Baroreceptor reflex in heart failure

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Abstract: Congestive heart failure is a syndrome that is usually initiated by a reduction in pump function of the heart, i.e. a decrease in cardiac output. Initially, a reduction in cardiac output leads to unloading of baroreceptor reflex that, in turn, increases heart rate through vago-sympathetic mechanisms and total peripheral resistance via an increase in sympathetic outflow to vascular beds. In this review we are thinking on how baroreceptor reflex plays a role in the abnormal control of the circulation in heart failure. This review and our recent studies suggest that: (1) baroreceptor reflex is blunted in heart failure; (2) central angiotensin II and reactive oxygen species play an important role in blunted baroreceptor reflex; (3) cardiac sympathetic afferent stimulation and chemoreceptor reflex inhibit baroreceptor reflex; and (4) exercise training normalizes abnormal reflexes in the heart failure state.

Key words: baroreceptor reflex; chemoreceptor reflex; heart failure; angiotensin II; reactive oxygen species; exercise training

心力衰竭状态下的动脉压力感受器反射

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摘 要: 心力衰竭是以心脏泵血功能降低(心输出量减少)为始动因素的临床综合征。心输出量降低首先引起动脉压力感受性反射失负荷，进而通过迷走-交感机制加快心率；同时，支配血管床的交感传出活动增强，进而增加总外周阻力。本文主要论述在心力衰竭状态下压力感受性反射在循环功能异常调控中的作用机制。本综述及我们近年的研究表明: (1) 在心力衰竭状态下压力感受性反射功能明显减弱; (2) 中枢血管紧张素 II 和活性氧在压力感受性反射功能失调中发挥关键作用; (3) 心交感传入刺激和化学感受性反射能抑制压力感受性反射; (4) 适当的运动可以部分纠正异常的心血管反射活动。

关键词: 压力感受器反射; 化学感受器反射; 心力衰竭; 血管紧张素 II; 活性氧; 运动训练

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Under normal conditions, the nervous control of the circulation takes place at two different levels. There is always a tonic level of sympathetic and vagal activity keeping the peripheral blood vessels in a state of mild constriction as well as providing an inotropic support for the heart and a suppression of heart rate. On the other hand, autonomic influences regulate myocardial and peripheral hemodynamics on a short-term basis due to the action of cardiac, arterial baro- and chemo-sensitive reflexes as well as pulmonary reflexes. This short term control is regulated by a complex network of afferent nerve endings which are located in the heart, lungs, and arteries and run in both vagal and sympathetic pathways, of central integration at the brain stem nuclei which regulate autonomic tone, and of the effector tissues which respond to the release of the neurotransmitters to evoke specific muscular or glandular effects. We have known a good deal about the normal function of each of these components from experimenta-
tion performed on both animals and humans\cite{41}. Unfortunately, much less is known about the behavior of these components of reflex functions in disease states.

Congestive heart failure is a syndrome that is usually initiated by a reduction in pump function of the heart, i.e. a decrease in cardiac output. Initially, a reduction in cardiac output leads to unloading of baroreceptors that, in turn, increases heart rate through vago-sympathetic mechanisms and total peripheral resistance via an increase in sympathetic outflow to vascular beds. This sympathoexcitation is sustained for the duration of the heart failure state.

It has been shown that the congestive heart failure state is characterized by an elevated sympathetic tone and a depressed cardiac vagal tone\cite{2,5}. In addition to the increased sympathetic outflow, which can be documented by both plasma norepinephrine measurements and by direct sympathetic nerve activity recordings in animals and humans\cite{25-27,67}, vasopressin, renin, angiotensin II (Ang II), and aldosterone are all elevated in congestive heart failure\cite{9,9}. Increased sympathetic tone decreases survival in patients with heart failure\cite{10}.

The baroreceptor reflex, which is a sympatho-inhibitory reflex, is blunted in the heart failure state\cite{11-17}. The blunted baroreceptor reflex are mediated by increased central Ang II in heart failure\cite{11,18-25}. Interestingly, in the normal state, cardiac vagal afferent stimulation blunts the baroreceptor reflex\cite{26-29}. In addition, the sympa-thoexcitatory chemoreceptor reflex, is also enhanced in the heart failure state\cite{30,31}. Is it possible that these sympatho-excitatory reflexes (cardiac sympathetic afferent reflex and chemoreceptor reflex) blunt baroreceptor reflex in heart failure?

1. Abnormal reflex control in heart failure

Cardiovascular reflexes may be playing a role in the abnormal control of the circulation in heart failure.

It is now well established that the arterial baroreflex is depressed in experimental and clinical heart failure\cite{3,13,14,16,18-20,32-36}. This depression has been shown for the control of heart rate and peripheral sympathetic nerve activity\cite{3,14,34-36}. The arterial baroreflex is only one reflex involved in these autonomic adjustments. Figure 1 shows that in rats with coronary ligated heart failure, baroreceptor reflex was determined by intravenous injection of phenylephrine (10 µg) following nitroglycerin (25 µg). Renal sympathetic nerve activity (RSNA) vs. arterial pressure relationship significantly blunted in rats with heart failure and baroreceptor reflex sensitive (Gain) was also decreased in heart failure. Figure 1 shows that baroreceptor reflex is significantly blunted in rats with coronary ligated heart failure. Representative recording shows renal sympathetic nerve activity (RSNA) decreases during mean arterial pressure (MAP) increasing by intravenous injection of phenylephrine (Fig. 1A) and baroreceptor reflex sensitivity (Gain) significantly decreased in rats with heart failure (Fig. 1B).

The mechanisms for arterial baroreceptor reflex depression in heart failure also include afferent and target organ sites\cite{13,14,37,38}. Baroreceptor reflex control of heart rate is depressed because of poor baroreceptor function as well as poor SA nodal responsiveness\cite{39}. It has been shown that β receptor down-regulation occurs in low output heart failure\cite{40}. In addition, it has also been reported that these receptors become uncoupled from their regulatory proteins in heart failure\cite{40,41}. Studies from our laboratory indicate that a process ensues during the development of chronic congestive heart failure which alters baroreceptor membrane function\cite{13,14}. The mechanism of this depression involves increased Na⁺-K⁺ ATPase activity. This finding is based on the evidence that a low dose of ouabain partially restores baroreceptor discharge sensitivity when perfused through isolated carotid sinuses of dogs with experimental heart failure but not of normal dogs\cite{13}. In addition, the phenomenon of post excitatory depression, which is related to Na⁺-K⁺ ATPase activity\cite{42}, is significantly prolonged in carotid sinus baroreceptors from dogs with heart failure. This also is reversed by low dose ouabain\cite{42}.

2. Central angiotensin II, reactive oxygen species and abnormal baroreceptor reflex in heart failure

The brain renin-Ang II system is now recognized as playing an important role in cardiovascular control, body fluid homeostasis, and certain behaviors\cite{43,44}. It is well accepted that central Ang II regulates, in part, sympathetic outflow, facilitates sympathetic neurotransmission, and modulates baroreceptor reflexes\cite{45-48}. Circulating Ang II is increased in severe heart failure\cite{40,51}. Increases in central Ang II enhances sympathetic outflow and blunts the baroreflex in the normal state\cite{32-34}. In the heart failure state, Ang II participates in several peripheral effects such as myocardial remodeling\cite{45}, vasoconstriction, vasopressin\cite{52}, and norepinephrine\cite{56} release. Ang II also has effects in the CNS to stimulate sympathetic outflow\cite{57} and reset the baroreflex\cite{56} in the heart failure state. Ang II type 1 receptor antagonism enhances baroreflex sensitivity and decreases baseline sympathetic outflow. Furthermore, a recent study from our laboratory has shown that the central gain of the cardiac sympathetic afferent reflex is enhanced in dogs.
with pacing-induced heart failure and that central administration of losartan normalizes this enhanced central gain. These data strongly suggest that central Ang II may be responsible for the enhanced cardiac sympathetic afferent reflex in the heart failure state.

Ang II receptors are densely distributed in the circumventricular organs, such as the subfornical organ (SFO), the organum vasculosum of the lamina terminalis (OVLT), the area postrema (AP) and several hypothalamic and brainstem nuclei (the paraventricular nuclei (PVN), the rostral ventrolateral medulla (RVLM), the caudal ventrolateral medulla (CVLM) and the nucleus tractus solitarius (NTS)). In a recent study Kaprielian et al. showed that the AT1 receptor mRNA is up-regulated in the atria of patients with end-stage heart failure. This is consistent with findings in animal models of heart failure. Therefore, one of the objectives of this proposal is to determine if central Ang II concentration, AT1 receptor binding and/or AT1 receptor protein is elevated in the brain (especially in the brainstem and hypothalamus) in rats with chronic heart failure. The production of Ang II by the PVN results in a tonic excitatory action and Ang II sensitive PVN neurons receive convergent baroreceptor inputs which may modulate their downstream effects. In addition, the baseline firing rate in Ang II sensitive PVN neurons was significantly higher in rats with heart failure. This higher rate could be normalized by intracarotid injection of losartan. In rats with heart failure, anterior third ventricular lesions attenuates sympathetic drive and improves baroreflex function. The latter studies suggest that Ang II plays a role in the central regulation of sympathetic activity.

Fig. 1. Baroreceptor reflex in heart failure. A: Original recording of arterial blood pressure (BP) changes induced by phenylephrine injection (10 µg i.v.) and RSNA reflex responses in a normal rat (left panel) and a rat with heart failure (right panel). B: Baroreceptor reflex function curve in normal and heart failure groups.
in modulation of sympathetic drive from the PVN in the heart failure state.

The blunted baroreceptor reflex can be reversed by AT1 receptor antagonism in rabbits with pacing induced heart failure\(^{(18)}\). The enhanced cardiac sympathetic afferent reflex sensitivity is also decreased by losartan in dogs and rats with heart failure\(^{(21,22,24)}\). In addition, Ang II concentration in plasma\(^{(29)}\) or CSF\(^{(11,23)}\) is increased in animals with heart failure.

Central AT1 receptors have been found to be involved in signal transduction pathways that rely on ROS\(^{(66-72)}\). A recent study has shown that the effects of central Ang II on arterial pressure, heart rate and drinking were abolished by pretreatment with adenoviral vectors encoding human mitochondrial superoxide dismutase (AdMnSOD) in the brain\(^{(73)}\). This suggests that central ROS mediates Ang II regulated cellular processes\(^{(72)}\) (most likely via activation of NAD(P)H oxidase).

Our recent studies have shown that intra cerebroventricular infusion of Ang II (10 ng in 1 µl,) significantly blunts baroreceptor reflex (Fig. 2) in the anesthetized normal rat and this blunted baroreceptor reflex can be partially restored by central ROS scavenging by tempol (10 µg in 1 µl, i.c.v).

\[\text{Ang II} \quad \text{ROS} \quad \text{tempol} \quad \text{baroreceptor reflex} \]

In rats with chronic heart failure, blunted baroreceptor reflex was also restored by central ROS scavenging by tempol (10 µg in 1 µl, i.c.v, Fig. 3).

3. Chemoreflex and cardiac sympathetic afferent reflex blunt baroreflex

While arterial baroreflex and atrial reflex abnormalities have been studied extensively there has been much less work examining ventricular reflexes in heart failure. Sanders and Ferguson have reported that the cardiopulmonary mechanoreflex is impaired in patients with heart failure\(^{(74)}\). The data from this laboratory have shown that the heart rate and arterial pressure responses to intracoronary injections of veratridine and prostacyclin are normal or enhanced in conscious dogs with pacing-induced heart failure\(^{(75)}\). Since veratridine stimulates cardiac vagal afferents with both chemically sensitive and mechanically sensitive endings, this experiment does not help to determine if cardiac chemoreflexes or mechanoreflexes are impaired in heart failure. In a study from this laboratory\(^{(76)}\), the bradycardia response to ascending aortic occlusion (mechanoreflex) was significantly blunted in sino-aortic denervated (SAD) dogs which were paced into heart failure, while the hypotensive and bradycardia responses to intracoronary injection of PGI\(_2\) (cardiac chemoreflex) were enhanced. In another study from this laboratory it was shown that left ventricular c-fiber chemosensitive vagal afferents were significantly sensitized to intracoronary administration of bradykinin and capsaicin\(^{(77)}\). In addition to ventricular reflexes of vagal origin, reflexes originating in cardiac sympathetic afferents have been described and extensively studied\(^{(78-82)}\). A comprehensive review of cardiac sympathetic afferent reflexes has been provided by Malliani\(^{(83)}\). Stimulation of these cardiac sympathetic afferents will elicit a sympatho-sympathetic excitatory reflex. Myocardial ischemia may stimulate these sympathetic afferent fibers that, in turn, increase sympathetic efferent outflow\(^{(79,84)}\). It has been shown that cardiac sympathetic afferents can be stimulated by a variety of substances that are released by the myocardium during ischemia. These include potassium, hydrogen ion, adenosine, bradykinin, and prostaglandins\(^{(79,84-86)}\). On the other hand, it has been shown that coronary flow is decreased\(^{(85,96)}\) and oxygen consumption is increased in experimental heart failure which is most likely...
induced by increased wall tension[95,97,98]. In the chronic heart failure state, increased oxygen consumption may elicit relative myocardial ischemia that, in turn, stimulates cardiac sympathetic afferents to increase sympathetic outflow. During the development of heart failure the extracellular milieu may change in such a way that substances released from the myocardium either sensitize or stimulate sympathetic afferents. As indicated above, recent studies from this laboratory have shown that the cardiac sympathetic afferent reflex is augmented in dogs and rats with chronic heart failure[23,24,99-103]. This enhanced cardiac sympathetic afferent reflex has been shown to possess two components; one at the receptor level[99] and one in the CNS[21]. Recent studies from Schultz and co-workers[30,31,104,105,106,107-109] have shown that the sensitivity of the arterial chemoreflex is augmented in rabbits with pacing-induced heart failure. This is emerging as an important contributor to sympatho-excitation in heart failure. Our recent data also confirm an augmentation of the peripheral chemoreflex in the rat model of heart failure. As was clearly shown by Schultz and colleagues, this enhancement is mediated by increased discharge of carotid body chemoreceptors in the heart failure

Fig. 4. Cardiac sympathetic afferent stimulation blunts baroreceptor reflex in normal state. A: Composite arterial baroreflex curves generated before and during epicardial application of capsaicin in normal rats. B: Baroreceptor reflex curve before and during capsaicin. Inset: Gain curves of these mean baroreflex curves.
The baroreflex and the chemoreflex interact in normal and disease states\cite{110-114}. As far as we know there are no studies that have examined the interaction between the cardiac sympathetic afferent reflex and the baroreflex or between the cardiac sympathetic afferent reflex and the chemoreflex in the heart failure state. In our recent studies, cardiac sympathetic afferent stimulation inhibited baroreceptor reflex (Fig. 4) in normal rats. In addition, blunted baroreceptor reflex in rats with heart failure can be restored by epicardial application of local anesthesia, lidocaine (Fig. 5). In both normal and heart failure groups baroreceptor reflex inhibition by cardiac sympathetic afferent stimulation can be prevented by central \( \text{AT}_1 \) receptor blockade, losartan\cite{115,116}.

4. Exercise training normalizes abnormal baroreceptor reflex in heart failure

Exercise training has been shown to have important beneficial effects in patients with heart failure\cite{117-120}. Heart failure patients engaged in an exercise training protocol have been shown to demonstrate improved exercise tolerance and an enhanced quality of life and survival\cite{121}. Exercise.

Fig. 5. Epicardial application of lidocaine restores blunted baroreceptor reflex in rats with heart failure. A: Representative recordings of the arterial baroreflex response before and during epicardial application of lidocaine (2% in 20 µl) in rats with heart failure. B: Baroreceptor reflex curve before and during lidocaine. Inset: Gain curves of these mean baroreflex curves.
training produced a decrease in plasma renin activity at rest and during submaximal exercise in patients with ischemic heart disease\(^{122}\). Recent studies have shown that chronic exercise reduces sympathetic nerve activity and enhances the blunted arterial baroreflex sensitivity in rabbits with pacing-induced heart failure\(^{11,20,123}\). In addition, lower plasma Ang II concentration by exercise training may contribute to the decrease in sympathetic nerve activity in the heart failure state\(^{11,20,123}\). Exercise training in rats with heart failure may decrease sympathetic outflow and the sensitivity of the cardiac sympathetic afferent reflex; it may reduce the augmented chemoreceptor reflex\(^{108,109}\) and enhance the blunted baroreceptor reflex if Ang II is indeed decreased. It has been shown that spinal administration of

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**Fig. 6.** Exercise training restores blunted baroreceptor reflex in rats with heart failure. *A*: Representative recordings of the arterial baroreflex response in a rat with heart failure (left panel) and a heart failure rat with exercise training. *B*: Composite arterial baroreflex curves generated in heart failure with and without exercise training. Inset: Gain curves of these mean baroreflex curves.
losartan attenuated the hemodynamic response to muscle contraction in anesthetized cats\cite{124}. Recent studies from Schultz’s laboratory have shown that exercise training in rabbits with CHF normalizes peripheral chemoreceptor sensitivity\cite{108,109}. Our data show that exercise training in rats with heart failure normalizes the blunted baroreceptor reflex. Figure 6 demonstrates the effects of exercise training on the baroreceptor reflex in rats with heart failure. Exercise training had a little beneficial effect in normal rats. However, there was a dramatic effect on the arterial baroreflex following exercise training in heart failure rats. These data suggest that exercise training reduces sympatho-excitation and that exercise training may have powerful effects on the interactions between baroreflex, chemoreflex and cardiac sympathetic afferent reflex. In addition, exercise training also restores the augmented peripheral chemoreceptor reflex and enhanced cardiac sympathetic afferent reflex. Since exercise training in the heart failure state reduces sympathetic nerve activity and Ang II concentration, it is of interest to determine the reduction in sympa-tho-excitation following exercise training. Figure 7 shows central AT1 receptor mRNA expression by RT-PCR and protein by Western blot techniques in the paraventricular nuclei (PVN), the rostral ventrolateral medulla (RVLM), and the nucleus tractus solitarius (NTS) in normal and heart failure rats with and without exercise training. AT1 receptor mRNA message and protein in these nuclei significantly increased in rats with heart failure and exercise training markedly decreased AT1 receptor mRNA and protein in heart failure state. Exercise training had a little or no beneficial effect in normal rats.

In this review, we have tried to promote the idea that baroreceptor reflex in the heart failure state is regulated by reflexes and neurohumoral mechanisms in addition to a decrease in the sensitivity of the traditional negative-feedback reflex. It is becoming increasingly clear that substances that are elevated in the heart failure state also participate in the chronic sympatho-excitation.

Taken in total these data suggest that: (1) baroreceptor reflex is blunted in heart failure, (2) central Ang II and reactive oxygen species play an important role in blunting baroreceptor reflex, (3) cardiac sympathetic afferent stimulation and chemoreceptor reflex inhibit baroreceptor reflex, and (4) exercise training normalizes abnormal reflexes in the heart failure state (Fig. 8).

![AT1 receptor mRNA expression and protein](image)

Fig. 7. A: RT-PCR detection of AT1 receptor mRNA expression in the PVN, RVLM and NTS in sham and heart failure rats with and without exercise training. AT1 receptor mRNA expression increased in heart failure. Exercise training decreased AT1 receptor mRNA expression in the heart failure state. B: Western blot detection of AT1 receptor protein in the PVN, RVLM and NTS in sham and heart failure rats with and without exercise training. AT1 receptor protein increased in heart failure and exercise training decreased AT1 receptor in heart failure rats.
Fig. 8. An illustration of summary in this review. Baroreceptor reflex is blunted in the heart failure state, the blunted baroreceptor reflex is mediated by central Ang II and ROS, cardiac sympathetic afferent stimulation blunts the baroreflex and exercise training, by reducing Ang II and ROS normalizes abnormal reflexes.

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