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Review

Heart failure as an autonomic nervous system dysfunction

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Summary In heart failure, it has been recognized that the sympathetic nervous system (SNS) is activated and the imbalance of the activity of the SNS and vagal activity interaction occurs. The abnormal activation of the SNS leads to further worsening of heart failure. Many previous clinical and basic studies have demonstrated that the abnormal activation of the SNS is caused by the enhancement of excitatory inputs including changes in: (1) peripheral baroreceptor and chemoreceptor reflexes; (2) chemical mediators that control sympathetic outflow; and (3) central sites that integrate sympathetic outflow. In particular, the abnormalities in central SNS regulation due to the renin angiotensin system–oxidative stress axis have recently been in focus. In the treatment of heart failure, the inhibition of the activated SNS, such as with beta-blockers and/or exercise training, is important. Furthermore, many experimental studies have demonstrated that vagal stimulation has beneficial effects on heart failure, and recently several clinical studies have also demonstrated that vagal stimulation is a possible novel therapy for heart failure. In conclusion, we must recognize that heart failure is a complex syndrome with an autonomic nervous system dysfunction, and that the autonomic imbalance with the activation of the SNS and the reduction of vagal activity should be treated.

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Introduction

The sympathetic nervous system (SNS) has a wide variety of cardiovascular actions, including heart rate acceleration, increase in cardiac contractility, reduction of venous capacitance, and constriction of resistance vessels [1,2]. On the contrary, the vagal activity affects the cardiovascular system by slowing heart rate [3]. The cardiac sympathetic nerve fibers are located at sub-epicardium and travel along the major coronary arteries representing the predominant autonomic component in the ventricles [1,2]. The parasympathetic fibers run with the vagal nerve at sub-endocardium after it crosses the atrial–ventricular groove and are mainly present in the atrial myocardium and less abundantly in the ventricular myocardium [4]. The sympathetic outflow to the heart and peripheral circulation is regulated by cardiovascular reflex [1,2]. Afferent fibers are usually carried toward the central nervous system by autonomic nerves, whereas efferent fibers travel from the central nervous system toward different organs either in autonomic or somatic nerves [1,2]. The main reflex responses originate from aortic arch and carotid baroreceptors (SNS inhibition), cardiopulmonary baroreceptors (diverse reflexes including the Bezold–Jarisch reflex, SNS inhibition), cardiovascular-low threshold poly-modal receptors (SNS activation), and peripheral chemoreceptors (SNS activation) [4].

This article reviews the autonomic imbalance of the activation of the SNS and the reduction of vagal activity, which is known to lead to further worsening of the prognosis for heart failure. Furthermore, in this article, we focus on the recent concept of treatments targeting autonomic nervous system dysfunction.

Sympathetic hyperactivity in heart failure – clinical research

In systolic dysfunction, neuronal and humoral hyperactivity occur to preserve cardiac output [1,2]. The neuronal response is the activation of the SNS and the reduction of vagal activity, and the humoral response is the increase in secretion of certain hormones, such as the renin–angiotensin–aldosterone axis [5]. In heart failure with preserved left ventricular ejection fraction (diastolic heart failure), there is limited information regarding chronic SNS activation [6]. However, the findings of a recent study indicate that, in patients with hypertension, SNS hyperactivity (increased muscle sympathetic nerve traffic) may contribute to the development of left ventricular diastolic dysfunction and accounts for the increased cardiovascular risk [7]. The SNS hyperactivity observed in heart failure is closely related to abnormalities in cardiovascular reflexes [1,2]. The sympathoinhibitory cardiovascular reflexes such as the arterial baroreceptor reflex

are significantly suppressed, whereas the sympathoexcitatory reflexes, including the cardiac sympathetic afferent reflex and the arterial chemoreceptor reflex, are augmented [8]. These abnormalities in cardiovascular reflexes are considered to increase the activity of the SNS in heart failure, and heart failure due to left ventricular systolic dysfunction has long been considered a state of generalized activation of the SNS to alter cardiac and peripheral hemodynamics that is initially appropriate, but ultimately pathological [2].

However, it is now recognized that: (1) the time course and magnitude of the activation of the SNS are target organ-specific, not generalized, and independent of ventricular systolic function; and (2) human heart failure is characterized by rapidly responsive arterial baroreflex regulation of muscle sympathetic nerve activity (MSNA), attenuated cardiopulmonary reflex modulation of MSNA, a cardiac sympathoexcitatory reflex related to increased cardiopulmonary filling pressure, and by individual variation in nonbaroreflex-mediated sympathoexcitatory mechanisms, including coexisting sleep apnea, myocardial ischemia, obesity, and reflexes from exercising muscle [2] (Fig. 1). Thus, the activation of the SNS in the setting of impaired systolic function reflects the net balance and interaction between appropriate reflex compensatory responses to impaired systolic function and excitatory stimuli that elicit adrenergic responses in excess of homeostatic requirements [2].

In human heart failure, a previous study has demonstrated that significant increases in internal jugular venous spillover of metabolites of norepinephrine and epinephrine, with a positive correlation between brain norepinephrine turnover and cardiac norepinephrine spillover [2]. These results suggest that activation of noradrenergic neurons projecting from the brain stem mediates the activity of the SNS, and that the central abnormalities have the possibility to activate the SNS in heart failure. The mechanisms in which the central abnormalities occur in heart failure have not been fully determined in clinical studies, and it has not been also fully determined whether the central abnormalities are caused by neuronal input or humoral factors. Further clinical novel studies are necessary.

Sympathetic hyperactivity in heart failure – basic research

Experimental models of heart failure, together with clinical data, have solidly established that sympathoexcitation and an abnormal cardiovascular reflex function contribute to the activation of the SNS in heart failure [9]. In animal studies, the primary mechanism in the activation of the SNS is also the reduced sensitivity of various sympathoinhibitory reflexes (e.g. arterial baroreflex and cardiopulmonary reflexes) [10]. Furthermore, circulating and local hormonal factors [angiotensin II, nitric oxide

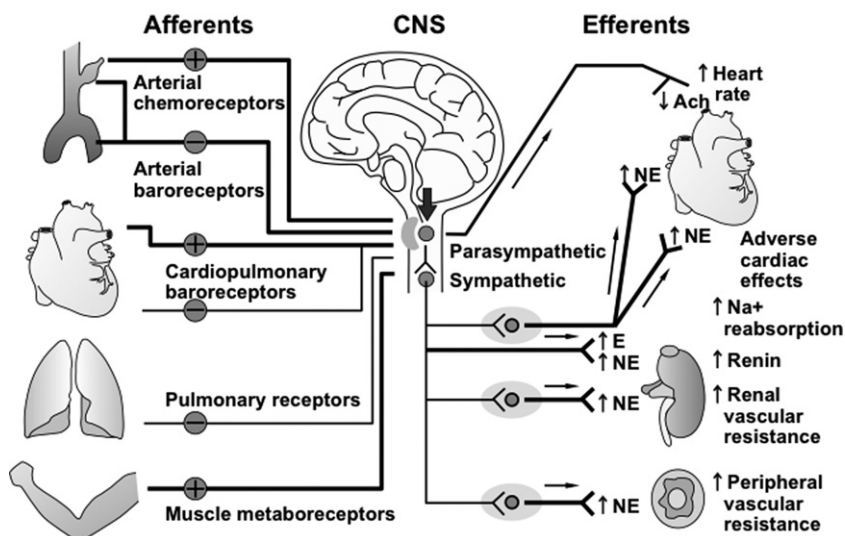


Figure 1 Mechanisms of the activation of the sympathetic nervous system in heart failure (modified from reference [2]). Afferent inputs from the arterial chemoreceptors, cardiopulmonary baroreceptors, and muscle metaboreceptors are activated, and afferent inputs from arterial baroreceptors, ventricular mechanoreceptors, and pulmonary receptors are inhibited. Central excitatory mechanisms are activated. Efferent mechanisms increase norepinephrine (NE) release and alter NE uptake. Ach, acetylcholine; CNS, central nervous system; E, epinephrine.

(NO), reactive oxygen species (ROS), arginine vasopressin, endothelin-1, atrial natriuretic peptide, prostaglandins, and aldosterone] are considered to modulate sympathetic outflow at several sites in the central nervous system. In addition, more recent data show direct central effects of pro-inflammatory cytokines on the activity of SNS [10–14].

The central nervous system receives inputs from a variety of sources in the body and activates mechanisms that play a major role in progressive cardiac remodeling and dysfunction [15]. For example, it has been demonstrated that the angiotensin II and aldosterone produced locally in the brain affect SNS activation and progression of systolic heart failure [16]. Angiotensin II type 1 receptors are found throughout the central nervous system and are expressed to a high degree in areas of the hypothalamus and medulla, which regulate sympathetic outflow [17]. It has already been demonstrated that angiotensin II initiates a positive feedback mechanism leading to up-regulation of the angiotensin II type 1 receptor, nitric oxide inhibition, and increased production of superoxide anion through the action of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase, leading to increased sympathetic outflow and progression in heart failure [10,13,14,18]. Previous studies have shown increases in angiotensin II type 1 receptor protein, mRNA, and angiotensin II binding in the rostral ventrolateral medulla (RVLM) and the nucleus tractus solitarius (NTS) in rabbits and rats with heart failure [10,19,20]. Furthermore, The balance between angiotensin-converting enzyme (ACE) and its homolog ACE2 or between angiotensin II type 1 and 2 receptor in the brain may be an important determinant of sympathoexcitation in heart failure [10,19,21,22]. Especially, in the brain, RVLM is well known as a vasomotor center, and it is well established that the angiotensin II type 1 receptor-induced ROS via NAD(P)H oxidase in the RVLM activates the SNS through the transcriptional pathways [12,13]. These mechanisms in the RVLM are also considered

to play a major role in activating the SNS in heart failure [10,14,19,20]. The angiotensin II type 1 receptor-induced ROS via NAD(P)H oxidase in the RVLM might be a novel target of therapy for heart failure through sympathoinhibition.

Parasympathetic dysfunction in heart failure

Acute myocardial ischemia represents a very useful model for a clear representation of what may appear as a complex relationship between sympathetic and vagal activity. The sensory endings of both vagal and sympathetic afferent fibers are mechanoreceptors and are thereby stimulated by the mechanical stretching associated with cardiac dilation [4]. Indeed, when the heart dilates, vagal and sympathetic afferent cardiac fibers increase their firing, and this afferent sympathetic excitation leads to the tonic and reflex inhibition of cardiac vagal efferent activity [4]. This phenomenon can be expected to occur whenever the heart dilates in heart failure probably due to the systolic dysfunction. In cases of diastolic dysfunction in which the heart does not dilate, the mechanisms in which the vagal activity is reduced have not been fully determined.

Therapy – sympathoinhibition

Beta-blockers can be broadly classified into generations: (1) first generation, which are nonselective and competitively block both the beta1- and beta2-receptors (propranolol, nadolol, timolol); (2) second generation, with much higher affinity for the beta1- than for the beta2-receptor (atenolol, metoprolol, bisoprolol); and (3) third generation, which may be selective (celiprolol, nebivolol) or nonselective (bucindolol, carvedilol, labetalol) but all cause peripheral vasodilation mediated via alpha1-receptor blockade (bucindolol, carvedilol, labetalol), beta2-receptor agonism

(celiprolol), or nitric oxide synthesis (nebivolol) [23]. Among all beta-blockers, bisoprolol (except in the USA), carvedilol, and metoprolol succinate (except in Canada) are almost universally approved for the treatment of chronic heart failure [24–29]. Chronic beta-blocker therapy improves left ventricular performance and reverses left ventricular remodeling, reduces risk of hospitalization, and improves survival [24–29].

In the Veterans Administration Cooperative Study, the patients with heart failure receiving the alpha1-blocker, prazosin, experienced worse outcomes than did those receiving the combined vasodilator therapy of hydralazine and isosorbide dinitrate [30]. Chronic use of prazosin has been reported to increase catecholamine levels, diminishing any potentially beneficial action mediated through inhibition of the alpha1-receptor [31]. In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study (ALLHAT collaborative), the other alpha1-blocker, doxazosin, was terminated early because of the higher heart failure incidence [32].

Central alpha2 receptor has been considered to be a possible target of treatment for heart failure, because the excitation of the central alpha2 receptor inhibits the activation of the SNS [33]. Clonidine is a centrally acting agent with alpha2-agonist actions. In modest doses of clonidine, it significantly attenuates cardiac and renal sympathetic tone in patients with heart failure [34]. Interestingly, chronic clonidine administration exerted marked sympathoinhibitory effects without further clinical deterioration in a small and short-term clinical study [34]. Large clinical trials are needed to evaluate the benefits. The other centrally acting sympathoinhibitory agent, moxonidine, acts through both alpha2- and imidazoline receptors [35]. However, in clinical trials, moxonidine led to increased mortality [36].

Angiotensin II and aldosterone production enhance the release and inhibit the uptake of norepinephrine at nerve endings [37]. ACE inhibitors have a predictable effect in increasing plasma renin and decreasing angiotensin II and aldosterone levels, whereas norepinephrine and vasopressin reduction is attributed to the hemodynamic improvement [38]. It should be determined whether angiotensin II type 1 receptor blockers have also the beneficial effects on the sympathetic hyperactivity in heart failure or not. Plasma aldosterone levels may be elevated as high as 20-fold in patients with heart failure, primarily due to increased production by the adrenal glands following stimulation by the high plasma angiotensin II concentrations. A previous large clinical trial has already shown the benefit with aldosterone antagonists in heart failure patients and this may be partially related to their effect on norepinephrine [39].

Exercise intolerance is a characteristic of patients with chronic heart failure, and skeletal myopathy contributes to the limitation of functional capacity in heart failure [1,2]. The activation of SNS and myogenic reflex engagement moderate the heart and muscle vasculature to maintain adequate blood pressure during exercise [40]. However, abnormal activation of the SNS contributes to the skeletal myopathy seen in heart failure, because SNS-mediated vasoconstriction at rest and during exercise restrains muscle blood flow, arteriolar dilation, and capillary recruitment, leading to underperfusion, ischemia, release of ROS, and

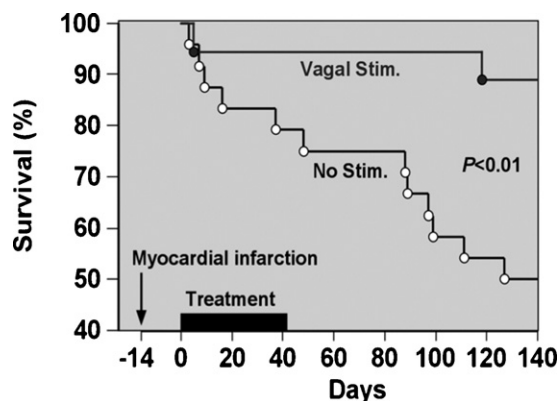


Figure 2 Effect of vagal nerve stimulation (Stim.) on survival curves of rats with heart failure treated with sham and vagal stimulation. Treatment started 14 days after coronary artery ligation. Vagal stimulation significantly improved survival rate (modified from reference [45]).

chronic inflammation [41]. Interestingly, current evidence suggests that exercise training improves central hemodynamics, peripheral muscle function, and symptoms and reduces the activity of the SNS even in patients treated with beta-blockers [42]. The HF-ACTION (Heart Failure – A randomized Controlled Trial Investigating Outcomes of exercise training) study, the first large, randomized, controlled trial to evaluate the effects of exercise training in heart failure patients, demonstrated that exercise training is safe and offers clinical benefits in this patient population [43]. The mechanisms for these beneficial effects of exercise in heart failure patients proposed include: (1) improvement in arterial and chemoreflex control; (2) significant reduction in central sympathetic outflow; (3) correction of central nervous system abnormalities; (4) increase in peripheral blood flow; (5) reduction of circulating cytokines; and (6) increase in muscle mass [44]. Experimental evidence suggests that the exercise training-induced beneficial effects on autonomic activity in heart failure may be due to an up-regulation in central antioxidative mechanisms and suppressed central pro-oxidant mechanisms [21].

Therapy – vagal stimulation

Chronic electrical vagal stimulation has been assessed in several animal studies. Rats with heart failure post myocardial infarction randomized to vagal stimulation showed significant improvement in left ventricular hemodynamics and decreased mortality from 50% to 14% in 140 days [45] (Fig. 2). In another study, therapy with vagal nerve electrical stimulation combined with beta-blockade improved left ventricular systolic function beyond that seen with beta-blockers alone [46]. More recently, Zhang et al. demonstrated that animals in the vagal stimulation group had significantly lower left ventricular end-diastolic and end-systolic volumes and higher left ventricular ejection fraction [47]. These experimental studies suggest that chronic vagal stimulation might have significant positive effects in the failing heart and heart failure. Interestingly, they also suggest the important concept that the mechanism(s) underlying the

protective effect of vagal stimulation involve something at least in part independent of the heart rate slowing.

In several clinical studies, favorable findings on quality of the New York Heart Association class, quality of life, and 6 min walk test were confirmed and a significant decrease in left ventricular end-systolic volume and a significant increase in left ventricular ejection fraction are indicated [48,49]. A large controlled multicenter study for USA and Europe is expected to provide soon a more precise definition of the role of vagal stimulation in heart failure.

Summary and future prospects

In heart failure, it has been recognized that autonomic nervous system dysfunction occurs. In the treatment of heart failure, the inhibition of the activated SNS, such as with beta-blockers and/or exercise training, is important. Furthermore, it has recently been demonstrated that vagal stimulation has beneficial effects on heart failure. We must recognize that heart failure is a complex syndrome with an autonomic nervous system dysfunction, and that the autonomic imbalance with the activation of SNS and the reduction in vagal activity should be focused on more in the aspects of treatment for heart failure. In this aspect, conservative pharmacological therapy is not sufficient, and device therapy and/or non-pharmacological therapy (exercise training, Waon-therapy [50]) are necessary.

The mechanisms by which autonomic nervous system dysfunction occurs in heart failure have not been fully determined. Especially, the central abnormalities need further examination in clinical and basic research. How does the brain "recognize" the condition of "heart failure"? What is the input into the brain, neuronal or humoral factors? The answers to these questions will contribute to a new and novel concept for the treatment of heart failure, "brain is a major target in the treatment of heart failure through sympathoinhibition".

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