REVIEW ARTICLE

Heart and Brain Interaction and Autonomic Modulation in Heart Failure

Pattara Rattanawong MD[1], Vichai Senthong MD, FACC[2]

[1] Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[2] Cardiovascular Unit, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Neurocardiac axis connects the heart and brain through insular cortex, the anterior cingulate cortex, the prefrontal cortex, the amygdala, sympathetic nervous system inhibition reflex, and cardiopulmonary baroreceptors. Sympathetic over-activation and dysregulation of fluid homeostasis through the brain and neurocardiac axis is the important causes of left ventricular remodeling and symptom aggravation in HF. Modulation of autonomic nervous system including activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system are manifestations of the clinical syndrome of HF. Activation of neurocardiac axis, especially the sympathetic nervous system, and neurohumoral systems, the renin-angiotensin-aldosterone system, by impaired cardiac function, play a major role in the progression of HF. β-blockers have been well studied and have been reported to reverse ventricular remodeling and decrease mortality in patients with HF. In addition, vagal stimulation showed effectiveness and favorable results in animal studies and may have subjective benefits in HF patients.

Keywords: Heart failure; Autonomic nervous system

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Heart and brain interaction

Neurocardiology was first described in 1985 as the interaction between the cardiovascular and autonomic nervous systems (ANS) in pathological states[1]. The neurocardiac axis, a complex neural interaction consisting of the insular cortex, the anterior cingulate cortex, the prefrontal cortex, and the amygdala was later discovered[2,3]. Baroreflex sensitivity, ECG changes, and heart rate variability (HRV) are also important tools for understanding the influence of the autonomic system on the interaction of heart and brain activity[4]. Sympathetic nervous system inhibition reflex includes arterial baroreceptors, originate from aortic arch and carotid baroreceptors, and cardiopulmonary baroreceptors (Bezold-Jarisch reflex). Sympathetic nervous system activation reflex includes cardiovascular low threshold polymodal receptors and peripheral chemoreceptors (Figure 1)[5].

The Insular Cortex

The insular cortex is a major region of the cerebral cortex that plays a crucial role in interoceptive processing, including motor control, homeostasis, cardiac perception, social emotion, interoceptive awareness, and self-consciousness[6,7]. Moreover, it also modulates the central autonomic network by increasing autonomic sympathetic activity via the right hemisphere of the insular cortex, thus causing cardiovascular autonomic dysfunction[8,9]. Heart rate variability has been found to be lower in patients with right hemisphere stroke with reduced bilateral insula volumes. This could be explained by alterations in autonomic nervous system function[10,11]. These patients also had increased risk of arrhythmias and sudden death due to autonomic imbalance[12]. The stellate ganglia play a major role in tachyarrhyth mia following insular cortex infarction[13]. In rabbits, structural changes in stellate ganglia from chronic sympathetic activation have been found to cause arrhythmogenesis leading to ventricular and atrial arrhythmia as a result of chronic increases in sympathetic activity[14]. A T wave repolarization dispersion during stellate ganglia activation is a prognostic marker of ventricular tachyarrhythmia, myocardial infarction, and sudden cardiac death[15,16]. Moreover, atrial fibrillation, atrioventricular block, ectopic beats, sinus bradycardia, an inverted T wave, and sudden cardiac death were common in patients with a right insular lesion. This supports the hypothesis that damage to the insula directly or indirectly affects cardiac function.

The Brain Stem

The brain stem, including the external lateral

Correspondence to:

Senthong V.

Cardiovascular Unit, Department of Medicine, Faculty of Medicine, Khon Kean University, Khon Kaen 40002, Thailand.

Phone: +66-43-363664

Email: vichais@kku.ac.th

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parabrachial nucleus in the pons and rostral ventrolateral medulla, plays a role in cardiac sympathetic stimulation through excitatory cardiovascular reflexes[17,18]. The medullary 5-hydroxytryptamine (5-HT) system in the brain stem creates an inherent susceptibility that could be exploited by exogenous stressors to further increase the risk of a life-threatening cardiorespiratory event[19]. Brain stem lesions are associated with cardiac autonomic dysfunction causing ventricular arrhythmias, myocardial infarction, bradycardias, and sudden death[3,19-21].

Prefrontal Cortex

Resting high-frequency HRV, which can be used to address the interaction of cardiovascular changes with the ANS modulation, can fluctuate with the resting state of prefrontal cortex neural activity[22]. The prefrontal cortex area is the region of distinct interest involved in ANS. Resting high-frequency HRV is more related to localized connectivity than the global resting state activity of intrinsic brain networks. Therefore, injury to brain regions such as the prefrontal cortex may consequently impair cardiac autonomic modulation[13]. Valenza et al. recently reported a study of cardiovascular autonomic responses to emotional and arousal processing at the prefrontal cortex and amygdala infract. The study showed significant arousal-dependent changes of electroencephalographic dynamics and instantaneous heart rate throughout the prefrontal cortex during positive and negative visual emotional elicitation stimuli[23].

Hippocampus

The hippocampus is significantly vulnerable to ischemic insult under ultralow flow cardiopulmonary bypass from ischemic stress[24]. Moreover, significant changes following early cerebral hyperperfusion and delayed cerebral hypoperfusion in the cortex, thalamus, hippocampus, and amygdala/piriform complex were reported in rats [52]. Cardiovascular risk factors, including hypertension, myocardial infarction, atrial fibrillation, and heart failure (HF), are associated with large hemispheric brain infarcts, while hippocampal infarcts are associated with large hemispheric brain infarcts, HF, and altered cardiovascular index as assessed in a postmortem study. This is likely due to the fact that large hemispheric infarcts, cardiovascular disease, and hippocampal infarcts share common risk factors[25]. Furthermore, the hippocampus and other brain regions are significantly susceptible to cerebral ischemia and neuronal degeneration, leading to clinical syndrome of myocardial infarction and HF[13].

Autonomic System and the Heart

Autonomic nervous system manifestations of the clinical syndrome of HF include activation of the sympathetic nervous system (SNS) and inhibition of the parasympathetic nervous system (PNS)[26]. The branches of SNS and PSN consist of afferent, efferent, and interneuron fibers. Sympathetic nervous system fiber innervation originates from the right and left stellate ganglia then travel along with the epicardial vascular structures into the epicardium, myocardium, and end as sympathetic nerve terminals at the endocardium.

The parasympathetic nervous system originates in the medulla treaveling down to the base of the heart carried by the right and left vagus nerves. Both right and left vagus nerves then divide into the superior and inferior cardiac nerves, eventually merging at the postganglionic sympathetic neurons to form a plexus at the base of the heart which is called the cardiac plexus[27].

The SNS has two mediators: norepinephrine (NE) and epinephrine. These mediators are produced from two sources in the body: the sympathetic nerve ending (which releases NE directly to into synaptic cleft) and adrenal medulla (which releases epinephrine and NE into the circulation). Therefore, the total amount of catecholamine presented to the cardiac adrenergic receptors (AR) consists of circulating NE and epinephrine plus NE released from the sympathetic nerve terminals[28]. Moreover, epinephrine, which is released into the circulation by the adrenal medulla, affects both the myocardium and the peripheral vessels[29].

The adrenergic receptors control central and peripheral augmentation of the NE (primary sympathetic neurotransmitter) and epinephrine (primary adrenal medullary hormone). There are three types of ARs: the α1-AR, the α2-AR, and the β-AR[30]. There are two main ARs found in the heart: β-AR (90% of the total cardiac AR) and α1-AR (10% of the total cardiac AR[31]. Previous studies in vitro, in animals, and in humans have shown that α1-ARs control adaptive and protective effects in the cardiac myocyte as well as prevent pathological remodeling in HF[31,32]. In HF, the SNS is over-activated and catecholamine levels are elevated. β-ARs are also down regulated and dysfunctional[32]. The β-ARs in human heart consist of β1-AR, β2-AR, and β3-AR. In human myocardium, 75% to 80% of total β-AR density is β1-AR[33]. Sympathetic activation through cardiac β-AR increases heart rate, myocardial contractility, impulse activity, and pacemaker activity[34]. β3-AR is now a novel target for cardiomyopathy HF due to its differential expression in myocardium to mediate negative inotropic effect, lipolysis, and thermogenesis in adipose tissue[35].

Muscarinic and preganglionic nicotinic receptors were activated by acetylcholine, the neurotransmitter of PSN[36]. Stimulation of PSN decreases heart rate, however, with minimal effect on cardiac contractility. It also inhibits

NE released from the adrenergic nerve terminal[37]. Thus, muscarinic receptors in the myocardium map play an important role in sympathetic modulation in HF patients[38,39].

Autonomic system and heart failure

Activation of the neurohumoral systems by impaired cardiac function, especially the SNS and renin-angiotensin-aldosterone system, plays a major role in the progression of HF. Beside activation of the SNS, neurohumoral signal modulation also activates the central nervous system (CNS) and plays another role in cardiac function regulation. The circumventricular organ in the lamina terminalis in the forebrain area predominantly sense thirst and sodium intake, which then regulate volume status in HF. This organ in the lamina terminalis area lack off the blood-brain barrier and is, thus, able to capture the signals of circulating neuropeptides in serum[40].

The center for fluid-balance regulation and sympathetic excitation is located at paraventricular nucleus of the hypothalamus near the third ventricle in the forebrain area[41]. The paraventricular nucleus is composed of different neuronal subgroups which project to the posterior pituitary where they release neuro-humoral transmitters including adrenocorticotropic hormone and arginine vasopressin. These neuro-humoral transmitters affect sodium and fluid retention[42]. The paraventricular nucleus also regulates the sympathetic drive through the nucleus tractus solitarius, which transmit vagal and baroreceptor reflex information to the paraventricular nucleus through afferent projection neurons where parvocellular neurons in the paraventricular nucleus interpret these data and then modulate sympathetic nerve activity[43]. Sympathetic over-activation from these neural networks causes left ventricular remodeling, cardiac dysfunction, vascular tree vasoconstriction, and sodium and fluid retention through renin release[40].

The majority of the information regarding the role of the SNS in the progression and prognosis of HF came from studies conducted on subjects with dilated cardiomyopathy with reduced ejection fraction[44-49]. Activation of the SNS in response to myocardial injury includes increased release and decreased uptake of NE at the adrenergic nerve endings. This activation affects the heart, kidney, and peripheral vascular bed. Catecholamine amplifies ventricular contractility and heart rate to maintain cardiac output. Sympathetic activation also increases systemic vascular resistance leading to vasoconstriction and increased venous tone to increasing of ventricular preload and, thus, maintains blood pressure. Norepinephrine and angiotensin II aggravate sodium reabsorption at the proximal tubular, which results in sodium retention and volume expansion in HF.

Chronic sympathetic over-activation results in myocardial mass hypertrophy and enlargement of the left ventricular chamber via cardiac myocyte enlargement, interstitial growth, and myocardium remodeling[50,51]. Therefore, chronic catecholamine exposure causes toxicity to cardiac myocytes[52]. Stimulation of β1-ARs increases apoptosis via a cAMP-dependent mechanism, whereas stimulation of β2-ARs inhibits apoptosis via an inhibitory G-protein (Gi) pathway[53-56]. Previous studies have demonstrated that the sympathetic nerve endings are likely damaged by NE-derived free radicals[57], and the toxic effects of norepinephrine on the sympathetic nerve terminals may be prevented by antioxidant therapy[57,58]. This NE-mediated cell toxicity was found to be diminished by a β-AR blockade and mimicked by selective stimulation of the β-AR whereas α-ARs were relatively less apparent[59]. β-blockers have been well studied and have been reported to reverse ventricular remodeling[60,61] and decrease mortality in patients with HF[62-64]. Therefore, one of the three β-blockers proven to reduce mortality (bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or previous symptoms of HF with reduced ejection fraction[65].

Heart failure and the brain

The heart is closely related to the brain. Therefore, it stands to reason that the brain may play an important role in the progression of HF. Two of the most important causes of left ventricular remodeling and symptom aggravation in HF are sympathetic over-activation and dysregulation of fluid homeostasis through the brain[40]. Impaired systolic function with low cardiac output in HF patients can diminish autoregulation of cerebral blood vessels and, thus, reduce cerebral blood flow[66]. Moreover, reduced cerebral blood flow is associated with cognitive impairment and abnormal cerebral metabolism, which indicate poor outcomes in HF[40].

Vagal stimulation as an autonomic nervous system interventions in heart failure

Nowadays, the strategy for HF treatment has mainly focused on the recovery of cardiac function. Since the pathophysiology of HF is a systemic disease that affects the whole body involving cardiovascular insufficiency and activation of neurotransmitter hormones, current treatment strategies, which are limited to the heart, may be unsuccessful[40].

Recent experimental studies in animals have found that chronic vagal stimulation has significant benefits in cases of HF[67,68]. In clinical studies, improvement with regard to New York Heart Association functional classification, quality of life, and 6 min walk test were reported, as well as a significant decrease in left ventricular end-systolic volume and a significant increase in left ventricular ejection fraction[69,70]. A recent randomized controlled trial also

reported that quality of life, New York Heart Association functional classification, and 6-min walking distance were favorably affected. However, overall mortality, HF hospitalization, and left ventricular end-systolic volume index were not[71]. As of this writing, four vagal nerve stimulation trials have been completed (CardioFit, ANTHEM-HF, NECTAR-HF, INOVATE-HF) and none of these trials raised safety issues. However, their findings differed with regard to efficacy[70-73]. Interestingly, subjective outcomes, such as New York Heart Association functional classification and quality of life improved in all studies. With regard to objective outcomes, CardioFit and ANTHEM-HF showed a positive outcome on echocardiographic parameters (left ventricular ejection fraction) whereas NECTAR-HF and INOVATE-HF did not show any difference between the groups who received vagal nerve stimulation therapy and the control groups[71,73]. A major variation among the three trials is the applied vagus nerve stimulation parameters[74]. It is possible that the lower stimulation intensity used in NECTAR-HF was associated with only a small recruitment effect of the vagus nerve fibers, which are important for the heart rate lowering mechanism as well as the anti-remodelling effect[75,76]. To date, the reasons for the ability to transfer effectiveness and favorable results of vagus nerve stimulation that have been obtained in animal studies to clinical practice using similar vagus nerve stimulation parameters are not fully understood[74].

Summary

The heart and brain are connected through a neurocardiac axis consisting of the insular cortex, the anterior cingulate cortex, the prefrontal cortex, and the amygdala. The important causes of left ventricular remodeling and symptom aggravation in HF are sympathetic over-activation and dysregulation of fluid homeostasis through the brain and neurocardiac axis. Autonomic nervous system manifestations of the clinical syndrome of HF include activation of the SNS and inhibition of the PNS. Activation of neurohumoral systems by impaired cardiac function, especially the SNS and the renin-angiotensin-aldosterone system, play a major role in the progression of HF. β-blockers have been well studied and have been reported to reverse ventricular remodeling and decrease mortality in patients with HF. In addition, vagal stimulation may have subjective benefits in HF patients.

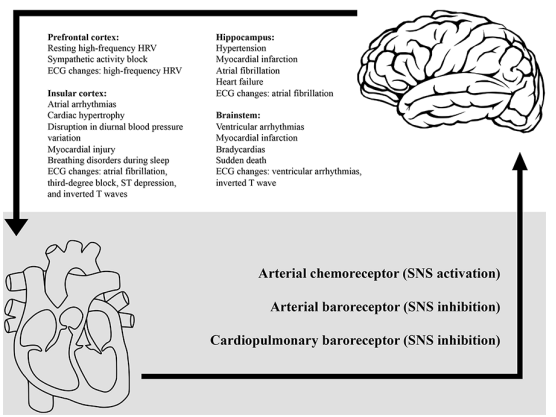

Figure 1. Heart and brain interaction (modified from reference (13) and (77)).

What is already known on this topic?

Modulation of the autonomic nervous system, including activation of the sympathetic nervous system and inhibition of the parasympathetic nervous system, are manifestations of the clinical syndrome of HF. Activation of the neurocardiac axis, especially the sympathetic nervous system, and neurohumoral systems, the renin-angiotensin-aldosterone system, by impaired cardiac function, play a major role in the progression of HF.

What this study adds?

β-blockers have been well studied and have been reported to reverse ventricular remodeling and decrease mortality in patients with HF. In addition, vagal stimulation showed effectiveness and favorable results in animal studies and may have subjective benefits in HF patients.

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Conflicts of interest

The authors declare no conflict of interest.

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