Published in final edited form as:

Heart Fail Clin. 2012 January ; 8(1): 87–99. doi:10.1016/j.hfc.2011.08.007.

Neurohumoral Stimulation

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Introduction

Neurohumoral activation has been recognized as one of the hallmarks in the compensatory response during the development of chronic heart failure (CHF), whatever its etiology¹⁻⁴. A large number of hormonal systems are activated in the CHF state, and virtually all vasoconstrictor substances are increased in CHF. These include Angiotensin II (Ang II), endothelin-1, vasopressin, and norepinephrine (NE). In addition, it is now well accepted that potent vasodilator systems are downregulated in the CHF state. Nitric oxide (NO) and its downstream target, cGMP are reduced and contribute to the general state of vasoconstriction in CHF. Furthermore, CHF has been viewed as a pro-inflammatory state as well as a condition characterized by high levels of oxidative stress⁵⁻⁷. In patients and animals with CHF, increased oxidative stress has been shown to occur in many tissues, including the heart and brain⁸⁻¹².

Based on measures from techniques such as microneurography and NE spillover, it is clear that sympathetic nerve activity is elevated in CHF^{13;14}. A clear indication of this phenomenon is illustrated in Figure 1, in which a profound increase in muscle sympathetic nerve activity correlates with the severity of cardiac dysfunction. These data also suggest that sympatho-excitation occurs early in the progression of the heart failure syndrome. The central origin of this sympatho-excitation is also well established in both animal and human studies¹⁵. Although there are differences in sympathetic outflow to various vascular beds in the CHF state it is generally well accepted that sympatho-excitation is a global phenomenon.

The temporal relationship between the development of heart failure and activation of these neurohumoral systems has not been precisely defined. It is not clear when a compensatory mechanism switches to a deleterious contributing factor in the progression of the disease. In this review, we hope to address these issues by evaluation of the contribution of various cardiovascular reflexes and cellular mechanisms to the sympatho-excitation in CHF. We will also shed light on some of the important central mechanisms that contribute to the increase in sympathetic nerve activity in CHF.

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Conflicts None

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Arterial Baroreflexes

The primary and most powerful short-term modulators of arterial pressure are the arterial baroreflexes (ABR). The sensory endings that mediate the ABR lie in the wall of the aortic arch and carotid sinus. This buffer reflex has been well characterized in humans and experimental animals. The maximum sensitivity of the ABR is defined by construction of full baroreflex curves in which the input (some parameter related to arterial pressure) is plotted against one of several output parameters (heart rate, sympathetic nerve activity, peripheral resistance, *etc.*). The maximum of the first derivative of the negative slope of this relationship defines the peak sensitivity. Usually the peak negative slope occurs close to the ambient arterial pressure.

As in some forms of severe hypertension, the ABR sensitivity is depressed in patients and animals with CHF¹⁶⁻¹⁸. This depression in baroreflex sensitivity in CHF occurs by several mechanisms. First, the sensitivity of the baroreceptor endings to pressure is reduced¹⁹⁻²¹. This phenomenon can only be studied in experimental models. In the dog pacing model of CHF, a reduced discharge sensitivity of single units dissected from the carotid sinus nerve has been demonstrated²². This decrease in sensitivity is mediated, in part, by an increase in Na⁺-K⁺ ATPase activity²¹ in baroreceptor afferent endings. Interestingly, aldosterone administered into the isolated carotid sinus reduced afferent discharge sensitivity by an apparent non-genomic effect²³. Because aldosterone is elevated in CHF and mineralocorticoid receptor antagonists have been proven to be an effective and important therapy it may well be that aldosterone contributes to baroreflex depression in the CHF state. Second, there is clear evidence that the central neural components that mediate the ABR are impaired in the CHF state. For instance, in dogs, stimulation of the carotid sinus nerve (thus bypassing the receptor endings) results in baroreflex responses that are impaired in CHF compared to normal animals²⁴. These data suggest central or efferent abnormalities in the control of baroreflex function in CHF.

Does ABR depression contribute to the sustained neurohumoral excitation in CHF or does it simply initiate this process at the beginning of the disease state? This question has been difficult to answer in humans. An attempt to address this issue was carried out by Grassi *et al.*²⁵ who evaluated muscle sympathetic nerve activity (MSNA) and ABR function in patients with mild (NYHA class I and II) and severe (NYHA class III and IV) CHF. Although there was a gradation in both resting MSNA and ABR sensitivity, patients with mild CHF clearly exhibited significant sympatho-excitation and baroreflex depression compared to aged matched control subjects. In a subsequent study, these investigators²⁶ showed that angiotensin converting enzyme (ACE) inhibition (benazepril; 10mg/d for 2 months) reduced sympathetic nerve activity in patients with mild CHF. Furthermore, benazepril treatment resulted in an enhancement in ABR sympatho-inhibition in response to increasing arterial pressure.

Given the facts that there is likely to be activation of the renin-angiotensin system early in the pathogenesis of CHF and that this activation may contribute to the central depression of ABR function one can raise the question is ABR depression a necessary prerequisite to the chronic elevation of sympathetic tone in CHF? This question has also been difficult to answer definitively. In studies carried out in dogs with CHF and complete baroreceptor denervation, Brändle *et al.*²⁷ showed increases in plasma NE induced by CHF that were the same with or without intact ABR function. In a related study, Levett *et al.*²⁸ showed similar NE increases in dogs with CHF following chronic cardiac denervation. Therefore, although cardiovascular reflex function is impaired in the CHF state it may not be the initiating factor that is responsible for early sympatho-excitation. In conscious rabbits with pacing-induced CHF we observed a late increase in renal sympathetic nerve activity (RSNA), (Figure 2).

This increase was associated with an increase in plasma Ang II levels. These latter data suggest a possible relationship between activation of the RAS and sympatho-excitation in CHF, at least in terms of late events.

Low Pressure Reflexes

Evidence for altered volume reflex in heart failure

Low pressure reflexes have been implicated in the control of salt and water balance in the normal state^{29;30}. In addition to the ABR, cardiovascular reflexes emanating from the low pressure side of the circulation may be very important in modulation of fluid balance and sympathetic outflow in CHF. In normal humans, translocation of blood from the periphery to the thoracic circulation evokes a brisk diuresis and natriuresis³¹⁻³⁴. Neural activity from sensory endings located in the atria and ventricles has been shown to be markedly reduced in animals with CHF³⁵⁻⁴². There are also data from humans with CHF suggesting that abnormal volume reflexes contribute to the chronic congestion and the sympatho-excitation of this disease⁴³⁻⁴⁵. Mechanical and chemical activation of atrial and ventricular reflexes have been shown to reduce sympathetic outflow and arginine vasopressin (AVP) secretion^{41;46;47}. Therefore, abnormalities in either the discharge characteristics of these endings or the central processing of neural information originating from these receptors may have profound effects on both sympathetic nerve activity and AVP secretion⁴¹.

The “volume reflex” can be defined as the renal response to an acute volume challenge. An impaired ability to excrete a sodium load is a salient feature of the heart failure condition. The renal response (diuresis and natriuresis) to acute volume expansion (with isotonic saline) is clearly blunted in various animal models of CHF⁴⁸⁻⁵⁰. It is important that, in addition to general sympathetic nerve activity, RSNA is also markedly elevated in CHF^{51;52}. There are several possible places in the volume reflex arc that could be altered in CHF. These include: 1) the receptors (including electromechanical coupling factors), 2) mechanical properties of the cardiac tissue where the receptors are located, 3) cardiac vagal afferent fibers, 4) the central neural processing of afferent input 5) efferent renal sympathetic nerve fibers, 6) the end-organ response to transmitter release and 7) the release and/or action of humoral factors such as atrial natriuretic peptide (ANP) and AVP on end-organ responses within the kidney.

Afferent limb of the volume receptor reflex

Even though the ABR is impaired in CHF, it is more likely that low pressure receptors mediate the volume reflex. Studies in our laboratory have addressed the hypothesis that the altered volume reflex in rats with CHF reflects reduced distensibility (compliance) of the right atrium and the veno-atrial junction, structures known to possess a large number of volume (stretch) receptors⁵⁰. The distensibility was assessed by measuring the stiffness constants of the pressure–volume curve, dp/dV , of the right atrium and veno-atrial junction in CHF rats and sham rats. The results illustrate that the stiffness constant, the slope of the change in pressure versus change in volume of the right atrium and veno-atrial junction, is significantly greater in CHF rats than in sham rats (Figure 3). These data suggest that CHF rats have stiffer right atria and veno-atrial junctions, which may reduce stimulation of the volume receptors to a volume load. Indeed, the decrease in diastolic compliance in the left atrium in CHF has been shown to limit the increase in receptor discharge as left atrial pressure increases during filling⁴⁰. In addition, gross morphological changes in atrial stretch receptors were observed in dogs with CHF⁴². Whether such a change in receptor discharge in CHF rats remains to be determined. Although the possibility of altered vagal afferent sensitivity in CHF has not been assessed in rats, the data available to date indicate that an

altered afferent limb of the volume reflex may contribute to the overall blunted diuretic and natriuretic response to volume load observed in CHF rats.

Central sites of integration for the volume receptor reflex

Anatomical, electrophysiological and histological evidence have clearly identified the nucleus tractus solitarius (NTS) as the primary site of termination for afferent vagal fibers⁵³. In addition, the forebrain has been examined thoroughly for its involvement in various aspects of fluid balance⁵⁴. The paraventricular nucleus (magnocellular subdivision of PVN - mPVN) and the supraoptic nucleus (SON) are known to produce AVP, an important humoral factor involved in fluid balance⁵⁵. In addition to these effects, the PVN (parvocellular subdivision of PVN - pPVN) has been implicated in the control of sympathetic outflow. Specifically, we demonstrated that lesioning the pPVN with kainic acid altered the renal sympatho-inhibition produced in response to acute volume expansion⁵⁶. Other areas in the forebrain, important in the control of fluid balance, are the subfornical organ and the organum vasculosum of the lamina terminalis⁵⁷. In addition, neurons in the PVN are known to function as integrators of autonomic outflow, particularly to the kidneys⁵⁵.

Relatively few studies have examined changes in the central structures of the brain associated with the volume reflex in CHF⁵⁸. In previous studies we found that rats with CHF had significantly elevated hexokinase activity (an index of metabolic activity) in the pPVN and mPVN compared to sham rats⁵⁹. Because the mPVN is a main site for AVP-synthesizing neurons, these changes are in accord with findings of increased serum levels of AVP reported in humans⁶⁰ and rats⁶¹ with CHF. In addition, rats with CHF exhibit a resetting of the osmotic regulation of AVP secretion in such a way that higher plasma AVP levels were observed at lower levels of plasma sodium or osmolality^{61;62}. Such a resetting of the osmotic regulation of AVP secretion may also contribute to the blunted volume reflex in rats with CHF. The effectiveness of tolvaptan in the treatment of chronic hyponatremia in CHF may be related to this mechanism⁶³. In addition, the increased neuronal activity in the pPVN of rats with CHF may contribute to the increased renal sympatho-excitation observed in this model of CHF^{59;64}.

Finally, it is of interest that the neuronal isoform of nitric oxide synthase (nNOS) within the PVN has been demonstrated to be an important contributor to the volume reflex-mediated renal sympatho-inhibition in normal rats⁶⁵ and that nNOS within the PVN of rats with CHF is decreased^{66;67}. It may well be that decreased nNOS within the PVN of rats with CHF may be responsible, in part, for the altered volume reflex in rats with CHF. Further studies are needed to elucidate the causal relationship between these parameters.

Efferent limb of the volume receptor reflex

The efferent mechanisms that regulate the reflex diuretic and natriuretic responses to volume expansion are neural and humoral^{48;50}. It has been well established that the neural component of the diuretic and natriuretic response to volume expansion is mediated, in part, by a decrease in RSNA^{48;50}. Since increased RSNA produces retention of salt and water, decreased RSNA can contribute to diuresis and natriuresis⁵⁰. Several humoral factors such as angiotensin II, aldosterone, AVP, and atrial natriuretic factor also contribute to the effector limb of the volume reflex.

Neural component

Data obtained primarily from rat experiments, indicate that sodium excretion from innervated kidneys is attenuated in rats with CHF compared to that of sham operated control rats; whereas, the sodium excretion from denervated kidneys of rats with CHF is similar to that from innervated kidneys of sham rats⁵⁰. Furthermore, urine flow and sodium excretion

from innervated kidneys, but not from denervated kidneys, were significantly lower in rats with CHF than those in sham rats⁵⁰. These results suggest that part of the blunted natriuresis to volume expansion in rats with CHF is due to the tonic impact of the renal nerves. The impaired natriuresis to volume expansion in innervated kidneys of rats with CHF may be due to 1) blunted afferent and central inhibition of RSNA or 2) a hyperactive effect at the neuro-effector junction sites to enhance sodium reabsorption. Recording of RSNA demonstrates that there is blunted inhibition of RSNA to a given increase in central venous pressure in rats with CHF compared to normal control rats⁵⁰. Since RSNA produces retention of sodium and water, decreased RSNA can contribute to diuresis and natriuresis during volume expansion. The influences of the renal nerves on excretory function are, in large part, mediated by α -1 adrenergic receptors. There are no studies to date reporting the density of adrenergic receptors in the kidneys of rats with CHF. Such an increased α -1 activity in the kidney of rats with CHF may contribute to the increased retention of sodium by the kidney when RSNA is elevated. Despite the accumulating evidence that the neural effector limb of the volume reflex is blunted in CHF, several key questions remain unanswered: Is the RSNA abnormally elevated before and during acute volume expansion in rats with CHF? Is CHF accompanied by an altered relationship between RSNA and the subsequent release of norepinephrine, which may be affected by various factors such as turnover of NE and, presynaptic excitation or inhibition? Is the renal excretory response to sympathetic nerve stimulation augmented in rats with CHF? Is renal noradrenergic receptor density increased in CHF? If so, is it specific to a particular tubular segment? Answers to all these questions will identify some of the specific mechanisms by which the renal sympathetic nerves are involved in sodium retention in response to acute volume expansion in CHF.

Humoral component

Several humoral abnormalities have been reported to accompany CHF^{43;60}. In light of the direct impact of atrial stretch on the release of atrial natriuretic peptide (ANP), of elevated basal ANP levels in CHF are relevant to the renal excretory response to volume expansion. Volume expansion does not increase ANP levels in CHF rats to the same extent that it does in sham rats⁶⁸. To determine whether or not renal responses to ANP are altered in the CHF state, the diuretic and natriuretic responses to ANP administration were assessed in innervated and denervated kidneys of anesthetized control and CHF rats⁵⁰. Compared with control rats, CHF rats exhibited significantly blunted diuretic and natriuretic responses to ANP, and this effect was independent of renal innervation⁵⁰. GFR measurements indicated that hemodynamic changes did not account for the blunted renal excretory responses in CHF rats. These results confirm that hemodynamic changes *per se* are not responsible for the altered volume reflex in rats with CHF and indicate that renal excretory responses to ANP are blunted in CHF regardless of the presence of renal nerves.

As stated above, we have previously shown that renal nerves contribute to the retention of sodium and water in rats with CHF⁵⁰. However, we also demonstrated that although renal denervation normalized the blunted renal diuretic and natriuretic responses to acute volume expansion, these responses from renal denervated kidneys of CHF rats were still significantly blunted when compared to the renal denervated control rats. These results suggest that in addition to the renal nerves, there are other factor/s that are involved in sodium retention during CHF. The excessive retention of sodium in CHF may result from either a reduced GFR or an enhanced tubular reabsorption or both. The key element involved in renal sodium retention is activation of apical ENaC in the collecting tubule by aldosterone and AVP. Elevated basal plasma aldosterone and AVP with increased sodium intake have been linked to CHF⁶⁹. However, the roles of various tubular segments and the molecular basis for the inappropriate sodium and water retention remain largely undefined

in CHF. In particular, there is very little, if any, information regarding the abundance and functional role of epithelial sodium channels (ENaC) in the kidneys of rats with CHF. Chronic administration of aldosterone increases the α -ENaC subunit and to a lesser extent the β and γ subunits⁷⁰ at the mRNA and protein levels. In contrast, AVP has a different effect from that observed with aldosterone. It primarily increases the expression of the β and γ subunits but not α to any great extent⁷¹. It has recently been reported that there is enhanced renal abundance and increased functional activity of ENaC subunits in animals with CHF⁷². This study demonstrated that the mRNA and protein levels of α , β , and γ subunits of ENaC were significantly increased in the cortex and outer medulla of the kidneys from rats with CHF. Immunohistochemistry confirmed the increased α -ENaC, β -ENaC and γ -ENaC subunits in the collecting duct segments in rats with CHF. These results are consistent with the observations that both aldosterone and AVP are increased in rats with CHF⁶⁹. Furthermore, the diuretic and natriuretic responses to the ENaC inhibitor benzamil were increased in the rats with CHF. Renal denervation unmasked a greater role for ENaC in CHF⁷². The observed increased expression of ENaC subunits associated with enhanced channel function suggest that dysregulation of renal ENaC subunits could be involved in the retention of sodium chloride and thus contribute to the pathogenesis and development of CHF.

The Central RAS and Sympatho-excitation in CHF

The RAS has been implicated in the central processing of sympathetic nerve activity⁷³⁻⁷⁶. In dogs with CHF, cerebrospinal fluid concentrations of Ang II are markedly elevated⁷⁷ and are substantially higher than those observed in dog plasma⁷⁸. These data raise the important question of the contribution of the central RAS to sympatho-excitation and ABR function in the setting of CHF. While this is difficult to assess in humans there are substantial data that strongly implicate activation of the central RAS system in animal's models of heart failure⁷⁹.

A wealth of evidence support the idea that all the components necessary to synthesize Ang II are located within the central nervous system⁸⁰. In studies carried out in rabbits with pacing-induced heart failure it was shown that expression of the AT1 receptor was increased in the rostral ventrolateral medulla (RVLM)^{81;82}. These data have also been confirmed in the rat paraventricular nucleus (PVN), RVLM and NTS⁸³⁻⁸⁵. Contributing to this central "angiotensinergic drive" in CHF is the finding that ACE is increased in the brain of animals with CHF⁸⁶. Recently, it has become clear that central Ang II contributes to oxidative stress which can activate sympathetic neurons^{10;87;88}. This effect may be very important because reducing central oxidative stress by overexpression of antioxidant enzymes in the setting of CHF not only reduces sympathetic outflow but also improves cardiac function^{11;81}.

Sympatho-excitatory Reflexes

Whereas baroreflexes provide a tonic inhibitory influence on sympathetic outflow, a number of other peripheral autonomic reflexes provide an excitatory influence. These include the cardiac sympathetic (spinal) afferent reflex, the peripheral (carotid body [CB]) chemoreflex, and the somatic afferent reflex (or ergoreflex) from exercising skeletal muscle (exercise pressor reflex). These sympatho-excitatory reflexes are enhanced in CHF and thus contribute in a 'feed-forward' manner to elevations in sympathetic outflow.

Cardiac Sympathetic Afferent Reflex

The cardiac sympathetic afferent reflex is difficult to study in humans, but the reflex is enhanced in CHF animals^{89;90}. The afferent signal arises from ischemically sensitive endings located mainly in the epicardial regions of the left ventricle. Under normal

conditions these afferents have little influence on sympathetic activity, but in CHF, they are sensitized to chemical mediators and become tonically active^{91;92}. The precise mechanisms by which these endings become sensitized in CHF are not yet understood. These afferent endings are known to be sensitized and activated by a variety of chemical mediators released from ischemic myocardium, including protons, bradykinin, prostaglandins, histamine, reactive oxygen species, ATP and adenosine⁹³. The failing heart enters into a progressive state of functional ischemia due to impaired coronary flow (as seen in patients with myocardial infarctions), increased wall stress secondary to volume overload, and increased myocardial energy expenditure sustained by tonically elevated cardiac sympathetic drive. Studies have confirmed that cardiac sympathetic afferent activity in CHF animals is enhanced in response to exogenous epicardial bradykinin via a prostaglandin intermediate⁹⁴. The sympathetic reflex in CHF is also enhanced in response to epicardial application of hydrogen peroxide and adenosine⁹². Further, volume expansion of the left ventricle enhances the reflex sympathetic activation in response to chemical stimulation of these afferent endings⁹⁵. Collectively, these studies suggest that the cardiac sympathetic afferent endings are sensitized to a variety of stimuli in CHF associated with cardiac stress.

In addition to an enhancement of the sensory limb of the reflex, it is also well established that the central gain of the cardiac sympathetic afferent reflex is enhanced in CHF^{89;92}. This phenomenon was verified by observing an enhanced sympathetic nerve activity in response to electrical stimulation of the cardiac sympathetic afferent nerve, which serves to control the neural input traveling to the CNS⁸⁹. Subsequent studies demonstrated that both increased central Ang II with downstream ROS activation and reduced central NO contribute to the increase in central gain of the cardiac reflex in CHF animals⁹⁶⁻⁹⁸. Central Ang II and NO effects on the reflex have been localized at the levels of the NTS, PVN^{99;100}, and RVLM¹⁰¹. However, it is likely that these central mediators are acting at multiple autonomic nuclei involved in integration of the reflex. The tonic elevation in cardiac afferent input also impacts the integration of inputs from peripheral reflexes at the level of the NTS through an AngII-AT1 receptor mechanism. Thus, cardiac sympathetic afferents also serve to enhance carotid body chemoreflex activation of sympathetic outflow and to impair baroreflex inhibition of sympathetic outflow in CHF^{84;102}.

Carotid Body Chemoreflex

Enhanced activation of sympathetic outflow and ventilation in response to CB chemoreflex activation is well documented in CHF. These changes were first shown in humans¹⁰³, but more recent studies in CHF animals have detailed the changes in carotid body chemoreceptor function that contribute to these effects¹⁰⁴. There is an enhanced CB sensitivity to hypoxia in addition to an elevation in resting afferent chemoreceptor nerve activity under resting normoxic conditions¹⁰⁵ that contributes to a tonic elevation of sympathetic outflow in CHF¹⁰⁶. The enhanced chemoreceptor nerve activity occurs as a result of synergistic effects within the CB of increased production of reactive oxygen species from elevated Ang II-driven NADPH oxidase activity^{107;108}, decreased cytosolic and mitochondrial superoxide dismutase expression^{109;110}, and decreased NO production via downregulation of nNOS^{105;111}.

The neuro-excitatory effect of Ang II- superoxide and the neuro-inhibitory effect of NO on CB chemoreceptors are consistent with their opposing effects on ion channel function in CB glomus cells, the sensory cell of the CB. Elevated superoxide derived from Ang II activation of NADPH oxidase and suppression of SOD activity inhibits voltage gated K⁺ currents in these cells in the CHF state¹¹². Conversely, NO, which normally acts on these cells to enhance voltage-gated K⁺ currents, is suppressed in CHF^{113;114}. The glomus cells also exhibit enhanced voltage-gated Ca⁺⁺ currents in CHF¹¹⁴, which is consistent with known effects of Ang II and NO on these channels. These changes would facilitate depolarization

of glomus cells to hypoxia and may also contribute to the elevation in resting nerve traffic that occurs from the CB in CHF.

A recent study has shown that a chronic reduction of CB blood flow, similar to that observed in CHF animals, induce changes in CB afferent and reflex function that mimic the CHF state¹¹⁵ (Figure 4). Thus the impairment in cardiac output and reduced local blood flow associated with CHF are implicated as a primary driving force for altered peripheral chemoreflex function in CHF. This relationship is further supported by evidence that the degree of chemoreflex enhancement is correlated with the degree of LV dysfunction¹¹⁶ and the reduction in carotid blood flow. Further studies are needed to elucidate the mechanisms of flow sensitivity in the CB and their impact on CB function and autonomic control in CHF.

Exercise Pressor Reflex

A third major reflex input to excitation of sympathetic nerve activity is the exercise pressor reflex or the ergoreflex. The ergoreflex originates from stimulation of mechanically (group III) and metabolically (group IV) sensitive endings in contracting skeletal muscle. There is substantial and uniform agreement that the ergoreflex is exaggerated in CHF¹¹⁷⁻¹¹⁹. However, the role of the mechanical and metabolic components of the sensory stimulus responsible for this exaggerated reflex in CHF remains controversial. Evidence from human and experimental animal studies suggests that the mechanoreceptor component to the reflex is enhanced whereas the metabolic component is blunted in CHF¹²⁰⁻¹²³. In contrast, other studies suggest that the metaboreflex component is enhanced in CHF¹²⁴⁻¹²⁶.

Direct recordings from group III and IV afferents from the triceps surae in rats provide some insight into this controversy. These studies have demonstrated that the activation of group III afferents in response to static contraction of the muscle is enhanced in CHF¹²⁷, whereas that of group IV afferents to static contraction and to chemical stimulation is blunted in CHF animals^{127;128}. These effects were related to increased purinergic 2X receptor sensitization of group III afferents, and reduced vanilloid receptor (VR1) mediation of group IV activation^{127;128}. Other studies have demonstrated that several other chemical mediators also contribute to the enhanced sensitivity of group III mechanosensitive afferents in CHF. These mediators include bradykinin¹²⁹, prostaglandins¹³⁰, and reactive oxygen species¹³¹.

It is important to point out that studies describing afferent neural responses have utilized static muscle contraction to activate the afferent sensory endings. In this regard, some of the controversy of the role of metabolic muscle afferents in mediating an exaggerated exercise pressor reflex in CHF may be related to the type of muscle work being performed. Important evidence indicates that a significant portion of the elevated muscle sympathetic nerve activation during rhythmic handgrip exercise in CHF patients can be attributed to metaboreceptors¹²⁵, whereas the metaboreceptor contribution was attenuated during static handgrip exercise¹²³. Metabolic derangements in exercising muscle are likely to be more manifest during rhythmic vs. static exercise¹³². Further studies are needed to evaluate the impact of rhythmic vs. static exercise on the exercise pressor reflex in CHF.

Summary

Targeting the sympathetic nervous system and hormonal activation has been at the center of treatment for CHF for many years. The control of neurohumoral activation in the setting of CHF is multifactorial, but clearly involves abnormalities in both peripheral sensors and the central nervous system. The arterial baroreflex and the volume reflex are major negative feedback systems that contribute to sympatho-excitation in CHF. In addition, excitatory reflexes such as the carotid body chemoreflex, the ergoreflex and the cardiac sympathetic

afferent reflex play a role in this sympatho-excitation. There are several peripheral and central humoral modulators that impact the sensitivity of these reflexes. AngII, NO and reactive oxygen species have been shown to be important regulators of cardiovascular reflex function in CHF. A critical question in this field is the contribution of these mechanisms to early heart failure and the progression of the disease process. This has been a difficult question to answer, especially in humans. Most experimental models of CHF are evaluated late in the progression of the disease. The role of the renin-angiotensin system early in CHF is still controversial. Additional human and animal studies are needed to evaluate neurohumoral activation in the earliest phases of CHF.

Acknowledgments

Some of the work shown in this paper was supported by a grant from the NIH; PO-1 HL62222.

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Figure 1.
Muscle sympathetic nerve activity (MSNA) recorded from the peroneal nerve of patients with increasing levels of cardiac dysfunction. Reprinted with permission from reference 13.

Figure 2.

Renal Sympathetic nerve activity in conscious rabbits during the progression of pacing-induced CHF (upper panel). There was a significant increase in RSNA after 3 weeks of pacing (* $p < 0.05$ compared to control; $n = 5$). The lower panel shows plasma Angiotensin II concentration for groups of rabbits examined before (black bars) and after each week of cardiac pacing. (* $p < 0.05$ compared to pre pace; $n = 5$)

Figure 3.

Relationship between the change in Renal Sympathetic Nerve Discharge (RSND) and change in Central Venous Pressure (CVP) in anesthetized sham operated control rats and coronary artery ligated rats with heart failure during acute volume expansion with isotonic saline. There was a significantly blunted renal sympho-inhibition in rats with heart failure ($P < 0.05$).

Figure 4.

The effects of normoxic and hypoxic states on renal sympathetic nerve activity (RSNA) and carotid body (CB) chemoreceptor discharge in sham, chronic heart failure (CHF) and chronic carotid occlusion (CAO) rabbits.

A. Representative recording of RSNA; B. RSNA response to hypoxia (n=12); C. Representative recording of CB chemoreceptor afferent discharge; D. CB chemoafferent response to hypoxia (n=6); DF, discharge frequency; AP, action potential. PaO₂, arterial oxygen partial pressure. CAO: bilateral carotid artery flow was decreased chronically (3 wk) to the same extent as that observed in CHF rabbits. Data are mean $\pm$ SEM. *P<0.05 CHF and CAO compared with sham group. Reprinted with permission from reference 112.