

Review

Chronic Baroreflex Activation: A Potential Therapeutic Approach to Heart Failure With Preserved Ejection Fraction

DIMITRIOS GEORGAKOPOULOS, PhD,¹ WILLIAM C. LITTLE, MD,² WILLIAM T. ABRAHAM, MD,³ FRED A. WEAVER, MD,⁴ AND MICHAEL R. ZILE, MD^{5,6}

Minneapolis, Minnesota; Winston-Salem, North Carolina; Columbus, Ohio; Los Angeles, California; Charleston, South Carolina

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a substantial public health issue, equal in magnitude to heart failure with reduced ejection fraction. Clinical outcomes of HFpEF patients are generally poor, related annual accrual of health care expenses amount to billions of dollars, and no therapy has been shown to be effective in randomized clinical trials. Baroreflex activation therapy (BAT) produced by stimulating the carotid sinuses using an implanted device (Rheos) is being studied for the treatment of hypertension, the primary comorbidity of HFpEF. Other potential benefits include regression of left ventricular hypertrophy, normalization of the sympathovagal balance, inhibition of the renin-angiotensin-aldosterone system, arterio- and venodilation, and preservation of renal function. This paper reviews the evidence suggesting that BAT may be a promising therapy for HFpEF and introduces the HOPE4HF trial (ClinicalTrials.gov Identifier: NCT00957073), a randomized outcomes trial designed to evaluate the clinical safety and efficacy of BAT in the HFpEF population. (*J Cardiac Fail* 2010;■:1–12)

Key Words: Baroreceptors, electrical stimulation, hypertrophy, autonomic nervous system.

Heart Failure With Preserved Ejection Fraction

Heart failure (HF) continues to be a major public health burden that is currently estimated to affect >5 million individuals in the United States and >6.5 million individuals in Europe.^{1,2}

More than one-half of HF patients exhibit left ventricular ejection fraction (EF) >40%–50%, and the term HF with

preserved EF (HFpEF) has been adopted for this condition. Symptoms and clinical outcomes of HFpEF are similar to HF with reduced EF (HFrEF). Both types of HF generally present with neurohormonal activation, deranged sympathovagal balance, increased left ventricular (LV) filling pressure, fluid retention, and exercise intolerance (Table 1). The principal factors which distinguish HFpEF from HFrEF are a higher prevalence of hypertension, female preponderance, older age, and concentric rather than eccentric hypertrophy.^{3,4} Although several therapies (eg, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and cardiac resynchronization therapy) have proven to be beneficial in HFrEF, none has been shown to be effective in randomized clinical trials of patients with HFpEF.

In the absence of specific treatments to improve HFpEF outcomes, current treatment guidelines call for aggressive use of conventional therapies to address the comorbidities of hypertension, elevated heart rate, vascular stiffness, renal dysfunction, diabetes, and increased diastolic filling pressures.⁵ Unfortunately, several trials of medical therapy have failed to show benefit in HFpEF, including the CHARM (Candesartan in Heart Failure) and I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection

From the ¹CVRx, Minneapolis, Minnesota; ²Cardiology Section, Wake Forest University School of Medicine, Winston-Salem, North Carolina; ³Ohio State University College of Medicine, Columbus, Ohio; ⁴Division of Vascular Surgery, University of Southern California Keck School of Medicine, Los Angeles, California; ⁵Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina and ⁶RHJ Department of Veterans Affairs Medical Center, Charleston, South Carolina.

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Reprint requests: Dimitrios Georgakopoulos, PhD, CVRx, Inc., 9201 West Broadway Avenue, Suite 650, Minneapolis, MN 55445. Tel: (763) 432-2335. E-mail: dgeorgakopoulos@cvr.com

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Table 1. Heart Failure With Preserved Ejection Fraction Strategies Targeted by Baroreceptor Activation Therapy

Therapeutic Strategy	Mechanisms by Which BAT Has Its Effect
Hypertension management	Arterial vasodilation, reduced central arterial stiffness
Heart rate control	Restored sympathovagal balance, arrhythmia suppression, left atrial remodeling
Inhibition of sympathetic nervous and renin-angiotensin-aldosterone systems	Renal nerve-mediated inhibition of renin secretion, renal artery vasodilation, reduced renal artery stiffness, reduced plasma norepinephrine
Venous congestion and LV filling pressure	Reduced venous neural tone leading to increased venous capacitance, reduced proximal tubule Na and H ₂ O reabsorption, suppressed nonosmotic release of vasopressin
Myocardial ischemia	Coronary artery vasodilation, LV hypertrophy regression, reduced heart rate and pressure-volume area (PVA)
Exercise intolerance	Reduced muscle sympathetic nerve activity, reduced arterial stiffness
Pulmonary hypertension	Decreased pulmonary vascular resistance, pulmonary artery stiffness
Obstructive sleep apnea	Reduced sympathetic tone, decreased carotid body sensitivity to hypoxia, reduced tension of upper airway smooth muscle ¹¹⁵

Fraction) studies. One potential underlying cause of failed therapies is iatrogenic sympathetic activation. A provocative study of hypertensive patients⁶ demonstrated that a combination of diuretic and angiotensin receptor blocker (ARB) therapy, despite normalizing systolic and diastolic blood pressures, persistently increased sympathetic activity as assessed by muscle sympathetic nerve activity. Similarly, use of dihydropyridine calcium-channel blockers commonly leads to peripheral edema and reflex tachycardia.⁷ A recent study of β -adrenergic blockade in HFpEF reported worse outcomes in women taking β -blockers compared with those who did not.⁸ Although these medications have not been studied in HFpEF clinical trials, they are common first-line treatment for the comorbidities associated with HFpEF.

HF prevalence, and that of HFpEF in particular, has increased as the population has aged.⁹ Aging itself is known to increase sympathetic activity, reduce parasympathetic control of heart rate, and reduce baroreflex sensitivity (BRS). Thus, patients may be naturally predisposed to be refractory to therapies that induce sympathetic activation. This notion is supported by a finding that depressed BRS is an independent predictor of outcome in HF that is not affected by the presence of a β -blocker.¹⁰ Such autonomic dysfunction has been demonstrated in essential and resistant hypertension patients. Therefore, it is likely that many HFpEF patients experience the same pathophysiology. In contrast to sympathomimetic drugs, a subanalysis of the DIG (Digitalis Investigation Group) trial suggests that low-dose digitalis may improve rates of HF hospitalization and mortality in HFpEF and HFrEF.¹¹ The putative benefits of digitalis may be explained by studies that have demonstrated a connection between digitalis and increased traffic in the carotid sinus nerve and related afferents, apparently by increasing sensitivity of arterial and cardio-pulmonary baroreceptors, the key modulators of autonomic tone. Therefore, therapies that reduce sympathetic activity, such as those that modulate the baroreflex, may hold promise for HFpEF.^{12,13}

An active implantable medical device has been developed to electrically elicit the baroreflex through stimulation of carotid baroreceptors. The Rheos System (CVRx, Minneapolis, Minnesota), which provides baroreflex activation therapy (BAT), resembles a pacemaker system and consists

of a pulse generator implanted in the pectoral region of the chest and ≥ 1 carotid sinus leads which are connected to the pulse generator via flexible wires and to the carotid sinus by an electrode with an insulative backer (Fig. 1). The effects of BAT are stimulus dependent and can be titrated to meet the needs of each patient through interactive device programming.

The first clinical application of BAT was for the treatment of resistant hypertension, defined as systolic blood pressure

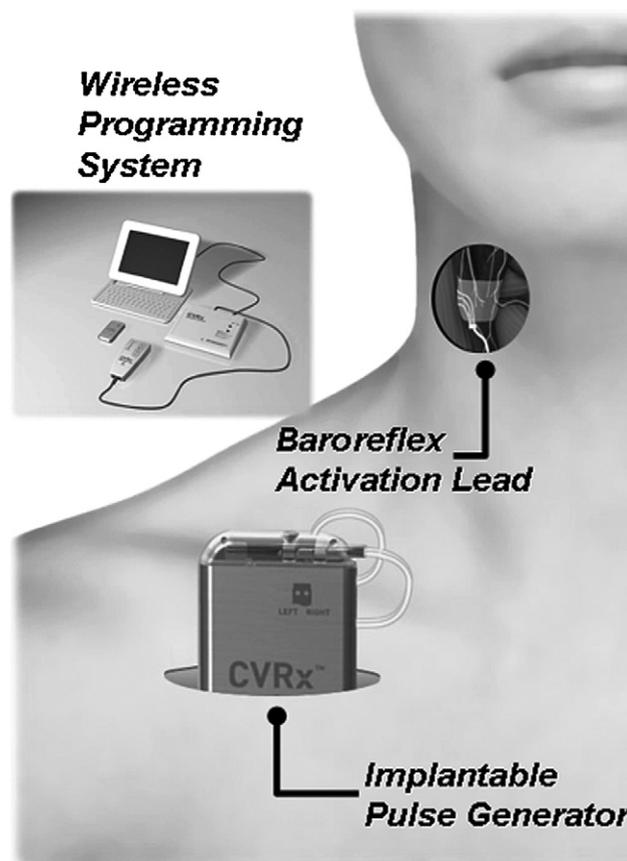


Fig. 1. The Rheos System, which enables chronic baroreflex activation as a therapy, consists of an implanted pulse generator and 2 carotid sinus leads. The pulse generator is implanted in the pectoral region, connected by a lead body to an insulated electrode that is in contact with the carotid sinus. The system is programmed with a wireless laptop computer-based system.

≥ 160 mm Hg despite maximum treatment with antihypertensive medications (≥ 3 drugs, ≥ 1 of which being a diuretic). As detailed in subsequent sections, results from feasibility studies have demonstrated substantial and persistent reductions in arterial pressures and heart rate.¹⁴ Echocardiographic data from a subset of patients exhibit reductions in left ventricular mass and other improvements in cardiac structure and function that occur contemporaneously with therapy.¹⁴ Although the effect of BAT on outcome has yet to be established, the LIFE (Lifestyle Interventions and Independence for Elders) trial has clearly linked regression of left ventricular mass with improvement in outcomes pertinent to HF.¹⁵ Regression of LV hypertrophy is associated with improvement in diastolic function, reduction of filling pressure, and improved balance between myocardial supply and demand. Reduced LV mass and associated reductions in filling pressure can silence high-threshold receptors responsible for sympathetic activation¹⁶ and enable cardiopulmonary stretch receptors to regain functionality, thereby further lowering sympathetic activity and cardiac norepinephrine (NE) spillover.¹⁷

Benefits of BAT therefore appear to extend beyond the lowering of blood pressure to systemic reduction of efferent sympathetic activity. Therefore, it is possible that BAT could succeed at improving outcomes in HFpEF where conventional therapies have failed. Because the sympathoinhibition of BAT is brought about by the baroreflex, it is instructive to inquire if there are other physiologic effects of this reflex relevant to HFpEF. The remainder of this review focuses on the physiology of baroreceptors and the potential therapeutic effects of chronically activating the baroreflex in HFpEF.

Baroreceptor Anatomy and Signaling

The baroreflex has been the subject of intense study for more than a century.^{18,19} Despite the volume of knowledge about the baroreflex, misconceptions remain. The baroreflex is typically associated only with blood pressure regulation. In addition, the baroreflex provides beat-to-beat regulation of circulatory homeostasis.²⁰

The baroreflex feedback signal originates predominantly in the carotid sinus and aortic arch. Baroreceptors are believed to be most concentrated at the medial-adventitial border of the arterial wall and are stimulated by arterial distention rather than directly by arterial pressure.²¹ They are exquisitely sensitive, having been documented to detect changes in distention corresponding to a 1 mm Hg pressure difference.²¹ Afferent fibers associated with baroreceptors innervate the nucleus of the solitary tract (NTS) in the medulla. Although reflexes arise from both carotid and aortic afferents, these converge at the same location in the NTS and drive the same pool of sympathetic motor neurons. Although previous studies have suggested different functions subserved by carotid and aortic baroreceptors,²² nerve traffic from the carotid afferents are capable of modulating sympathetic nerve activity on their own and of having a dominant effect in interactions with other cardiovascular

reflexes.^{20,23} Therefore, the present review focuses primarily on the carotid baroreceptors.

The baroreflex functions as a negative feedback loop. Stimulation of baroreceptors (equivalent to a rise in blood pressure) by distention or electric current propagates via the carotid sinus (Hering) nerve through the glossopharyngeal nerve (cranial nerve IX) to the ipsilateral NTS. Through a series of interneurons, an excitatory signal is transmitted to the caudal ventrolateral medulla which, in turn, inhibits activity in the rostral ventrolateral medulla (RVLM), the principal site of sympathetic outflow in the brainstem. The RVLM sends projections down the spinal column to the intermediolateral cell group which, by way of the paravertebral column, carries sympathetic efferent traffic to all major organs and tissues. Thus, inhibition at the RVLM results in reduced sympathetic activity to the heart, blood vessels, adrenal glands, kidneys, lungs, and other organs.²²

In addition to regulating sympathetic outflow, baroreceptor-related traffic ascends the carotid sinus nerve to the nucleus ambiguus and vagal motor nucleus to modulate parasympathetic efferent traffic to the heart and other organs through the vagus nerves.²⁴ Through the simultaneous activation of vagal and sympathetic outflows, the baroreflex is the primary cardiovascular reflex involved in the regulation of short-term and possibly long-term blood pressure in humans.^{24,25} Projections also exist from the NTS to the supraoptic and paraventricular nuclei in the hypothalamus, the nuclei responsible for vasopressin synthesis. Through this pathway, the baroreflex inhibits the nonosmotic release of vasopressin.²⁶ Vasopressin has been shown to play an important role in HFpEF, contributing to increased peripheral resistance and hyponatremia.²⁷

Baroreflex responses can also be modulated by afferent input to the NTS from skeletal muscle, kidney, cardiopulmonary, and chemoreceptors (Fig. 2). Sympathetic outflow is ultimately determined by integration of all afferent traffic. However, input from the carotid sinus baroreceptors is a dominant influence, and only when input from carotid sinus receptors is diminished do other receptors begin to dominate regulation of sympathetic outflow.²⁸

Recently, the protein ASIC2 has been implicated as the molecular mediator of baroreceptor stretch transduction.²⁹ Transgenic null mice lacking the ASIC2 ion channel display diminished parasympathetic heart rate modulation, enhanced sympathetic control of heart and vascular resistance, reduction in baroreflex gain, and elevated blood pressure. It is unknown if baroreceptor dysfunction is responsible for neurohormonal activation in HF,³⁰ but the pathology observed from ASIC2 null mice raises the possibility that baroreceptor dysfunction may participate in the natural history of cardiovascular diseases, including HFpEF. If baroreceptor dysfunction is a factor in the disease process, electrical activation that bypasses impaired receptors may be an ideal therapy.

Hemodynamic modulation by the baroreflex is accomplished by regionally specific changes in sympathetic outflow. Rather than being a generalized “fight or flight”

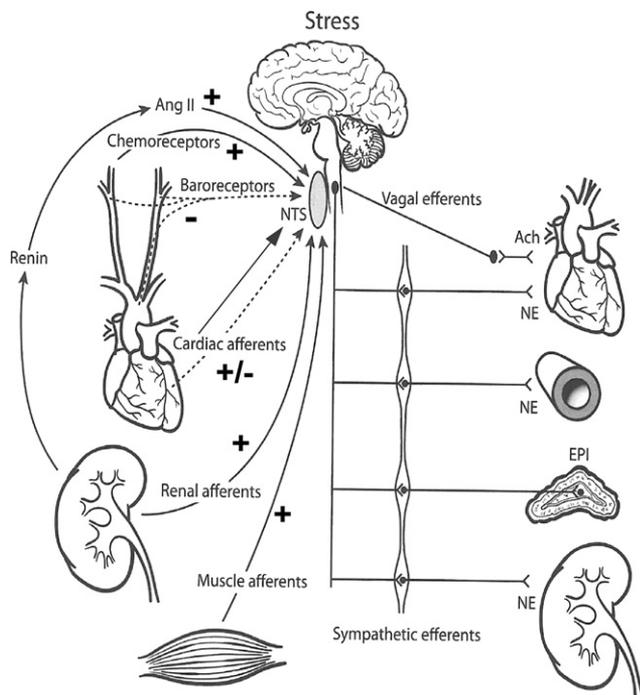


Fig. 2. Schematic depicting the primary determinants of central sympathetic outflow. Dashed arrows represent inhibitory influences, and solid arrows represent excitatory influences. Cardiac afferents can be either inhibitory arising from vagal cardiopulmonary receptors or excitatory from high threshold receptors innervated by sympathetic afferents. Note that baroreflex activation not only influences sympathetic outflow directly but also modulates factors involved in sympathetic excitation through hemodynamic effects. Modified from Kaplan and Victor, *Clinical hypertension*, Lippincott (2010).

withdrawal of sympathetic tone, efferent outflow is centrally orchestrated by means such as frequency coding to specifically modulate each target system. Frequency coding produces not only modulation of NE release, but also release of cotransmitters, such as dopamine, neuropeptide Y (NPY), adenosine triphosphate, and calcitonin gene-related peptide,³¹ so that the various proportions of each transmitter can be selectively controlled.³² Further refinement is achieved by the distribution of receptors at each organ relative to sites of transmitter release. Such refinement is frequently observed in organs, in which arteries and veins exhibit distinct receptor populations or altered distributions of receptors.³³ Unlike pharmacologic therapies that act in a nonspecific manner regarding target organ effects, stimulating the baroreflex with BAT alters release of transmitters in region-specific and regulated proportions.

Therapeutic Targets of Baroreflex Activation in HFpEF

Sympathetic Nervous System

Congestive heart failure is traditionally defined as a pathophysiologic state in which the heart is unable to supply

perfusion commensurate with requirements of tissue metabolic demand or when such perfusion can be achieved only by the heart operating at elevated filling pressures. The syndrome of heart failure is not synonymous with LV systolic dysfunction. Indeed, diastolic abnormalities can promote circulatory congestion in the face of normal or elevated ejection fraction.

When flow to peripheral tissues is sufficiently reduced at rest or during exertion, compensatory mechanisms mediated by increased activity of the sympathetic nervous system (SNS) are invoked, such as retention of sodium and water by the kidneys, increased cardiac output due to elevated heart rate and myocardial contractility, and diversion of perfusion to vital beds owing to vasoconstriction. As a result of these compensatory mechanisms, levels of circulating NE, angiotensin II, and vasopressin are increased. The shift in neurohormonal balance promotes venous congestion and increased load on the heart, thereby further reducing peripheral flow, impairing diastolic relaxation, and increasing LV filling pressure. In addition, neurohormonal activation promotes adverse cardiac remodeling.³⁴ This vicious cycle continues unabated until filling pressures rise sufficiently to initiate pulmonary edema and, ultimately, decompensation. This process is the final common pathway for acute decompensated HF regardless of EF.^{35,36}

HF patients experience little benefit from the parasympathetic nervous system, whose tone is decreased and efferent traffic inhibited by increased SNS activity. Rather, the syndrome is characterized by chronic activation of the SNS leading to elevated plasma NE in peripheral (eg, antecubital) veins and the coronary sinus, driven by spillover from the heart, arteries, and kidneys.³⁷ Excess plasma catecholamines are similarly prevalent in essential and obesity-related hypertension. Vasoconstriction in skeletal muscle mediated by the SNS, in addition to increasing cardiac load, leads to microvascular rarefaction, which may be a potential mechanism for reduced delivery of glucose and a substrate for impaired functional capacity, insulin resistance, and hyperinsulinemia.^{38,39}

Cardiac sympathetic stimulation contributes to development of LV hypertrophy and increases myocardial automaticity, which can promote ventricular tachyarrhythmias and sudden death. Thus, the level of sympathetic drive to the failing heart is a major determinant of prognosis and is the basis for β -adrenergic blockade as a therapy.⁴⁰ Cardiac pathology is also affected by elevated NPY, a cotransmitter of NE simultaneously released by efferent sympathetic nerve terminals. It has been shown that NPY can inhibit parasympathetic tone by modulating release of acetylcholine through stimulation of prejunctional α -1 receptors on vagal nerve endings.^{41,42} Although no pharmacologic therapy exists for excess NPY, levels are modulated by the baroreflex in parallel with NE because of reduced sympathetic tone.

The elevated LV filling pressures characteristic of HF can lead to further sympathetic activation by reducing baroreflex gain in the NTS due to dysfunction of

sympathoinhibitory cardiopulmonary afferents and activation of sympathetic afferents.^{17,43} Compounding the pathology, excess plasma NE promotes hypertrophy of vascular smooth muscle, thereby increasing arterial stiffness and LV afterload.²⁶ Further contributing to neurohormonal activation are the chemoreceptors, whose sensitivity to hypoxia becomes elevated.⁴⁴

As illustrated in Fig. 2, sympathetic outflow from the NTS is determined by the convergence of signals from somatic, renal, chemoreceptor, and cardiac afferents. Although it is controversial whether carotid baroreceptors dysfunction is responsible for initiating sympathoexcitation in many cardiovascular diseases,¹⁸ it may contribute to it by either resetting to maintain SNS activation or generating insufficient afferent signaling to compete with other inputs to the NTS. Some of the benefits that cardiac glycosides, such as digitalis, confer to HF patients may be a result of sensitizing carotid, aortic, and cardiopulmonary receptors so that afferent traffic is increased.^{45,46} In addition, chronic baroreflex stimulation has been shown to increase BRS, thereby further potentiating the therapeutic effect.⁴⁷

BAT has been shown to directly affect SNS traffic and autonomic balance to the heart. Wustmann et al⁴⁷ reported analyses of serial 24-hour ambulatory electrocardiogram recordings in hypertensive patients receiving BAT. Over the course of 12 months, patients exhibited a reduced low frequency–high frequency ratio, corresponding to diminished sympathetic activity. Patients also developed increased heart rate turbulence, indicating increased parasympathetic activity and BRS.

Baroreflex effects on sympathetic activity can be quantified with muscle sympathetic nerve activity (MSNA).⁴⁸ MSNA provides a direct measurement of postganglionic SNS traffic elicited by NE release, in the form of spontaneous bursts of discharge targeted to skeletal muscle vasculature. Traffic observed in MSNA has been shown to be highly regulated by the carotid baroreceptors. Although sympathetic efferent activity may differ among target organs, it has been shown that changes in MSNA induced by baroreflex activation are similar to changes observed in cardiac and renal sympathetic nerve activity.⁴⁹ MSNA has recently been shown to be elevated in both hypertension and HF.⁵⁰

Heusser et al⁵¹ have reported effects on MSNA in 12 patients with resistant hypertension treated with BAT for a minimum of 3 months. Even after long-term therapy, acute activation of BAT elicited sustained decreases in MSNA that were quickly reversible when therapy was withdrawn. Furthermore, changes in MSNA were positively correlated with the reduction of systolic blood pressure (SBP; Fig. 3A). As emphasized in an accompanying editorial,⁵² the reduction in pressure was not due to reduced cardiac output. Rather, it was an effect of vasodilation with a concomitant reduction in heart rate. This distinguishes the effects of BAT from drugs such as selective β -blockers, which reduce pressure acutely by reducing cardiac output through a reduction in heart rate and cardiac

contractile function. Interrelationships of BP and heart rate assessed by cross-spectral and sequence techniques further demonstrated that baroreflex regulation of heart rate was unimpaired by acute activation of BAT. Indeed, heart rate variability tended to increase, suggestive of improved cardiac sympathovagal balance. Acute modulation of the renin-angiotensin-aldosterone system (RAAS) was also observed as renin levels dropped acutely by 20%.⁵¹

Modulation of SNS activity driven by baroreflex activation also affects kidney function by altering renal nerve activity. One mechanism by which this may occur is through altering the properties of the pressure-natriuresis curve by redistribution of blood flow from the renal cortex to the medulla, the portion of the kidney most sensitive to ischemia due to its escape from autoregulation.⁵³ Changes in renal sympathetic efferent activity, along with renal artery vasodilation, are presumably the means by which the baroreflex reduces activation of the RAAS. Consequent reduction in plasma angiotensin will further decrease central sympathetic outflow.⁵⁴

SNS activation is also known to affect immune function by promoting activation of T cells, which release reactive oxygen species which reduce the bioavailability of nitric oxide, thereby exacerbating vasoconstriction.⁵⁵ Activated T cells may also constitute an important part of the mechanism linking increased SNS activation with fibrosis and associated structural remodeling of arteries and the myocardium. Fibrotic effects of activated T cells may be exacerbated by oxidative stress from plasma angiotensin and catecholamines secondary to sympathetic activation.⁵⁶

The Heart

The heart is preferentially targeted by SNS activation early in the course of the development of HF as assessed by spillover of NE and, as has recently been shown, NPY.⁵⁷ The increase in NPY is further evidence of increased cardiac sympathetic nerve activity as opposed to a reduction in neuronal reuptake.⁵⁷ Increasing NE spillover is believed to be the consequence of diminished sympathoinhibition from cardiopulmonary receptor feedback as a result of damage from ischemia and/or hypertrophy and enhanced activation of high-threshold receptors due to elevated filling pressures.⁵⁸ Elevated sympathetic activity also inhibits vagal modulation of the heart, resulting in diminished heart rate variability, and has been shown to contribute to diastolic dysfunction.⁵⁹

To assess effects of BAT on cardiac function, LV pressure-volume (PV) relationships⁶⁰ were measured using the conductance catheter technique in normotensive canines. Figure 3B shows that the initiation of BAT from steady state (dashed PV loop) results in a gradual fall in BP until a new steady state is reached (solid PV loop) which was maintained for 8–10 minutes. BAT resulted in increased stroke volume, small reduction in end-diastolic volume, and a reduction in LV filling pressures. Cardiac output was preserved despite a reduction in heart rate of $\sim 20\%$. The slope of the end-systolic pressure

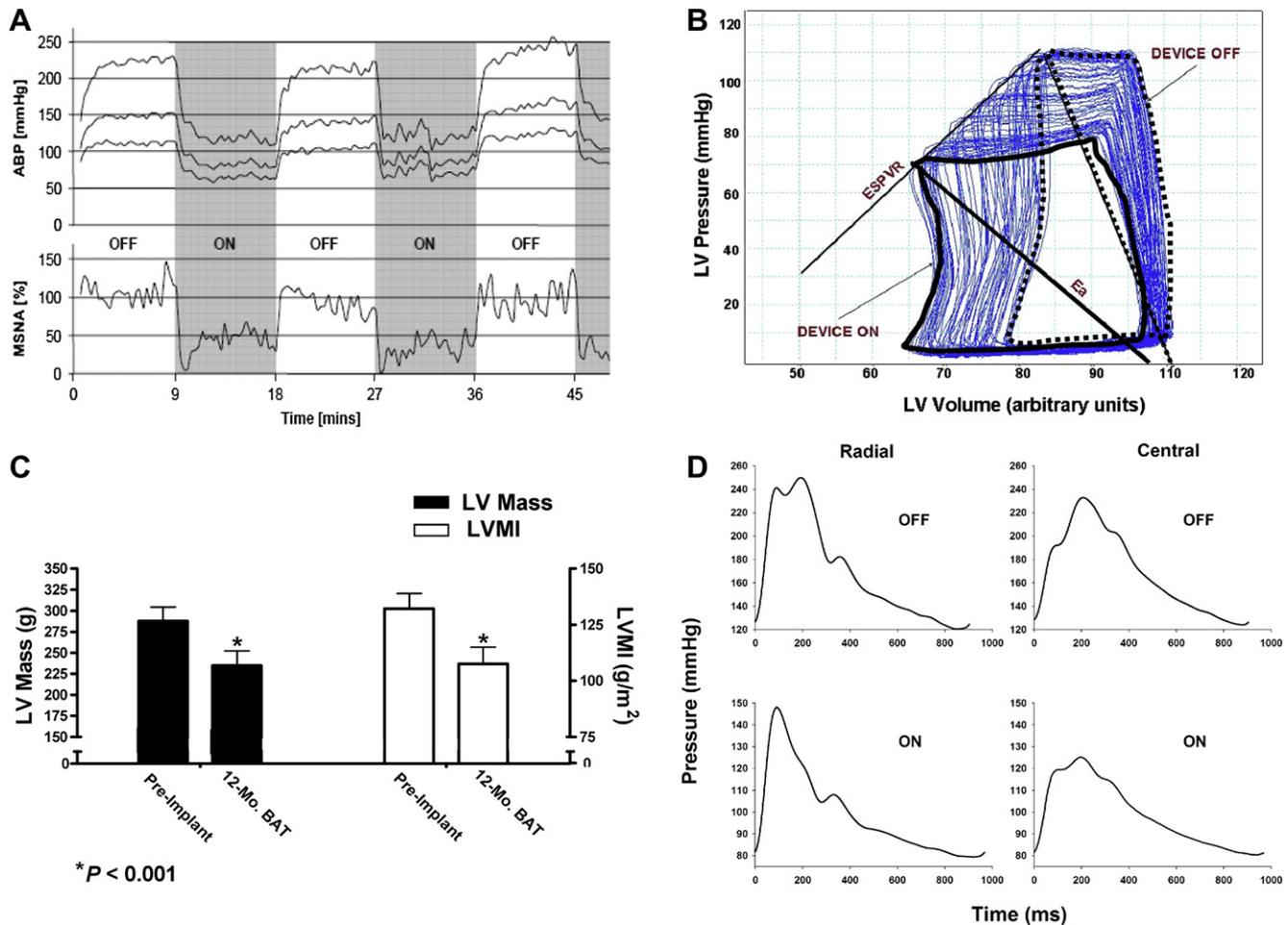


Fig. 3. Baroreflex activation therapy (BAT) exhibits several high-level effects that may be beneficial for patients with preserved-ejection-fraction heart failure. **(A)** Acute impact of BAT on muscle sympathetic nerve activity, showing rapid reductions in sympathetic traffic concomitant with pressure reduction induced by activation of BAT.⁴⁷ **(B)** Acute effects of BAT on cardiac pressure-volume relationships in normotensive dogs, demonstrating increased stroke volume, maintained end-diastolic volume, and a large reduction in arterial resistance (Ea). No effects were observed on cardiac contractility assessed by the ESPVR. **(C)** Chronic effects of BAT on cardiac structure in resistant hypertension patients, demonstrating significant reductions in LV mass (*solid bars*) and LV mass index (*open bars*). **(D)** Impact of acute BAT on central pressure waveform derived from radial tonometry, demonstrating reduction in augmentation index and elevated diastolic pressure despite the decrease in heart rate owing to attenuation of reflected wave amplitude and timing and improved arterial stiffness. Pulse pressure amplification was also increased after BAT, indicating a greater reduction in central blood pressure relative to peripheral.

volume relationship (ESPVR, a load-independent measure of contractility) was unchanged compared with the preload reduction at baseline before BAT (data not shown), indicating no effect on myocardial contractile function. This finding was important in that a reduction in contractility would limit the increase in stroke volume, thereby resulting in a fall in cardiac output. However, any increase in contractility would result in an increase in myocardial oxygen consumption.

In this series of studies in normotensive canines with acute BAT activation, cardiac efficiency increased due to preserved cardiac output that required less energy to accomplish as a result of reduced afterload (Fig. 3B: reduction in Ea, a measure of arterial load). Specifically, the ratio of stroke work to PV area increased by 35%. This increase was due to maintenance of stroke work and a reduction in PV area (PVA), indicating a reduction in myocardial

oxygen consumption (MVO_2), because MVO_2 is directly related to PVA.⁶¹ Stroke work was preserved, because end-diastolic volume was maintained nearly constant relative to baseline and BAT induced vasodilation, allowing extraction of potential energy available during contraction that would normally have been liberated as heat. These effects are distinct from those of β -adrenergic blockade, which reduces the ESPVR along with heart rate, thereby reducing cardiac work at the expense of cardiac output.

It is important to note that the effects on heart rate with BAT were mediated not by sympathetic withdrawal, but by increased parasympathetic tone, because it has been demonstrated to be blocked by atropine.⁶² It has further been shown that the baroreflex causes coronary artery dilation through both sympathetic and parasympathetic mechanisms.⁶³ A study of patients receiving carotid sinus nerve

stimulation demonstrated in the clinical setting that cardiac output is unaffected by baroreflex activation.⁶⁴ Reduced heart rate is offset by increased stroke volume facilitated by vasodilation.⁶⁵

Reduced ventricular loading due to the baroreflex has been shown clinically^{64,65} to reduce myocardial oxygen consumption. Increased coronary flow further increases oxygen availability. Refractory angina patients with carotid sinus nerve stimulators experienced complete relief of symptoms upon stimulation, resulting in increased exercise duration.^{64,65} Nitrates did not alleviate symptoms in this cohort. High-rate pacing in these ischemic patients resulted in rapid increases in LV end-diastolic pressure and tension-time index. Carotid sinus nerve stimulation promptly reversed these effects.⁶⁴ Thus, metabolic benefits conferred by the baroreflex to the heart are more profound than a mere lowering of heart rate. These metabolic effects may be beneficial to HFpEF patients, whose delayed LV relaxation and impaired ventriculovascular coupling be linked to impaired cardiac energy reserve.⁶⁶

In a pacing model of HF, LV end-diastolic pressures were directly observed to be reduced by BAT compared with control subjects not receiving BAT.⁶⁷ Similarly, surges in plasma NE and angiotensin II that occurred concomitantly with increased filling pressure were suppressed. The net result of these benefits on the pacing model was to double the survival of canines treated with BAT (68.1 ± 7.4 vs 37.3 ± 3.2 days; $P < .01$). Importantly, there were no differences in SBP, and the improved outcomes were independent of heart rate.

Significant structural remodeling has been observed in the microembolization model of HF when treated with BAT. Compared with control HF animals that did not receive intervention, dogs treated with BAT exhibited reduced myocyte cross-sectional area, fibrosis, and LV chamber size.⁶⁸ These observations further support the notion that BAT may demonstrate clinical benefit, because all therapies that have been successful in the treatment of HF induce remodeling.⁶⁹ In addition to structural benefits, molecular remodeling was observed. BAT up-regulated RNA message for β_1 receptors and normalized the nitric oxide synthase (NOS) profile by elevating message for endothelial NOS while decreasing that for inducible NOS.⁷⁰

Reduction of sympathetic activity is expected to reduce myocardial automaticity. This expectation was confirmed in the microembolization model of HF, which demonstrated that chronic BAT increased threshold to induce ventricular tachyarrhythmias compared with control. The increased threshold for induction was reversed when BAT was withdrawn.⁷¹ Clinical antiarrhythmic effects of baroreflex activation have also been documented: Patients implanted with carotid sinus nerve stimulators experienced cessation of supraventricular tachycardia when therapy was applied.⁷²

Clinical experience with BAT has documented therapeutic benefits corresponding to mechanisms observed in preclinical studies. Among the >400 patients implanted worldwide, 18 patients with stage II resistant hypertension

have completed follow-up through 4 years of Rheos therapy.⁷³ In these 18 patients, a sustained and significant reduction in SBP (mean reduction at 4 years: -53 ± 9 mm Hg), diastolic blood pressure (DBP; mean reduction at 4 years: -30 ± 6 mm Hg), and heart rate (mean reduction at 4 years: -5 ± 2 beats/min) has been observed. Importantly, 12/18 patients (67%) achieved an SBP <140 mm Hg, and antihypertensive medication usage has gradually decreased such that the average number of medications used has been reduced by 1.6. No unexpected system- or procedure-related serious adverse events have occurred during follow-up of these patients. Thus, BAT has been shown clinically to address one of the primary treatment goals in HFpEF.

Results from other cohorts receiving BAT have indicated that electrical stimulation of the carotid baroreflex may provide incremental physiologic benefits beyond those of simply lowering blood pressure and heart rate. In an echocardiography substudy in which all patients had stage II hypertension and stage A-B HFpEF (baseline LVEF $66 \pm 5\%$), LV mass index (LVMI) decreased from a baseline of 138.8 ± 35.4 g/m² by 17.8 ± 16.0 g/m² ($n = 33$) and 24.6 ± 17.9 g/m² ($n = 21$) at 3 and 12 months, respectively ($P < .001$).⁷⁴ In absolute terms, LV mass decreased by >50 g at 12 months from a baseline of ~ 300 g (Fig. 3C). The magnitude of this reduction is greater than what has been observed from therapies such as ACE inhibitors or angiotensin-receptor blockers.⁷⁵ Left atrial diameter and mitral A-wave velocity (surrogate for late ventricular filling velocity) were also significantly reduced, suggesting an improvement in LV filling pressures. This improvement in left atrial structure and function may confer additional benefits in patients who experience atrial fibrillation. Stroke work was reduced by 15% at both 3 and 12 months, and the rate-pressure product (surrogate for myocardial oxygen demand) was significantly reduced, suggesting that BAT reduced global cardiac workload. Baseline 6-minute hall walk distance (6MHW; mean 438 ± 153 m) was near the clinical threshold for reduced capacity. Treatment with BAT resulted in a statistically and clinically significant improvement in 6MHW distance (mean increase: $+37 \pm 60$ m).⁷⁶

A definitive trial of this technology has been underway since 2007 in patients with resistant hypertension (Rheos Pivotal Trial, ClinicalTrials.gov identifier: NCT00442286). Endpoints include: for efficacy: 1) the percentage of patients with ≥ 10 mm Hg drop in blood pressure after 6 months; and 2) the percentage of patients with a sustained response at 12 months; and for safety: 1) system- and procedure-related serious adverse event—free rate in the first 30 days after procedure; 2) serious hypertension-related adverse event and serious system-related adverse event—free rate >30 days after implantation through 12 months after randomization; and 3) serious therapy-related adverse event—free rate through 6 months after randomization. An interim analysis of this trial by the Data Safety Monitoring Board found that efficacy endpoint (1) was unlikely to be met owing to the higher than expected number of responders in those

randomized to have the device turned off for the first 6 months. This interim analysis also showed that the 30-day safety endpoint (1) was unlikely to be met even as the majority of clinical events were ones that resolved.

Final results of this study will be available in 2011 when the last study subject completes the 12-month endpoint. Until the results are published, any conclusions concerning the magnitude and durability of effect of this technology must be considered to be tentative.

Arteries and Veins

As previously discussed, reductions in BP by BAT are brought about in part by reductions in systemic vascular resistance. This effect is achieved by reducing sympathetic outflow to arteries in skeletal muscle, thereby dilating the bed primarily responsible for arterial resistance. Modulation of blood flow distribution by BAT is regional rather than systemic, with vasodilation preferentially occurring in skeletal muscle.

Regional distribution of perfusion is known to be deranged in canine models of heart failure as well as in the clinical setting.^{77–79} A recent magnetic resonance imaging study of skeletal muscle perfusion in patients with HFpEF⁸⁰ found that exercise tolerance correlated with the extent of skeletal muscle vasodilation, suggesting clinical impaired perfusion. BAT may be uniquely positioned to target this pathology.

Central conduit arteries are richly innervated with sympathetic nerves.^{81–83} Studies have shown that stimulation of baroreceptors can affect smooth muscle tone in central conduit vessels.^{81,84} BAT has been observed to modulate smooth muscle in conduit arteries. Figure 3D illustrates the effects of BAT on a central pressure waveform calculated from radial artery tonometry in a hypertensive patient with a history of HFpEF. Initiation of BAT produces a reduction in augmentation index, despite a reduced heart rate, which results in systolic pressure dropping at a ratio of 3:1 compared with diastolic pressure (Fig. 3D). The implication of this effect is that BAT acutely reduces arterial stiffness, which is primarily thought to reside in conduit arteries. It has previously been shown that reduced late systolic loading improves diastolic function⁸⁵ through increased relaxation time. Furthermore, reduction in pulsatile load and the magnitude of the reflected wave have been shown to correlate with regression of LV mass and prevention of target organ damage.⁸⁶

Despite substantial reduction in pressure, coronary perfusion increased as assessed by the subendocardial viability ratio.⁸⁷ Although systolic pressure dropped ~100 mm Hg, the patient experienced no symptoms. Accompanying the large reduction in peripheral pressure was greater reduction in central pressure, thereby restoring pulse amplification. Given the recent finding that aortic diameter correlates with exercise tolerance in HFpEF,⁸⁸ reduced conduit artery stiffness resulting from BAT might further increase a patient's exercise tolerance.

In the echocardiography cohort described previously, reductions in arterial stiffness (calculated as stroke volume/pulse pressure) and increased diameter of the left ventricular outflow tract were observed at 3 and sustained after 12 months of BAT.⁸⁹ Thus, the reduced pulsatile load resulting from BAT may have contributed to the substantial reductions observed in LV mass. These effects on arterial properties may be relevant in HF, because it has recently been shown that HFpEF patients have elevated central aortic stiffness.⁹⁰

Studies have documented that baroreflex activation can modulate resistance in the pulmonary vascular bed by almost 20% in normotensive canines.⁹¹ The baroreflex can also modulate pulsatile properties of the lung, as evidenced by alteration of the characteristic impedance of the pulmonary artery.⁹² This may have important implications in HF, because pulmonary hypertension is common, particularly in HFpEF. Unloading of the RV by reducing pulmonary artery afterload may enhance LV filling and reduce LV pressures by reducing effects of pericardial constraint.⁹³

Some of the most important effects of baroreceptor stimulation pertain to veins. The venous system is the principal blood reservoir, normally containing 70%–80% of blood volume. In animal models of HF, it has been shown that total vascular capacitance is decreased, independent of blood volume.⁹⁴ Baroreceptor activation has been shown to reduce venous smooth muscle tone and increase venous capacitance, the magnitude of the increase being similar to that observed with nitrates.⁹⁵ Increased capacitance is achieved through dilation of venules,⁹⁶ which are particularly prominent in the splanchnic circulation. An increase in venous capacitance shifts fluid from the central compartment to the periphery, resulting in reduced central venous pressure (CVP). This effect may be especially important in HF, because it has been shown that LV filling pressure, independently of cardiac contractile function, can be increased only by reducing venous capacitance.⁹⁷ This mechanism may be the means by which sodium nitroprusside therapy improves outcomes in HF.⁹⁸ Indeed, recent studies of acute decompensated HF have shown that CVP is the strongest predictor of future hospitalization and a key determinant of renal function.⁹⁹

From a standpoint of therapeutic goals, combined vasodilation has been the cornerstone of HF therapy for decades. Although drugs have afforded the ability to accomplish these goals grossly and with unintended consequences, BAT provides a method to precisely modulate the degree of unloading using the body's physiologic regulatory pathways. BAT likely provides benefits beyond contemporary medical therapy by using mechanisms that are as yet unidentified or unexploited. For example, BAT has been shown to exert effects through vascular postjunctional α_2 -adrenergic receptors¹⁰⁰ for which no pharmacologic therapy has yet been developed.

Renal Effects and Volume Regulation

Kidney disease is a common comorbidity in HF which increases the likelihood of poor outcome. Baroreflex

effects, as manifested in efferent renal traffic, modulate renin secretion via a β -adrenergic receptor-mediated mechanism similar to β -blockers, but also via α_1 -adrenergic receptors, which reduce sodium and water reabsorption in the nephron.¹⁰¹

Lohmeier et al have reported several series of dogs treated with BAT. Models have included normal dogs and dogs with obesity hypertension, and reduced renal mass hypertension.^{102–104} BAT is titrated to achieve a 20 mm Hg reduction in mean arterial pressure (MAP). In all series, BAT reduced plasma NE along with MAP and was further shown to not elicit changes in plasma renin and urinary sodium excretion, even in normotensive animals. This is consistent with other reports of shifts in the renal blood flow/glomerular filtration rate (GFR) pressure relationship in which the autoregulation capacity of the kidney is maintained at lower pressures.¹⁰⁵ Measurements of urinary sodium excretion at various levels of MAP and salt intake allowed construction of pressure-natriuresis curves. The curves demonstrated that BAT shifts the relationship leftward, so that there is no sodium retention despite the lower MAP (T. E. Lohmeier, personal communication, 2009). One possible mechanism responsible for this effect is the maintenance of renal medullary flow, which has been proposed as the mediator of pressure-natriuresis.¹⁰⁶ Infusion of the nitric oxide (NO) inhibitor L-NAME has been shown to reduce medullary flow, leading to a sustained increase in blood pressure while renal cortical flow was unaltered.¹⁰⁷ In normotensive dogs made hypertensive by chronic L-NAME infusion, BAT was able to reduce blood pressure to near baseline values over a period of 4 weeks (CVRx data on file) suggesting that BAT was able to restore sodium balance. Possible mechanisms assessing NO-dependent and -independent mechanisms require further study.

BAT has been clinically observed to provide renoprotective benefits in patients with stage 1-3 chronic kidney disease (CKD). In addition to similar reductions in BP and LV mass as the general cohort, no significant change in the estimated GFR was observed in 24 CKD patients receiving BAT for 1 year.¹⁰⁸ This effect was observed across all stages of CKD in the cohort. Given the close relationship between decline in kidney function and worsening cardiac outcome, these results provide substantive support for the use of BAT in HF patients with compromised kidney function.

Modulation of renal nerve traffic by the baroreflex also affects mechanical properties of the renal arteries. BAT has been shown to acutely reduce renal vascular resistance as well as stiffness quantified by renal artery pulse wave velocity,^{109,110} the latter effect being important in minimizing pulsatile energy reaching the glomerular capillaries.¹¹¹ This may be particularly important in that renal autoregulation appears to be influenced to a greater extent by pulsatile pressure than absolute pressure.^{112,113}

The benefits of BAT on renal vascular resistance have also been documented in a canine pacing model of HF. In this model, a treadmill exercise protocol was performed

during which renal artery blood flow was measured. Preliminary results indicate that over the course of 4 weeks, a graded response was observed to progressive levels of exercise, during which renal artery resistance increased nearly 4-fold with increasing levels of intensity in HF control animals. In canines treated with BAT, the increase in renal artery resistance was blunted, so that blood flow was maintained near baseline levels (I. H. Zucker, personal communication, 2009). This effect may offer further benefits to exercise tolerance that are not conferred by drugs, whereby vasodilators commonly used to improve cardiac output in HF do not improve renal blood flow.¹¹⁴

Clinical Limitations

With the current generation of the Rheos device, implantation requires surgical exposure of the carotid sinus; however, the technique is simpler than a common surgical procedure, carotid endarterectomy, because there is no vascular access. Application of current to the carotid baroreceptors has occasionally been observed to elicit symptoms in patients such as facial tingling, coughing, and tooth pain, all symptoms of extraneous stimulation of cranial nerves. These effects either subside in a few minutes or programming parameters can usually be adjusted to circumvent this. Given the multiple effects of BAT, medication adjustments of β -blockers, diuretics, and RAAS inhibitors may be required to optimize therapeutic benefits.

Summary

At present, no therapy has been demonstrated to be effective in the treatment of HFpEF. Consensus guidelines call for treatment of comorbidities, the foremost of which is hypertension. As described in the present review, baroreflex effects can affect many of the major comorbidities and pathologies, including hypertension (Table 1). BAT is a device-based therapy that chronically excites carotid baroreceptors to modulate hemodynamics. Feasibility studies of BAT have demonstrated significant reductions in arterial pressure that are maintained for ≥ 4 years of follow-up. By leveraging the well documented abilities of the baroreflex to modulate a host of physiologic properties, BAT offers benefits to HFpEF patients beyond BP control.

As previously demonstrated in patients with resistant hypertension, BAT reduces afterload, consequently reducing filling pressures, LV mass, and left atrial size. Accompanying these structural changes are chronic reductions in sympathetic nerve activity and plasma NE, increased parasympathetic nerve activity, and improved heart rate variability. Dilation of arteries and veins promotes skeletal muscle and coronary perfusion, normalizes blood flow distribution, and lowers central venous pressure, a key determinant of clinical outcome. Autonomic and circulatory changes promote preservation of renal function through maintenance of euolemia and suppression of vasopressin

release. Baroreflex-mediated changes may also ameliorate pulmonary hypertension and sleep apnea.

As a result of this wide spectrum of potential benefit, BAT is being evaluated as a therapy for HFpEF in the CVRx Health Outcomes Prospective Evaluation for Heart Failure With EF $\geq 40\%$ (HOPE4HF) trial (ClinicalTrials.gov Identifier: NCT00957073). HOPE4HF is a prospective randomized trial of ~ 540 subjects at up to 70 U.S. sites and up to 20 sites outside of the U.S. Subjects will be randomized in a 2:1 ratio to receive BAT plus medical management (device arm) or to receive medical management alone (medical management arm). The primary efficacy endpoint will be measured by the time from randomization to cardiovascular death or heart failure event, defined as a heart failure hospitalization or an emergency department or clinic visit requiring intravenous therapy for the treatment of heart failure.

Because the symptomology and pathophysiology of HFpEF and HF with reduced EF share much in common, it is likely that BAT will also benefit HF patients whose EF is $< 40\%$. Future studies will explore possible therapeutic benefit in this population.

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References

- Croft JB, Giles WH, Pollard RA, Keenan NL, Casper ML, Anda RF. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. *Arch Intern Med* 1999;159:505–10.
- Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003;89:49–53.
- Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. *J Cardiac Fail* 2007;13:569–76.
- Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. *Annu Rev Med* 2004;55:373–94.
- Adams KF, Lindenfeld J, Arnold JMO, Baker DW, Barnard DH, Baughman KL, et al. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Cardiac Fail* 2006;12:10–38.
- Fu Q, Zhang R, Witkowski S, Arbab-Zadeh A, Prasad A, Okazaki K, et al. Persistent sympathetic activation during chronic antihypertensive therapy: a potential mechanism for long term morbidity? *Hypertension* 2005;45:513–21.
- McCormack PL, Wagstaff AJ. Lacidipine: a review of its use in the management of hypertension. *Drugs* 2003;63:2327–56.
- Farasat SM, Bolger DT, Shetty V, Menachery EP, Gerstenblith G, Kasper EK, et al. Effect of beta-blocker therapy on rehospitalization rates in women versus men with heart failure and preserved ejection fraction. *Am J Cardiol* 2010;105:229–34.
- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251–9.
- La Rovere MT, Pinna GD, Maestri R, Robbi E, Caporotondi A, Guazzotti G, et al. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. *J Am Coll Cardiol* 2009;53:193–9.
- Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci MD, et al. Digoxin and reduction in mortality and hospitalization and heart failure: a comprehensive post-hoc analysis of the DIG trial. *Eur Heart J* 2006;27:178–86.
- Esler M, Kaye D. Increased sympathetic nervous system activity and its therapeutic reduction in arterial hypertension, portal hypertension and heart failure. *J Auton Nerv Syst* 1998;72:210–9.
- Sleight P. The importance of the autonomic nervous system in health and disease. *Aust N Z J Med* 1997;27:467–73.
- Lovett EG, Shafer J, Kaufman CL. Chronic activation by the Rheos System: an overview of results from European and North American feasibility studies. *Conf Proc IEEE Eng Med Biol Soc* 2009;2009:4626–30.
- Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;114:345–52.
- Grassi G, Giannattasio C, Cleroux J, Cuspidi C, Sampieri L, Bolla GB, et al. Cardiopulmonary reflex before and after regression of left ventricular hypertrophy in essential hypertension. *Hypertension* 1988;12:227–37.
- Azevedo ER, Newton GE, Floras JS, Parker JD. Reducing cardiac filling pressure lowers norepinephrine spillover in patients with chronic heart failure. *Circulation* 2000;101:2053–9.
- Eckberg DL, Sleight P. Human baroreflexes in health and disease. New York: Oxford University Press; 1992.
- Kirchheim HR. Systemic arterial baroreceptor reflexes. *Physiol Rev* 1976;56:100–77.
- Eckberg DL. Arterial baroreflexes and cardiovascular modeling. *Cardiovasc Eng* 2008;8:5–13.
- Angell-James JE, George MJ. Carotid sinus baroreceptor reflex and baroreflex control of the circulation in experimental cardiovascular disease. *J Physiol* 1978;275:38P–9P.
- Ito CS, Scher AM. Regulation of arterial blood pressure by aortic baroreceptors in the unanesthetized dog. *Circ Res* 1978;42:230–6.
- Mancia G, Shepherd JT, Donald DE. Interplay among carotid sinus, cardiopulmonary and carotid body reflexes in the dog. *Am J Physiol Heart Circ Physiol* 1976;230:H19–24.
- Guyenet PG. The sympathetic control of blood pressure. *Nat Rev Neurosci* 2006;7:335–46.
- Jacobsen TN, Morgan BJ, Scherrer U, Vissing SF, Lange RA, Johnson N, et al. Relative contributions of cardiopulmonary and sinoaortic baroreflexes in causing sympathetic activation in the human skeletal muscle circulation during orthostatic stress. *Circ Res* 1993;73:367–78.
- Persson PB, Kirchheim HR. Baroreceptor reflexes: integrative functions and clinical aspects. Berlin: Springer-Verlag; 1991.
- Farmakis D, Filippatos G, Kremastinos DT, Gheorghiadu M. Vasopressin and vasopressin antagonists in heart failure and hyponatremia. *Curr Heart Fail Rep* 2008;5:91–6.
- Korner PI. Essential hypertension and its causes: neural and nonneural mechanisms. Oxford: Oxford University Press; 2007.
- Lu Y, Ma X, Sabharwal R, Snitsarev V, Morgan D, Rahmouni K, et al. The ion channel ASIC2 is required for baroreceptor and autonomic control of the circulation. *Neuron* 2009;64:885–97.
- Higgins CB, Vatner SF, Eckberg DL, Braunwald E. Alterations in the baroreceptor reflex in conscious dogs with heart failure. *J Clin Invest* 1972;51:715–24.

31. Morris MJ, Cox HS, Lambert GW, Kaye DM, Jennings GL, Meredith IT, et al. Region-specific plasma NPY concentrations and overflows at rest and during sympathetic activation in man. *Hypertension* 1997;29:137–43.
32. Janig W. Integrative action of the autonomic nervous system: neurobiology of homeostasis. New York: Cambridge University Press; 2006.
33. Birch D, Turmaine M, Boulou P, Burnstock G. Sympathetic innervation of human mesenteric artery and vein. *J Vasc Res* 2008;45:323–32.
34. Burns J, Sivanathan MU, Ball G, Mackintosh AF, Mary DASG, Greenwood JP. Relationship between central sympathetic drive and magnetic resonance imaging–determined left ventricular mass in essential hypertension. *Circulation* 2007;115:1999–2005.
35. Kumar R, Gandhi SK, Little WC. Acute heart failure with preserved systolic function. *Crit Care Med* 2008;36:S52–6.
36. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008;118:1433–41.
37. Eckberg DL. Baroreflexes and the failing human heart. *Circulation* 1997;96:4133–7.
38. Toussaint JF, Koelling TM, Schmidt CJ, Kwong KK, LaRaia PJ, Kantor HL. Local relation between oxidative metabolism and perfusion in leg muscles of patients with heart failure studied by magnetic resonance imaging and spectroscopy. *J Heart Lung Transplant* 1998;17:892–900.
39. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 2008;118:968–76.
40. Cohn JN. Beta-blockers in heart failure. [abstract]. *Eur Heart J* 1998;19(Suppl F):F52–5.
41. Potter EK. Cardiac vagal action and plasma levels of neuropeptide Y following intravenous injection in the dog. *Neurosci Lett* 1987;77:243–7.
42. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992;327:1912–8.
43. Sopher SM, Smith ML, Eckberg DL, Fritsch JM, Dibner-Dunlap ME. Autonomic pathophysiology in heart failure: carotid baroreceptors-cardiac reflexes. *Am J Physiol Heart Circ Physiol* 1990;259:H689–96.
44. Schultz HD, Li YL. Carotid body function in heart failure. *Resp Physiol Neurobiol* 2007;157:171–85.
45. Quest JA, Gillis RA. Effect of digitalis on carotid sinus baroreceptor activity. *Circ Res* 1974;35:247–55.
46. Thames MD, Miller BD, Abboud FM. Sensitization of vagal cardiopulmonary baroreflex by chronic digoxin. *Am J Physiol Heart Circ Physiol* 1982;243:H815–8.
47. Wustmann K, Kucera JP, Scheffers I, Mohaupt M, Kroon AA, de Leeuw PW, et al. Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension. *Hypertension* 2009;54:530–6.
48. Wallin BG, Charkoudian N. Sympathetic neural control of integrated cardiovascular function: insights from measurement of human sympathetic nerve activity. *Muscle Nerve* 2007;36:595–614.
49. Kamiya A, Kawada T, Yamamoto K, Michikami D, Ariumi H, Miyamoto T, et al. Muscle sympathetic nerve activity averaged over 1 minute parallels renal and cardiac sympathetic nerve activity in response to a forced baroreceptor pressure change. *Circulation* 2005;112:384–6.
50. Grassi G, Arenare F, Pieruzzi F, Brambilla G, Mancia G. Sympathetic activation in cardiovascular and renal disease. *J Nephrol* 2009;22:190.
51. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010;55:619–26.
52. Mancia G, Parati G, Zanchetti A. Electrical carotid baroreceptor stimulation in resistant hypertension. *Hypertension* 2010;55:607–9.
53. Cowley AW, Roman RJ. Renal mechanisms in hypertension. In: Zanchetti A, Mancia G, editors. *Handbook of hypertension*. Amsterdam: Elsevier; 1997. p. 740–83.
54. Zucker IH, Schultz HD, Patel KP, Wang W, Gao L. Regulation of central angiotensin type 1 receptors and sympathetic outflow in heart failure. *Am J Physiol* 2009;297:H1557–66.
55. Tracey KJ. The inflammatory reflex. *Nature* 2002;420:853–9.
56. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. *Med Clin North Am* 2009;93:569–82.
57. Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transitions from mechanisms to medical management. *J Appl Physiol* 2010;108:227–37.
58. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 2009;54:375–85.
59. Grassi G, Seravalle G, Quarti-Trevano F, dell’Oro R, Arenare F, Spaziani D, et al. Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. *Hypertension* 2009;53:205–9.
60. Georgakopoulos D, Wagner D, Cates AW, Irwin E, Lovett EG. Effects of electrical stimulation of the carotid sinus baroreflex using the Rheos device on ventricular-vascular coupling and myocardial efficiency assessed by pressure-volume relations in nonvagotomized anesthetized dogs. *Conf Proc IEEE Eng Med Biol Soc* 2009;2009:2025–9.
61. Suga H. Ventricular energetics. *Physiol Rev* 1990;70:247–70.
62. Eckberg DL, Fletcher GF, Braunwald E. Mechanism of prolongation of the R-R interval with Electrical stimulation of the carotid sinus nerves in man. *Circ Res* 1972;30:131–8.
63. Ito BR, Feigl EO. Carotid Baroreceptor reflex coronary vasodilation in the dog. *Circ Res* 1985;56:486–95.
64. Dunning AJ. *Electrostimulation of the carotid sinus nerve in angina pectoris*. Amsterdam: Excerpta Medica; 1971.
65. Braunwald E, Vatner SF, Braunwald NS, Sobel BE. Carotid Sinus Nerve Stimulation in the treatment of angina pectoris and supraventricular tachycardia. *Calif Med* 1970;112:41–50.
66. Phan TT, Abozguia K, Shivu GN, Mahadevan G, Ahmed I, Williams L, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol* 2009;54:402–9.
67. Zucker IH, Hackley JF, Cornish KG, Hiser BA, Anderson NR, Kieval R, et al. Chronic baroreceptor activation enhances survival in dogs with pacing-induced heart failure. *Hypertension* 2007;50:904–10.
68. Sabbah HN, Imai M, Irwin ED, Serdar DJ, Sharov VG, Rossing MA, et al. Chronic electrical activation of the carotid baroreflex improves left ventricular systolic function and prevents progressive chamber dilation in dogs with advanced heart failure. [abstract]. *Circulation* 2005;112:557.
69. Anand I, Florea VG. Traditional and novel approaches to management of heart failure: successes and failures. *Cardiology Clinics* 2008;26:59–72.
70. Gupta RC, Imai M, Cody RJ, Irwin ED, Rossing MA, et al. Baroreflex activation therapy normalizes gene expression of components of the beta-adrenergic receptor signaling pathway in LV myocardium of dogs with chronic heart failure. [abstract]. *Eur Heart J* 2007;28:818–9.
71. Wang M, Zaca V, Jiang A, Ihsar I, Ebinger M, Sabbah MB, et al. Long-term baroreflex activation therapy increases the threshold for the induction of lethal ventricular arrhythmias in dogs with chronic advanced heart failure. [abstract]. *Circulation* 2008;118:S-721.
72. Braunwald E, Sobel BE, Braunwald NS. Treatment of paroxysmal supraventricular tachycardia by electrical stimulation of the carotid-sinus nerves. *N Engl J Med* 1969;281:885–7.
73. Kroon AA, Schmidli J, Tordoir J, Mohaupt M, Allemann Y, Jordan J, et al. Sustained blood pressure reduction by baroreflex activation

- therapy with a chronically implanted system: 4-year data from the Rheos DEBuT-HT study in patients with resistant hypertension. *J Hypertens* 2010;28(e-suppl A):278.
74. Bisognano JD, de Leeuw P, Bach DS, Lovett EG, Kaufman CL. Improved functional capacity and cardiovascular structure after baroreflex activation therapy in resistant hypertension patients with symptomatic heart failure: results from European and United States trials of the Rheos System. [abstract]. *J Cardiac Fail* 2009;15:S62.
 75. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 2009;54:1084–91.
 76. Bisognano JD, de Leeuw P, Bach DS, Lovett EG, Kaufman CL. Improved functional capacity and cardiovascular structure after baroreflex activation therapy in resistant hypertension patients with symptomatic heart failure: results from the European and United States trials of the Rheos System. *J Cardiac Fail* 2009;15:S63.
 77. Creager MA, Hirsch AT, Dzau VJ, Nabel EG, Cutler SS, Colucci WS. Baroreflex regulation of regional blood flow in congestive heart failure. *Am J Physiol Heart Circ Physiol* 1990;27:H1409–14.
 78. Abboud FM, Mark AL, Heistad DD, Eckberg DL, Schmid PG. Selectivity of autonomic control of the peripheral circulation in man. *Trans Am Clin Climatol Assoc* 1975;86:184–97.
 79. Vatner SF, Franklin D, Van Citters RL, Braunwald E. Effects of carotid sinus nerve stimulation on blood-flow distribution in conscious dogs at rest and during exercise. *Circ Res* 1970;27:495–503.
 80. Puntawangkoon C, Kitzman DW, Kritchevsky SB, Hamilton CA, Nicklas B, Leng X, et al. Reduced peripheral arterial blood flow with preserved cardiac output during submaximal bicycle exercise in elderly heart failure. *J Cardiovasc Magn Reson* 2009;11:48–59.
 81. Gerova M, Gero J, Dolezel S, Blazkova-Huzulakova I. Sympathetic control of canine abdominal aorta. *Circ Res* 1973;33:149–59.
 82. Aars H. Effects of altered smooth muscle tone on aortic diameter and aortic baroreceptor activity in anesthetized rabbits. *Circ Res* 1971;28:254–62.
 83. Peterson LH, Jensen RE, Parnell J. Mechanical properties of arteries in vivo. *Circ Res* 1960;8:622–39.
 84. Cox RH, Bagshaw RJ. Carotid Sinus control of pulsatile hemodynamics in halothane-chloralose anesthetized dogs. *Am J Physiol Heart Circ Physiol* 1980;238:H294–9.
 85. Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. *J Am Coll Cardiol* 2007;50:1570–7.
 86. Hashimoto J, Nichols WW, O'Rourke MF, Imai Y. Association between wasted pressure effort and left ventricular hypertrophy in hypertension: influence of arterial wave reflection. *Am J Hypertens* 2008;21:329–33.
 87. Hoffman JJ, Buckberg GD. The myocardial supply:demand ratio—a critical review. *Am J Cardiol* 1978;41:327–32.
 88. Rerkpattanapipat P, Hundley WG, Link KM, Brubaker PH, Hamilton CA, Darty SN, et al. Relation of aortic distensibility determined by magnetic resonance imaging in patients ≥ 60 years of age to systolic heart failure and exercise capacity. *Am J Cardiol* 2002;90:1221–5.
 89. de Leeuw PW, Bisognano JD, Bach DS, Lovett EG. Device-Based Reduction in blood pressure is associated with increased diameter of the left ventricular outflow tract: results from European and United States trials of the Rheos Hypertension System. [abstract]. *Circulation* 2008;118:S-887.
 90. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. *J Cardiac Fail* 2009;15:658–64.
 91. Shoukas AA. Carotid sinus baroreceptors reflex control and epinephrine. Influence on capacitive and resistive properties of the total pulmonary vascular bed of the dog. *Circ Res* 1982;51:95–101.
 92. Pace JB, Cox RH, Alvarez-Vara F, Karreman G. Influence of sympathetic nerve stimulation on pulmonary hydraulic input power. *Am J Physiol Heart Circ Physiol* 1972;222:H196–201.
 93. Atherton JJ, Moore TD, Lele SS, Thomson HL, Galbraith AJ, Belenkie I, et al. Diastolic ventricular interaction in chronic heart failure. *Lancet* 1997;349:1720–4.
 94. Ogilvie RI, Zobrowska-Sluis D. Effect of chronic rapid ventricular pacing on total vascular capacitance. *Circulation* 1992;85:1524–30.
 95. Juro I. Cardiovascular physiology: nerve, flow and pressure. Tokyo: Igaku Shoin; 1972.
 96. Haase EB, Shoukas AA. Carotid sinus baroreceptor reflex control of venular pressure-diameter relations in rat intestine. *Am J Physiol Heart Circ Physiol* 1991;260:H752–8.
 97. Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis. *Am J Physiol Heart Circ Physiol* 1993;34:H1819–28.
 98. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, et al. Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol* 2008;52:200–7.
 99. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009;53:589–96.
 100. Lohmeier TE, Hildebrandt DA, Dwyer TM, Iliescu R, Irwin ED, et al. Prolonged activation of the baroreflex decreases arterial pressure even during chronic adrenergic blockade. *Hypertension* 2009;53:833–8.
 101. DiBona GF. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R633–41.
 102. Lohmeier TE, Hildebrandt DA, Dwyer TM, Barrett AM, Irwin ED, Rossing MA, et al. Renal denervation does not abolish sustained baroreflex-mediated reductions in arterial pressure. *Hypertension* 2007;49:373–9.
 103. Lohmeier TE, Dwyer TM, Irwin ED, Rossing MA, Kieval RS. Prolonged activation of the baroreflex abolishes obesity-induced hypertension. *Hypertension* 2007;49:1307–14.
 104. Lohmeier TE, Hildebrandt DA, Dwyer TM, Irwin ED, Rossing MA, Kieval RS. Prolonged activation of the baroreflex abolishes reduced kidney mass, salt-induced hypertension. [abstract]. *Hypertension* 2007;50:e85.
 105. Just A, Wittmann U, Ehmke H, Kirchheim HR. Autoregulation of renal blood flow in the conscious dog and the contribution of the tubuloglomerular feedback. *J Physiol* 1998;506:275–90.
 106. Cowley AW. Role of the renal medulla in volume and arterial pressure regulation. *Am J Physiol Regul Integr Comp Physiol* 1997;273:R1–15.
 107. Matson DL, Lu S, Nakanishi K, Papanek PE, Cowley AW. Effect of chronic renal medullary nitric oxide inhibition on blood pressure. *Am J Physiol Regul Integr Comp Physiol* 1994;266: H1918–H26.
 108. Sica D, Rothstein M, Bisognano JD, Nadim MK, Lovett EG, Kaufman C, et al. Baroreflex activation therapy preserves eGFR in hypertensive patients with stage 2 and 3 chronic kidney disease: results from European and United States trials of the Rheos System. *J Am Soc Nephrol* 2009;20:11A. Abstract.
 109. Segers P, Wagner D, Ludwig K, Cates AW, Georgakopoulos D. Electrical carotid baroreceptor activation lowers renal artery impedance and stiffness in an acute canine model. [abstract]. *Artery Res* 2009;3:S35.
 110. Bakris GL, Nadim M, Georgakopoulos D, Sica D. Electrical stimulation of the carotid baroreceptors using the Rheos System decreases renal artery stiffness. *J Am Soc Nephrol* 2009;20:1A.
 111. Mitchell GF. Clinical achievements of impedance analysis. *Med Biol Eng Comput* 2009;47:153–63.
 112. Loutzenhiser R, Bidani A, Chilton L. Renal myogenic response: kinetic attributes and physiological role. *Circ Res* 2002;90:1316–24.
 113. Farasat SM, Valdes C, Shetty V, Muller DC, Egan JM, Metter EJ, et al. Is longitudinal pulse pressure a better predictor of 24-hour urinary albumin excretion than other indices of blood pressure? *Hypertension* 2010;55:415–21.
 114. Elkayam U, Ng TMH, Hatamizadeh P, Janmohamed M, Mehra A. Renal vasodilatory action of dopamine in patients with heart failure: magnitude of effect and site of action. *Circulation* 2008;117:200–5.
 115. Schultz HD, Pisarri TE, Coleridge HM, Coleridge JC. Carotid sinus baroreceptors modulate tracheal smooth muscle tension in dogs. *Circ Res* 1987;60:337–45.