European Journal of Heart Failure (2017) **19**, 1361–1378
doi:10.1002/ejhf.921

POSITION STATEMENT

The autonomic nervous system as a therapeutic target in heart failure: a scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology

Marc van Bilsen[1†], Hitesh C. Patel[2,3,4†], Johann Bauersachs[5], Michael Böhm[6], Martin Borggrefe[7,8], Dirk Brutsaert[9], Andrew J.S. Coats[10,11], Rudolf A. de Boer[12], Gilles W. de Keulenaer[13], Gerasimos S. Filippatos[14], John Floras[15], Guido Grassi[16,17], Ewa A. Jankowska[18,19], Lilian Kornet[20], Ida G. Lunde[21], Christoph Maack[6], Felix Mahfoud[6], Piero Pollesello[22], Piotr Ponikowski[18,19], Frank Ruschitzka[23], Hani N. Sabbah[24], Harold D. Schultz[25], Petar Seferovic[26], Riemer H.J.A. Slart[27,28], Peter Taggart[29], Carlo G. Tocchetti[30], Linda W. Van Laake[31], Faiez Zannad[32,33], Stephane Heymans[34,35], and Alexander R. Lyon[2,3]*

[1]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Hospital, Maastricht, the Netherlands; [2]National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, London, UK; [3]National Heart and Lung Institute, Imperial College London, London, UK; [4]Baker Heart and Diabetes Institute, Melbourne, Vic, Australia; [5]Department of Cardiology and Angiology, Medical School Hannover, Hannover, Germany; [6]Clinic for Internal Medicine III, Cardiology, Angiology and Intensive Internal Medicine, Homburg, Germany; [7]First Department of Medicine, Cardiology Division, University Medical Centre Mannheim, Mannheim, Germany; [8]German Centre for Cardiovascular Research, Mannheim, Germany; [9]Department of Cardiology, Antwerp University, Antwerp, Belgium; [10]Department of Medicine, Monash University, Melbourne, Vic, Australia; [11]Department of Medicine, University of Warwick, Coventry, UK; [12]Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands; [13]Laboratory of Physiopharmacology, University of Antwerp, Antwerp, Belgium; [14]Department of Cardiology, School of Medicine, National and Kapodistrian University of Athens, Athens University Hospital Attikon, Athens, Greece; [15]University Health Network and Sinai Health System Division of Cardiology, Peter Munk Cardiac Centre, Toronto General and Lunenfeld–Tanenbaum Research Institutes, University of Toronto, Toronto, ON, Canada; [16]Clinica Medica, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy; [17]IRCCS Multimedica, Milan, Italy; [18]Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [19]Centre for Heart Diseases, Military Hospital, Wroclaw, Poland; [20]Medtronic, Inc., Bakken Research Centre, Maastricht, the Netherlands; [21]Institute for Experimental Medical Research, Oslo University Hospital, University of Oslo, Oslo, Norway; [22]Critical Care, Orion Pharma, Espoo, Finland; [23]University Heart Centre, University Hospital Zurich, Zurich, Switzerland; [24]Department of Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, MI, USA; [25]Department of Cellular and Integrative Physiology, University of Nebraska College of Medicine, Omaha, NE, USA; [26]Department of Cardiology, Belgrade University Medical Centre, Belgrade, Serbia; [27]Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; [28]Department of Biomedical Photonic Imaging, Faculty of Science and Technology, University of Twente, Enschede, the Netherlands; [29]Department of Cardiovascular Science, University College London, Barts Heart Centre, London, UK; [30]Department of Translational Medical Sciences, Federico II University, Naples, Italy; [31]Department of Cardiology, Heart and Lungs Division, and Regenerative Medicine Centre, University Medical Centre Utrecht, Utrecht, the Netherlands; [32]INSERM, Centre for Clinical Investigation 9501, Unit 961, University Hospital Centre, Nancy, France; [33]Department of Cardiology, Nancy University, University of the Lorraine, Nancy, France; [34]Netherlands Heart Institute, Utrecht, the Netherlands; and [35]Department of Cardiovascular Sciences, Leuven University, Leuven, Belgium

Received 9 February 2017; revised 23 April 2017; accepted 24 May 2017; online publish-ahead-of-print 26 September 2017

*Corresponding author. National Heart and Lung Institute, Imperial College London, Sydney Street, London SW3 6NP, UK. Tel: +44 (0) 20 7352 8121 ext 2396, Fax: +44 (0) 20 7351 8776, Email: a.lyon@ic.ac.uk

[†]These authors contributed equally to this work.

Despite improvements in medical therapy and device-based treatment, heart failure (HF) continues to impose enormous burdens on patients and health care systems worldwide. Alterations in autonomic nervous system (ANS) activity contribute to cardiac disease progression, and the recent development of invasive techniques and electrical stimulation devices has opened new avenues for specific targeting of the sympathetic and parasympathetic branches of the ANS. The Heart Failure Association of the European Society of Cardiology recently organized an expert workshop which brought together clinicians, trialists and basic scientists to discuss the ANS as a therapeutic target in HF. The questions addressed were: (i) What are the abnormalities of ANS in HF patients? (ii) What methods are available to measure autonomic dysfunction? (iii) What therapeutic interventions are available to target the ANS in patients with HF, and what are their specific strengths and weaknesses? (iv) What have we learned from previous ANS trials? (v) How should we proceed in the future?

Keywords Heart failure • Sympathetic • Parasympathetic • Devices and nerve ablation • Autonomic dysfunction

Introduction

Complex autonomic nervous system (ANS) imbalances exist in chronic heart failure (HF).[1] These can be simplified as excessive sympathetic nervous system (SNS) activation and withdrawal of parasympathetic nervous system (PNS) activity. These changes may initially be considered as short-term compensatory responses to the haemodynamic alterations that result from abnormal cardiac function. However, in chronic disease, this imbalance of SNS and PNS activity drives maladaptive remodelling and promotes further deterioration in cardiac function.[1]

Longitudinal studies in HF patients demonstrated that the worse the ANS imbalance, the greater the risk for mortality, although not all HF patients have autonomic imbalance.[2–5] Treatments which improve prognosis (by reducing levels of risk for mortality and/or hospitalization) in HF concomitantly attenuate the effects of SNS activation and/or improve PNS modulation. These treatments include the administration of angiotensin-converting enzyme (ACE) inhibitors,[6] angiotensin receptor blockers,[7] beta-blockers,[8,9] spironolactone,[10] digoxin,[11] ivabradine[12] and cardiac resynchronization therapy (CRT).[13]

However, mortality and morbidity rates in patients with HF remain unacceptably high despite the availability of many evidence-based treatments.[14] The ANS remains an important target worthy of further research because: (i) current drug therapies do not adequately reverse the autonomic imbalances seen in HF; (ii) drug interactions and intolerances limit the initiation and up-titration of current evidence-based treatments shown to affect ANS balance, and (iii) patients with chronic illness may be non-compliant to pharmacological treatments, which introduces a role for therapies that do not rely on patient compliance.

Several therapies are being developed and tested to attenuate cardiac dysfunction through the modulation of components of the autonomic cardiovascular reflexes by: (i) enhancing vagus nerve activity by direct electrical stimulation; (ii) attenuating renal afferent sympathetic outflow via renal nerve ablation; (iii) attenuating the chemoreceptor reflex by carotid body resection, and (iv) enhancing baroreceptor activity via direct electrical stimulation. In addition to these surgical and electrical device-based interventions, strategies to diminish the chemoreceptor reflex with adaptive servo-ventilation (ASV) in patients with sleep apnoea are being investigated and drugs that stimulate parasympathetic activity, primarily by blocking the enzymatic breakdown of the neurotransmitter acetylcholine (ACh), are being tested. The interventional and device-based therapies targeting the ANS are summarized in *Figure 1*. The respective roles of these new treatments are yet to be established; early trial results are variable and predominantly disappointing, despite a logical pathophysiological hypothesis.

Pathophysiology of autonomic dysfunction in heart failure

The set points for sympathetic and vagal efferent discharge are altered within the central nervous system (CNS) in patients with chronic HF. The peripheral nervous system also displays altered responses. Specifically, there is impaired vagal nerve-controlled heart rate modulation, and augmented chemoreceptor, skeletal muscle (mechanic and metabolic) and renal afferent reflexes. These complex interactions between the various limbs of the central and peripheral ANS in HF have been reviewed previously[1] and are summarized in *Figure 2*.[1]

The consequences of the disequilibrium of the SNS and PNS in human HF are myocyte dysfunction caused by excessive β-adrenergic receptor (βAR) stimulation with apoptosis and βAR desensitization,[15] altered kinase and phosphatase activity,[16] neurohumoral activation,[17] increased susceptibility to arrhythmia,[18] inflammation[19] and abnormal nitric oxide synthase (NOS) signalling,[20] all of which lead to a worse clinical outcome and reduced survival.[2]

Techniques to measure autonomic dysfunction in heart failure patients

Objective assessment of the ANS would be invaluable, not only in the identification of subpopulations of patients with a diagnosis of HF and with significant autonomic maladaptation, but also in the monitoring of the effects of any treatments directed at the ANS. However, there are no reference-standard, reliable, clinically available methods with which to measure the functionality of the ANS.[21] There are several different techniques, each of which

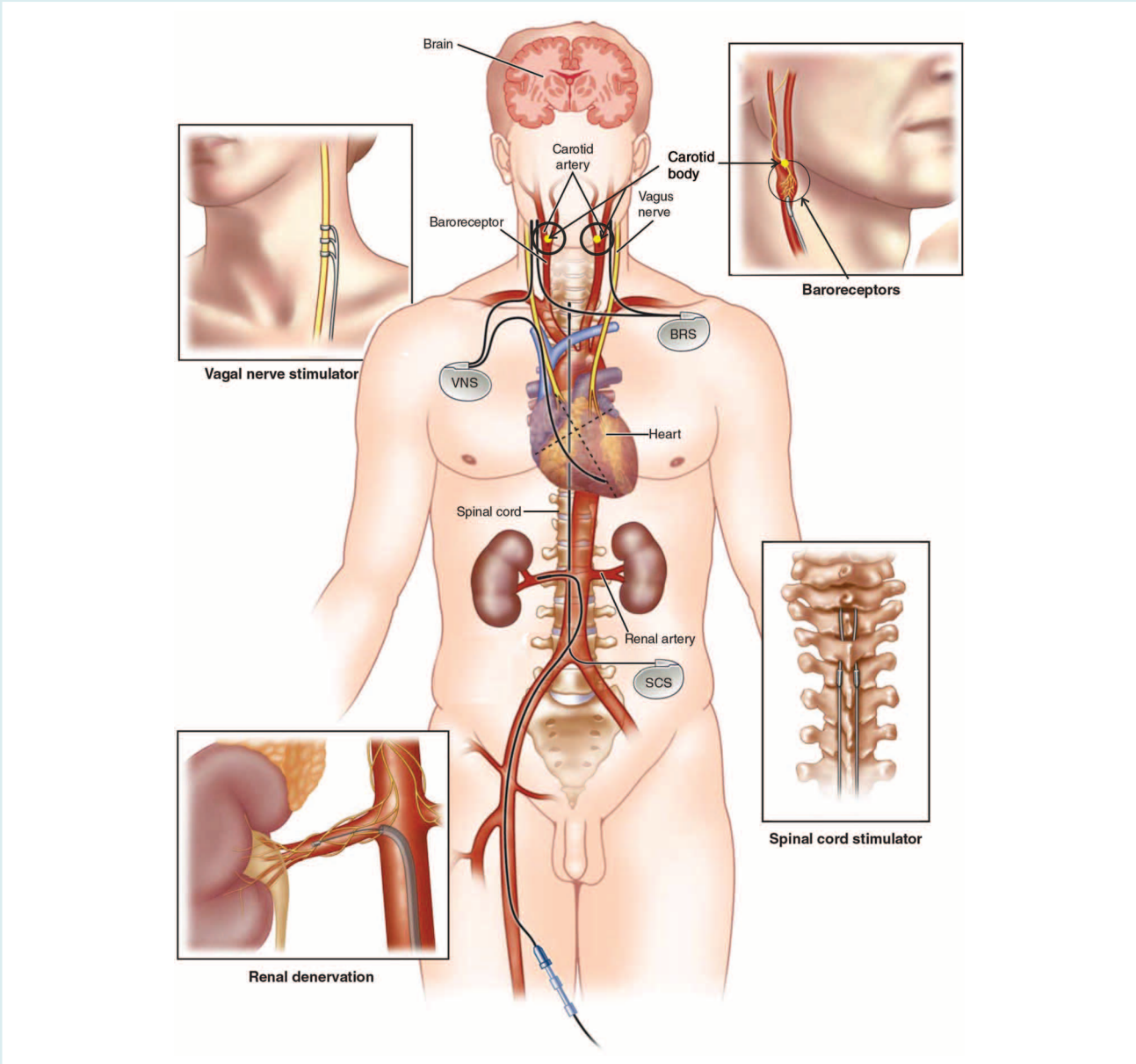

Figure 1 Schematic illustrating the various invasive device-based therapies targeting different limbs of the autonomic nervous system currently under investigation to treat chronic heart failure, including vagal nerve stimulation (VNS), baroreceptor stimulation (BRS), renal nerve denervation and carotid body resection. SCS, spinal cord stimulation. (Adapted from Patel *et al.*[21] with permission.)

provides a unique insight into different limbs of the SNS and PNS, with differing strengths and limitations.[1,21] These techniques can be dichotomized into non-invasive and invasive measurements.

Non-invasive techniques

An elevated resting heart rate is associated with SNS activation and PNS withdrawal and is a risk factor (not just a risk marker) of worse prognosis in HF.[22] In the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT), the lowest risk was observed in patients with heart rates of <60 b.p.m.[23] International guidelines advocate the initiation of treatment in symptomatic HF patients who are in sinus rhythm and have a heart rate of >70 b.p.m. to achieve a resting heart rate of <60 b.p.m.[14]

Dynamic assessment of heart rate, blood pressure and respiratory ventilation frequency provides further data on the functionality of the ANS. Blood pressure and heart rate responses to simple manoeuvres such as standing (SNS and PNS), deep breathing (PNS), hand grip stress (SNS) and Valsalva's manoeuvre (baroreceptor, SNS, PNS), are different in healthy individuals compared with those with HF.[24] However, to date none have proven prognostic importance, although recent data suggest that chronotropic incompetence has prognostic value.[25]

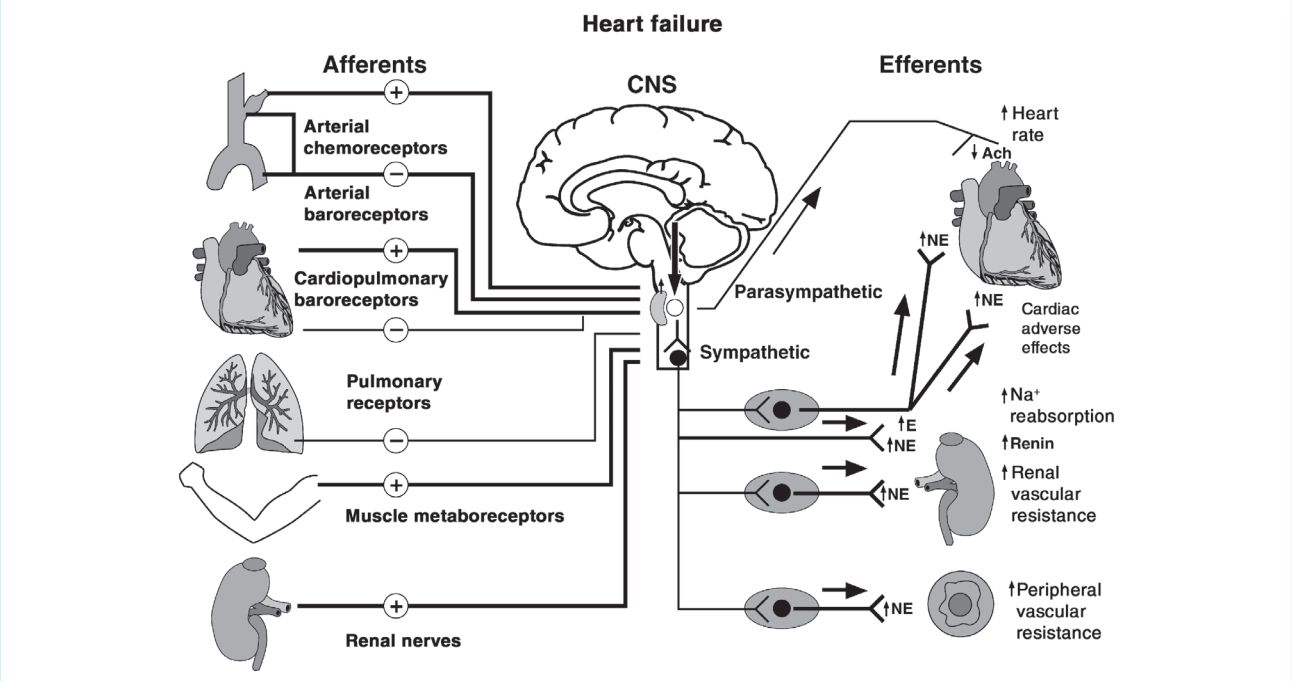

Figure 2 Mechanisms involved in the autonomic disturbances of heart failure with reduced ejection fraction (HFrEF). Input from arterial and cardiac mechano- and chemoreceptor afferents, arterial chemoreceptor, pulmonary stretch receptor, muscle metabo- and mechanoreceptor, and renal afferent nerves converse to modulate sympathetic outflow about a centrally mediated set point increase, involving an angiotensin II-AT1 receptor–NADPH–superoxide pathway. As systolic dysfunction progresses, input effecting sympatho-inhibition by stimulating ventricular and a population of atrial mechanoreceptor nerve afferents decreases (thin line), whereas inhibitory modulation of efferent sympathetic nerve traffic by arterial baroreceptors (thick line) is preserved. Efferent vagal heart rate responses to arterial baroreflex perturbations are attenuated (thin line). Excitatory (+) afferent input arises from: a normally quiescent atrial reflex, activated by increases in cardiac filling pressures; chemically sensitive ventricular afferent nerve endings, triggered by ischaemia; augmented sympatho-excitatory input from arterial chemoreceptors; exercising skeletal muscle in heart failure, and renal afferent nerves (thick lines). The central set point for sympathetic outflow (downward arrow) is raised further by central chemoreceptor sensitization, by sleep apnoeas and possibly by obesity. Efferent mechanisms for increased norepinephrine (NE) spillover include pre-junctional facilitation of its release and impaired NE uptake. The time course through which these mechanisms are engaged differs among individuals. Relatively asymptomatic systolic dysfunction is characterized by a selective increase in cardiac NE release, and a reduction in tonic and reflex vagal heart rate modulation; as heart failure advances, there is a generalized increase in sympathetic nerve traffic to the heart, adrenal, kidney, skeletal muscle and other vascular beds (thick arrow shafts, thick lines). Ach, acetylcholine; CNS, central nervous system; E, epinephrine; Na^+, sodium. (Reproduced with permission from Floras and Ponikowski[1]).

The ANS also regulates beat-to-beat heart rate variability (HRV). HRV analysis is relatively simple to perform, requiring only consecutive RR intervals, but there are several important obstacles to its widespread adoption into both clinical and academic practice.[26,27] Although a reduced HRV has been shown to be associated with shortened survival in HF, this parameter is not a direct quantification of SNS activity (as provided by the spillover technique and microneurography).[28] Secondly, HRV is influenced by both the SNS and PNS, including both pre-synaptic and post-synaptic pathways, and hence HRV will not be a specific correlate of cardiac SNS function.[27] Thirdly, as HF progresses, analysis of HRV using conventional methods is limited by the presence of atrial fibrillation, biventricular pacing, frequent ectopy and the increasing influence of respiratory rhythm-driven very low-frequency oscillations. In patients who remain in sinus rhythm, HRV is reduced. Finally, the optimal technique for calculating HRV remains unclear. Time domain, frequency domain and non-linear analyses of heart rate data collected in short (10 min) or longer (24 h) time intervals are being applied, and currently the use of short-segment electrocardiography (ECG) for spectral HRV and 24-h ECG for time domain analyses are well defined. These issues raise the question of how HRV may be effectively employed in patients with HF, both clinically and for research purposes.[27,28]

Heart rate varies as a reflex response to blood pressure fluctuations due to the effects of baroreceptor function, and the lack of adequate reflex vagal activation has the best prognostic value. The sensitivity of the baroreceptor can be tested through interventions that can acutely affect blood pressure, such as the peripheral administration of a vasopressor (phenylephrine) or vasodilator (nitroglycerine) drug, or by imposing a mechanical stimulus (Valsalva's manoeuvre, lower body negative pressure, neck suction).[29] It is important to note that a pressure rise rapidly and primarily activates the parasympathetic limb, whereas a pressure drop activates the sympathetic limb of the baroreceptor

reflex arc. If a continuous registration of blood pressure is available in conjunction with heart rate, the sensitivity of the baroreflex regulation of heart rate can also be determined in a simple, non-invasive, automated manner by computing the slope of the regression line relating spontaneous changes in the RR interval to the antecedent systolic blood pressure (SBP).[29] A technique to assess the baroreflex that accounts for the influence of increased arterial wall stiffness with age has also been established.[30]

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are two modalities available for the imaging of cardiac sympathetic nerves. SPECT is the more widely available and utilizes meta-iodo-benzylguanidine (^{123}I-MIBG), a radiolabelled norepinephrine analogue. Two semi-quantitative parameters (ratios as opposed to absolute values) are derived: washout rate, and heart–mediastinum ratio (HMR). Patients with a higher washout rate (indicative of higher adrenergic drive) and lower late HMR (indicative of neuronal function, including uptake and release of ^{123}I-MIBG) have a worse prognosis in HF.[31]

Imaging by PET achieves higher temporal and spatial resolution than SPECT and has the added benefit of allowing absolute quantification of pre- and post-synaptic sympathetic innervation.[32] Recently, ^{11}C-metahydroxyphedrine PET was successfully applied to quantify the inhomogeneity in myocardial sympathetic innervation to identify patients at risk for sudden cardiac death.[33] However, dedicated PET facilities are not widely available and many of the PET radiotracers (e.g. ^{11}C-epinephrine and ^{11}C-phenylephrine) have short half-lives and thus their generation requires the availability of an on-site cyclotron, which can be prohibitively expensive. The development of longer-living PET tracers to detect sympathetic innervation is underway, including β-receptor imaging. Although several radiotracers (e.g. ^{11}C-methiodide quinuclidinyl benzilate, ^{11}C-donepezil) are available to image the cardiac PNS, they need further development and validation and as such have not been widely adopted.[34,35]

Invasive techniques

Norepinephrine is the key neurotransmitter of the SNS. Plasma and urine norepinephrine levels provide a global and non-organ-specific assessment of the SNS. Their uses as biomarkers are limited as only 20% of the norepinephrine released at the sympathetic synaptic cleft ultimately enters the circulating blood pool, and only 2% is eventually excreted in the urine.[36] Nonetheless, a higher plasma norepinephrine level, which is suggestive of both heighted sympathetic nerve activity as well as diminished plasma clearance as a result of reduced cardiac output, is associated with worse prognosis in HF.[2]

Organ-specific quantification of synaptic norepinephrine release is performed using the spillover technique. This technique has limited acceptance outside the research setting because it requires an infusion of radiolabelled norepinephrine and the use of a catheterization suite, enabling blood sampling across an organ of interest (e.g. for cardiac spillover, blood samples from the coronary sinus and the aorta are required).[36] ACh is the main neurotransmitter of the PNS, but, unlike norepinephrine, it is too unstable to be sampled and assayed in plasma.

Non-adrenergic non-cholinergic (NANC) neurotransmitters are also co-released by the ANS and may be used as biomarkers of the ANS. Neuropeptide Y (NPY) has an excitatory effect and is found in peripheral organs richly innervated with sympathetic fibres. This substance has been found to be elevated in patients with HF.[37] At the cardiac level, vasoactive intestinal peptide (VIP) is released with vagal nerve firing and is associated with coronary artery vasodilatation and increased flow.[38]

A direct method of quantifying peripheral sympathetic nerve firing in man has been established and is known as muscle sympathetic nerve activity (MSNA). An electrode is placed into the sympathetic nerves (usually of the peroneal nerve) innervating a skeletal muscle.[21] Efferent SNS discharges (from multiple or single units) to these muscles can be quantified as bursts/min or bursts/100 heart beats. This is an operator-dependent and time-consuming technique and is within the capacity of only a few centres around the world. When performed correctly with acceptable reproducibility, MSNA recordings have provided invaluable mechanistic data. Skin sympathetic nerve activity can also be recorded, but the haemodynamic perturbations of HF have little influence on its discharge and there are so far no data associating the activity of these efferent nerves with subsequent mortality.[39] There are no suitable peripheral parasympathetic nerves in man from which to record.

Ventricular arrhythmia is a common cause of sudden death or morbidity in patients with HF. Electrophysiology catheters have been used to measure myocardial electrical patterns, including action potential duration, restitution curves and periodic repolarization dynamics. This provides more granular and spatial data beyond a simple heart rate and HRV. Data from this technique have highlighted the regional heterogeneity in myocardial sympathetic innervation, which is a critical component of re-entrant arrhythmia.[40,41]

Therapeutic interventions targeting the autonomic nervous system

There are now devices available that target several of the autonomic reflexes, particularly at the cervical vagus nerve, renal sympathetic nerves, carotid body and baroreceptor. In addition, ASV and exercise training, as well as pharmacological approaches to influence parasympathetic tone, will be included in this discussion.

Vagus nerve stimulation

Vagus nerve anatomy and function

The vagus nerve contains both afferent (to the CNS) and efferent parasympathetic fibres (from the CNS), as well as sympathetic fibres. Post-ganglionic efferent fibres innervate the sinoatrial and atrioventricular nodes, as well as the atrial and ventricular myocardium. Afferent fibres synapse either centrally or at the baroreceptors modulating both PNS and SNS activity. Increased

vagus nerve activity is associated with a lower heart rate and a decreased refractory period in the atria and an increased refractory period in the left ventricle (LV), and at the same time favourably affects nitric oxide (NO) balance and cytokine release.[42,43]

Preclinical studies

In animal models of pacing-induced HF, impaired vagal control of heart rate occurs at an early stage in the HF process.[44,45] In cats, single-fibre recordings of vagal and sympathetic efferents to the heart demonstrated that stimulation of the right vagus concomitantly led to firing of the left vagus, but also had a reflex cardiac sympathoinhibitory effect.[46] Vagal nerve stimulation (VNS) in dogs reduced ventricular fibrillation and LV dimensions and improved ejection fraction (EF) and survival following ischaemia- and pacing-induced HF.[47,48]

Clinical studies: heart failure

In chronic human HF, reductions in HRV,[49] baroreflex sensitivity for heart rate[50] and heart rate turbulence (HRT)[51] provide evidence of attenuated vagally mediated heart rate modulation. Furthermore, there is evidence of vagal withdrawal prior to acute decompensation in HF.[52]

In the USA, implantable vagal nerve stimulators have been available for use in patients with epilepsy since 1997 and depression since 2005. This familiarity and an established safety record encouraged studies in human HF. The most important features of these clinical studies are listed in *Table 1* and are discussed below.

The initial experience was a safety and feasibility study, which, after extension, recruited 32 patients, the CardioFit Multicentre Trial.[53] Recruited patients were in sinus rhythm with symptomatic HF with a reduced EF (HFrEF), and without CRT. The surgical procedure involved implantation of a right ventricle (RV) pacing lead and a stimulation lead to the right cervical vagus, which was then attached to a CardioFit system (CardioFit™, BioControl Medical Ltd, Yehud, Israel). The RV lead is necessary as vagal stimulation is timed to 'ON' at a certain delay from the sensed R-wave. The procedure was well tolerated by all patients. There were no serious adverse events related to the procedure. However, the stimulation delivered by the device was frequently associated with local side effects with symptoms in the head and neck. The average current achieved was 4.1 ± 1.2 mA. There were also some statistically significant improvements in surrogate secondary endpoints at 6 months, although these should be interpreted with caution as they derive from an open-label uncontrolled study. They include decreases in heart rate, New York Heart Association (NYHA) class and HF symptom score, and increases in 6-min walking test (6MWT) distance and EF.[53]

NECTAR-HF was the first published sham-controlled, blinded, randomized controlled trial (RCT) of VNS.[54] Patients were randomized 2:1 following the implant of the Precision VNS device (Precision™ VNS, Boston Scientific, Marlborough, MA, USA), which was turned either 'ON' or 'OFF' in a blinded manner. The protocol required the up-titration of stimulation current and follow-up for 6 months. The primary endpoint was LV end-systolic dimension as an assessment of LV remodelling. The trial used a one-arm crossover design whereby those initially randomized to device 'OFF' then crossed over to device 'ON'. Current amplitude of 1.42 ± 0.8 mA was reached after 3 months. Data for 86 patients at 6-month follow-up showed that the trial was neutral with respect to LV remodelling, natriuretic peptide levels, peak oxygen uptake on exercise and mean heart rate. Heart failure symptom score and NYHA class improved in those patients who received VNS therapy; but these endpoints are subjective and the findings should be interpreted with caution as the study was imperfectly blinded. Most patients experienced local neck discomfort or coughing when the device was activated. The infection rate from the device was 7.4% in the first 6 months, which may be related to operator experience.[54]

ANTHEM-HF studied another VNS device, the Demipulse Model 103 (Cyberonics Inc, Houston, TX, USA), which delivers continuous stimulation independent of the R-wave and hence does not require an RV lead.[55] This trial enrolled patients with HFrEF (LVEF $\leq$40%). In comparison with the previous two trials described, this study randomized patients to a VNS on the right or the left vagus. Sixty patients were randomized and the primary endpoint was change in LVEF and end-systolic volume. An average current amplitude of 2.0 ± 0.6 mA was achieved. Mean EF improved but end-systolic volume did not change at 6 months. Differences between right or left stimulation were absent, and heart rate was not affected. Consistent with the previous studies, the subjective endpoints of symptom score, 6MWT distance and NYHA class all improved in the context of an unblinded and uncontrolled study.[55] This trial also raised some safety issues as a result of the occurrence of an implant-related death caused by a stroke 3 days after the procedure, possibly related to carotid artery manipulation. Stimulation-related symptoms were common and were managed by appropriate titration of the dose.[55]

A subgroup of 25 patients from ANTHEM-HF underwent advanced Holter analysis that suggested the VNS therapy reduced heart rate and microvolt T-wave alternans (MTWA) and increased the high-frequency component of HRV and HRT.[56] The latter two changes suggest vagal nerve activation. An interesting observation is that the changes in HRV and HRT preceded the changes in MTWA (a marker of arrhythmic risk in HF), which suggests that ANS modification may have a cardioprotective effect against arrhythmogenesis in HF.

INOVATE-HF is the largest and only Phase 3 trial of VNS in HF.[57] The trial patient population had symptomatic HFrEF with NYHA class III HF, sinus rhythm and an EF of $\leq$40%. Patients with atrial fibrillation or pacing were not eligible. A protocol amendment during the trial allowed the recruitment of those who failed to respond to CRT. A total of 707 patients were randomized at a ratio of 3:2 for implant of the CardioFit VNS device (CardioFit™, BioControl Medical Ltd, Yehud, Israel) or ongoing medical therapy with no sham implant procedure. The primary efficacy endpoint was time to all-cause mortality or first HF hospitalization. The INOVATE-HF trial was stopped after a mean follow-up period of 16 months as a result of futility. At 6 months, the mean current amplitude achieved was 3.9 ± 1.0 mA. The primary endpoint occurred in 30.3% of the active arm and 25.8% of the control arm and there was no difference in survival curves between the two

Table 1 Trials in autonomic device therapies for heart failure

Trial name	Device	Trial design	Inclusion criteria	Exclusion criteria	Follow-up period primary outcome	Details study design	Outcomes	Results
Vagal Nerve Stimulation								
CardioFit (n=32)	CardioFit™, BioControl Medical Ltd, Israel	Multi-centre, open-label, non-controlled	EF ≤35% NYHA II–III	AF, CRT being planned	6 months	Stimulation 4.1 mA at 0.9 Hz at a sensed interval from the R-wave	1. System/ procedure related adverse events 2. NYHA, QoL, 6MWT, LV volumes	- 3 deaths unrelated to procedure - Device related pain, dysphonia, cough (n=12) - Improvements in NYHA, QoL, 6MWT, EF, heart rate
NECTAR-HF (n=96)	Precision™, Boston Scientific, USA	Multi-centre, randomized (2:1), sham-controlled	EF ≤35% NYHA II–III, LVEDD ≥5.5 cm	AF, CRT for less than one year or being planned	6 months	Stimulation 1.42 mA at 20 Hz	1. LVESD 2. LVESV, EF, peak VO_2, NT-proBNP, QoL, 6MWT	- No change in LVESD. - Improvement in QoL and NYHA - 7.4% device related infection - No interference with ICD therapies - Device related coughing and facial paraesthesia affected blinding
ANTHEM-HF (n=60)	IPG 103, Cyberonics, USA	Multi-centre, randomized, open-label, controlled	EF ≤40% NYHA II–III LVEDD 5-8 cm QRS <150 ms		6 months	Stimulation 2.0 mA at 10 Hz	1. Procedure related complications 2. LVESV and EF 3. NYHA, QoL, 6MWT	- 1 procedure related death secondary to stroke - Improvements in LVESD, EF, NYHA, QoL, 6MWT
INOVATE-HF (n=707)	CardioFit™, BioControl Medical Ltd, Israel	Multi-centre, randomized (3:2), open-label, controlled	EF ≤40% NYHA III LVEDD 5-8 cm	AF	16 months	Stimulation 3.9 mA at 0.9 Hz at a sensed interval from the R-wave	1. All-cause mortality or HFH 2. Freedom from procedure complications 3. NYHA, 6MWT, LVESV, QoL	- No benefit in reducing mortality/HFH - No safety issues - Improvements in: NYHA, 6MWT, QoL

Table 1 Continued

Trial name	Device	Trial design	Inclusion criteria	Exclusion criteria	Follow-up period primary outcome	Details study design	Outcomes	Results
Renal Sympathetic Denervation								
REACH-Pilot (n=7)	Symplicity™, Medtronic, USA	Single centre, open-label, uncontrolled	SHF NYHA III–IV	eGFR <35 ml/min	6 months	Minimum 4 ablations per artery	1. Safety	- No safety concerns in the first 5 days or over subsequent 6 months post RDN - Improvement in 6MWT
RDT-PEF (n=25)	Symplicity™, Medtronic, USA	Single centre, randomized, open-label, controlled	EF >40% NYHA II–III BNP >35 ng/L or increased LAV/LVH	eGFR <45 ml/min Contraindications to cardiac MRI	12 months	Median 5 ablations per artery	1. QoL, peak VO_2, BNP, E/e', LAV, LVM 2. Safety	- Underpowered - No effect of co-primary endpoints though a signal for improvement at 3 months which did not last to 12 months - 2 patients needed renal artery angioplasty during procedure due to intense spasm
Baroreceptor Activation Therapy								
Gronda *et al.* (n=11)	Barostim neo™, CVRx Inc, USA	Single centre, open-label, uncontrolled	EF ≤40% NYHA III	No indications for CRT eGFR <30 ml/min	6 months		1. Reduction SNS activity 2. Safety, BRS, EF, haemodynamics	- Improvements in MSNA and BRS - Improvements in QoL, 6MWT, EF
Barostim neo HF and Barostim HOPE4HF (n=146)	Barostim neo™, CVRx Inc, USA	Multi-centre, randomized, open-label, controlled	EF ≤35% NYHA III	Carotid artery stenosis >50% eGFR <30 ml/min Recent CRT implant	6 months		1. Safety (MANCE) 2. NYHA, QoL, 6MWT	- Procedure was safe. MANCE free rate 9.2% - Improvements in NYHA, QoL, 6MWT
Carotid Body Resection								
Niewinski *et al.* (n=10)	Surgical resection	Single centre, open-label, uncontrolled	EF ≤45% NYHA II–III CRS >0.6 L/min/SpO_2	Carotid artery stenosis >50% COPD stage III/IV	1 month (primary) 12 months (safety)		1. Reduction SNS activity and CRS 2. Safety, QoL, peak VO_2, EF, overnight oximetery	- Improvements in MSNA and CRS - 2 deaths, 4 worsening overnight oximetry

AF, atrial fibrillation; BNP, B-type natriuretic peptide; BRS, baroreceptor sensitivity; COPD, chronic obstructive pulmonary disease; CRS, chemoreceptor sensitivity; CRT, cardiac resynchronization therapy; EF, left ventricle ejection fraction; eGFR, estimated glomerular filtration rate; HFH, hospitalization for heart failure; LAV, left atrial volume; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVESV, left ventricle end-systolic volume; LVH, left ventricle hypertrophy; LVM, left ventricular mass; MANCE, major adverse neurological and cardiovascular events; MRI, magnetic resonance imaging; MSNA, muscle sympathetic nerve activity; 6MWT, six minute walk test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association class; QoL, quality of life questionnaires; RDN, renal denervation; SHF, systolic heart failure; SNS, sympathetic nervous system; VO_2, oxygen uptake.

groups. In secondary endpoint analyses, those who received VNS had improvements in NYHA class, symptom questionnaire score and 6MWT distance, but there was no effect on LV structural remodelling (LV end-systolic volume). A pre-specified subgroup analysis suggested a trend for females to do worse with VNS, but this may be related to the worse HF profile of women at baseline. No safety concerns were raised in this trial.[57]

An important limitation of strategies to stimulate the vagal nerve refers to the finding in animal studies that part of the abnormality lies anatomically between the preganglionic neuron and the synapse at the end-organ.[58] It is important to consider this, given the neutral findings of clinical trials stimulating the preganglionic vagal fibres.

In summary, despite a wealth of preclinical data supporting the therapeutic benefit of VNS in HF, it has not been translated to patients. Perhaps the most important hurdle that must be overcome before this technology can advance refers to the identification of the ideal VNS stimulation protocol and therapeutic dose. The four clinical trials described here each achieved different maximally tolerated stimulation currents, ranging from 1.4 mA to 4.1 mA.[53–55,57] Further complexity refers to possible variations in the duty cycle (the proportion of time stimulation is applied), stimulation frequency, synchronization to the cardiac cycle, which nerves are preferentially activated (efferent, afferent or both) by the stimulation leads and whether the right or left vagus is used. These issues require rigorous preclinical and Phase 2 dose–response studies to identify the optimal treatment settings for safety and efficacy. Patient selection is also critical to identifying the HF patients most likely to respond (e.g. HF patients with reduced or absent vagal tone). Finally, it has been demonstrated in animal models of HF that the preganglionic neuron and the synapse at the end-organ constitute the anatomical substrate for the disturbances in vagal control.[58] It is important to recollect these data in the context of the neutral or early-stage studies that are ongoing with respect to vagal activation in HF.

Renal sympathetic denervation

Renal nerve anatomy and function

The kidneys are innervated by both efferent and afferent sympathetic nerves. Stimulation of the efferent nerves has been shown to increase renin secretion through the direct action of norepinephrine on β-adrenoreceptors on juxtaglomerular cells, to promote sodium and water reabsorption at the tubular level via activation of α-adrenoreceptors, and to reduce renal blood flow and glomerular filtration through vasoconstriction, all of which are important mechanisms in the pathophysiology of HF.[59]

There are two main types of afferent nerves, both predominately found in the renal pelvis; one is chemosensitive and responds to nociception (adenosine, ischaemia, acidosis, inflammation, oxidative stress and angiotensin II) and the other is mechanosensitive (also found in the renal cortex) and responds to stretch. Activation of the afferent system stimulates CNS centres known to be involved in cardiovascular regulation. Conversely, interrupting the afferent nerves in diseased states reduces central sympathetic outflow, particularly to the heart, kidneys and peripheral vasculature.

The renal sympathetic nerves run in close proximity to the renal artery. The number of renal nerves is greater at the proximal artery (nearest to its origin at the aorta) and gradually decreases towards the distal renal artery.[60] The nerves approximate closer to the renal artery lumen as they progress from the aorta to the renal hilum. Prior to any renal artery bifurcation, 90% of the renal nerves are within 6.4 mm of the renal artery lumen. However, after any bifurcation, 90% of the nerves are within 3 mm of the lumen. A larger proportion of nerves pass anterior, superior and inferior to the renal artery as opposed to posterior to it.[60,61]

The proximity of the nerves to the renal artery lumen make them amenable to destruction using transcatheter ablative techniques with radiofrequency or ultrasound energy or alcohol injection.[62]

Preclinical studies

Surgical renal denervation (RDN) improves natriuresis in HF models.[63] In animals submitted to surgical RDN and induced HF, lower LV filling pressures, higher EFs and better renal perfusion were observed.[64] In rats, surgical denervation was more efficacious than metoprolol, perindopril or losartan in preventing adverse cardiac structural remodelling following a myocardial infarction.[65]

Few studies have reported the effects of transcatheter RDN compared with control in HF models. In one study, RDN in dogs attenuated the fall in EF and systolic function compared with control.[66] Dogs receiving RDN developed less myocardial fibrosis and showed lower plasma norepinephrine, aldosterone, natriuretic peptides and angiotensin II.[66] Animals that underwent RDN prior to developing HF were less likely to have inducible ventricular fibrillation or atrial fibrillation than those that did not undergo RDN.[67]

Clinical studies: hypertension

The majority of experience with RDN in man has been derived in the context of treatment-resistant hypertension (TRH) using the single-electrode Symplicity™ catheter (Medtronic, Minneapolis, MN, USA).[68,69] The initial first-in-man study and open-label RCT showed the treatment to have profound effects on blood pressure,[69] which in further work were coupled mechanistically to improvements in renal norepinephrine spillover, MSNA and cardiac remodelling.[70,71] However, the subsequent larger RCT SYMPLICITY HTN-3, which included a blinded sham control, failed to show any beneficial effect of RDN on blood pressure.[72]

The reasons for this unexpected discrepancy have been debated.[73–75] In retrospect, a number of factors in the SYMPLICITY HTN-3[72] trial design may be relevant, including a failure to require patient selection based on objective evidence that sympathetic activity was high and contributory to the hypertension. Another important issue is that RDN may not have been successfully achieved either through the use of a defunct single-electrode catheter or by the operator's failure to apply ablation to the correct segment of the renal artery.[61] The single-electrode design did not allow the operator to create a circumferential lesion effortlessly. In the SYMPLICITY HTN-3 trial, the largest trial to date in hypertension, only 5.2% of patients received a circumferential ablation.[72] It is hoped that the newer catheter systems, which have unique

designs that enable circumferential/helical denervation, will overcome this shortfall. The latest human cadaveric data suggest that the renal nerves are closer to the renal artery in the distal vessel and hence this may be the preferred location for denervation.[60] This goes against the initial protocol of performing RDN only in the proximal main renal artery before any bifurcation. Recent data in animals have shown that a greater and less variable reduction in renal SNS outflow is achieved if RDN is performed in the main and branch vessels.[76] Finally, the large blood pressure reduction in the sham control arm emphasizes the importance of sham controls for these device and intervention trials.

Clinical studies: heart failure

Two published papers have examined the role of RDN in human HF (*Table 1*). The REACH-Pilot was a proof-of-concept study that performed RDN in seven patients with HF and a mean EF of 43%.[77] As safety was an overarching concern, these patients were kept in hospital for 5 days after the procedure for close monitoring and then were seen at short intervals for a follow-up of 6 months. The study concluded that RDN was safe in HF patients; in particular, there was no significant hypotension or irreversible renal dysfunction.

The RDT-PEF study followed and randomized 25 patients with HF with preserved EF (HFpEF) to RDN vs. usual care.[78] The study was underpowered as a result of challenges in recruitment and the primary composite outcome was neutral. However, there was a signal of improvement at 3 months in peak oxygen uptake and E/e' on Doppler echocardiography that disappeared at 12 months. There was no effect of RDN on plasma norepinephrine or other MIBG parameters.[78] Several other trials concerning HF, with both preserved and reduced EF, are currently recruiting. The outcomes of these trials will help inform the medical community regarding the clinical prospects of this technology.

Other non-controlled studies, not necessarily examining patients with HF, have suggested that RDN may have ancillary effects that would be beneficial in HF, such as LV remodelling.[79]

In summary, there is a plethora of preclinical data supporting the value of attenuating the renal nerves in HF. These data are in the process of translation into man. It is vital that consensus is reached prior to the launch of any new studies of the optimal RDN technique. In light of the currently available data, we would not recommend using a single-electrode catheter and suggest current research trials deploy a strategy of delivering therapy to both the main renal artery and the main branches where safely accessible, or use catheters that target the nerves using different modalities such as ultrasound or chemical ablation by injection of alcohol. Current safety data pertaining to the new catheters and the more comprehensive denervation approach are minimal and hence further data are required in future studies.

Baroreceptor activation therapy

Baroreceptor anatomy and function

The baroreceptors are mechanoreceptors located in the carotid sinus (an out-pouching of the internal carotid artery) and aortic arch that respond to beat-to-beat changes in SBP or pulse pressure. When activated by stretch, they transmit sensory signals to the vasomotor centre in the brain stem via the vagal nerve (aortic baroreceptors), the nerve of Hering and the glossopharyngeal nerve (carotid sinus baroreceptors). This initiates an efferent reflex response, resulting in both sympathetic inhibition (via the spinal cord and sympathetic chain) and parasympathetic activation (via efferent pathways in the vagus nerve). In hypertension the baroreceptor response to blood pressure resets, whereas in HF it is diminished. It is hypothesized that electrical stimulation of the carotid sinus nerve distal to the mechanoreceptor will circumvent such attenuation and intensify afferent input to the brain stem, thereby reflexively inducing augmented parasympathetic tone and attenuated sympathetic nerve firing.

Preclinical studies

Baroreceptor activation therapy (BAT) has been used in canine HF models of coronary artery microembolism and rapid pacing. The BAT device used in the majority of these studies was the Rheos™ system (CVRx, Minneapolis, MN, USA). This system involves the surgical implantation of stimulating electrodes circumferentially around both carotid sinuses, which are then connected to an implantable pulse generator.

In dogs with HF, BAT reduces mortality, attenuates neurohumoral activation, improves systolic and diastolic LV function, reduces functional mitral regurgitation and reduces the vulnerability of the myocardium to ventricular tachyarrhythmia.[80,81] Beneficial effects of BAT on myocardial NOS isoform expression (eNOS up, iNOS and nNOS down) have also been reported.[81]

Clinical studies: hypertension

Baroreceptor activation therapy was first applied to treat patients with TRH. The initial pilot studies and Phase 2 studies demonstrated that when the device was turned 'ON', a rapid decrease in blood pressure ensued, along with a reduction in heart rate and low-frequency power, an increase in high-frequency power, and changes in HRT suggestive of modulation of both the SNS and PNS.[82,83] LV hypertrophy also regressed.[84] The procedure was considered to be safe for patients, although a learning curve in the device implant procedure was clearly evident as eight of the 42 patients recruited into the initial feasibility study experienced either procedural or device-related serious adverse events.[83]

These smaller studies were followed by a double-blind RCT, the Rheos Pivotal Trial, which recruited 265 patients with TRH.[85] All recruited patients underwent a device implant; however, in two-thirds of patients, the device was turned 'ON' at 1 month, whereas in the remainder, the device was kept 'OFF'. The co-primary endpoints (two efficacy and three safety) were not all met. A marked placebo effect was observed, whereby SBP dropped at 6 months by 9 ± 29 mmHg in the 'OFF' arm vs. 16 ± 29 mmHg in the 'ON' arm ($P = 0.08$). Safety was also an issue as 9% of patients developed either temporary or permanent facial nerve injury. After 6 months of follow-up, the device was turned 'ON' in those patients initially randomized to device 'OFF'. One-year open-label

data now available suggest that BAT has variable effects on blood pressure in that some patients show no response. However, 76% of patients were classified as responders according to evidence of either SBP reductions of >20 mmHg or the achievement of target blood pressure.[86] The technology has since undergone modification and the next generation of the device, Barostim neo™ (CVRx, Minneapolis, MN, USA), is smaller and requires the implantation of a single stimulating electrode, preferably on the right carotid body. This is expected to reduce the incidence of implant complications, including facial nerve damage.

Clinical studies: heart failure

The human HF studies of BAT (*Table 1*) have used the new-generation single-electrode device, Barostim neo™, with no serious safety concerns. The initial proof-of-concept study recruited 11 patients with NYHA class III HF and a mean EF of 31%.[87] In this open-label study, improvements were seen at 3 and 6 months in MSNA, 6MWT distance, HF symptom score and LVEF. These favourable effects were coupled with a significant reduction in muscle sympathetic nerve traffic, documenting the occurrence of an adrenergic deactivation. There was no effect on heart rate or blood pressure. The data were confirmed at a later follow-up examination carried out about 2 years after Barostim neo™ implantation, which showed a trend towards reduced hospitalization in the treatment arm.[83,88]

Abraham and colleagues reported on a multicentre, randomized, open-control trial that randomized 146 patients with an EF of ≤35%.[89] At 6-month follow-up (data available for 118 patients), patients who received BAT had greater improvements in NYHA class, HF questionnaire score and 6MWT distance than those randomized to the control group. These changes were mirrored in a statistical improvement in natriuretic peptide levels and increase in SBP in the active arm. However, LVEF did not increase significantly in the treatment group relative to the control group. By contrast with VNS, with BAT up-titration of stimulation strength does not seem to be limited by patient discomfort.

The authors performed a subgroup analysis focusing on the effects of BAT in patients who also underwent CRT.[90] BAT was safe in patients who had concomitant CRT; however, BAT may be less effective in this group compared with patients not treated with CRT.[90]

In summary, the role of BAT in the management of HF has yet to be established. The clinical data currently available are restricted to two small studies, neither of which were blind-controlled and hence were susceptible to various biases.[73] Further direction will be provided with the currently recruiting cardiovascular outcome trial, Barostim therapy for Heart Failure (BeAT-HF; ClinicalTrials.gov ID: NCT02627196). Mechanistic studies examining the role of BAT in HFpEF are also underway.

Carotid body removal

Carotid body anatomy and function

Peripheral chemoreceptors are found predominately in the carotid body, which is a discrete 1.5–3.0-mm ovoid structure found at the bifurcation of the carotid artery. Peripheral chemoreceptors are sensitive to hypoxia and to a lesser degree to hypercapnia and acidosis.[91] In health, when the chemoreceptors are activated, signals are sent to the CNS, effecting an increase in minute ventilation (to counteract hypoxia) and an increase in sympathetic outflow to the vasculature (to maintain blood pressure and organ perfusion as hypoxia is associated with vasodilatation). In HF, this reflex becomes maladaptive, presumably because reduced blood flow to the carotid body sensitizes the chemoreceptors, which increases their tonic firing rate, as well as responsiveness to hypoxia.[92] Sensitization, which may involve adenosine, as this purine is produced under hypoxic conditions, is a potent stimulus to the peripheral chemoreflex. Indeed, circulating adenosine levels were increased in HFrEF patients.[93]

Clinically, chemoreceptor sensitivity can be determined as the change in minute ventilation as a proportion of the amount of induced hypoxia or hypercapnia.[94] When activated by this pathway, there is an SNS response with increased MSNA, hypertension and tachycardia.[95] Tonic discharge of the chemoreceptors can also be measured by the administration of low-dose dopamine or hyperoxia, both of which have an inhibitory effect.[96,97]

Preclinical studies

Various models of HF have demonstrated the development of altered chemoreflexes, as well as autonomic dysfunction and periodic breathing disorders following the onset of HF.[98,99] However, if the sensory input from the peripheral chemoreceptor is altered through ablation, these maladaptive processes are partially reversed. Bilateral carotid body ablation at 2 weeks after induction of myocardial infarction in rats increased the survival rate from 45% to 85%, normalized central sympathetic outflow and baroreceptor sensitivity, and reduced the incidence of apnoea and ventricular arrhythmias.[98] Bilateral cryogenic ablation of the carotid bodies in rabbits with pacing-induced HF reduced resting renal sympathetic nerve activity, improved respiratory control and LV function, while reducing cardiac arrhythmias.[100] Collectively, these findings certainly support the strategy of targeting the peripheral chemoreceptors as a novel therapy in HF.

Clinical studies: heart failure

In human HF, increased peripheral chemosensitivity is associated with poor prognosis, central sleep apnoea (CSA), exercise intolerance, cardiac arrhythmia, sympathetic activation and reduced baroreceptor sensitivity.[94,101–103] Suppression of the chemoreflex with high concentration inspired oxygen in 12 patients with HF improved exercise tolerance and reduced minute ventilation.[104]

During the 1940s to 1970s, surgical carotid body resection was performed largely as a palliative procedure in the treatment of chronic lung disease. In some patients, the perception of shortness of breath was reduced and exercise tolerance improved.[105] The historic follow-up data for >15 000 patients submitted to carotid body resection revealed a very low mortality rate, albeit in the presence of probable publication bias. These data and background

led to a first-in-man single-case study of a unilateral carotid body resection for HFrEF.[106] The procedure was well tolerated and without complication. The patient experienced an improvement in symptoms, exercise function, HRV and chemoreceptor sensitivity following this procedure.[106]

This was followed by an open-label and uncontrolled study conducted in 10 patients of NYHA class II and III status, with an EF of ≤45%, and with augmented peripheral chemosensitivity of >0.6 L/min/SpO_2.[107] Four patients underwent unilateral and six underwent bilateral carotid body removal.[107] During the follow-up period, two patients died (it is unclear whether these deaths reflected the natural history of HF in the individual patients or were related to the procedure) and one patient withdrew. At 1 month follow-up, MSNA and chemosensitivity were reduced (ventilator response to hypoxia). These reductions were sustained at 2 months, but without improvement in exercise time, HF symptom score, natriuretic peptide levels or EF. From the perspective of safety, an increase in the arterial partial pressure of carbon dioxide was reported, and four patients experienced worsening of minimal oxygen saturations at night, necessitating the introduction of ASV in one. The authors concluded that nocturnal hypoxia might be less frequently encountered if only unilateral carotid body resection (rather than bilateral) is performed.[107] They suggest the risks of this invasive, non-reversible procedure should be carefully weighed against its limited clinical efficacy before further clinical studies using this intervention are launched.

In summary, dampening peripheral chemosensitivity with carotid body resection may be an appropriate target in the management of HF, but data supporting this strategy are sparse. Device-based approaches to target the carotid body transvenously are under investigation in ongoing clinical studies.

Treatment of sleep apnoea

Sleep-related breathing disorders are common in HF and affect approximately 50% of patients with chronic HFrEF and in receipt of contemporary evidence-based drug or device-based therapy. Obstructive and central sleep apnoea differ with respect to their aetiology (collapse of the pharynx vs. withdrawal of central drive to muscles of respiration during sleep) and their acute effect on stroke volume (a reduction vs. an increase), but have several features in common, including breathing instability, a nocturnal autonomic pathology in which recurring cycles of apnoea (that silences pulmonary-stretch receptors that inhibit sympathetic outflow reflexively), inducing progressive hypoxia and hypercapnia (eliciting chemoreflex-mediated sympatho-excitation) and arousal with hyperpnoea (inducing centrally generated sympathetic excitation and vagal withdrawal), elicit and entrain clusters of intense sympathetic nerve firing, and, during wakefulness, sustained upward resetting of central sympathetic outflow.[108,109]

Treatment of obstructive sleep apnoea

Obstructive sleep apnoea (OSA) occurs in approximately a quarter of all HF patients and is associated with a worse prognosis.[110,111] One of the consequences of OSA, intermittent hypoxia, has been shown to directly affect carotid body function, centrally activating the SNS.[112] This SNS hyperactivity may be attenuated if OSA is abolished by therapies such as continuous positive airway pressure (CPAP) or ASV.[113,114] CPAP restores both daytime and night-time autonomic balance in HF,[113] improves EF,[115] improves HRV[116] and enhances norepinephrine reuptake by cardiac sympathetic nerve terminals.[117] ASV therapy is currently being evaluated in a multicentre cardiovascular endpoint-driven RCT (ADVENT-HF; ClinicalTrials.gov ID: NCT01128816).[118] At the time of writing, 417 patients with LVEF of ≤45% and predominantly NYHA class II symptoms, of whom approximately two-thirds have OSA and one-third have CSA, have been randomly allocated to receive or not receive ASV in addition to optimal medical therapy. Data are reviewed at 6-month intervals by a data safety monitoring board. At their meeting on 24 November 2016, no adverse safety signals were detected for either type of sleep apnoea and trial continuation was recommended. It is important to distinguish between the populations that are being recruited into the ADVENT-HF trial and those entering SERVE-HF (see below).

Treatment of central sleep apnoea

The development of ASV algorithms capable of substantially reducing the apnoea–hypopnoea index of patients with CSA refractory to CPAP sparked renewed interest in its treatment. In SERVE-HF, the largest trial performed thus far, 1325 patients with an EF of ≤45% and CSA detected by either home polygraphy without sleep monitoring or in-laboratory attended polysomnography were randomly allocated minute ventilation-triggered ASV (mv-ASV) with initial settings of 5 cmH_2O expiratory positive airway pressure and 3 cmH_2O inspiratory pressure support, delivered predominantly through a full-face mask.[119] Approximately 70% of participants were classified as having NYHA class III symptoms and mean follow-up was 31 months. Compliance with mv-ASV was 3.7 h/night. There was considerable dropout (29% in the mv-ASV group) and crossover (16% from the control to treatment arms). The primary endpoint in the time-to-event analysis by allocation strategy was the composite of first occurrence of death from any cause, cardiac transplantation, implantation of a ventricular assist device, resuscitation for sudden cardiac death, appropriate lifesaving defibrillator shock, or unplanned hospitalization for HF. This primary endpoint did not differ between groups, but all-cause mortality and cardiovascular mortality were significantly higher in the group allocated mv-ASV than in the control group [hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.06–1.55 ($P = 0.01$); HR 1.34, 95% CI 1.90–1.65 ($P = 0.006$), respectively]. In a secondary multi-state modelling analysis, the risk for cardiovascular death without prior hospitalization (therefore presumed to be sudden death) was greatest in those with an LVEF of ≤30% allocated mv-ASV (HR 5.2, 95% CI 2.11–12.89; $P = 0.026$).[120] Neither the primary nor this secondary SERVE-HF publication reported any representations of cardiovascular autonomic regulation or primary or secondary outcomes for those using or not using mv-ASV, respectively.

The use of ms-ASV to treat CSA, particularly in Europe, has essentially ceased following the publication of the SERVE-HF results, and ASV has a class III indication (contraindicated) in the recent European Society of Cardiology (ESC) HF guidelines.[14] Attention has turned to the study of alternative therapies for CSA within the context of clinical trials. Modalities under investigation include peripheral chemoreceptor reflex attenuation by supplementary oxygen, peak flow-triggered ASV (pf-ASV), and phrenic nerve stimulation. Transvenous unilateral phrenic nerve stimulation has been demonstrated, in both non-randomized[121] and randomized[122] studies, to reduce the severity of CSA, but no data concerning the impact of this intervention (which was not without initial discomfort or device- and procedure-related adverse events) on either sympathetic or vagal nerve function have been forthcoming.

Pharmacological restoration of autonomic nervous system imbalance

In addition to devices and ablation strategies, a number of new pharmacological approaches targeting ANS dysfunction are being developed. The attenuation of the effects of neurally released and circulating norepinephrine on β-1 and β-2 adrenoreceptors is the most obvious established example in chronic HF and beta-blockers have had a class 1 indication for HFrEF for over 10 years, which has been reinforced in the current 2016 ESC guidelines for chronic HF.[14]

Stimulation of the parasympathetic branch of the ANS is more difficult to achieve pharmacologically. Parasympathetic innervation of the heart is mediated primarily by ACh binding to the M2 muscarinic ACh receptor (M2-AChR). Although parasympathetic fibres are also found throughout the ventricles, the majority are located in the sinoatrial node, the atrial myocardium, the atrioventricular node, and the ventricular conducting system.

The importance of the PNS in cardiac physiology is exemplified by observations that both knockout of the M2-AChR and knockdown of the vesicular ACh transporter in mice are associated with the development of marked cardiac dysfunction.[123] ACh also modulates sympathetic tone by acting as a preganglionic neurotransmitter for the SNS and by inhibiting the release of norepinephrine from adrenergic nerve terminals. Indeed, muscarinic stimulation with intracoronary ACh decreases cardiac norepinephrine spillover.[124] ACh has an independent negative lusitropic effect and at the same time antagonizes the effects of β-adrenergic stimulation.[125]

Acetylcholine released into the synaptic cleft has a very short half-life. One strategy to stimulate PNS activity is to block the degradation of ACh in the synaptic cleft by means of acetylcholine esterase inhibitors (ChEIs). Centrally acting ChEIs, like donezepil, are able to pass the blood–brain barrier and are being used clinically to treat Alzheimer's disease. Retrospective analysis revealed that cardiovascular mortality risk was lower in Alzheimer's disease patients treated with donezepil.[126] In a subsequent small study in 49 dementia patients, donezepil lowered plasma BNP levels in a subgroup of patients with subclinical HF (baseline BNP >60 pg/mL).[127] In a large Swedish cohort of Alzheimer's disease patients, the application of ChEI significantly lowered the risk for myocardial infarction and cardiovascular death.[128] In preclinical studies, donepezil attenuated LV dysfunction and neurohumoral activation in rats with HF[129] and the effect was additive when the treatment was administered in combination with losartan therapy.[130]

Pyridostigmine, a ChEI that does not cross the blood–brain barrier and thus only acts peripherally, increased HRV in healthy humans.[131] Pyridostigmine increased HRV and reduced ventricular arrhythmias in HF patients.[132]

Collectively, these findings indicate that ChEIs ameliorate the sympatho–vagal balance and improve haemodynamics in HF. An important caveat is that ChEI will also stimulate sympathetic cervical, splanchnic and lumbar ganglionic neurotransmission. Indeed, an increase in MSNA was reported after application of edrophonium, a short-acting ChEI.[133]

The beneficial effects of ChEI may also be related to the anti-inflammatory effects exerted through the so-called inflammatory reflex. ACh (and nicotine) inhibits the synthesis and secretion of proinflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNFα) by stimulating the α7 nicotinic acetylcholine receptor (α7-nAChR) on monocytes/macrophages in the spleen (and perhaps also in other tissues, including the injured heart).[134] Selective agonists of the α7-nAChR have been shown to exert a potent anti-inflammatory effect. This mechanism of action may explain much of the observed therapeutic effects of VNS.

Digoxin (digitalis) is a more established drug used in patients with HF that has vagomimetic properties.[11,135] In preclinical studies, the digoxin analogue digitoxin inhibited inflammation and had vasoprotective effects.[136] This effect is seen at lower drug concentrations than the more direct positive inotropic and pro-arrhythmic effects observed at higher concentrations. Digitoxin may be advantageous, especially in patients with chronic kidney disease, because the kidney contributes much less to its clearance than it does to clearance of digoxin.[14] At lower doses digitalis may still be of therapeutic value in patients suffering from advanced HF. Acutely, digoxin reduces heightened cardiac sympathetic activity in patients with severe HFrEF.[137] A large prospective randomized trial, the DiGIT-HF trial (EudraCT no. 2013-005326-38) is currently ongoing to further investigate the role of digitoxin in patients with HFrEF.

Caffeine has also been investigated in HF and has been shown to prolong exercise duration.[138] This is probably related to its non-selective adenosine antagonistic properties. Adenosine is a potent stimulus to the peripheral chemoreflex and a purine, the circulating concentration of which is increased in HFrEF.[93]

Exercise training and autonomic function

It is also noteworthy that supervised exercise training is another effective and non-invasive way to improve overall autonomic balance in HF patients.[139,140] A recent small study (26 patients) showed that a 16-week exercise training protocol improved the baroreflex control of MSNA in patients with chronic HF,[141] thereby confirming earlier findings in animal models of HF and illustrating

the potential of exercise training as a non-invasive means to restore ANS imbalance in HF patients. This topic will be reviewed in detail by the Heart Failure Association (HFA) Committee on Exercise and Training (in preparation).

Conclusions

Detailed understanding of the pathophysiological role of ANS imbalance in preclinical models and clinical studies in HF patients raises the normalization of ANS balance as an obvious therapeutic strategy for the treatment of HF. There are roles for new drug therapies, in addition to beta-blockers, and for surgical techniques, including stimulation devices, aimed at reducing SNS reflex activity or promoting PNS activity. A wealth of preclinical studies provides the proof of principle that translation of this approach is worthwhile. However, delineating the mechanisms responsible for the beneficial effects seen in preclinical studies remains challenging. Do these benefits derive merely from a reduction in workload attributable to the lowering of afterload and the reduction in heart rate? Or are other injurious processes, such as cardiac inflammation, also directly targeted by some of these interventions?

Clinical studies have been low in number, often open label, and have enrolled limited numbers of patients. Several trials have been disappointing and have reported minimal or no benefit. One obvious question concerns whether we are selecting the correct patients to treat. The milieu of inhibitory and excitatory autonomic reflexes in HF differs between individuals in terms of magnitude, variation and time course.[1] To identify the subgroups that will benefit from ANS modulation based on just one test will be difficult. As discussed, the assessment of ANS imbalance in patients is not easy, is certainly not common practice, and can be performed in various ways, each with its advantages and disadvantages. The same holds for measuring the effectiveness of the intervention in terms of its direct effect on ANS activity. Ideally, it would be preferable to measure nerve activity directly to identify patients with abnormal nerve firing patterns and document alterations following the intervention. However, this technique is invasive and has been applied for the measurement of only SNS activity, not PNS activity. There is no adrenergic or autonomic biomarker with the pragmatic utility, sensitivity and specificity of natriuretic peptides in the diagnosis of HF. We still lack a measure that can be used in clinical practice on a routine basis and research to develop new, preferably non-invasive techniques to measure SNS and PNS activity is required. In this respect, the recent developments in SPECT and PET imaging offer hope, and applying a variety of these methods will help improve the selection of patients for specific therapeutic modalities by ensuring the presence of an imbalance worthy of treating.

Important variables that require optimization in the context of electrical device stimulation or nerve ablation are the anatomical location of the intervention and the stimulation protocol in the case of treatment with electrical devices. Vagal stimulation and renal nerve denervation depend on the site of the intervention, which affects outcome. Should we preferentially stimulate the cervical vagal nerve or a more specific cardiac branch? Treatment effectiveness will depend on the way in which stimulation is applied in terms of frequency, and impulse amplitude. The optimal settings remain to be defined. In general, current amplitude influences the number and type of fibres that will be stimulated and, as current amplitude increases, additional, smaller fibre types will be recruited. Duty time (intermittent, continuous, day/night or random stimulation) is likely to be another important variable that requires further study to identify the optimal treatment stimulation dose.

Trial design is another issue.[142,143] Marked placebo and Hawthorne effects exist. The nature of surgical and device-based interventions is such that blinding is hard to achieve. Patients are often aware of the stimulus. Cervical vagal nerve stimulation can cause local pain, and baroreceptor stimulation causes laryngeal activation, voice hoarseness and throat discomfort.

Collectively, although neuromodulation is promising from a conceptual perspective and despite the many preclinical studies in support of the concept, there are several hurdles to be overcome with respect to both neuromodulation strategy and trial design before neuromodulation can find its place as a proven clinical treatment. It is also important to note that supervised exercise training is another non-invasive way of improving overall autonomic balance in HF patients.[139,140] Finally, it is important to recognize that some forms of excessive sympatholysis may be harmful, as demonstrated in the MOXCON trial.[144]

Most trials to date have assessed treatment effects in patients suffering from HFrEF and receiving optimal medical therapy. As shown previously for CRT,[145] it is important to note that the techniques discussed above may act synergistically with other therapies. Neuromodulation has primarily been tested in HFrEF patients, a group in which the presence of ANS imbalance is evident. It will be interesting to learn if neuromodulation will be beneficial in other patient groups, including those with acute HF and HFpEF.

Addressing these challenges in preclinical and clinical studies that are appropriately designed to optimize treatment dose, delivery, patient selection and the monitoring of direct 'on target' effects on SNS and/or PNS will serve to clarify where the range of ANS therapies will find their individual places in the armamentarium of treatments for patients with HF.

Acknowledgements

The authors would like to thank the staff in the Brussels office of the European Society of Cardiology, who supported them during the aftermath of the tragic events of 22 March 2016 in Brussels. We dedicate this article to the memory of the people who lost their lives that morning in the airport and underground train in Brussels.

Funding

This was supported by the Heart Failure Association of the ESC.

References

1. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. *Eur Heart J* 2015;**36**:1974–1982.

2. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;**311**:819–823.
3. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;**351**:478–484.
4. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, Boveda S, Massabuau P, Fauvel M, Senard JM, Bounhoure JP. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *Eur Heart J* 2000;**21**:475–482.
5. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. *Eur Heart J* 2005;**26**:906–913.
6. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Pozzi M, Morganti A, Carugo S, Mancia G. Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. *Circulation* 1997;**96**:1173–1179.
7. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, Kurabayashi M. Effects of candesartan on cardiac sympathetic nerve activity in patients with congestive heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2005;**45**:661–667.
8. Azevedo ER, Kubo T, Mak S, Al-Hesayen A, Schofield A, Allan R, Kelly S, Newton GE, Floras JS, Parker JD. Nonselective versus selective beta-adrenergic receptor blockade in congestive heart failure: differential effects on sympathetic activity. *Circulation* 2001;**104**:2194–2199.
9. Cohen-Solal A, Rouzet F, Berdeaux A, Le Guludec D, Abergel E, Syrota A, Merlet P. Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure. *J Nucl Med* 2005;**46**:1796–1803.
10. Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1995;**76**:1259–1265.
11. Brouwer J, van Veldhuisen DJ, Man in't Veld AJ, Dunselman PH, Boomsma F, Haaksma J, Lie KI. Heart rate variability in patients with mild to moderate heart failure: effects of neurohormonal modulation by digoxin and ibopamine. The Dutch Ibopamine Multicenter Trial (DIMT) Study Group. *J Am Coll Cardiol* 1995;**26**:983–990.
12. Bohm M, Borer JS, Camm J, Ford I, Lloyd SM, Komajda M, Tavazzi L, Talajic M, Lainscak M, Reil JC, Ukena C, Swedberg K. Twenty-four-hour heart rate lowering with ivabradine in chronic heart failure: insights from the SHIFT Holter substudy. *Eur J Heart Fail* 2015;**17**:518–526.
13. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;**108**:266–269.
14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
15. Gorelik J, Wright PT, Lyon AR, Harding SE. Spatial control of the betaAR system in heart failure: the transverse tubule and beyond. *Cardiovasc Res* 2013;**98**:216–224.
16. El-Armouche A, Gocht F, Jaeckel E, Wittkopper K, Peeck M, Eschenhagen T. Long-term beta-adrenergic stimulation leads to downregulation of protein phosphatase inhibitor-1 in the heart. *Eur J Heart Fail* 2007;**9**:1077–1080.
17. Elsner D, Kromer EP, Riegger GA. Effects of vagal blockade on neurohumoral systems in conscious dogs with heart failure. *J Cardiovasc Pharmacol* 1990;**15**:586–591.
18. Schwartz PJ, Motolese M, Pollavini G, Lotto A, Ruberti UGO, Trazzi R, Bartorelli C, Zanchetti A; TISDP Group. Prevention of sudden cardiac death after a first myocardial infarction by pharmacologic or surgical antiadrenergic interventions. *J Cardiovasc Electrophysiol* 1992;**3**:2–16.
19. Sloan RP, McCreath H, Tracey KJ, Sidney S, Liu K, Seeman T. RR interval variability is inversely related to inflammatory markers: the CARDIA study. *Mol Med* 2007;**13**:178–184.
20. Binkley PF, Nunziatta E, Liu-Stratton Y, Cooke G. A polymorphism of the endothelial nitric oxide synthase promoter is associated with an increase in autonomic imbalance in patients with congestive heart failure. *Am Heart J* 2005;**149**:342–348.
21. Patel HC, Rosen SD, Lindsay A, Hayward C, Lyon AR, di Mario C. Targeting the autonomic nervous system: measuring autonomic function and novel devices for heart failure management. *Int J Cardiol* 2013;**170**:107–117.
22. Bohm M, Reil JC. Heart rate: surrogate or target in the management of heart failure? *Heart* 2013;**99**:72–75.
23. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;**376**:886–894.
24. Patel H, Ozdemir BA, Patel M, Xiao HB, Poole-Wilson PA, Rosen SD. Impairment of autonomic reactivity is a feature of heart failure whether or not the left ventricular ejection fraction is normal. *Int J Cardiol* 2011;**151**:34–39.
25. Magri D, Corra U, Di Lenarda A, Cattadori G, Maruotti A, Iorio A, Mezzani A, Giannuzzi P, Mantegazza V, Gondoni E, Sinagra G, Piepoli MF, Fiorentini C, Agostoni P. Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. *Eur J Heart Fail* 2014;**16**:201–209.
26. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;**17**:354–381.
27. Notarius CF, Floras JS. Limitations of the use of spectral analysis of heart rate variability for the estimation of cardiac sympathetic activity in heart failure. *Europace* 2001;**3**:29–38.
28. Notarius CF, Butler GC, Ando S, Pollard MJ, Senn BL, Floras JS. Dissociation between microneurographic and heart rate variability estimates of sympathetic tone in normal subjects and patients with heart failure. *Clin Sci (Lond)* 1999;**96**:557–565.
29. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. *Ann Noninvasive Electrocardiol* 2008;**13**:191–207.
30. Kornet L, Hoeks AP, Janssen BJ, Houben AJ, De Leeuw PW, Reneman RS. Neural activity of the cardiac baroreflex decreases with age in normotensive and hypertensive subjects. *J Hypertens* 2005;**23**:815–823.
31. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. *Eur Heart J* 2008;**29**:1147–1159.
32. Noordzij W, Slart RH. PET imaging of the autonomic myocardial function: methods and interpretation. *Clin Transl Imaging* 2015;**3**:365–372.
33. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, Hutson AD, Dekemp RA, Haka MS, Sajjad M, Cimato TR, Curtis AB, Cain ME, Canty JM Jr. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol* 2014;**63**:141–149.
34. Mazzadi AN, Pineau J, Costes N, Le Bars D, Bonnefoi F, Croisille P, Porcher R, Chevalier P. Muscarinic receptor upregulation in patients with myocardial infarction: a new paradigm. *Circ Cardiovasc Imaging* 2009;**2**:365–372.
35. Wang JQ, Miller MA, Fei X, Stone KL, Lopshire JC, Groh WJ, Zipes DP, Hutchins GD, Zheng QH. Facile synthesis and initial PET imaging of novel potential heart acetylcholinesterase imaging agents [^{11}C]pyridostigmine and its analogs. *Nucl Med Biol* 2004;**31**:957–964.
36. Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988;**11**:3–20.
37. Feng QP, Hedner T, Andersson B, Lundberg JM, Waagstein F. Cardiac neuropeptide Y and noradrenaline balance in patients with congestive heart failure. *Br Heart J* 1994;**71**:261–267.
38. Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. *Cardiovasc Res* 2001;**49**:27–37.
39. Robinson EA, Rhee KS, Doytchinova A, Kumar M, Shelton R, Jiang Z, Kamp NJ, Adams D, Wagner D, Shen C, Chen LS, Everett TH, Fishbein MC, Lin SF, Chen PS. Estimating sympathetic tone by recording subcutaneous nerve activity in ambulatory dogs. *J Cardiovasc Electrophysiol* 2015;**26**:70–78.
40. Vaseghi M, Lux RL, Mahajan A, Shivkumar K. Sympathetic stimulation increases dispersion of repolarization in humans with myocardial infarction. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1838–H1846.
41. Rizas KD, Nieminen T, Barthel P, Zurn CS, Kahonen M, Viik J, Lehtimaki T, Nikus K, Eick C, Greiner TO, Wendel HP, Seizer P, Schreieck J, Gawaz M, Schmidt G, Bauer A. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. *J Clin Investig* 2014;**124**:1770–1780.
42. Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation* 2008;**118**:863–871.

43. Huang W, Shivkumar K, Vaseghi M. Device-based autonomic modulation in arrhythmia patients: the role of vagal nerve stimulation. *Curr Treat Options Cardiovasc Med* 2015;**17**:379.
44. Kinugawa T, Dibner-Dunlap ME. Altered vagal and sympathetic control of heart rate in left ventricular dysfunction and heart failure. *Am J Physiol* 1995;**268**:R310–R316.
45. Sabbah HN, Ilsar I, Zaretsky A, Rastogi S, Wang M, Gupta RC. Vagus nerve stimulation in experimental heart failure. *Heart Fail Rev* 2011;**16**:171–178.
46. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. *Circ Res* 1973;**32**:215–220.
47. Hamann JJ, Ruble SB, Stolen C, Wang M, Gupta RC, Rastogi S, Sabbah HN. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. *Eur J Heart Fail* 2013;**15**:1319–1326.
48. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, Van Wagoner DR, Mazgalev TN. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail* 2009;**2**:692–699.
49. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;**59**:256–262.
50. Mortara A, La Rovere MT, Pinna GD, Prpa A, Maestri R, Febo O, Pozzoli M, Opasich C, Tavazzi L. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation* 1997;**96**:3450–3458.
51. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr, Schomig A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;**353**:1390–1396.
52. Adamson PB, Smith AL, Abraham WT, Kleckner KJ, Stadler RW, Shih A, Rhodes MM. Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device. *Circulation* 2004;**110**:2389–2394.
53. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J* 2011;**32**:847–855.
54. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J* 2015;**36**:425–433.
55. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 2014;**20**:808–816.
56. Libbus I, Nearing BD, Amurthur B, KenKnight BH, Verrier RL. Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the ANTHEM-HF study. *Heart Rhythm* 2016;**13**:721–728.
57. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF Trial. *J Am Coll Cardiol* 2016;**68**:149–158.
58. Bibevski S, Dunlap ME. Ganglionic mechanisms contribute to diminished vagal control in heart failure. *Circulation* 1999;**99**:2958–2963.
59. Bohm M, Ewen S, Kindermann I, Linz D, Ukena C, Mahfoud F. Renal denervation and heart failure. *Eur J Heart Fail* 2014;**16**:608–613.
60. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014;**64**:635–643.
61. Tzafriri AR, Mahfoud F, Keating JH, Markham PM, Spognardi A, Wong G, Fuimaono K, Bohm M, Edelman ER. Innervation patterns may limit response to endovascular renal denervation. *J Am Coll Cardiol* 2014;**64**:1079–1087.
62. Patel H, Dhillon P, Mahfoud F, Lindsay A, Hayward C, Ernst S, Lyon A, Rosen S, di Mario C. The biophysics of renal sympathetic denervation using radiofrequency energy. *Clin Res Cardiol* 2014;**103**:337–344.
63. DiBona GF, Sawin LL. Role of renal nerves in sodium retention of cirrhosis and congestive heart failure. *Am J Physiol* 1991;**260**:R298–R305.
64. Pettersson A, Hedner J, Hedner T. Renal interaction between sympathetic activity and ANP in rats with chronic ischaemic heart failure. *Acta Physiol Scand* 1989;**135**:487–492.
65. Hu J, Li Y, Cheng W, Yang Z, Wang F, Lv P, Niu C, Hou Y, Yan Y, Ge J. A comparison of the efficacy of surgical renal denervation and pharmacologic therapies in post-myocardial infarction heart failure. *PLoS One* 2014;**9**:e96996.
66. Dai Z, Yu S, Zhao Q, Meng Y, He H, Tang Y, Wang X, Xiao J, Huang C. Renal sympathetic denervation suppresses ventricular substrate remodelling in a canine high-rate pacing model. *EuroIntervention* 2014;**10**:392–399.
67. Zhao Q, Yu S, Huang H, Tang Y, Xiao J, Dai Z, Wang X, Huang C. Effects of renal sympathetic denervation on the development of atrial fibrillation substrates in dogs with pacing-induced heart failure. *Int J Cardiol* 2013;**168**:1672–1673.
68. Patel HC, Hayward C, Vassiliou V, Patel K, Howard JP, Di Mario C. Renal denervation for the management of resistant hypertension. *Integr Blood Press Control* 2015;**8**:57–69.
69. Symplicity HTN-2 Investigators; Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–1909.
70. Mahfoud F, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, Fries P, Dreysse S, Wellnhofer E, Schneider G, Buecker A, Schneeweis C, Doltra A, Schlaich MP, Esler MD, Fleck E, Bohm M, Kelle S. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. *Eur Heart J* 2014;**35**:2224–2231.
71. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013;**61**:457–464.
72. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–1401.
73. Patel HC, Hayward C, Ozdemir BA, Rosen SD, Krum H, Lyon AR, Francis DP, di Mario C. Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials: implications for trials of renal denervation. *Hypertension* 2015;**65**:401–406.
74. Luscher TF, Mahfoud F. Renal nerve ablation after SYMPLICITY HTN-3: confused at the higher level? *Eur Heart J* 2014;**35**:1706–1711.
75. Floras JS. Renal denervation for drug-resistant hypertension: suffering its original sin, seeking redemption. *Can J Cardiol* 2014;**30**:476–478.
76. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Bohm M, Melder RJ. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. *J Am Coll Cardiol* 2015;**66**:1766–1775.
77. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol* 2013;**162**:189–192.
78. Patel HC, Rosen SD, Hayward C, Vassiliou V, Smith GC, Wage RR, Bailey J, Rajani R, Lindsay AC, Pennell DJ, Underwood SR, Prasad SK, Mohiaddin R, Gibbs JS, Lyon AR, Di Mario C. Renal denervation in heart failure with preserved ejection fraction (RDT-PEF): a randomized controlled trial. *Eur J Heart Fail* 2016;**18**:703–712.
79. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Bohm 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.
80. Zucker IH, Hackley JF, Cornish KG, Hiser BA, Anderson NR, Kieval R, Irwin ED, Serdar DJ, Peuler JD, Rossing MA. Chronic baroreceptor activation enhances survival in dogs with pacing-induced heart failure. *Hypertension* 2007;**50**:904–910.
81. Sabbah HN, Gupta RC, Imai M, Irwin ED, Rastogi S, Rossing MA, Kieval RS. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in dogs with advanced heart failure. *Circ Heart Fail* 2011;**4**:65–70.
82. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, Peters T, Sweep FC, Haller H, Pichlmaier AM, Luft FC, Jordan J. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010;**55**:619–626.
83. Scheffers IJ, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG, Luft FC, Haller H, Menne J, Engeli S, Ceral J, Eckert S, Erglis A, Narkiewicz K, Philipp T, de Leeuw PW. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol* 2010;**56**:1254–1258.
84. Bisognano JD, Kaufman CL, Bach DS, Lovett EG, de Leeuw P. Improved cardiac structure and function with chronic treatment using an implantable device in

resistant hypertension: results from European and United States trials of the Rheos system. *J Am Coll Cardiol* 2011;**57**:1787–1788.
85. Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, de Leeuw PW, Sica DA. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. *J Am Coll Cardiol* 2011;**58**:765–773.
86. Bakris GL, Nadim MK, Haller H, Lovett EG, Schafer JE, Bisognano JD. Baroreflex activation therapy provides durable benefit in patients with resistant hypertension: results of long-term follow-up in the Rheos Pivotal Trial. *J Am Soc Hypertens* 2012;**6**:152–158.
87. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, Lovett EG, Mancia G, Grassi G. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *Eur J Heart Fail* 2014;**16**:977–983.
88. Gronda E, Seravalle G, Trevano FQ, Costantino G, Casini A, Alsheraei A, Lovett EG, Vanoli E, Mancia G, Grassi G. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. *J Hypertens* 2015;**33**:1704–1708.
89. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Muller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015;**3**:487–496.
90. Zile MR, Abraham WT, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Muller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy. *Eur J Heart Fail* 2015;**17**:1066–1074.
91. Prabhakar NR, Peng YJ. Peripheral chemoreceptors in health and disease. *J Appl Physiol (1985)* 2004;**96**:359–366.
92. Ding Y, Li YL, Schultz HD. Role of blood flow in carotid body chemoreflex function in heart failure. *J Physiol* 2011;**589**:245–258.
93. Funaya H, Kitakaze M, Node K, Minamino T, Komamura K, Hori M. Plasma adenosine levels increase in patients with chronic heart failure. *Circulation* 1997;**95**:1363–1365.
94. Ponikowski P, Chua TP, Anker SD, Francis DP, Doehner W, Banasiak W, Poole-Wilson PA, Piepoli MF, Coats AJS. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation* 2001;**104**:544–549.
95. Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Leuenberger UA. Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. *Chest* 2007;**131**:1406–1413.
96. Seals DR, Johnson DG, Fregosi RF. Hyperoxia lowers sympathetic activity at rest but not during exercise in humans. *Am J Physiol* 1991;**260**:R873–R878.
97. Olson LG, Hensley MJ, Saunders NA. Ventilatory responsiveness to hypercapnic hypoxia during dopamine infusion in humans. *Am Rev Respir Dis* 1982;**126**:783–787.
98. Del Rio R, Marcus NJ, Schultz HD. Carotid chemoreceptor ablation improves survival in heart failure: rescuing autonomic control of cardiorespiratory function. *J Am Coll Cardiol* 2013;**62**:2422–2430.
99. Piccirillo G, Ogawa M, Song J, Chong VJ, Joung B, Han S, Magri D, Chen LS, Lin SF, Chen PS. Power spectral analysis of heart rate variability and autonomic nervous system activity measured directly in healthy dogs and dogs with tachycardia-induced heart failure. *Heart Rhythm* 2009;**6**:546–552.
100. Marcus NJ, Del Rio R, Schultz EP, Xia XH, Schultz HD. Carotid body denervation improves autonomic and cardiac function and attenuates disordered breathing in congestive heart failure. *J Physiol* 2014;**592**:391–408.
101. Chua TP, Ponikowski PP, Harrington D, Chambers J, Coats AJ. Contribution of peripheral chemoreceptors to ventilation and the effects of their suppression on exercise tolerance in chronic heart failure. *Heart* 1996;**76**:483–489.
102. Chua TP, Ponikowski P, Webb-Peploe K, Harrington D, Anker SD, Piepoli M, Coats AJ. Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex. *Eur Heart J* 1997;**18**:480–486.
103. Despas F, Lambert E, Vaccaro A, Labrunee M, Franchitto N, Lebrin M, Galinier M, Senard JM, Lambert G, Esler M, Pathak A. Peripheral chemoreflex activation contributes to sympathetic baroreflex impairment in chronic heart failure. *J Hypertens* 2012;**30**:753–760.
104. Moore DP, Weston AR, Hughes JM, Oakley CM, Cleland JG. Effects of increased inspired oxygen concentrations on exercise performance in chronic heart failure. *Lancet* 1992;**339**:850–853.
105. Vermeire P, de Backer W, van Maele R, Bal J, van Kerckhoven W. Carotid body resection in patients with severe chronic airflow limitation. *Bull Eur Physiopathol Respir* 1987;**23** (Suppl 11):165–166.
106. Niewinski P, Janczak D, Rucinski A, Jazwiec P, Sobotka PA, Engelman ZJ, Fudim M, Tubek S, Jankowska EA, Banasiak W, Hart EC, Paton JF, Ponikowski P. Carotid body removal for treatment of chronic systolic heart failure. *Int J Cardiol* 2013;**168**:2506–2509.
107. Niewinski P, Janczak D, Rucinski A, Tubek S, Engelman ZJ, Piesiak P, Jazwiec P, Banasiak W, Fudim M, Sobotka PA, Javaheri S, Hart EC, Paton JF, 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.
108. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009;**373**:82–93.
109. Yumino D, Kasai T, Kimmerly D, Amirthalingam V, Floras JS, Bradley TD. Differing effects of obstructive and central sleep apneas on stroke volume in patients with heart failure. *Am J Respir Crit Care Med* 2013;**187**:433–438.
110. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. *J Card Fail* 2009;**15**:279–285.
111. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Relationship between sleep apnoea and mortality in patients with ischaemic heart failure. *Heart* 2009;**95**:819–824.
112. Prabhakar NR. Carotid body chemoreflex: a driver of autonomic abnormalities in sleep apnoea. *Exp Physiol* 2016;**101**:975–985.
113. Usui K, Bradley TD, Spaak J, Ryan CM, Kubo T, Kaneko Y, Floras JS. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol* 2005;**45**:2008–2011.
114. Ruttanaumpawan P, Gilman MP, Usui K, Floras JS, Bradley TD. Sustained effect of continuous positive airway pressure on baroreflex sensitivity in congestive heart failure patients with obstructive sleep apnea. *J Hypertens* 2008;**26**:1163–1168.
115. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003;**348**:1233–1241.
116. Gilman MP, Floras JS, Usui K, Kaneko Y, Leung RS, Bradley TD. Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea. *Clin Sci (Lond)* 2008;**114**:243–249.
117. Hall AB, Ziadi MC, Leech JA, Chen SY, Burwash IG, Renaud J, deKemp RA, Haddad H, Mielniczuk LM, Yoshinaga K, Guo A, Chen L, Walter O, Garrard L, DaSilva JN, Floras JS, Beanlands RS. Effects of short-term continuous positive airway pressure on myocardial sympathetic nerve function and energetics in patients with heart failure and obstructive sleep apnea: a randomized study. *Circulation* 2014;**130**:892–901.
118. Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, Fleetham J, John Kimoff R, Leung RS, Lorenzi Filho G, Mayer P, Mielniczuk L, Morrison DL, Ryan CM, Series F, Tomlinson GA, Woo A, Arzt M, Parthasarathy S, Redolfi S, Kasai T, Parati G, Delgado DH, Bradley TD. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J Heart Fail* 2017;**19**:579–587.
119. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;**373**:1095–1105.
120. Eulenburg C, Wegscheider K, Woehrle H, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H, Cowie MR. Mechanisms underlying increased mortality risk in patients with heart failure and reduced ejection fraction randomly assigned to adaptive servoventilation in the SERVE-HF study: results of a secondary multistate modelling analysis. *Lancet Respir Med* 2016;**4**:873–881.
121. Jagielski D, Ponikowski P, Augostini R, Kolodziej A, Khayat R, Abraham WT. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnoea: 12 months' experience with the remede(R) System. *Eur J Heart Fail* 2016;**18**:1386–1393.
122. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, Abraham WT. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet* 2016;**388**:974–982.
123. Lara A, Damasceno DD, Pires R, Gros R, Gomes ER, Gavioli M, Lima RF, Guimarães D, Lima P, Bueno CR, Vasconcelos A, Roman-Campos D, Menezes CAS, Sirvente RA, Salemi VM, Mady C, Caron MG, Ferreira AJ, Brum PC, Resende RR, Cruz JS, Gomez MV, Prado VF, de Almeida AP, Prado MAM, Guatimosim S. Dysautonomia due to reduced cholinergic neurotransmission causes cardiac remodeling and heart failure. *Mol Cell Biol* 2010;**30**:1746–1756.
124. Azevedo ER, Parker JD. Parasympathetic control of cardiac sympathetic activity: normal ventricular function versus congestive heart failure. *Circulation* 1999;**100**:274–279.

125. Newton GE, Parker AB, Landzberg JS, Colucci WS, Parker JD. Muscarinic receptor modulation of basal and beta-adrenergic stimulated function of the failing human left ventricle. *J Clin Investig* 1996;**98**: 2756–2763.
126. Sato K, Urbano R, Yu C, Yamasaki F, Sato T, Jordan J, Robertson D, Diedrich A. The effect of donepezil treatment on cardiovascular mortality. *Clin Pharmacol Ther* 2010;**88**:335–338.
127. Kubo T, Sato T, Noguchi T, Kitaoka H, Yamasaki F, Kamimura N, Shimodera S, Iiyama T, Kumagai N, Kakinuma Y, Diedrich A, Jordan J, Robertson D, Doi YL. Influences of donepezil on cardiovascular system – possible therapeutic benefits for heart failure-DOnepezil Cardiac TEst Registry (DOCTER) Study. *J Cardiovasc Pharmacol* 2012;**60**:310–314.
128. Nordström P, Religa D, Wimo A, Winblad B, Eriksdotter M. The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease. *Eur Heart J* 2013;**34**:2585–2591.
129. Okazaki Y, Zheng C, Li M, Sugimachi M. Effect of the cholinesterase inhibitor donepezil on cardiac remodeling and autonomic balance in rats with heart failure. *J Physiol Sci* 2010;**60**:67–74.
130. Li M, Zheng C, Kawada T, Inagaki M, Uemura K, Sugimachi M. Adding the acetylcholinesterase inhibitor, donepezil, to losartan treatment markedly improves long-term survival in rats with chronic heart failure. *Eur J Heart Fail* 2014;**16**:1056–1065.
131. Nobrega AC, dos Reis AF, Moraes RS, Bastos BG, Ferlin EL, Ribeiro JP. Enhancement of heart rate variability by cholinergic stimulation with pyridostigmine in healthy subjects. *Clin Autonom Res* 2001;**11**:11–17.
132. Behling A, Moraes RS, Rohde LE, Ferlin EL, Nóbrega ACL, Ribeiro JP. Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmia and enhances heart rate variability in heart failure. *Am Heart J* 2003;**146**: 494–500.
133. Floras JS. Inhibitory effect of atrial natriuretic factor on sympathetic ganglionic neurotransmission in humans. *Am J Physiol* 1995;**269**:R406–R412.
134. Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. *J Exp Med* 2012;**209**:1057–1068.
135. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397–403.
136. Jagielska J, Salguero G, Schieffer B, Bavendiek U. Digitoxin elicits anti-inflammatory and vasoprotective properties in endothelial cells: therapeutic implications for the treatment of atherosclerosis? *Atherosclerosis* 2009; **206**:390–396.
137. Newton GE, Tong JH, Schofield AM, Baines AD, Floras JS, Parker JD. Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol* 1996;**28**:155–161.
138. Notarius CF, Morris B, Floras JS. Caffeine prolongs exercise duration in heart failure. *J Card Fail* 2006;**12**:220–226.
139. Haack KK, Zucker IH. Central mechanisms for exercise training-induced reduction in sympatho-excitation in chronic heart failure. *Auton Neurosci* 2015;**188**:44–50.
140. Corra U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, Lambrinou E, Pieske B, Piotrowicz E, Schmid JP, Seferovic PM, Anker SD, Filippatos G, Ponikowski PP. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the committee on exercise physiology and training of the heart failure association of the ESC. *Eur J Heart Fail* 2014;**16**:929–941.
141. Groehs RV, Toschi-Dias E, Antunes-Correa LM, Trevizan PF, Rondon MU, Oliveira P, Alves MJ, Almeida DR, Middlekauff HR, Negrao CE. Exercise training prevents the deterioration in the arterial baroreflex control of sympathetic nerve activity in chronic heart failure patients. *Am J Physiol Heart Circ Physiol* 2015;**308**:H1096–H1102.
142. Zannad F, Stough WG, Mahfoud F, Bakris GL, Kjeldsen SE, Kieval RS, Haller H, Yared N, De Ferrari GM, Pina IL, Stein K, Azizi M. Design considerations for clinical trials of autonomic modulation therapies targeting hypertension and heart failure. *Hypertension* 2015;**65**:5–15.
143. Smith S, Rossignol P, Willis S, Zannad F, Mentz R, Pocock S, Bisognano J, Nadim Y, Geller N, Ruble S, Linde C. Neural modulation for hypertension and heart failure. *Int J Cardiol* 2016;**214**:320–330.
144. Cohn JN, Pfeffer MA, Rouleau J, Sharpe N, Swedberg K, Straub M, Wiltse C, Wright TJ. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003;**5**:659–667.
145. Hai OY, Mentz RJ, Zannad F, Gasparini M, De Ferrari GM, Daubert J-C, Holzmeister J, Lam CSP, Pochet T, Vincent A, Linde C. Cardiac resynchronization therapy in heart failure patients with less severe left ventricular dysfunction. *Eur J Heart Fail* 2015;**17**:135–143.