ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3327–3338
Published online 18 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13361

ESC AND HFA PAPER

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

Ana Jorbenadze[1], Marat Fudim[2,3], Felix Mahfoud[4], Phillip B. Adamson[5], Tarek Bekfani[6], Rolf Wachter[7], Horst Sievert[8], Piotr P. Ponikowski[9], John G. F. Cleland[10] and Stefan D. Anker[11,12]*

[1]*Tbilisi Heart and Vascular Clinic, Tbilisi, Georgia;* [2]*Division of Cardiology, Duke University Medical Center, Durham, NC, USA;* [3]*Duke Clinical Research Institute, Durham, NC, USA;* [4]*Department of Internal Medicine III, Cardiology, Angiology, and Intensive Care Medicine, Saarland University, Saarbrücken, Germany;* [5]*Abbott, Los Angeles, CA, USA;* [6]*Department of Internal Medicine I, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Magdeburg, Otto von Guericke University, Magdeburg, Germany;* [7]*Clinic and Polyclinic for Cardiology, University Hospital Leipzig, Leipzig, Germany;* [8]*CardioVascular Center Frankfurt, Frankfurt, Germany;* [9]*Centre for Heart Diseases, University Hospital, Wroclaw, Poland;* [10]*Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK;* [11]*Division of Cardiology and Metabolism – Heart Failure, Cachexia & Sarcopenia, Department of Cardiology, Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany;* [12]*Berlin-Brandenburg Centre for Regenerative Therapies (BCRT), Charité – Universitätsmedizin Berlin, Berlin, Germany*

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

Received: 7 January 2021; Revised: 14 March 2021; Accepted: 29 March 2021
**Correspondence to: Stefan D. Anker, Department of Cardiology (CVK) and Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK), partner site Berlin, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany. Tel: +49-30-450 553407; Fax: +49-30-450 553951. Email:* s.anker@cachexia.de

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.

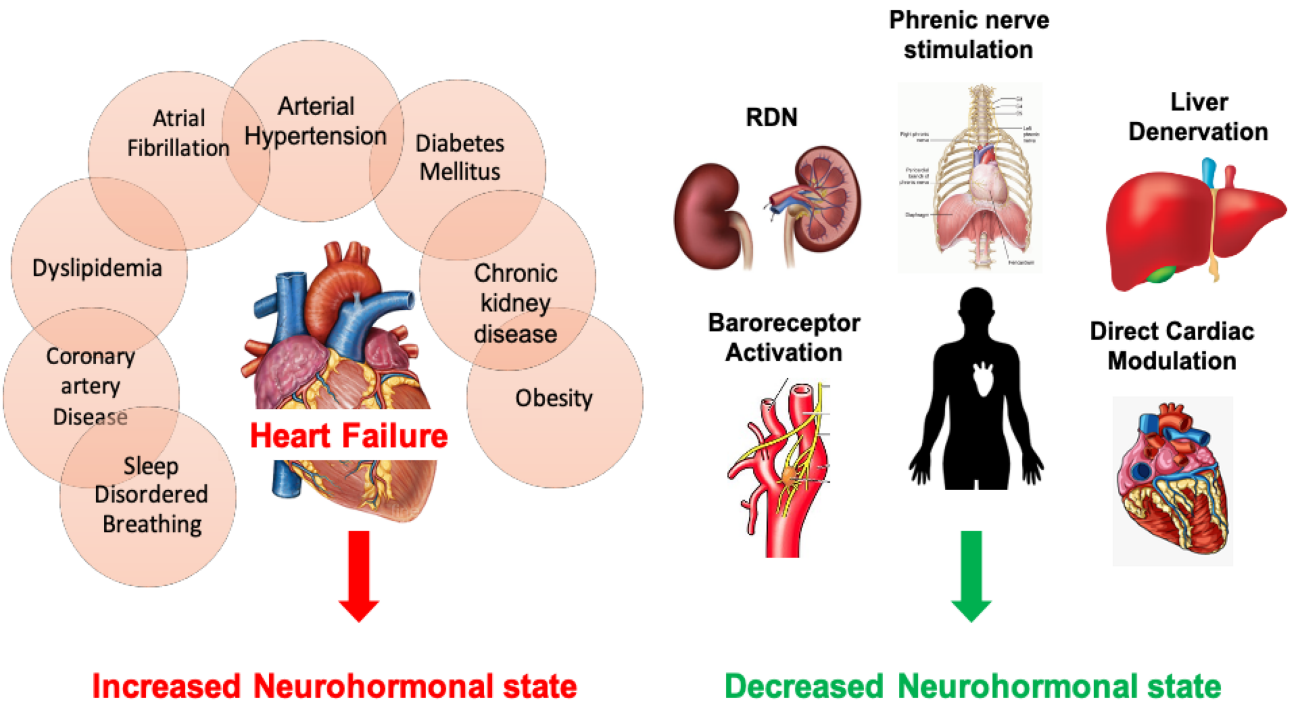
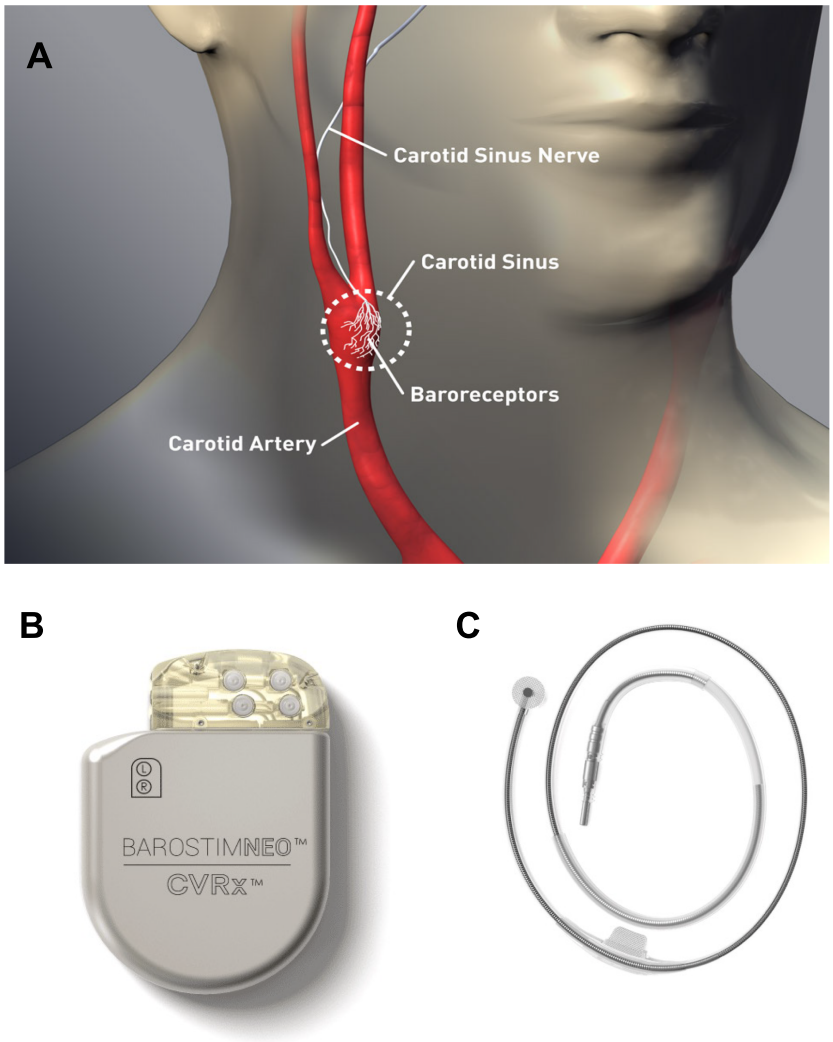


Figure 2 Baroreceptor activation therapy. (A) Anatomy of the carotid sinus, carotid artery and baroreceptors. (B) A pulse generator placed under the skin near the clavicle. (C) A lead attaching onto the carotid artery.



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

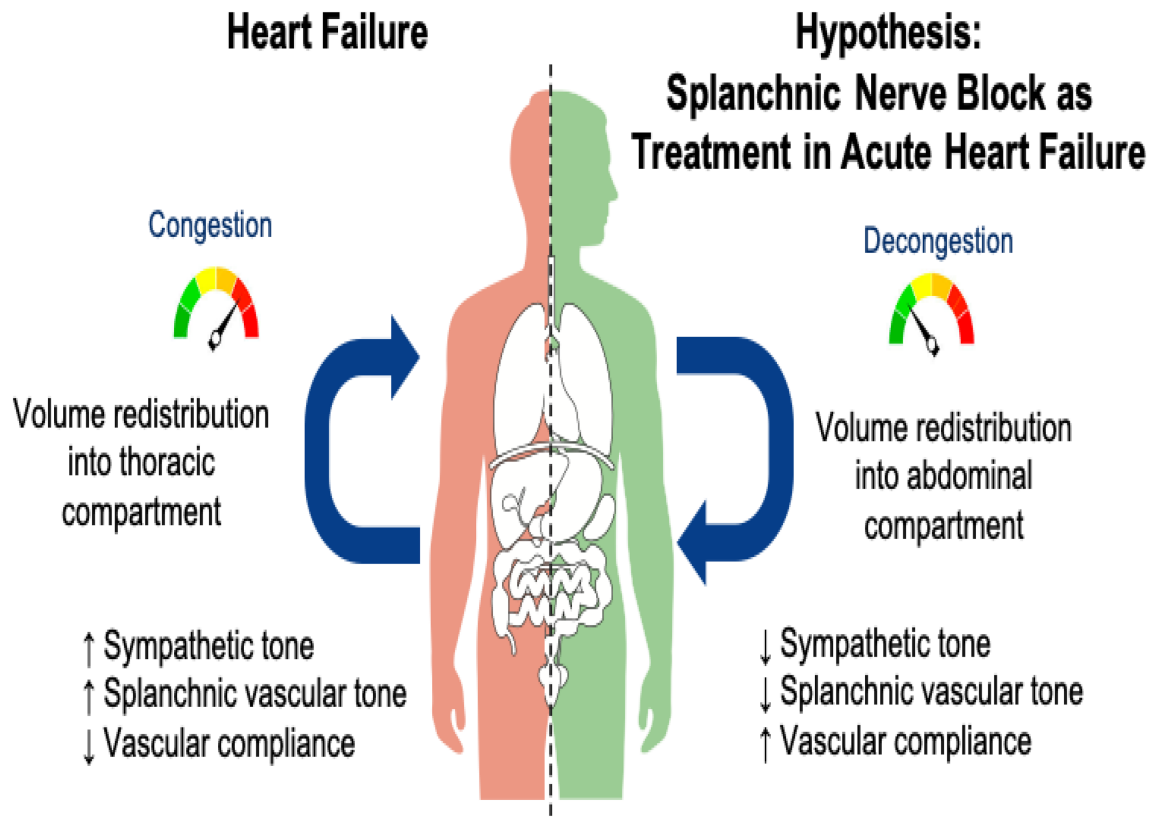
patients included had little or no weight gain prior to hospitalization for acute decompensation.[23] Studies of intra-cardiac pressure monitoring devices demonstrated that intra-cardiac pressure elevation precedes any significant weight gain by several weeks.[24] This implies that disrupted intravascular 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]

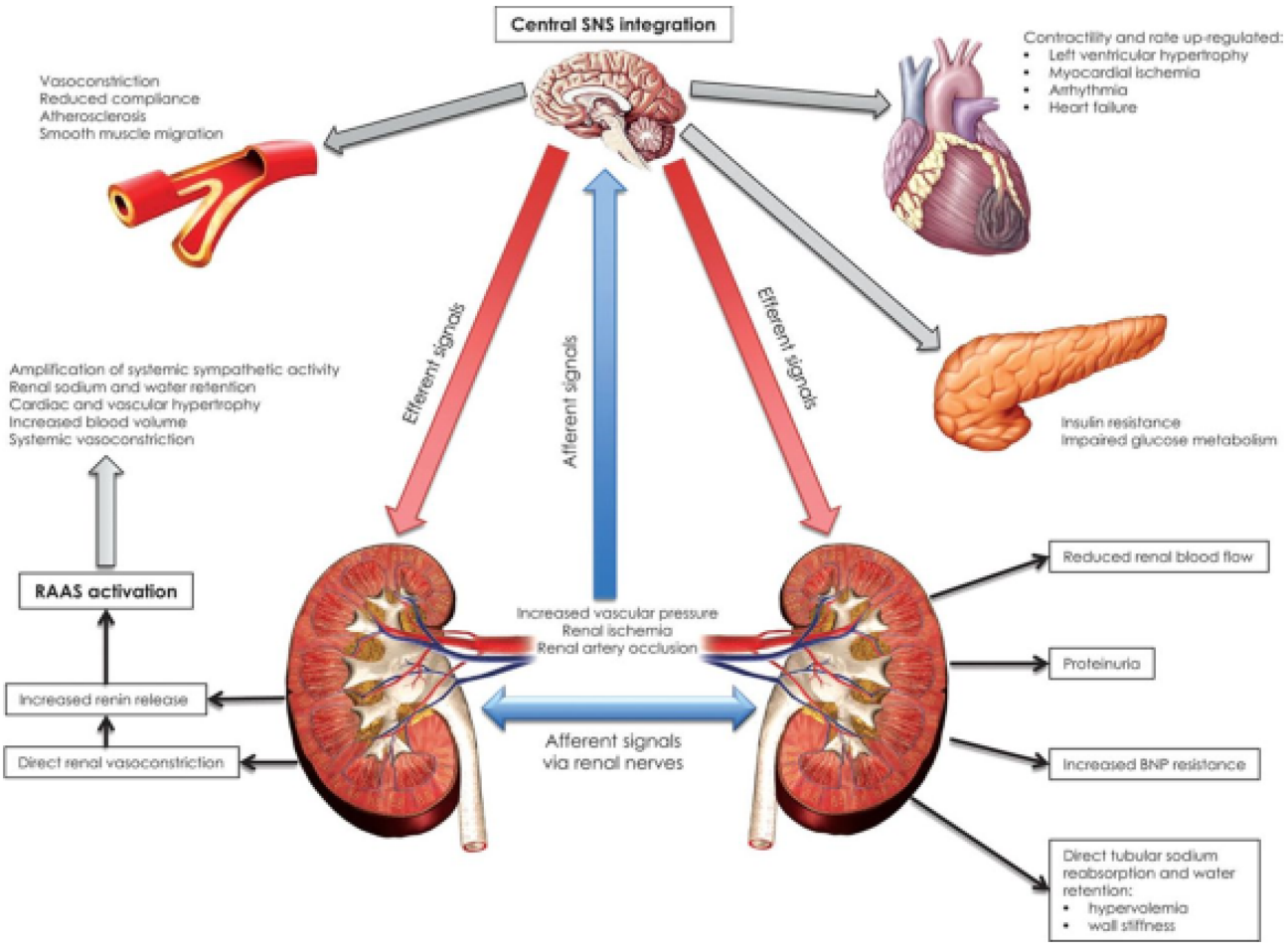
The evidence to support the utility of RDN to suppress ventricular arrhythmia is limited mostly to animals. In a porcine model of acute coronary ischemia, RDN reduced the ventricular tachycardia burden when compared with a sham procedure (86% vs. 17%, P = 0.029).[57] The potential of RDN to suppress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

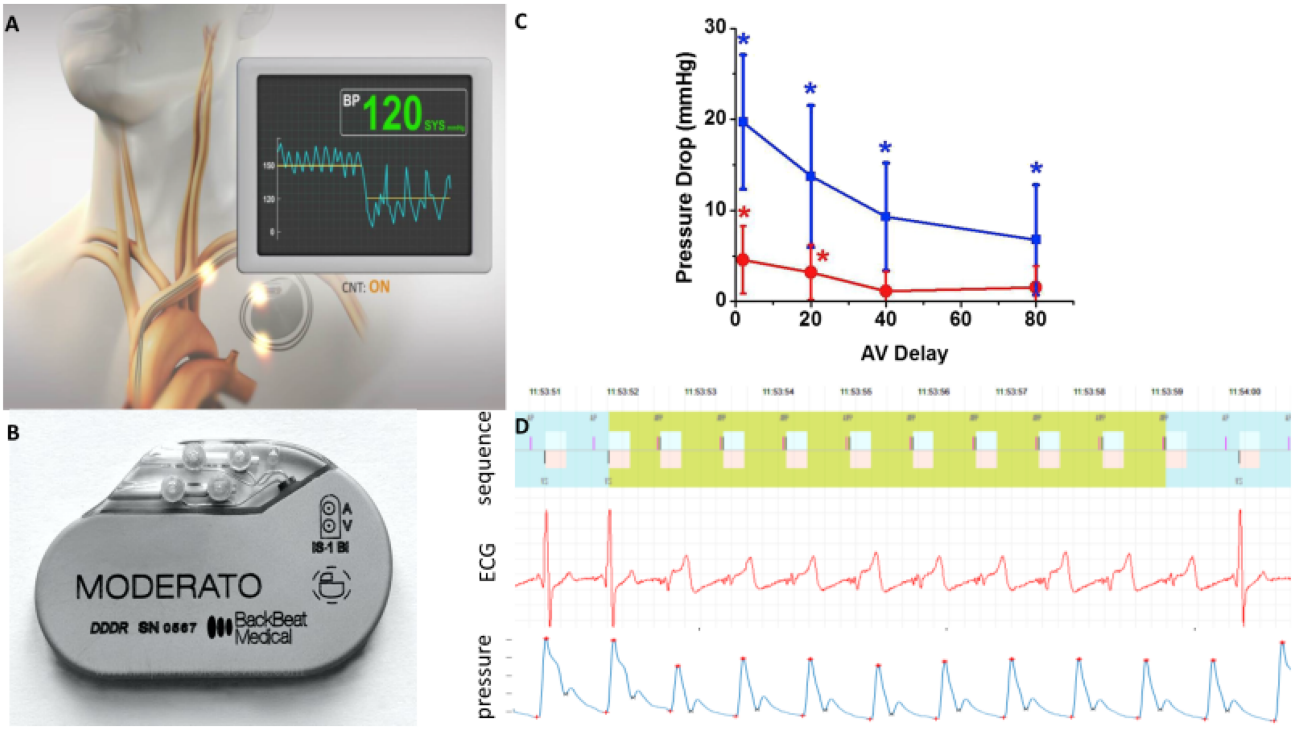


contraction determines 15% of the ventricular filling.[62] Ultrashort atrioventricular delays lower blood pressure, and longer atrioventricular delays modulate the autonomic reflex responses via baro/stretch receptors. According to the Frank–Starling law, pressure generation by the heart is dependent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

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.

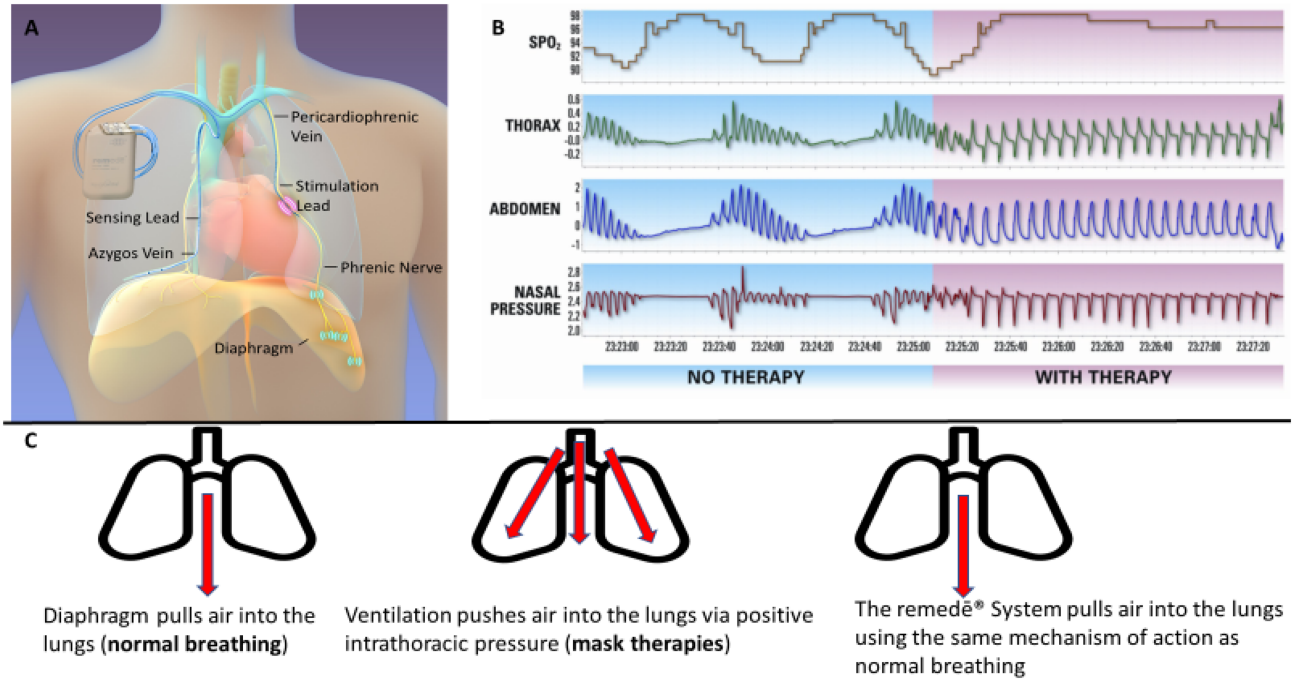
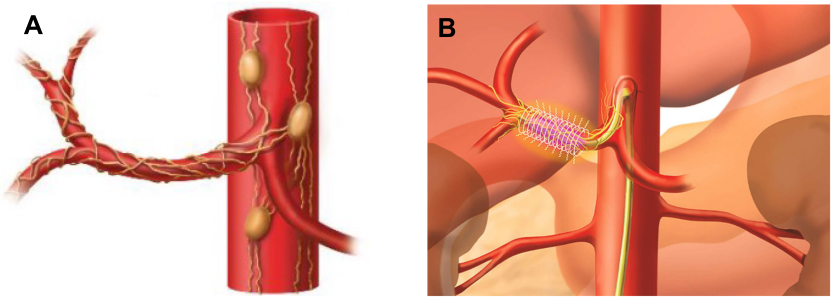


Figure 7 Hepatic denervation, Metavention. (A) Nerves surrounding the common hepatic artery (CHA). (B) Radiofrequency energy is passed through the vessel walls to disrupt sympathetic nerves leading to the liver.



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

AJ No COI. **MF** is supported by an American Heart Association Grant, 17MCPRP33460225, NIH T32 grant 5T32HL007101, Mario Family Award and Translating Duke Health Award and consulting fees from AxonTherapies, Daxor and Galvani. **FM** is supported by Deutsche Gesellschaft für Kardiologie (DGK) and Deutsche Forschungsgemeinschaft (SFB TRR219) and has received scientific support and speaker honoraria from Bayer, Boehringer Ingelheim, Medtronic and ReCor Medical. **JGFC** reports research grants from Medtronic; share options from HeartFelt Technologies; research collaboration with Sensible Medical; equipment loan from Mespere; and personal honoraria from Medtronic and Servier. **PBA** is an Abbott employee. **RW** reports having been an investigator or consultant for or received fees from Bayer, Berlin Chemie, Bristol-Myers-Squibb, Boehringer Ingelheim, Boston Scientific, CVRx, Daiichi, Gilead, Johnson & Johnson, Medtronic, Novartis, Pfizer, Sanofi and Servier outside the submitted work. He received research grants from Boehringer Ingelheim, Deutsche Forschungsgemeinschaft, European Union and Bundesministerium für Bildung und Forschung (BMBF). **HS** reports study honoraria to institution, travel expenses and consulting fees 1 < 25. 000 €: 4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Append Medical, Axon, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Cardiac Success, Cardimed, Celonova, Comed B.V., Contego, CVRx,

Dinova, Edwards, Endologix, Endomatic, Hemoteq, Hangzhou Nuomao Medtech, Holistick Medical, K2, Lifetech, Maquet Getinge Group, Medtronic, Mokita, Occlutech, Recor, Renal Guard, Terumo, Trisol, Vascular Dynamics, Vectorious Medtech, Venus, Venock, Vivasure Medical. **PP** reports research funding from Vifor Pharma and serving as consultant for Vifor Pharma, Amgen, Abbott, Servier, Novartis, Berlin Chemie, Bayer, Pfizer, Cibiem, Coridea, Impulse Dynamics and Renal Guard Solutions. **SDA** reports grants and personal fees from Vifor Int, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from Servier, grants and personal fees from Abbott Vascular, personal fees from Impulse Dynamics and personal fees from Cardiac Dimensions, outside the submitted work. All other authors report no disclosures. **TB** No COI.

Funding

Open Access funding enabled and organized by Projekt DEAL.

References

1. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction in older adults. *Heart Fail Clin* 2017; **13**: 485–502.
2. Branca L, Sbolli M, Metra M, Fudim M. Heart failure with mid-range ejection fraction: pro and cons of the new classification of Heart Failure by European Society of Cardiology guidelines. *ESC Heart Fail* 2020; **7**: 381–399.
3. Fudim M, O'Connor CM, Dunning A, Ambrosy AP, Armstrong PW, Coles A, Ezekowitz JA, Greene SJ, Metra M, Starling RC, Voors AA, Hernandez AF, Michael Felker G, Mentz RJ. Aetiology, timing and clinical predictors of early vs. late readmission following index hospitalization for acute heart failure: insights from ASCEND-HF. *Eur J Heart Fail* 2018; **20**: 304–314.
4. Shear FE. Novel paradigms in the therapeutic management of heart failure with preserved ejection fraction: clinical perspectives. *Am J Cardiovasc Dis* 2019; **9**: 91–108.
5. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. *Eur Heart J* 2015; **36**: 1974–82b.
6. Grosman-Rimon L, Billia F, Wright E, Carasso S, Elbaz-Greener G, Kachel E, Rao V, Cherney D. Neurohormones, inflammatory mediators, and cardiovascular injury in the setting of heart failure. *Heart Fail Rev* 2019; **25**: 685–701.
7. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019; **393**: 61–73.
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**: 1413–1424.
9. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020; **382**: 1883–1893.
10. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27**: 2338–2345.
11. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467.
12. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392.
13. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP, McMurray JJV. Angiotensin receptor neprilysin inhibition in heart failure With preserved ejection fraction: rationale and design of the PARAGON-HF trial. *JACC Heart Fail* 2017; **5**: 471–482.
14. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc* 2019; **8**: e013389.
15. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**: 658–666.
16. Gronda E, Francis D, Zannad F, Hamm C, Brugada J, Vanoli E. Baroreflex activation therapy: a new approach to the management of advanced heart failure with reduced ejection fraction. *J Cardiovasc Med (Hagerstown)* 2017; **18**: 641–649.
17. Creager MA, Creager SJ. Arterial baroreflex regulation of blood pressure in patients with congestive heart failure. *J Am Coll Cardiol* 1994; **23**: 401–405.
18. Paton JF, Sobotka PA, Fudim M, Engelman ZJ, Hart EC, McBryde FD, Abdala AP, Marina N, Gourine AV, Lobo M, Patel N. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. *Hypertension* 2013; **61**: 5–13.
19. Niewinski P, Janczak D, Rucinski A, Jazwiec P, Sobotka PA, Engelman ZJ, Fudim M, Tubek S, Jankowska EA, Banasiak W, Hart EC. Carotid body removal for treatment of chronic systolic heart failure. *Int J Cardiol* 2013; **168**: 2506–2509.
20. Niewinski P, Janczak D, Rucinski A, Tubek S, Engelman ZJ, Piesiak P, Jazwiec P, Banasiak W, Fudim M, Sobotka PA, Javaheri S, Hart ECJ, Paton JFR, Ponikowski P. Carotid body resection for sympathetic modulation in systolic heart failure: results from first-in-man study. *Eur J Heart Fail* 2017; **19**: 391–400.

21. Funakoshi K, Hosokawa K, Kishi T, Ide T, Sunagawa K. Striking volume intolerance is induced by mimicking arterial baroreflex failure in normal left ventricular function. *J Card Fail* 2014; **20**: 53–59.
22. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020; **76**: 1–13.
23. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007; **116**: 1549–1554.
24. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008; **118**: 1433–1441.
25. Adamson PB, Magalski A, Braunschweig F, Böhm M, Reynolds D, Steinhaus D, Luby A, Linde C, Ryden L, Cremers B, Takle T, Bennett T. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. *J Am Coll Cardiol* 2003; **41**: 565–571.
26. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ Heart Fail* 2011; **4**: 669–675.
27. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc* 2017; **6**.
28. Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol* 1993; **265**: H1819–H1828.
29. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; **3**: 588–595.
30. Delorme EJ, Mac PA, Mukherjee SR, Rowlands S. Measurement of the visceral blood volume in dogs. *Q J Exp Physiol Cogn Med Sci* 1951; **36**: 219–231.
31. Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008; **108**: 735–748.
32. Bapna A, Adin C, Engelman ZJ, Fudim M. Increasing blood pressure by greater splanchnic nerve stimulation: a feasibility study. *J Cardiovasc Transl Res* 2019.
33. Fudim M, Yalamuri S, Herbert JT, Liu PR, Patel MR, Sandler A. Raising the pressure: hemodynamic effects of splanchnic nerve stimulation. *J Appl Physiol (Bethesda, Md: 1985)* 2017; **123**: 126–127.
34. Barnes RJ, Bower EA, Rink TJ. Haemodynamic responses to stimulation of the splanchnic and cardiac sympathetic nerves in the anaesthetized cat. *J Physiol* 1986; **378**: 417–436.
35. Fudim M, Ganesh A, Green C, Jones WS, Blazing MA, DeVore AD, Felker GM, Kiefer TL, Kong DF, Boortz-Marx RL, Hernandez AF, Patel MR. Splanchnic nerve block for decompensated chronic heart failure: splanchnic-HF. *Eur Heart J* 2018; **39**: 4255–4256.
36. Fudim M, Jones WS, Boortz-Marx RL, Ganesh A, Green CL, Hernandez AF, Patel MR. Splanchnic nerve block for acute heart failure. *Circulation* 2018; **138**: 951–953.
37. Fudim M, Boortz-Marx RL, Ganesh A, DeVore AD, Patel CB, Rogers JG, Coburn A, Johnson I, Paul A, Coyne BJ, Rao SV. Splanchnic nerve block for chronic heart failure. *JACC Heart Fail* 2020; **8**: 742–752.
38. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**: R245–R253.
39. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; **391**: 2346–2355.
40. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L, Wang Y, Jay D, Skeik N, Schwartz R, Rader F, Dohad S, Victor R, Sanghvi K, Costello J, Walsh C, Abraham J, Owan T, Abraham A, Fisher NDL, Mauri L, Sobieszczky P, Williams J, Bloch MJ, Roongsritong C, Todoran T, Basile J, Powers E, Hodskins E, Fong P, Laffer C, Gainer J, Robbins M, Reilly JP, Cash M, Goldman J, Aggarwal S, Ledley G, Hsi D, Martin S, Portnay E, Calhoun D, McElderry T, Maddox W, Oparil S, Huang PH, Jose P, Khuddus M, Zentko S, O'Meara J, Barb I, Garasic J, Drachman D, Zusman R, Rosenfield K, Devireddy C, Lea J, Wells B, Stouffer R, Hinderliter A, Pauley E, Potluri S, Biedermann S, Bangalore S, Williams S, Zidar D, Shishehbor M, Effron B, Costa M, Kirtane AJ, Radhakrishnan J, Lobo MD, Saxena M, Mathur A, Jain A, Sayer J, Iyer SG, Robinson N, Edroos SA, Levy T, Patel A, Beckett D, Bent C, Davies J, Chapman N, Shun-Shin M, Howard J, Sharp ASP, Joseph A, D'Souza R, Gerber R, Faris M, Marshall AJ, Elorz C, Lurz P, Höllriegel R, Fengler K, Rommel KP, Mahfoud F, Böhm M, Ewen S, Lucic J, Schmieder RE, Ott C, Schmid A, Uder M, Rump LC, Stegbauer J, Kröpil P, Azizi M, Sapoval M, Cornu E, Fouassier D, Gosse P, Cremer A, Trillaud H, Papadopoulos P, Pathak A, Honton B, Lantelme P, Berge C, Courand PY, Daemen J, Feyz L, Blankestijn PJ, Voskuil M, Rittersma Z, Kroon AA, van Zwam WH, Persu A, Renkin J. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018; **391**: 2335–2345.
41. Mahfoud F, Mancia G, Schmieder R, Narkiewicz K, Ruilope L, Schlaich M, Whitbourn R, Zirlik A, Zeller T, Stawowy P, Cohen SA, Fahy M, Böhm M. Renal denervation in high-risk patients with hypertension. *J Am Coll Cardiol* 2020; **75**: 2879–2888.
42. Bohm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, Tsioufis K, Pocock S, Konstantinidis D, Choi JW, East C. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020; **395**: 1444–1451.
43. Sardar P, Bhatt DL, Kirtane AJ, Kennedy KF, Chatterjee S, Giri J, Soukas PA, White WB, Parikh SA, Aronow HD. Sham-controlled randomized trials of catheter-based renal denervation in patients with hypertension. *J Am Coll Cardiol* 2019; **73**: 1633–1642.
44. Fudim M, Ali-Ahmed F, Patel MR, Sobotka PA. Sham trials: benefits and risks for cardiovascular research and patients. *Lancet* 2019; **393**: 2104–2106.
45. Sata Y, Head GA, Denton K, May CN, Schlaich MP. Role of the sympathetic nervous system and its modulation in renal hypertension. *Front Med (Lausanne)* 2018; **5**: 82.
46. Waldron NH, Fudim M, Mathew JP, Piccini JP. Neuromodulation for the treatment of heart rhythm disorders. *JACC Basic Transl Sci* 2019; **4**: 546–562.
47. Fudim M, Sobotka AA, Yin YH, Wang JW, Levin H, Esler M, Wang J, Sobotka PA. Selective vs. global renal denervation: a case for less is more. *Curr Hyperten Rep* 2018; **20**: 37.
48. McArdle MJ, deGoma EM, Cohen DL, Townsend RR, Wilensky RL, Giri J. Beyond blood pressure: percutaneous renal denervation for the management of sympathetic hyperactivity and associated disease states. *J Am Heart Assoc* 2015; **4**: e001415.
49. Táborský MLM, Václavík J. The effect of renal denervation in patients with advanced heart failure: Oloumoc I study [Internet]. *Eur Soc Cardiol Meet* 2012; **2012**: 2012.
50. Schirmer SH, Sayed MM, Reil JC, Lavall D, Ukena C, Linz D, Mahfoud F, Böhm

M. Atrial remodeling following catheter-based renal denervation occurs in a blood pressure- and heart rate-independent manner. *JACC Cardiovasc Interv* 2015; **8**: 972–980.
51. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012; **59**: 901–909.
52. Mahfoud F, Bohm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L, Schlaich M, Williams B, Fahy M, Mancia G. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 2019; **40**: 3474–3482.
53. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. *JACC Heart Fail* 2019; **7**: 447–456.
54. Wei Y, Xu J, Zhou G, Chen S, Ouyang P, Liu S. Renal denervation suppresses the inducibility of atrial fibrillation in a rabbit model for atrial fibrosis. *PLoS ONE* 2016; **11**: e0160634.
55. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1163–1170.
56. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, Pokushalov EA, Romanov AB. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020; **323**: 248–255.
57. Linz D, Wirth K, Ukena C, Mahfoud F, Pöss J, Linz B, Böhm M, Neuberger HR. Renal denervation suppresses ventricular arrhythmias during acute ventricular ischemia in pigs. *Heart Rhythm* 2013; **10**: 1525–1530.
58. Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, Sobotka PA, Gawaz M, Böhm M. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. *Clin Res Cardiol* 2012; **101**: 63–67.
59. Verloop WL, Spiering W, Vink EE, Beeftink MMA, Blankestijn PJ, Doevendans PA, Voskuil M. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. *Hypertension* 2015; **65**: 751–757.
60. Neuzil P, Merkely B, Erglis A, Marinskis G, de Groot JR, Schmidinger H, Rodriguez Venegas M, Voskuil M, Sturmberger T, Petru J, Jongejan N, Aichinger J, Kamzola G, Aidietis A, Gellér L, Mraz T, Osztheimer I, Mika Y, Evans S, Burkhoff D, Kuck KH, the BackBeat Study Investigators, the BackBeat Study Investigators, Simon J, Dujka L, Machalek L, Király Á, Molnár L, Kovács A, Szabó M, Kupics K, Ansaberga I, Ansabergs J, Nesterovics N, Barysiene J, van Cruijsen M, Schellevis MM, Pezawas T, Flores E, Fullerton D, Beeftink MMA, Meine M, Ascheim DD, Dizon J, Hanon S, Hastings H. Pacemaker-mediated programmable hypertension control therapy. *J Am Heart Assoc* 2017; **6**.
61. Lohmeier TE, Iliescu R. The baroreflex as a long-term controller of arterial pressure. *Physiology (Bethesda)* 2015; **30**: 148–158.
62. Alhogbani T, Strohm O, Friedrich MG. Evaluation of left atrial contraction contribution to left ventricular filling using cardiovascular magnetic resonance. *J Magn Reson Imaging* 2013; **37**: 860–864.
63. Wendling P. MODERATO II: pacemaker-based therapy tamps down hypertension. Medscape. October 01 2019. Presented at the TCT Congress (2019).
64. Kuck K-H. MODERATE II - double-blind, randomized study of neuromodulation therapy in patients with hypertension. Presented at the TCT Congress (2019).
65. Kuck K-H. Safety and efficacy of BackBeat™ cardiac neuromodulation therapy (CNT™) in patients with hypertension: final results of a double-blind randomized trial. 2019. Presented at the TCT Congress (2019).
66. Farrell PC, Richards G. Recognition and treatment of sleep-disordered breathing: an important component of chronic disease management. *J Transl Med* 2017; **15**: 114.
67. Coats AJS. Monitoring for sleep-disordered breathing in heart failure. *Eur Heart J Suppl* 2019; **21**: M36–M39.
68. Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, Abraham WT. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. *J Am Coll Cardiol* 2015; **65**: 72–84.
69. Bradley TD, Floras JS, Investigators A-H. The SERVE-HF trial. *Can Respir J* 2015; **22**: 313.
70. Ding N, Zhang X. Transvenous phrenic nerve stimulation, a novel therapeutic approach for central sleep apnea. *J Thorac Dis* 2018; **10**: 2005–2010.
71. Costanzo MR, Augostini R, Goldberg LR, Ponikowski P, Stellbrink C, Javaheri S. Design of the remede system pivotal trial: a prospective, randomized study in the use of respiratory rhythm management to treat central sleep apnea. *J Card Fail* 2015; **21**: 892–902.
72. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg LR, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, Abraham WT, remedē System Pivotal Trial Study Group. Sustained 12 month benefit of phrenic nerve stimulation for central sleep apnea. *Am J Cardiol* 2018; **121**: 1400–1408.
73. Fudim M, Spector AR, Costanzo MR, Pokorney SD, Mentz RJ, Jagielski D, Augostini R, Abraham WT, Ponikowski PP, McKane SW, Piccini JP. Phrenic nerve stimulation for the treatment of central sleep apnea: a pooled cohort analysis. *J Clin Sleep Med* 2019; **15**: 1747–1755.
74. Fox H, Oldenburg O, Javaheri S, Ponikowski P, Augostini R, Goldberg LR, Stellbrink C, Mckane S, Meyer TE, Abraham WT, Costanzo MR. Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea. *Sleep* 2019; **42**.
75. Costanzo MR, Ponikowski P, Coats A, Javaheri S, Augostini R, Goldberg LR, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, McKane S, Abraham WT, for the remedē System Pivotal Trial Study Group. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail* 2018; **20**: 1746–1754.
76. Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. *Hippokratia* 2009; **13**: 9–19.
77. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. *Prog Cardiovasc Dis* 2014; **56**: 369–381.
78. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. *Transl Res* 2017; **183**: 57–70.
79. Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic fatty liver disease and the heart: JACC state-of-the-art review. *J Am Coll Cardiol* 2019; **73**: 948–963.
80. Hurr C, Simonyan H, Morgan DA, Rahmouni K, Young CN. Liver sympathetic denervation reverses obesity-induced hepatic steatosis. *J Physiol* 2019; **597**: 4565–4580.
81. Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. *Compr Physiol* 2013; **3**: 655–665.
82. Kraft G, Vrba A, Scott M, Allen E, Edgerton DS, Williams PE, Vafai SB, Azamian BR, Cherrington AD. Sympathetic denervation of the common hepatic artery lessens glucose intolerance in the fat- and fructose-fed dog. *Diabetes* 2019; **68**: 1143–1155.
83. Mahfoud F. Early feasibility of the Metavention integrated radio frequency nerve ablation system to improve hyperglycemia and fatty liver in type II diabetic subjects (Metavention). September 26, 2019. Presented at the TCT Congress (2019).