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Invited review

Cardiac sympathetic nerve terminal function in congestive heart failure[1]

Chang-seng LIANG[2]

School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642, USA

Key words

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[1] Project supported by a grant from USPHS National Heart, Lung, and Blood Institute (No HL-68151).
[2] Correspondence to Prof Chang-seng LIANG.
Phn 1-585-341-7706.
Fax 1-585-341-4216.
E-mail chang-seng_liang@urmc.rochester.edu

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Abstract

Increased cardiac release of norepinephrine (NE) and depleted cardiac stores of NE are two salient features of the human failing heart. Researches from my laboratory have shown that these changes are accompanied by a functional defect of NE uptake in the cardiac sympathetic nerve terminals. Our studies have shown that the decrease of NE uptake is caused by reduction of NE transporter density in the sympathetic nerve endings, and this change is responsible, at least in part, for the increased myocardial interstitial NE, decreased myocardial adrenoceptor density, and increased myocyte apoptosis in experimental cardiomyopathies. We have also provided evidence in both intact animals and cultured PC12 cells that the decrease of NE transporter is induced by the actions of oxidative metabolites of exogenous NE, involving endoplasmic reticulum stress and impaired N-glycosylation of the NE transporter. This change in the cardiac sympathetic NE uptake function, as demonstrated by [^{123}I] metaiodobenzylguanidine in human studies, may not only serve as an important prognostic variable in patients with congestive heart failure, but also be used as a surrogate for the efficacies of various therapeutic interventions for heart failure. Finally, increasing evidence suggests and further studies are needed to show that the cardiac sympathetic nerve terminal function may be a direct target for pharmacologic treatment of congestive heart failure.

Introduction

It has been long recognized that cardiac norepinephrine (NE) is depleted in patients with congestive heart failure[1,2]. Early studies have shown that NE depletion is associated with increased release of cardiac NE secondary to heightened sympathetic nervous activity and decreased synthesis of NE in patients with congestive heart failure[2–5]. It was thought initially that the heightened sympathetic activity was an important adaptive mechanism to support the failing myocardium, and that the subsequent depletion of cardiac NE stores contributed to the progressive deterioration of cardiac function and the decreased myocardial contractility seen in chronic heart failure. However, it was later discovered that the intrinsic contractility of the heart muscle remains normal after depletion of myocardial NE by reserpine treatment or cardiac denervation[6]. Thus, normal cardiac stores of NE are not essential for maintaining the intrinsic myocardial contractility, and NE depletion does not account for the myocardial depression in heart failure. However, as an overwhelming majority of NE is stored in the intraneuronal storage vesicles, tissue content of NE does not accurately reflect myocardial interstitial NE concentration which is elevated in heart failure. Recent studies from our laboratory and others have provided new insights into cardiac sympathetic nerve terminal function in heart failure, and it has been suggested that abnormal NE uptake in the sympathetic nerve ending plays an important pathophysiological role in dilated cardiomyopathy. The findings further indicate that the change in NE uptake in chronic heart failure is maladaptive, and might be a novel therapeutic target in the treatment of congestive heart failure.

Reduction of NE uptake transporter in heart failure

Myocardial uptake of NE is known to be reduced in the failing heart. In experimental heart failure produced by aortic constriction, Spann *et al*[7] showed that the intravenous infusion of NE resulted in a much smaller increase in cardiac NE in guinea pigs with heart failure than normal animals, but the increase of NE in the kidneys did not differ between the 2 groups of animals. They attributed the organ-specific difference of tissue NE uptake to a diminished number of sympathetic nerves and/or binding sites in the failing heart. We now know that the primary defect is caused by a reduction of neuronal NE transporter (NET) density at the sympathetic nerve endings[8]. Since the NE uptake mechanism is responsible for a rapid removal of interstitial NE after the sympathetic release of NE, this defect of NE uptake has been used to explain, at least in part, the selective increase of the cardiac washout of NE. The amount of NE in the myocardial interstitial space is also expected to increase and causes greater actions on the postsynaptic adrenergic receptors. NET, a 617 amino acid protein, comprises of 12 transmembrane domains at the sympathetic nerve endings[9]. It is a member of the Na^+ and Cl^--dependent family of neurotransmitter transporters. It takes up NE from the interstitial space back to the adrenergic nerve terminals with the stoichiometric exchange of Na^+ and Cl^- against their electrochemical gradients[10].

Our laboratory has studied the pre- and postsynaptic function of the cardiac sympathetic nerves for many years. Our interest began with a novel observation in experimental, right ventricle heart failure dogs produced by tricuspid avulsion, and progressive pulmonary artery constriction where myocardial β-receptor density was reduced only in the failing right ventricle[11]. The chamber-specific reduction of myocardial β-receptor density was later confirmed in the failing human right ventricles associated with primary pulmonary hypertension[12]. We speculated that the decrease of myocardial β-receptors occurred because of a chamber-specific reduction of cardiac sympathetic NE uptake activity, leading to an increase of interstitial NE of the failing right ventricular myocardium. Indeed, we have shown that myocardial neuronal NE uptake activity as measured by the tissue accumulation of [^{3}H]NE *ex vivo* is reduced only in the failing right ventricular myocardium, and this change correlated with the reduction of myocardial β-receptors (Figure 1)[13]. We later studied the cardiac sympathetic nerve terminal dysfunction in heart failure by measuring the NE binding site density and numbers of sympathetic neuronal marker NE and tyrosine hydroxylase, using sucrose-potassium phosphate-glycoxylic acid-induced NE histofluorescence and tyrosine hydroxylase immunocytochemistry, respectively[13,14]. The sympathetic neuronal markers were reduced in the failing ventricle (Figure 2). In contrast, the contralateral non-failing left ventricle is relatively spared without reductions of myocardial β-receptors, NE uptake activity, NE uptake binding sites, or the numbers of neuronal profiles of NE and tyrosine hydroxylase. The NE uptake binding site density also did not change in the kidneys of the heart failure animals. These findings suggest that the changes in cardiac sympathetic nerve endings are produced by a local mechanism, and is organ- and chamber-specific, occurring only in the failing ventricle.

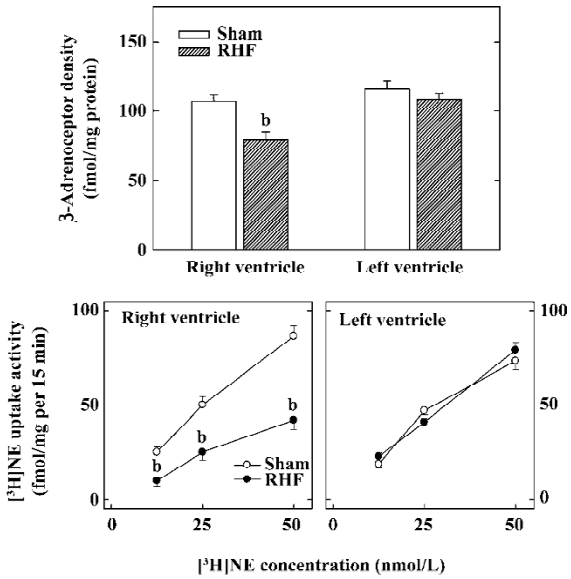

Figure 1. Chamber-specific reduction of myocardial β-adrenoceptors in the failing right ventricle of the right-heart failure (RHF) dogs (upper panel). β-Adrenoceptor density was measured using the [^{3}H] dihydroalprenolol ligand binding assay. Sympathetic nerve-specific ^{3}H uptake activity (representing tissue [^{3}H] NE uptake) at 3 different concentrations of [^{3}H] NE, using fresh tissue slices taken from the right and left ventricular free walls of sham-operated and RHF dogs (lower panels). Mean±SEM. n=20–30. $^bP<0.05$ *vs* sham-operated dogs. Modified with permission from Liang *et al*[13].

We have extended our observations in right ventricle heart failure animals to dogs with biventricular heart failure produced by rapid ventricular pacing[14]. In these animals, we also produced direct proof that myocardial interstitial NE increased in the failing heart, and that the interstitial NE correlated inversely with number of myocardial β-receptors (Figure 3)[15], indicating that the changes in the myocardial β-adrenoceptor density is agonist induced, secondary to the

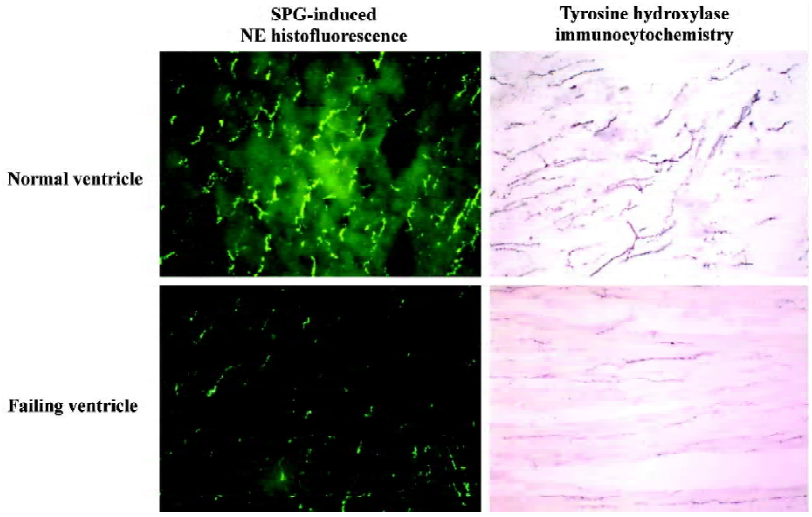

Figure 2. Representative myocardial tissue microphotographs showing reductions of sucrose-potassium phosphate-glyoxylic acid (SPG)-induced NE histofluorescence and tyrosine hydroxylase immunoreactive profiles in the failing ventricular myocardium.

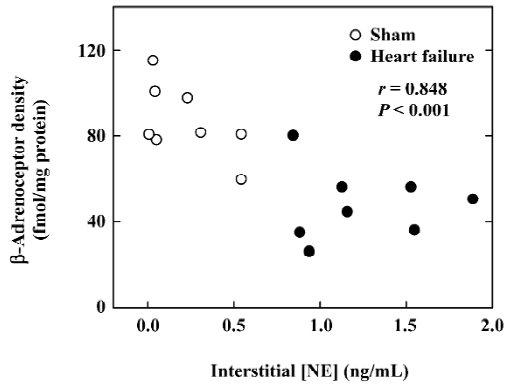

Figure 3. Scatterplot showing a significant inverse correlation between interstitial NE concentration and β-adrenoceptor density in heart failure and sham-operated animals. *r*=correlation coefficient. Adapted with permission from Delehanty *et al*[15].

reduction of NE neuronal uptake.

The functional importance of the NE uptake site was further studied in rabbits at various time intervals after the start of rapid ventricular pacing[16]. We found that rapid ventricular pacing caused early sympathetic nervous system activation, followed in sequence by the reduced myocardial NE uptake, loss of neuronal NE, and downregulation of myocardial β-adrenoceptors. However, there was no significant reduction of the protein gene product 9.5, a panneuronal marker, suggesting that the anatomic integrity of the cardiac sympathetic nerves probably is intact, and the changes of sympathetic neurotransmitters within the nerve endings are caused by functional abnormalities that are potentially reversible with either effective therapy or the removal of a primary insult that causes heart failure. The interdependence of increased sympathetic stimulation, decreased cardiac NE uptake, and myocardial β-adrenoceptor downregulation is further discussed in a study by Leineweber *et al*[17] who found that neurohumoral activation is essential for the reduction of myocardial β-receptors in the hypertrophied right ventricle produced by monocrotaline. This study, which is similar to our earlier studies of right ventricle heart failure, is characterized by a chamber-specific reduction of myocardial NE uptake sites[18].

Significance of NE re-uptake for cardiac function in heart failure

The physiological significance of the NE re-uptake mechanism in the regulation of myocardial β-receptor density and postsynaptic β-adrenergic inotropic responsiveness was further studied in heart failure animals treated with desipramine[19] and selegiline[20]. Desipramine is a NET inhibitor. In the present study, it increased myocardial interstitial NE in heart failure, and caused further reductions of myocardial β-adrenoceptor density and β-adrenergic subsensitivity. In contrast, selegiline, which is a central α_2-agonist with a neuroprotective effect, attenuated the increase in plasma NE and the decrease of myocardial β-receptor density and improved cardiac mechanical function in pacing-induced cardiomyopathy. These findings support the concept that interstitial NE is a modifiable variable, important in the mediation of agonist-induced postsynaptic events seen in heart failure.

To study the mechanism responsible for the NE uptake inhibition in heart failure, experiments have been conducted in our laboratory to show that the reductions of cardiac sympathetic transmitters and NET can be induced by exog-

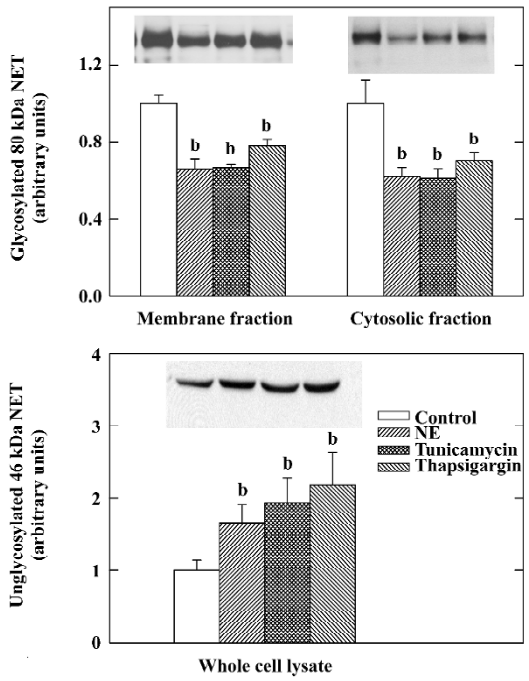

Figure 4. Effects of NE, tunicamycin, and thapsigargin on 2 populations of the NET protein in PC12 cells. NE treatment reduced the 80 kDa NET protein in the membrane and cytosolic fractions of the PC12 cells (upper panel). The 46 kDa NET protein was increased in the whole cell lysate after NE, tunicamycin, and thapsigargin treatment (lower panel). Optical density readings were normalized against a control sample in arbitrary units. Mean±SEM; n=6–8 in each group. $^bP<0.05$ *vs* control group without drug treatment, as measured by ANOVA and Bonferroni simultaneous confidence intervals for all comparisons. Modified with permission from Mao *et al*[25].

enous NE[21,22] and inhibited by desipramine[19,23] and antioxidants[22,24] in intact animals. Studies also have been conducted in cultured rat neuroblastoma cells (PC12) cells, indicating that NE reduces NE uptake activity and the NET protein in a dose-dependent fashion[25]. The changes of NE on the NET protein are reproduced by well-known endoplasmic reticulum stressors such as tunicamycin and thapsigargin (Figure 4). These effects of NE are most likely caused by endoplasmic reticulum stress, the resultant reduced glycosylation and the trafficking of NET to the cell membrane[26]. Our studies[26] have also shown that the reduction of the NET protein by NE in PC12 cells was not associated with changes in NET mRNA, suggesting that the NET protein downregulation is a post-transcriptional event. These findings are consistent with an earlier study of experimental heart failure in which the reduction of the cardiac NET protein in aortic-banded rats was associated with no change of NET mRNA in the left stellate ganglion[27]. NET gene expression also was unchanged in the stellate ganglia of rats with cardiac hypertrophy induced by pressure overload, despite a marked reduction of NE uptake site density in the hypertrophied left ventricle[28]. There is also evidence that the effects of NE on NET are associated with an increase in reactive oxygen species, and can be attenuated by the free-radical scavenger mannitol, or antioxidant enzymes superoxide dismutase and catalase. The findings suggest that the cardiac sympathetic nerve terminal dysfunction is probably caused by increased interstitial NE in heart failure, and the neuronal damage effect of NE involves the uptake of NE or its oxidative metabolites into the sympathetic nerve endings. More recently, endothelin-1 also has been shown to inhibit cardiac NE uptake and promote NE release from the failing heart via ET_A receptors[29]. Endothelin blockade also improves survival in experimental heart failure[30,31], but no long-term beneficial effects of either ET_A-specific[32] or non-specific endothelin receptor inhibitors[33] have been demonstrated in human heart failure.

Myocardial metaiodobenzylguanidine scintigraphy and its clinical utility in heart failure

Recently, radio-iodinated metaiodobenzylguanidine (MIBG), a structural analogue of NE, has been used to study the integrity and function of the cardiac sympathetic nervous system[34]. MIBG shares the same reuptake mechanism and storage site with NE. Thus, its uptake into the myocardium reflects both the distribution of cardiac sympathetic innervation and the extent of neuronal NE uptake activity. The failing heart is characterized by reduced distribution and washout of MIBG[35]. Abnormal MIBG uptake, calculated by the ratio of heart and mediastinum uptake, correlates with reduced myocardial contractile reserve in patients with dilated cardiomyopathy[36]. Similarly, c-11-HED, a PET-based NE analog, is significantly correlated to the NET density, and has been used to demonstrate regional variations of NE content in cardiomyopathy[37]. Thus, the MIBG and HED-PET patterns can be used as a non-invasive means to investigate the changes of cardiac sympathetic innervation in the hearts of cardiomyopathic patients. Studies have now shown that cardiac sympathetic nerve innervation, as demonstrated by MIBG scintigraphy, is an independent predictor for adverse clinical outcomes, including mortality in patients with heart failure[38,39]. Improvements in MIBG patterns also have been shown to occur in patients who respond favorably to carvedilol[40], metoprolol[41], spironolactone[42,43], enalapril[44], and cardiac resynchronization therapy[45]. In contrast, bucindolol therapy, which showed only marginal survival benefits[46], did not improve the sym-

pathetic nerve function as measured by MIBG[47]. However, because prior studies involved only small numbers of patients, the application of MIBG scintigraphy in heart failure remains investigational. In a recent editorial, Motherwell *et al*[48] discussed the proper use of MIBG scintigraphy and the limitations of current imaging protocols, as well as need of a better understanding of the kinetics of MIBG and standardization of imaging techniques and analyses in cardiac imaging. They concluded that a large multicenter trial with a standardized imaging protocol is required to establish the clinical utility of the MIBG in congestive heart failure in patients.

Therapeutic implications

Long-term β-blocker therapy is now widely accepted as a pillar in the treatment of systolic heart failure. Effective utilization of β-receptor blockers can not only improve left ventricular systolic function, but also increase survival in patients with chronic heart failure secondary to left ventricular systolic dysfunction[49–52]. Given the overwhelming success of the β-adrenoceptor blocker therapy, attempts have been made to determine if similar or greater beneficial effects can be derived from potent sympatholytic agents such as moxonidine, which has been shown to decrease peripheral sympathetic outflow and circulating plasma NE by stimulating the brain stem imidazoline-1 receptor[53]. Unfortunately, despite early enthusiasm with the centrally-acting sympatholytic agents[54,55], moxonidine therapy was considered detrimental because it tended to increase mortality and morbidity in chronic systolic heart failure in a large clinical trial[56]. Thus, the sympathetic nervous system activation can be both adaptive and maladaptive, depending on the degree of basal sympathetic activation and the extent of sympa-tholysis or β-receptor blockade. Furthermore, generalized sympathetic nervous system inhibition probably has limited therapeutic utility, and localized adrenergic inhibition at the cardiac receptor level is the preferred mode of therapy for heart failure.

Alternatively, the results of several recent studies suggest that without directly affecting the central sympathetic drive, cardiac function in heart failure may be modified by agents or interventions that upregulate the neuronal NET in the myocardium. Kreusser *et al*[57] reported that an injection of nerve growth factor into the stellate ganglia of rats with heart failure produced by transverse aortic constriction, improved NE uptake, repleted cardiac NE stores, and increased left ventricular fractional shortening. The number of cardiac sympathetic nerves, however, was unaffected. In a separate study[58], adenoviral gene transfer was used to overexpress NET in the myocardium of rabbits with pacing-induced cardiomyopathy. This resulted in increased NE uptake capacity and the reversal of β-receptor downregulation in the cardiac tissue. Local overexpression of cardiac NET also improved the systolic function and contractile reserve of the cardiomyopathic hearts. These findings not only confirm the importance of NET in the initiation or progression of cardiomyopathy, but also suggest that cardiac NET may be a novel therapeutic target in the treatment of congestive heart failure. Future research should be directed at the development of pharmacological agents or interventions that reduce the cardiac noradrenergic drive while preserving the integrity and NE reuptake function of the sympathetic nerve terminals.

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