

Angiotensin II, Oxidative Stress, and Sympathetic Nervous System Hyperactivity in Heart Failure

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ABSTRACT

In congestive heart failure (CHF), sympathetic nervous system is hyperactive. This article reviews current understandings about central and peripheral neural mechanisms underlying sympathetic hyperactivation in this pathological condition. During the development of CHF, renin-angiotensin system (RAS) activities and angiotensin II–mediated oxidative stress become enhanced. Here, on the basis of findings obtained from animal studies, it is examined how RAS overactivation and oxidative stress in central and peripheral nervous systems of CHF mediate sympathetic hyperactivation. Mechanisms by which exercise training in CHF ameliorates RAS overactivation, oxidative stress and sympathetic hyperactivation are also investigated.

Key words angiotensin II; heart failure; superoxide; sympathetic nervous system

Congestive heart failure (CHF) is a common and lethal syndrome earmarked by systemic perfusion insufficient to meet the peripheral organs' metabolic demands as a result of attenuated cardiac pump function. This disease binds enormous medical resources and therefore is a major public health problem in developed countries including Japan. In Japan, as the incidence of CHF increases with age, the disease pandemic is expected to be evident by 2030.¹

In CHF, sympathetic nervous system becomes hyperactive at rest as well as during exercise. Elevated plasma norepinephrine levels seen in patients with CHF have been reported.² The microneurographic experiments performed by Leimbach and colleagues

provided direct evidence for increased discharges of muscle sympathetic postganglionic neurons in resting patients with CHF.³ The level of sympathoexcitation seen during voluntary exercise is also excessive in CHF patients compared to that in control subjects.^{4,5} While sympathetic hyperactivation can initially be interpreted as short-term compensatory responses to hemodynamic alterations due to impaired cardiac function, chronic hyperactivation of sympathetic nervous system drives maladaptive remodeling, and promotes further deterioration in cardiac function and disease progression.⁶ The level of sympathetic hyperactivation at rest is a possible index to predict the mortality of CHF patients.⁷ Exaggerated sympathoexcitatory responses to exercise are a cause of exercise intolerance, a primary symptom of this disease.⁸ Therapeutic interventions that inhibit sympathetic hyperactivation favorably alter the natural course of the disease.

Sympathetic hyperactivation in CHF involves dysfunction of regulatory neural mechanisms of sympathetic nervous system. However, it has not been fully understood how function of neural mechanisms becomes abnormal in CHF. Nevertheless, evidence has suggested that increased angiotensin II (AngII) and AngII-induced superoxide overproduction in central and peripheral nervous systems play a role in enhancing sympathetic vasomotor tone in CHF. Renin-angiotensin system (RAS) activity and oxidative stress become increased during the development of CHF.⁹ There is an interaction between the RAS activity and oxidative stress. Griendling et al. firstly demonstrated that stimulation of AngII receptor type 1 (AT1R) activated NADPH oxidases and increased superoxide production.¹⁰ Moreover, superoxide can increase the sensitivity of neuronal cells that respond to excitatory input.¹¹ Thus, increased AngII likely has an excitatory effect on neural cells through action of superoxide. In this article, mechanisms by which RAS overactivation and AngII-mediated oxidative stress in central and peripheral nervous systems of CHF lead to sympathetic hyperactivation at rest and during exercise are discussed on the basis of findings obtained from animal studies. Moreover, mechanisms by which exercise training in CHF, currently acknowledged as an effective therapeutic treatment, ameliorates RAS overactivation,

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Abbreviations: ACE, angiotensin converting enzyme; AngII, angiotensin II; AT1R, angiotensin II receptor type 1; BBB, blood-brain barrier; CHF, congestive heart failure; EPR; exercise pressor reflex; MLR, mesencephalic locomotor region; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus of the hypothalamus; RAS, renin-angiotensin system; RVLM, rostral ventrolateral medulla; SFO, subfornical organ; SNA, sympathetic nerve activity; SOD, superoxide dismutase

oxidative stress, and sympathetic hyperactivation are also examined.

Central nervous system dysfunction due to RAS overactivation and oxidative stress in CHF

In CHF, plasma AngII levels are elevated in CHF due to the reduced renal blood flow and sodium delivery to the distal tubule that leads to renin release. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I. In turn, angiotensin converting enzyme (ACE) cleaves angiotensin I to form the active octapeptide AngII. Renin release is further exacerbated by sympathetically mediated renal vasoconstriction. As discussed below, increased plasma AngII likely acts on central cardiovascular pathways that lack blood-brain barrier (BBB), thereby playing a role in causing sympathetic hyperactivation.

There are various hierarchical brain sites that are known to generate sympathetic vasomotor tone. One of the most major among them is the paraventricular nucleus of the hypothalamus (PVN). The PVN contains cells that monosynaptically target the spinal cell column, in which cell bodies of sympathetic preganglionic neurons are located, and cells that innervate the rostral ventrolateral medulla (RVLM), another cardiovascular region.¹² In rats with CHF after myocardial infarction, neurons in the PVN were hyperactive compared with healthy controls, and intracarotid artery injection of AT1R antagonist losartan reduced PVN neuronal activities to a larger degree than that in controls.¹³ These observations suggest that plasma AngII causes PVN neural overactivities, thereby mediating sympathetic hyperactivation. Nevertheless, the PVN is located inside the BBB. Thus, the effect of increased plasma AngII to elevate the PVN neuronal activity is likely explained by its action on neurons upstream to the PVN that regulate PVN neuronal excitabilities. Neurons in the BBB-lacking subfornical organ (SFO) contain AT1R abundantly and send axonal projections to the PVN (SFO-PVN neurons).¹⁴ Zimmerman et al. showed that hypertension caused by chronic and systemic infusion of AngII in mice was correlated with significant elevations of superoxide production in the SFO, and that adenoviral-mediated delivery of cytoplasmically targeted superoxide dismutase (SOD) selectively to the SFO prevented the hypertension and increased superoxide production.¹⁵ These observations lead to the hypothesis that in CHF, elevated plasma AngII stimulates AT1R located on SFO-PVN neurons and increases superoxide production, thereby enhancing SFO-PVN neuronal activities. In turn, sympathoexcitatory PVN neurons receive enhanced excitatory inputs from SFO-PVN neurons, and sympathetic nerve

activity (SNA) is elevated in CHF (Fig. 1). The finding by Lindley et al. verifies the role played by brain oxidative stress in enhancing excitabilities of SFO and PVN neurons, thereby causing sympathetic hyperactivation in CHF.¹⁶ They demonstrated that intracerebroventricular administration of an adenoviral vector encoding SOD in CHF mice not only inhibited neural hyperactivation in the PVN and SFO with CHF but also decreased urinary norepinephrine levels.

Endogenous AngII production is also increased in the PVN of CHF. All components of the RAS such as renin and angiotensinogen are abundantly expressed within the brain.¹⁷ Expressions of ACE and AT1R are upregulated in the brain regions including the PVN of CHF rats.¹⁸ The upregulation of ACE in central nervous system of CHF may be due to, at least in part, the increase in plasma aldosterone,¹⁹ that is released from the zona glomerulosa of the adrenal glands in response to plasma AngII, and penetrates the BBB unlike AngII. Intracerebroventricular administration of a selective antagonist of aldosterone mineralocorticoid receptor in CHF rats reduced expression of ACE and AT1R as well as NADPH oxidases-induced superoxide production in the PVN.¹⁸ Moreover, neurotransmitters released from SFO-PVN neurons include glutamate and AngII.^{14, 20} Since SFO-PVN angiotensinergic neurons are considered to be excessively excited in CHF as stated above, angiotensinergic neurotransmission is likely enhanced in the PVN of CHF. Finally, Zheng et al. reported that AngII microinjected into the rat PVN increased SNA and that losartan microinjected into the PVN decreased SNA to a larger degree in CHF rats than those in healthy controls.²¹ Taken together, the endogenous AngII upregulation in the PVN of CHF is likely part of sympathetic hyperactivation (Fig. 1).

The RVLM contains neurons directly projecting to the spinal intermediolateral cell column, in which cell bodies of sympathetic preganglionic neurons are located. The basal activity of the RVLM sympathetic premotor neurons is a major mechanism responsible for the generation of resting sympathetic vasomotor tone.²² In the RVLM, there is a high density of ACE and AT1R.^{23, 24} In the RVLM of CHF, expressions of ACE, AT1R, and NADPH oxidases become upregulated.^{23, 25} Gao et al. showed that cerebroventricular infusion of simvastatin, which impairs RAS hyperactivity,²⁶ decreased expressions of AT1R and NADPH oxidase proteins and ameliorated superoxide production in the RVLM of CHF rabbits.²⁵ Blunted oxidative stress in the RVLM was associated with the decreased basal SNA. Thus, endogenous AngII mechanisms and therefore the superoxide pathway in the RVLM likely underlie sympathetic hyperactivation in

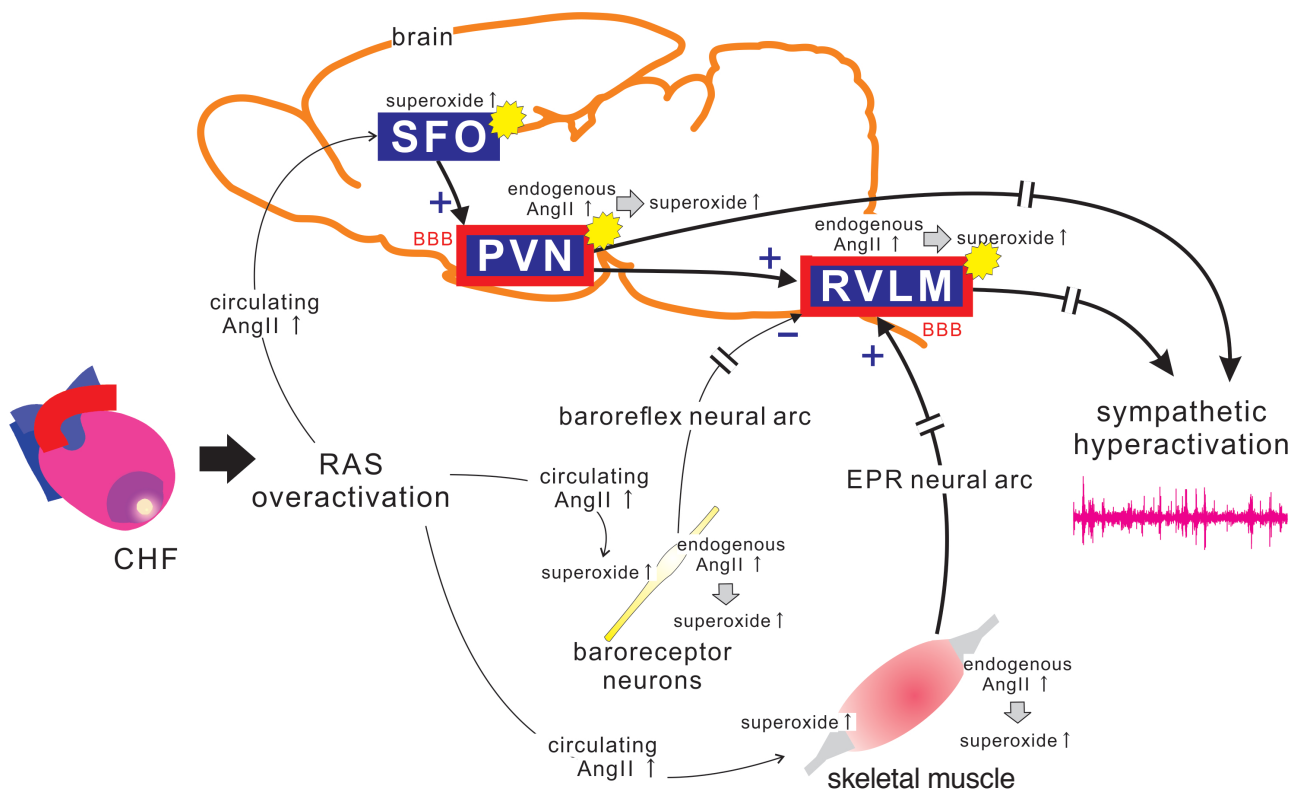


Fig. 1. A schema for the involvement of RAS overactivation and oxidative stress in central and peripheral neural mechanisms that underlie the level of sympathetic nerve activities in CHF based on works cited in text. AngII, angiotensin II; BBB, blood-brain barrier; CHF, congestive heart failure; EPR; exercise pressor reflex; PVN, paraventricular nucleus of the hypothalamus; RAS, renin-angiotensin system; RVLM, rostral ventrolateral medulla; SFO, subformal organ.

CHF (Fig. 1).

Oxidative stress in the RVLM of CHF mediates not only resting sympathetic hyperactivity but also exaggerated sympathoexcitation in response to exercise. Sympathoexcitatory responses to exercise are mediated by a feedforward neural mechanisms termed central command. Central command evokes parallel modifications of motor and autonomic functions during exercise, and excites the central cardiovascular pathways containing the RVLM.²⁷ We previously reported that central command-elicited sympathoexcitation becomes exaggerated in CHF by demonstrating that renal sympathoexcitation in response to electrical stimulation of the mesencephalic locomotor region (MLR), stimulation of which evokes fictive locomotion under paralysis, was larger in rats with CHF than that in controls.²⁸ Subsequently, we demonstrated that administration within the RVLM of Tempol, a SOD mimetic, reduced MLR stimulation-elicited sympathoexcitation in CHF, suggesting the role of superoxide overproduction in the RVLM in enhancing central command-elicited sympathetic outflow in CHF.²⁹

Of note, a recent report by Biancardi et al. suggested that circulating AngII plays a role in increasing BBB permeability, thereby facilitating its access to central cardiovascular regions.³⁰ They found that, the BBB permeability was increased along with downregulated key BBB protein constituents in the PVN and RVLM of spontaneously hypertensive rats that have increased plasma AngII as do CHF animal models. The BBB disruption was prevented by oral administration of losartan. In CHF, it is hypothesized that plasma AngII can extravasate into central cardiovascular regions inside the BBB, thereby stimulating the AT1R in the PVN and/or RVLM and mediating sympathetic hyperactivation as does endogenous AngII. Future studies are required to test this hypothesis.

Baroreflex dysfunction due to overactivation of RAS and oxidative stress in CHF

We need to note the important roles of reflex mechanisms that regulate central cardiovascular pathway activities and therefore the level of sympathetic vasomotor tone. The arterial baroreflex is a homeostatic mechanism

by which the level of SNA changes through sensing the alteration of tension in arterial vascular walls. Arterial baroreceptors are located in the arterial blood vessels including aortic baroreceptor neurons in the nodose ganglion and carotid baroreceptor neurons in the petrosal ganglion. They sense the mechanical deformation of arterial vascular walls associated with arterial pressure changes, thereby exciting or inhibiting aortic baroreceptor neurons. In turn, neural signals are sent to central cardiovascular pathways through the nucleus tractus solitarius (NTS). When barosensitive afferents transmit excitatory signals to the NTS due to the elevation of arterial pressure, the NTS send excitatory signals to the caudal ventrolateral medulla, that sends inhibitory signals to the RVLM. Patients with CHF exhibit the attenuated baroreflex sensitivity, which contributes to sympathetic hyperactivation.^{31, 32}

Intravenous infusion of AngII has the effect to downregulate the baroreflex control of SNA in healthy animals.³³ DiBona et al. demonstrated that, in rats with CHF, intravenous administration of AT1R antagonist losartan partially restored the impaired baroreflex control of SNA,³⁴ suggesting that increased plasma AngII in CHF mediates arterial baroreflex dysfunction (Fig. 1).

Enhanced AngII-NADPH oxidase-superoxide signaling in the periphery of CHF likely mediates dysfunction of aortic baroreceptor neurons. Via whole cell patch-clamp recordings, AngII enhanced the density of hyperpolarization-activated currents, and decreased membrane excitabilities in the aortic baroreceptor neurons.³⁵ Moreover, either losartan or apocynin, a NADPH oxidase inhibitor, blunted the AngII-induced increases in the hyperpolarization-activated currents and decreases in the membrane excitability in the aortic baroreceptor neurons. In their subsequent study,³⁶ AT1R expression and local AngII concentration in the nodose ganglia were upregulated in CHF. Moreover, local microinjection of losartan into the nodose ganglia of CHF significantly increased the sensitivity of arterial baroreflex that was impaired. Furthermore, local application of AngII in the nodose ganglia from healthy rats mimicked CHF to depress the arterial baroreflex function. These results suggest that elevation of AngII associated with AT1R overexpression in the nodose ganglia contributes to the aortic baroreceptor dysfunction and subsequent downregulation of the arterial baroreflex sensitivity in CHF rats. This group also reported that adenoviral gene transfection of manganese SOD into the nodose neurons reduced the elevation of mitochondrial superoxide in CHF rats, and partially reversed the suppressed cell excitabilities.³⁷ Mitochondria-derived superoxide overproduction in the aortic baroreceptor neurons of CHF

also likely impairs arterial baroreflex control of SNA.

Exercise pressor reflex dysfunction due to overactivation of RAS and oxidative stress in CHF

Elevated AngII concentration in the periphery of CHF plays a role in exaggerating sympathoexcitation in response to exercise by acting on neural arc of the exercise pressor reflex (EPR). The EPR originates in exercising skeletal muscle from chemical and mechanical activation of nerve endings of thin fiber muscle afferents (i.e., group III and IV). Signals from the nerve endings project to the dorsal horn of the spinal cord and then to the central cardiovascular pathways. In turn, muscle afferent engagement during exercise reflexly causes sympathoexcitatory and pressor responses.³⁸ Smith et al. reported that the reflex pressor response to contraction of hindlimb skeletal muscle of CHF rats was larger than that of controls, suggesting the exaggerated EPR.³⁹ We previously found that exaggerated EPR in CHF is mediated by oxidative stress in skeletal muscle by showing that Tempol infused into the hindlimb circulation significantly reduced sympathoexcitatory responses to hindlimb skeletal muscle contraction in CHF rats but not in healthy controls.⁴⁰ Subsequently, we reported that subcutaneous administration of AngII for two weeks enhanced the reflex sympathoexcitatory response to skeletal muscle contraction in rats, suggesting the role of increased plasma AngII in enhancing the EPR.⁴¹ The enhanced EPR response was reduced by pretreatment with Tempol of exercising skeletal muscle. Taken together, AngII-mediated oxidative stress in skeletal muscle in CHF is considered an important factor to exaggerate sympathoexcitatory responses to exercise via the EPR arc (Fig. 1).

Beneficial effects of exercise training in CHF to ameliorate RAS activation, oxidative stress, and sympathetic hyperactivation

Exercise training interventions in patients with CHF have currently been an accepted adjunct to an evidence based management program. This therapy not only reduces symptoms and improves self-reported measures of quality of life without adverse events but also alleviates sympathetic hyperactivation.⁴²

Alleviated sympathetic hyperactivity in CHF after exercise training is due to, at least in part, its effect to reduce plasma AngII. Liu et al. showed that exercise training lowered resting sympathetic hyperactivity and improved arterial baroreflex dysfunction in conscious rabbits with CHF but not in healthy controls.⁴³ Intravenous infusion of losartan enhanced baroreflex sensitivity in CHF rabbits that were not exercise trained but had

no effect in CHF rabbits that were exercise trained. Concomitant with this effect, exercise training lowered the elevated plasma AngII concentration in CHF rabbits, and there was a significant positive correlation between SNA and plasma AngII. These observations suggest that exercise training ameliorates baroreflex dysfunction and alleviates sympathetic hyperactivity by lowering plasma AngII.

Exercise training in CHF can also normalize angiotensinergic mechanisms in central nervous system. Kar et al. reported that overexpression of ACE in the PVN of CHF rabbits was decreased after exercise training.²³ Zheng et al. found that renal sympathoexcitation in response to microinjection of AngII into the PVN was larger in CHF rats than in healthy controls, and the enhanced sympathoexcitatory response was normalized after exercise training.⁴⁴ Moreover, losartan microinjected into the PVN reduced SNA in CHF rats had no effect in healthy controls and CHF animals after exercise training. Finally, overexpression of AT1R in the PVN of CHF was reduced after exercise training. Reduced RAS activity in the PVN of CHF after exercise training is likely part of alleviated sympathetic hyperactivity.

In the RVLM of CHF, exercise training reduced overexpressions of ACE and AT1R,^{23, 45} suggesting that RAS overactivation are suppressed. Mousa et al. reported that, in CHF rabbits that were exercise trained, subcutaneous infusion of AngII to experimentally maintain plasma AngII levels near levels of untrained rabbits with CHF prevented the effects of exercise training to ameliorate baroreflex dysfunction and sympathetic hyperactivity and cancelled exercise training-downregulated AT1R expression in the RVLM.⁴⁵ These observations suggest that the beneficial effects of exercise training on resting sympathetic hyperactivity and baroreflex dysfunction in CHF are a result of, at least in part, concomitant reductions of RAS activities in the RVLM. Gao et al. reported that exercise training increased expression of Cu,Zn SOD and decreased expression of NADPH oxidase subunit gp91^{phox} in the RVLM of CHF rabbits.⁴⁶ Thus, an upregulation in antioxidative mechanisms and suppressed prooxidant mechanisms in the RVLM contribute to beneficial effects of exercise training to ameliorate sympathetic hyperactivity in CHF.

In patients with CHF, exercise training interventions also ameliorate acutely elicited sympathoexcitatory responses to exercise that are exaggerated.⁴⁷ This effect is likely a result of normalizations of central command and EPR dysfunction.^{29, 48} We previously demonstrated that the normalization of central command dysfunction in CHF after exercise training was due to its antioxidative effects in the RVLM.²⁹ Tempol microinjected into the

RVLM reduced central command-elicited sympathoexcitation in rats with CHF but had no effect in CHF animals after exercise training. Moreover, since the EPR becomes exaggerated by AngII-mediated oxidative stress in skeletal muscle,⁴¹ ameliorated RAS overactivation in skeletal muscle after exercise training⁴⁹ likely underlies the normalization of the EPR dysfunction in CHF.

Conclusion

This article focused on RAS overactivation and AngII-mediated oxidative stress in central and peripheral nervous systems, which play an important role in causing sympathetic hyperactivation in CHF. Mechanisms underlying beneficial effects of exercise training on RAS overactivation, oxidative stress and sympathetic hyperactivity in CHF were also examined. However, questions have still remained unanswered. For example, mechanisms underlying upregulation of proteins related to RAS activity and oxidative stress in central and peripheral nervous systems of CHF have remained to be investigated. Mechanisms by which exercise training in CHF downregulates the protein expressions are also unknown. These issues need to be addressed in future studies.

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The author declares no conflict of interest.

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