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# Extra-cardiac targets in the management of cardiometabolic disease: Device-based therapies

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## Abstract

Heart failure (HF) does not occur in a vacuum and is commonly defined and exacerbated by its co-morbid conditions. Neurohormonal imbalance and systemic inflammation are some of the key pathomechanisms of HF but also commonly encountered co-morbidities such as arterial hypertension, diabetes mellitus, cachexia, obesity and sleep-disordered breathing. A cornerstone of HF management is neurohormonal blockade, which in HF with reduced ejection fraction has been tied to a reduction in morbidity and mortality. Pharmacological treatment effective in patients with HF with reduced ejection fraction did not show substantial effects in HF with preserved ejection fraction. Here, we review novel device-based therapies using neuromodulation of extra-cardiac targets to treat cardiometabolic disease.

**Keywords** Heart Failure; Comorbidities; Autonomic Nervous System; Neuromodulation

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## Introduction

Our understanding of the pathomechanisms that lead to or aggravate heart failure (HF) signs and symptoms has evolved. It is increasingly well understood that heart failure with reduced ejection fraction (HFrEF) and even more so heart failure with preserved ejection fraction (HFpEF) are not merely the results of cardiac structure abnormalities. In patients with HF, neurohormonal activation and increased levels of inflammatory mediators promote ventricular remodelling, vascular dysfunction and development of HF. Yet, HF is not a disease state in isolation, but rather a syndrome closely linked to co-morbid conditions that in themselves can lead to a progression of the disease, consequently independently increasing morbidity and mortality. Across the whole spectrum of left ventricular ejection fraction (LVEF), HF is characterized by a high burden of co-morbid disease. Although both HFpEF and HFrEF are marked by a high burden of co-morbidities, patients with HFpEF tend to be older, more frequently hypertensive and obese.[1,2] Beyond the high burden of co-morbid disease, the significance of extra-cardiac disease is highlighted by the fact that in a large acute HF trial, the majority of 30-day readmissions were for non-HF causes and one-third of readmissions occurred in the first 7 days.[3]

Neurohormonal imbalance and systemic inflammation are some of the key mechanisms of HF but also commonly encountered co-morbidities such as arterial hypertension, diabetes mellitus, cachexia, obesity and sleep-disordered breathing (SDB).[4,5] A cornerstone of HF management is neurohormonal blockade, which in HFrEF has been tied to a reduction in morbidity and mortality. In many cases, the progression of the syndrome can be significantly slowed by available pharmacological treatments but not stopped, despite the fact that substantial advances have been made in the

field.[6,7] Additional pathways mostly independent of neurohormonal modulation are the sodium glucose cotransport inhibitors[8] and soluble guanylate cyclase activators.[9] Pharmacological treatment effective in patients with HFrEF did not show substantial effects in HFpEF (CHARM-Preserved, PEP-CHF, I-PRESERVE, TOPCAT, PARAGON).[10–13] Central treatment options aiming to reduce morbidity or mortality in patients with HFpEF are diuretics for symptom control and aggressive management of co-morbidities.[14] Hemodynamic monitoring strategies that aim to trend and optimize volume/pressures and personalize medical intervention have been some of the few successful strategies for HFpEF.[15]

Several new approaches have emerged in recent years for the treatment of HF and related co-morbid diseases (*Figure 1*). Here, we review novel device-based therapies applying neuromodulation of extra-cardiac targets to treat cardiometabolic disease. The review reflects discussions among representatives from academia, regulatory agencies and industry at the Device-Heart Failure (D-HF) meeting (Paris, France, December 2019).

## Baroreceptor activation therapy

The baroreflex originates from the carotid sinus and aortic arch. Baroreceptors sense arterial distension as a surrogate of a pressure change. Afferent fibres from baroreceptors innervate the nucleus of the solitary tract in the medulla. Activation of the baroreflex modulates the efferent sympathetic and parasympathetic activity via the rostral ventrolateral medulla and nucleus ambiguous.[16] The arterial baroreflex is the key reflex mechanism to regulate autonomic tone of most organ systems such as the heart, blood vessels, adrenal glands, kidneys and lungs. The arterial baroreflex is impaired in patients with HF and hypertension and signifies an imbalance between sympathetic and parasympathetic tone.[5,17] The baroreflex is not the only autonomic reflex (i.e. chemoreflex) to be impaired in HF and co-morbid diseases but rather the downstream manifestation of cardiac injury, tissue hypoxia and metabolic dysregulation with resultant neurohormonal imbalance.[18–20] Isolated injury to the baroreflex alone can induce HF in preclinical models.[21]

Baroreflex activation therapy (BAT) (Barostim Neo System, CVRx, Inc.) results in a centrally mediated reduction of sympathetic outflow and increased parasympathetic activity to the heart via a physiological reflex pathway. The device has two parts that are surgically implanted: a pulse generator that is placed under the skin near the clavicle and a lead that is attached onto the carotid artery. The safety and effectiveness of BAT were investigated in the BeAT-HF pivotal study (#NCT02627196) (*Figure 2*). Subjects with HF were defined by the New York Heart Association (NYHA) as functional Class III with LVEF $\leq$ 35% and NT-proBNP$<$1600 pg/ml despite

**Figure 1** Central figure. Heart failure and co-morbid diseases are characterized by an elevated sympathetic tone. Co-morbidities contribute to heart failure progression by an additional dysregulation of the neurohormonal state. Novel device-based therapies targeting neurohormonal dysregulation present a new therapeutic avenue for the treatment of HF and related co-morbidities.

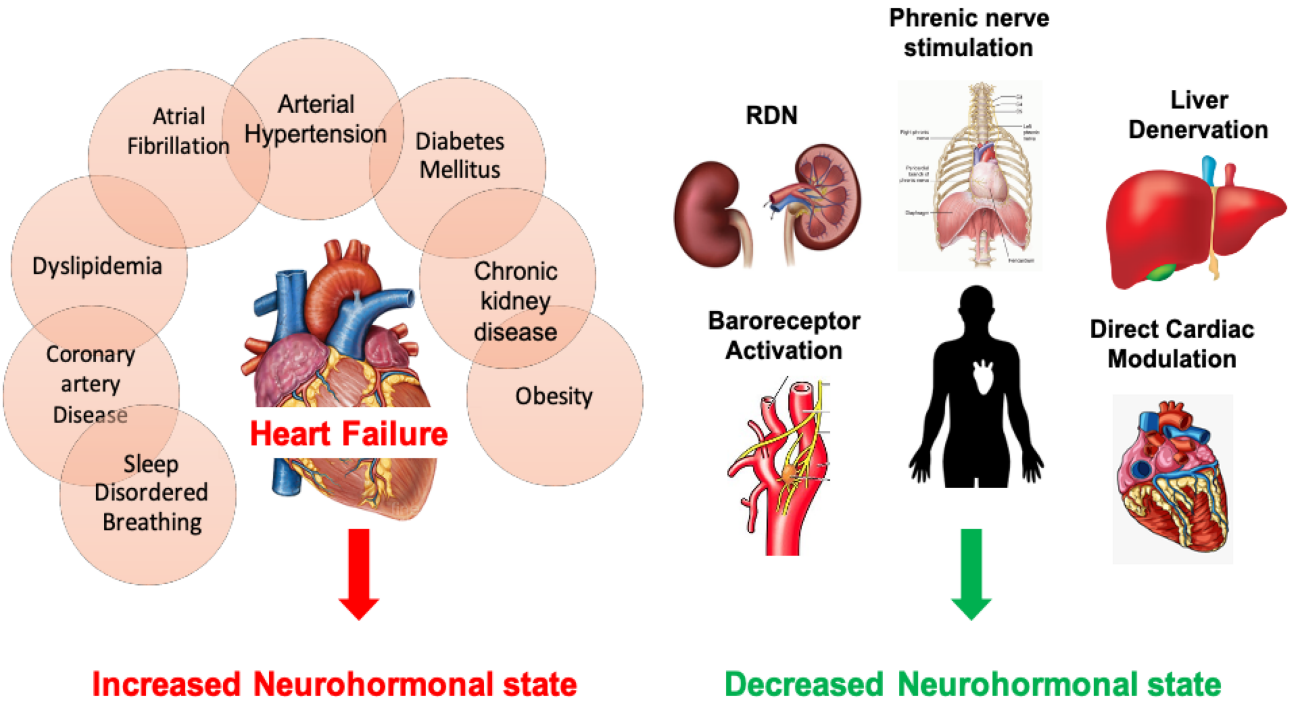



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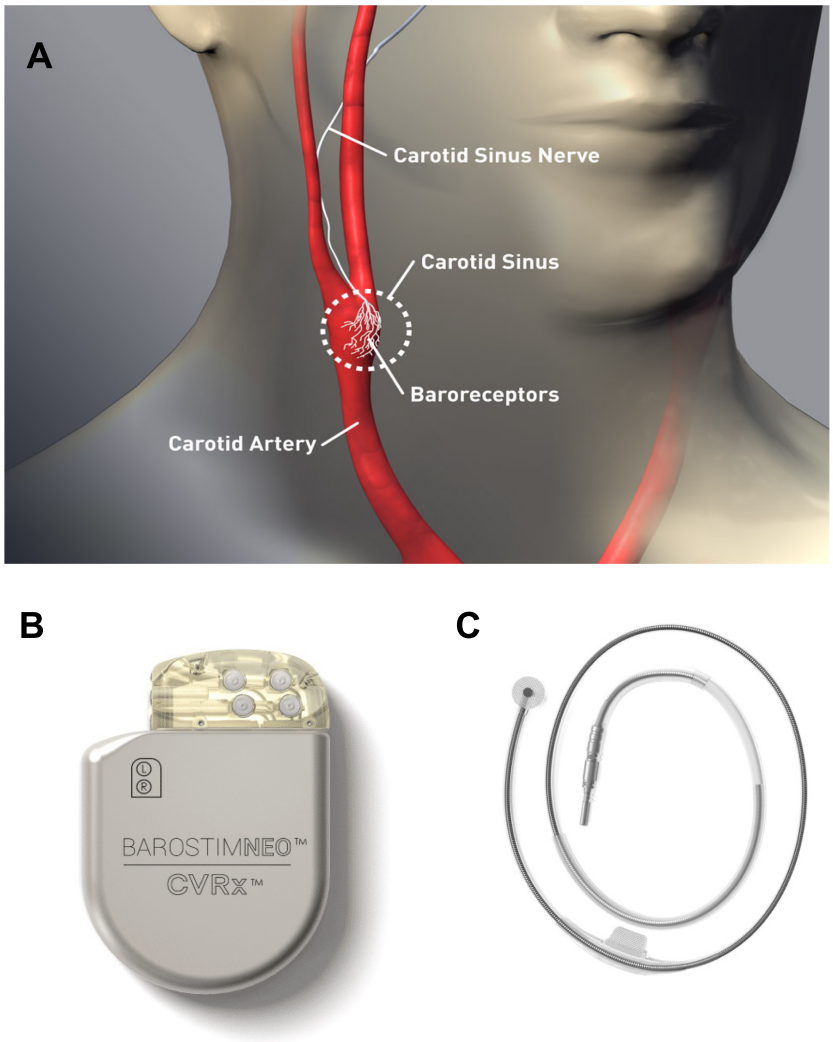
**Figure 2** Baroreceptor activation therapy. (A) Anatomy of the carotid sinus, carotid artery and baroreceptors. (B) A pulse generator placed under the skin near the clavicle. (C) A lead attaching onto the carotid artery.




being treated with the appropriate HF guideline-directed therapy and were enrolled in this prospective randomized controlled trial. The treatment group had a 24.6% (95% confidence interval: −38% to −9%; $P = 0.004$) reduction in NT pro-BNP at 6 months. Further, barostimulation therapy was associated with a greater improvement in the Minnesota Living with Heart Failure Questionnaire quality of life (QOL) score and functional capacity score at 6 months ($P < 0.001$ for both) compared with the control group.[22] In August 2019, the Food and Drug Administration (FDA) announced approval of the Barostim Neo BAT system using the pre-market approval pathway.

Ongoing activities include a continued enrollment for the post-market outcome phase. Further, in Germany, there is an ongoing post-market companion study, Barostim Therapy Improves Cardiac Remodelling in Heart Failure (BiRD-HF), which aims to assess cardiac remodelling in HFrEF patients. Finally, a non-surgical approach to the lead implantation is under development.

## Splanchnic nerve modulation for HF

Abnormalities in volume compliance and control are central to the pathophysiology of both HFpEF and HFrEF. Current strategies for HF management rely on the classical paradigm that salt and fluid retention is the culprit of intravascular fluid expansion and cardiac decompensation. There is increasing evidence suggesting that fluid homeostasis and control of intravascular fluid distribution are equally important. For example, in one study, over half of the 134 HF

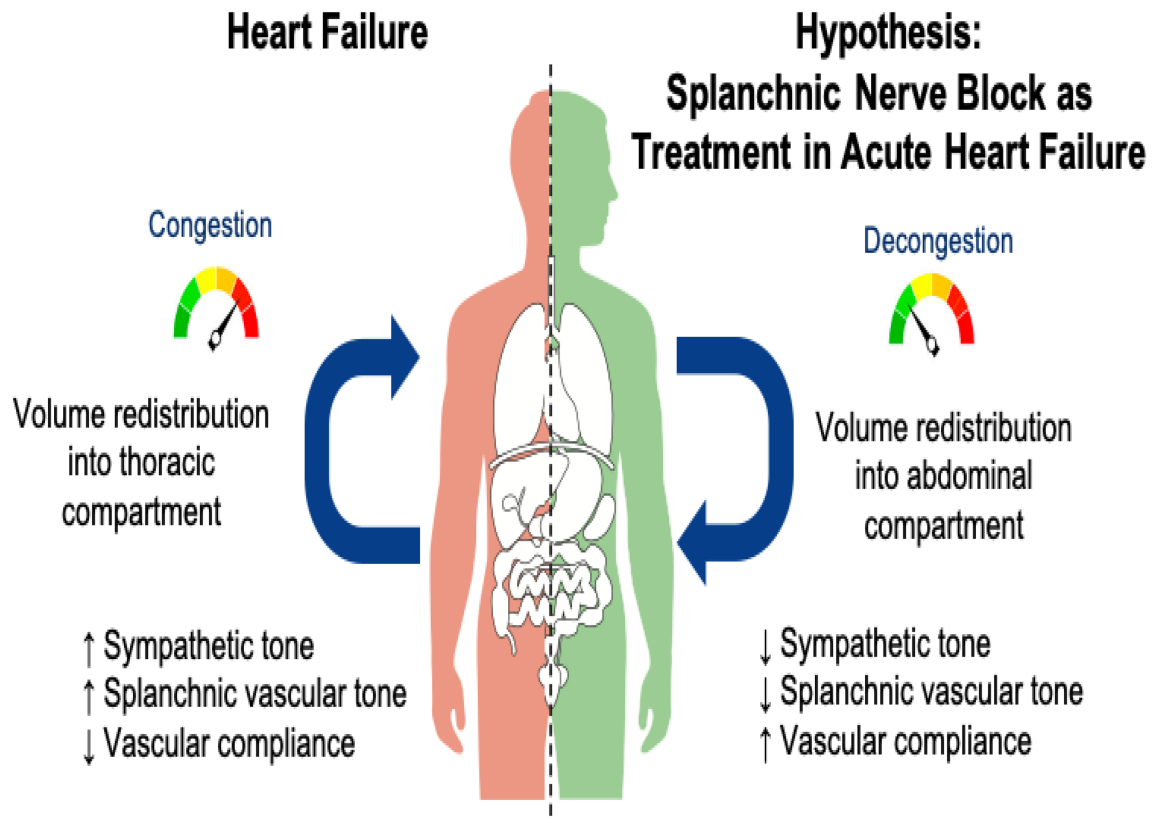
patients included had little or no weight gain prior to hospitalization for acute decompensation.[23] Studies of intra-cardiac pressure monitoring devices demonstrated that intra-cardiac pressure elevation precedes any significant weight gain by several weeks.[24] This implies that disrupted intravascular fluid distribution might play a significant role in the process of HF decompensation even in the absence of increases of total body salt and water.[24–27] The mechanism of volume redistribution may also apply to exercise and be a key driver of exercise-induced wedge pressure elevation.[28,29]

The splanchnic (abdominal) compartment contains a large portion of the intravascular blood volume[30] and functions as a reservoir and is a central contributor to volume redistribution in HF[23,24,26,27] (*Figure 3*). Sympathetic fibres regulate the effective distribution of blood in and out of the splanchnic compartment.[23,24,31–33] The splanchnic nerves contain the sympathetic fibres that control arterial and venous vascular tone.[34] The splanchnic vascular compartment and greater splanchnic nerves (GSN) were identified as a potential therapeutic target in HF.

Recently, the role of volume redistribution in the congestion of HF was evaluated by Fudim et al.[27] in a number of small physiological investigations, including decompensated chronic HF (splanchnic HF-1: ClinicalTrials.gov #: NCT02669407; $n$ = 11),[35,36] and chronic HF (splanchnic HF-2: NCT03453151; $n$ = 15).[37] These studies investigated the physiological effects of short-term pharmacological splanchnic nerve block. In patients hospitalized for acute HF, bilateral temporary splanchnic nerve block with lidocaine reduced resting cardiopulmonary filling pressures and improve the cardiac output without complications.[35,36] In patients with ambulatory HF, splanchnic nerve blockade reduced peak exercise wedge pressure from 34.8 ± 10.0 to 25.1 ± 10.7 mmHg ($P < 0.001$). Changes in intracardiac pressures were associated with improvement in the cardiac index (at peak exercise increased from 3.4 ± 1.2 to 3.8 ± 1.1 L/min/m$^2$; $P$ = 0.011) and peak oxygen consumption $VO_2$ (from pre-block: 9.1 ± 2.5 to post-block: 9.8 ± 2.7 mL/kg/min; $P$ = 0.053). In total, these results support the role of intravascular volume distribution in the pathophysiology of acute and chronic HF.

In a separate investigation, two centres in Europe studied for the first time the feasibility of permanent right GSN ablation for the treatment of HFpEF (surgical resection of the GSN in subjects having HFpEF: ClinicalTrials.gov #: NCT03715543; $n$ = 11). The 6-month data were presented at the Device Therapies for Heart Failure 2018 (Frankfurt, Germany, December 14–15), and 12-month data presented

**Figure 3** Volume redistribution concept in heart failure and splanchnic nerve modulation as a novel therapeutic intervention.



at EuroPCR 2019 (Paris, France, May 21–24), demonstrating that right-sided GSN surgical resection was safely applied and resulted in improvements in key physiological indicators of patient health. The sustained benefit at 12-month follow-up compared includes a reduction of exercise induced pulmonary capillary wedge pressure, QOL and an increased cardiopulmonary exercise duration. The studies to date suggest the potential therapeutic use of splanchnic sympathetic nerve blockade in chronic HF irrespective of LVEF and certain forms of decompensated HF. These studies provide the rationale for development of minimally invasive tools to enable further investigation in randomized controlled trials.

## Renal denervation for HF and arrhythmias

Efferent sympathetic nervous fibres to the kidney arise from the thoracic sympathetic ganglia and form a network within the renal arterial adventitia. Sympathetic stimulation of the juxtaglomerular apparatus leads to volume retention, sodium reabsorption, decreased renal blood flow and renin–angiotensin–aldosterone (RAAS) system activation. Sensory afferent fibres travel from the kidney to the central nervous system. Afferent renal input regulates the sympathetic outflow and controls systemic haemodynamics and reflexive sympathetic efferent activity. Multiple animal models have demonstrated that renal denervation (RDN) effectively reduces the sympathetic nervous system outflow to the kidney, thus restoring physiological natriuresis and diuresis and reducing renin release.[38] To date, there is an abundance of human data to support the efficacy of RDN to reduce the sympathetic tone and treat hypertension.[39–42] Despite the lack of efficacy of RDN in the Symplicity HTN-3 trial, RDN was effective in lowering blood pressure in several sham-controlled trials such as RADIANCE SOLO, SPYRAL HTN ON and SPYRAL HTN OFF[43,44] in patients with and without concomitant antihypertensive medication. Although the role of renal sympathetic nerves has been studied most extensively in the regulation of blood pressure and the pathogenesis of hypertension,[45–47] the impact of the renal sympathetic nerves reaches far beyond blood pressure control (*Figure 4*).

The potential for RDN in HFrEF was demonstrated in a pilot study: the Renal Artery Denervation in Chronic Heart Failure (REACH) study (NCT01639378).[48] Seven patients with New NYHA Class III–IV HF with left ventricle (LV) ejection fraction 28%–58% without hypertension were enrolled. At 6 months after the procedure, there were no major adverse events. The study also showed improved 6-min walk test results (221 ± 33 to 249 ± 34 months, $P$ = 0.03). In a randomized study of patients with NYHA Class II–IV HF ($n$ = 51), RDN decreased NT-proBNP levels and improved echocardiographic parameters and NYHA class when compared with optimal medical therapy.[49] There are also promising clinical data on left atrial and left ventricular remodelling following RDN.[50,51] In addition, RDN was safe in terms of the deterioration of renal function (Symplicity HTN trial).[52]

Atrial fibrillation (AF) is the most common arrhythmia in HF irrespective of the LVEF. It increases the risk of thromboembolic complications and may impair cardiac function, leading to worsening symptoms of HF.[53] In animals, RDN decreased the inducibility of AF.[54] In humans, Pokushalov et al.[55] compared pulmonary vein isolation (PVI) alone and in combination with RDN in a small cohort ($n$ = 27) of hypertensive patients with AF. The addition of RDN decreased AF episodes compared with PVI alone (69% vs. 29%, $P$ = 0.033).[55] The ERADICATE-AF (The Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation) trial randomized 302 patients to RDN with catheter ablation, compared with catheter ablation alone. Complementary RDN resulted in a statistically significantly greater proportion of patients who were free from AF at 12 months (72.1% vs. 56.5%).[56]

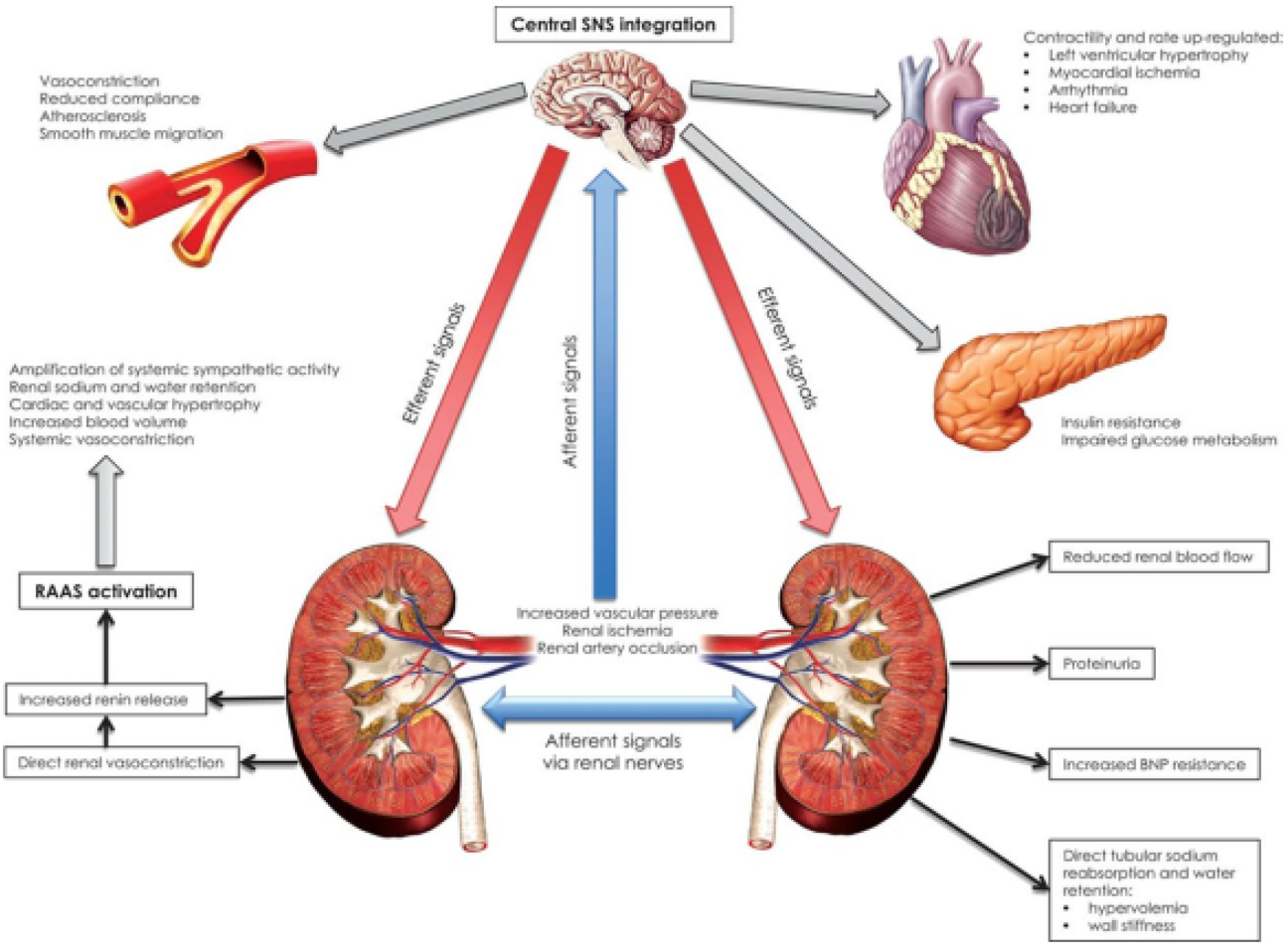
The evidence to support the utility of RDN to suppress ventricular arrhythmia is limited mostly to animals. In a porcine model of acute coronary ischemia, RDN reduced the ventricular tachycardia burden when compared with a sham procedure (86% vs. 17%, $P$ = 0.029).[57] The potential of RDN to suppress ventricular tachycardia in humans has been explored only in case reports.[58]

It appears possible that RDN could provide an upstream therapy not only in hypertension but also in other sympathetically mediated diseases such as HF, cardiac arrhythmias and diabetes.[59] Most of the options are at an advanced experimental stage, and the potential in this treatment should be explored further by well-designed randomized clinical trials. Several clinical studies in these indications are ongoing (NCT03418415, NCT04264403, NCT04055285). Additional efforts include development of novel ablation techniques and technologies.[47]

## Cardiac neuromodulation therapy

Cardiac neuromodulation therapy is a novel approach to hypertensive management and may be applicable to a wide range of hypertensive patients.[60] BackBeat neuromodulation therapy uses an implantable pulse generator that connects to the heart with standard pacing leads. BackBeat therapy itself is a repeating sequence of paced heartbeats with variable atrioventricular delays. Reduction of blood pressure is achieved by modulating LV filling due to alternation between a shorter and a longer atrioventricular delay.[60,61] Changes in atrioventricular delay can modulate LV filling. Atrial

**Figure 4** Renal denervation therapy. Increased end organ sympathetic outflow via efferent pathways causes renal sodium and water retention, systemic vasoconstriction and cardiac and vascular hypertrophy. Renal denervation reduces sympathetic tone, showing potential in treatment of sympathetically mediated diseases including HF. BNP, brain natriuretic peptide; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

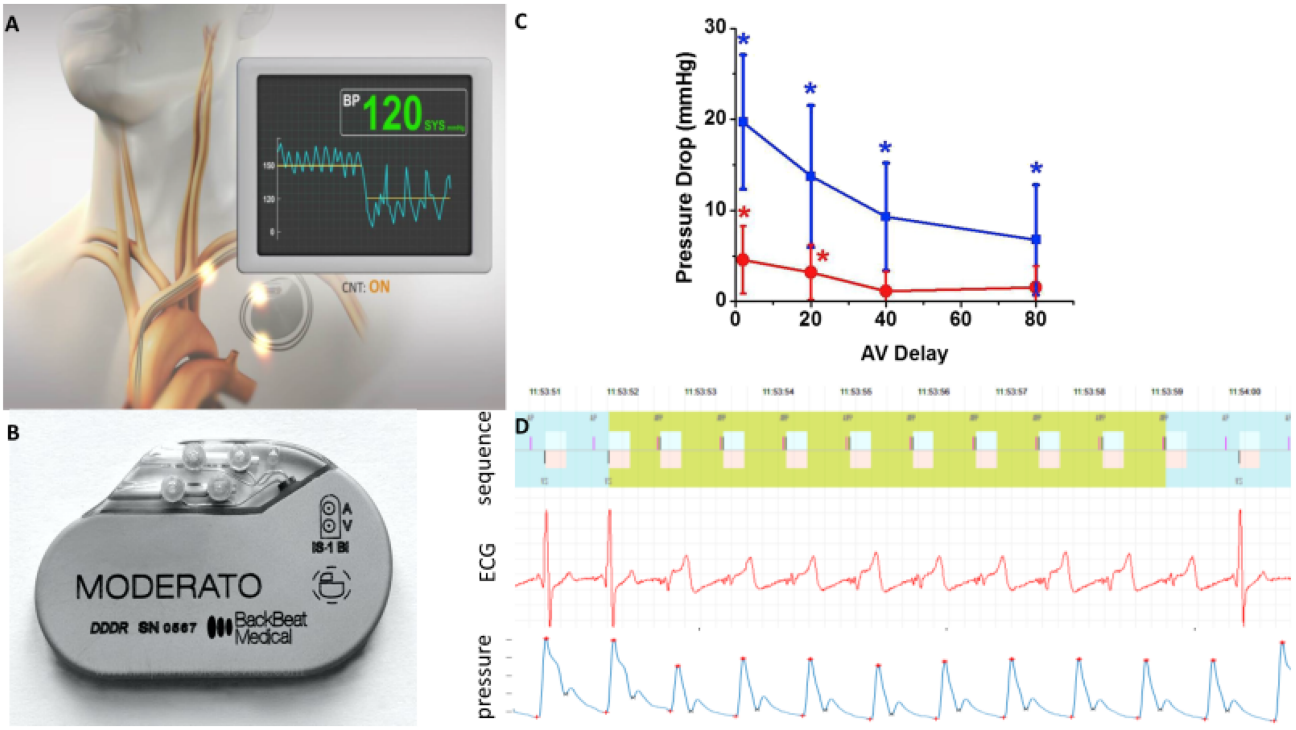



contraction determines 15% of the ventricular filling.[62] Ultrashort atrioventricular delays lower blood pressure, and longer atrioventricular delays modulate the autonomic reflex responses via baro/stretch receptors. According to the Frank–Starling law, pressure generation by the heart is dependent on LV preload.

The pacemaker-based programmable hypertension control (PHC) therapy was evaluated in a single-arm Moderato I study (NCT02282033) (2013–2017) (*Figure 5*). Patients indicated for dual-chamber pacing with office systolic blood pressure >150 mmHg, despite stable medical therapy, were implanted with a Moderato pulse generator that delivers PHC therapy.[60] BackBeat CNT reduced 24-h ambulatory systolic blood pressure by 10.1 mmHg among 27 patients, with the effect maintained for up to 2 years. There was a marked reduction in cardiac end-diastolic volume and heart rate with no change in LVEF.[63]

The Moderato II trial is a prospective, randomized, double-blind study that compares BackBeat with drug therapy in nine European centres. The study enrolled patients with hypertension and indicated for dual-chamber pacemaker implantation and who remained hypertensive 30 days after implantation. The objective was to compare the efficacy and safety of BackBeat CNT in hypertensive patients with an indication for a pacemaker. The primary outcome of blood pressure reduction after 6 months was 11.1 mmHg in the BackBeat CNT group and 3.1 mmHg in the control group ($P < 0.01$). Systolic blood pressure, at the end of 6 months, was reduced by 12.4 mmHg in the BackBeat CNT group and 0.1 mmHg in the control group ($P = 0.02$).[64] The study has

**Figure 5** Cardiac neuromodulation therapy BackBeat. (A,B) Implantable pulse generator that connects to the heart with standard pacing leads and delivers BackBeat CNT to lower blood pressure. (C,D) A repeating sequence of paced heartbeats with variable AV delays, ultrashort AV delay beats to lower blood pressure and longer AV delay to modulate autonomic reflex responses via baro/stretch receptors.




shown a high responder rate in 88.5% patients with isolated systolic hypertension. In September 2019, the Moderato implantable pulse generator system received a CE Mark approval. A pivotal, double-blind study is planned in patients with hypertension.[65]

## Phrenic nerve stimulation for central sleep apnoea

SDB is common and thought to play a significant role in congestive HF. SDB has two main types, namely, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), although these two commonly overlap.[66]

The difference between OSA and CSA is that OSA is mainly an anatomical problem (a thick neck and large tongue result in a proclivity to having obstructions of the upper airway), whereas CSA is principally due to a loss of neural drive to breathe during sleep, thus leading to alternating phases of apnoea and hyperpnoea. CSA significantly reduces QOL and increases the risk of co-morbidities and hospitalizations. Approximately 75% of CSA patients have HF and patients with HF and co-morbid CSA also have double the risk of death.[67]

CSA can cause the progression of HF by at least two known mechanisms: apnoea-induced hypoxia/reoxygenation (causing endothelial dysfunction and inflammation leading to thrombosis, left ventricular hypertrophy and adverse cardiac remodelling) and arousal-induced catecholamine release (leading to RAAS activation, sodium retention, increased HF, arrhythmia and cardiac myocyte hypertrophy). Taken together or individually, these conditions enhance adverse cardiac remodelling and the further progression of HF.[68]

Initially, adaptive servo-ventilation (ASV) type masks were recommended to treat CSA (CANPAP). Following the SERVE-HF trial, ASV became contraindicated in HFrEF patients with predominant CSA. The ASV group experienced significantly higher all-cause and cardiovascular mortality than the control group (HR 1.28 [$P$ = 0.01] and HR 1.34 [$P$ = 0.006], respectively) and had no improvement in QOL.[69] There are few other treatment options for CSA, with limited randomized data supporting those options. These include theophylline, acetazolamide, oxygen and CPAP/BIPAP, some of which showed arrhythmogenic potential that could lead to cardiac arrhythmias.[67,68,70]

An alternative approach to treat moderate to severe CSA in HFrEF is a fully implantable neurostimulation system (remedē System, Respicardia, Inc.).[71] It stimulates the phrenic nerve to move the diaphragm causing inspiration by activating the diaphragm to generate negative pressure in the chest (similar to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natural breathing). The system turns on automatically at night, ensuring nightly compliance and adherence over time. It consists of a pulse generator implanted below the clavicle and a stimulation lead placed either in the left pericardiophrenic or right brachiocephalic vein, as well as an optional sensing lead, which helps to optimize therapy (*Figure 6*).

The pivotal trial, studying the safety and effectiveness of treatment with transvenous phrenic nerve stimulation (PNS) in subjects with moderate to severe sleep apnoea, showed a reduction in AHI events and improvements with all the major sleep respiratory metrics, daytime sleepiness and QOL.[72]

To better characterize the efficacy and safety with the prospective experience of PNS in CSA with and without concomitant HF, pooled analysis was conducted using data from the pilot and pivotal studies.[72–74]Twelve-month safety and 6- and 12-month effectiveness based on polysomnography data, QOL and cardiac function was evaluated. Among 208 combined patients, a remedē device implant was successful in 95% of the subjects, the apnoea–hypopnoea index (AHI) reduction was seen at 6 months, and improvement in sleep variables, daytime sleepiness and QOL was maintained through 12 months of follow-up. In patients with HF and ejection fraction $\leq$ 45%, PNS was associated with improvement in systolic function from 27.0% (23.3, 36.0) to 31.1% (24.0, 41.5) at 12 months ($P$ = 0.003).[73,75]

The US FDA granted its official approval of the remedē System in October 2017. In agreement with the FDA, ongoing patients were asked to enrol into the remedē System Post Approval Study. The patients will be followed up for 5 years to evaluate the long-term safety, long-term effectiveness and survival rate.[74] In March 2019, Respicardia announced initial enrolments in a non-randomized post-market study (NCT03884660) to collect clinical data on the safety and effectiveness of the remedē System. At least 500 subjects will be studied at approximately 50 sites in the United States and Europe.

## Hepatic denervation therapy

The non-alcoholic fatty liver disease (NAFLD) is a spectrum of disorders ranging from a simple steatosis to non-alcoholic steatohepatitis (NASH).[76] The worldwide prevalence of NAFLD is estimated to be ~25%. The pathogenesis of NAFLD and metabolic syndrome share pathophysiological mechanisms, with focus on insulin resistance as a key factor.[76] Metabolic syndrome can lead to significant neurohormonal changes that include activation of the RAAS and sympathetic nervous systems and altered levels of pro-inflammatory cytokines that consequently cause microvascular dysfunction and vascular calcification.[77,78] NAFLD and metabolic syndrome can increase the risk of Type II diabetes mellitus, insulin resistance and atherosclerosis, which significantly increase the risk for incident HF and the risk of cardiovascular death.[79,80] Treatment of

**Figure 6** Phrenic nerve stimulation with remedē System. (A) Parts of remedē System: pulse generator implanted below clavicle, stimulation lead placed either in left pericardiophrenic or right brachiocephalic vein and a sensing lead helping to optimize the therapy. (B) Breathing with the therapy off compared with the therapy on. (C) Comparison of normal inspiration with CSA therapies.

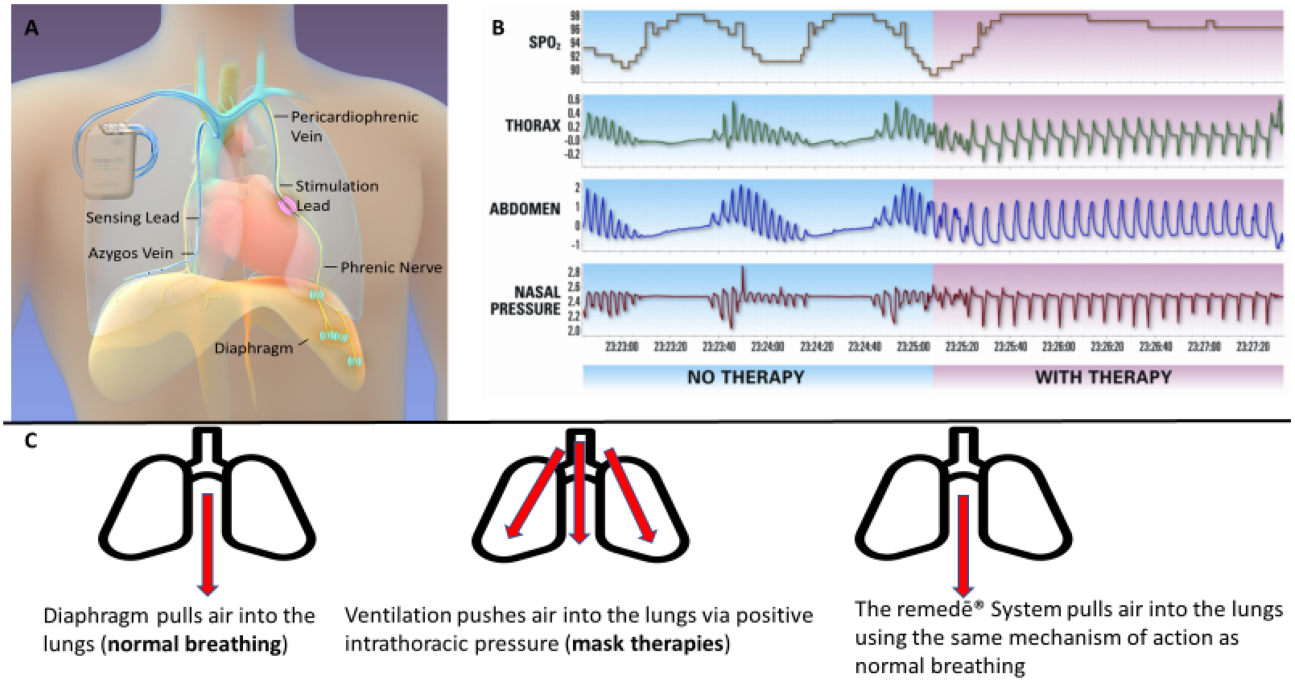
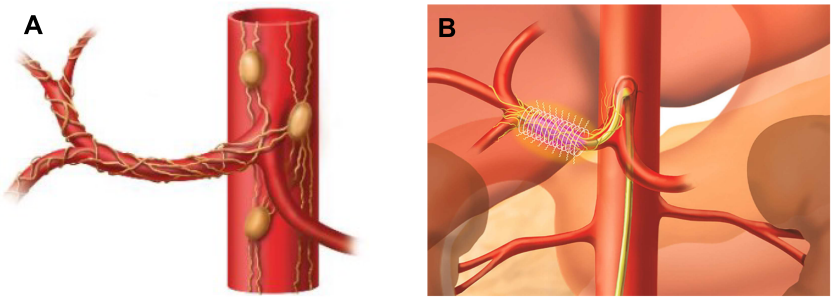


**Figure 7** Hepatic denervation, Metavention. (A) Nerves surrounding the common hepatic artery (CHA). (B) Radiofrequency energy is passed through the vessel walls to disrupt sympathetic nerves leading to the liver.




the metabolic syndrome might not only prevent HF but also ameliorate the severity of the HF syndrome (*Figure 7*).

The liver is innervated by both afferent and efferent autonomic nerves. The sympathetic innervation is postganglionic and originates in the celiac and superior mesenteric ganglia that receive preganglionic fibres from the intermediolateral column of the spinal cord (T7–T12). The parasympathetic nerves branch off the vagus nerve. The anterior plexus forms a network of nerves surrounding the hepatic artery that originates from the left portion of the celiac plexus and the right abdominal branch of the vagus.[81] Nerves surrounding the common hepatic artery (CHA) are predominately efferent sympathetic (~95%). Hepatic manifestation of SNS overactivity are abnormalities of glucose and lipid handling that characterize the metabolic syndrome and Type II diabetes mellitus. As described in some animal studies, removal of the sympathetic nerves has shown reduced obesity-induced hepatic steatosis[80] and improvements in glucose tolerance.[82]

Hepatic denervation therapy (HDN), introduced by Metavention, uses a standard cardiac catheterization procedure to position a dedicated radiofrequency catheter in the CHA. The integrated multi-electrode denervation system is a newly designed system in which integrated, monopolar multi-electrode design forms a single lesion with full circumferentially and has active cooling to protect the endothelium.[83]

The use of intravascular hepatic denervation (iRFAblation System) for the treatment of metabolic syndrome and NAFLD will be studied in the DeLIVER study. This is a prospective, single-arm, multicentre study testing the Metavention Integrated Radio Frequency Nerve Ablation System as a treatment for hyperglycaemia in Type II diabetic subjects in New Zealand (ACTRN12619001524189A). A singular, intravascular procedure that provides the disruption of overactive hepatic sympathetic nerve activity shows new perspective in the treatment of metabolic diseases, including diabetes and NASH.

In conclusion, the use of devices in HF has been long established. Device-based therapy modifying non-cardiovascular co-morbidities can be a route to improved outcomes in HF, lower HF hospitalization and healthcare costs. Although the side effect profile is mostly limited to the procedure itself, the potential adverse impact of neuromodulation on human physiology remains in most cases to be established. Because the reviewed device-based therapies are in all cases small to moderate sized, ongoing and future efforts to establish device safety and efficacy are very important. In many cases, post-approval surveillance studies/registries will help determine just that.

## Conflict of interest

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