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# Chronic heart failure: a disease of the brain

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## Abstract

The underlying mechanism for clinical and biochemical manifestations of chronic heart failure (HF) may be due in part to neurohumoral adaptations, such as activation of the renin-angiotensin-aldosterone and sympathetic nervous systems in the periphery and the brain. Internet search and discussion with colleagues are the methods for this study. Since chronic HF is associated with autonomic imbalance with increased sympathetic nerve activity and a withdrawal of parasympathetic activity, it may be considered a brain disease. This phenomenon may be the result of an increased systemic and cerebral angiotensin II signaling because plasma angiotensin II is increased in humans and animals with chronic HF. The increase in angiotensin II signaling enhances sympathetic nerve activity through actions on both central and peripheral sites during chronic HF. Activation of angiotensin II signaling in different brain sites such as the paraventricular nucleus (PVN), rostral ventrolateral medulla (RVLM), and area postrema (AP) may increase the release of norepinephrine, oxidative stress, and inflammation leading to increased cardiac contractility. It is possible that blocking angiotensin II type 1 receptors decreases sympathetic nerve activity and cardiac sympathetic afferent reflex when therapy is administered to the PVN. The administration of an angiotensin receptor blocker by injection into the AP activates the sympatho-inhibitory baroreflex indicating that receptor blockers act by increasing parasympathetic activity. In chronic HF, in peripheral regions, angiotensin II elevates both norepinephrine release and synthesis and inhibits norepinephrine uptake at nerve endings, which may contribute to the increase in sympathetic nerve activity. Increased circulating angiotensin II during chronic HF may enhance the sympatho-excitatory chemoreflex and inhibit the sympatho-inhibitory baroreflex resulting in worsening of HF. Increased circulating angiotensin II signaling can directly act on the central nervous system via the subfornical organ and the AP to increase sympathetic outflow resulting in to neurohumoral dysfunction, resulting in to heart failure.

**Keywords** Cardiac failure · Hypertrophy of heart · Neurohumoral dysfunction · Brain-heart interactions

## Introduction

Heart failure (HF) results due to compensatory mechanisms utilized by the body in an attempt to adjust for a primary deficit in cardiac output [1, 2]. The underlying mechanism for clinical and biochemical manifestations of HF may be due in part to neurohumoral adaptations, such as activation of the renin-angiotensin-aldosterone and sympathetic nervous systems by the low-output state. These can contribute to vasoconstriction for maintenance of the systemic blood pressure for the perfusion of vital organs [1–4]. Metabolic and electrophysiologic disturbances may occur during restoration of cardiac output by increase in myocardial contractility and heart rate and expansion of the extracellular fluid volume in an attempt to restore the cardiac output under influence of sympathetic and parasympathetic nervous system [3–6]. The sympathetic nervous system has a wide variety of cardiovascular actions, including heart rate acceleration, increase in cardiac contractility, reduction of venous capacitance, and constriction

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of resistance vessels [3, 4]. However, parasympathetic fibers run along the vagus nerve at sub-endocardium, after it crosses the atrial-ventricular grove and mainly present in the atrial myocardium, and its activity affects the cardiovascular system by reducing the heart rate. 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 [3, 4].

In HF, elevation in diastolic pressure is transmitted to the atria and to the pulmonary and systemic venous circulations; the ensuing elevation in capillary pressure promotes the development of pulmonary congestion and peripheral edema [1, 2]. The increase in peripheral resistance increases left ventricular afterload which may both directly depress cardiac function and enhance the rate of deterioration of myocardial function [1, 2]. These alterations in the cardiovascular function are associated with rise in catecholamines, cortisol, and angiotensin II with a decrease in parasympathetic activity due to decline in vagal control of the heart [1–4].Catecholamine-stimulated inflammation enhances angiotensin II signaling and cardiac contractility with increased heart rate which can worsen cardiovascular function and brain dysfunction. It is possible that, the induction of maladaptive fetal isoforms of proteins involved in contraction and hypertrophy might become worst due to inflammation [2–7]. There is evidence that vagal control of the heart is impaired early in HF with a parallel reduction in buffering of sympathetic outflow [6, 7]. It is also known that the time course and magnitude of sympathetic activation are target organ specific not generalized and independent of ventricular systolic function [5–7]. Nutrient deficiency either primary or due to cardiac cachexia can further damage the cardiomyocyte and neuronal dysfunction leading to worsening of HF [8–10]. In view of these facts, we examine the available evidence regarding brain dysfunction in chronic HF.

## Heart failure, a brain disease

Plasma angiotensin II is increased in humans and animals with chronic HF [3]. The increase in angiotensin II signaling enhances sympathetic nerve activity through actions on both central and peripheral sites during chronic HF. The major parts of the brain that are involved in chronic HF are the paraventricular nucleus (PVN); the rostral ventrolateral chronic HF may be considered a brain disease because it is associated with autonomic imbalance with increased sympathetic nerve activity and a withdrawal of parasympathetic activity [3, 4]. It is possible that sympathetic activation 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. These observations pose the possibility of an updated model of cardiovascular neural regulation in chronic HF due to ventricular systolic dysfunction with implication for diagnosis, therapy, and evolving new therapies [6, 7].Many previous clinical and basic studies have demonstrated that the abnormal activation of the sympathetic nervous system is caused by the enhancement of excitatory inputs including changes in peripheral baroreceptor and chemoreceptor reflexes, chemical mediators that control sympathetic outflow, and central sites that integrate sympathetic outflow [6, 7]. The abnormalities in central sympathetic nervous system regulation due to the renin angiotensin system-oxidative stress axis have recently been of great interest. The clinical benefits of ACE-I or ARB on HF may be by central sympathetic nervous system regulation by inhibiting renin-angiotensin system-oxidative stress which could be due to antioxidant activity and class effects. The abnormal activation of the sympathetic system leads to further worsening of HF. Therefore, treatment of HF, by inhibition of the activated sympathetic nervous system, with beta-blockers and/or exercise training, is important. It is clear from several studies that HF is a complex syndrome with an autonomic nervous system dysfunction and that the autonomic imbalance with the activation of the sympathetic nervous system and the decline of vagal activity should be treated.

This phenomenon may be the result of an increased systemic and cerebral angiotensin II signaling, since medulla (RVLM), the caudal ventrolateral medulla (CVLM), the area postrema (AP), the hypothalamus (HPT), and the nucleus of the solitary tract (NTS) (Fig. 1).

Angiotensin II signaling is enhanced in different brain sites such as the PVN, RVLM, and AP. Blocking angiotensin II type 1 receptors may decrease sympathetic nerve activity and cardiac sympathetic afferent reflex when therapy is administered to the PVN (Fig. 2).The administration of an angiotensin receptor blocker by an injection into the AP activates the sympatho-inhibitory baroreflex indicating that receptor blockers act by increasing parasympathetic activity. In chronic HF, in peripheral regions, angiotensin II elevates both norepinephrine release and synthesis and inhibits norepinephrine uptake at nerve endings, which may contribute to the increase in sympathetic nerve activity. Increased circulating angiotensin II during chronic HF may enhance the sympatho-excitatory chemoreflex and inhibit the sympatho-inhibitory baroreflex resulting in worsening of HF. It is possible that increased circulating angiotensin II can directly act on the central nervous system via the subfornical organ and the AP to increase sympathetic outflow. Inhibition of angiotensin II formation and its type 1 receptor by drug therapy has been shown to have beneficial effects in patients with chronic HF [3, 4].

The autonomic imbalance is associated with receptor alterations, which may have profound effects on cardiomyocyte biology and function [4]. In patients with HF with a dilated left ventricle, inhibition of the sympathetic drive to the heart through β-receptor blockade and increase in parasympathetic

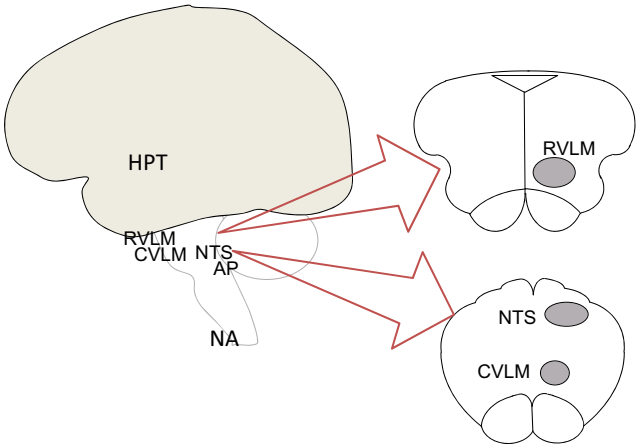


**Fig. 1** Locations of the rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), area postrema (AP), hypothalamus (HPT), and nucleus of the solitary tract (NTS) (modified from Google images)

activity via vagal stimulation has become a standard component of therapy. Beta-blockers are quite effective in inhibiting the ventricular structural remodeling process and prolonging life among these patients. In this connection, several devices for selective modulation of sympathetic and vagal activity have recently been developed in an attempt to alter the natural history of HF. However, the amount of optimal sympathetic and parasympathetic activity to be maintained in HF is not clearly known. In patients with HF, a profound decrease in adrenergic support with excessive blockade of the sympathetic nervous system may result in adverse outcomes such as stroke, acute coronary syndrome, and sudden cardiac death (SCD).

There is a need to find out the contributory role of the autonomic functional alterations on the course of HF. Milovanovic et al. use excellent techniques to assess autonomic nervous system activity, and the evidence for clinical effectiveness of pharmacological and device interventions was discussed during the Neurocard 2014 conference, held from Oct 16 to 18, 2014 in Belgrade, Serbia. The potential future role of autonomic nervous system modifiers in the management of HF is awaited. However, diet and lifestyle factors can have significant influence on brain function and predispose heart disease [8–10]. Further studies have emphasized that following an injury to the cardiomyocyte during an ischemic attack, an intense inflammatory response occurs, which leads to further injury and progression of the cardiac dilatation and dysfunction in association with increased consumption of antioxidant nutrients to antagonize oxidative stress [5–10] (Fig. 3). Cell debris released during tissue injury, such as extracellular ATP, induces conformational changes in components of inflammation, such as the cryopyrin

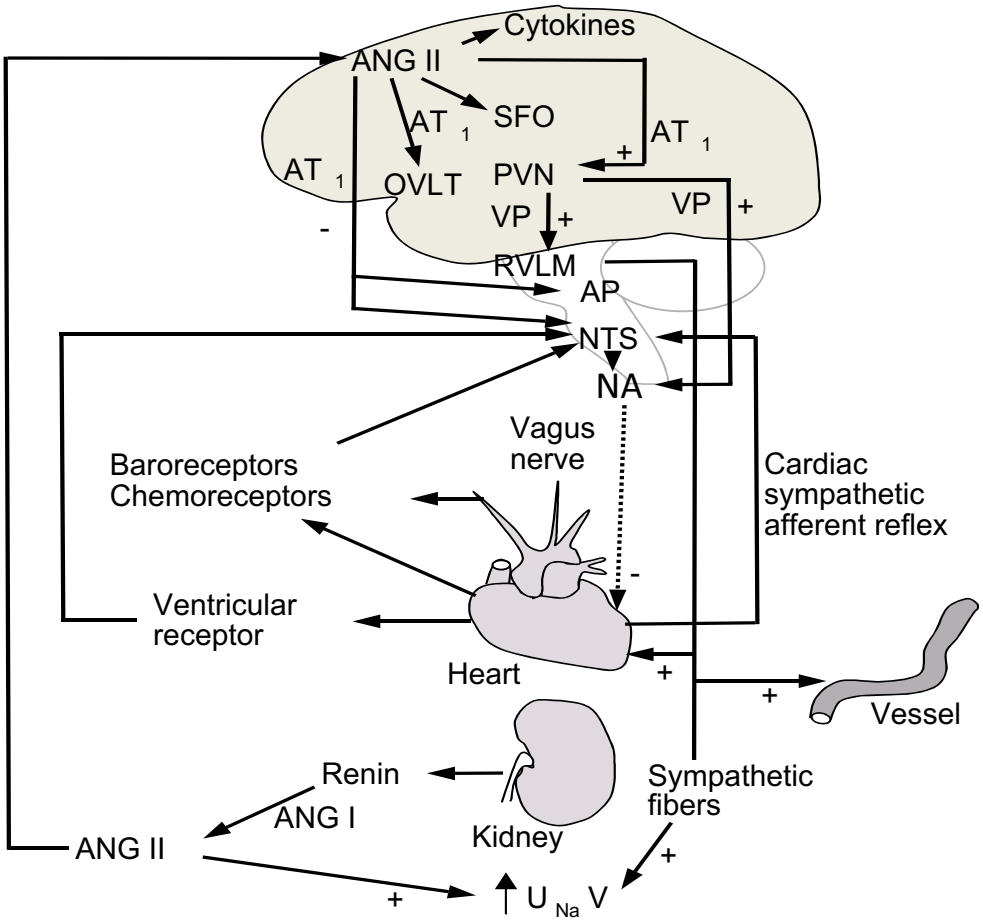


**Fig. 2** Central angiotensin II stimulates vasopressin (VP) and cytokines, which stimulate rostral ventrolateral medulla (RVLM) and nucleus tractus solitarius (NTS) area postrema (AP), leading to autonomic imbalance in chronic heart failure (modified from Google image)

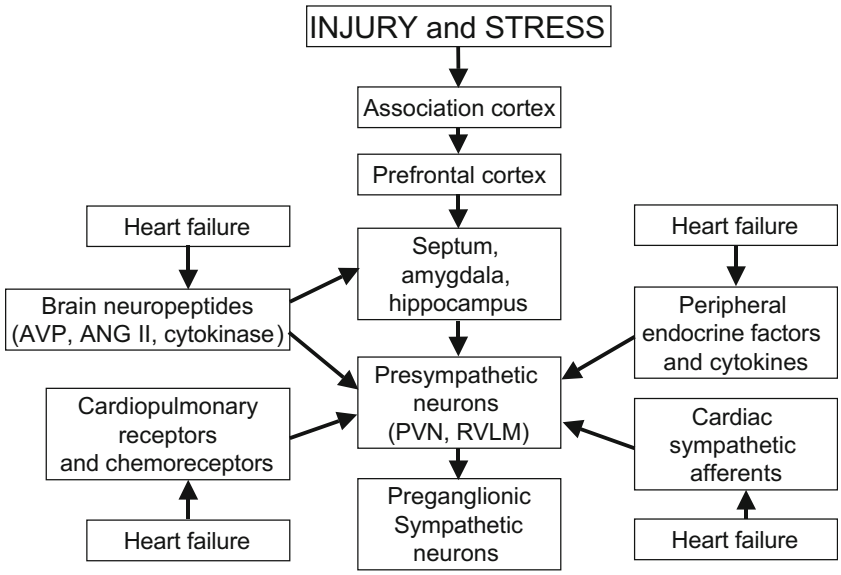


**Fig. 3** Stress during infarction stimulates cortex and other areas of brain causing heart failure, which stimulates brain neuropeptides and peripheral endocrine factors which further stimulate the brain causing worsening of heart failure (Google image)

Nlrp3, a sensor protein, the adaptor protein ASCs that trigger activation of caspase-1, and effector proteins which are pro-inflammatory [5, 10].

Vagal nerve stimulation in experimental study has revealed cytokine modulation and nitric oxide elaboration [11]. Chronic vagal stimulation has been used for the treatment of low ejection fraction HF. Results of the neural cardiac therapy for HF (NECTAR-HF) are a randomized controlled trial [12, 13] where patients were randomized in a 2:1 ratio to receive vagus nerve stimulation therapy (VNS ON) or control (VNS OFF) for a 6-month span. Of the 96 implanted patients, 87 had paired datasets for the primary endpoint. Change in LVESD from reference to 6 months was $-0.04 \pm 0.25$ cm in the therapy group compared with $-0.08 \pm 0.32$ cm in the control group ($P = 0.60$). Despite no other benefits observed, there were statistically significant improvements in quality of life gauged by the Minnesota Living with Heart Failure Questionnaire ($P = 0.049$), the New York Heart Association class ($P = 0.032$), and the SF-36 Physical Component ($P = 0.016$) in the therapy group. In conclusion, VNS as delivered in HF patients failed to demonstrate a significant beneficial effect on primary and secondary endpoint measures of cardiac remodeling and functional capacity in symptomatic HF patients. However, quality-of-life measures showed significant improvement. Thus, it is clear that controlling brain-related mechanisms has a better role among patients of HF with preserved ejection fraction compared to those with very low ejection fraction [11–17].

## Arterial baroreflex sensitivity

Secondly, HF is characterized by rapidly responsive arterial baroreflex regulation of muscle sympathetic nerve activity, attenuated cardiopulmonary reflex modulation of muscle sympathetic nerve activity, and a cardiac sympatho-excitatory reflex related to increased cardiopulmonary filling pressure. There may be an individual variation on baroreflex-mediated sympatho-excitatory mechanisms, including coexisting sleep apnea, myocardial ischemia, obesity, and reflexes from exercising muscles in patients with HF [16, 17]. It is interesting that modulation of parasympathetic activation as potential therapy for HF has received some attention. The arterial baroreflex regulates blood pressure and heart rate through sensing mechanical alteration of arterial vascular walls by baroreceptor terminals in the aortic arch and carotid sinus. There are aortic baroreceptor neurons in the nodose ganglion (NG), which serve as the main afferent component of the arterial baroreflex. Clinical and experimental studies indicate that the sensitivity of arterial baroreflex is blunted in the HF, which is a possible risk factor for SCD. In HF, functional alterations of baroreceptor neurons are involved in the arterial baroreflex dysfunction, and circulating angiotensin II (Ang II) and local Ang II concentration in the nodose ganglion is elevated, with overexpression of AT1R mRNA and protein in the ganglion [17]. There is impairment of the arterial baroreflex and Ang II-superoxide-NFκB signaling pathway that regulates the neuronal excitability of aortic baroreceptors through influencing the expression and activation of $Na_v$ channels in aortic baroreceptors. Thus, arterial baroreflex sensitivity in the CHF could be a new target in the treatment of HF.

Chronic baroreflex activation therapy (BAT) on left ventricular (LV) function and chamber remodeling and the effects of long-term therapy on ventricular arrhythmias and on potential modifiers of the HF state that include maladaptations of both the nitric oxide and β-adrenergic receptor signal transduction pathways are important in HF [16]. The results of the preclinical studies conducted to date have shown that in dogs with advanced HF, monotherapy with BAT improves global LV systolic and

diastolic function and partially reverses LV remodeling both globally and at cellular and molecular levels. In addition, BAT therapy was shown to markedly increase the threshold for lethal ventricular arrhythmias in dogs with chronic HF. These benefits of BAT support the continued exploration of this therapeutic modality for treating patients with chronic HF and those with increased risk of sudden cardiac death.

Further studies indicate that donepezil, an acetylcholinesterase inhibitor used against Alzheimer disease, can also provide benefits to HF patients [14]. In a recent study in patients with high level of BNP, the BNP levels decreased after administration of donepezil (116.39 ± 76.58 pg/mL at baseline to 82.24 ± 46.64 pg/mL at first evaluation; $P = 0.011$) with the tendency to be reduced in the follow-up period [14]. Donepezil seemed to be safe in patients with dementia without symptomatic heart disease and significantly decreased plasma BNP levels in patients with subclinical chronic HF. In a cohort consisting of 7073 subjects (mean age, 79 years) from the Swedish Dementia Registry with the diagnoses of Alzheimer's dementia, follow-up after 503 days, 831 subjects in the cohort suffered MI or died [15]. Those patients who were taking the highest recommended ChEI doses (donepezil, 10 mg; rivastigmine, > 6 mg; galantamine, 24 mg) had the lowest risk of MI (HR, 0.35; 95% CI, 0.19–0.64), or death (HR, 0.54; 95% CI, 0.43–0.67) compared with those who had never used ChEIs. Cholinesterase inhibitor use was associated with a reduced risk of MI and death in a nationwide cohort of subjects diagnosed with Alzheimer's dementia. These associations were stronger with increasing ChEI dose indicating that brain-mediated mechanisms appear to be important in the pathogenesis of MI and death. The two clinical trials suggest that anti-Alzheimer drugs are effective against chronic HF and reduce a risk of cardiovascular death [14, 15].

Recently, defective disposal of misfolded proteins has been reported to be involved in the pathogenesis of neurodegenerative diseases, cystic fibrosis, and HF, which damage the cardiomyocyte in the same way as they do with neurons [18]. There are striking similarities between cardiomyocytes in patients with HF and neurons in patients with Alzheimer's disease, raising the possibility that some treatment approaches being developed for Alzheimer's may also help reverse the damage from HF. The damage in Alzheimer's disease involves a process of wear and tear on the brain; the same sort of wear and tear affects the heart, causing inflammation and HF. Neuronal networks represent physiological mechanisms, selected by evolution to control inflammation, that can be exploited for the treatment of inflammatory and infectious disorders which are basic causes of injury and inflammation in the cardiomyocytes [7, 11].

In the PARADIGM HF trial, the substantial beneficial effects of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril may be related to modulation of brain-body connections via neprilysin inhibition [19]. Neprilysin inhibition can enhance the availability of several endogenous protective vasoactive peptides, including neuregulin, natriuretic peptides, bradykinin, and adrenomedullin that are degraded by neprilysin [19, 20]. Combined inhibition of the renin–angiotensin system and neprilysin shows greater effects than using a single agent [19, 20]. Molecularly, LCZ696 includes moieties of valsartan and sacubitril, from which it is classified as an angiotensin receptor-neprilysin inhibitor (ARNI) [18–20]. The PARADIGM-HF investigators randomized over 8000 patients with depressed LV systolic function NYHA class II–IV to treatment with LCZ696 or enalapril on top of other evidence-based therapies. Patients who received the newer agent (LCZ696) compared with the one used earlier (enalapril) showed a 20% drop in cardiovascular (CV) death or HF hospitalization ($P < 0.001$) over 27 months. All-cause mortality also dropped by 20% ($P < 0.001$). It is proposed that above combined therapy may have increased the concentrations of brain-derived protective substances (vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin) antagonizing the neurohumoral overactivation responsible for HF [19, 20]. This robust finding provides strong support for an approach using multiple agents targeting brain-body connections for controlling neurohumoral overactivation. The efficacy of this (and any other) treatment could be further enhanced by chronotherapy in which central circadian clock controls metabolic and physiological function of the neuron cardiomyocytes. Omega-3 fatty acids and flavonoids that are abundant in the Mediterranean diet are known to work by activating nitric oxide signaling in the neurons as well as in other tissues, protecting the neurons and cardiomyocytes [21, 22]. Cellular deficiency of nutrients appears to be important in the adverse outcomes, particularly during cardiac cachexia [8–10]. Further studies showed that the Mediterranean diet can bring about improved cardiac autonomic function and prevent HF among high-risk patients with coronary artery disease [21, 22]. Hence, improving the nutritional status of these patients might further increase the efficacy of angiotensin receptor neprilysin inhibitor LC696 in the management of HF [23]. Alterations in receptor activation from this autonomic imbalance in HF may have a profound effect. In a population-based study among twins, consisting of 276 middle-aged men, time- and frequency-domain measures of HRV were calculated [21]. After adjusting for energy intake, other nutritional factors, shared genes, and common environment, a 1-unit higher score for Mediterranean food intake was significantly associated with 3.9 to 13% higher time- and frequency-domain HRV parameters, showing that Mediterranean diet can increase heart rate variability [21].The Indo-Mediterranean diet-heart study showed a positive association of an alpha linolenic-acid-rich diet with the circadian rhythm of cardiac events among 1000 high-risk patients including HF patients [22].

## Chronocardiology and heart failure

The Indo-Mediterranean diet heart study reported a significant decline in cardiac events in the second quarter of the 24-h scale in the Indo-Mediterranean diet group as compared to the control group and subgroups in the same group, indicating that the suprachiasmatic circadian clock appears to be important in the pathogenesis and management of HF [22].

In one study among patients with chronic HF, circadian variability of RR and QT intervals was altered because of neurohumoral activation and functional and structural remodeling of the heart. In order to evaluate the prognostic significance of circadian variability of the RR and QT intervals, 121 patients with stable chronic HF in sinus rhythm provided a 24-h Holter electrocardiogram [24]. During the follow-up span of 34 ± 17 months, 40 (33%) patients died of cardiac causes, 10 of which were sudden. As compared to survivors, patients who died of cardiac causes had reduced circadian variability of QT interval (10 ± 10 ms vs. 21 ± 13 ms) and a later maximum RR interval (4.1 ± 0.9 AM vs. 2.3 ± 2.1 AM) [23]. Patients with chronic HF may have decreased RR interval complexity and loss of its circadian rhythm, in addition to decreased frequency-domain RR interval variability and its abnormal circadian rhythm [25]. In another study, simultaneous analysis of Holter ECG and physical activity revealed that in patients with HF, sympathovagal balance shifted toward sympathotonic conditions and their physical activity could become subject to intrinsic ultradian dynamics of body's homeostasis [26].

SCD is a catastrophic event in cardiovascular disease. It has a circadian pattern prominent in the early morning, which has been thought to be due to a surge of sympathetic stimulation. In advanced HF with chronic sympathetic activation, SCD did not show a morning peak, suggesting that circadian sympathetic activation did not strongly influence these events [27]. It is known that spironolactone therapy given in addition to angiotensin-converting enzyme inhibitors improves survival in chronic HF. In order to evaluate the circadian effects of aldosterone blockade on autonomic tone and QT dispersion in chronic HF, 28 patients with NYHA class II to IV chronic HF received spironolactone (50 mg/day) and placebo for 4 weeks each in a double-blind crossover fashion. Spironolactone reportedly reduced heart rate and improved HRV and QT dispersion in chronic HF. Its effects were particularly prominent during the morning hours [28]. In a recent study, among patients with advanced HF (NYHA III but not NYHA II), nocturnal melatonin secretion was negatively correlated with NTproBNP, indicating involvement of the central circadian clock [29]. Hristova et al. have reported a circadian twist in echocardiographic myocardial function in the forenoon, indicating that time-adjusted therapy with pharmacological and nutraceuticals may be an additional approach for providing greater benefit because bioactivity of a therapy, determined by the suprachiasmatic central circadian clock, appears to be more important than bioavailability [30–32]. The brain-related mechanisms of sympathetic activation in heart failure are mediated by the renin-angiotensin system, nitric oxide, and pro-inflammatory cytokines [33–36]. Any dysregulation of the renin-angiotensin system and the vasopressinergic system may interact in enhancing cardiovascular disorders [34]. In an experimental study, beneficial effect of renal denervation on cardiac remodeling may be due to prevention of the downregulation of phosphoinositide 3-kinase/AKT/endothelial nitric oxide synthase signaling pathway [35]. The clinical implications are that renal denervation regulates the progression of atrial electrical and structural remodeling and suppresses the atrial fibrillation inducibility [35]. It is possible that atrial fibrillation and HF may be associated with a higher risk of mortality, and renal denervation might be an alternative therapeutic strategy in selected patients, particularly when medical therapy for HF with atrial fibrillation is ineffective.

In brief, chronic HF appears to be mediated by autonomic dysfunction, characterized by high sympathetic and low parasympathetic activity and neurohumoral activation. An increased systemic and cerebral angiotensin II signaling can enhance sympathetic nerve activity through actions on both central and peripheral sites during development of HF, which may influence different brain sites such as the PVN, the RVLM, and the AP as well as possibly, the circadian clock, leading to chronic HF. The role of neprilysin inhibitor in NYHA class IV HF alone needs further evaluation, preferably in a chronotherapeutic trial to develop more evidence regarding the role of brain function in patients with HF.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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