Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers

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Abstract
Heart failure (HF) is a complex clinical syndrome characterized by the activation of at least several neurohumoral pathways that have a common role in maintaining cardiac output and adequate perfusion pressure of target organs and tissues. The sympathetic nervous system (SNS) is upregulated in HF as evident in dysfunctional baroreceptor and chemoreceptor reflexes, circulating and neuronal catecholamine spillover, attenuated parasympathetic response, and augmented sympathetic outflow to the heart, kidneys and skeletal muscles. When these sympathoexcitatory effects on the cardiovascular system are sustained chronically they initiate the vicious circle of HF progression and become associated with cardiomyocyte apoptosis, maladaptive ventricular and vascular remodeling, arrhythmogenesis, and poor prognosis in patients with HF. These detrimental effects of SNS activity on outcomes in HF warrant adequate diagnostic and treatment modalities. Therefore, this review summarizes basic physiological concepts about the interaction of SNS with the cardiovascular system and highlights key pathophysiological mechanisms of SNS derangement in HF. Finally, special emphasis in this review is placed on the integrative and up-to-date overview of diagnostic modalities such as SNS imaging methods and novel laboratory biomarkers that could aid in the assessment of the degree of SNS activation and provide reliable prognostic information among patients with HF.
Heart failure (HF) is a complex clinical syndrome characterized by the symptoms such as breathlessness, fatigue and ankle edema and signs like elevated jugular venous pressure, lung crepitations during auscultation and peripheral edema. The central hemodynamic consequence of HF is the inability of a heart to support required metabolic demands and perfusion of organs and tissues due to structural and/or functional cardiac abnormalities that predispose to decreased cardiac output (CO) and/or increased intracardiac filling pressures during the rest or exercise. HF nowadays represents a relevant clinical entity and global pandemic that affects more than 26 million adults worldwide while its general prevalence in population accrues to about 2% with yearly incidence of approximately 0.2% in Western countries. Projected burden of HF, assuming the stable incidence of this syndrome in persons ≥65 years was already surpassed by the actual burden of the HF in the United States and it is expected that more than 8 million people will have this condition in the United States by 2030. This increase in HF prevalence observed worldwide might be attributed not necessarily to increased HF incidence but to phenomena such as advancing age of the population and increased comorbidity burden coupled with improved HF survival due to progress in HF treatment and diagnosis while the decreased incidence of HF according to some data might partially be the consequence of more efficacious treatment of acute coronary syndromes, lower severity of index HF events and improvements in HF primary prevention programs.

Despite the advancements in therapeutic management, HF is still characterized by the rather high morbidity and mortality rates and considerable healthcare expenditures while these outcomes appear to be strongly dependent on the region of the world, healthcare infrastructure and the level of quality/access to specialized HF care. Of note, HF is at least as deadly or even deadlier than some of the common malignancies in both men and women. Among patients, HF with worse mortality outcomes than those with prostate and bladder cancer while among women those with HF had worse mortality outcomes than female patients suffering from breast cancer. Survival after a diagnosis of HF has shown only modest improvement in the 21st century, with an increase in average survival rates between 6.4% to 7.2% during nearly two decades thus clearly indicating that our clinical efforts to improve outcomes in HF substantially lag behind advancements in other severe conditions such as cancer. In support to this notion, a recent data from the United States nationwide temporal analysis showed that age-adjusted death rates for HF did not change significantly, in fact there even emerges a trend of the slight rise of HF-related mortality recently, after nearly 15 years of modest but gradual decline in HF-related
mortality since the late nineties\[13\]. Similarly, recent longitudinal data acquired from the Framingham Heart Study and Cardiovascular Health Study showed that HF incidence was relatively stable for almost two decades and this was true for mortality outcomes as well (including cardiac death, non-cardiac death, and all-cause mortality)\[14\]. This study also showed that the incidence of heart failure with reduced ejection fraction (HFrEF) significantly declined whereas the incidence of heart failure with preserved ejection fraction (HFpEF) significantly increased over time in both sexes. Approximately 50% of community patients with HF nowadays have an HFpEF clinical phenotype while multimorbidity seems to be a stronger driver for HFpEF onset although it is a highly prevalent phenomenon in both HFrEF and HFpEF. Likewise, both phenotypes portend a comparable 5-year mortality\[15\]-\[17\]. Finally, the proportion of those dying of non-cardiovascular causes seems to be higher in HFpEF than HFrEF and this holds for non-cardiovascular-related 30-d readmissions that are more common among HFpEF compared with HFrEF patients\[18\]-\[20\].

Taken together, these recent trends strongly suggest that HF is a clinical entity that will continue to impose a significant burden on modern societies, urging for the advances in our understanding of its complex pathophysiology and development of new treatments. Equally important, the discovery and implementation of biomarkers that might aid in the diagnosis, prognosis, and risk stratification of patients with HF is required in a contemporary clinical practice\[21\]-\[23\]. For these reasons, aims of the present review are to provide recent updates regarding the HF pathophysiology with the special emphasis on novel biomarkers that might reflect the sympathetic nervous system (SNS) activation as one of the constituent neurohumoral pathways that are upregulated to preserve CO in the setting of a failing heart.

PATHOPHYSIOLOGY AND COMPENSATORY MECHANISMS IN HEART FAILURE

Any abnormality or combination of abnormalities that cause structural, mechanical, or electrical dysfunction of the heart carry the potential to induce HF. Most commonly HF is the consequence of the myocyte injury caused by coronary artery disease, uncontrolled arterial hypertension and diabetes mellitus, however, adverse myocardial remodeling can be triggered and sustained by valvular dysfunction, tachyarrhythmias (especially atrial fibrillation/flutter), interatrial and interventricular conduction abnormalities or pulmonary disorders such as chronic obstructive pulmonary disease or pulmonary arterial hypertension\[9\]. Less common etiologies include cardiomyopathies, myocarditis, infections, systemic toxins, and cardiotoxic drugs that are nowadays increasingly used in various chemotherapeutic regimens\[24,25\]. At least several pathophysiological mechanisms are at play in the setting of failing myocardium such as increased hemodynamic overload, ventricular dysfunction due to subclinical or overt ischemia, pathologic ventricular remodeling, upregulated neurohumoral activation, impaired intracellular calcium cycling and accelerated apoptosis of cardiac myocytes, imbalance in the formation and breakdown of the extracellular matrix, and various genetic predilections\[9\].

Clinically, a majority of patients with HF have both systolic and the diastolic dysfunction occurring at the same time and these two pathophysiological mechanisms often overlap but even in the isolation of each other, they cause a similar degree of HF signs and symptoms\[26,27\]. For the didactic purposes, in the systolic dysfunction, the primary pathomorphological substrate is the loss of functional myocardium (primary myocyte injury) most commonly due to ischemic disease and myocardial infarction causing impaired contractility and insufficient emptying of the ventricles consequently leading to increased left ventricular (LV) end-diastolic and end-systolic volumes and rise in end-diastolic pressure (LVEDP) within the left ventricle further decreasing stroke volume and left ventricular ejection fraction (LVEF)\[25,26\]. An increase in LVEDP might retrogradely increase left atrial (LA) pressure which consequently increases pressure in the pulmonary circulation, and if this cascade progresses even further can induce right heart failure, congestive hepatopathy and affect portal and peripheral circulation thus altogether precipitating fluid extravasation leading to pulmonary and/or splanchnic and peripheral congestion.

On the other hand, in diastolic dysfunction, the contractile ability of the heart might be preserved, however, functional mechanisms that are responsible for the adequate filling of the heart are impaired. It is estimated that up to 50% of patients presenting with signs and symptoms of HF have normal or near-normal LVEF but exhibit abnormalities predominantly in diastolic function\[27,28\]. Even more, those with normal
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LVEF by conventional transthoracic echocardiography and verified diastolic dysfunction can often have subclinical contractile dysfunction that is captured only by the means of myocardial deformation studies such as LV global longitudinal strain and speckle tracking techniques or advanced cardiac imaging methods such as cardiac magnetic resonance[35-38]. These filling abnormalities may occur due to impairments in early diastolic relaxation of the LV (an active energy-consuming process) and/or increased stiffness and rigidity of the LA and LV (a passive process independent of energy) coupled with reduced arterial compliance in both major vessels such as the aorta and peripheral arteries[32,33]. Among patients with HFrEF both processes of active relaxation and increased passive stiffness are impaired and are predominant pathophysiological mechanisms leading to diastolic dysfunction[40-42]. These abnormalities altogether act synergistically to produce a rise in the LVEDP thus causing significant venous congestion in HFrEF patients that is as severe as among those with HFrEF[43]. Of note, significant increase in passive LV stiffness is propagated by aberrations in collagen-dependent and titin-dependent deposition cellular pathways[44]. Similarly, longstanding elevated ventricular pressures further perpetuate LA dilation that is clinically detected as an increased LA volume at rest and reduced LA filling during submaximal exercise[45]. Also, peripheral oxygen extraction is blunted in HFrEF resulting in exercise intolerance while reduced peak oxygen uptake and increased perfusion/ventilation mismatch carry important prognostic information and assist in the selection of patients that might require advanced HF interventions such as heart transplantation or deployment of ventricular assist devices[46,47].

A complex interaction of highly prevalent comorbidities such as salt-sensitive hypertension, obesity, diabetes mellitus, metabolic syndrome, iron deficiency, chronic obstructive pulmonary disease and, atrial fibrillation (AF), combined with natural pathophysiological effects of aging can give rise to systemic proinflammatory state that affects coronary microvasculature and endothelium by upregulating cytokine-mediated inflammation pathways[48-50]. In this proposed pathophysiological scheme, pioneered by Paulus and Tschöpe[49] in 2013, endothelial inflammation of coronary microvasculature acts as a central transitioning mechanism by which synergistic effects of comorbidities are translated onto heart thus causing secondary myocyte injury that ultimately leads to structural and functional alterations of the myocardium in HFrEF[45]. According to the postulated model, coronary microvascular endothelial inflammation reduces nitric oxide (NO) bioavailability and cyclic guanosine monophosphate (cGMP) content and reduces protein kinase G activity in adjacent cardiomyocytes thus highlighting NO-cGMP-PKG signaling pathway disruption as the key culprit in HFrEF pathophysiology. This disruption leads to the onset of cardiac hypertrophy and increased resting tension (Fpassive) of cardiomyocytes due to hypophosphorylation of titin and increased myocardial nitrosative/oxidative stress[45-47]. Furthermore, hypophosphorylation of constitutive myofilament proteins and increased calcium sensitivity of sarcomeres causes increased LV stiffness and abnormal relaxation contributing to HFrEF onset while these derangements are not present in normal myocardium[48]. Graziani et al[49] also proposed that microvascular dysfunction is the common pathophysiological pathway contributing to both microvascular angina and HFrEF[49]. Of note, endothelial dysfunction represents a pathological vascular phenotype of all systemic arteries that encompasses damaging effects of vasoconstrictive, prothrombotic and proinflammatory substances and mediators on the endothelial vascular lining and diminished reparability of endothelium thus further acting as an independent pathobiological driver of atherosclerosis and overt cardiovascular disease[48-52].

Furthermore, a novel pathophysiological concept of endothelial-to-mesenchymal transition has been recently proposed describing a process by which endothelial cells undergo a series of molecular events that lead to a loss of their endothelial properties and a consequent shift in phenotype toward mesenchymal cells such as myofibroblasts, smooth muscle cells, and osteoblasts[49]. Accumulation of these cells promotes plaque formation and atherosclerosis by secreting proinflammatory cytokines and metalloproteinases and increasing extracellular matrix and collagen deposition thereby affecting the structure and function of cardiac valves, native vein grafts that are used in coronary artery bypass graft surgery and inducing interstitial cardiac fibrosis, diastolic dysfunction, endocardial fibroelastosis and contributing even to the development of pulmonary arterial hypertension[49-51]. From the molecular perspective, it seems that activation of transforming growth factor-beta plays a key role in the initiation of endothelial-to-mesenchymal transition cascade and tissue fibrosis through its interaction with SMAD-2/3/4 and SLUG signaling pathways[52,53]. Furthermore, endothelial cells in which the EndoMT pathway was experimentally activated had significantly elevated secretion of proinflammatory
cytokines such as interleukin-6, interleukin-8 and tumor necrosis factor-alpha thus likely representing an integrative pathophysiological cross-talk between fibrosis and inflammation[9,24]. In summary, EndoMT might be the key link in interaction between inflammation, endothelial dysfunction, and chronic cardiac fibrosis, and thus might become a viable target for novel therapeutic solutions for cardiovascular disease[25,26].

Altogether, these converging and mutually complementary pathophysiological mechanisms may contribute to a net effect of stiffening of cardiac myocytes and overt interstitial fibrosis thus directly inducing myocardial dysfunction during diastole and subsequent HF development.

In order to maintain adequate tissue perfusion in the setting of the failing heart, several compensatory mechanisms are activated to increase CO via the Frank-Starling mechanism, increased ventricular volume and wall thickness through the process of ventricular remodeling and augmenting mean arterial pressure (MAP) by activating several neurohormonal pathways and cytokine systems[67,68]. These compensatory mechanisms are initially able to compensate for impaired myocardial function, however, they inflict deleterious effects on cardiac structure and function if chronically activated leading to further worsening of HF and progressive clinical deterioration of a patient. Neurohumoral systems that are upregulated act to promote beneficial short-term changes in heart, kidneys, and vasculature to maintain cardiovascular homeostasis[69]. They encompass the activation of the renin-angiotensin-aldosterone system (RAAS), arginine-vasopressin (anti-diuretic) system, kallikrein-kininogen-kinin system, activation of natriuretic peptides system, neprilysin signaling pathway, endothelin pathway, and cytokine systems[69,70]. Finally, the upregulation of adrenergic/SNS pathways and blunted responsiveness of the parasympathetic nervous system (PNS), also collectively known as autonomic nervous system (ANS) imbalance, is one of the hallmark neurohumoral disturbances that are operative in HF and is of central interest in this review[71,72]. The summary of the most common etiologies, pathophysiological effects, and compensatory mechanisms in HF is shown in Figure 1.

It is worth of brief mentioning that evidence-based treatments such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor neprilysin inhibitors, ivabradine, sodium/glucose cotransporter 2 inhibitors, digoxin, and cardiac resynchronization therapy (CRT) devices are developed around our understanding of compensatory and maladaptive mechanisms in HF[1,73]. Importantly, these treatment modalities were found successful in reducing mortality rates and hospitalizations in patients with HFrEF, however, no evidence-based pharmacologic treatments with clear beneficial effects on these endpoints were observed in patients with HFpEF while current guidelines stipulate symptom control with diuretics and efficacious management of comorbidities such as arterial hypertension, AF, obesity, and diabetes in this population[74].

Recent European Society of Cardiology and Heart Failure Association expert panel issued a scientific position statement in which ANS imbalance is recognized as an important contributor to cardiac disease progression and is designated as a prognostic parameter and a therapeutic target in HF by the means of novel pharmacologic and/or device therapies[75]. Furthermore, heart and brain are in bidirectional interaction meaning that depressed cardiac function affects cerebral structures and functional capacity while dysregulation of neuro-cardiac reflexes significantly affects the cardiovascular system thus aggravating and further sustaining the progression of HF[76]

PHYSIOLOGY OF SYMPATHETIC NERVOUS SYSTEM AND ITS MEDIATORS

In the advent of our understanding of HF, this syndrome was largely perceived as a hemodynamic disorder thus all treatment strategies were primarily directed toward the correction of hemodynamic abnormalities. However, since hemodynamic derangements could not fully explain the progression and long-term effects of the disease, a neurohormonal hypothesis was developed in which neurohumoral mechanisms encompassing RAAS and SNS activation were emphasized as independent drivers of cardiac dysfunction and progression of HF[77].

SNS activation is a fundamental physiological response to stress conditions (also known as the fight-or-flight response) such as hypovolemia, hypoglycemia, hypoxia or cardiovascular dysfunction[78]. SNS activity can modify and induce a wide spectrum of
potent hemodynamic effects such as an increase in heart rate (positive chronotropic effect), augmentation of cardiac contractility (positive inotropic effect), accelerated cardiac relaxation (positive lusitropic effect), enhanced (shortened) atrioventricular conduction (positive dromotropic effect), reduced venous capacitance and peripheral vasoconstriction of resistance and cutaneous vessels\(^\text{[71,79]}\). The actions of SNS are dominantly mediated by secreted neurotransmitters such as norepinephrine (NE) that is released by sympathetic nerve terminals and, to a lesser degree, by the adrenal medulla and by epinephrine (EPI) that is chiefly released into peripheral circulation by the adrenal medulla.

Peripheral target organs are regulated by the two major sets of neurons serially connected to control the motor outflow of the SNS: (1) Preganglionic neurons that originate in the brainstem or the spinal cord; and (2) Postganglionic neurons that are part of sympathetic ganglia that are located outside of the central nervous system (CNS). Intrathoracic and extracardiac ganglia including stellate ganglia, middle cervical ganglia, and T2-T4 thoracic ganglia modulate the sympathetic outflow to the heart while sympathetic afferent impulses are carried through the dorsal root ganglia and reach the spinal cord, brain stem, and higher CNS centers. Cardiac sympathetic nerve fibers innervate myocardium at the subepicardial level, follow the path of major coronary arteries and are a predominant autonomic component in the ventricular tissue while parasympathetic nerve fibers, along with vagus nerve, run through subendocardium crossing the atrioventricular groove and are significantly more abundant in the atrial than ventricular myocardium thus exerting negative chronotropic effect with minimal effects on cardiac contractility\(^\text{[79]}\). Furthermore, sympathetic innervation has a relatively higher density in the anatomical areas around sinoatrial node and coronary sinus while its density gradually increases from the base of the ventricle to the apex (positive base-to-apex gradient)\(^\text{[80,81]}\). Intrinsinc cardiac ganglia are located epicardially and receive innervation from post-ganglionic sympathetic and pre-ganglionic parasympathetic connections while most of sympathetic efferent and parasympathetic preganglionic fibers exhibit a large degree of intermixing thus most of the nerves reaching the heart in the mediastinum have mixed fibers (both sympathetic and parasympathetic components)\(^\text{[82]}\).

The degree of SNS activation and sympathetic outflow to the heart and peripheral circulation, under physiological conditions, is regulated by a complex integration of...
autonomic cardiovascular reflexes. These reflexes include arterial baroreflexes, cardiopulmonary mechanosensitive reflexes, cardiac chemoreflexes, peripheral and central chemoreceptor reflexes, pulmonary stretch reflexes, cardio-cardiac reflexes and reflexes that are afferently projected from skeletal muscles. All of these reflexes have a common role in fine-tuning and maintaining adequate heart rate, mean arterial blood pressure, vascular tone, ventilation, and respiratory drive in response to various hemodynamic changes. These reflexes are listed with a summary of their function and potential impairment in HF (Table 1). According to modern pathophysiological findings, any depression of ventricular systolic function (irrespective of the underlying etiology) is augmenting cardiac reflex sympathoexcitation in chronic HF but might also be a leading culprit for the acute HF onset. For example, a physiological response to the sudden increase in the cardiac filling pressures should act to vasodilate venous capacitance vessels to accommodate for excessive fluid, however, paradoxical sympathetic discharge in HF instead causes vasoconstriction of venous pool (mainly splanchnic circulation) and redistributes fluid to cardiopulmonary pool thus precipitating congestion and causing dyspnea. For this reason, it could be that rapid increase in the effective circulating volume from the mobilization of fluid from the splanchnic bed is the dominant driving force behind increased central venous pressure and congestion encountered during HF decompensation episode and might depend on an external fluid gain to a lesser degree. Finally, cardiovascular-low threshold polymodal receptors are sensory endings localized in all cardiac chambers and large thoracic vessels that detect both mechanical and chemical stimuli and act in positive-feedback fashion with stimulatory effects on SNS.

In terms of principal neurotransmitters that propagate the effects of SNS, NE is ejected in the synaptic cleft upon the stimulation from stellate ganglia via postganglionic fibers thus activating adrenergic receptors (ARs) in the heart and physiologically augmenting contractile strength, chronotropy, dromotropy and increasing mean arterial perfusion pressure. About 80% to 90% of released NE is reuptaken by the noradrenaline transporter 1 which is a monoamine transporter that clears NE from sympathetic nerve terminals/chromaffin cells while about 10% to 20% of remaining NE content is spilled into circulation. This NE turnover and metabolism can be evaluated with imaging methods such as scintigraphy by using radiolabelled guanethidine analogs of NE. Similarly, sympathetic fibers that innervate the adrenal gland stimulate chromaffin cells in the adrenal medulla that act as modified post-ganglionic fibers to release catecholamines in response to stressors or exercise. This efflux of catecholamines from adrenal medulla is predominantly comprised of EPI (about 80%) while NE makes up the remaining 20% with small amounts of dopamine being released into peripheral circulation as well. EPI and NE bind to specific ARs that are proteins embedded within the cell membrane with 7 transmembrane structures coupled to heterotrimeric G proteins. A total of two classes of ARs (alpha- and beta-adrenergic receptors) with 9 subtypes have been identified thus far: three α receptors, three α receptors and three β receptors (β1, β2, and β3). A healthy human heart mostly consists of β1 (75%-80%) and β2 (20%-25%) adrenergic receptors and they represent the key effectors behind positive chronotropic and inotropic effects of catecholamines while β3 adrenergic receptors (comprising less than 5% of total beta-receptor density) have been postulated to exert negative inotropic effects through upregulation of nitric oxide synthase pathway in human ventricle. It has been recently confirmed that β1 and α receptors are present in all ventricular cardiomyocytes. Alpha-1 adrenergic receptors (α1) and alpha-2 adrenergic receptors (α2) are chiefly expressed in vascular smooth muscle cells proximal and distal to sympathetic nerve terminals, respectively, and their activation elicits vasoconstriction of peripheral arteriolar and venous vessels while in the brain stem they modulate sympathetic outflow. A recent study by Becker et al. showed that activation of neuronal endothelin B receptors can increase arterial blood pressure mediated through α1-adrenergic receptor signaling showing that abnormalities of endothelin system have a cross-talk with adrenergic systems in hypertension and HF.

Beta-adrenergic receptors act as powerful regulators of cardiac output and upon acute stimulation by catecholamines they facilitate fight-or-flight response while their chronic stimulation results in maladaptive and pathologic cardiac remodeling. Activation of β adrenergic receptors induces the activation of the stimulatory G protein (Gs) which further activates adenylyl cyclase leading to an increase in levels of intracellular cyclic adenosine monophosphate and activation of protein kinase A that phosphorylates several target proteins within the cardiomyocyte such as phospholamban, L-type calcium channels, troponin I, contractile proteins, and the cardiac ryanodine receptor and this mainly is the mechanism by which β receptors regulate cardiac contractility/relaxation and heart rate. Furthermore, activation of
Table 1 Cardiovascular reflexes and their pathophysiological implications in heart failure

| Type of neurally-mediated cardiovascular reflex | Proposed mechanism of action | Pathophysiological consequence in heart failure |
|-----------------------------------------------|-----------------------------|-----------------------------------------------|
| Arterial baroreceptor reflexes                | In HF acts as a response to perceived reduction in stroke volume or diastolic blood pressure; It is implicated that reduced carotid sinus and aortic arch afferent nerve firing as a response to systolic stretch disinhibits efferent sympathetic discharge; This reflex is impaired in terms of heart rate control, however, efferent sympathetic nerve activity might be preserved in human HF, even in advance stage | ↓ Reduced reflex vagal response; ↓ reduced heart rate variability; ↑ increased cardiac NE spillover; ---no change in renal NE spillover; ↑mean sympathetic discharge to peripheral muscles is increased |
| Cardiac chemosensitive reflexes               | Myocardial ischemia and reperfusion elicits increased sympathoexcitatory response by chemically (reactive oxygen species) stimulating sympathetic afferent fibers in both anterior and infero-posterior regions of the left ventricle; Platelet activation and local release of serotonin (5-HT) through a SHT3 receptor mechanism and regional changes in pH from lactic acid stimulate sympathetic afferents in myocardium; Cardiac sympathetic afferent reflex is enhanced in HF and acts in the positive-feedback fashion | ↑ Increased shift and predominance of sympathetic efferent discharge; ↓ parasympathetic depletion; ↑ sympathetic activation; ↑ increased blood pressure; ↑ adverse left-ventricular remodeling; ↑ increased propensity for malignant arrhythmias and sudden cardiac death |
| Cardiopulmonary mechanosensitive reflexes     | Normally elicited by the stretch of unmyelinated afferents sensitive to mechanical input, located intracardially and within pulmonary veins; It is implicated that impairment of this reflex decreases efferent sympathoinhibition to periphery; Cardiac-specific myelinated afferent are responsible for observed sympathoexcitatory effects characteristic by the increased local cardiac NE spillover due to increased filling pressures (e.g. ↑ high LA pressure); Bezold-Jarisch reflex – mediated by nonmyelinated vagal afferent pathways – acts in sympathoinhibitory fashion and promotes reflex bradycardia, vasodilation and hypotension | ↓ Reduced cardiopulmonary reflex regulation of central sympathetic outflow to peripheral tissues (dominantly skeletal muscles); ↑ paradoxical excitation and increase in sympathetic outflow in the setting of high LA pressure |
| Cardio-cardiac reflexes                       | Coronary occlusion elicits the activity of preganglionic fibers in left thoracic sympathetic ramus communicans (T3) and increases discharge towards heart via efferent sympathetic innervation | ↑ Increased myocardial oxygen consumption; ↑ facilitation of malignant arrhythmias; --- might also have a protective effect in sense that they augment contractility, therefore, opposing ventricular dilatation and/or impending cardiogenic shock |
| Peripheral and central chemoreceptor reflexes | These receptors monitor partial pressures of oxygen and CO2 within arterial vessels and close to heart and escalate afferent sensory discharge according to changes; Peripheral chemoreceptors – dominantly respond to hypoxia; Central chemoreceptors – dominantly respond to hypercapnia; Peripheral and central receptor chemosensitivity is significantly increased in HF and is linked to augmented MSNA | ↑ Increased ventilation; ↑ increased sympathetic outflow; ↑ increased heart rate and systolic blood pressure; ↓ suppressed inhibition of sympathetic outflow that is mediated by arterial baroreflexes; ↑ increased peripheral and central chemoreflex-mediated sympathoexcitation is linked to poor 4-yr survival in HF patients |
| Pulmonary stretch receptor reflex             | Fast and shallow breathing (high respiratory rate and low tidal volume) decreases stimulation of sympathoinhibitory reflex that is initiated with lung stretch; HF patients with such breathing had increased MSNA burst frequency or amplitude; There is a correlation between decrease in resting tidal volume and attenuated sympathoinhibitory effect of lung inflation reflex with increased sympathoexcitation | ↓ Decreased the resting tidal volume; ↓ attenuated sympathoinhibitory effect of lung inflation reflex |
| Reflexes originating from skeletal muscles    | Autonomic responses of skeletal muscles during exercise are modulated by skeletal ergo-receptors in order to optimize muscle work; HF patients had augmented afferent reflexes originating from skeletal muscles | ↑ Increase in the efferent ventilatory and sympathoneural responses to exercise |

HF: Heart failure; LA: Left atrium; MSNA: Muscle sympathetic nerve activity; NE: Norepinephrine.
and they mediate unique downstream cellular effects once activated by catecholamines as they are mostly expressed in white adipose tissue where they mobilize stored fatty acids and regulate the release of adipokines while in brown adipose tissue they stimulate adaptive nonshivering thermogenesis\[^{109}\]. A study by Napp \textit{et al.}\[^{109}\] showed that \(\beta_3\) adrenergic receptors were mostly expressed in the endothelium of failing myocardium thus negative inotropic effect was most likely elicited by the NO liberation from the cardiac endothelial cells while \(\beta_3\) stimulation itself seemed to deactivate rather than activate endothelial NOS\[^{109}\]. A study by Dessy \textit{et al.}\[^{106}\] showed that \(\beta_3\) receptors are abundantly expressed in the microvasculature of human coronary arteries in which their activation caused vasodilatation through NO-dependent pathway and vessel hyperpolarization\[^{106}\]. Of note, the expression of \(\beta_3\) adrenergic receptors in diverse cardiovascular pathologies seems to be upregulated and resistant to desensitization while in normal heart their activation resulted with a moderate negative inotropic effect\[^{105,110}\]. Similarly, in septic cardiomyopathy, functional \(\beta_3\) receptors were upregulated and they increased negative inotropic response to \(\beta_3\) agonists\[^{105}\]. Furthermore, in the setting of HF, activation of these receptors conferred beneficial effects with respect to excitation-contraction coupling and electrophysiological and mechanical remodeling of cardiomyocytes while also mediating vasodilatative pathways when \(\beta_1\) and/or \(\beta_3\) receptors are inoperativel\[^{105}\]. In the clinical and translational realm, relevant studies confirmed these initial findings as they showed that the third-generation beta-blocker, nebivolol, exhibited agonistic action on \(\beta_3\) adrenergic receptors in human ventricle thus providing evidence that highly selective blockade of \(\beta_3\) receptors coupled with NO-dependent endothelial vasodilatation and neoangiogenesis in coronary microcirculation could improve cardiac energetic\[^{109,110}\]. Taken together, in the HF context, \(\beta_3\) adrenergic stimulation might confer cardioprotection by attenuating excessive catecholaminergic stimulation mediated by \(\beta_1\) adrenoceptors thereby presenting an attractive therapeutic target. The physiological effects of beta-adrenergic receptors are summarized and shown in Figure 2.

Finally, the expression of \(\beta_3\)-adrenergic receptors is physiologically modulated through G protein-coupled receptor kinases (GRKs), \(\beta\)-arrestins and complex intracellular signalosome\[^{111}\]. GRK family consists of seven different protein kinases that canonically recognize and phosphorylate agonist-activated G protein-coupled receptor signaling and initiate downstream \(\beta\)-arrestin-mediated cellular pathways\[^{112}\]. \(\beta\)-arrestins have a crucial role in the desensitization of activated seven transmembrane receptors such as \(\beta_3\)-adrenergic receptors, and they are key mediators of receptor endocytosis, ubiquitylation, and G-protein-independent cellular signaling\[^{112}\]. Therefore, it becomes obvious that the normal expression of GRKs is a cellular prerequisite to maintain physiological homeostasis regarding \(\beta_3\)-adrenergic receptor turnover by phosphorylation, degradation or clathrin-mediated receptor downregulation and internalization\[^{111}\].

**SYMPATHETIC NERVOUS SYSTEM PATHOPHYSIOLOGY AND ADRENERGIC DYSREGULATION IN HEART FAILURE**

A chronic SNS overactivity is one of the key pathophysiological mechanisms that are operative in HF. In the acute phase, this upregulated SNS activity is an essential compensatory response initiated in order to counteract reduced contractility, however, in the long-term, it becomes a major contributor to cardiac dysfunction as it promotes maladaptive cardiac hypertrophy and cell death.

In a seminal study performed more than three decades ago, Swedberg \textit{et al.}\[^{117}\] showed that patients with chronic HF (CHF) had significantly higher arterial and coronary sinus venous NE concentrations compared to patients without HF while the net myocardial NE release in patients with CHF was about 20 times higher than in patients without CHF\[^{117}\]. This was subsequently confirmed by Viquerat \textit{et al.}\[^{118}\] demonstrating that endogenous plasma levels of NE and dopamine were significantly higher among patients with CHF compared to patients without CHF thus reflecting enhanced sympathetic activity in response to failing heart\[^{118}\]. Such overt sympathetic activity in HF closely paralleled increases in pulmonary artery pressures while activation of noradrenergic neurons in the brain might also be an underlying CNS mechanism of generalized sympathoexcitatory response observed in HF\[^{118,119}\]. In fact, it has been shown that the RAAS axis is the major regulator of the SNS activity in the brain \textit{via} angiotensin II type 1 receptors\[^{120}\]. This likely occurs due to the upregulated expression of angiotensin II type 1 receptors (promoting sympathoexcitation) and
Figure 2 The function and physiological actions of beta-adrenergic receptors and adrenergic signaling. β: Beta; G: Inhibitory alpha subunit of G protein; Gs: Stimulatory alpha subunit of G protein; NO: Nitric oxide.

decreased expression of angiotensin II type 2 receptors (promoting sympathoinhibition) in the rostral ventrolateral medulla[122]. Likewise, historical studies showed that 24-h urinary excretion of NE, EPI, and their O-methylated metabolites – normetanephrine and metanephrine was significantly higher in patients with congestive HF and reflected functional disease severity as assessed by the New York Heart Association (NYHA) class[123,124]. Furthermore, there is not only a significant increase in circulating catecholamines but there is also an augmented neuronal NE spillover due to increased cardiac sympathetic nerve activity (SNA) while renal SNA nearly reached its maximum in the state of HF and showed to be an independent predictor of mortality in HF[125-127]. Recent research efforts demonstrated that NE spillover does not only depend on increases in SNA but it also partially occurs due to mechanisms controlling NE release and reuptake in the synapse and these mechanisms seem to be deranged in HF[128]. Increased NE spillover is in most cases paralleled by the reduced neuronal NE reuptake thus higher net concentrations of NE are present in the sympathetic synaptic cleft which further desensitizes myocardial β-adrenergic receptors[129,130]. A study by Hasking et al[131] further showed that cardiac and renal NE spillover in subjects with congestive HF was increased by 540% and 206%, respectively, compared to patients without HF while adrenomedullary-mediated EPI spillover was also markedly increased among these patients[131].

As previously mentioned, in a failing human heart, an important pathophysiological characteristic is a decreased sensitivity of β-adrenergic receptors to catecholamines while β-receptors are downregulated and decreased in their density and quantity[132]. For example, β1 adrenergic receptors are reduced up to 50% in HF and there is a 200% increase in Gi-mediated cellular pathways with concomitant significant upregulation of GRK2 activity (also known as β-adrenergic receptor kinase 1 or βARK1) that further promotes adrenergic receptor internalization[133]. Myocardial GRK2 activity and expression have been increased in the failing heart as shown in several studies[134]. Conversely, experimental inhibition of βARK1 resulted in a marked reversal of ventricular dysfunction[135]. Finally, a wide variety of HF phenotypes and different response to HF treatment might suggest variants and functional polymorphisms of beta and alpha-adrenergic receptor genes[79]. Some pharmacogenomic studies suggested that polymorphisms in β1-adrenergic receptors might affect susceptibility to HF such as Gly389 allele and Gly389 homozygotes; improved response to β-blocker treatment among Arg389 homozygotes while none of the candidate polymorphisms was an independent predictor of prognosis in HF[136,137].
Likewise, specific β₂-adrenergic receptor polymorphisms were linked with lower myocardial infarction rate and improved reverse left ventricular remodeling among patients with HF\cite{138,139}.

From the structural perspective, catecholamine spillover is cardiotoxic and its overexpression promotes senescence and inflammation of cardiomyocytes, upregulates tumor suppressor p53 pathway, and production of adhesion molecules by endothelial cells and macrophages and mediates cardiac dysfunction\cite{140}. Chronic and persistent stimulation by catecholamines in HF causes interstitial fibrosis, myocyte hypertrophy, oxidative stress, and impairs the responsiveness and function of cardiac β-adrenergic receptors\cite{141}. Engelhardt and colleagues experimentally demonstrated that increased chronic stimulation of β₁ adrenergic signaling resulted in a significant cardiomyocyte hypertrophy and apoptosis resulting in a marked loss of contractility and progressive reduction of LVEF with histological and functional deficits typical of HF\cite{142}. Catecholamine toxicity and generalized autonomic storm also have an important pathophysiological role in causing acute stress-related cardiomyopathies such as Takotsubo cardiomyopathy, acute LV dysfunction associated with subarachnoid hemorrhage, pheochromocytoma, and exogenous catecholamine administration as well as acute LV dysfunction in critically ill\cite{143}. Contrary to this, activation of β₂ adrenergic receptors delivered an antiapoptotic signal to cardiac myocytes through G_{i}-dependent coupling to phosphoinositol 3-kinase\cite{144}. Furthermore, it seems that the number of β₂-adrenergic receptors does not change significantly in HF\cite{145}. These findings suggest that a fine balance between proapoptotic and antiapoptotic pathways initiated by differential adrenergic signaling is of fundamental importance for physiological cardiomyocyte function\cite{146}.

Importantly, studies have shown that the activation of SNS in the course of heart failure exhibits specific temporal dynamics and regional sympathetic profile. Rundqvist et al\cite{147} showed that a selective increase in cardiac NE spillover (defined as increased amounts of NE at neuroeffector junctions) in patients with mild-to-moderate CHF was higher for more than a three-fold compared to healthy subjects while total body and renal NE spillover, as well as sympathetic outflow to skeletal muscles, were not different in HF patients compared to healthy controls\cite{148}. This study clearly showed that in the early stages of HF, selective increase in cardiac adrenergic drive precedes generalized sympathetic hyperactivity and outflow towards the periphery (skeletal muscles and kidneys) which is characteristic of advanced HF. In the early stages of HF, such cardiac sympathoexcitation might trigger ventricular arrhythmias and is associated with poor prognosis\cite{149,150}. Furthermore, local cardiac NE spillover might be the first component required for further β-receptor downregulation and depletion, adverse myocardial remodeling, depletion of NE stores, and impairment in G-protein signaling pathways, as discussed earlier. This might further drive hemodynamic deterioration and progressive LV dysfunction. Even more, blunted response and withdrawal of parasympathetic cardiac control seem to precede sympathetic activation during the development of HF. In support of this claim, in the tachycardia-induced model of HF, Ishise et al\cite{151} showed that parasympathetic withdrawal occurs rapidly and correlates with the decline in LV contractility and plasma NE increased gradually as LV diastolic function worsened while all of these changes recovered toward baseline values once pacing was ceased\cite{152}. The proposed mechanism was that depressed contractility resulted in the attenuated stimulation to the carotid sinus baroreceptor which diminished vagal efferent activity towards the heart thus demonstrating parasympathetic tonic withdrawal. Together, these findings suggest that in the course of SNS dysfunction in HF, sympathovagal imbalance might occur earliest as evidenced in parasympathetic withdrawal while sympathetic hyperactivity likely first occurs at the cardiac level before it is propagated to peripheral tissues and organs as observed in the advanced stages in HF.

Furthermore, dysfunction of cardiac reflexes is a hallmark of SNS hyperactivity in HF and it occurs to a similar degree regardless of HF etiology (ischemic or nonischemic)\cite{153,154}. There is a diminished baroreflex sensitivity in HF characterized by the marked suppression of inhibitory SNS reflexes such as arterial baroreceptor reflex while excitatory SNS reflexes such as those fired from peripheral chemoreceptors are enhanced\cite{155}. Floras et al\cite{156} showed that a failing heart reacts to increased cardiopulmonary filling pressures through responsive and sensitive arterial baroreflex that elicits potent sympathoexcitatory hemodynamic actions\cite{157}. Furthermore, even among patients with mild CHF, an SNS-inhibiting baroreceptor function is already significantly impaired thus implying that baroreflex dysfunction might be one of the earliest constitutive phases in SNS activation during the natural course of CHF\cite{158}. Reduction in baroreflex sensitivity is even more severe if obesity and arterial hypertension are present among HF patients\cite{159}. Conversely, baroreflex activation
therapy in HF, encompassing the deployment of a device electrically stimulating carotid sinus, succeeded in improving muscle sympathetic nervous activity and relevant clinical indices thus showing that modulation of autonomic balance in HF might improve relevant outcomes\textsuperscript{123,124,125}.

Collectively, these findings are of clinical relevance because ANS imbalance and predominance of sympathetic excitation cause electrophysiological perturbations in the vulnerable cardiac syncytium and can initiate arrhythmogenesis\textsuperscript{156}. For example, simultaneous stimulation of both sympathetic and parasympathetic systems can trigger AF while increased sympathetic stimulation is a contributing culprit to initiation of ventricular fibrillation (VF) or ventricular tachycardias (VT) or sudden cardiac death (SCD)\textsuperscript{156}. Beat-to-beat variability of ventricular action potential duration is increased with elevated sympathetic activity in HF patients and might precipitate ventricular arrhythmias while beta-blocker, bisoprolol, attenuated these effects\textsuperscript{156,157}. It was previously shown by Brunner-La Rocca et al\textsuperscript{158} that high cardiac sympathetic activity in HF was an independent risk factor for sudden death, especially if sympathetic innervation was intact\textsuperscript{159}. Sympathetic denervation in the heart combined with the presence of high NE levels is tightly correlated to progression of HF and SCD\textsuperscript{156}. From the other way around, stellate ganglion blockade was effective in the acute reduction of ventricular arrhythmia burden and suppression of electrical storm thus clinically validating the concept that attenuation of sympathetic outflow to the heart from sympathetic ganglia can indeed mitigate the risk of future arrhythmic events\textsuperscript{156,159,160}. These clinical observations were inspired by the previous animal study demonstrating that spontaneous high-amplitude discharge activity from left stellate ganglion was strongly associated with the induction of malignant ventricular arrhythmias\textsuperscript{161}. Modern state-of-the-art neuromodulation strategies that are capable of mitigating VT/VF and atrial arrhythmias are, therefore, focused on increasing parasympathetic drive and inhibiting sympathetic neurotransmission\textsuperscript{162,163}.

Finally, it should also be noted that the widespread SNS activation also affects the function of skeletal muscles and promotes exercise intolerance in HF. Of note, diminished exercise capacity in terms of reduced peak oxygen uptake is present among HF subjects and is related to increased efferent sympathetic traffic to skeletal muscles, compared to control subjects\textsuperscript{164}. This study also showed that resting muscle SNA is inversely related to peak oxygen uptake thus suggesting that there is a peripheral neurogenic limit to exercise in HF. As later validated, this reduced exercise capacity in HF is more dependent on sympathetic outflow to skeletal muscles than to cardiac sympathetic outflow, as assessed by NE spillover\textsuperscript{165}. Furthermore, a subsequent study showed that muscle SNA was significantly higher while peak oxygen uptake was significantly lower in patients with ischemic vs nonischemic cardiomyopathy\textsuperscript{166}. The most recent clinical study also demonstrated that the α-adrenergic-mediated vasoconstriction in HFrEF patients elicited a marked decrease in exercising skeletal muscle blood flow thus contributing to reduced exercise capacity in this population\textsuperscript{167}. Finally, HF patients present with a high degree of chronotropic incompetence and attenuated heart rate response to exercise which is partially due to postsynaptic desensitization of the β-adrenergic receptor pathways\textsuperscript{168}.

CARDIAC IMAGING AND SYMPATHETIC ACTIVATION IN HEART FAILURE

A noninvasive in vivo imaging modalities can assess sympathetic innervation of the heart and for these purposes single-photon emission computed tomography and positron emission tomography (PET) are used by employing radiolabeled analogs of NE. The myocardial uptake of these radioanaloggs dominantly represents presynaptic nerve function and their density in the heart. The most commonly used single-photon emission computed tomography tracer is $^{123}$I-metiodobenzylguanadine ($^{123}$I-mIBG) while most common PET tracer in clinical use is $^{11}$C-hydroxyephedrine ($^{11}$C-HED)\textsuperscript{169}.

Recent studies demonstrated that impaired myocardial sympathetic innervation and regional sympathetic denervation, as detected by the presence of $^{11}$C-HED by PET imaging, were independently associated with grade 2-3 diastolic dysfunction and contractile dysfunction and fibrotic burden among patients with HFpEF, respectively\textsuperscript{170,171}. Similarly, data from prospective HF cohort studies demonstrated that diminished $^{123}$I-mIBG uptake quantified as the reduced heart-to-mediastinum uptake ratio (H/M, indicating neuronal function including uptake and release of $^{123}$I-mIBG) or increased myocardial $^{123}$I-mIBG washout rate (indicating higher adrenergic drive) were strong markers of abnormal myocardial sympathetic innervation and consistent predictors of poor prognosis among patients with HF\textsuperscript{172-174}. Furthermore,
HEART RATE VARIABILITY

Heart rate variability (HRV) is an established and widely used noninvasive method for the assessment of autonomic modulation of heart rate. It uses electrocardiographic (ECG) signal to measure subtle variations in the beat-to-beat heart intervals and is considered as a surrogate parameter of the complex interaction between CNS and cardiovascular system\cite{191,192,193}. These periodic oscillations in heart rate signals are transformed into different frequency areas and their relative intensity is reported as a numerical value\cite{194,195,196}. Briefly, low-frequency power (LF) and high-frequency power (HF), as well as the LF/HF ratio, are the most commonly used parameters in HRV analysis\cite{188,189}. In most of the studies, HF power is regarded as a surrogate of PNS activity while LF power is modulated by both SNS and PNS. Likewise, high LF power values are associated with increased sympathetic activity while the LF/HF ratio reflects global sympathetic/vagal balance\cite{197}. Generally, decreased HRV is associated with various pathologies and decreased life expectancy in several studies\cite{198,199}.

Regarding cardiovascular diseases, depressed HRV has been associated with autonomic neuropathy, heart transplantation, congestive HF, MI, and other incident cardiac conditions\cite{195,196,197}. Most data for low HRV and increased mortality have been corroborated from studies investigating populations with cardiovascular diseases such as post-MI patients, patients with HF and those experiencing SCD, and in contrast to this, such associations of HRV were historically more diluted when it comes to risk stratification among the general asymptomatic population\cite{190}. However, a recent study by Hillebrand et al\cite{191} showed that low HRV was associated with a 32%-45% increased risk of a first cardiovascular event in populations without known cardiovascular disease\cite{192,193}. In a similar fashion, abnormal HRV parameters were independently associated with incident CHF in asymptomatic older adults\cite{194}.

In the setting of a failing heart, HRV is significantly reduced in most patients and associated with the high risk of death due to progressive HF, SCD and syndrome

the ADMIRE-HF study confirmed that H/M remained as a significant and independent predictor of all-cause mortality and the composite endpoint of death or death-equivalent events among nearly thousand NYHA II-III HF subjects during the median of 24 mo follow-up\cite{180}.

An elegant study by Wakabayashi et al\cite{181} exploring \(^{123}\)I-mIBG kinetics in terms of underlying HF etiology showed that \(^{123}\)I-mIBG activity provided independent long-term prognostic information for both ischemic and non-ischemic etiologies of HF with lower H/M values having a greater impact on cardiac death among patients with ischemic compared to non-ischemic cardiomyopathy\cite{182,183}. In concordance with such findings among HF patients with ischemic cardiomyopathy, \(^{123}\)-HED PET-based studies revealed that regional myocardial sympathetic denervation and volume of denervated myocardium accurately predicted the risk of sudden cardiac arrest thus clearly correlating SNS innervation abnormalities with future arrhythmogenic events\cite{184,185}. Similar findings were confirmed by another research group showing that denervated myocardium quantified using PET strongly predicted the risk of sudden cardiac arrest, independent of LVEF, infarct volume and other clinical variables among HF patients with ischemic cardiomyopathy and with LVEF < 35% that were eligible for implantable cardioverter-defibrillator device for primary prevention\cite{186}. Finally, the most recent study conducted among patients admitted for acute decompensated heart failure and prospectively enrolled in the OPAR registry demonstrated that patients with cardiac sympathetic nerve dysfunction, defined as low late H/M, had a significantly greater risk of future adverse cardiac events, irrespective of clinical phenotype based on the LVEF values\cite{187}. This study also showed that even a mild impairment in cardiac contractility (as shown in borderline LVEF values represented in HFmrEF cohort) was associated with sympathetic nerve dysfunction and was independently linked to poor outcomes thus suggesting that use of beta-blocker therapy in patients with HFmrEF phenotype is a viable pharmacotherapeutic option, as also supported by expert consensus statement and data from a large meta-analysis\cite{188,189}.

Taken together, these studies suggest that non-invasive cardiac imaging with norepinephrine analogs provides a reliable estimation of cardiac sympathetic nerve activity and this activity is strongly associated with clinical outcomes, regardless of clinical phenotypes or if HF is of chronic or acute onset. Such findings validate the concept that SNS overactivity is an important pathophysiological target in HF that must be efficaciously treated to improve outcomes and prevent sudden cardiac death.

In the setting of a failing heart, HRV is significantly reduced in most patients and associated with the high risk of death due to progressive HF, SCD and syndrome.
LABORATORY BIOMARKERS OF SYMPATHETIC NERVOUS SYSTEM ACTIVATION IN HEART FAILURE

Laboratory biomarkers that can be measured in the peripheral circulation of HF patients can give us insight on underlying pathophysiological mechanisms that are occurring in patients with both acute and chronic HF. Since HF is a complex syndrome characterized by the high prevalence of comorbidities an integrated approach using multiple biomarkers could aid in the diagnosis, accurate risk stratification regarding mortality and future hospitalizations and perhaps enable optimal tailoring of pharmacotherapeutic and/or device therapies for the individual HF patient. A wide array of novel biomarkers reflecting pathophysiological processes of myocardial stretch, matrix remodeling, myocyte injury, oxidative stress, inflammation, neurohumoral activation, and renal dysfunction are becoming increasingly studied and integrated into the process of care for HF patient and clinical decision-making.

The early adoption of these novel biomarkers in modern clinical practice has a great potential to complement traditional biomarkers that are regularly used in the workup of HF patients such as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), high sensitivity cardiac troponin (hs-cTn), soluble suppression of tumorigenicity 2 or C-reactive protein. In this last section of the review, we will focus on both established and novel laboratory biomarkers that are implicated in the pathophysiology of SNS activation in HF and as such might be potentially used in clinical practice. The summary of pathophysiological effects, cellular mechanisms of action, circulating levels, and association of selected biomarkers with outcomes in HF is presented in Table 2.

**Norepinephrine**

As previously discussed, circulating plasma levels and urinary excretion of norepinephrine (NE) are significantly higher among patients with congestive HF compared to those without, reflecting elevated sympathetic drive. A recent study by Matsushita et al. showed that the endogenous catecholamine surge might be the cause of urgently presenting acute HF by eliciting an abrupt and excessive rise in blood pressure leading to increased after-overload and volume-shift lung congestion. A few decades ago, Cohn and colleagues showed that plasma NE has been independently related to subsequent risk of mortality among patients with chronic congestive HF and was also higher among those that had progressive HF compared to patients that died suddenly. This was later confirmed in the V-HEFT II study that enrolled patients with congestive HF showing that plasma NE was an independent predictor of prognosis and plasma NE values > 900 pg/mL were associated with significantly greater mortality risk compared to lower NE tertiles. In the longitudinal follow-up of patients with HF from the Val-HeFT trial, changes of...
Table 2 Selected biomarkers in respect to their pathophysiological effects, cellular mechanisms, circulating levels and outcomes in heart failure

| NE | NPY | GAL | ET-1 | CST |
|----|-----|-----|------|-----|
| Pathophysiological effects in heart failure or cardiovascular diseases | | | | |
| ↑ Promotes cardiac hypertrophy; ↑ promotes induction of fetal genes in myocardial remodeling; ↑ mediates and enhances apoptosis of cardiac myocytes in vitro; ↑ promotes arterial vasocstriction; ↑ promotes tachyphylaxis; ↑ increased cardiac and renal spillover in HF; ↓ impaired oxygen utilization and exercise efficiency in patients with stable HF; ↑ increased sympathetic nerve activity and reduced clearance of norepinephrine | ↑ Vasoconstruction; ↑ promotes adverse cardiac remodeling; ↑ increased spillover; ↑ promotes angiogenesis; ↑ associated with increased platelet aggregation and adhesion following thrombosis; ↑ stimulates atherosclerosis; ↑ promotes vasocstruction of coronary microvasculature; ↑ enhancing the NE-mediated effect of sympathetic discharge, associated with the increased incidence of ventricular arrhythmia; ↑ enhances inhibition of vagally-mediated bradycardia through Y2 receptors; ↑ potentiates arrhythmias following STEMI, despite beta-blocker therapy | ↓ Reduces cardiac cholinergic neurotransmission; ↓ reduces acetylcholine bioavailability in the synapse junctions; ↓ reduces vagally-mediated bradycardia; ↓ promotes antithrombotic phenotype on endocardial endothelial cells; ↑ increased cardioprotective activity against ischemia-reperfusion injury in H9C2 cardiomyoblasts in vitro | ↑ Promotes vasconstriction (most potent vasoconstrictor in humans); ↑ promotes vascular and cardiac hypertrophy; ↓ decreases NE reuptake thus propagating adrenergic effects; ↓ reduces coronary flow; ↓ promotes inotropic and chronotropic responses in cardiomyocytes; ↓ promotes mitogenic actions; ↓ activation of endothelin-dependent pathways is observed in HF; ↓ correlates with hemodynamic impairment and severity of pulmonary hypertension in HF; ↓ promotes angiogenesis | ↓ Decreases arterial blood pressure (direct and indirect vasoconstriction); ↓ inhibits catecholamine release; ↓ decreases NPY and ATP release; ↓ attenuates cardiac inotropy and chronotropy; ↓ promotes angiogenesis; ↓ blunts atherosclerosis; ↓ reduces inflammation; ↓ reduces thrombogenicity; ↓ promotes VSMC proliferation; ↓ decreases arrhythmogenic events; ↓ decreases ventricular remodeling |
| Cellular mechanism | Activation of α and β adrenergic receptors (G protein-coupled) | Activation of G protein-coupled post-synaptic Y1-Y6 receptors (Y2 is also pre-synaptic) on sympathetic nerve endings | Activation of G protein-coupled receptors – GAL1R, GAL2R, GAL3R (ET\(_B\) receptors(both G protein-coupled) | Acts on neuronal nicotinic acetylcholine receptor (nAChR) |
| Circulating levels in HF vs controls | ↑ Circulating plasma levels;↑ urinary excreted levels | ↑ Circulating plasma levels | → Not significantly different plasma levels | Plasma levels;↑ renal tissue levels |
| Association with mortality and morbidity in HF | ↑ High NE levels were associated with significantly increased mortality and morbidity in patients with congestive HF; ↑ circulating NE levels positively correlate with HF syndrome severity | ↑ Elevated levels in coronary sinus were associated with composite endpoint of VAD implantation, death, and cardiac remodeling in patients with stable chronic HF undergoing CRT implantation | Not established (no studies available) | ↑ Increased ET-1 levels associated with higher HF syndrome severity;↑ increased ET-1 levels associated with mortality in HF |
| | | | | ↑ Increased CST levels were independently associated with all-cause and cardiac mortality in patients with chronic HF; ↑ correlates with NYHA functional class |

NE: Norepinephrine; NPY: Neuropeptide Y; GAL: Galanin; ET-1: Endothelin; CST: Catestatin; CRT: Cardiac resynchronization therapy; FU: Follow-up; HF: Heart failure; NYHA: New York Heart Association; STEMI: ST-elevation myocardial infarction; VAD: Ventricular assist device; VSMC: Vascular smooth muscle cell.
Neuropeptide Y

Neuropeptide Y (NPY) is a sympathetic co-transmitter with a longer half-life than NE and is widely distributed in the CNS and peripheral nervous system with pleiotropic physiological actions. In the cardiovascular system, NPY is co-released from cardiac sympathetic nerve terminals along with catecholamines (predominantly NE) and galanin[214]. These sympathetic nerves supply vasculature, cardiomyocytes and endocardial endothelial cells in the ventricle while NPY physiologically modulates cardiovascular function, potentiates pressor effects of angiotensin II, elicits arterial and venous constriction, blunts parasympathetic activity, augments cardiomyocyte calcium loading, participates in cardiomyocyte remodeling and promotes angiogenesis[215-219]. NPY and galanin have a direct ability to modulate vagus nerve to release acetylcholine and control heart rate while NPY plasma levels had a strong correlation with coronary microvascular function among patients with ST-elevation myocardial infarction[224]. Maisel and colleagues were the first to report on elevated levels of plasma NPY in patients with congestive HF and this was later confirmed in several subsequent studies[225-227].

In the recent clinical study by Ajijola et al[228], NPY was sampled from the coronary sinus (CS) among patients with stable CHF during the elective CRT device implantation[229]. Researchers sought to answer if NPY as a peptide involved in adrenergic signaling is associated with outcomes among patients with stable CHF. They found that patients with NPY CS levels > 130 pg/mL had significantly worse outcomes compared to those with lower NPY CS levels, even after adjusting for age, estimated glomerular filtration rate (eGFR), and LVEF (HR: 9.5, 95%CI: 2.92-30.5, P < 0.001) during the median follow-up of 28.8 mo while the composite endpoint consisted of death, ventricular assist device placement and cardiac transplant. Most of the signal from the composite endpoint was driven by death events and interestingly, CRT data at 6-mo follow-up showed that CS NPY levels did not significantly differ between CRT responders and non-responders (P = 0.76). Finally, immunohistochemical analyses revealed that sympathetic ganglia (stellate and middle cervical ganglion) of CHF patients contained less NPY compared to ganglia tissue obtained from healthy donors while no significant difference was observed in the NPY production between both groups as examined by the measured NPY mRNA levels. This study showed that CS NPY levels were elevated in stable CHF patients and associated with adverse outcomes and relevant clinical and laboratory characteristics while increased stellate ganglia sympathetic discharge was likely the culprit for these elevated levels.

Although CS NPY levels provided robust prognostic information among stable CHF patients, a problem in clinical practice arises in the peripheral venous sampling of NPY since those levels are not cardiac-specific and are mostly of hepatomesenteric origin since NPY has been identified as a stimulator to food intake[230]. In cardiac failure, there is an increase in resting NPY spillover within the myocardium, however, the net overflow of NPY to plasma was dominantly from hepatic circulation, but not the cardiac, forearm or cerebral circulations showing a marked difference in regional distribution of NPY content[224]. It has also been shown that sympathetic activation by exercise produced only a modest increase in cardiac NPY overflow without the concomitant change in arterial NPY concentrations finally concluding that plasma NPY concentrations are less sensitive than those of plasma NE in terms of quantifying SNS responses regulating the systemic circulation and cardiac hemodynamics in HF, as implied in some previous studies[231,232,233]. Finally, a recent preclinical study showed that NPY blockade by experimental Nur77 agent protected against adverse cardiac remodeling by limiting NPY-mediated signaling (NPY-NPY[α]) in the cardiomyocytes[224], Most important characteristics and effects of NPY are depicted in the Figure 3. In the future, antagonists of NPY receptors Y1 and Y2 might be a feasible therapeutic option in acute myocardial infarction but also during chronic HF and hypertension[224]. These pharmacotherapeutic options would complement beta-blockers and implantable vagus nerve stimulators to improve outcomes in patients with cardiovascular diseases[224].

Galanin

Similarly to NE and NPY, galanin is an adrenergic co-transmitter with a short half-life (about 5 min) released from peripheral postganglionic neurons and is implicated in attenuation of cardiac cholinergic tonus after burst sympathetic activity thus contributing to autonomic imbalance and the pathophysiological phenomenon known as “sympathovagal crosstalk”[224,233]. This phenomenon can remain chronically activated and sustained even in the presence of beta-adrenergic blockade thereby it could be a valid therapeutic target in the spectrum of neurohumoral activation in...
HF. Furthermore, nerve terminals of parasympathetic neurons in the heart express both galanin receptors and NPY receptors (NPY Y2) which, upon activation, reduce acetylcholine release. During the prolonged sympathetic activation there is a release of a slowly diffusing co-transmitter galanin, together with NPY, that bind to these receptors and reduce cholinergic neurotransmission in the heart. Furthermore, galanin through its receptors interacts with other neuropeptides such as NPY and angiotensin II and their receptors, namely Y1 and AT1, thus having a potential role in neurochemical modulation of central cardiovascular control.

A recent prospective case-control study in the clinical realm showed that unlike pro-BNP, copeptin and NPY, galanin levels were similar among patients with HF patients and control subjects while pro-BNP was the only significant determinant of galanin levels in HF patients. Authors postulated that galanin most likely has a predominant paracrine modulatory function at the level of peripheral cardiac sympathetic nerves, therefore, its circulating levels in plasma might not reflect the degree of its local involvement in sympathovagal crosstalk. Finally, since natriuretic peptides promote catecholamine release from cardiac sympathetic neurons, authors suggested biological plausibility of their finding that galanin positively correlated with BNP.

On the other hand, galanin promoted anti-thrombotic phenotype on cultured endocardial endothelial cells from HF patients through attenuation of von Willebrand factor extrusion and multimer expression while this effect was not elicited by the NPY. One preclinical study in the animal model of HF showed that galanin receptor type 1 agonist improved cardiac function and attenuated ventricular remodeling.

Most important characteristics and effects of galanin are depicted in Figure 3. Due to the scarcity of studies examining the role of galanin in HF, future preclinical and clinical studies are warranted to further elucidate its biological functions and its potential as a biomarker in HF.

**Endothelin**

Endothelins represent a family of three similar 21 amino acid length peptides – endothelin 1 (ET-1), 2 (ET-2) and 3 (ET-3) of which ET-1 and ET-2 bind to G-protein coupled endothelin receptors A (ETa) and B (ETb) on vascular smooth muscle cells with equal affinity to both while ET-3 exhibits lower affinity for ETa relative to ETb receptor. Of all endothelins, ET-1 is predominantly produced by vascular tissue, has inotropic, chemotactic and mitogenic properties, induces collagen synthesis by cardiac fibroblasts, and is biologically the most potent vasoconstrictor in the human cardiovascular system. Furthermore, autocrine binding of ET-1 to ETb receptors promotes NO and prostaglandin release and consequent relaxation of vascular smooth muscle cells. ET-1 plays a role in neuronal development, growth, and function while...
biologically promoting vascular and cardiac hypertrophy, inflammatory responses and is an independent factor contributing to exacerbation of the cardiovascular disease\[25-26\]. The main source of ET-1 and its precursor, big endothelin-1 (BigET-1) are pulmonary vascular endothelial cells, therefore, elevated plasma levels of ET-1 or bigET-1 might closely reflect the degree of pulmonary endothelial dysfunction in HF while ET-1 was significantly overexpressed in the lungs of patients with pulmonary hypertension\[27-28\]. Stangl et al\[29\] demonstrated that in severe congestive HF lungs act as a producer while coronary and peripheral circulation act as consumers of BigET-1 and ET-1 while short-term vasodilator therapy decreased endotoxins and restored pulmonary, coronary, and peripheral balance\[29\]. Endothelin receptors are also expressed in the CNS and central administration of endothelin modulated endocrine and cardiovascular regulation, behavior and MAP\[30\]. In the preclinical experiment, an injection of ET-1 in different regions of the brainstem of normotensive rats resulted in a differential response in heart rate, arterial blood pressure, and respiratory frequency indicating that endothelin has a modulatory role in cardiovascular function\[30\].

Previous studies showed that HF is associated with high levels of ET-1 in plasma and renal tissue and these levels correlated with syndrome severity, especially with the extent of pulmonary hypertension, and overall contributed to the progression of chronic HF\[25-26\]. In a preclinical study, infusion of tezosentan (ET-1 antagonist) significantly decreased MAP in both normal and HF animals and reduced cardiac sympathetic nerve activity (CSNA) in normal animals; however, no decrease was observed in HF animals\[30\]. Therefore, this study showed that endogenous levels of ET-1 contribute to the baseline levels of CSNA in healthy animals, however, this correlation was absent in experimentally induced HF. Contrary to this, a non-selective experimental ET-1 and ET-2 antagonist (TAK-004) suppressed sympathetic activity and improved arterial baroreflex function in rats with HF\[30\]. Similarly, the addition of ACE inhibitor to ET\(_\alpha\) receptor antagonist significantly improved cardiac failure after extensive MI in a rat model of congestive HF, compared with ACE inhibition monotherapy\[30\]. A cross-talk between the endothelin system and the adrenergic system has been demonstrated as activation of ET\(_\alpha\) receptors on sympathetic neurons caused an increase in arterial blood pressure through vasoconstriction mediated by \(\alpha_2\)-adrenergic receptors\[30\]. Sympathoexcitatory effects are also promoted through the interaction of ET-1 with ET\(_\alpha\) receptors as this resulted in cardiomyocyte hypertrophy through adrenergic signaling pathways and massive NE release while it also contributed to impaired responsiveness of renal mechanosensory nerves in congestive HF\[25-26\]. In the rat model of HF, endogenous ET-1 impaired NE reuptake through activation of ET\(_\alpha\) receptors while in a healthy heart ET\(_\alpha\)-mediated inhibition of NE reuptake was countered, but to a lesser degree, by the ET\(_\alpha\)-mediated silencing of NE release resulting in a net increase in left ventricular contractility suggesting that fine balance between NE reuptake and exocytotic release is modulated by endothelin signaling as it was also suggested in previous studies\[26,30\].

However, while endothelin pathway inhibition seemed promising in animal and preclinical models of HF, these observations did not translate to human clinical studies as ET-1 antagonist tezosentan did not improve symptoms or clinical outcomes in patients with acute HF although ET-1 levels were independently associated with short term in-hospital outcomes and 180-d mortality in patients hospitalized for acute HF, as demonstrated in ASCEND-HF substudy\[25-26\]. A predictive value of BigET-1 in patients with left ventricular dysfunction after AMI on the composite endpoint of cardiovascular death or hospitalization for worsening HF has been demonstrated in the subanalysis from EPHESUS study, however, neurohumoral antagonist – eplerenone seemed to have no significant effect in modifying BigET-1 levels at follow-up\[20\]. Authors proposed that levels of BigET-1 (as a precursor of ET-1) likely reflect the degree of ET-1 synthesis while BigET-1 is also a more feasible laboratory biomarker due to its longer half-life than that of ET-1\[20\]. This notion has been confirmed in a previous study that established how elevated plasma ET-1 levels in human CHF dominantly represent the elevation of Big-ET-1 while ET activity was not changed in CHF compared to a healthy state\[20\]. Furthermore, increased ET-1 levels were detected only in moderate or severe CHF and not among asymptomatic patients or those with mild CHF while plasma concentrations in range 5-40 pmol/L seemed to exhibit vasoactive effects\[20\]. Previous studies confirmed that BigET-1 provided prognostic information regarding the cardiovascular mortality during the 12-mo follow-up (HR: 1.42, 95%CI: 1.04-1.95, \(P = 0.03\)) all-cause mortality during the 23-mo follow-up (HR: 1.49, 95%CI: 1.20-1.84, \(P = 0.0003\)) and the composite endpoint of mortality and morbidity (HR: 1.43, 95%CI: 1.20-1.69, \(P < 0.001\)) at 23 mo, however, in the latter study BNP remained the strongest neurohormonal prognostic factor\[30\]. In the small study that enrolled patients with severe CHF, Big-ET-1 and ET-1 levels were
higher at baseline than in patients with mild to moderate CHF or healthy subjects and were found as robust independent predictors of survival, even beyond natriuretic peptide levels[271].

When 32 studies with 18497 HF patients were summarized in the meta-analysis, it was shown that plasma ET-1 and its related peptides were associated with poor prognosis and mortality in diverse spectrum of HF populations[272]. On the other hand, a meta-analysis of randomized clinical trials showed that neurohumoral antagonism of ET receptors in HF patients improved cardiac output, pulmonary and systemic hemodynamics but had a modest effect on clinical outcomes[273]. Therefore, these data suggest that there is a significant discrepancy between these observations – on one hand, ET signaling has been consistently associated with poor outcomes and prognosis in HF and on the other hand, pharmacological targeting of these adverse pathways seems less impressive in improving outcomes.

Perhaps there is a need to fine-tune and identify which subgroups of HF patients would have the greatest benefit from drugs interfering with ET pathways. In that regard, ET-1 and its fragments have shown some potential as valuable biomarkers among HFpEF patients with pulmonary hypertension or pulmonary dysfunction as its levels were associated with the degree of pulmonary hemodynamic derangements, reduced functional reserve of the right ventricle, diminished cardiac output and impaired cardiac response to exercise and peak oxygen consumption[274-276]. Even in the general population, elevated plasma ET-1 levels were in strong relation with elevated pulmonary artery systolic pressures on the echocardiogram and correlated with mortality and incident HF[277].

Therefore, current data suggest that activation of the endothelin system may play an important role in the pathophysiology of pulmonary hypertension in HFpEF and that it might present a viable target and a step towards precision medicine approach in HFpEF[278]. Regarding the potential ET pathway inhibition in HFpEF, thus far there are limited but encouraging preliminary reports. In the preclinical murine model of HFpEF, dual ET₁/ET₅ blockade by macitentan improved HFpEF by abrogating aldosterone-induced cardiomyocyte hypertrophy and reducing stiffness through decreased expression of type 1 collagen and titin n2B in the left ventricle[279]. In the clinical domain, in patients with HFpEF, ET₅ receptor antagonist sitaxsentan improved exercise tolerance, however, failed to decrease left ventricular mass or improve diastolic function while the study was not powered for mortality and rehospitalization analyses[279]. A small and prematurely stopped study showed that ET receptor blocker bosentan did not improve outcomes in HFpEF patients with pulmonary hypertension[280]. Therefore, due to the size and scarcity of available studies, a question whether ET-1 antagonists would improve outcomes in HFpEF yet remains to be answered by future and adequately powered randomized controlled trials. It is possible that neurohumoral biomarkers such as endothelin and its derivatives will enable us a more precise phenotyping of HFpEF patients to identify those that have a significantly impaired pulmonary function and that would receive the greatest benefit from ET pathway-oriented therapeutic interventions. The summary of synthesis, cellular effects, and pathophysiological implications of ET-1 are presented in Figure 4.

Catestatin
Catestatin (CST) is a product of precursor hormone chromogranin A (ChgA) and was isolated in 1997 by Mahata et al[281]. Its principal physiological action is the negative regulation of catecholamine release into circulation through the mechanism of non-competitive and reversible antagonism of neuronal nicotinic cholinergic receptors (nACHR)[281,282]. Its precursor molecule, ChgA, and other soluble secretory proteins are co-stored and co-released with catecholamines from vesicles in the neuroendocrine, endocrine and immune cells and sympathetic neurons thus have an important modulatory role of the adrenergic system[283]. Upon stimulation of chromaffin cells or sympathetic axons, a marked elevation of ChgA levels was detected[284]. Levels of ChgA are elevated in peripheral blood of patients with chronic HF and AMI and correlate with mortality and poor outcomes[285-287]. Even more, an intramyocardial production of ChgA is established in humans and was associated with negative inotropic and lusitropic effects on the mammalian heart thus providing evidence for neuroendocrine regulation of cardiac function by ChgA[288]. Furthermore, immunohistochemical biopsy studies showed that ChgA is co-localized with BNP in the dilated and hypertrophic left ventricle while ChgA levels correlated with end-diastolic left ventricular pressures[289].

CST is a 21 amino acid fragment derived from ChgA (ChgA213-234) and is secreted by neuroendocrine tissues and nerve endings while it is widely distributed in the secretory granules of skin, sensory organs, and myocardium[290]. Its most important
ECE: Endothelin converting enzyme; ET-1: Endothelin-1; NE: Norepinephrine; NO: Nitric oxide; PGI$_2$: Prostacyclin (prostaglandin I$_2$); VSMCs: Vascular smooth muscle cells.

physiological effect is the autocrine action on the chromaffin cells in the adrenal medulla and adrenergic neurons by which it modulates spillover of catecholamines (primarily NE) into peripheral circulation while concomitantly exhibiting paracrine and endocrine effects since it can be readily measured in the venous and arterial blood\cite{290}. Furthermore, CST is potent regulator of arterial blood pressure since it exerts direct vasodilative effect in humans \textit{in vivo}, activates histamine release from mast cells and stimulates production of NO within endothelial cells\cite{291-293}. Once secreted outside of the cell through the process of exocytosis, extracellular post-translational proteolytic processing of the ChgA molecule will release several bioactive peptides and CST that will ultimately bind nAChR receptors of chromaffin cells in autocrine fashion thus antagonizing ACh actions in the periphery as depicted in Figure 5\cite{295}.

In the perspective of previously discussed catecholamine storage vesicle neurotransmitters, Mahapatra and colleagues demonstrated that CST inhibited nicotinically triggered exocytotic release of several co-transmitters from chromaffin granules such as NPY, adenosine triphosphate, chromogranins and catecholamines thereby demonstrating that CST is a potent regulator of neuropeptide transmission in the sympathochromaffin system\cite{296}. However, in the CNS, CST exhibits both sympathoexcitatory and procholinergic effects depending on the region of medulla where its expressed\cite{297,298}. Of established cardiovascular effects, CST suppresses beta-adrenergic activation and acts in a negative inotropic and chronotropic fashion, stimulates angiogenesis and proliferation of vascular smooth muscle cells, decreases thrombogenicity of endothelial cells, suppresses atherosclerosis and inflammation while also exerts cardioprotective effects by abrogating cardiomyocyte ischemia-reperfusion injury\cite{299-301}. A very recent study by Alam \textit{et al.}\cite{307} showed that CST has a direct and independent inhibiting effect on hypertrophy elicited by NE in the cultured H9c2 cardiac myoblasts and that is involved in the regulation of a large number of fetal genes that are upregulated during the process of myocardial hypertrophy\cite{307}. Furthermore, the same study showed that CST effectively blunted stimulative effects of NE and other mitogenic signals on $\beta_1$ and $\beta_2$ adrenergic receptors thus providing novel evidence that CST has a direct modulatory effect on adrenergic transmission at
the level of adrenergic receptors. Similarly, in the model of rat heart, CST activated \( \beta_2 \) and \( \beta_3 \) adrenergic receptors thus upregulating the activity of eNOS and consequently increasing cyclic GMP and phosphodiesterase type 2 (PDE2) levels\(^{308}\).

In line with its sympatholytic effects, chronic administration of exogenous CST improved autonomic function, shortened QT interval, and action potential duration and reduced the incidence of experimentally-induced ventricular arrhythmias in a rat model of myocardial infarction\(^{309}\). Similarly, in the rat model of hyperadrenergic hypertension, rats with ablated ChgA gene showed significantly longer QT interval, R-amplitude, and QRS time-voltage and this was accompanied by increased resting heart rate and QT variability thus demonstrating that arrhythmogenic ventricular assault develops in the status of low circulating CST levels\(^{310}\). These preclinical observations were clinically validated as elevated CST levels were an independent predictor of complicated malignant arrhythmias among AMI patients\(^{311}\). This observation might seem counterintuitive at first, however, it could be explained in the sense that CST levels reflect a compensatory response for the increased SNS activity and excess catecholamine discharge and are attempting to restore autonomic balance. Therefore, circulating CST levels likely “mirror” biological catecholamine turnover and degree of sympathetic activity as CST co-localizes and is co-released with catecholamines and other neuropeptides. Finally, cardioprotective effects of CST are likely pathophysiologically overpowered by sympathetic discharge in conditions in which cardiovascular homeostasis is disrupted such as AMI or decompensated HF, despite the relatively high circulating CST levels.

There are only a few available studies that examined the role of CST in HF and investigated its prognostic role in this syndrome.

In the first study by Zhu et al\(^{312}\) CST levels gradually decreased from stage A to C of HF while there was a significant difference between stage A and B in terms of CST concentrations with a cut-off value of 19.73 ng/mL providing 90% sensitivity and 50.9% specificity for the detection of B stage of HF\(^{312}\). This finding is of clinical relevance since stage B presumes structural cardiac disorder but without symptoms, while stage A assumes patients at high risk for developing HF but without functional or structural heart disorder. Therefore, this study showed that there is a utility for

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**Figure 5** Mechanism of cestatin autocrine modulation of chromaffin cell in the adrenal medulla during sympathetic stimulation. ACh: Acetylcholine; ATP: Adenosine triphosphate; Ca\(^{2+}\): Calcium; ChgA: Chromogranin A; nAchR: Neuronal type of nicotinic cholinergic receptors; Na\(^{+}\): Sodium; NPY: Neuropeptide Y.
decreased CST levels implying structural heart disease among asymptomatic patients. In the study by Liu et al\cite{313} performed in the similar setting, CST was found higher in patients with HF compared to control subjects and it positively correlated with functional syndrome burden as assessed by the NYHA class\cite{313}. Furthermore, etiology of HF (ischemic or not) and NYHA class predicted plasma CST levels while BNP provided better area under the curve value than CST in terms of detecting moderate to severe HF diagnosis (area under the curve values of 0.831 and 0.626, respectively). Adding CST to BNP did not improve diagnostic accuracy.

Recently, Borovac et al\cite{314} showed in CATSTAT-HF study, that patients with acutely decompensated HF had higher serum CST levels if they belonged to a higher NYHA functional class while circulating CST levels were significantly higher among patients with ischemic vs non-ischemic etiology of disease thus likely reflecting an augmented SNS neurohumoral activation in patients with ischemic etiology of the disease (in the study defined as those with the history of myocardial infarction)\cite{314}. The same study revealed that CST levels did not differ in respect to LVEF phenotypes while CST levels independently correlated with NYHA class, waist-to-hip ratio, HbA1c, LDL cholesterol, non-HDL cholesterol, high sensitivity cardiac troponin I and the heart rate at admission and rest. Finally, higher CST levels were strongly associated with favorable echocardiographic profile as they positively correlated with smaller LV volumes and dimensions, as well as with decreased left ventricular mass and smaller dimensions of the left atrium and this finding clinically validates the concept that CST locally has cardioprotective effects, attenuates adverse ventricular remodeling and acts in antihypertrophic fashion, as these biological effects were postulated in a few earlier preclinical studies\cite{307,315}.

**CONCLUSION**

Finally, the prognostic value of CST as a biomarker was demonstrated among chronic HF patients. In the multivariate Cox regression analysis, plasma CST was an independent risk factor for all-cause death (HR: 1.84, 95% CI: 1.02-3.32, \( P = 0.042 \)) and cardiac death (HR: 2.41, 95% CI: 1.26-4.62, \( P = 0.008 \)), respectively, during the median follow-up of 52.5 mo\cite{316}. If patients had both high CST and BNP levels during hospitalization the risk of all-cause death increased 3-fold while the risk of cardiac death increased 4-fold.

Based on these findings it is plausible that CST could be a reliable indirect marker of SNS activity and it is likely that high CST levels reflect advanced disease burden and high sympathoexcitatory profile of an individual HF patient. Furthermore, CST provides complementary prognostic information to natriuretic peptides in terms of mortality in HF and could aid in the risk stratification of chronic HF patients. However, since the latter finding is based on only one clinical study further large-scale studies are required to validate these findings and clarify the role of circulating CST levels in predicting HF prognosis. Finally, patients with elevated CST levels might be suitable candidates for the introduction or up-titration of sympatholytic agents such as beta-adrenergic blockers, however, the effects of neurohumoral antagonists on circulating CST levels are yet to be determined.

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**REFERENCES**

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]
Borovac JA et al. Sympathetic system activation in heart failure

2 Braunwald E. Heart failure. JACC Heart Fail 2013; 1: 1-20 [PMID: 24621794 DOI: 10.1016/j.hfc.2012.10.002]

3 Savarese G, D’Amario D. Sex Differences in Heart Failure. Adv Exp Med Biol 2018; 1065: 529-544 [PMID: 30051405 DOI: 10.1007/978-3-7973-92-32-2]

4 Benjamini EJ, Blaha MJ, Chiueh SE, Cushman M, Das SR, Deo R, de Ferrari GD, Floyd J, Forman M, Gillespie C, Isací CR, Jimenez MC, Jordan LC, Judd SE, Lackland DT, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Paliapannan L, Pandey DK, Thigaarajan RR, Reeves MJ, Ritchey M, Rodd JG, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017; 135: e1-e603 [PMID: 28122885 DOI: 10.1161/CIR.0000000000000485]

5 Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev 2017; 3: 7-11 [PMID: 28785469 DOI: 10.15420/cfr.2016:25:2]

6 Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespiollo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018; 391: 572-580 [PMID: 29174292 DOI: 10.1016/s0140-6736(17)32520-5]

7 Lesyk W, Kriza C, Kolominsky-Rabas P. Cost-of-illness studies in heart failure: a systematic review 2004-2016. BMC Cardiovasc Disord 2018; 18: 74 [PMID: 29716540 DOI: 10.1186/s12872-018-0815-3]

8 Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lamas CSP, Sato N, Shahos A, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014; 63: 1123-1133 [PMID: 24491699 DOI: 10.1016/j.jacc.2013.11.053]

9 Taylor CJ, Ryan R, Nichols L, Gale N, Hobbs FR, Marshall T. Survival following a diagnosis of heart failure in primary care. Fam Pract 2017; 34: 161-168 [PMID: 28137015 DOI: 10.1093/fampra/cmw089]

10 Dookainah B, Teo K, Zhu J, Roy A, AlHabib KF, Elsayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusuf K, Orlandini A, Libston AS, Fung Y, Amlagtwary M, Damasceno A, Tibazarwa K, Denman J, Liu S, Yacoub MH, Huffman MD, Haskens K, Grinfelds A, McKelvie R, Bangdiwala SI, Yusuf S; INTER-CHF Investigators. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Health 2017; 5: e665-e672 [PMID: 28476564 DOI: 10.1016/S1473-3099(17)30190-1]

11 Mamas MA, Serrin M, Watson MC, Couts A, Wilde K, Burton C, Kadam UT, Kwok CS, Clark AB, Murchie P, Buchan I, Hamford PC, Miyki PK. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. Eur J Heart Fail 2019; 17: 1095-1104 [PMID: 28470862 DOI: 10.1002/ejhf.822]

12 Taylor CJ, Ordóñez-Mena JM, Routle AF, Lay-Flurrie S, Jones NR, Marshall T, Hobbs FDR. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ 2019; 364: 1223 [PMID: 30706447 DOI: 10.1136/bmj.l223]

13 Mensah GA, Weis GS, Sorte PD, Fine LJ, Rosenberg Y, Kaufmann PG, Mussolino ME, Hsu LL, Addou E, Engelgas MM, Gordon D. Decline in Cardiovascular Mortality: Prognostic Causes and Implications. Circ Res 2017; 120: 366-380 [PMID: 28104770 DOI: 10.1161/CIRCRESAHA.116.309115]

14 Tsao CW, Lyass A, Ensorro D, Larson MG, Ho JE, Kizer JR, Gottschales JS, Paity BM, Vasan RS. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail 2018; 6: 678-685 [PMID: 30007560 DOI: 10.1016/j.jchf.2018.03.008]

15 Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017; 14: 591-602 [PMID: 28492288 DOI: 10.1038/nrc2981-61]

16 Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart Failure With Preserved Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol 2017; 70: 2476-2486 [PMID: 29141781 DOI: 10.1016/j.jacc.2017.08.074]

17 Henning RJ. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. World J Cardiol 2020; 12: 7-25 [PMID: 31984124 DOI: 10.4330/wjc.v12.i1.7]

18 Goyal P, Loop M, Chen L, Brown TM, Durant RW, Stafford MM, Leitan EB. Causes and Temporal Patterns of 30-Day Readmission Among Older Adults Hospitalized With Heart Failure With Preserved or Reduced Ejection Fraction. J Am Heart Assoc 2018; 7 [PMID: 29866028 DOI: 10.1161/JAHA.117.007785]

19 Ibrahim NE, Januzzi JL Jr. Established and Emerging Roles of Biomarkers in Heart Failure. Circ Res 2018; 123: 614-629 [PMID: 30355136 DOI: 10.1161/CIRCRESAHA.118.312706]

20 Ziaiean B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016; 13: 368-378 [PMID: 26935038 DOI: 10.1038/nrccardio.2016.25]

21 Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol 2012; 21: 365-371 [PMID: 22227365 DOI: 10.1016/j.carpath.2011.11.007]

22 Cuomo A, Rodolico A, Galdieri A, Russo M, Campi G, Franco R, Bruno D, Aram L, Carramante A, Attanasio U, Tochetti C, Varrielli G, Mercaldo CD. Heart Failure and Cancer: Mechanisms of Cofailure and New Cardiotoxic Drugs in Cancer Patients. Circ Res Fail Rev 2019; 5: 112-118 [PMID: 31179022 DOI: 10.1542/circ.2018.32.2]

23 De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation 2011; 123: 1996-2004; discussion 2005 [PMID: 21555722 DOI: 10.1161/CIRCULATIONAHA.110.981451]

24 Aziz F, Tk LA, Enweluzo C, Dutta S, Zaeem M. Diastolic heart failure: a concise review. J Clin Med Res 2013; 5: 327-334 [PMID: 23986796 DOI: 10.4021/jocmr1532w]

25 Federmann M, Hess OM. Differentiation between systolic and diastolic dysfunction. Eur Heart J 1994; 15 Suppl D: 2-6 [PMID: 7713107 DOI: 10.1093/eurheartj/15.suppl_d.2]

26 Bloom MW, Greenberg B, Jaarsma T, Januzzi JL, Lam CSP, Maggioni AP, Trochu JN, Butler J. Heart
failure with reduced ejection fraction. *Nat Rev Dis Primers* 2017; 3: 17058 [PMID: 28836616 DOI: 10.1038/nrdp.2017.35]

Ozouman M, Lee DS, Lin PP. Diastolic heart failure: mechanisms and controversies. *Clin Pract Cardiol* 2008; 5: 375-386 [PMID: 18542106 DOI: 10.1007/s00467-014-0325-6]

Yoon S, Eom GH. Heart failure with preserved ejection fraction: present status and future directions. *Exp Mol Med* 2019; 51: 1-9 [PMID: 31885781 DOI: 10.1038/s12276-019-0332-2]

Buggey J, Alenzi F, Yoon HJ, Phelan M, DeVore AD, Khouri MG, Schulte PJ, Velazquez EJ. Left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: outcomes following an acute heart failure hospitalization. *ESC Heart Fail* 2017; 4: 432-439 [PMID: 29154416 DOI: 10.1002/ehf2.12159]

DeVore AD, McNulty S, Alenzi F, Essnl M, Vader JM, Oh JK, Lin G, Redfield MM, Lewis G, Semigran MJ, Amstrom KJ, Hernandez AF, Velazquez EJ. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. *Eur J Heart Fail* 2017; 19: 893-900 [PMID: 28194841 DOI: 10.1002/ejhf.754]

Nagueh SF, Chang SM, Nabi F, Shah DJ, Estep JD. Cardiac Imaging in Patients With Heart Failure and Preserved Ejection Fraction. *Circ Cardiovasc Imaging* 2017; 10 [PMID: 28838962 DOI: 10.1161/CIRCIMAGING.117.006547]

Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation* 2002; 105: 1503-1508 [PMID: 11941262 DOI: 10.1161/01.01.20105290]

Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2014; 11: 507-515 [PMID: 24958077 DOI: 10.1038/nrcardio.2014.83]

Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; 350: 1953-1959 [PMID: 15128895 DOI: 10.1056/NEJMoa032566]

Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation* 2015; 131: 1247-1259 [PMID: 25657629 DOI: 10.1161/CIRCULATIONAHA.114.013215]

Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignon P, Badoz M, Sadoun M, Launay JM, Gayat E, Lam CSP, Cohen-Solal A, Mebazaa A, Seronde MF. Aclutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail* 2018; 20: 738-747 [PMID: 29251818 DOI: 10.1002/ejhf.1050]

Reddy VNY, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melonenovsky V, Olson TP, Borlaug BA. Arterial Stiffening With Exercise in Patients With Heart Failure and Preserved Ejection Fraction. *Am Coll Cardiol* 2017; 70: 136-148 [PMID: 28683960 DOI: 10.1016/j.jacc.2017.05.029]

Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weinier RB, Houstis NE, Esman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015; 8: 286-294 [PMID: 25344549 DOI: 10.1161/CIRCHEARTFAILURE.114.001822]

Malhotra R, Bakken K, D'elia E, Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. *JACC Heart Fail* 2016; 4: 607-616 [PMID: 27289406 DOI: 10.1016/j.jchf.2016.03.022]

Reddy VNY, Olson TP, Obokata M, Melonenovsky V, Borlaug BA. Hemodynamic Correlates and Diagnostic Role of Cardiopulmonary Exercise Testing in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2018; 6: 665-675 [PMID: 29803552 DOI: 10.1016/j.jchf.2018.03.003]

Banning AP, Lewis NP, Northridge DB, Elborn JS, Henderson AH. Perfusion/ventilation mismatch during exercise in chronic heart failure: an investigation of circulatory determinants. *Br Heart J* 1995; 74: 27-33 [PMID: 7662449 DOI: 10.1136/hrt.74.1.27]

P'Amario D, Migliaro S, Borvac IA, Restivo A, Vergallo R, Galli M, Leone AM, Montone RA, Niccoli G, Aspromonte N, Crea F. Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction. *Front Physiol* 2019; 10: 1347 [PMID: 31749710 DOI: 10.3389/fphys.2019.01347]

Gevaert AB, Boen JRA, Segers VF, Van Craenenbroeck EM. Heart Failure With Preserved Ejection Fraction: A Review of Cardiac and Noncardiac Pathophysiology. *Front Physiol* 2019; 10: 638 [PMID: 31191343 DOI: 10.3389/fphys.2019.00638]

Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; 62: 263-271 [PMID: 23688677 DOI: 10.1016/j.jacc.2013.02.092]

Fransen C, Chen S, Unger A, Korkmaz HI, De Keulenaeer GW, Tschöpe C, Leite-Moreira AF, Musters R, Niessen HW, Linke WA, Paulus WJ, Hamdani N. Myocardial Microvascular Inflammatory Endothelial Activation in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail* 2016; 4: 312-324 [PMID: 26682792 DOI: 10.1016/j.jchf.2015.10.007]

van Heerbeek L, Hamdani N, Falcão-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circulation* 2012; 126: 830-839 [PMID: 22906602 DOI: 10.1161/CIRCULATIONAHA.111.076675]

Kötter S, Gout L, Von Frieling-Salewsky M, Müller AE, Helling S, Marcus K, Dos Remedios C, Linke WA, Krüger M. Differential changes in titin domain phosphorylation increase myofilament stiffness in failing human hearts. *Cardiovasc Res* 2013; 99: 648-656 [PMID: 23764881 DOI: 10.1093/cvr/cvt144]

Hamdani N, Bishu KG, von Frieling-Salewsky M, Redfield MM, Linke WA. Deranged myofilament phosphorylation and function in experimental heart failure with preserved ejection fraction. *Cardiovasc Res* 2013; 97: 464-471 [PMID: 23231008 DOI: 10.1093/cvr/cvs353]

Graziani F, Varone F, Crea F, Richeldi L. Treating heart failure with preserved ejection fraction: learning from pulmonary fibrosis. *Eur J Heart Fail* 2018; 20: 1385-1391 [PMID: 30085383 DOI: 10.1002/ejhf.1286]

Leuecker TM, Jones SP. Endothelial dysfunction as a nexus for endothelial cell-cardiomyocyte
miscommunication. Front Physiol 2014; 5: 328 [PMID: 25206341 DOI: 10.3389/fphys.2014.00328]

Gevaert AB, Lemmens K, Vrints CJ, Van Craenenbroeck EM. Targeting Endothelial Function to Treat Heart Failure with Preserved Ejection Fraction: The Promise of Exercise Training. *Oxid Med Cell Longev* 2017; 2017: 4865756 [PMID: 28706575 DOI: 10.1155/2017/4865756]

Gimbrone MA Jr, Garcia-Cardena G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res* 2016; 118: 620-636 [PMID: 26892962 DOI: 10.1161/CIRCRESAHA.115.306301]

Kovacic JC, Dimmeler S, Harvey RP, Finkel T, Aikawa E, Krenning G, Baker AH. Endothelial to Mesenchymal Transition in Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; 73: 190-209 [PMID: 30624892 DOI: 10.1016/j.jacc.2019.08.089]

Wirrig EE, Yatsev KE. Conserved transcriptional regulatory mechanisms in aortic valve development and disease. *Arterioscler Thromb Vasc Biol* 2014; 34: 737-741 [PMID: 24665126 DOI: 10.1161/ATVBAHA.113.302071]

Spillmann F, Miteva K, Pieske B, Tschöpe C, Van Linhout S. High-density lipoproteins reduce endothelial-to-mesenchymal transition. *Arterioscler Thromb Vasc Biol* 2015; 35: 1774-1777 [PMID: 26088574 DOI: 10.1161/ATVBAHA.115.305887]

Murdock CE, Chaubey S, Zeng L, Yu B, Ivetic A, Walker SJ, Vanhoutte D, Heymans S, Grieve DJ, Cave AC, Brewer AC, Zhang M, Shah AM. Endothelial NADPH oxidase-2 promotes interstitial cardiac fibrosis and diastolic dysfunction through proinflammatory effects and endothelial-mesenchymal transition. *J Am Coll Cardiol* 2014; 63: 2734-2741 [PMID: 24681145 DOI: 10.1016/j.jacc.2014.02.572]

Cooley BC, Nevado J, Mellad J, Yang D, St Hilaire C, Negro A, Fang F, Chen G, San H, Walts AD, Schwartzebeck RL, Taylor B, Lanzer JD, Wragg A, Elagha A, Beltran LE, Berry C, Feil R, Virmani R, Ladich E, Kovacic JC, Boehm M. TGF-β signaling mediates endothelial-to-mesenchymal transition (EndMT) during vein graft remodeling. *Clin Sci (Lond)* 2013; 6: 227ra34 [PMID: 24622534 DOI: 10.1126/scitransmed.3006927]

Xu X, Friehs I, Zhong Hu T, Melnychenko I, Tampe B, Alnour F, Iascone M, Kalluri R, Zeisberg M, Del Nido PJ, Zeisberg EM. Endocardial fibroelastosis is caused by aberrant endothelial to mesenchymal transition. *Circ Res* 2015; 116: 857-866 [PMID: 25587097 DOI: 10.1161/CIRCRESAHA.116.305629]

Good RB, Gilibane AJ, Trinder SL, Denton CP, Coghlan G, Abraham DJ, Holmes AM. Endothelial to Mesenchymal Transition Contributes to Endothelial Dysfunction in Pulmonary Arterial Hypertension. *Am J Pathol* 2015; 185: 1850-1858 [PMID: 25956031 DOI: 10.1016/j.ajpath.2015.03.019]

Jiang Y, Zou X, Hu R, Dai A. TGF-β1-induced SMAD2/3/4 activation promotes RELM-β transcription to modulate the endothelium-mesenchymal transition in human endothelial cells. *Int J Biochem Cell Biol* 2018; 105: 52-60 [PMID: 30120989 DOI: 10.1016/j.biocel.2018.09.029]

Piera-Velazquez S, Mendoza FA, Jimenez SA. Endothelial to Mesenchymal Transition (EndoMT) in the Pathogenesis of Human Fibrotic Diseases. *J Clin Med* 2016; 5 [PMID: 27077889 DOI: 10.3390/jcm5040045]

Yoshimura A, Wakabayashi Y, Mori T. Cellular and molecular basis for the regulation of inflammation by TGF-beta. *J Biochem* 2017; 147: 781-792 [PMID: 20410014 DOI: 10.1093/jb/mvx041]

Cho JG, Lee A, Chang W, Lee MS, Kim J. Endothelial to Mesenchymal Transition Represents a Key Link in the Interaction between Inflammation and Endothelial Dysfunction. *Front Immunol* 2016; 7: 294 [PMID: 27915588 DOI: 10.3389/fimmu.2016.00294]

Hulshoff MS, Xu X, Krenning G, Zeisberg EM. Epigenetic Regulation of Endothelial-to-Mesenchymal Transition in Chronic Heart Disease. *Arterioscler Thromb Vasc Biol* 2018; 38: 1986-1996 [PMID: 30354260 DOI: 10.1161/ATVBAHA.118.112376]

Hartupe J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol* 2017; 14: 30-38 [PMID: 27708278 DOI: 10.1038/nrcardio.2016.163]

Volpe M, Carnovale M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci (Lond)* 2016; 130: 57-77 [PMID: 26637405 DOI: 10.1042/CS20150469]

Jhund PS, McMurray JJ. The nephrilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. *Heart* 2016; 102: 1342-1347 [PMID: 27207980 DOI: 10.1136/heartjnl-2014-306775]

Orsborne C, Chaggar PS, Shaw SM, Williams SG. The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future. *Postgrad Med J* 2017; 93: 29-37 [PMID: 27867172 DOI: 10.1136/postgradmedj-2016-134045]

Goldsmith SR. The role of vasopressin in congestive heart failure. *Cleve Clin J Med* 2006; 73 Suppl 3: S18-S23 [PMID: 16970149 DOI: 10.3949/ccjm.73.suppl_3.319]

Lee CS, Tkacs NC. Current concepts of neurohormonal activation in heart failure: mediators and mechanisms. *AACC Adv Crit Care* 2008; 19: 364-85; quiz 366-7 [PMID: 18981739 DOI: 10.1097/01.AACN.0000340718.93742.c4]

Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. *Circadi Clin 2014; 32: 33-45, vii [PMID: 24286577 DOI: 10.1016/j.circadhyp.2013.09.010]

Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. *Eur Heart J* 2015; 36: 1974-1982 [PMID: 25975567 DOI: 10.1093/eurheartj/ehv087]

Seferovic PS, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Céldor JG, de Boer RA, Drexel H, Ben Gal T, Hill I, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piot P, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filipatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; 21: 1169-1186 [PMID: 31129923 DOI: 10.1002/ejhf.1531]

Yancey CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EL, Wilkoff BL: American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology
Borovac JA et al. Sympathetic system activation in heart failure

Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147-e239 [PMID: 23747842 DOI: 10.1016/j.jacc.2013.05.019]

van Bilsen M, Patel HC, Bauerachs J, Böhm M, Borußreif M, Bruunsgaard H, de Boer RA, de Keulenaer GW, Filipatos GS, Floras JS, Grassi G, Jankowska EA, Kornel L, Lunde IG, Maack C, Mahfoud F, Pollesello P, Ponikowski P, Ruschitzka F, Sabbah HN, Schultz HD, Seferovic P, Stirling RHU, Taggart P, Tocchetti CG, Van Laake LW, Zamad F, Heymans S, Lyon AR. The autonomic nervous system as a therapeutic target in heart failure: a scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2017; 19: 1361-1378 [PMID: 28949064 DOI: 10.1002/ejhf.921]

Doehner W, Ural D, Hauseuler KG, Čelutkienė J, Bestetti R, Cavusoglu Y, Peña-Duque MA, Glavas D, Iacoviello M, Laufs U, Alvear RM, Bhukwem A, Piepoli MF, Rosen SD, Tsivgoulis G, Vitale C, Yilmaz MB, Anker SD, Filipatos G, Seferovic P, Coats AJS, Ruschitzka F. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Eur J Heart Fail 2018; 20: 199-215 [PMID: 29280256 DOI: 10.1002/ejhf.1100]

Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1999; 22: 248-254 [PMID: 10315488 DOI: 10.1016/S0735-1097(92)90167-J]

de Lucia C, Piedepalumbo M, Paolisso G, Koch WJ. Sympathetic nervous system in age-related cardiovascular dysfunction: Pathophysiology and therapeutic perspective. Int J Biochem Cell Biol 2019; 108: 29-33 [PMID: 30693431 DOI: 10.1016/j.biocell.2019.01.004]

Triposkádlis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol 2009; 54: 1747-1762 [PMID: 19874988 DOI: 10.1016/j.jacc.2009.05.015]

Angelakos ET, King MP, Millard RW. Regional distribution of catecholamines in the hearts of various species. Ann N Y Acad Sci 1969; 156: 219-240 [PMID: 5316805 DOI: 10.1111/j.1749-6632.1969.tb0730a.x]

Pierpoint GL, DeMaster EG, Reynolds S, Pederson J, Cohn JN. Ventricular myocardial catecholamines in primates. J Lab Clin Med 1985; 106: 205-210 [PMID: 4020248]

Janes RD, Brandys JC, Hopkins DA, Johnstone DE, Murphy DA, Armour JA. Anatomy of human extrinsic cardiac nerves and ganglia. Am J Cardiol 1986; 57: 299-309 [PMID: 3946219 DOI: 10.1016/0002-9149(86)90908-2]

Heesch CM. Reflexes that control cardiovascular function. Am J Physiol 1999; 277: S234-S243 [PMID: 10864250 DOI: 10.1152/advances.1999.277.6.S234]

Burchell AE, Sobotta PA, Hart EC, Nightingale AK, Dunlap ME. Chemobypersensitivity and autonomic modulation of venous capacitance in the pathophysiology of acute decompensated heart failure. Curr Heart Fail Rep 2013; 10: 139-146 [PMID: 23504401 DOI: 10.1007/s11897-013-0135-y]

Fallick C, Sobotta PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail 2011; 4: 696-675 [PMID: 21934091 DOI: 10.1161/CIRCHEARTFAILURE.111.961789]

Malliani A, Montano N. Emerging excitatory role of cardiovascular sympathetic afferents in pathophysiological conditions. Hypertension 2002; 39: 63-68 [PMID: 11799080 DOI: 10.1161/hy0102.099206]

Leineweber K, Wangemann T, Giessler C, Bruck H, Dhein S, Kostelka M, Mohr FW, Silber RE, Brodde OE. Age-dependent changes of cardiac neuronal noradrenaline reuptake transporter (uptake1) in the human heart. J Am Coll Cardiol 2002; 40: 1459 [PMID: 12392837 DOI: 10.1016/s0735-1097(02)92168-x]

Torres GE, Gaimednínov RR, Caron MG. Plasma membrane monoamine transporters: structure, regulation and function. Nat Rev Neurosci 2003; 4: 13-25 [PMID: 12511858 DOI: 10.1038/nrn1008]

Rengo G, Pagano G, Vitale DF, Formisano R, Komici K, Petraglia L, Parisi V, Femminella GD, de Lucia C, Paolillo S, Cannavo A, Aruta E, Pellegroino T, Della Ragione R, Dicafi F, Scioccola N, Ferrara N. Impact of aging on cardiac sympathetic innervation measured by 123I-mIBG imaging in patients with systolic heart failure. Eur J Nucl Med Mol Imaging 2016; 43: 2392-2400 [PMID: 27287990 DOI: 10.1007/s00259-016-3432-3]

Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, Agostoni D, Weiland F, Chandha H, Narula J; ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol 2010; 55: 2212-2222 [PMID: 20188504 DOI: 10.1016/j.jcc.2010.01.014]

de Diego AM, Gandia L, García AG. A physiological view of the central and peripheral mechanisms that regulate the release of catecholamines at the adrenergic medulla. Acta Physiol (Oxf) 2008; 192: 287-301 [PMID: 18005392 DOI: 10.1111/j.1748-1716.2007.01807.x]

Philipp M, Hein L. Adrenergic receptor knockout mice: distinct functions of 9 receptor subtypes. Pharmacol Ther 2004; 101: 65-74 [PMID: 14729393 DOI: 10.1016/j.pharmthera.2003.10.004]

Rooke B, Gauhther C. beta3-adrenoceptors in the cardiovascular system: putative roles in human pathologies. Pharmacol Ther 2006; 111: 652-673 [PMID: 16480771 DOI: 10.1016/j.pharmthera.2005.12.002]

Rockman HA, Koch WJ, LeKowitz RJ. Seven-transmembrane-spanning receptors and heart function. Nature 2002; 415: 206-212 [PMID: 11805844 DOI: 10.1038/41506a]

Gauhther C, Lehblas V, Kolbzik L, Trochu JN, Khandouri N, Bri A, Balligand JL, Le Marec H. The negative inotropic effect of beta3-adrenoceptor stimulation is mediated by activation of a nitric oxide synthase pathway in human ventricle. J Clin Invest 1998; 102: 1377-1384 [PMID: 9769330 DOI: 10.1172/JCI32191]

Myagmar BE, Flynn JM, Cowley PM, Swigant PM, Montgomery MD, Thai K, Nair D, Gupta R, Deng DX, Hosoda C, Melov S, Baker AJ, Simpson PC. Adrenergic Receptors in Individual Ventricular Myocytes: The Beta-1 and Alpha-1B Are in All Cells, the Alpha-1A Is in a Subpopulation, and the Beta-2 and Beta-3 Are Mostly Absent. Circ Res 2017; 120: 1103-1115 [PMID: 28219977 DOI: 10.1161/CIRCRESAHA.116.310414]
Borovac JA et al. Sympathetic system activation in heart failure

10.1161/CIRCREHA.117.310520

Reid JL. Alpha-adrenergic receptors and blood pressure control. Am J Cardiol 1986; 57: 6E-12E [PMID: 2869681 DOI: 10.1016/0002-9149(86)90716-2]

Reed BK, Speed JS, Powell M, Pollock DM. Activation of neuronal endothelin B receptors mediates pressor response through alpha-1 adrenergic receptors. Physiol Rev 2017; 5 [PMID: 28219980 DOI: 10.14814/phy2.13077]

Woo AH, Xiao RP. β-Adrenergic receptor subtype signaling in heart: from bench to bedside. Acta Pharmacol Sin 2012; 33: 335-341 [PMID: 22286918 DOI: 10.1089/aps.2011.201]

Ali DC, Naveed M, Gordon A, Majeed F, Saeed M, Ogubke MI, Atif M, Zubair HM, Changxing L. β-Adrenergic receptor, an essential target in cardiovascular diseases. Heart Fail Rev 2020; 25: 343-354 [PMID: 31079410 DOI: 10.1007/s10741-019-09825-x]

Madamanchi A. Beta-adrenergic receptor signaling in cardiac function and heart failure. McGill J Med 2007; 10: 99-104 [PMID: 18523538]

Baruscotti M, Barbùti A, Bucchi A. The cardiac pacemaker current. J Mol Cell Cardiol 2010; 48: 55-64 [PMID: 19591835 DOI: 10.1016/j.yjmcc.2009.06.019]

Santulli G, Iaccarino G. Pinpointing beta adrenergic receptor in ageing pathophysiology: victim or executioner? Evidence from crisis scenes. Immun Ageing 2013; 10: 10 [PMID: 23497415 DOI: 10.1186/1477-4472-10-10]

Collins S, Cao W, Robidoux J. Learning new tricks from old dogs: beta-adrenergic receptors teach new lessons on firing up adipose tissue metabolism. Mol Endocrinol 2004, 18: 2123-2131 [PMID: 15243132 DOI: 10.1210/me.2004-0193]

Napp A, Brixius K, Pott C, Ziskoven C, Boeck B, Mehlhorn U, Schwinger RH, Bloch W. Effects of the beta3-adrenergic agonist BRL 37344 on endothelial nitric oxide synthase phosphorylation and force of contraction in human failing myocardium. J Card Fail 2009; 15: 57-67 [PMID: 19181295 DOI: 10.1016/j.cardfail.2008.09.006]

Dessy C, Moniotte S, Ghisdal P, Havaux X, Noirhomme P, Balligand JL. Endothelial beta3-adrenoceptors mediate vasorelaxation of human coronary microarteries through nitric oxide and endothelium-dependent hyperpolarization. Circulation 2004; 110: 948-954 [PMID: 15302798 DOI: 10.1161/01.CIR.0000139331.85766.AF]

Dessy C, Balligand JL. Beta3-adrenergic receptors in cardiac and vascular tissues emerging concepts and therapeutic perspectives. Adv Pharmacol 2010; 59: 135-163 [PMID: 20935201 DOI: 10.1016/S1054-5558(10)50057-7]

Imbrogno S, Angelone T, Adamo C, Puleri E, Tota B, Cerra MC. Beta3-adrenoceptor in the eel (Anguilla anguilla) heart: negative inotropy and NO-cGMP-dependent mechanism. J Exp Biol 2006; 209: 4966-4973 [PMID: 17142685 DOI: 10.1242/jeb.02595]

Moniotte S, Belge C, Sikkali B, Massion PB, Rozec B, Dessy C, Balligand JL. Sepsis is associated with an upregulation of functional beta3 adrenoceptors in the myocardium. Eur J Heart Fail 2007; 9: 1163-1171 [PMID: 17999941 DOI: 10.1016/j.ejheart.2007.10.006]

Gauthier C, Rozec B, Manoury B, Balligand JL. Beta-3 adrenoceptors as new therapeutic targets for cardiovascular pathologies. Curr Heart Fail Rep 2011; 8: 184-192 [PMID: 21633786 DOI: 10.1007/s11897-011-0064-0]

Rozec B, Erfanian M, Laurent K, Trochu JN, Gauthier C. Nebivolol, a vasodilating selective beta(1)-blocker, is a beta(3)-adrenoceptor agonist in the nonfailing transplanted human heart. J Am Coll Cardiol 2009; 53: 1532-1538 [PMID: 19385654 DOI: 10.1016/j.jacc.2008.11.057]

Dessy C, Saliez J, Ghisdal P, Danageau G, Lobysheva HI, Fréart F, Belge C, Jnaoui K, Noirhomme P, Feron O, Balligand JL. Endothelial beta3-adrenoceptors mediate nitric oxide-dependent vasorelaxation of coronary microvessels in response to the third-generation beta-blocker nebivolol. Circulation 2005; 112: 1198-1205 [PMID: 16167060 DOI: 10.1161/CIRCULATIONAHA.104.532960]

de Lucia C, Eguchi A, Koch WJ. New Insights in Cardiac β-Adrenergic Signaling During Heart Failure and Aging. Front Pharmacol 2018; 9: 904 [PMID: 30147654 DOI: 10.3389/fphar.2018.00904]

Gurevich VV, Gurevich EV. GPCR Signaling Regulation: The Role of GRKs and Arrestins. Front Pharmacol 2019; 10: 125 [PMID: 30837883 DOI: 10.3389/fphar.2019.00125]

Shukla AK, Xiao K, Lefkowitz RJ. Emerging paradigms of β-arrestin-dependent seven transmembrane receptor signaling. Trends Biochem Sci 2011; 36: 457-469 [DOI: 10.1016/j.tibs.2011.06.003]

Sato PY, Chuprun JK, Schwartz M, Koch WJ. The evolving impact of g protein-coupled receptor kinases in cardiac health and disease. Physiol Rev 2015; 95: 377-404 [PMID: 25834229 DOI: 10.1152/physrev.00015.2014]

Swedberg K, Viquerat C, Rouleau J-L, Roizen M, Atherton B, Parmley WW, Chatterjee K. Comparison of myocardial catecholamine balance in chronic congestive heart failure and in angina pectoris without failure. Am J Cardiol 1984; 54: 783-786 [PMID: 6488628 DOI: 10.1016/0002-9149(84)90208-5]

Viquerat CE, Daly P, Swedberg K, Evers C, Currar D, Parmley WW, Chatterjee K. Endogenous catecholamine levels in chronic heart failure. Relation to the severity of hemodynamic abnormalities. Am J Med 1985; 78: 455-460 [PMID: 3976704 DOI: 10.1016/0002-9343(85)90339-9]

Kaye DM, Lambert GW, Lefkowitz JI, Morris M, Jennings G, Esler MD. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. J Am Coll Cardiol 1994; 23: 570-578 [PMID: 8113536 DOI: 10.1016/0735-1097(94)90738-2]

Aggarwal A, Esler MD, Lambert GW, Hastings J, Johnston L, Kaye DM. Norepinephrine turnover is increased in suprabulbar subcortical brain regions and is related to whole-body sympathetic activity in human heart failure. Circulation 2002; 105: 1031-1033 [PMID: 11877349 DOI: 10.1161/01.ha.0000057253]

Zucker IH, Schultz HD, Patel KP, Wang W, Gao L. Regulation of central angiotensin type 1 receptors and sympathetic outflow in heart failure. Am J Physiol Heart Circ Physiol 2009; 297: H1557-H1566 [PMID: 19717736 DOI: 10.1152/ajpheart.00703.2009]

Gao L, Wang WZ, Wang W, Zucker IH. Imbalance of angiotensin type 1 receptor and angiotensin II type 2 receptor in the rostral ventrolateral medulla: potential mechanism for sympathetic overactivity in heart
Borovac JA et al. Sympathetic system activation in heart failure

failure. Hypertension 2008; 52: 708-714 [PMID: 18763398 DOI: 10.1161/HYPERTENSIONAHA.108.116228]

123 Møller W, Tschada R, Manthey J, Ablasser A, Kühler W. Catecholamines in Patients with Heart Failure. Delius W, Gerlach E, Grobecker H, Kühler W. Catecholamines and the Heart. Berlin, Heidelberg: Springer 1981; 236-246 [DOI: 10.1007/978-3-642-68321-3_22]

124 Chidsey CA, Braunwald E, Morrow AG. Catecholamine Excretion and Cardiac Stores of Norepinephrine in Congestive Heart Failure. Am J Med 1965; 39: 442-451 [PMID: 14338295 DOI: 10.1016/0002-9343(65)90211-1]

125 Ramchandra R, Hood SG, Denton DA, Woods RL, McKinley MJ, Mcallen RM, May CN. Basis for the preferential activation of cardiac sympathetic nerve activity in heart failure. Proc Natl Acad Sci USA 2009; 106: 924-928 [PMID: 19136653 DOI: 10.1073/pnas.0811929106]

126 Kaye DM, Letkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. J Am Coll Cardiol 1995; 26: 1257-1263 [PMID: 7594040 DOI: 10.1016/0735-1979(95)00332-0]

127 Ramchandra R, Barrett CJ. Regulation of the renal sympathetic nerves in heart failure. Front Physiol 2015; 6: 238 [PMID: 26388778 DOI: 10.3389/fphys.2015.00238]

128 Ramchandra R, Hood SG, Xing D, Lambert GW, May CN. Mechanisms underlying the increased cardiac norepinephrine spillover in heart failure. Am J Physiol Heart Circ Physiol 2018; 315: H340-H347 [PMID: 29701999 DOI: 10.1152/ajpheart.00009.2018]

129 Cohn JN, Levine TB, Oliviari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311: 819-823 [PMID: 6382011 DOI: 10.1056/NEJM198409273111130]

130 Chidsey CA, Harrison DC, Braunwald E. Augmentation of the plasma nor-epinephrine response to exercise in patients with congestive heart failure. N Engl J Med 1962; 267: 650-654 [PMID: 13878934 DOI: 10.1056/NEJM196209272670305]

131 Hasking GJ, Estler MD, Jennings GL, Burton D, Johns JA, Kornet PJ. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardioselective sympathetic nervous activity. Circulation 1986; 73: 615-621 [PMID: 3948363 DOI: 10.1161/01.cir.73.4.615]

132 Bristow MR, Ginsburg R, Minobe W, Cubiciotti RS, Sageman GS, Lurie K, Billingham ME, Harrison DC, Stinson EB. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med 1982; 307: 205-211 [PMID: 6283349 DOI: 10.1056/NEJM198207223070401]

133 Freedman NJ, Lefkowitz RJ. Anti-beta(1)-adrenergic receptor antibodies and heart failure: causation, not just correlation. J Clin Invest 2004; 113: 1379-1382 [PMID: 15146232 DOI: 10.1172/JCI21748]

134 Mangnool S, Parichatikanond W, Karote H. Naphthalene Targeted Treatment of Heart Failure: Focus on GPR55 and β-Arrestins Affecting [JAR Signaling. Front Pharmacol 2018; 9: 1336 [PMID: 30538631 DOI: 10.3389/fphar.2018.01336]

135 Shah AS, White DC, Emanu S, Kypson AP, Lillie RE, Glower DD, Lefkowitz RJ, Koch WJ. In vivo ventricular gene delivery of a beta-adrenergic receptor kinase inhibitor to the failing heart reverses cardiac dysfunction. Circulation 2001; 103: 1311-1316 [PMID: 11238278 DOI: 10.1161/01.cir.103.13.1311]

136 Liu WN, Fu KL, Gao HY, Wang Y, Wang ZH, Jiang GH, Zhang Y, Zhang W, Zhong M. β1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to β-blocker therapy and prognosis. PLoS One 2012; 7: e37659 [PMID: 22815685 DOI: 10.1371/journal.pone.0037659]

137 Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, Rohde LE. Impact of beta-1 adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol 2008; 102: 726-732 [PMID: 18773997 DOI: 10.1016/j.amjcard.2008.04.070]

138 Metaux S, Missouri C, Mavrogianis D, Milios A, Oikonomou E, Toli E, Kormali L, Vlismas A, Drakakis P, Tschada R, Manthey J, Lefkowitz RJ, Kübler W. Catecholamines in Patients with Heart Failure. Circulation 2015; 131: 1311-1316 [PMID: 26388778 DOI: 10.1161/01.cir.131.1311]

139 Liu WN, Fu KL, Gao HY, Wang Y, Wang ZH, Jiang GH, Zhang Y, Zhang W, Zhong M. β1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to β-blocker therapy and prognosis. PLoS One 2012; 7: e37659 [PMID: 22815685 DOI: 10.1371/journal.pone.0037659]

140 Pezzali N, Curnis A, Specchia C, Carubelli V, Covolo L, Donato F, Auricchio A, Regoli F, Metra M. Adrenergic receptor gene polymorphism and left ventricular reverse remodelling after cardiac resynchronization therapy: preliminary results. Europace 2013; 15: 1475-1481 [PMID: 23729404 DOI: 10.1093/europace/eul056]

141 Katsuumi G, Shimizu I, Yoshida Y, Hayashi Y, Ikegami R, Suda M, Wakasugi T, Nakao M, Minamino T. Catecholamine-Induced Senescence of Endothelial Cells and Bone Marrow Cells Promotes Cardiac Dysfunction in Mice. Int Heart J 2018; 59: 837-844 [PMID: 29794381 DOI: 10.1536/ihj.17-313]

142 Bonnefont-Rousselot D, Mahmoudi A, Mugenot N, Varoquaux O, Le Nahour G, Fouret P, Lechat P. Catecholamine effects on cardiac remodelling, oxidative stress and fibrosis in experimental heart failure. Redox Rep 2002; 7: 145-151 [PMID: 12189045 DOI: 10.1179/13510002022500389]

143 Engelhardt S, Hein L, Wiesmann F, Lohse MJ. Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. Proc Natl Acad Sci USA 1999; 96: 7059-7064 [PMID: 10359838 DOI: 10.1073/pnas.96.12.7059]

144 Richard C. Stress-related cardiomyopathies. Ann Intensive Care 2011; 1: 39 [PMID: 21933374 DOI: 10.1186/2110-5820-1-39]

145 Chelsey A, Lundberg MS, Asai T, Xiao RP, Ohtani S, Lakatta EG, Crow MT. The beta(2)-adrenergic receptor delivers an antiapoptotic signal to cardiac myocytes through Gi(-)-dependent coupling to phosphatidylinositol 3’-kinase. Circ Res 2000; 87: 1172-1179 [PMID: 11170775 DOI: 10.1161/01.res.87.12.1172]

146 Liggert SB, Tepe NM, Asai T, Lorenz JN, Canning AM, Jantz TD, Mitrani S, Yatani A, Dorn GW 2nd. Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level. Circulation 2000; 101: 1707-1714 [PMID: 10758054 DOI: 10.1161/01.cir.101.14.1707]

147 Communal C, Singh K, Sawyer DB, Colucci WS. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. Circulation 1999;
WJC | https://www.wjgnet.com

100: 2210-2212 [PMID: 10577992 DOI: 10.1161/01.cir.100.22.2210]

Rundqvist B, Elam M, Bergmann-Sverrisdottr Y, Eisenhofer G, Friberg P. Increased cardiac adrenergic drive precedes generalized sympathetic activation in human heart failure. *Circulation* 1997; 95: 169-175 [PMID: 8984433 DOI: 10.1161/01.cir.95.1.169]

Meredith IT, Broughton A, Jennings GL, Esler MD. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 1991; 325: 618-624 [PMID: 1861695 DOI: 10.1056/nejm199108293250905]

Ishie H, Asano H, Ishizaka S, Joho S, Kameyama T, Umeno K, Inoue H. Time course of sympathovagal imbalance and left ventricular dysfunction in conscious dogs with heart failure. *J Appl Physiol* (1985) 1998, 84: 1234-1241 [PMID: 9516189 DOI: 10.1152/jappl1988.84.4.1234]

Ferguson DW, Berg WJ, Roach PJ, Oren RM, Mark AL. Effects of heart failure on baroreflex control of sympathetic neural activity. *Am J Cardiol* 1992; 69: 523-531 [PMID: 1736619 DOI: 10.1016/0002-9149(92)90098-c]

Grassi G, Saravalle G, Bertinieri G, Turri C, Stella ML, Scopelliti F, Mancia G. Sympathetic and reflex abnormalities in heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy. *Clin Sci (Lond)* 2001; 101: 141-146 [PMID: 11473487]

Ferguson DW, Abboud FM, Mark AL. Selective impairment of baroreflex-mediated vasoconstrictor responses in patients with ventricular dysfunction. *Circulation* 1984; 69: 451-460 [PMID: 6692307 DOI: 10.1161/01.cir.69.3.451]

Floras JS. Arterial baroreceptor and cardiopulmonary reflex control of sympathetic outflow in human heart failure. *Ann N Y Acad Sci* 2001; 940: 500-513 [PMID: 11458705 DOI: 10.1111/1749-6632.2001.tb03701.s]

Grassi G, Saravalle G, Cattaneo BM, Lanfranchi A, Vailati S, Giannattasio C, Del Bo A, Sala C, Bolla GB, Pozzi M. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. *Circulation* 1995; 92: 3206-3211 [PMID: 7586305 DOI: 10.1161/01.hyp.92.11.3206]

Grassi G, Saravalle G, Quarti-Trevano F, DellOrso R, Bolla G, Mancia G. Effects of hypertension and obesity on the sympathetic activation of heart failure patients. *Hypertension* 2003; 42: 873-877 [PMID: 14568990 DOI: 10.1161/01.HYP.0000098660.26184.63]

Gronda E, Saravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, Lovett EG, Mancia G, Grassi G. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *J Eur Heart Fail* 2014; 16: 977-983 [PMID: 25067799 DOI: 10.1002/ehjhf.138]

Gronda E, Francis D, Zannaf F, Hamm C, Bregada J, Vanoji E. Baroreflex activation therapy: a new approach to the management of advanced heart failure with reduced ejection fraction. *J Cardiovasc Med (Hagerstown)* 2017; 18: 641-649 [PMID: 28737621 DOI: 10.2459/JCM.0000000000000544]

Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res* 2014; 114: 1004-1021 [PMID: 24625726 DOI: 10.1161/CIRCRESAHA.113.302549]

Franciosi S, Perry FKG, Roston TM, Armstrong KR, Claydon VE, Sanatani S. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. *Auton Neurosci* 2017; 205: 1-11 [PMID: 28392310 DOI: 10.1016/j.autneu.2017.03.005]

Porter B, Bishop MJ, Claridge S, Behar J, Sieniewicz BJ, Webb J, Gould J, O'Neill M, Rinaldi CA, Razavi R, Gill JS, Taggart P. Autonomic Modulation in Patients with Heart Failure Increases Beat-to Beat Variability of Ventricular Action Potential Duration. *Front Physiol* 2017; 8: 328 [PMID: 28616676 DOI: 10.3389/fphys.2017.00328]

Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. *Eur Heart J* 2001; 22: 1136-1143 [PMID: 11428854 DOI: 10.1053/euh.2000.2407]

Fukada K, Karazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. *Circ Res* 2015; 116: 2005-2019 [PMID: 26044253 DOI: 10.1161/CIRCRESAHA.116.304679]

Fudim M, Booritz-Mars R, Ganesh A, Waldron NH, Qudsi YJ, Patel CB, Milano CA, Sun AY, Mathew JP, Piccini JP. Stellate ganglion blockade for the treatment of refractory ventricular arrhythmias: A systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2017; 28: 1460-1467 [PMID: 28833780 DOI: 10.1111/jce.13324]

Meng L, Tseng CH, Shivkumar K, Ajijola O. Efficacy of Stellate Ganglion Blockade in Managing Electrical Storm: A Systematic Review. *JACC Clin Electrophysiol* 2017; 3: 942-949 [PMID: 29270467 DOI: 10.1016/j.jcell.2017.06.096]

Fudim M, Qudsi YJ, Waldron NH, Booritz-Mars RL, Ganesh A, Patel CB, Podgoreanu MV, Sun AY, Milano CA, Tong BC, Harpole DH Jr, Mathew JP, Piccini JP. Stellate Ganglion Blockade for the Treatment of Refractory Ventricular Arrhythmias. *JACC Clin Electrophysiol* 2020; 6: 562-571 [PMID: 3243942]

Zhou S, Jung BC, Tan AY, Trang VQ, Ghomieh G, Han SW, Lin SF, Fishbein MC, Chen PS, Chen LS. Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death. *Heart Rhythm* 2008; 5: 131-139 [PMID: 18055272 DOI: 10.1016/j.hrthm.2007.09.007]

Wu P, Vaseghi M. The autonomic nervous system and ventricular arrhythmias in myocardial infarction and heart failure. *Pacing Clin Electrophysiol* 2020; 43: 172-180 [PMID: 31823401 DOI: 10.1111/pacem.13856]

Waldron NH, Fudim M, Mathew JP, Piccini JP. Neuromodulation for the Treatment of Heart Rhythm Disorders. *JACC Basic Transl Sci* 2019; 4: 546-562 [PMID: 31468010 DOI: 10.1016/j.jatbs.2019.02.009]

Notarius CF, Ando S, Rongen GA, Floras JS. Resting muscle sympathetic nerve activity and peak oxygen uptake in heart failure and normal subjects. *Eur Heart J* 1999; 20: 880-887 [PMID: 10329093 DOI: 10.1053/eur.1998.1447]

Notarius CF, Azvedo ER, Parker JD, Floras JS. Peak oxygen uptake is not determined by cardiac noradrenaline spillover in heart failure. *Eur Heart J* 2002; 23: 800-805 [PMID: 12009720 DOI: 10.1053/eu.2001.2942]

Notarius CF, Spaak J, Morris BL, Floras JS. Comparison of muscle sympathetic activity in ischemic and nonischemic heart failure. *J Card Fail* 2007; 13: 470-475 [PMID: 17675061 DOI: 10.1016/j.cardfail.2007.03.014]
Borovac JA et al. Sympathetic system activation in heart failure

172 Barrett-O’Keefe Z, Lee JF, Ives SJ, Trinity JD, Witman MAH, Rossman MJ, Groot HJ, Sorensen JR, Morgan DE, Nelson AD, Stehlik J, Richardson RS, Wray DW. β-Adrenergic receptor regulation of skeletal muscle blood flow during exercise in heart failure patients with reduced ejection fraction. *Am J Physiol Regul Integr Comp Physiol* 2019; 316: R512-R524 [PMID: 30789790 DOI: 10.1152/ajpregu.00345.2018]

173 Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. *Circulation* 1989; 80: 314-323 [PMID: 2546698 DOI: 10.1161/01.cir.80.2.314]

174 Boutagy NE, Sinusas AJ. Imaging of the Cardiac Sympathetic Nervous System Has Potential Value in the Evaluation of Patients with Heart Failure with Preserved Ejection Fraction. *J Nucl Med* 2017; 58: 781-783 [PMID: 28232609 DOI: 10.2967/jnumed.116.186130]

175 Matsunari I, Aoki H, Nomura Y, Takeda N, Chen WP, Taki J, Nakajima K, Nekolla SG, Kinuya S, Kajinami K. Iodine-123 metaiodobenzylguanidine imaging and carbon-11 hydroxyephedrine positron emission tomography compared in patients with left ventricular dysfunction. *Circ Cardiovasc Imaging* 2010; 3: 595-603 [PMID: 20534790 DOI: 10.1161/CIRCIMAGING.109.205358]

176 Aikawa T, Naya M, Obara M, Manabe O, Tomiyama Y, Magota K, Yamada S, Katoh C, Tamaki N, Tsutsui H. Impaired Myocardial Sympathetic Innervation Is Associated with Diastolic Dysfunction in Heart Failure with Preserved Ejection Fraction. 18F-Hydroxyephedrine PET Study. *J Nucl Med* 2017; 58: 784-790 [PMID: 27811122 DOI: 10.2967/jnumed.116.178558]

177 Aikawa T, Naya M, Obara M, Oyama-Manabe N, Manabe O, Magota K, Ito YM, Katoh C, Tamaki N. Regional interaction between myocardial sympathetic denervation, contractile dysfunction, and fibrosis in heart failure with preserved ejection fraction: 18F-hydroxyephedrine PET study. *Eur J Nucl Med Mol Imaging* 2017; 44: 1897-1905 [PMID: 28653180 DOI: 10.1007/s00259-017-3760-y]

178 Shah AM, Bourgouin M, Narula J, Jacobson AF, Solomon SD. Influence of ejection fraction on the prognostic value of sympathetic innervation imaging with iodine-123 MIBG in heart failure. *JACC Cardiovasc Imaging* 2012; 5: 1139-1146 [PMID: 23153914 DOI: 10.1016/j.jcmg.2012.02.019]

179 Nakata T, Nakajima K, Yamashina S, Yamada T, Morose M, Kasama S, Matsu S, Matsui S, Travin MI, Jacobson AF. A pooled analysis of multicenter cohort studies of (123I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. *JACC Cardiovasc Imaging* 2013; 6: 772-784 [PMID: 23845574 DOI: 10.1016/j.jcmg.2013.02.007]

180 Verberne HJ, Breuwer LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. *Eur Heart J* 2008; 29: 1147-1159 [PMID: 18349024 DOI: 10.1093/eurheartj/ehn113]

181 Narula J, Gerson M, Thomas GS, Cerequera MD, Jacobson AF. 18I-MIBG Imaging for Prediction of Mortality and Potentially Fatal Events in Heart Failure: The ADMIRE-HF Study. *J Nucl Med* 2015; 56: 1011-1018 [PMID: 26069309 DOI: 10.2967/jnumed.115.156406]

182 Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchishahi K, Travin MI, Shimamoto K. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. *J Nucl Med* 2001; 42: 1757-1767 [PMID: 11752070]

183 Fallavollita JA, Hevey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashare TL Jr, Hutson AD, Decempi RA, Haka MS, Sajjad M, Cimato TR, Curtis AB, Cain ME, Canty JM Jr. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac death in ischemic cardiomyopathy. *J Am Coll Cardiol* 2014; 63: 141-149 [PMID: 24076296 DOI: 10.1016/j.jacc.2013.07.096]

184 Fallavollita JA, Dare JD, Carter RL, Baldwa S, Canty JM Jr. Denervated Myocardium Is Preferentially Associated With Sudden Cardiac Death in Ischemic Cardiomyopathy: A Pilot Competing Risks Analysis of Cause-Specific Mortality. *Circ Cardiovasc Imaging* 2017; 10 [PMID: 28794139 DOI: 10.1161/CIRCIMAGING.117.006446]

185 Cain ME. Impact of denervated myocardium on improving risk stratification for sudden cardiac death. *Trans Am Clin Climatol Assoc* 2014; 125: 141-53; discussion 153 [PMID: 25125727]

186 Seo M, Yamada T, Tanuki S, Watanabe T, Morita T, Furukawa Y, Kawasaki M, Kikuchi A, Kawai T, Abe M, Nakamura I, Yamamoto K, Kayama K, Kawashima H, Tanabe K, Kimura T, Ueda K, Sakamoto D, Sakata Y, Fukumani M. Prognostic significance of cardiac I-123-metiodobenzylguanidine imaging in patients with reduced, mid-range, and preserved left ventricular ejection fraction admitted for acute decompensated heart failure: a prospective study in Osaka Prefectural Acute Heart Failure Registry (OPAR). *Eur Heart J Cardiovasc Imaging* 2020 [PMID: 32091079 DOI: 10.1093/eurheartj/ehaa025]

187 Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JVF, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson A, Wikstrand J, Kotecha D. Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018; 39: 26-35 [PMID: 29040525 DOI: 10.1093/eurheartj/ehx564]

188 Ernst G. Heart-Rate Variability-More than Heart Beats? *Front Public Health* 2017; 5: 240 [PMID: 28955705 DOI: 10.3389/fpubh.2017.00240]

189 Shaffer F, McCrery R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol* 2014; 5: 1040 [PMID: 25324790 DOI: 10.3389/fpsyg.2014.01040]

190 Rajendra Acharya U, Paul Joseph K, Kannathala N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comp* 2006; 44: 1031-1051 [PMID: 17111118 DOI: 10.1007/s11517-006-0119-0]

191 Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health* 2017; 5: 258 [PMID: 29034226 DOI: 10.3389/fpubh.2017.00258]

192 Stys A, Stys T. Current clinical applications of heart rate variability. *Clin Cardiol* 1998; 21: 719-724 [PMID: 9789691 DOI: 10.1023/a:10490211005]

193 Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996; 94: 2850-2855
Neuropeptide Y rapidly enhances \([\text{Ca}^{2+}]_i\) transients and \(\text{Ca}^{2+}\) sparks in adult rat ventricular myocytes through Y1 receptor and PLC activation.

Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukkema JW, Middeldorp S, Rosendaal FR, Dekkers OM. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Eurocepe* 2013; 18: 742-749 [PMID: 23370966 DOI: 10.1093/eurocepe/esu341]

Patel VN, Pierce BR, Bodapati RK, Brown DL, Ives DG, Stein PK. Association of Holter-Derived Heart Rate Variability Parameters With the Development of Congestive Heart Failure in the Cardiovascular Health Study. *JACC Heart Fail* 2017; 5: 423-431 [PMID: 28396041 DOI: 10.1016/j.jchf.2016.12.015]

Nolan J, Batin PD, Andrews R, Lindsay SJ, Brookesby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998; 98: 1510-1516 [PMID: 9769304 DOI: 10.1161/01.CIR.98.15.1510]

Palacios M, Friedrich H, Götz E, Vallverdu M, de Luna AB, Cannial P, Hoyer D. Changes of autonomic information flow due to idiopathic dilated cardiomyopathy. *Physiol Meas* 2007; 28: 677-688 [PMID: 17664621 DOI: 10.1088/0967-3334/28/6/006]

La Rovere MT, Pinna GD, Maestri R, Mortara A, Caporomilla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opsasich C, Riccardi PG, Traversi E, Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003; 107: 565-570 [PMID: 12566367 DOI: 10.1161/01.cir.0000047275.25917-5]

Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banaasiak W, Wrabcz K, Coats AJ. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79: 1645-1650 [PMID: 9202356 DOI: 10.1016/s0002-9149(97)89315-4]

Ponikowski P, Anker SD, Amadi A, Chua TP, Cerquetani E, Ondusova D, O'Sullivan C, Adamopoulos S, Piepoli M, Coats AJ. Heart rhythms, ventricular arrhythmias, and death in chronic heart failure. *J Card Fail* 1996; 2: 177-183 [PMID: 8891855 DOI: 10.1016/1071-9144(96)80039-x]

Aronson D, Mittleman MA, Berger AJ. Measures of heart period variability as predictors of mortality in hospitalized patients with compensated congestive heart failure. *Am J Cardiol* 2004; 93: 59-63 [PMID: 14697467 DOI: 10.1016/j.amjcard.2003.09.013]

Pouset F, Copie X, Lechat P, Jaillon P, Hetzel M, Guize L, Le Heuzey JY. Effects of bisoprolol on heart rate variability in heart failure. *Am J Cardiol* 1996; 77: 612-617 [PMID: 8610612 DOI: 10.1016/0002-9149(97)89316-2]

Aronson D, Burger AJ. Effect of beta-blockade on heart rate variability in decompensated heart failure. *Int J Cardiol* 2001; 79: 31-39 [PMID: 1139339 DOI: 10.1016/s0167-5273(01)00401-6]

Hayano J, Yuda E. Pitfalls of assessment of autonomic function by heart rate variability. *J Physiol Anthropol* 2019; 38: 3 [PMID: 30867063 DOI: 10.1186/s40101-019-0193-2]

Lombardi F, Mortara A. Heart rate variability and cardiac failure. *Heart* 1998; 80: 213-214 [PMID: 9875973 DOI: 10.1136/hrt.80.3.212]

Sarkhene M, Wang Y, Wei J, Huang Y, Li M, Li L, Achaempong E, Zhengcan Z, Xiaoyuan Q, Yunsheing X, Jingyuem X, Xiumei G, Guanwei F. Biomarkers in heart failure: the past, current and future. *Heart Fail Rev* 2019; 24: 867-903 [PMID: 31183637 DOI: 10.1007/s10719-019-09807-z]

Iqbal N, Wentworth B, Choudhary R, Landa Ade L, Kipper B, Fard A, Maisel AS. Cardiac biomarkers: new tools for heart failure management. *Cardiovasc Diag Ther* 2012; 2: 147-164 [PMID: 22482708 DOI: 10.9787/issn.2223-3652.2012.06.03]

Matsushita M, Shirakabe A, Kobayashi N, Okazaki H, Shibata Y, Goda H, Shigihara S, Asano K, Tani K, Kimachi K, Okajima F, Hata N, Axi K, Shimura W. Mechanisms of Urgent Hospitalization for Acute Heart Failure. *Int Heart J* 2020; 61: 316-324 [PMID: 32173711 DOI: 10.1536/jih.19-5123]

Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; 87: VI40-VI48 [PMID: 8500238]

Anand IS, Fisher LD, Chiappelli A, Latini R, Masson S, Maggioni AP, Glauser RD, Tognoni G, Cohn JN; Val-HeFT Investigators. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation* 2003; 107: 1278-1283 [PMID: 12562948 DOI: 10.1161/01.cir.0000054164.99831.00]

Givertz MM, Braunwald E. Neurohormones in heart failure: predicting outcomes, optimizing care. *Eur Heart J* 2004; 25: 281-282 [PMID: 14984914 DOI: 10.1093/eurheartj/ehj.2003.12.013]

Hjeddal P. Plasma catecholamines--analytical challenges and physiological limitations. *Baillieres Clin Endocrinol Metab* 1993; 7: 307-353 [PMID: 8489483 DOI: 10.1016/0950-351X(93)80179-x]

Haberer BA, Anderson ME, Birren SJ, Fukuda K, Herring N, Hoover DB, Kanazawa H, Paterson DJ, Ripplinger CM. Molecular and cellular neurocardiology: development, and cellular and molecular adaptations to heart disease. *J Physiol* 2016; 594: 3853-3875 [PMID: 27060296 DOI: 10.1113/JP271840]

Tan CMJ, Green P, Troupoul N, Lewandowski AJ, Leeson P, Herring N. The Role of Neuropeptide Y in Cardiovascular Health and Disease. *Front Physiol* 2018; 9: 1281 [PMID: 30283345 DOI: 10.3389/fphys.2018.01281]

Herring N, Lokale MN, Danson EJ, Paterson DJ. Neuropeptide Y reduces acetylcholine release and vagal bradycardia via a Y2 receptor-mediated, protein kinase C-dependent pathway. *J Mol Cell Cardiol* 2008; 44: 477-485 [PMID: 17996892 DOI: 10.1016/j.yjmcc.2007.10.001]

Heredia Mendel P, Delgado C, Perriere L, Perrier R, Richard S, Vassort G, Bénitah JP, Goméz AM. Neuropeptide Y rapidly enhances [Ca^{2+}]_i transients and Ca^{2+} sparks in adult rat ventricular myocytes through Y1 receptor and PLC activation. *J Mol Cell Cardiol* 2005; 38: 205-212 [PMID: 15623437 DOI: 10.1016/j.yjmcc.2004.11.001]
Borovac JA et al. Sympathetic system activation in heart failure

218 Tatemoto K. Neuropeptide Y: complete amino acid sequence of the brain peptide. Proc Natl Acad Sci USA 1982; 79: 5485-5489 [PMID: 6957876 DOI: 10.1073/pnas.79.18.5485]

219 Alasvand M, Javannard SH, Rashidi B, Khazaee M. Myocardial capillary density after neuropeptide Y antagonist administration in normal and high-fat diet C57BL/6 mice. Adv Biomed Res 2016; 5: 165 [PMID: 27995184 DOI: 10.4103/2277-0175.190998]

220 Saraf R, Mahmood F, Amir R, Matyal R. Neuropeptide Y is an angiogenic factor in cardiovascular regeneration. Eur J Pharmacol 2016; 776: 64-70 [PMID: 26875634 DOI: 10.1016/j.ejphar.2016.02.033]

221 Jacques D, D’Orelles-Juste P, Magder S, Bkailly G. Neuropeptide Y and its receptors in ventricular endocardial endothelial cells. Can J Physiol Pharmacol 2017; 95: 1224-1229 [PMID: 28731862 DOI: 10.1139/cjpp-2017-0290]

222 Feng Q, Lambert ML, Callow ID, Arnold JM. Venous neuropeptide Y receptor responsiveness in patients with chronic heart failure. Clin Pharmacol Ther 2000; 67: 292-298 [PMID: 10741633 DOI: 10.1016/0002-9149(99)00307-4]

223 Feng QP, Sun XY, Hedner T. Cardiovascular responses and interactions by neuropeptide Y in rats with congestive heart failure. Blood Pressure 1996; 5: 312-318 [PMID: 8879605 DOI: 10.1016/0803-7056(96)80786-5]

224 Shanks J, Herrington N. Peripheral cardiac sympathetic hyperactivity in cardiovascular disease: role of neuropeptides. Am J Physiol Regul Integr Comp Physiol 2013; 305: R1411-R1420 [PMID: 24050254 DOI: 10.1152/ajpregu.00118.2013]

225 Feng QP, Hedner T, Andersson B, Lundberg JM, Waagstein F. Cardiac neuropeptide Y and noradrenaline balance in patients with congestive heart failure. Br Heart J 1994; 71: 261-267 [PMID: 8142196 DOI: 10.1136/hrt.71.3.261]

226 Ullman B, Lindvall K, Lundberg JM, Sigurdsson A, Swedberg K. Response of plasma neuropeptide Y and noradrenaline to dynamic exercise and ramipril treatment in patients with congestive heart failure. Clin Physiol 1994; 14: 123-134 [PMID: 8205743 DOI: 10.1111/j.1475-097x.1994.tb00498.x]

227 Maisel AS, Scott NA, Motulsky HJ, Michel MC, Boublik JH, Rivier JE, Ziegler M, Allen RS, Brown MR. Elevation of plasma neuropeptide Y levels in congestive heart failure. Am J Med 1989; 86: 43-48 [PMID: 2910096 DOI: 10.1016/0002-9343(89)90228-3]

228 Ajijola OA, Chatterjee NA, Gonzales MJ, Gormbein J, Liu K, Li D, Paterson DJ, Shvickum K, Singh JP, Herrington N. Coronary Sinus Neuropeptide Y Levels and Adverse Outcomes in Patients with Stable Chronic Heart Failure. JAMA Cardiol 2019 [PMID: 31876927 DOI: 10.1001/jamacardio.2019.4717]

229 Morton GJ, Schwartz MW. The NPY/AgRP neuron and energy homeostasis. Int J Obes Relat Metab Disord 2001; 25 Suppl 5: S56-S62 [PMID: 11840217 DOI: 10.1038/sj.ijo.0801915]

230 Morris MJ, Cox HS, Lambert GW, Kaye DM, Jennings GL, Meredith IT, Estler MD. Region-specific neuropeptide Y overflows at rest and during sympathetic activation in humans. Hypertension 1997; 29: 137-143 [PMID: 9039093 DOI: 10.1161/01.hyp.29.1.137]

231 Dubois-Randé JL, Cornoy E, Merlet P, Benvenuti C, Carville C, Hittinger L, Maquen-Mavier I, Bohuon C, Castaigne A. Relationship among neuropeptide Y, catecholamines and haemodynamics in congestive heart failure. Eur Heart J 1992; 13: 1233-1238 [PMID: 1396834 DOI: 10.1093/oxfordjournals.eurheartj.a060142]

232 Medzikovic L, van Roomen C, Baartscheer A, van Loemen PB, de Vos J, Bakker ENTP, Koenis DS, Damanafshah A, Cremers EE, Arkenbout EK, de Vries CJM, de Waard V. Nur77 protects against adverse cardiac remodelling by limiting neuropeptide Y signalling in the sympathoadrenal-cardiac axis. Cardiovasc Res 2018; 114: 1617-1628 [PMID: 29850786 DOI: 10.1093/cvr/cvy125]

233 Smith-White MA, Iisnaa TP, Potter EK. Galanin and neuropeptide Y reduce cholinergic transmission in the heart of the anaesthetised mouse. Br J Pharmacol 2003; 140: 170-178 [PMID: 12967946 DOI: 10.1038/sj.bjp.0705404]

234 Herring N, Cranley J, Lokale MN, Li D, Shanks D, Alston EN, Girard BM, Carter E, Parsons RL, Habecker M, Chatterjee NA, Gonzales MJ, Gornbein J, Liu K, Li D, Paterson DJ, Singh JP, Herrington N. Coronary Sinus Neuropeptide Y Levels and Adverse Outcomes in Patients with Stable Chronic Heart Failure. JAMA Cardiol 2019 [PMID: 31876927 DOI: 10.1001/jamacardio.2019.4717]

235 Chan NY, Robadour PA, Levi R. Natriuretic peptide-induced catecholamine release from cardiac sympathetic neurons: inhibition by histamine H3 and H4 receptor activation. J Pharmacol Exp Ther 2012; 343: 568-577 [PMID: 22927376 DOI: 10.1124/jpet.111.198747]

236 Tyrrell C, Toyooka A, Khan F, Thornburg KL, Mudd JO, Hasan W. The neuropeptide galanin promotes an anti-thrombotic phenotype on endocardial endothelial cells from heart failure patients. Auton Neurosci 2017; 206: 35-42 [PMID: 28720509 DOI: 10.1016/j.autneu.2017.07.002]

237 Chen A, Li M, Song L, Zhang Y, Luo Z, Zhang W, Chen Y, He B. Effects of the Galanin Receptor Antagonist M40 on Cardiac Function and Remodeling in Rats with Heart Failure. Cardiovasc Ther; 2015; 33: 288-293 [PMID: 26170727 DOI: 10.1111/1755-5922.12144]

238 Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS, Pollock DM, Webb DJ, Maguire JJ. Endothelin. Pharmacol Rev 2016; 68: 357-418 [PMID: 26956245 DOI: 10.1124/pr.115.118335]

239 Agapitov AV, Haynes WG. Role of endothelin in cardiovascular disease. J Renin Angiotensin Aldosterone Syst 2002; 3: 1-15 [PMID: 11984741DOI: 10.1037/sj.pnas.2002.001]

240 Dhaun N, Webb DJ. Endothelins in cardiovascular biology and therapeutics. Nat Rev Cardiol 2019; 16: 491-502 [PMID: 30867577 DOI: 10.1038/s41591-019-0176-3]

241 Koseki C, Imai M, Hiraoka Y, Yanagisawa M, Masaki T. Autoradiographic distribution in rat tissues of binding sites for endothelin: a neuropeptide? Am J Physiol 1989; 256: R858-R866 [PMID: 2650570 DOI: 10.1152/ajpheart.1989.256.5.R858]
Brain natriuretic peptide plasma concentrations predict clinical outcomes in patients with left ventricular failure. Rossignol P; EPHESUS Investigators. Combined baseline and one-month changes in big endothelin-1 and brain natriuretic peptide plasma concentrations predict clinical outcomes in patients with left ventricular failure: an ASCEND-HF biomarker substudy. Eur J Heart Fail 2016; 18: 290-297 [PMID: 26663359 DOI: 10.1002/ejhf.456]

Olivier A, Girend N, Michel JB, Ketelslegers JM, Fey R, Vincent J, Bramlage P, Pitt B, Zannad F, Rossignol P, EPHESUS Investigators. Combined baseline and one-month changes in big endothelin-1 and brain natriuretic peptide plasma concentrations predict clinical outcomes in patients with left ventricular failure. Circulation 2006; 112: 1132-1138 [PMID: 16745537 DOI: 10.1161/01.01.0000077269-9071]
dysfunction after acute myocardial infarction: Insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Int J Cardiol* 2017; 241: 344-350 [PMID: 28284500 DOI: 10.1016/j.ijcard.2017.02.018]

266 Plumpotn C, Haynes WG, Webb DJ, Davenport AP. Measurement of C-terminal fragment of big endothelin-1: a novel method for assessing the generation of endothelin-1 in humans. *J Cardiovasc Pharmacol* 1995; 26 Suppl 3: S34-S36 [PMID: 8587408]

267 Wei CM, Lerman A, Rodeheffer RJ, McGregor CG, Brandt RR, Wright S, Heublein DM, Kao PC, Edwards WD, Burnett JC Jr. Endothelin in human congestive heart failure. *Circulation* 1994; 89: 1580-1586 [PMID: 8149524 DOI: 10.1161/01.cir.89.4.1580]

268 McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. *Circulation* 1992; 85: 1374-1379 [PMID: 15325440 DOI: 10.1161/01.cir.85.4.1374]

269 Pankowska EA, Filipatos GS, von Haehling S, Papassotiriou I, Morgenthaler NG, Ciccoira M, Scheffold JC, Rozentzi P, Ponikowska B, Doehner W, Banasiak W, Hartmann O, Struck J, Bergmann A, Anker SD, Ponikowski P. Identification of chronic heart failure patients with a high 12-month mortality risk using biomarkers including plasma C-terminal pro-endothelin-1. *PLoS One* 2011; 6: e14506 [PMID: 21264211 DOI: 10.1371/journal.pone.0014506]

270 Masson S, Latini R, Anand IS, Barlera S, Judd D, Salio M, Perticini F, Perini G, Tognoni G, Cohn JN, Val-HeFT investigators. The prognostic value of big endothelin-1 in more than 2,300 patients with heart failure enrolled in the Valsartan Heart Failure Trial (Val-HeFT). *J Card Fail* 2006; 12: 375-380 [PMID: 16762803 DOI: 10.1016/j.cardfail.2006.02.013]

271 Van Beneden R, Gurnd O, Selvais PL, Ahn SA, Robert AR, Ketelslegers JM, Poulou HG, Rousseau MF. Superiority of big endothelin-1 and endothelin-1 over natriuretic peptides in predicting survival in severe congestive heart failure: a 7-year follow-up study. *J Card Fail* 2004; 10: 490-495 [PMID: 15599830 DOI: 10.1016/j.cardfail.2004.01.001]

272 Zhang CL, Xue S, Qiao X, An YM, Zhang Y, Li L, Guo XB, Zhang FC, Wu LL. Plasma endothelin-1-related peptides as the prognostic biomarkers for heart failure: A PRISMA-compliant meta-analysis. *Cardiology (Baltimore)* 2017; 96: e1342 [PMID: 28996406 DOI: 10.1159/000489342]

273 Xiong B, Nie D, Cao Y, Zou Y, Yao Y, Tan J, Qian J, Rong S, Wang C, Huang J. Clinical and Hemodynamic Effects of Endothelin Receptor Antagonists in Patients With Heart Failure. *Int J Heart* 2017; 58: 400-408 [PMID: 28535681 DOI: 10.1536/ijh.16-307]

274 Chowdhury MA, Moukarbel GV, Gupta R, Frank SM, Anderson AM, Liu LC, Khouri SJ. Endothelin 1 Is Associated with Heart Failure Hospitalization and Long-Term Mortality in Patients with Heart Failure with Preserved Ejection Fraction and Pulmonary Hypertension. *Cardiology* 2019; 143: 124-133 [PMID: 31514818 DOI: 10.1159/000501100]

275 Obokata M, Kane GC, Reddy YNV, Mel노novsky V, Olson TP, Jarolim P, Borlaug BA. The neurohumoral basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J* 2019; 40: 3707-3717 [PMID: 31513270 DOI: 10.1093/eurheartj/ehz626]

276 Jankowich MD, Wu WC, Choudhary G. Association of Elevated Plasma Endothelin-1 Levels With Pulmonary Hypertension, and Heart Failure in African American Individuals: The Jackson Heart Study. *JAMA Cardiol* 2016; 1: 461-469 [PMID: 27438323 DOI: 10.1001/jamacardio.2016.09962]

277 Omland T. Targeting the endothelin system: a step towards a precision medicine approach in heart failure with preserved ejection fraction? *Eur Heart J* 2019; 40: 3718-3720 [PMID: 31682255 DOI: 10.1093/eurheartj/ehz765]

278 Valero-Munoz M, Li S, Wilson RM, Boldbaatar B, Iglarz M, Sam F. Dual Endothelin-A/Endothelin-B Receptor Blockade and Cardiac Remodeling in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail* 2016; 9 [PMID: 27810862 DOI: 10.1161/CIRCHEARTFAILURE.116.003381]

279 Zile MR, Bourge RC, Redfield MM, Zhou D, Baicu CF, Little WC. Randomized, double-blind, placebo-controlled study of sitaxsentan to improve impaired exercise tolerance in patients with heart failure and a preserved ejection fraction. *JACC Heart Fail* 2014; 2: 123-130 [PMID: 24720918 DOI: 10.1016/j.jchf.2013.12.002]

280 Koller B. Steringer-Mascherbauer R, Ebner CH, Weber T, Ammer M, O'Connor DT. The chromogranin-secretogranin family. *J Clin Invest* 2019; 134: 433-441 [PMID: 27816421 DOI: 10.1172/JCI95680]

281 Mahata SK, O'Connor DT, Mahata M, Yoo SH, Taupenot L, Wu H, Gill BM, Parmer RJ. Novel autocrine feedback control of catecholamine release. A discrete chromogranin a fragment is a noncompetitive nicotinic cholinergic antagonist. *J Clin Invest 1997; 100: 1623-1633 [PMID: 9294131 DOI: 10.1172/JCI139680]

282 Taupenot L, Harper KL, O'Connor DT. The chromogranin-secretogranin family. *N Engl J Med* 2003; 348: 1134-1149 [PMID: 12646671 DOI: 10.1056/NEJMra021405]

283 Mahata SK, Corti A. Chromogranin A and its fragments in cardiovascular, immunometabolic, and cancer regulation. *Ann N Y Acad Sci* 2019; 1455: 34-58 [PMID: 31588572 DOI: 10.1111/nyas.14249]

284 Takiyuddin MA, Brown MR, Dinh TQ, Cervenka JH, Braun SD, Parmer RJ, Kennedy B, O'Connor DT. Sympatho-renal secretion in humans: factors governing catecholamine and storage vesicle peptide corelease. *J Auton Pharmacol* 1994; 14: 187-200 [PMID: 7929473 DOI: 10.1111/j.1474-8675.1994.tb00601.x]

285 Cecconi C, Ferrari R, Bachi T, Oppasch C, Volterra M, Colombo B, Parinello G, Corti A. Chromogranin A in heart failure; a novel neurohumoral factor and a predictor for mortality. *Heart* 2002; 86: 967-974 [PMID: 12069452 DOI: 10.1053/ehj.2001.2977]

286 Omland T, Dickstein K, Syversen U. Association between plasma chromogranin A concentration and long-term mortality after myocardial infarction. *Am J Med* 2003; 114: 25-30 [PMID: 12543286 DOI: 10.1016/s0002-9345(02)01425-0]

287 Estensen ME, Hognestad A, Syversen U, Squire I, Ng L, Kjekshus J, Dickstein K, Omland T. Prognostic value of plasma chromogranin A levels in patients with complicated myocardial infarction. *Am Heart J* 2006; 152: 927.e1-927.e6 [PMID: 17070161 DOI: 10.1016/j.ahj.2006.05.008]
Improves Autonomic Function and Exerts Cardioprotective Effects in Myocardial Infarction Rats. Angelone T

norepinephrine in H9c2 cardiac myoblasts by modulating the adrenergic signaling. pathway in ischemic-reperfused myocardium.

stress-induced apoptosis: A novel mechanism by activating the beta2 adrenergic receptor and PKB/Akt

prevents endothelial inflammation and promotes thrombus resolution in acute pulmonary embolism in mice.

through the Ca2+-calcineurin-NFAT signaling pathway.

acts as a novel angiogenic cytokine via a basic fibroblast growth factor-dependent mechanism.

Bahlmann FH, Patsch JR, Wolf D, Schratzberger P, Mahata SK, Kirchmair R. The neuropeptide catestatin

pathway and preserving mitochondrial membrane potential.

protective effects on rat cardiomyocytes undergoing ischemia/reperfusion by stimulating PI3K-Akt-GSK3β

Bassino E

Cardiovasc Res

induced antiadrenergic mechanism triggered by the endothelial PI3K-eNOS pathway in the myocardium. 

Bassino E

Physiol

attenuates sympathetic barosensitivity and the chemoreflex in rat CVLM.

Gaede AH

2010; 33-43 [PMID: 15438435 DOI: 10.1093/cvr/cvr129]

Imbrogno S, Garofalo F, Cerra MC, Mahata SK, Tota B. The catecholamine release-inhibitory peptide catestatin (chromogranin A344-363) modulates myocardial function in fish. J Exp Biol 2010; 213: 3636-3643 [PMID: 20952611 DOI: 10.1242/jeb.045567]

Bassino E, Fornero S, Gallo MP, Gallina C, Femmini S, Levi R, Tota B, Alloart G. Catestatin: A novel catestatin-

Bassino E

2012; 102: R365-R372 [PMID: 22129620 DOI: 10.1152/jappl.00409.2011]

Bassino E, Fornero S, Gallo MP, Ramella R, Mahata SK, Tota B, Levi R, Alloart G. A novel catestatin-induced antiadrenergic mechanism triggered by the endothelial PI3K-eNOS pathway in the myocardium. Cardiovase: Res 2011; 91: 617-624 [PMID: 21543850 DOI: 10.1093/cvr/cvr129]

improve sympathetic and somatosympathetic reflex.

Leuck M, Kirchmair R, Pasqua T, Tota B, Angelone T, Cerra MC, Nowosielski Y, Mätzler R, Theurl M, Kirchmair R, Pasqua T, Gentile S, Tota B; Mahata SK, O'Connor DT. The chromogranin A fragment catestatin: specificity, potency and mechanism to inhibit exocytic secretion of multiple catecholamine storage vesicle co-transmitters. J Hypertens 2006; 24: 895-904 [PMID: 16612252 DOI: 10.1097/01.jhy.0000222760.99582.e0]

Gaede AH, Pilowski PM. Catestatin in rat RVLM is sympathoexcitatory, increases barosensitivity, and attenuates chemosensitivity and the somatosympathetic reflex. Am J Physiol Regul Integr Comp Physiol 2010; 299: R1538-R1545 [PMID: 20926765 DOI: 10.1152/ajpregu.00335.2010]

Gaede AH, Pilowski PM. Catestatin, a chromogranin A-derived peptide, is sympathoinhibitory and attenuates sympathetic barosensitivity and the chemoreflex in rat CVLM. Am J Physiol Regul Integr Comp Physiol 2012; 302: R365-R372 [PMID: 22129620 DOI: 10.1152/jappl.00409.2011]

Bassino E, Fornero S, Gallo MP, Ramella R, Mahata SK, Tota B, Levi R, Alloart G. A novel catestatin-induced antiadrenergic mechanism triggered by the endothelial PI3K-eNOS pathway in the myocardium. Cardiovase: Res 2011; 91: 617-624 [PMID: 21543850 DOI: 10.1093/cvr/cvr129]

Imbrogno S, Garofalo F, Cerra MC, Mahata SK, Tota B. The catecholamine release-inhibitory peptide catestatin (chromogranin A344-363) modulates myocardial function in fish. J Exp Biol 2010; 213: 3636-3643 [PMID: 20952611 DOI: 10.1242/jeb.045567]

Bassino E, Fornero S, Gallo MP, Gallina C, Femmini S, Levi R, Tota B, Alloart G. Catestatin exerts direct protective effects on rat cardiomyocytes undergoing ischemia/reperfusion by stimulating PI3K-Akt-GSK3β pathway and preserving mitochondrial membrane potential. PLoS One 2015; 10: e0119790 [PMID: 25774921 DOI: 10.1371/journal.pone.0119790]

Theurl M, Schgoer W, Albrecht K, Jeschke J, Egger M, Beer AG, Vasilievich D, Rong S, Wolf AM, Bahllmann FH, Patrck JR, Wolf D, Schratzberger P, Mahata SK, Kirchmair R. The neuropeptide catestatin acts as a novel angiogenic cytokine via a basic fibroblast growth factor-dependent mechanism. Circ Res 2010; 107: 1326-1335 [PMID: 20930149 DOI: 10.1161/CIRCRESAHA.110.219493]

Guo X, Zhou C, Sun N. The neuropeptide catestatin promotes vascular smooth muscle cell proliferation through the Ca2+-calcium-free-NFAT signaling pathway. Biochem Biophys Res Commun 2011; 407: 807-812 [PMID: 21443664 DOI: 10.1016/j.bbrc.2011.03.104]

Chen H, Liu D, Ge L, Wang T, Ma Z, Han Y, Duan Y, Xu X, Liu W, Yuan J, Liu J, Li R, du R. Catestatin prevents endothelial inflammation and promotes thrombus resolution in acute pulmonary embolism in mice. Biosci Rep 2019; 39 [PMID: 31682263 DOI: 10.1042/BSR20192236]

Chen Y, Wang X, Yang C, Su X, Yang W, Dai Y, Han H, Jiang J, Lu L, Wang H, Chen Q, Jin W. Decreased circulating catestatin levels are associated with coronary artery disease: The emerging anti-inflammatory role. Atherosclerosis 2019; 281: 78-88 [PMID: 30658195 DOI: 10.1016/j.atherosclerosis.2018.12.025]

Chu SY, Peng F, Wang J, Liu L, Meng L, Zhao J, Han XN, Ding WH. Catestatin in defense of oxidative-stress-induced apoptosis: A novel mechanism by activating the beta2 adrenergic receptor and PKB/Akt pathway in ischemic-reperfused myocardium. Peptides 2020; 123: 170200 [PMID: 31730792 DOI: 10.1016/j.peptides.2019.170200]

Alam MJ, Gupta R, Mahapatra NR, Goswami SK. Catestatin reverses the hypertrophic effects of norepinephrine in H9c2 cardiac myoblasts by modulating the adrenergic signaling. Mol Cell Biochem 2020; 464: 205-219 [PMID: 31792650 DOI: 10.1007/s11010-019-01066-3]

Angeleno T, Quintieri AM, Pasqua T, Gentile S, Tota B, Mahata SK, Cerra MC. Phosphodiesterase type-2 and NO-dependent S-nitrosylation mediate the cardioinhibition of the antiplatelet hypertensive catestatin. Am J Physiol Heart Circ Physiol 2012; 302: H431-H442 [PMID: 22058158 DOI: 10.1152/ajpheart.00491.2011]

Wang D, Liu T, Shi S, Li R, Shan Y, Huang Y, Hu D, Huang C. Chronic Administration of Catestatin Improves Autonomic Function and Exerts Cardioprotective Effects in Myocardial Infarction Rats. J Cardiovasc Pharmacol Ther 2016; 21: 526-535 [PMID: 26821570 DOI: 10.1017/jcph.2016.117]

Dev NB, Mir SA, Gayen JR, Siddiqua JA, Mustapic M, Vaingankar SM. Cardiac electrical activity in a genetically "humanized" chromogranin a monogenic mouse model with hyperadrenergic hypertension. J Cardiovasc Transl Res 2014; 7: 483-493 [PMID: 24821335 DOI: 10.1007/s12265-014-9563-7]
Pei Z, Ma D, Ji L, Zhang J, Su J, Xue W, Chen X, Wang W. Usefulness of catestatin to predict malignant arrhythmia in patients with acute myocardial infarction. *Peptides* 2014; **55**: 131-135 [PMID: 24631953 DOI: 10.1016/j.peptides.2014.02.016]

Zhu D, Wang F, Yu H, Mi L, Gao W. Catestatin is useful in detecting patients with stage B heart failure. *Biomarkers* 2011; **16**: 691-697 [PMID: 22050388 DOI: 10.3109/1354750X.2011.629038]

Liu L, Ding W, Li R, Ye X, Zhao J, Jiang J, Meng L, Wang J, Chu S, Han X, Peng F. Plasma levels and diagnostic value of catestatin in patients with heart failure. *Peptides* 2013; **46**: 20-25 [PMID: 23702300 DOI: 10.1016/j.peptides.2013.05.003]

Borovac JA, Glavas D, Susilovic Grabovac Z, Supe Domic D, D’Amario D, Bozic J. Catestatin in Acutely Decompensated Heart Failure Patients: Insights from the CATSTAT-HF Study. *J Clin Med* 2019; **8** [PMID: 31366074 DOI: 10.3390/jcm8081132]

Meng L, Ye XJ, Ding WH, Yang Y, Di BB, Liu L, Hao Y. Plasma catecholamine release-inhibitory peptide catestatin in patients with essential hypertension. *J Cardiovasc Med (Hagerstown)* 2011; **12**: 643-647 [PMID: 21508854 DOI: 10.2459/JCM.0b013e328346c142]

Peng F, Chu S, Ding W, Liu L, Zhao J, Cui X, Li R, Wang J. The predictive value of plasma catestatin for all-cause and cardiac deaths in chronic heart failure patients. *Peptides* 2016; **86**: 112-117 [PMID: 27771336 DOI: 10.1016/j.peptides.2016.10.007]
