Heart Failure as a Disruption of Dynamic Circulatory Homeostasis Mediated by the Brain

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Summary

Circulatory homeostasis is associated with interactions between multiple organs, and the disruption of dynamic circulatory homeostasis could be considered as heart failure. The brain is the central unit integrating neural and neurohormonal information from peripheral organs and controlling peripheral organs using the autonomic nervous system. Heart failure is worsened by abnormal sympathoexcitation associated with baroreflex failure and/or chemoreflex activation, and by vagal withdrawal, and autonomic modulation therapies have benefits for heart failure. Recently, we showed that baroreflex failure induces striking volume intolerance independent of left ventricular dysfunction. Many studies have indicated that an overactive renin-angiotensin system, excess oxidative stress and excess inflammation, and/or decreased nitric oxide in the brain cause sympathoexcitation in heart failure. We have demonstrated that angiotensin II type 1 receptor (AT1R)-induced oxidative stress in the rostral ventrolateral medulla (RVLM), which is known as a vasomotor center, causes prominent sympathoexcitation in heart failure model rats. Interestingly, systemic infusion of angiotensin II directly affects brain AT1R with sympathoexcitation and left ventricular diastolic dysfunction. Moreover, we have demonstrated that targeted deletion of AT1R in astrocytes strikingly improved survival with prevention of left ventricular remodeling and sympathoinhibition in myocardial infarction-induced heart failure. From these results, we believe it is possible that AT1R in astrocytes, not in neurons, have a key role in the pathophysiology of heart failure. We would like to propose a novel concept that the brain works as a central processing unit integrating neural and hormonal input, and that the disruption of dynamic circulatory homeostasis mediated by the brain causes heart failure. (Int Heart J 2016; 57: 145-149)

Key words: Sympathetic nerve activity, Baroreflex, Renin-angiotensin system

What is “heart failure”? In terms of homeostasis, heart failure could be considered as a disruption of dynamic circulatory homeostasis associated with interactions between multiple organs. In the system of dynamic circulatory homeostasis, no one doubts that the brain is the central unit integrating neural and neurohormonal information from peripheral organs and controlling peripheral organs using the autonomic nervous system. Heart failure is worsened by autonomic nervous system dysfunction as excess sympathoexcitation and/or vagal nerve withdrawn. Actually, β-blockers are known to result in established improvement of survival in heart failure with reduced ejection fraction. This review article focuses on the mechanisms of sympathoexcitation in heart failure, and the expected potential of the therapies for heart failure targeting the brain.

Excess Sympathoexcitation in Heart Failure

Excess sympathoexcitation occurs in heart failure with left ventricular systolic and diastolic dysfunction. The mechanisms in sympathoexcitation are arterial baroreflex failure, attenuation of cardiopulmonary reflex modulation, cardiac sympathoexcitatory reflex related to increased cardiopulmonary filling pressure, sleep apnea, myocardial ischemia, obesity, and/or reflexes from exercising muscle.

Sympathetic nerve activation is determined by the negative feedback loop system of baroreflex control. The native arterial baroreceptor senses a change in arterial pressure (AP) and transmits the message to the vasomotor center via afferent nerves (the aortic depressor nerves and the carotid sinus nerves). The vasomotor center modulates the sympathetic outflow depending on the inputs from the baroreceptors (central arc. of baroreflex). The efferent sympathetic nerve firing facilitates the cardiovascular actuators and induces resultant AP change (peripheral arc. of baroreflex). This negative feedback loop is the biological mechanism that stabilizes AP. Previous studies have demonstrated that sympathoexcitation with baroreflex failure is involved in the pathogenesis of heart fail-
ure. Patients with heart failure and preserved ejection fraction (HFpEF) are supersensitive to volume overload, and flash pulmonary edema often occurs transiently which is rapidly resolved by intravascular volume reduction. The stressed blood volume and systemic blood pressure are controlled by several systems. Among them, the baroreflex system is an important and powerful regulator. We developed a baroreflex failure model in rats with normal left ventricular function, and assessed the left atrial pressure (LAP) responses to volume overload. We investigated the effect of baroreflex failure on LAP and systemic AP responses to volume loading in rats with normal left ventricular function in which baroreflex failure was mimicked by maintaining constant carotid sinus pressure (CSP). In anesthetized Sprague-Dawley rats, we isolated bilateral carotid sinus nerves and controlled CSP by a servo-controlled piston pump. We mimicked normal baroreflex (NORM) by matching CSP to instantaneous AP, and baroreflex failure (FAIL) by maintaining CSP at a constant value regardless of AP. We infused dextran stepwise (infused volume: Vi) until LAP reached 15 mmHg and obtained the LAP-Vi relationship. We estimated the critical Vi when LAP reached 20 mmHg. In FAIL, critical Vi decreased markedly from 19.4 ± 1.6 mL/kg to 15.6 ± 1.6 mL/kg (P < 0.01), while AP at the critical Vi increased (194 ± 6 mmHg versus 163 ± 6 mmHg, P < 0.01). In addition, we also demonstrated that baroreflex failure with salt loading caused a transient increase in LAP of normal rats. Sakamoto, et al clearly demonstrated that baroreflex modulates both cardiac function and vascular function to regulate AP and that baroreflex-induced changes in vascular resistance and stressed blood contribute to AP regulation far greater than changes in contractility and heart rate. These results strongly suggest that baroreflex failure could induce volume intolerance independent of left ventricular systolic function, and that baroreflex failure would be the main cause of flash pulmonary edema in HFpEF.

In addition, we examined the effects of an artificial (bionic) baroreflex system we recently developed in the absence of native baroreflex. The bionic baroreceptor consists of an AP sensor, a neuro-stimulator, and a regulator. The bionic pressure sensor senses AP and the regulator translates AP into neuro-stimulation. Previously we determined that our bionic baroreflex system restores the pressure buffering function, and that the bionic baroreceptor would be an attractive therapy for orthostatic hypotension caused by baroreceptor impairment in rats. In the present examination, our bionic baroreflex system was able to fully reverse the physiological volume intolerance in the FAIL animals (critical Vi: 23.1 ± 1.7 mL/kg, and systolic AP at critical Vi: 206 ± 7 mmHg). These results suggest that the bionic baroreflex system would be an attractive therapeutic tool for preventing flash pulmonary edema in HFpEF caused by baroreflex failure. Interestingly, vagal afferent nerve stimulation apparently restores baroreflex function. It is worth noting that baroreflex dysfunction occurs in heart failure, and conveys independent prognostic information of heart failure. Age, heart rate, blood pressure, gender, body mass index, and smoking are independent and common factors affecting baroreflex and heart rate. We also reported that baroreflex sensitivity would be useful for identifying potential responders to inotropic phosphodiesterase-III inhibitor in patients with heart failure. Inhibition of oxidative stress in the vasomotor center improved the impaired baroreflex sensitivity. In HFpEF, baroreflex sensitivity is reduced and impaired heart rate recovery. Patients with HFpEF have multiple arteriosclerotic risk factors, and stiffened arterial walls in the baroreceptor regions impair baroreflex function.

This results strongly suggest that baroreflex failure should be considered as the cause and result of heart failure, and that heart failure is a dysfunction of dynamic circulatory homeostasis mediated mainly by the central arc (brain) of the baroreflex. Baroreflex failure could become a therapeutic target in heart failure, and our bionic baroreflex system in particular has the potential to be a therapy for HFpEF.

Renal Afferent Nerve in Heart Failure

The renal afferent nerve would be a powerful input into the central mechanisms of sympathetic regulation. The brain has been shown to receive inputs from renal afferent nerves. There are multiple triggers in heart failure activating afferent nerves, such as increased venous pressure and reduced kidney perfusion, and previous studies have demonstrated that sympathoinhibitory mechanoreceptor reno-renal reflex is blunted in heart failure due to high levels of circulating angiotensin II and activation of endothelin A. Blunting of the inhibitory reno-renal reflex may be a mechanism by which sodium is retained and efferent sympathetic drive to non-renal vascular beds is stimulated in heart failure. Considering these results, the renal afferent nerve is an important sympathoexcitatory factor in heart failure.

Central Mechanisms of Sympathoexcitation in Heart Failure

With respect to abnormal sympathetic activation in chronic heart failure, we should focus on the central mechanism, because sympathetic nervous system activation is determined by the brain. Previous studies have demonstrated that the central renin-angiotensin system is the major system that regulates the sympathetic nervous system in heart failure. Angiotensin II type 1 receptors (AT1R) are found in the areas of the hypothalamus and medulla that regulate sympathetic outflow. The rostral ventrolateral medulla (RVLM) in particular is a well known vasomotor center, and oxidative stress in the RVLM causes sympathetic activation. In animals with heart failure, AT1R-induced oxidative stress causes sympathoexcitation. Furthermore, the balance between angiotensin-converting enzyme (ACE) and its homolog ACE2 or between AT1R and angiotensin II type 2 receptor in the brain determines sympathetic outflow in heart failure. Circulating angiotensin II also exaggerates central sympathoexcitation in heart failure. We recently reported that circulating angiotensin II in heart failure is capable of inducing sympathoexcitation via in part AT1R in the brain, subsequently leading to left ventricular diastolic dysfunction. The brain may sense the neurohormonal factors and determine sympathetic outflow.

Brain inflammation associated with the central renin-angiotensin system and/or oxidative stress is also involved in the mechanisms of sympathoexcitation in heart failure. Brain
Heart failure is a complex syndrome with sympathetic overexertion, and no one doubts that excess sympathoexcitation causes heart failure (Figure). There are several other mechanisms of abnormal sympathoexcitation in heart failure. Dysfunction of nitric oxide (NO) in the brain occurs in heart failure, and overexpression of NO synthase in the brain causes sympathoinhibition in heart failure. The small G protein Rho/Rho kinase pathway, mineralocorticoid receptors and/or Na sensitivity, or toll-like receptor 4 in the brain have also been shown to cause sympathoexcitation in heart failure.

In the brain, astrocytes are more abundant than neurons, and have neuronal and vascular connections, suggesting that astrocytes can splice neural and hormonal inputs into the brain much like a central processing unit. Recently, we have demonstrated that targeted deletion of AT1R in astrocytes strikingly increases sympathetic outflow. Heart failure is a disruption of brain-mediated dynamic circulatory homeostasis.

**Figure.** Our concept of brain-mediated dynamic circulatory homeostasis. The inputs into the brain are afferent nerves and neurohormonal factors from peripheral organs (heart, kidney, and vasculature). The output from the brain is efferent nerves. In the brain, the renin-angiotensin system, oxidative stress, inflammation, nitric oxide, and other factors mediate sympathetic outflow. Heart failure is a disruption of brain-mediated dynamic circulatory homeostasis.

There is no conflict of interest to report.

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