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

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Abstract:

Despite improvements in medical and device treatment, heart failure continues to pose an enormous burden on patients and healthcare 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 specifically to target the sympathetic and parasympathetic branches of the ANS. The Heart Failure Association of the European Society of Cardiology recently organised an expert workshop, bringing together clinicians, trialists and basic scientists to discuss the ANS as a therapeutic target in heart failure. The questions addressed were: (a) what are the abnormalities of ANS in heart failure patients? (b) which methods are available to measure autonomic dysfunction? (c) which therapeutic interventions are available to target the ANS in patients with heart failure, and what are their specific strengths and weaknesses? (d) what have we learned from previous ANS trials? and (e) how should we proceed in the future?

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 short-term compensatory responses to the haemodynamic alterations that result from abnormal cardiac function. However, chronically 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 mortality risk.[2-6] Treatments which improve prognosis (reduction in mortality and/or hospitalisation) in HF, concomitantly attenuate the effects of SNS activation and/or improve PNS modulation. These treatments include angiotensin converting enzyme inhibitors,[7, 8] angiotensin receptor blockers,[9-11] beta-blockers,[12, 13] spironolactone,[14] digoxin,[15] ivabradine[16] and cardiac resynchronisation therapy (CRT).[17]

However, mortality and morbidity in patients with HF remains unacceptably high despite many evidence-based treatments being available.[18, 19] The ANS remains an important target worthy of further research because: 1) current drug therapies do not adequately reverse the autonomic imbalances seen in HF; 2) drug interactions and intolerances limit initiation/uptitration of current evidence-based treatments shown to affect ANS balance; and 3) chronically, patients may be non-compliant to pharmacological treatments introducing a role for therapies that do not rely on patient compliance.

Several therapies are being developed and tested to attenuate cardiac dysfunction via modulation of components of the autonomic cardiovascular reflexes by: 1) enhancing vagal nerve activity by direct electrical stimulation; (2) attenuating renal afferent sympathetic outflow via renal nerve ablation; 3) attenuating the chemoreceptor reflex by carotid body resection; 4) enhancing baroreceptor activity via direct electrical stimulation. In addition to these surgical and electrical device interventions; 5) diminishing the chemoreceptor reflex with adaptive servo-ventilation (ASV) in patients with sleep apnoea; and 6) drugs are being tested that stimulate parasympathetic activity, primarily by blocking the enzymatic breakdown of its neurotransmitter acetylcholine (ACh). The role of these new treatments is

yet to be established with early trial results being 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 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 and are summarised in Figure 1.[1]

The consequences of the disequilibrium of the SNS and PNS in human HF are myocyte dysfunction,[20] neurohumoral activation,[21] increased susceptibility to arrhythmia,[22] inflammation[23] and abnormal nitric oxide synthase (NOS) signalling,[24] all leading to worse clinical outcome and reduced survival.[2]

Techniques to measure autonomic dysfunction in heart failure patients

Objectively assessing the ANS would be invaluable not only to identify subpopulations of patients with a diagnosis of HF that have significant autonomic maladaptation but also to monitor the effects of any treatments directed at the ANS. However, there remain no gold-standard reliable, clinically available methods to measure the ANS.[25] There are several different techniques, each providing a unique insight into different limbs of SNS and PNS, with differing strengths and limitations.[1, 25] These techniques can be dichotomised into non-invasive and invasive measurements.

Non-invasive

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.[26] In the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT) the lowest risk was observed in patients with heart rates lower than 60 beats per minute (bpm).[27] International guidelines advocate starting treatment in symptomatic HF patients who are in sinus rhythm and have a rate >70 bpm to achieve a resting heart rate of <60 bpm.[18]

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 to those with HF.[28] However, so far it has not been tested whether these haemodynamic changes are of prognostic importance.

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.[29, 30] Though a reduced HRV has been shown to be associated with shortened survival in HF, this parameter only reflects modulation of neuronal outflow rather than a direct quantification of SNS activity (as provided by the spillover technique and microneurography).[31] 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.[30] 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. For those patients that remain in sinus rhythm, the heart rate variability is reduced. Finally, the optimal technique for calculating HRV remains unclear. Time domain, frequency domain, and non-linear analysis on heart rate data collected from short (ten minutes) or longer time (24 hour) time intervals are being applied. These issues raise the question how HRV may be effectively employed in patients with HF clinically and for research purposes?[30, 31]

Heart rate varies as a reflex response blood pressure fluctuations due to the effects of baroreceptor function. The sensitivity of the baroreceptor can be tested through interventions that can acutely affect blood pressure such as 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).[32] It is important to note that a pressure rise rapidly and primarily activates the parasympathetic limb, while 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 R-R

interval to the antecedent systolic blood pressure.[32] A technique to assess the baroreflex that accounts for the influence of increased arterial wall stiffness with age has also been established.[33]

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are two modalities available to image cardiac sympathetic nerves. SPECT is the more widely available and utilises meta-iodo-benzylguanidine (^{123}I-MIBG), a radiolabeled 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.[34, 35]

PET achieves a higher temporal and spatial resolution than SPECT with the added benefit of allowing absolute quantification of pre- and post-synaptic sympathetic innervation.[36] 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.[37] However, dedicated PET facilities are not widely available, and many of the PET radiotracers (e.g. ^{11}C-epinephrine and ^{11}C-phenylephrine) have a short half-life, requiring an on-site cyclotron to generate them, which can be prohibitively expensive. Longer-living PET tracers to detect sympathetic innervation are underway, including beta-receptor imaging. Though several radiotracers (^{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.[38, 39 40-42]

Invasive

Norepinephrine (NE) 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.[43] Nonetheless, a higher plasma norepinephrine level, which is suggestive of both heighted sympathetic nerve activity as well as diminished plasma clearance due to 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, as it requires an infusion of radiolabelled norepinephrine and the use of a catheterisation 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).[43] Acetylcholine is the main neurotransmitter of the PNS, but in contrast to 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.[44] At the cardiac level, vasoactive intestinal peptide (VIP) is released with vagal nerve firing and is associated with coronary artery vasodilatation and increased flow.[45]

A direct method of quantifying peripheral sympathetic nerve firing has been established in man 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.[25] Efferent SNS discharges (from multiple or single unit) to these muscles can be quantified as bursts/min or bursts/100 heart beats. This is an operator-dependent and time consuming technique and there are only a few centres around the world capable of performing this investigation. When performed correctly with acceptable reproducibility, MSNA recordings have provided invaluable mechanistic data. Skin sympathetic nerve activity can also be recorded, but the hemodynamic perturbations of HF have little influence on its discharge and there are so far no data associating the activity of these efferent nerves to subsequent mortality.[46] 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 repolarisation dynamics. This provides more granular and spatial data beyond a simple heart rate and heart rate variability. Data from this technique have highlighted the regional heterogeneity in

myocardial sympathetic innervation, which is a critical component of re-entrant arrhythmia.[47, 48]

Therapeutic interventions targeting the ANS

There are now devices available that target several of the autonomic reflexes in particular at the following sites: cervical vagus nerve, the renal sympathetic nerves, the carotid body and baroreceptor. In addition, we will discuss adaptive servo-ventilation as well as pharmacological approaches to influence parasympathetic tone.

Vagus Nerve Stimulation

Vagal nerve anatomy and function

The vagus nerve contains both afferent (to the central nervous system) and efferent parasympathetic fibres (from the central nervous system) as well as sympathetic fibres. Post-ganglionic efferent fibres innervate the sino-atrial and atrio-ventricular 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 an increased refractory period in the atria and left ventricle, and at the same time favourably affects nitric oxide (NO) balance and cytokine release.[49, 50]

Preclinical studies

In animal models of pacing-induced HF, impaired vagal control of heart rate occurs at an early stage in the HF process.[51, 52] 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.[53] Vagal nerve stimulation (VNS) in dogs reduced ventricular fibrillation and left ventricular dimensions and improved ejection fraction and survival following ischemia- and pacing-induced HF.[54, 55]

Clinical studies- Heart Failure

In chronic human HF, reductions in heart rate variability[56], baroreflex sensitivity for heart rate[4] and heart rate turbulence[57], provide evidence of attenuated vagally-mediated heart rate modulation. Furthermore, there is evidence of vagal withdrawal prior to acute decompensation in HF.[58]

Implantable vagal nerve stimulators were already available for use in the US for 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 that after extension recruited 32 patients, the CardioFit Multicentre trial.[59] Recruited patients had symptomatic HF with a reduced ejection fraction (HFrEF), sinus rhythm and were without cardiac resynchronisation therapy. The surgical procedure involved implantation of a right ventricle pacing lead and a stimulation lead to the right cervical vagus, which was then attached to a CardioFit system. The right ventricular 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 does achieved was 4.1 ± 1.2mA. There were also some statistically significant improvements in surrogate secondary endpoints at six months though these have to be interpreted with caution in an open label uncontrolled study (decrease in: heart rate, New York Heart Failure Association (NYHA) class, HF symptom score; increase in: six minute walk test distance, ejection fraction).

NECTAR-HF was the first published sham-controlled, blinded, randomised controlled trial of VNS.[60] Patients were randomised 2:1 following implant of the Precision VNS device, either turned 'ON' or 'OFF' in a blinded manner. The protocol required up-titration of stimulation current and follow up for six months. The primary endpoint was left ventricular end-systolic dimension as an assessment of LV remodelling. The trial had a one arm crossover design with those initially randomised to device 'OFF' then crossed over and had stimulation turned 'ON'. Current amplitude of 1.42 ± 0.8 mA was reached after three months. Data from 86 patients at six months follow-up showed that the trial was neutral with respect to left ventricular 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 there was imperfect blinding in this study. Most patients experienced local neck discomfort or coughing when the device was activated. Infection rate

from the device was 7.4% in the first six months, which may be related to operator experience.

ANTHEM-HF studied another VNS device, Demipulse Model 103, which delivers continuous stimulation independent of the R wave and hence a right ventricular lead is not required.[61] This trial enrolled patients with HFrEF (LVEF ≤40%). In comparison to the previous two trials described, this study randomised patients to a VNS on the right or the left vagus. Sixty patients were randomised and the primary endpoint was change in left ventricular ejection fraction and end-systolic volume. Average current amplitude of 2.0±0.6mA was achieved. Mean ejection fraction improved but end-systolic volume did not change at six months. Differences between right or left stimulation were absent, and heart rate was not affected. Consistent with the previous studies the subjective endpoints of symptoms score, six minute walk distance and NYHA class all improved in the context of an unblinded and uncontrolled study. This trial also raised some safety issues as there was an implant-related death caused by a stroke three days after the procedure, possibly related to carotid artery manipulation. Stimulation-related symptoms were common and were managed by appropriate titration of the dose.

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 heart rate turbulence (HRT).[62] 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) suggesting 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.[63] The trial patient population had symptomatic HFrEF with NYHA class III HF, sinus rhythm and an ejection fraction ≤40%. Patients with atrial fibrillation or pacing were not eligible. A protocol amendment during the trial allowed those who failed to respond to cardiac resynchronisation therapy to be recruited. In total 707 patients were randomised 3:2 for implant of CardioFit VNS device or on-going medical therapy with no sham implant procedure. The primary efficacy endpoint was time-to-all-cause mortality or first HF hospitalisation. The INOVATE-HF trial was stopped after a mean follow up period of 16 months due to futility. At six-

months the mean current amplitude was 3.9 ± 1.0mA. The primary endpoint occurred in 30.3% of the active arm and 25.8% of the control arm with no difference in the survival curves between the two groups. In secondary endpoint analyses, those who received VNS had improvements in NYHA class, symptom questionnaire score and six minute walk test 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, possibly related to the significant differences between the men and women in other baseline characteristics. No safety concerns were raised in this trial.

In summary, despite a wealth of pre-clinical data supporting the therapeutic benefit of VNS in HF, this has not been translated to patients. Perhaps the most important hurdle that needs to be overcome before this technology can advance is to identify the ideal VNS stimulation protocol and therapeutic dose. The four described clinical trials each achieved different maximally tolerated stimulation currents, ranging from 1.4 to 4.1 mA. There is further complexity with variations possible in the duty cycle (the proportion of time stimulation is applied), stimulation frequency, synchronisation to the cardiac cycle, which nerves do the stimulation leads preferentially activate (efferent, afferent or both) 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. 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.[64] This data is important to recollect on the background 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, promote sodium and water reabsorption at the tubular level via activation of α-adrenoreceptors, and reduce renal blood flow and glomerular filtration through vasoconstriction, which are all important mechanisms in the pathophysiology of HF.[65]

There are two main types of afferent nerves, both predominately found in the renal pelvis; one is chemosensitive and responds to nociception (adenosine, ischemia, 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 central nervous system centres known to be involved in cardiovascular regulation. Conversely, interrupting the afferent nerves in diseased states reduces central sympathetic outflow particularly to the heart, the 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 its origin at the aorta) and gradually decreases towards the distal renal artery.[66] 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.[66-68]

The proximity of the nerves to the renal artery lumen make them amenable to destruction using transcatheter ablative techniques using radiofrequency or ultrasound energy or alcohol injection.[69]

Preclinical studies

Surgical renal denervation improves natriuresis in HF models.[70] Animals who received surgical renal denervation and then had HF induced had lower left ventricular filling pressures, higher ejection fractions and better renal perfusion.[71] In rats surgical denervation was more efficacious than metoprolol, perindopril or losartan in preventing adverse cardiac structural remodelling following a myocardial infarction.[72]

Few studies have reported the effects of transcatheter renal denervation (RDN) compared to control in HF models. In these studies RDN in dogs attenuated the fall in ejection fraction and systolic function compared to control.[73, 74] The dogs receiving RDN developed less myocardial fibrosis and showed lower plasma norepinephrine, aldosterone, natriuretic peptides and angiotensin II.[73, 74] Animals that underwent RDN prior to developing HF were less likely to have inducible ventricular fibrillation or atrial fibrillation than those who did not undergo RDN.[75, 76]

Clinical studies- Hypertension

The majority of experience with RDN in man is for the treatment resistant hypertension (TRH) using the single electrode Symplicity™ catheter.[77, 78] The initial first-in-man study and randomised open-label controlled trial showed the treatment to have profound effects on blood pressure[78, 79], which in further work was coupled mechanistically to improvements in renal norepinephrine spillover, MSNA and cardiac remodelling.[79-81] However, the subsequent larger randomised controlled trial SYMPLICITY-HTN 3 which included a blinded sham control failed to show any beneficial effect of RDN on blood pressure.[82]

The reasons for this unexpected discrepancy have been debated.[83-86] In retrospect, a number of factors in the SYMPLICITY-HTN 3 trial design may be relevant, including not requiring patient selection based on objective evidence that sympathetic activity was high and contributing to the hypertension. Another important issue is that RDN may have not been successfully achieved, either due to using a defunct single electrode catheter and/or the operator not applying ablation to the correct segment of the renal artery.[68] The single electrode design did not allow the operator effortlessly to create a circumferential lesion. In the SYMPLICITY HTN-3 trial, the largest trial to date in hypertension, only 5.2% of patients received a circumferential ablation. It is hoped that the newer catheter systems, which have unique designs that enable circumferential/helical denervation, will overcome this shortfall. Secondly, the latest human cadaveric data suggests that the renal nerves are closer to the renal artery in the distal vessel and hence this might be the preferred location for denervation.[66] This goes against the initial dogma of performing RDN only in the proximal main renal artery before any bifurcation. Recent data in animals has shown that a greater and less variable reduction in renal SNS outflow is achieved if RDN is performed in the main and branch vessels.[87]

Clinical studies- Heart failure

There have been two papers published examining the role of RDN in human HF (Table 1). The REACH-pilot was the proof of concept study that performed RDN on seven patients with HF and a mean ejection fraction of 43%.[88] As safety was an overarching concern, these patients were kept in hospital for five days after the procedure for close monitoring and then were seen at short intervals for a follow-up of six months. The study concluded that the RDN

was safe in HF patients; in particular there was no significant hypotension or irreversible renal dysfunction.

The RDT-PEF study followed and randomised 25 patients with HF with preserved ejection fraction (HFpEF) to RDN versus usual care.[89] The study was underpowered due to recruitment challenges and the primary composite outcome was neutral. However, there was a signal of improvement at three 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 either mIBG parameters. Several other trials concerning HF, both with preserved and reduced ejection fraction, are currently recruiting. The outcome 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 left ventricular remodelling and electrical remodelling.[90-92]

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. With the current 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 also to the main branches where safely accessible, or to use catheters that target the nerves using different modalities such as ultrasound or chemical ablation by injection of alcohol.. The safety data pertaining to the new catheters and the more comprehensive denervation approach is minimal and hence is required in future studies.[93]

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 systolic blood pressure 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) and via 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 brainstem, 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. This system involves 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 left ventricular function, reduces functional mitral regurgitation and reduces the vulnerability of the myocardium to ventricular tachyarrhythmia.[94-96] Beneficial effects of BAT on myocardial NOS isoform expression (eNOS up, iNOS and nNOS down) also have been reported.[95]

Clinical studies- hypertension:

BAT was first applied to treat patients with medical treatment resistant hypertension (TRH). The initial pilot studies and phase II studies demonstrated that when the device was turned 'ON', blood pressure rapidly decreased along with a reduction in heart rate and low frequency power, an increase in high frequency power, and changes in heart rate turbulence suggestive of modulation of both the SNS and PNS.[97-99] Left ventricular hypertrophy also regressed.[100] The procedure was considered to be safe for patients, although a learning curve to device implant was clearly evident with 8 of the 42 patients recruited into the initial feasibility study experiencing either procedural or device-related serious adverse events.[99]

These smaller studies were followed by a double-blind randomised control trial (Rheos Pivotal Trial), which recruited 265 patients with TRH.[101] All recruited patients underwent a device implant, however the device was turned 'ON' in two-thirds at one month whilst the remainder were kept 'OFF'. The co-primary end-points (two efficacy and three safety) were

not all met. A marked placebo effect was observed with systolic blood pressure dropping at six months by 9±29 mmHg in the 'OFF' arm versus 16±29 mmHg in the 'ON' arm (p=0.08 for difference). Safety was also an issue as 9% of patients developed either temporary or permanent facial nerve injury. After six months of follow-up those patients that were initially randomised to device 'OFF' had it turned 'ON'. One year open-label data now available suggest that BAT therapy has variable effects on blood pressure with some patients showing no response, however, 76% of patients were classified as responders with either systolic blood pressure reductions of >20mmHg or through achievement of target blood pressure.[102] The technology has since undergone modification and the next generation of the device Barostim neo™ is smaller and requires implantation of a single stimulating electrode preferably on the right carotid body. It is expected that this will 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 ejection fraction of 31%.[103] In this open-label study improvements were seen at 3 and 6 months in MSNA, six minute walk test distance, HF symptom score and left ventricular ejection fraction. 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 seen 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.[83,104]

Abraham and colleagues reported on a multi-centre randomised, open-control trial that randomised 146 patients with an ejection fraction ≤ 35%.[105] At six months follow up (data available for 118 patients), patients who received BAT had greater improvements in NYHA class, HF questionnaire score and six minute walk test distance than those randomised to control. These changes were mirrored with a statistical improvement in natriuretic peptide levels and increase in systolic blood pressure in the active arm. Left ventricular EF, however, did not increase significantly relative to control. In contrast to VNS, with BAT up-titration of stimulation strength does not seem to be limited by patient discomfort.

The authors also performed a subgroup analysis focusing on the effects of BAT in patients who also had cardiac resynchronisation therapy (CRT).[106] BAT was safe in patients who had concomitant CRT, however, BAT might be less effective in this group compared to those patients not treated with CRT.

In summary, the role of BAT in the management of HF has yet to be established. The clinical data currently available is restricted to two small studies neither of which were blinded-controlled and hence were susceptible to various biases.[84] Further direction will be provided with the currently recruiting cardiovascular outcome trial, Barostim therapy for Heart Failure (BeAT-HF, ClinicalTrials.gov Identifier: NCT02627196). Mechanistic studies examining the role of BAT in HF with preserved ejection fraction (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 1.5-3mm ovoid structure found at the bifurcation of the carotid artery. Peripheral chemoreceptors are sensitive to hypoxia and to a lesser degree hypercapnia and acidosis.[107] In health when the chemoreceptors are activated, signals are sent to the central nervous system, effecting an increase in minute ventilation (to counteract hypoxia) and 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, the hypothesis being that reduced blood flow to the carotid body sensitises the chemoreceptors, which increases their tonic firing rate as well as responsiveness to hypoxia.[108] Sensitisation, 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.[109].

Clinically chemoreceptor sensitivity can be determined as the change in minute ventilation as a proportion of the amount of induced hypoxia or hypercapnia.[110, 111] When activated by this pathway there is a SNS response with increased MSNA, hypertension and tachycardia.[112, 113] Tonic discharge of the chemoreceptors can also be measured by administering low dose dopamine or hyperoxia, both having an inhibitory effect.[114-116]

Preclinical studies

Various models of HF demonstrated the development of altered chemoreflexes as well as autonomic dysfunction and periodic breathing disorders following the onset of HF.[117-119] However, if the sensory input from the peripheral chemoreceptor is altered through ablation, these maladaptive processes are partially reversed. Bilateral carotid body ablation (CBA) two weeks after induction of myocardial infarction in rats increased survival rate from 45% to 85% and normalised central sympathetic outflow and baroreceptor sensitivity, reduced the incidence of apnoea and ventricular arrhythmias.[117] Bilateral cryogenic ablation of the carotid bodies in rabbits with pacing-induced HF reduced resting renal sympathetic nerve activity, improved respiratory control and left ventricular function, while reducing cardiac arrhythmias.[120] Collectively, these findings certainly support the strategy to target 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, exercise intolerance, cardiac arrhythmia, sympathetic activation and reduced baroreceptor sensitivity.[110, 121-123] Suppression of the chemoreflex with high concentration inspired oxygen in 12 patients with HF improved exercise tolerance and reduced minute ventilation.[124] Adaptive servo-ventilation has also been shown to be useful and this is discussed in a later section.

Surgical carotid body resection was performed largely as a palliative procedure in the 1940-70s as a treatment for chronic lung disease. In some of these patients the perception of shortness of breath was reduced and exercise tolerance improved.[125] The historic follow-up data of >15,000 patients undergoing carotid body resection revealed a very low mortality rate albeit in the presence of likely publication bias. This data and background led to a first-in-man single case study of a unilateral carotid body resection for HF with reduced ejection fraction.[126] The procedure was well tolerated and without complication. The patient experienced an improvement in symptoms, exercise function, heart rate variability and chemoreceptor sensitivity following this procedure.

This was followed by a ten patients (NYHA II-III, EF≤45%, augmented peripheral chemosensitivity >0.6 L/min/SpO2) open-label and uncontrolled study. Four patients received unilateral carotid body removal and six bilateral.[127] During the follow-up period two patients died (it is unclear whether these reflect the natural history of HF in the individual

patients or are related to the procedure) and one patient withdrew. At one month follow-up, MSNA and chemosensitivity was reduced (ventilator response to hypoxia), which was sustained at two months, but without improvement in exercise time, HF symptom score, natriuretic peptide levels or EF. From the safety point of view, 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 servo-adaptive ventilation in one. The authors concluded that nocturnal hypoxia might be less frequently encountered if only unilateral carotid body resection (compared to bilateral) is performed. They suggest carefully considering the risks (invasive, non-reversible procedure) against limited clinical efficacy before launching further clinical studies using this intervention.

In summary, dampening peripheral chemosensitivity with carotid body resection may be an appropriate target in the management of HF, however, supportive data are sparse. Device-based approaches to target the carotid body transvenously are being investigated in ongoing clinical studies.

Treatment of Sleep Apnoea

Obstructive sleep apnoea (OSA) is present in approximately a quarter of all HF patients and when present is associated with a worse prognosis.[128, 129] One of the consequences of OSA, intermittent hypoxia, has been shown to directly affect carotid body function, centrally activating the SNS.[130] This SNS hyperactivity may be attenuated if OSA is abolished by therapies such as continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV) [131, 132] CPAP restores both daytime and night time autonomic balance in HF,[131] improve ejection fraction,[133] improve HRV and[134] enhance norepinephrine reuptake by cardiac sympathetic nerve terminals.[135] ASV therapy is currently being evaluated in a multi-centre cardio-vascular endpoint-driven randomised controlled trial (ADVENT HF, ClinicalTrials.gov Identifier: NCT01128816). At the time of writing, 417 patients with left ventricular EF≤ 45% and predominantly NYHA Class II symptoms, of whom approximately 2/3 have OSA and 1/3 central sleep apnoea (CSA), have been randomly allocated to receive or not receive ASV in addition to optimal medical therapy. Data are reviewed 6-monthly by a data safety monitoring board. At their November 24, 2016 meeting no adverse safety signal was 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 ADVENT-HF

to those that entered SERVE-HF. The latter, which recruited patients with CSA and predominantly Class III symptoms, found ASV to increase the secondary end-point of all-cause and cardiovascular mortality.[136]

Pharmacological restoration of ANS 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 beta-1 and 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 and reinforced in the current 2016 ESC guidelines for chronic HF.[18]

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 AV-node, and the ventricular conducting system.

The importance of the PNS for cardiac physiology is exemplified by the observations that knockout of the M2-AChR and knockdown of the vesicular ACh transporter in mice both are associated with the development of marked cardiac dysfunction.[137] ACh also modulates sympathetic tone by acting as preganglionic neurotransmitter for the SNS and by inhibiting the release of norepinephrine from adrenergic nerve terminals. Indeed, muscarinic stimulation with intracoronary ACh decreases cardiac NE spillover.[138] ACh has an independent negative lusitropic effect and at the same time antagonizes the effects of beta-adrenergic stimulation.[139]

ACh 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 (ChEI). Centrally acting acetylcholine esterase inhibitors, 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 patients treated with donezepil.[140] In a subsequent small study with 49 dementia patients donezepil lowered plasma BNP levels in a subgroup of patients with subclinical HF

(baseline BNP >60 pg/ml).[141] In a large Swedish cohort of Alzheimer patients the application of ChEI significantly lowered the risk for MI and cardiovascular death.[142] In preclinical studies Donepezil attenuated LV dysfunction and neurohumoral activation in rats with HF[143], and the effect was additive when applied in combination with losartan therapy. [144]

Pyridostigmine (PYR), a ChEI that does not cross the blood-brain barrier and thus only acts peripherally, increased HR variability in healthy humans.[145] PYR increased HR variability and reduced ventricular arrhythmias in HF patients.[146]

Collectively, these findings indicate that ChEIs ameliorate the sympatho-vagal balance and improve heamodynamics in HF. An important caveat is that ChEI will also stimulate sympathetic cervical, splanchnic and lumbar ganglionic neurotransmission. Indeed, an increase in MSNA activity was reported after application of edrophonium, a short-acting CheI.[147]

The beneficial effects of ChEI may also be related to the anti-inflammatory effects exerted via the so-called inflammatory reflex. ACh (and nicotine) inhibits the synthesis and secretion of pro-inflammatory cytokines such as IL-6 and TNFα by stimulating the α7 nicotinic acetylcholine receptor (α7-nAChR) on monocytes/macrophages in the spleen (but perhaps in other tissues as well, including the injured heart).[148] 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.[15, 149] In preclinical studies the digoxin analogue- digitoxin inhibited inflammation and had vasoprotective effects.[150] 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, as compared to digoxin the kidney contributes much less to its clearance.[18] At lower doses digitalis might still be of therapeutic value in patients suffering from advanced HF. Acutely, digoxin reduces the heightened cardiac sympathetic activity of patients with severe HFrEF.[151] There is currently an on-going, large prospective randomized trial, the DiGIT-HF trial

(EudraCT no 2013-005326-38) to further investigate the role of digitoxin in patients with HF and a reduced ejection fraction.

An important limitation of drugs (or devices) to stimulate the vagal nerve is that in animal studies it has been demonstrated that the abnormality anatomically lies between the preganglionic neuron and the synapse at the end-organ.[64] This data is important to recollect on the background of the neutral or early stage studies that are ongoing with respect to vagal activation in HF.

Caffeine has also been investigated in HF and shown to prolong exercise duration.[152] This is likely related to its non-selective adenosine antagonistic properties. Adenosine is a potent stimulus to the peripheral chemoreflex and a purine whose circulating concentration is increased in HFrEF.[109]

Conclusions

The detailed understanding of the pathophysiological role of ANS imbalance in preclinical models and clinical studies in HF patients raises normalization of ANS balance as an obvious therapeutic strategy for the treatment of HF. There is a role 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. It remains a challenge to delineate the mechanisms responsible for the beneficial effects seen in preclinical studies. Is it merely a reduction in workload due 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 with a limited number of patients enrolled. Several trials have been disappointing with minimal or no benefit reported. One obvious question is 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, 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 one would like to measure nerve activity directly to identify patients with abnormal nerve firing patterns and document alterations following the intervention. This technique however is invasive and has only been applied for the measurement of SNS activity, not for PNS activity. There is no adrenergic or autonomic biomarker with the pragmatic utility, sensitivity, and specificity in heart failure as seen with natriuretic peptides for diagnosis. A measure that can be used in clinical practice on a routine basis is still lacking and research to develop new, preferentially non-invasive, techniques to measure SNS and PNS activity are required. In this respect the recent developments in SPECT/PET imaging are hopeful.

Important variables that require optimization in case of electrical device stimulation or nerve ablation are the anatomical location of the intervention and the stimulation protocol in case of electrical devices. Vagal stimulation and renal nerve denervation depend on the site of intervention which affects outcome. Should we preferably stimulate the cervical vagal nerve, or a more specific cardiac branch? Treatment effectiveness will depend on the way 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 fibers that will be stimulated, and as current amplitude increases, additional, smaller fiber types will be recruited. Duty time (intermittent, continuous, day/night, or random stimulation) is likely to be another important variable that requires more studies to identify the optimal treatment stimulation dose.

Trial design is another issue.[153, 154] Marked placebo and Hawthorne effects exist. The nature of the surgical and device 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 promising from a conceptual point of view, and despite many preclinical studies in support of the concept, there are several hurdles to be overcome, both with respect to neuromodulation strategy and trial design, before neuromodulation will find its place as a proven clinical treatment. It is also important to note that supervised exercise training is another non-invasive way to improve overall autonomic balance in HF patients.[155,

[156] Finally, it is also important to recognize that some forms of excessive sympatholysis might be harmful, as demonstrated in the MOXCON trial.[157, 158]

Most trials to date have assessed treatment effects in patients suffering from HFrEF and getting optimal medical therapy. As shown for cardiac resynchronisation therapy before [159], 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 patient group in which the presence of ANS imbalance is evident. It will be interesting to learn if neuromodulation will be beneficial for other patient groups including acute HF and HFpEF.

Addressing these challenges with correctly designed preclinical and clinical studies to optimise treatment dose, delivery, patient selection and monitoring direct 'on target' effects on SNS and/or PNS will serve to provide the answers to where the range of ANS therapies will find their individual places in the armamentarium of treatments for patients with heart failure.

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Figure Legends

Figure 1: Mechanisms involved in the autonomic disturbances of 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 (arrow pointing down) is raised further by central chemoreceptor sensitization, by sleep apnoeas, and possibly by obesity. Efferent mechanisms for increased NE spillover include pre-junctional facilitation of its release and impaired NE uptake. The time course through which these mechanisms are engaged differs between 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; NE, norepinephrine. (Reproduced with permission from Floras and Ponikowski[1]).

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