New devices in heart failure: an European Heart Rhythm Association report

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Karl-Heinz Kuck* (Chairperson) (Germany), Pierre Bordachar (France), Martin Borggrefe (Germany), Giuseppe Boriani (Italy), Haran Burri (Switzerland), Francisco Leyva (UK), Patrick Schauerte (Germany), Dominic Theuns (The Netherlands), Bernard Thibault (Canada)

Document Reviewers: Paulus Kirchhof (Review Coordinator) (UK), Gerhard Hasenfuss (Germany), Kenneth Dickstein (Norway), Christophe Leclercq (France), Cecilia Linde (Sweden), Luigi Tavazzi (Italy), Frank Ruschitzka (Switzerland)

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Several new devices for the treatment of heart failure (HF) patients have been introduced and are increasingly used in clinical practice or are under clinical evaluation in either observational and/or randomized clinical trials. These devices include cardiac contractility modulation, spinal cord stimulation, carotid sinus nerve stimulation, cervical vagal stimulation, intracardiac atrioventricular nodal vagal stimulation, and implantable hemodynamic monitoring devices. This task force believes that an overview on these technologies is important. Special focus is given to patients with HF New York Heart Association Classes III and IV and narrow QRS complex, who represent the largest group in HF compared with patients with wide QRS complex. An overview on potential device options in addition to optimal medical therapy will be helpful for all physicians treating HF patients.

Keywords
Heart failure devices • Narrow QRS complex • Pressure monitoring • Cardiac contractility modulation

Introduction
The Committee for scientific documents of the European Heart Rhythm Association felt, that several new devices for the treatment of heart failure (HF) patients have been introduced and are increasingly used in clinical practice or are under clinical evaluation in either observational and/or randomized clinical trials. So far, most of these technologies, if not all, have not been addressed in guidelines or position papers. Recently, several expert consensus documents and guidelines on device therapy in HF have been published followed by the publication of the 2012 EHRA/HRS consensus statement and new 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy in 2013. Therefore, this position paper does not include any recommendation on cardiac resynchronization therapy (CRT) in heart failure.

Recommendations should represent evidence-based medicine. However, except for cardiac contractility modulation (CCM), no data based on randomized trials are available, and for none of the new devices clinical outcome data, in particular mortality data, are available.

Nevertheless, this task force believes that an overview on these new technologies is important and necessary. Special focus is given to patients with HF New York Heart Association (NYHA) Classes III and IV and narrow QRS complex, who represent the largest group in HF compared with patients with wide QRS complex. Therefore, the task force believes that an overview on potential device options in addition to optimal medical therapy (OMT) would be helpful for all physicians treating HF patients.

Cardiac contractility modulation
Cardiac resynchronization therapy improves symptoms, quality of life (QoL), exercise tolerance, and reduces hospitalizations in patients with advanced HF and prolonged electrical activation (i.e.

* Corresponding author. Tel: +49-(0)40-1818 852305; fax: +49-(0)40-1818 854444, E-mail: kuckkh@aol.com

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increased QRS duration). The results of a recent study showed that patients with mechanical dyssynchrony detected by tissue Doppler imaging but a normal QRS duration did not benefit from CRT. While the results of outcome trials of CRT in patients with a normal QRS duration are negative including Echo-CRT, a QRS \( \geq 120 \) ms remains as one of the criterion for selecting patients for CRT. Patients with a QRS duration \( > 120 \) ms represent 31\% of HF patients in a recent trial. The indications for CRT have been summarized in a recent update of ESC guidelines on devices in heart failure.

Although CRT is indicated in patients with a prolonged QRS duration, up to 60\% of patients with HF have a normal QRS duration. According to European registries published recently, even in the broad QRS population, those cared in hospital cardiology setting and meeting the current indications to CRT therapy were 6\%, and among them approximately one-third only were actually implanted with a CRT device. Therefore, although the last ESC guidelines on HF extended the indications to CRT in chronic heart failure, a substantial proportion of patients remain either not eligible for CRT or simply do not respond. At a time when pharmacological therapy for HF has made only little advances, it is appropriate to explore whether new device-based therapies have anything else to offer to patients with heart failure.

**Background**

Cardiac contractility modulation signals are non-excitatory signals which, when applied during the absolute refractory period, enhance the strength of left ventricular (LV) contraction and improve exercise tolerance as well as QoL in patients with heart failure. As the signals influence cell function without any affecting activation sequence, the effects are independent of QRS duration and should be additive to those of CRT.

**Concept of cardiac contractility modulation**

Cardiac contractility modulation signals are electrical impulses delivered during the absolute refractory period (Figure 1). Cardiac contractility modulation signals used in clinical practice are delivered \( \approx 30 \) ms after detection of the QRS complex onset and consist of two biphasic \( \pm 7 \) V pulses spanning a total duration of \( \approx 20 \) ms. These signals do not elicit a new action potential or contraction, as is the case with extra- or postextrasystolic contractions. Moreover, they do not affect the sequence of electrical or mechanical activation, nor do they recruit additional contractile elements. On this basis, CCM signals are referred to as ‘non-excitatory’.

**Implantation technique**

Cardiac contractility modulation signals are provided by a pacemaker-like impulse generator (OPTIMIZER III, IMPULSE Dynamics) that connects to the heart via two standard active-fixation leads placed endocardially on the right ventricular (RV) septum (Figure 2). An additional right atrial lead is used to detect the timing of atrial activation which, upon detection by an algorithm, ensures appropriate timing of CCM signal delivery without the risk of inducing ventricular arrhythmias. Cardiac contractility modulation pulses contain 50–100 times the amount of energy delivered in a standard pacemaker impulse and are, therefore, readily identified by body surface electrocardiography (Figure 1). Aside from the superimposed electrical artefact, there is generally no significant effect on the underlying ECG signal. Within several minutes of the acute CCM signal application, a mild increase in ventricular contractile strength can be detected as indexed by increases in LV pressure (LVP) and the rate of rise of LVP (\( \frac{dP}{dt_{\text{max}}} \)). Haemodynamic responses to acute CCM signal application are measured with a micromanometer catheter (Millar Instruments) placed in the LV. An increase in the maximum rate of LVP rise (\( \frac{dP}{dt_{\text{max}}} \), an index of systolic function) of at least 5\% is defined as a significant response to CCM. If such changes cannot be achieved, even after repositioning of the electrodes, the device is not implanted. The acute change \( \frac{dP}{dt_{\text{max}}} \) is independent of QRS duration. Moreover, in patients with prolonged QRS duration, the acute contractile effects of CCM are additional to those of CRT, as expected from a therapy that exerts its effects on substrates other than dyssynchrony.
The impact of a HF therapy on myocardial energetics is an important factor to consider in long-term safety and efficacy. Therefore, the acute effects of CCM on myocardial energetics were investigated in a clinical study in which myocardial oxygen uptake (MVO₂) and LV ejection fraction (EF) were measured in nine patients exposed to acute CCM signals. In this study, acute CCM was associated with an increase in dP/dt max from ~630 to ~800 mmHg/s (an ~20% increase). Despite an acute increase in contractility, there was no detectable increase in myocardial oxygen consumption. These data were compared with those of Nelson et al., who had also measured MVO₂ and dP/dt max during temporary RV and biventricular pacing (BIV) pacing. In this study, contractility was increased first by applying CRT and then dobutamine to achieve a comparable increase in dP/dt max. As expected from its effects on calcium cycling, dobutamine increased both dP/dt max and MVO₂. In contrast, CCM increased dP/dt max but not MVO₂. Thus, like CRT, the acute, modest increase in contractility achieved by CCM does not increase energy demands. In addition to acute haemodynamic effects noted above, improvement in global ventricular function has also been reported during chronic CCM signal application. In one study, 30 patients with ejection fraction (EF) < 35% and NYHA III symptoms despite OMT underwent three-dimensional echocardiography at baseline and 3 months after CCM treatment. Left ventricular ejection fraction (LVEF) increased by 4.8 ± 3.6% and LV end-systolic volumes decreased by 11.5 ± 10.5%, respectively. These findings indicate that LV reverse remodelling could be achieved by CCM in the background of optimum medical therapy.

**Mechanisms of action**

Several recent studies have sought to define the mechanisms by which CCM signals impact on regional and global myocardial function. Early studies had shown that electromagnetic fields can impact on protein–protein interaction and gene expression. Since the CCM-induced increases in contractility are not associated with an increase in MVO₂, CCM signals may have a direct impact on cellular physiology beyond typical acute effects on calcium handling that underlie pharmacological inotropic effects. To explore this hypothesis, myocardial samples were initially obtained for molecular (northern blot) and biochemical (western blot) analyses from an animal model of HF in both acute and chronic studies. Samples were taken from the interventricular septum (near the site of CCM signal delivery) and in a remote area on the LV free wall. Emphasis was placed on genes and proteins of high abundance whose tissue content were known to be significantly altered in heart failure. It was demonstrated that one of the most rapid effects of CCM is that near the site of signal delivery. There is, within minutes, increases in phosphorylation of phospholamban, a key protein that modulates the activity of sarco-endoplasmic reticulum calcium ATPase type 2a (SERCA2a) which in turn modulates calcium handling by the sarcoplasmic reticulum. Shortly thereafter, changes in gene expression can be demonstrated. For example, the expression of SERCA2a was decreased in untreated HF animals in both the interventricular septum (‘near’) and remote from the LV free wall (‘remote’). For tissue obtained from animals with acute (4 h) CCM treatment, SERCA2a expression increased in the region near the site of CCM signal administration, but not in the remote region. After 3 months, however, SERCA2a expression was improved in both near and remote regions. These findings were reproduced by other genes whose expression is decreased in chronic heart failure. Brain natriuretic peptide (BNP) expression was also examined but in this case, BNP was overexpressed in untreated heart failure, decreased acutely only in the region near the CCM pacing site, and decreased in both the near and remote sites with chronic CCM treatment. The fact that gene expression is improved in the short term only near the area of treatment implies that the effects of CCM treatment are local and direct. However, in the long run, where expression is improved in both near and remote sites, two possible factors may contribute. First, changes in gene expression in remote areas may be secondary to the global haemodynamic benefits provided by chronic regional CCM treatment. Alternatively, there may be some direct effect that is transmitted to remote sites via gap junctions. These findings concerning the molecular effects of CCM treatment in an animal model of HF were confirmed in a study with right endomyocardial biopsies performed in patients with heart failure. Most interestingly, improvements in gene expression correlated with improvements in peak VO₂ and Minnesota Living with Heart Failure Questionnaire (MLWHFQ). These correlations were present for patients with coronary artery disease (CAD) and reduced LV function and in patients with idiopathic cardiomyopathy. These findings indicate that CCM treatment reversed cardiac maladaptive foetal gene programme and normalized expression of key sinus rhythm (SR) Ca⁺⁺⁺ cycling and stretch response genes.

**Chronic signal application in heart failure patients**

Following three small pilot studies of chronic CCM signal application, a multicentre randomized, double-blind, double-crossover study was performed in HF patients with EF ≤ 35% and NYHA Class II or III symptoms despite OMT (the FIX-HF-4 study). One hundred and sixty-four subjects with EF < 35% and NYHA Class II (24%) or III (76%) symptoms received a CCM pulse...
These differences represent a statistically significant positive treatment effect in a cross-over study design confirmed that 428 patients recruited from 50 sites in the US (FIX-HF-5 study). The second randomized study of CCM was a multicentre study involving 35% of the small sample size, the trends suggest greater effects than in the larger subgroup of patients with EF ≥ 25% (Tables 1 and 2). Long-term results from the observational study in 54 patients with advanced HF have shown no adverse effect of CCM on long-term survival.

Patients were randomly assigned to Group 1 (n = 80, CCM treatment 3 months, sham treatment second 3 months) or Group 2 (n = 84, sham treatment 3 months, CCM treatment second 3 months). The co-primary endpoints were changes in peak oxygen consumption (VO2peak) and MLWHFQ. Baseline EF (29.3 ± 6.69% vs. 29.8 ± 7.8%), VO2peak (14.1 ± 3.0 vs. 13.6 ± 2.7 mL/kg/min) and MLWHFQ (38.9 ± 27.4 vs. 36.5 ± 27.1) were similar between groups. VO2peak increased similarly in both groups during the first 3 months (0.40 ± 3.0 vs. 0.37 ± 3.3 mL/kg/min), suggesting a placebo effect. During the next 3 months, however, VO2peak decreased in the group switched to sham (–0.86 ± 3.06 mL/kg/min) and increased in patients switched to active treatment (0.16 ± 2.50 mL/kg/min). At the end of the second phase of the study, the difference in peak VO2 between groups was approximately 1 mL/kg/min. After performing statistical testing for carryover effects and period effects, data from both study phases could be formally combined to arrive at a net treatment mean (+SD) treatment effect on VO2peak of 0.52 ± 1.39 mL/kg/min (P = 0.032). Quality of life, assessed using the MLWHFQ, behaved similarly, trending only slightly better with treatment (–12.06 ± 15.33 vs. –9.70 ± 16.71) during the first 3 months, again consistent with a large placebo effect. During the second 3 months, MLWHFQ increased in the group switched to sham (+4.70 ± 16.57) and decreased further in patients switched to active treatment (–0.70 ± 15.13) (a reduction in scores denoting an improvement in QoL). As was the case for VO2peak, formal statistical testing of data from a cross-over study design confirmed that these differences represent a statistically significant positive treatment effect (P = 0.030). Serious cardiovascular adverse events (AEs) were tracked carefully in both groups. The study met its primary endpoint using the formal analysis of a cross-over study design; both exercise tolerance and QoL improved significantly during the on periods compared with the off periods. The most frequently reported AEs were episodes of decompensated heart failure, atrial fibrillation (AF), bleeding at the OPTIMIZER System implant site and pneumonia. Importantly, there were no significant differences between ON and OFF phases in the number or types of AEs. The second randomized study of CCM was a multicentre study involving 428 patients recruited from 50 sites in the US (FIX-HF-5 study). Patients were characterized by NYHA Class III (89%) or IV (11%), QRS duration averaging 101 ms and EF averaging 25%. Patients were required to be receiving stable optimized medical therapy, defined as a beta-blocker, angiotensin converting enzyme-inhibitor (ACE-I) or angiotensin receptor blocker and a diuretic for at least 3 months (unless intolerant); the daily dose of each medication could not vary by more than a 50% reduction or 100% increase over the prior 3 months. Patients were randomized (1:1 and stratified for ischaemic or non-ischaemic underlying aetiology) to OMT plus CCM (n = 215) or OMT alone (n = 213). The primary safety endpoint was the test of non-inferiority between groups at 12 months for the composite of all-cause mortality and all-cause hospitalizations (12.5% allowable delta). Efficacy was assessed by changes in exercise tolerance and QoL at 6 months compared with baseline. Exercise tolerance was indexed by ventilator anaerobic threshold (VAT, which was the declared primary endpoint) and by peak VO2 (pVO2). Quality of life was assessed by the MLWHFQ. Furthermore, the primary analysis of these endpoints was a ‘responders analysis’ which was between-group comparison of the percent of patients whose VAT increased by ≥20%. The study groups (OMT vs. CCM) were comparable for age (58 ± 13 vs. 59 ± 12 years), congestive heart failure (CHF) aetiology (67 vs. 65% ischaemic aetiology), QRS duration (101 ± 0.5 vs. 101 ± 0.6 ms), EF (26 ± 7 vs. 26 ± 7%), VAT (11.0 ± 2.2 vs. 11.0 ± 2.2 mL/kg/min), pVO2 (14.7 ± 2.9 vs. 14.8 ± 3.2 mL/kg/min), and other important baseline characteristics. The safety endpoint of the study was met; by the end of 1-year follow-up, 52% of patients in the treatment group and 48% of patients in the control group met a study-specified safety endpoint, which was non-inferior by both a Blackwelder’s test of non-inferiority and by a log-rank test comparing Kaplan–Meier survival curves. Regarding efficacy, pVO2 was 0.7 mL/kg/min greater (P = 0.024) and MLWHFQ was 9.7 points better (P < 0.0001) in the treatment group than in the control group. However, the primary endpoint of this study was not reached. There was no difference for VAT between the groups (neither based on a responders analysis or a comparison of mean changes between the groups). The study protocol indicated that efficacy effects would be explored in specific patient subsets. This analysis showed that particularly large effects on both VAT and pVO2 were observed in patients with a baseline EF ≥ 25% and NYHA Class III symptoms. In this subgroup (which consisted of 97 OMT and 109 CCM group patients, nearly half of the entire study cohort), VAT was 0.64 mL/kg/min greater (P = 0.03), pVO2 was 1.31 mL/kg/min greater (P = 0.001), and MLWHFQ was 10.8 points better (P = 0.003) in the treatment group than in the control groups. Regarding the results of the ‘responders analysis’ 5.8% of OMT and 20.5% of CCM patients exhibited a ≥20% increase in VAT, a difference of 14.7%, at 6 months (P = 0.007). Furthermore, in this subgroup, the effects on exercise tolerance and QoL were sustained through the entire 12-month follow-up period of the study. This finding has interesting implications related to the purported mechanisms of action. Cardiac contractility modulation signals are applied to one region of the heart and are believed to have direct and relatively rapid local effects. It is hypothesized that secondary remote effects are achieved, over time, when the local effect is large enough to have a sufficient effect on global function. Heart size increases as EF decreases; it can therefore be speculated that the larger the heart the less the impact on global function and the less effective the therapy. To further test this hypothesis, an additional subgroup analysis was performed. There were 38 patients in the FIX-HF-5 study with an EF ≥ 35%. These patients were admitted to the study because the EF determined at the investigative site was <35%; however, all analyses were based on the core lab EF assessment. Eighteen of the patients were in the treatment group and 20 patients were in the control group. In this subgroup, efficacy parameters were even more greatly improved by CCM: peak VO2 was 2.96 mL/kg/min greater (P = 0.03), VAT was 0.57 mL/kg/min greater (P = ns), and MLWHFQ score was 18 points better (P = 0.06) in the CCM group compared with the OMT group. Although not all of these differences were statistically significant in view of the small sample size, the trends suggest greater effects than in the larger subgroup of patients with EF ≥ 25% (Tables 1 and 2). Long-term results from the observational study in 54 patients with advanced HF have shown no adverse effect of CCM on long-term survival.
Combining cardiac contractility modulation with cardiac resynchronization therapy

As discussed above, CCM signals applied in the acute setting to HF patients simultaneously receiving CRT provide additive effects on LV contractility indexed by \( \frac{dP}{dt}_{\text{max}} \). In view of the fact that symptoms persist in more \( \approx 30\% \) of patients with prolonged QRS duration receiving CRT, it can be postulated that addition of CCM treatment may provide an option for these patients. The initial experience of combining CCM in a CRT non-responders has been published. It was demonstrated that the implantation procedure is technically feasible, that the OPTIMIZER and CRT defibrillator (CRT-D) devices can coexist without interference and that acute haemodynamic and clinical improvements can be observed. These preliminary results, however, have to be confirmed in a prospective study that is

Table 1 New therapeutic devices in heart failure

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Effects and status of trials</th>
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<tbody>
<tr>
<td><strong>Cardiac contractility modulation (CCM)</strong></td>
<td><strong>Enhances the strength of LV contraction</strong></td>
</tr>
<tr>
<td>CCM signals are non-excitatory signals delivered to the LV ( \sim 30 \text{ ms after QRS onset} )</td>
<td><strong>Decreases LV volumes and increases EF</strong></td>
</tr>
<tr>
<td>Effects are independent of QRS duration and additive to those of CRT</td>
<td><strong>Improves exercise tolerance and quality of life</strong></td>
</tr>
<tr>
<td>CCM signals acutely affect calcium handling but also expression of proteins and genes involved in Ca handling</td>
<td><strong>RCTs: FIX-HF-4, FIX-HF-5</strong></td>
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| **Spinal cord stimulation** | **Improves cardiac work efficiency, decreases myocardial oxygen demand** |
| Stimulation of afferent spinal nerve fibres | **Reduces risk of ischaemic ventricular arrhythmia** |
| Increase of central vagal tone and decrease of sympathetic tone via central reflex activation | **SCS-HEART (ongoing non-RCT)** |
| **Carotid sinus nerve stimulation** | **DEFEAT-HF (ongoing RCT)** |
| Stimulation of afferent fibres coupled to arterial baroreceptors | **Improves systolic and diastolic LV function** |
| Increase of central vagal tone and decrease of sympathetic tone via central reflex activation | **Slight decrease of heart rate and blood pressure** |
| **Cervical vagal nerve stimulation** | **XR-1 Heart Failure Study; HOPE4HF study (ongoing RCTs)** |
| Stimulation of cervical pre-ganglionic parasympathetic fibres | **Antiarrhythmic, rate slowing, antifibrotic, anti-inflammatory, and reverse remodelling effects** |
| Direct activation of overall cardiac vagal tone | **Decreases LV volumes and increases EF** |
| **Intracardiac AV-nodal vagal stimulation** | **Improves exercise tolerance and quality of life** |
| Stimulation of post-ganglionic cardiac parasympathetic nerves selectively innervating AV node | **CardioFit study (non-RCT)** |
| **Implantable haemodynamic monitoring devices** | **INNOVATE-HF (ongoing RCT)** |
| **RV-pressure monitoring** | **Dynamic ventricular rate control during AF** |
| Monitors: | **AV nodal selective** |
| Systolic and diastolic RV pressure | **May avoid inappropriate shock delivery in patients with AF and ICD/CRT-D** |
| RV \( \frac{dP}{dt} \) | **AVNS study (ongoing non-RCT)** |
| Pulmonary artery diastolic pressure | **Non-significant reduction of all CHF-related events (COMPASS-HF)** |
| Heart rate | **Reduces death and CHF events** |
| Patient activity | **Adequate adjustment of drug-therapy results in improvement of NYHA class and LVEF (HOMEOSTASIS study)** |
| Core body temperature | **Reduces significantly rate and duration of CHF-related hospitalization (CHAMPION study)** |

Table 2 Implantable haemodynamic monitoring devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Characteristics</th>
<th>Clinical outcome</th>
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<tbody>
<tr>
<td><strong>RV-pressure monitoring</strong></td>
<td>Monitors:</td>
<td><strong>Non-significant reduction of all CHF-related events (COMPASS-HF)</strong></td>
</tr>
<tr>
<td>Systolic and diastolic RV pressure</td>
<td><strong>Reduces death and CHF events</strong></td>
<td></td>
</tr>
<tr>
<td>RV ( \frac{dP}{dt} )</td>
<td><strong>Adequate adjustment of drug-therapy results in improvement of NYHA class and LVEF (HOMEOSTASIS study)</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure</td>
<td><strong>Reduces significantly rate and duration of CHF-related hospitalization (CHAMPION study)</strong></td>
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</tr>
<tr>
<td>Heart rate</td>
<td><strong>CardioFit study (non-RCT)</strong></td>
<td></td>
</tr>
<tr>
<td>Patient activity</td>
<td><strong>AV nodal selective</strong></td>
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</tr>
<tr>
<td>Core body temperature</td>
<td><strong>May avoid inappropriate shock delivery in patients with AF and ICD/CRT-D</strong></td>
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| **LA-pressure monitoring (Heart-POD)** | Monitors: | **Non-significant reduction of all CHF-related events (COMPASS-HF)** |
| LA pressure | **Reduces death and CHF events** |
| Intracardiac electrogram | **Adequate adjustment of drug-therapy results in improvement of NYHA class and LVEF (HOMEOSTASIS study)** |
| Body temperature | **Reduces significantly rate and duration of CHF-related hospitalization (CHAMPION study)** |

| **Pulmonary artery pressure (CardioMEMS)** | Monitors PAP | **Non-significant reduction of all CHF-related events (COMPASS-HF)** |

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underway to systematically investigate the effects of CCM in CRT non-responders.

Clinical perspectives

Two large-scale studies have validated the safety and suggested the effectiveness of CCM therapy. Results of these trials show that CCM improves exercise tolerance as indexed by peak VO₂. Other indices of exercise tolerance (e.g. 6 min hall walk) and QoL (NYHA class and MLWHFQ) have also been shown to improve. Data from both clinical trials suggest that mortality rates are unaffected by CCM therapy. However, the aim of these studies was to demonstrate an absence of increase in mortality as a safety end-point and was not powered to show a mortality benefit. The level of recommendation would be substantially higher if a gain in mortality can be demonstrated. In this respect, a specific subgroup of HF patients (EF ≥ 25%) is more likely to respond favourably. Moreover, more research is probably required to determine the optimal pacing configuration (single or bipolar stimuli, optimal delay from the pacing spike, optimal duration of each phase, and optimal amplitude of the signal), the optimal daily duration of application, the optimal localization of the pacing sites, and the optimal number of pacing sites to gain the maximal benefit from this therapy. The potential interest of CCM in early stages of HF has not been investigated.

Required technical improvement

Some technical limitations should be solved in the future: (i) with the last version of the device, CCM cannot be delivered in patients with AF or frequent ectopy, as it is designed to inhibit CCM delivery on arrhythmias and relies on detection of a P-wave. A future device is supposed to incorporate an algorithm that does not rely on P-wave detection and therefore could be used in patients with AF. (ii) The development of a device combining CCM with implantable cardioverter defibrillator (ICD) functions would be desirable in this population of HF patients. Future studies will be required to define whether CCM is additive to CRT pacemaker or CRT-D in patients with wide QRS.

This would be facilitated by the development of a single device that incorporates pacing, antitachycardia therapies, and CCM. (iii) A simple peri-implantation method to guide lead positioning would be desirable, beyond the invasive LV dP/dt max measurement.

Neuromodulation

Heart failure is associated with significant perturbances of the autonomic balance with predominant sympathetic activation over the parasympathetic system.33 – 35 Several indirect markers of cardiac vagal tone like heart rate variability, heart rate turbulence, baroreflex sensitivity are suppressed in CHF which in turn is predictive for a worse outcome of CHF.36,37 Likewise, an increase of cardiac vagal sensitivity is confirmed in patients with refractory angina44 associated with end-stage CAD45 – 48 and in the absence of CAD (syndrome X)49,50 Positive effects have also been demonstrated in the peripheral vascular beds: patients with severe pain due to distal atherosclerosis,51,52 in Raynaud’s disease, and at the level of cerebral vasculature.53 – 55

Spinal cord stimulation

Background

Preliminary work suggests some benefits from neuromodulation with SCS in HF patients.42 Spinal cord stimulation has been used for over 40 years in the management of chronic intractable pain.43 According to the American Association of Neurosurgical Surgeons (aans.org), as many as 50 000 neurostimulators are implanted worldwide every year. Among multiple indications, the benefits have been confirmed in patients with refractory angina44 associated with end-stage CAD45 – 48 and in the absence of CAD (syndrome X)49,50 Positive effects have also been demonstrated in the peripheral vascular beds: patients with severe pain due to distal atherosclerosis,51,52 in Raynaud’s disease, and at the level of cerebral vasculature.53 – 55

parasympathetic efferent activity and tone. Such input is likely provided by sensory afferent fibres from arterial baroreceptors or respiratory sensory neurons,40 but spinal cord afferent fibres may also connect to the brainstem and modulate cardiac vagal tone (Figure 3).41 Thus, attempts to therapeutically increase the cardiac parasympathetic tone by electrical neural stimulation may operate at any part of this integrative circuit. This has led to four neurostimulation approaches, two of which are focusing on reflex activation of the parasympathetic tone and sympathetic inhibition via afferent fibres, electrical neural stimulation [spinal cord stimulation (SCS), carotid sinus nerve stimulation], while two are concentrating on efferent parasympathetic stimulation (cervical vagal and intracardiac vagal stimulation).
More recently, Issa et al. showed improved LVEF, therefore decreasing oxygen myocardial demand. Since there is little evidence that SCS improves ischemia:59,60 SCS seems to affect the balance between oxygen demand and supply. There is little evidence that SCS improves the coronary blood flow in ischemic patients.61 – 63 Other factors acting in the balance between oxygen requirements and supplies have to play an important role. Spinal cord stimulation applied at the low cervical (C7–C8) and/or high thoracic (T1–T6) level exerts effects through reflex activation of the vagus nerve and sympathetic (Figure 4).64

Overall, the cumulated effects on both the sympathetic and the parasympathetic system seems to be a re-equilibrium of the balance in favour of the latter.65 – 72 Other positive effects via the cytokines and the NO/NOS system73 – 75 have been identified and appear to be far more complex than just the suppression of the nociceptive influx associated with myocardial ischemia:59,60 SCS seems to affect the balance between oxygen demand and supply. Since there is little evidence that SCS improves the coronary blood flow in ischemic patients.61 – 63 other factors acting in the balance between oxygen requirements and supplies have to play an important role. Spinal cord stimulation applied at the low cervical (C7–C8) and/or high thoracic (T1–T6) level exerts effects through reflex activation of the vagus nerve and sympathetic (Figure 4).64

Mechanisms of action
Spinal cord stimulation compared positively with surgical66 and laser endo-myocardial revascularization48,57 in patients with severe refractory angina associated with severe CAD without any increase in adverse ischemic events. This suggests that the improvement in symptoms and the clinical condition of these patients was mediated only partially through the ‘gate-control’ mechanisms described by Melzack and Wall in 1965.58,59 The involved mechanisms remain incompletely understood and appear to be far more complex than just the suppression of the nociceptive influx associated with myocardial ischemia:59,60 SCS seems to affect the balance between oxygen demand and supply. Since there is little evidence that SCS improves the coronary blood flow in ischemic patients.61 – 63 other factors acting in the balance between oxygen requirements and supplies have to play an important role. Spinal cord stimulation applied at the low cervical (C7–C8) and/or high thoracic (T1–T6) level exerts effects through reflex activation of the vagus nerve and sympathetic (Figure 4).64

Overall, the cumulated effects on both the sympathetic and the parasympathetic system seems to be a re-equilibrium of the balance in favour of the latter.65 – 72 Other positive effects via the cytokines and the NO/NOS system73 – 75 have been identified and there may even be some direct protective mechanisms on the myocardium during ischemia.64,72,76 Despite, all that is known from the abundant data accumulated over the last 30 years on ischemic patients (and animals), very little is known about the effects of SCS on the systolic function of the LV. In 1993, Kujacic et al. found by echocardiography, that the LVEF decreased less with adenosine infusion under SCS compared with the control situation in 15 patients with severe multivessel CAD. Interestingly, the baseline LVEF was also slightly higher at rest under SCS (48%) than without SCS (44%) (P value not provided).77 In 2001, Gersbach et al. showed improved cardiac output, reduced peripheral resistance, and increased cardiac work efficiency, therefore decreasing oxygen myocardial demand. More recently, Issa et al. found in a canine model of HF that SCS reduced the risk of ischemic ventricular arrhythmias. Interestingly, they also found, in accordance with the previous reference, that SCS reduced the sinus rate and the systolic blood pressure (consistent with anti-sympathetic effects).79 In 2009, the same group confirmed the long-term (5–10 weeks) beneficial effects of SCS in the same animal model. Compared with medical treatment or to controls, SCS resulted in a significant improvement of LVEF, clinical parameters (blood pressure and body weight), serum levels of BNP and norepinephrin, and fewer episodes of non-sustained VTs detected by the implanted ICD.80 Liu et al. used nine adult pigs in which HF was induced by myocardial infarction and 4 weeks of rapid pacing. The animals were studied 24 h after rapid pacing was turned off. Haemodynamic and echocardiographic data were collected at baseline (HF), after two sets of 15 min of SCS separated by 30 min of recovery. They found that SCS, in this acute model, significantly improved LVEF and maximum positive dP/dt while decreasing myocardial oxygen consumption. By echocardiography, the benefits in terms of LV function were present both globally and regionally, i.e. associated with better intra-ventricular synchrony assessed by speckle tracking.81 Finally, to our knowledge, there is only one recent report in patients. In 2009, at the HF Society meeting, Jesus et al. presented their initial experience with SCS in four patients with advanced HF: all patients were reported to have improved clinically and three increased the distance they covered during the 6 min walk test.

Technology and implant technique
The North-American Neuromodulation Society (NANS) has established guidelines concerning the training requirements for implantation and follow-up of SCS devices.82 The technique is well described.83 – 86 The procedure is performed under sedation with the patient lying prone on an X-ray compatible table allowing anteroposterior and lateral views. The peridural space is accessed at the L1–L2 level with a needle. The lead(s) is (are) advanced under fluoroscopic guidance up to the desired level in a posterior and median/para-median position close to the dorsal horn fibres (Figure 4). The impulse generator is usually implanted subcutaneously in the low back or high buttock with tunnelling of the leads down to that region. Complications are observed in up to 38% of the patients.51,83,87,88 Longer-term lead migration or breakage or other problems with the impulse generator can happen in 20–30% of the patients with a need for surgical correction in most of the cases. There are case reports of patients who were implanted with pacemakers89 – 92 or ICD’s93 – 95 and received a spinal stimulation system. Although electromagnetic interference is possible, using SCS is safe in these patients provided the sensing of the cardiac device is programmed in the bipolar mode, that the sensitivity is set at 0.3 mV and that the SCS is implanted contra-laterally and at a sufficient distance.96

Verification of the cardiac device is nevertheless advised to minimize the risks. Interestingly, their experiments with dogs, Lopshire et al.80 implanted 60 animals with both systems (SCS and ICD) and no interference was noted. Two companies produce the two types of devices and neither company cites SCS as contra-indicated in the presence of an implanted cardiac device. Of note, a SCS device could nevertheless be damaged by ICD discharges, probably due to important muscular contraction.75
Table 3 Major findings reported with SCS

| Spinal cord stimulation has been shown to have positive impact on cardiac ischaemia due to CAD: |
| 1. The mechanisms involved go beyond suppression of the nociceptive stimuli |
| 2. SCS has limited impact on coronary blood flow, therefore the mechanisms must lie somewhere else |
| 3. SCS has a profound positive impact on the cardiac sympathetic/parasympathetic balance |
| 4. SCS also affects positively the NO/NOS and cytokines system at the myocardiocardial level |

Spinal cord stimulation has shown some effects on LV function and ventricular arrhythmias:

1. One preliminary report on four HF patients who improved clinically with SCS
2. SCS was associated with smaller deterioration of LVEF due to adenosine administration in patients with multivessel CAD
3. SCS was associated with better invasive haodynamic evaluation in patients with normal LV function
4. SCS was associated with reduced risk of ventricular arrhythmias and LV function improvement in animal models of HF

Clinical perspectives

Spinal cord stimulation, via complex mechanisms, appears promising in pre-clinical experiments to improve the systolic function of the LV and to decrease the ventricular arrhythmias associated with this condition. According to Clinicaltrials.org, there are at the present time two ongoing clinical studies that are directly addressing the role—and possible benefits—of SCS in severely afflicted HF patients. SCS-HEART is a non-randomized feasibility study that aims to determine the safety of SCS in 20 patients with a LVEF between 20 and 35%, in NYHA functional class III, and who already have an ICD implanted. Results should be available in the second part of 2014. On the other hand, DEFEAT-HF (sponsored by Medtronic) is a single blind randomized study involving similar patients but that will compare SCS ‘ON’ vs. ‘OFF’ in 250 recipients. Results are also expected for the end of 2014. Until these studies are completed, it remains impossible to recommend this therapy in HF patients outside of the current recognized indications (Table 3).

Carotid sinus nerve stimulation

Background

Baroreceptors are embedded into the wall of arterial vessels and can be preferentially found in the aortic arch at the origins of the brachiocephalic or left subclavian artery, in the brachiocephalic artery at its bifurcation into the right subclavian and right common carotid artery, in the carotid sinuses, along both common carotid arteries, and in both common carotid arteries at the origin of the superior thyroid artery. They respond to changes in arterial pressure and mediate their signals via afferent rapid conducting (2.5–60 m/s) myelinated A fibres and slow conducting (<2.5 m/s) non-myelinated C fibres to the brainstem1 where they connect to efferent vagal neurons. A-type receptors respond to normal arterial pressures and are regularly discharging at high frequency (>100 Hz) synchronously to the pulsatile pressure wave. By contrast, C-type baroreceptor respond to higher threshold values of the mean arterial pressure with irregular firing at lower frequency of 20–30 Hz. Increases of arterial blood pressure elicit a reflexatory activation of efferent vagal fibres resulting in a decrease of the sinus heart rate. The baroreflex activation is considered as powerful contributor to the baseline parasympathetic tone. During human HF, this baroreflex is profoundly suppressed and worsens with deterioration of CHF. Thus, electrical stimulation of afferent carotid sinus nerves, which connect baroreceptors to the brainstem, may evolve as a tool for increasing cardiac vagal tone during HF.

Mechanisms of action

Electrical stimulation of the baroreceptor fibres (carotid sinus nerve fibres) elicits a graded response decrease of heart rate and arterial pressure via parasympathetic efferent activation and sympathetic withdrawal and has recently been clinically introduced for treatment of resistant arterial hypertension. The potential of electrical carotid sinus nerve stimulation to shift the autonomic balance towards a higher parasympathetic tone has also been investigated in HF models. In fact, chronic low-intensity carotid sinus stimulation, which lowers blood pressure by only 10–15 mm Hg and which does not critically decrease heart rate was able to improve survival in dogs with pacing-induced HF. In addition, LV systolic and diastolic function improved due to reverse LV geometric and interstitial remodelling. In parallel, the downregulation of B1 receptor density in CHF was almost normalized to control levels and serum catecholamine levels declined which may be taken as evidence for a direct or reflexatory decrease of the systemic sympathetic tone in these models.

Technology and implant technique

The first systems consisted of an implantable battery powered pulse generator that was placed subcutaneously in the pectoral region as well as two leads with finger-shaped bipolar electrodes that are surgically implanted circumferentially around each carotid sinus. The electrode wires (leads) were tunnelled subcutaneously to the impulse generator near the collarbone. The impulse generator delivered rectangular pulses (3, 5, or 7 V while keeping constant current). The size of the finger electrodes and the need to wrap around the vessel increased the risk of causing injury to the surrounding nerves. The next generation of BAT—the Neo system—was thus developed.

However, the implantable pulse generator (Figure 5) provides extended battery longevity (longevity of Rheos system 1 year, Neo system 3 years) and a smaller size pulse generator. Instead of two leads, the Neo system consists of only one lead that requires less dissection of the carotid artery for implantation. The iridium oxide-coated unipolar electrode is flat and disk-shaped with a 6 mm diameter (providing stimulation currents of 2, 5, or 8 mA while keeping the stimulation voltage constant). The implant procedure can be done in local anaesthesia with sedation.
Clinical data

The Rheos system was the first baroreceptor stimulation system by CVRx implanted in hypertensive patients. The Rheos system was so far evaluated in three multicentre clinical studies in patients with resistant hypertension: the DEBuT-HT/DEBuT-HET in Europe\textsuperscript{110} and the Rheos Feasibility Trial and Rheos Pivotal Trial\textsuperscript{107} which mostly included patients in the USA. The Rheos pivotal trial is in long-term follow-up by now.\textsuperscript{111} The randomized part of the trial with a 12-month blinded follow-up was published in 2011:\textsuperscript{107} 265 patients with resistant hypertension received the device and were either randomized to immediate BAT or delayed BAT following the 6-month visit. Three of the five pre-specified co-primary endpoints were met: long-term sustained response to baroreceptor activation therapy, with 88% responders after 12 months of follow-up, incidence of short-term AEs (6-month follow-up), and long-term AEs (12-month follow-up). The study did not meet the endpoints for acute responders (54 vs. 46% responders after 6-month follow-up) and procedural safety (event-free rate 74.8%). A majority of these events were related to the carotid sinus lead placement and involved transient or permanent nerve injury that occurred during the implant. The majority (76%) of procedure-related AEs resolved completely.

To date, there exist no randomized clinical data evaluating the effectiveness of BAT in patients with systolic HF. In addition to experimental data,\textsuperscript{111–113} several sub-studies and single-centre data indicated beneficial physiological effects of BAT beyond just blood pressure reduction.\textsuperscript{114–116}

Clinical perspectives

The CVRx Neo system has received the CE mark in the fourth quarter of 2011. With the Neo system, a verification study for the treatment of patients with resistant hypertension was conducted in Europe and Canada. Thirty patients had a 6-month follow-up and showed average systolic blood pressure reduction of 26 mmHg. In the USA, the HOPE4HF study\textsuperscript{117} is planned with the primary endpoint assessing the effects of BAT on HF hospitalizations in patients with HF and preserved EF.

In patients with systolic HF, the randomized XR-1 Heart Failure Study has started patient recruitment. One hundred and forty subjects are planned to be randomized 1 : 1 at either device therapy or medical therapy alone at up to 30 sites in Europe and Canada. Main inclusion criteria are LVEF ≤ 35%, HF NYHA Class III, optimal stable HF therapy for at least 4 weeks, and patient’s age between 18 and 80.

Primary endpoint is to determine whether BAT with the Neo system produces a change in LVEF from screening through 6 months for subjects treated with BAT therapy relative to standard of care. Secondary endpoints are 6 month changes in the following measures: 6 min hall walk test, NYHA classification, quality of life, using the Minnesota Living With Heart Failure Questionnaire, NT-proBNP, creatinine levels, central pressure and haemodynamic parameters, echocardiographic parameters and indices of rhythm status derived from 24 h Holter recordings, and additional echocardiographic parameters. The primary safety objective is to describe safety by estimating the rate of all system- and procedure-related complications. The primary exclusion criteria are significant stenosis or former surgery of carotid arteries, severe chronic obstructive lung disease, terminal renal failure, and acute cardiac decompensation. Interestingly patients with the combination of narrow QRS complex and permanent AF can be included in this study—a patient group that cannot be considered for CRT or CCM therapy.

Cervical vagal nerve stimulation

Background

The efferent cardiac parasympathetic signalling chain comprises preganglionic parasympathetic neurons originating in the brainstem, which course inside the vagal nerve and connect via nicotinergic acetylcholine receptors to post-ganglionic neurons, which are aggregated in circumscribed cardiac ganglionic plexus inside the heart. Post-ganglionic fibres then innervate the cardiac target cells via muscarinergic acetylcholine receptors.
During CHF, the density of cardiac muscarinergic receptors is increased, which is most probably due to an adaptive upregulation secondary to a decreased efferent vagal input. However, the post-ganglionic vagal nerve transmission seems to be intact in HF: selective electrical stimulation of post-ganglionic vagal nerve fibres to the sinus node leads to a larger decrease of the sinus rate in HF dogs than in controls, which would be in line with an increased number of muscarinergic receptors in HF. By contrast, electrical stimulation of pre-synaptic cervical vagal fibres led to a smaller decrease of the sinus rate in CHF animals as compared with control animals. Thus, pre- to post-ganglionic parasympathetic efferent neurotransmission via nicotinergic acetylcholine receptors seems to be impaired during CHF. Importantly, these nicotinergic receptors are agonist dependent and chronic exposure to a nicotinic agonist during HF has been shown to reestablish efferent parasympathetic neural control of the sinus node. These experiments form a pathophysiological rationale to apply electrical pre-ganglionic cervical vagal nerve stimulation to reestablish the diminished cardiac vagal tone in CHF.

**Mechanisms of action**

Several studies in various chronic HF animal models have shown a reduction of the progression of HF and a survival benefit with cervical vagal nerve stimulation. Major contributing mechanisms are detailed as follows:

1. **Antiarrhythmic effects**: Vagal nerve stimulation increases the ventricular refractory period in humans, leads to a prolongation of the epicardial action potential duration, and decreases ventricular vulnerability to ventricular fibrillation. These electrophysiological effects may contribute to its potent antifibrillatory effects as demonstrated during cervical vagal nerve stimulation experiments in post-infarction animal models. In addition, vagal nerve stimulation in HF reduces the loss of Cx43, which may prevent proarrhythmic conduction delays and dispersion of action potential duration.

2. **Rate slowing effects**: Vagal nerve stimulation exerts profound negative chronotropic and dromotropic effects. Since an increased heart rate is associated with adverse prognosis in CHF, a reduction of heart rate both in SR and AF might contribute beneficial therapeutic effects in CHF.

3. **Antifibrotic effects**: In a coronary microembolization-induced HF model, chronic cervical vagal nerve stimulation has been shown to decrease ventricular replacement fibrosis and to blunt the development of CHF-associated cellular hypertrophy of remaining myocytes.

4. **Anti-inflammatory effects**: Vagal nerve stimulation has potent anti-inflammatory effects. Recently, vagal nerve stimulation was shown to blunt HF-associated increases of tumour necrosis factor-α, interleukin-6, and C-reactive protein in two animal models of HF.

5. **Reverse remodelling**: Vagal nerve stimulation decreases ventricular end-systolic and end-diastolic diameters and improves LVEF. Chronic vagal stimulation has also been shown to reduce NT-proBNP levels in a dog HF model and biventricular weight in a rat HF model.

**Figure 6** (A) Chest X-ray of an implanted cervical vagal nerve stimulator in a patient with severely reduced LV systolic function. The device has been implanted via the right side and consists of a ventricular sensing lead and a cervical vagal nerve electrode. On the left side an ICD had been previously implanted. (B) Example of a cervical vagal stimulator. The device carries two electrodes: one conventional RV screw-in pace/sense electrode monitors the heart rate during vagal nerve stimulation, while the other cuff electrode is wrapped around the cervical vagal nerve. (C) Local implantation site of the CVS: there are two incisions, one for exposure of the cervical vagal nerve and a second one for implanting the RV electrode. The vagal electrode is tunnelled subcutaneously to the impulse generator, which is implanted below the collarbone. (D) Exposed cervical vagal nerve.
Technology and implant technique

Implanting the stimulation lead in the neck is the unique component of this treatment, and important issues concerned are discussed below, assuming that placing a RV sensing lead and the implantable stimulator are done routinely by many cardiologists who are trained in implanting pacemakers (Figure 6):

1. A surgeon with knowledge and understanding of the neck anatomy should be appointed for this procedure. Often, neurosurgeons, ENT, or head and neck surgeons; or vascular or cardiothoracic surgeons who perform carotid endarterectomy will be good candidates.
2. The surgical approach should favour exposure of the vagus nerve rather than the carotid artery, upon dissection of the carotid sheath.
3. Manipulation of the nerve should be minimized, with working posterior and around the nerve favoured over its lifting when placing the stimulation lead cuff.
4. Attention should be given to proper selection of the cuff electrode size, as its fitting on the nerve is important to the vagus functionality: too tight a cuff might damage the nerve, while too loose one does not allow stimulation currents concentration in the nerve, creating side effects and decreasing treatment effectiveness. Training in proper use of the tools available for determining appropriate cuff size: including, the nerve diameter gauge and impedance measurements and allowed ranges should be performed.
5. Fixation of the stimulation lead should be performed via suture sleeves to stable fascia and not to muscles with wider range of motion. Care should be taken to leave sufficient slack as strain relief.

Figure 6 shows an example of a patient with an implantable vagal nerve stimulator.

Clinical data

The first multicentre, open-label phase II, two-staged study (8-patient feasibility phase plus 24-patient safety and tolerability phase) enrolled 32 NYHA Class II–IV patients (age 56 ± 11 years, LVEF 23 ± 8%). Right cervical vagal nerve stimulation (VNS) with an implantable system started 2–4 weeks after implant, slowly raising intensity; patients were followed 3 and 6 months thereafter with optional 1-year follow-up. Overall, 26 serious AEs occurred in 13 of 32 patients (40.6%), including three deaths and two clearly device-related AEs (post-operative pulmonary oedema, need of surgical revision). Expected non-serious device-related AEs (cough, dysphonia, and stimulation-related pain) occurred early but were reduced and disappeared after stimulation intensity adjustment. There were significant improvements \((P = 0.001)\) in NYHA class QoL, 6 min walk test \((from \ 411 + 76 \ to \ 471 + 111 \ m)\), LVEF \((from \ 22 + 7 \ to \ 29 + 8\%\), and LV systolic volumes \((P = 0.02)\). These improvements were maintained at 1 year.131

Several scientific articles have summarized the use of cervical vagal nerve stimulator (CVS) in patients with CHF.131–133 Naturally, the data provided in those articles are limited, due to the small patient cohort and the non-randomized nature of first in man and safety and feasibility studies; however important considerations can be drawn from them:

(1) Patients with mild-to-moderate HF can tolerate the higher current amplitudes and other parameters used in chronic vagal stimulation vs. the parameters used for treatment of epilepsy.
(2) Vagal stimulation may generate side effects like hoarseness, voice alteration, and increased cough. The majority of side effects are related to the underlying disease or a multitude of co-morbidities.
(3) In patients with both CVS and ICD, no interferences from vagal stimulation were recognized by the ICD nor were detectable on the intracardiac electrogram of the device.
(4) CVS increased parasympathetic tone of subjects with HF (as measured by heart rate variability on 24 h Holter recordings; and as inferred by reduction of resting heart rate).
(5) Vagal stimulation improved subjective, as well as objective clinically relevant parameters of functional class, quality of life, submaximal exercise capacity, and cardiac structure and function in a first clinical study.

Unresolved issues

Atrial proarrrhythmia

At the atrial level, an increased vagal tone substantially shortens the atrial refractory period and increases the heterogeneity of refractory periods in the atria.132,133 Whether this might promote the occurrence of AF especially in HF patients with a diseased atrial substrate is unknown. Experimental evidence in healthy dogs, however, suggests that the occurrence of AF during cervical vagal nerve stimulation depends on the intensity of vagal stimulation with no AF occurrence at lower level stimulation.135 Data on the occurrence of AF during vagal stimulation in HF patients need to be gathered prospectively.

Selectivity of neural stimulation

The cervical vagal nerve contains efferent and afferent fibres coursing not only to the thoracic but also to or from the abdominal viscera.136 So far, the issue of concomitant stimulation of efferent parasympathetic fibres to the gastrointestinal tract has not yet been thoroughly investigated. Such inadvertent stimulation might increase gastric acid secretion or increase intestinal motility. Likewise, afferent electrical stimulation or block of the vagal nerve below the diaphragm has been shown to decrease food intake and to reduce weight gain.137,138 Since these fibres potentially course through the cervical vagal nerve inadvertent stimulation or block of these fibres may occur during vagal nerve stimulation for HF possibly inducing weight loss masking as cardiac cachexia.

Clinical perspectives

CVS has not yet undergone randomized control studies. The currently performed increase of vagal tone in CHF (INOVATE-HF; NCT 01303718) prospective randomized controlled trial should provide data to determine whether patients with HF will be able to benefit from this new treatment method. Due to the inherent issues of blinding of patients and healthcare providers to the activity of a nerve stimulator, an open-label study design has been elected and authorized by regulatory authorities in the USA and Europe (Germany and Serbia). The purpose of the INOVATE-HF study is to demonstrate the long-term safety and efficacy of vagus nerve stimulation with the CardioFitTM system for the treatment of subjects with HF. Up to 650 patients with LV systolic dysfunction...
(EF < 40%) and HF NYHA Class III despite OMT are included in 60 centres. Patients are randomized 3:2 in active vs. control and followed for at least 12 months. The planned study duration is about 5.5 years. The two co-primary safety endpoints are freedom from procedure- and system-related events through 90 days post-implant > 75% and time to first event in all-cause mortality and complications resulting in prolonged hospitalization. The primary efficacy endpoint of the study is a composite of all-cause mortality and unplanned HF hospitalization equivalent using a time to first event analysis, when a pre-specified number of events have been accumulated in both arms. That design enables more thorough examination of safety issues related to the implant and activation of this new treatment modality, a necessity in the current regulatory environment. In addition to safety, that design enables more accurate comparison of the effect of chronic vagal stimulation on clinical outcome parameter, that include mortality and HF hospitalizations.

Given the substantial theoretical background coupled with the beneficial effect of increased vagal tone on patients longevity in patients with HFr and in patients post-MI, it is conceivable that in patients whose baseline vagal tone is low and in whom the parasympathetic tone is increased via VNS, clinical benefit may be observed.

Intracardiac atrioventricular nodal vagal stimulation

Background

Thirty to forty percent of patients with CHF eventually will develop AF. Rapid ventricular rates during AF may further deteriorate HF or decrease the degree of LV resynchronization in patients with cardiac resynchronization devices and may ultimately lead to inappropriate shock delivery in up to 5% of ICD recipients. Long-term selective atrioventricular (AV) nodal vagal stimulation for ventricular rate control has been developed as potential adjunctive treatment modality for these patients.

Mechanisms and experimental models

Post-ganglionic cardiac vagal fibres, which preferentially supply the AV node reside in an inferior right ganglionated plexus (IRGP) at the postero-inferior interatrial septum. This makes them amenable to stimulation from the endocardial surface, thus resulting in a graded response negative dromotropic effect. Chronic stimulation of the IRGP in animal models provides reliable and well-tolerated ventricular rate control in dogs and has been shown to be haemodynamically superior to His bundle ablation and RV pacing probably because ventricular conduction over the His–Purkinje system is maintained.

Technology and implant technique

The IRGP is located at the epicardial surface of the heart between the ostium of the coronary sinus and the entrance of the inferior vena cava. For chronic electrostimulation of this plexus, atrial pacing leads of current technology can be screwed into the IRGP from the right atrial endocardial site at the postero-inferior interatrial septum either by using specifically shaped guiding catheters or manually shaped conventional mandrins.

Clinical data

Recently, the feasibility of such an approach was shown in a series of chronic human implants in HF patients with AF. A prospective multicentre study (AVNS: AV node stimulation study, NCT01095952), which investigates whether short-term probatory AV nodal vagal stimulation may avoid inappropriate shock delivery in patients with resynchronization defibrillators is ongoing.

Electrical determinants of neurostimulation

Electrical stimulation of parasympathetic pre- or post-ganglionic efferent fibres obeys the same fundamental laws as myocardial electrostimulation with the exception that the chronaxie time of 180 μs is shorter. In contrast to the myocardial action potential, the action potential of neurons is very short lasting only 10–20 ms. Thus, transmitter release and physiological effects may be elicited by electrical stimulation at higher frequencies, which typically is set to 20–50 Hz during cervical vagal stimulation for seizures or depression. 100 Hz for carotid sinus stimulation, or 4–20 Hz for cervical vagal stimulation in HF. For post-ganglionic effervent parasympathetic stimulation the frequency-responsivity curve is bell-shaped with an optimum at 40 Hz. Since most stimulated nerve structures contain afferent and efferent autonomic fibres with varying fibre diameter and conduction velocities, efforts have been undertaken to preferentially stimulate efferent fibres. For example, cervical vagal nerve stimulation for treatment of HF aims to stimulate afferent parasympathetic B fibres coursing towards the heart but tries to avoid afferent A and C fibre excitation. This can be achieved by hyperpolarizing the nerve fibres at the anode thus preventing excitation and simultaneously depolarizing fibres at the cathode. Since larger afferent A fibres (diameter 5–20 μm) are more sensitive to hyperpolarization than smaller efferent B fibres (1–3 μm) inside the vagal nerve preferential efferent stimulation can be accomplished. Besides electrode configuration, the applied stimulus strength also affects differential recruitment of A–C fibres and changes the frequency dependence of afferent neural stimulation. Finally, the application of biphasic impulses may bare the benefit of decharging the membrane with the second phase of the impulse thus preventing damage to the neurocytes.

Implantable haemodynamic monitoring devices

Clinical management to prevent acute decompensated heart failure (ADHF) and/or hospitalization in ambulatory HF patients remains challenging. There is an urgent need to develop strategies to reduce hospitalizations and re-admission rates for HF. Frequent monitoring of physiological data is imperative in the management of HF. The development of wireless and remote technology makes it possible to frequently monitor and transfer data via telemonitoring. The concept of telemonitoring involves patient-activated automatic devices which provide physiological parameters such as weight, blood pressure, heart rate, rhythm, and activity logs. Results of studies using telemonitoring have been contradictory. A meta-analysis demonstrated that telemonitoring may provide
better outcomes compared with usual care, with a reduction in mortality and HF hospitalizations.\(^{158}\) Recently, the value of telemonitoring has been challenged by two randomized clinical trials. The results of the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial showed no significant difference in all-cause mortality (primary endpoint) or in the composite of cardiovascular death or HF hospitalization.\(^{159}\) The study of Chaudhry et al.\(^{160}\) demonstrated that telemonitoring failed to reduce HF hospital admissions, duration of hospital stay, or the frequency of admissions. One explanation might be the insensitivity of daily weight monitoring to predict HF hospitalization, which is \(\sim 20\%\).\(^{161}\)

Another strategy is the use of cardiac implantable devices (defibrillators and CRT) to stratify the risk of ADHF based on a single parameter as thoracic impedance\(^{162,163}\) or heart rate variability,\(^{160}\) or a combination of parameters.\(^{164,165}\) These parameters, single or combined, have a sensitivity of 60%–70%, a predictive positive value up to 7.8%, and false-positive alarms ranging from 1.8 to 2.7 per patient-year of monitoring. Although these parameters enable physicians to identify patients at increased risk of ADHF, they do not impact patient outcomes and are not sufficiently accurate to adjust treatment. A new approach to monitor the status of ambulatory HF patients and preventing potential hospitalizations may involve implantable devices providing real-time haemodynamic data to the clinician. Device companies began to develop new implantable devices designed to collect haemodynamic data. These investigational devices include RV, left atrial pressure (LAP), and pulmonary artery pressure (PAP) sensors.

### Right ventricular pressure monitoring

#### The device, implantation, and monitored data

The Chronicle (model 9520, Medtronic Inc.) is an implantable haemodynamic monitor. The system consists of a specialized transvenous lead that has a sensor incorporated near the tip to measure intracardiac pressure and a programmable device similar in size and shape to a pacemaker. Details of the components have been previously described.\(^{166}\) The device is able to monitor and telemeter systolic and diastolic RV pressure, RV dP/dt (positive and negative), to estimate pulmonary artery diastolic pressure, to monitor heart rate and patient’s activity, and to measure core body temperature. In addition, continuous remote monitoring of data is available. The implantation procedure is similar to that of a single-lead pacemaker. The device is positioned subcutaneously in the pectoral area and the lead is placed transvenously in the RV outflow tract or septum. The patient is furnished with a small external device, which aids in correcting for barometric pressure. The monitor capabilities includes pressure sensing circuitry and a memory to store continuous pressure trends, as well as specific triggered events such as bradyarrhythmias, tachyarrhythmias, or patient-activated episodes. The device continuously measures and stores RV systolic, diastolic, and pulse pressure, estimated pulmonary arterial diastolic pressure (ePAD), RV dP/dt, pre-ejection interval, and systolic time interval. The ePAD is defined as the RV pressure at the time of pulmonary valve opening or maximal RV dP/dt and has been shown to correlate with PA diastolic pressures (\(r = 0.87\) at baseline and 1 year), thus reflecting LV filling pressure.\(^{167,168}\) In addition, heart rate, patient activity levels, and central venous temperature are also monitored and stored.

#### Clinical data

The early clinical experience with this implantable haemodynamic monitor was obtained on 32 HF patients followed for 17 months.\(^{169}\) In this non-controlled study monitoring of RV pressures at long term showed either marked variability or minimal time-related changes. However, during clinical events due to volume-overload events, RV systolic pressures increased on average by 25%, occurring around 4 ± 2 days before the HF exacerbations requiring hospitalization. In this patient cohort use of haemodynamic data lead to a significant reduction of hospitalizations in comparison with previous patients’ history and this was the basis for planning the COMPASS-HF study (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure).\(^{170}\)

The COMPASS-HF study was a multicentre, single-blinded trial in which all 274 participants received the implantable haemodynamic monitoring, but were randomized to either an intervention arm in which the device diagnostic data were used for patient management on the basis of a set of recommendations (\(n = 134\)) or to a control (\(n = 140\)) group (no access to device diagnostics data for the first 6 months of the study). The enrolment criteria for this trial included HF with NYHA functional class III or IV, regardless of LVEF with optimized standard medical therapy for at least 3 months before enrolment. During the study three study visits over 6 months were planned. A decrease in HF-associated events was the primary endpoint and lack of system-related complications and pressure-sensor failures were the safety endpoints. Although healthcare providers were not blinded to treatment assignment, blanking of patients was maintained using both written communications and telephonic contacts.

The study results showed that the two safety endpoints were met (system-related complications in only 8% of cases), but the primary efficacy endpoint was not met because the Chronicle group had a non-significant 21% lower rate of all HF-related events compared with the control group (\(P = 0.33\)). This finding is partly explained by a lower than expected event rate. A retrospective analysis showed a 36% reduction (\(P = 0.03\)) in the relative risk of first HF-related hospitalization in the chronicle group with no difference with regard to LVEF (\(\geq 50\%\)).

#### Clinical perspectives

In March 2007, FDA’s Circulatory System Devices Panel voted against the approval of Chronicle implantable haemodynamic monitor because its use was not proved to significantly improve clinical outcomes in the COMPASS-HF randomized, controlled trial. The following step has been the planning of a trial designed to test the potential usefulness of combining the haemodynamic monitoring capabilities of an implantable monitoring device with an ICD in patients at risk of sudden cardiac death. Indeed, a new trial, REDUCE-CEHF, was designed to enrol 850 patients (then increased to 1300) with indication for an ICD (NYHA functional class II or III with reduced LVEF) to test the hypothesis that the use of RV pressure-guided patient management would reduce HF-related events.
hospitalization and emergency department or urgent clinic visit requiring parenteral therapy). Because of technical complications, REDUCEHf was prematurely ended after enrolment of 400 patients. Data analysis showed no benefit from haemodynamic monitoring and a lower than expected event rate. Demonstrating the efficacy of HF disease management programmes using RV pressure monitoring was particularly difficult and many issues appear to condition the ability to demonstrate a substantial clinical benefit. These factors include the degree of HF severity in the tested population, the quality of comparative usual care (with a potential low-external validity if the trial is managed by highly specialized centres), the choice of the primary endpoint (the need for medical visits may actually increase during continuous monitoring in view of earlier detection of worsening HF, but this may imply avoidance of subsequent hospitalizations), as well as the specific characteristics of the disease management programme adopted. Moreover, it is possible that a substantial improvement in patient care will require to couple the information provided by an implantable haemodynamic sensor to an effect or capable of promptly instituting an appropriate therapy, thus ‘closing the loop’ and limiting the need for interventions of healthcare providers.

**Left atrial pressure monitoring**

Patients admitted for decompensated HF usually have elevated LAP causing pulmonary congestion and oedema. The rise in LAP is usually gradual and precedes the onset of symptoms. Therefore, monitoring of LAP has the potential to forecast and abort HF decompensation by adjusting drug therapy.

**The device**

The HeartPOD (St Jude Medical) comprises an implantable sensor lead that measures pressure, intracardiac electrograms, and temperature, coupled to a coil antenna positioned in the subcutaneous tissue (Figure 7). Folding proximal and distal nitinol anchors fix the sensor lead onto the interatrial septum. The device is either standalone or coupled to a CRT-D unit. A handheld patient advisory module (PAM) powers the implanted device (which has no battery) by radio-frequency wireless transmission. The PAM also measures the atmospheric pressure, that is then subtracted from the pressure measured in the implant to obtain LAP. During interrogation, physiological waveforms of LAP and intracardiac electrograms are captured in the memory of the PAM for periods of up to 20 s. The PAM has the capacity to store ~3 months of data with six daily interrogations.

**Implantation**

The device is implanted by cardiac catheterization and transseptal puncture, and requires special training. Access may either be (i) entirely femoral, with implantation of the sensor module in a lower right abdominal pocket, (ii) entirely superior with transseptal puncture performed by a deflectable sheath and a special puncture screw, or (iii) combined, with the transseptal puncture performed by femoral access and lead transfer to a superior access using a snare. The device was implanted successfully in 82 of 84 (98%) subjects included in the HOMEOSTASIS study, without any reported major periprocedural cardiac or neurological AEs. Post-implantation, patients are maintained on daily aspirin, as well as clopidogrel for ≥6 months. The bulk of foreign body material in the left atrium is less compared with septal defect closure devices, and post-mortem examination shows that fibrous tissue subsequently covers most of the pressure sensor (Figure 8), thus limiting thromboembolic risk.

**Clinical data**

The first human experience with the HeartPOD is reported in the HOMEOSTASIS study, which is a prospective, multicentre, observational open-label registry in patients with NYHA III/IV HF, regardless of LVEF. The first human experience with the HeartPOD is reported in the HOMEOSTASIS study, which is a prospective, multicentre, observational open-label registry in patients with NYHA III/IV HF, regardless of LVEF.
82 patients. Correlation between simultaneous measurement of LAP and pulmonary artery wedge pressure was high at 3 months ($r = 0.97$) and at 12 months ($r = 0.99$). Freedom from device failure was 95% ($n = 37$) at 2 years and 88% ($n = 12$) at 4 years. Causes of device failure were related to either measurement issues (artefacts or drift) or to communication malfunction. The clinical impact of the HeartPOD on patient outcome was reported in 40 patients. After a 3-month observation period, patients entered a 3-month titration period where vasodilator and diuretic drug therapy was adjusted by a physician based upon the LAP readings. A ‘stability’ period was then followed during $\geq 6$ months, whereby drug therapy, sodium and fluid intake, activity level, or physician contact was adjusted based upon five ranges of LAP readings that had been individually adjusted by the physician during the titration period. Compared with the observation period, the annual rate in death or HF events was significantly decreased during the titration and stability periods (0.68 vs. 0.28 per year; $P = 0.041$). Also, there were improvements in NYHA class ($-0.7 \pm 0.8$, $P < 0.001$) and LVEF ($7 \pm 10\%$, $P < 0.001$). Even though these results are encouraging, it should be stressed that the study was not randomized. The ongoing LAPTOP-HF study is a randomized clinical trial recruiting up to 730 patients with maximally treated NYHA III HF (irrespective of LVEF) randomized 1:1 to receive a HeartPOD vs. a PAM only (for reminding drug therapy), that aims to show a reduction in worsening HF and hospitalizations. Successful extraction of the HeartPOD has been reported, although details are not provided. A locking stylet may be used, if necessary with an extraction sheath. The presence of an atrial septal defect after extraction is a possible issue, although the fibrotic membrane covering the HeartPOD may limit this complication.

**Clinical perspectives**

Self-titration of HF therapy by patients based upon LAP readings (similar to diabetics adjusting insulin levels with glycaemia) is a paradigm shift in HF management. This strategy of course requires patient participation and compliance, and may not be suitable for many individuals. Patients with diastolic HF are a therapeutic challenge, in whom volume overload may rapidly cause pulmonary congestion. Analysis of the LAPTOP-HF data in this subset of patient will clarify whether titration of diuretics based upon LAP readings improves outcome. LAP data may be of use to optimize AV delays in CRT-HeartPOD devices (as the left atrial A-wave is recorded), but has not as yet been tested.

In conclusion, preliminary data relating to the HeartPOD show good mid-term device function and hold promise for improving patient self-management in HF. These data however need to be confirmed by the ongoing randomized LAPTOP-HF trial. Device implantation requires special training, and techniques are still evolving. The presence of a lead allows extraction (contrary to PAP monitor), but further experience is required to better evaluate procedural complications.

**Pulmonary artery pressure monitoring**

**The device**

The CardioMEMS heart failure sensor (CardioMEMSInc.) consists of a coil and a pressure-sensitive capacitor housed in a hermetically sealed silica capsule covered in medical-grade silicone. Two wired nitinol loops at the ends of the capsule serve as anchors to prevent distal migration of the sensor.

[Figure 9](#) The CardioMEMS sensor consists of a coil and a pressure-sensitive capacitor housed in a hermetically sealed silica capsule covered in medical-grade silicone. Two wired nitinol loops at the ends of the capsule serve as anchors to prevent distal migration of the sensor.
antenna, which is held against the patient’s body. The antenna powers the implanted device, continuously measures its resonant frequency, which is then converted to a pressure waveform. The interrogating device measures the atmospheric pressure, which is subtracted from the pressure measured by the implanted sensor. The CardioMEMS sensor is designed to measure PAP.

Sensor delivery system and implantation
The CardioMEMS sensor is supplied pre-loaded and attached to a tether wire at the end of the delivery catheter. The sensor is implanted by using a venous femoral approach. First, a Swan–Ganz catheter is advanced into the deployment site in the pulmonary artery. After identification of the target artery, a guidewire (0.018–0.025 inch) is placed through the Swan–Ganz catheter to allow the sensor delivery catheter system to be advanced. The delivery catheter is advanced over the wire and released in the target vessel. After removal of the delivery catheter, the Swan–Ganz catheter is replaced into the pulmonary artery proximal to the sensor. Subsequently, the implanted sensor is calibrated using PAPs acquired from the Swan–Ganz catheter.

Experimental data
Animal studies with follow-up up to 6 months showed good correlation between sensor-based measurements and invasive pressure evaluations, and no propensity for in situ thrombus formation (K. Robinson et al. 2005, unpublished results). The first human implant of a wireless pressure sensor for monitoring PAP was performed in 2007.178 At 60 days post-implantation, no complications were observed and there was no evidence of pulmonary thrombosis. Subsequently, an observational cohort study was performed in 12 ambulatory HF patients to evaluate the accuracy of sensor-based determinations compared with measurements obtained by Swan–Ganz catheterization and echocardiography.179 The results of this study demonstrated high correlation between simultaneous sensor-based PAP measurements and Swan–Ganz catheterization at baseline ($r^2 = 0.90$) and at 60 days follow-up ($r^2 = 0.94$). The correlation between sensor and echocardiography was good ($r^2 = 0.75$). Systolic pressure obtained by the sensor tended to be higher than those measured by Swan–Ganz catheterization, which can be explained by differences in measurement method and sampling rate.

Clinical data
Recently, the results CardioMEMS HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III Heart Failure Patients (CHAMPION) prospective, multicentre, randomized, single-blind clinical trial were published.180 All patients ($n = 550$) received the device implantation but physicians were blinded to daily PAP measurements in the control group ($n = 280$). The goal was to evaluate the efficacy and safety of the PAP sensor. The study met the safety endpoints; freedom from device- or system-related complications was 98.6% and overall freedom from pressure-sensor failures was 100%. The primary efficacy endpoint was the rate of HF hospitalizations over 6 months. The use of daily PAP measurements reduced the rate of HF hospitalizations by 30% (hazard ratio 0.70, 95% confidence interval, 0.60–0.84; $P < 0.001$). Over the entire randomization period, the rate of HF hospitalizations was reduced by 39% in the treatment group. When admitted for HF, patients in the treatment group had significantly shorter length of stay compared with those in the control group (2.2 ± 6.8 vs. 3.8 ± 11.1 days, $P = 0.02$). The CHAMPION study was the first study where the use of diagnostic data significantly reduced HF events. Two trial design issues are worth noting, which distinguish the CHAMPION trial from other device diagnostic studies. The issues include, (i) target population risk, and (ii) intensity of intervention. The target population in CHAMPION focused on HF patients with sustained NYHA Class III symptoms for at least 90 days prior to enrollment. Low-risk NYHA Class II and end-stage NYHA IV patients were excluded from the study. In addition, patients with chronic kidney disease (estimated glomerular filtration rate < 25 mL/min/1.73 m²) were excluded due to non-response to changes in medications in the outpatient setting. The major difference between the CHAMPION trial and other device diagnostic studies can be attributed to the intensity of intervention. The CHAMPION trial had specific pressure targets that providers were supposed to achieve using neurohormonal, diuretic, and/or vasodilator therapy. A significantly higher number of medication changes were observed in the treatment group compared with the control group (9.1 ± 7.4 vs. 3.8 ± 4.5 per patient, $P < 0.001$).

Clinical perspectives
In November 2011, FDA’s Circulatory System Devices Panel voted against the approval of the CardioMEMS implantable haemodynamic monitor because its use was not proved to significantly improve clinical outcomes in the randomized, single-blind CHAMPION trial. The greatest concern is the trial’s design, which made it impossible to distinguish any treatment effect from the device itself in the single-blind trial. Physicians knew which patients had the device and specific treatment recommendations were made in the treatment group and not in the control group. Ambulatory HF patients are at high risk for hospital admission. There is an urgent need to develop strategies to reduce hospitalizations and re-admission rates for HF. New technologies for invasive haemodynamic monitoring have been developed as an adjunct to clinical follow-up. The results of studies with implantable haemodynamic monitoring devices show great promise as adjunctive tools in the management of HF patients. The technology of haemodynamic monitoring is not incorporated in current defibrillators or devices with CRT. Future studies have to evaluate whether a role exists for combining impedance measurements by current cardiac devices with haemodynamic sensors.

Conflict of interest: The disclosure forms of the authors and reviewers are available on the EHRA website www.escardio.org.

References
3. Brignole M et al. ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the
New devices in heart failure: an European Heart Rhythm Association report

European Society of Cardiology (ESC), Developed in collaboration with the European Heart Rhythm Association (EHRA). European 2013;15:1070–118.


McMurray JJ et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2010 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.


Sabbah HN et al. Cardiac contractility modulation with the impulse dynamics signal: studies in dogs with chronic heart failure. Heart Fail Rev 2001;6:45–53.


chronic pacemaker treatment for cardiac arrhythmias. 2003;
poraneous double spinal cord stimulation.
verter defibrillator in a patient with continuous spinal cord stimulation.
stimulation on pacing-induced angina pectoris.
calcitonin-gene-related peptide in the human heart and the effects of spinal cord
responses to different stressors in canine ventricles.
Comp Physiol
failure.
implications for its therapeutic use in angina pectoris.
Neuromodulation targets intrinsic cardiac neurons to attenuate
Jacques F et al. Spinal cord stimulation causes potentiation of right vagus nerve
effects on atrial chronotropic function and repolarization in canines. J Cardiovasc
Southernland EM et al. Preemptive, but not reactive, spinal cord stimulation
mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic
Binkley PF et al. A polymorphism of the endothelial nitric oxide synthase promoter
is associated with an increase in autonomic imbalance in patients with congestive
Markos F et al. Nitric oxide facilitates vagal control of heart rate via actions in the
cardiac parasympathetic ganglia of the anaesthetised dog. Exp Physiol 2002; 87:
49–52.
Li W et al. Inflammatory cytokines and nitric oxide in heart failure and potential
Elliasson T et al. Myocardial turnover of endogenous opioids and
calcitonin-gene-related peptide in the human heart and the effects of spinal cord
Kujacic V et al. Assessment of the influence of spinal cord stimulation on left ventricular
Issa ZF et al. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular
arrhythmias in a postinfarction heart failure canine model. Circulation 2005; 111:
3217–20.
Henderson JM et al. Nans training requirements for spinal cord stimulation devices:
Bedder MD et al. Spinal cord stimulation surgical technique for the nonsurgically
Mehdialina et al. Retrospective review of 707 cases of spinal cord stimulation: indi-
Ferrerot P et al. Spinal cord stimulation affects T-wave alternans in patients with isch-
Enggaard TP et al. Spinal cord stimulation for refractory angina in patients implanted
Ooi YC et al. Simultaneous use of neurostimulators in patients with a preexisting cardiovascular implantable electronic device. Neuromodulation 2011; 14:20–5; dis-
Kirchheim HR. Systemic arterial baroreceptor reflexes. Physiol Rev 1976; 56:
100–77.
Czachurski J et al. Localization of neurons with baroreceptor input in the medial
solitary nucleus by means of intracerebral application of horseradish peroxidase in the
Andresen MC et al. Nucleus tractus solitarius—gateway to neural circulatory
Kollai M et al. Relation between baroreflex sensitivity and cardiac vagal tone in
Eckberg DL et al. Defective cardiac parasympathetic control in patients with heart
Bristow MR et al. Decreased catecholamine sensitivity and beta-adrenergic
Brunner-La Rocca HP et al. Effect of cardiac sympathetic nervous activity on mode of
Creager MA et al. Arterial baroreflex regulation of blood pressure in patients with
Marin-Neto JA et al. Abnormal baroreflex control of heart rate in decompensated
congestive heart failure and reversal after aspersion. J Am Coll Cardiol 1991; 16:
64–10.
Fan W et al. Graded and dynamic reflex summation of myelinated and unmyelinated
Bisogno JD et al. Baroreflex activation therapy lowers blood pressure in patients
with resistant hypertension: results from the double-blind, randomized, placebo-
Tordoir JH et al. An implantable carotid sinus baroreflex activating system: surgical
technique and short-term outcome from a multi-center feasibility trial for the treat-
Ilig KA et al. An implantable carotid sinus stimulator for drug-resistant hyperten-
sion: surgical technique and short-term outcome from the multicenter phase II
Scheffers JM et al. Novel baroreflex activation therapy in resistant hypertension:
results of a European multi-center feasibility study. J Am Coll Cardiol 2010; 56:
1254–8.
Zucker IH et al. Chronic baroreceptor activation enhances survival in dogs with
Sabbah HN et al. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in
Wang M et al. Long-term baroreflex activation therapy increases the threshold for
the induction of lethal ventricular arrhythmias in dogs with chronic advanced heart
Wustmann K et al. Effects of chronic baroreflex stimulation on the autonomic
cardiovascular regulation in patients with drug-resistant arterial hypertension.
Heusser K et al. Chronic baroreflex activation: a potential therapeutic approach
to heart failure with preserved ejection fraction carotid baroreceptor stimulation,
sympathetic activity, baroreflex function, and blood pressure in hypertensive
Brandt MC et al. Baroreflex activation as a novel therapeutic strategy for
Georgakopoulos D et al. Chronic baroreflex activation: a potential therapeutic ap-
Vatner DE et al. Physiological and biochemical evidence for coordinate increases in
Bibeysi S et al. Ganglionic mechanisms contribute to diminished vagal control in
Bibeysi S et al. Prevention of diminished parasympathetic control of the heart in
Vanoli E et al. Vagal stimulation and prevention of sudden death in conscious dogs
Li M et al. Vagal nerve stimulation markedly improves long-term survival after
New devices in heart failure: an European Heart Rhythm Association report

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