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# Cognitive Function and Heart Failure: The Role of the Adrenergic System

Grazia D. Femminella[1], Ciro Candido[1], Maddalena Conte[1], Sandra Provenzano[1], Carlo Rengo[2], Enrico Coscioni[3] and Nicola Ferrara[1, 4,*]

*From: [1]Division of Geriatrics, Department of Translational Medical Sciences, Federico II University of Naples, Italy; [2]Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University of Naples, Italy; [3]Division of Cardiac Surgery, San Giovanni di Dio Ruggi d'Aragona, Salerno, Italy; [4]Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Telese Terme (BN), Italy*

**Grazia D. Femminella**

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**Abstract:** ***Background:*** Heart Failure (HF) and cognitive impairment (CI) represent two high incident diseases worldwide, with extremely elevated mortality and morbidity rates. Their prevalence is expected to further increase in the next years due to the aging population, thus they pose enormous clinical, social and economic challenges. Sympathetic nervous system hyperactivity is known to play a pivotal role in HF pathophysiology and progression. In fact, increased cardiac and circulating catecholamine levels are responsible for several molecular and structural abnormalities with detrimental effects on the failing heart. The ~~poof~~ proof of this latter concept is represented by the clinical success of β-Blocker therapy that is able to attenuate HF-related morbidity and mortality. Recently, adrenergic system alterations have been implied also in the pathogenesis of CI and dementia opening the window for new fascinating and promising therapeutic opportunities.

***Objective:*** Assess the state of the art on the relationship between cognitive impairment and heart failure.

***Method:*** In the present manuscript, we propose an updated review of literature and patent on the role of sympathetic nervous system derangement in the pathogenesis of HF and CI.

***Conclusion:*** We have discussed recent findings allowing the identification of new molecular targets that hopefully will contribute to the generation of effective therapeutic strategies for HF and dementia.

In this article, the patents US20100048479, US7060871, WO2006052857, US7351401, US5721243, WO1994009155, US5449604, WO1999058981, US5985581, EP2319511, EP2377534, EP2650303, WO2006004939, WO2010132128 and EP1779858 are summarized.

**Keywords:** β-Blocker, cognitive impairment, dementia, GRK2, heart failure, sympathetic nervous system.

## INTRODUCTION

### Epidemiology of Heart Failure and Cognitive Impairment

Heart Failure (HF) is an important public health problem and its prevalence is expected to progressively increase due to population ageing [1]. HF can be defined as a complex clinical syndrome in which patients have several symptoms and signs resulting from any structural or functional cardiac disorder that causes inability of the heart to provide adequate blood flow to other organs. Several epidemiological studies have investigated incidence and prevalence of HF, frequently reporting conflicting results, probably due, at least in part, to the different diagnostic criteria adopted. According to a recent review about 37.7 million people are estimated to be living with HF in the world [2]. Data from the American Heart Association (AHA) indicate a prevalence of 5.1 million people with HF only in the United States [3], with the prevalence in African-Americans that is higher than in Caucasian [4]. The prevalence of HF reported in ESC guidelines is 1-2% in the developed world, increasing to ≥10% among patients 70 years of age or older, while the incidence was evaluated as 0.5-1% subjects/year [5]. The Framingham Heart Study showed trends toward increasing HF prevalence in older people: it was estimated 0.8% at age 50-59 years, rising to 6.6% at ages 80 to 89 years, with similar values (respectively 0.8% and 7.9%) in women [6]. This trend is paralleled by an increase in the rate of hospitalization due to HF, which is the major cause of hospitalization in patients older than 65 years. In elderly subjects with HF one of the most common medical conditions associated is cognitive impairment (CI) [7]. Rait *et al.* have examined the prevalence of CI in subjects aged 75 years and over in the UK [8]. CI assessed by Mini-Mental State Examination (MMSE) showed a prevalence of 18.3% for mild impairment and of

*Address correspondence to this author at the Department of Translational Medical Sciences, University of Naples Federico II, Via S. Pansini, 5 - 80131 - Naples, Italy; Tel: +39-0817462339; Fax: +39-0817462339; E-mail: nicola.ferrara@unina.it

 

3.3% for moderate to severe impairment, with a higher prevalence in women. The prevalence of CI in HF patients, as well as cardiac dysfunction, increases with aging and its incidence varies widely from 25% to 70-80% according to presence of comorbidities, methods adopted to assess cognition and study designs [9-12]. It seems that the different cognitive domains (attention, executive function, learning and memory, language, visuospatial functioning and psychomotor speed) are affected in patients with HF. Also, the severity of cognitive dysfunction is correlated to HF severity and several brain changes observed in dementia are also found in patients with HF. Among them, increased cortical atrophy, cerebral infarcts, white matter changes and metabolic alterations have been identified in HF subjects and might contribute to cognitive decline onset and progression. Data from recent studies also demonstrate that cognitive deficits in HF are, at least in part, reversible. Improved clinical management and close monitoring of cardiovascular function might prevent cognitive deterioration in HF patients, as suggested by studies that have shown improved cognitive function in persons with HF as a result of cardiac transplantation ~~pacemaker and~~ cardiac assist device implantation and initiation of treatment with ACE inhibitors [13]. In this review we aim to explore the relationship between HF and dementia, with a particular focus on the possible role of the adrenergic system.

## Cardiac Adrenergic System: Anatomy and Physiology

The autonomic nervous system (ANS) is the part of the nervous system that regulates visceral functions to maintain the body homeostasis and to allow reactions and adaptation to external and internal stressors. The ANS is divided into sympathetic (or adrenergic) nervous system (SNS) and parasympathetic (or cholinergic) nervous system. These branches have different neurotransmitters that generally exert opposite effects on target tissue through the activation of adrenergic and cholinergic receptors. SNS exerts relevant cardiovascular effects, such as increase heart rate and contractility, lowering venous capacitance and vasoconstriction. Instead the parasympathetic nervous system has minimal effects on contractility and acts mainly by inducing bradycardia through vagal impulses [14].

Cardiac anatomic distribution of ANS fibers is different for the two branches: adrenergic nerve travel in the epicardium, run along coronary arteries and reach mainly the ventricular myocardium, while cholinergic nerve fibers travel with vagus nerve in the subendocardium and reach primarily the atria and at a lesser extent the ventricular myocardium. Accordingly, the heart rate is under the control of both parts of the ANS, whereas myocardial contractility is regulated almost exclusively by the SNS [15].

The two branches of the ANS are composed of afferent, efferent and interneuronal fibers, involved in cardio-cardiac reflexes. Afferent fibers run to the central nervous system via the autonomic nerves, while efferent fibers reach target organs with autonomic or somatic nerves. The principal reflex responses derive from the aortic arch, the carotid baroreceptors, the cardiopulmonary baroreceptors, the cardiovascular low-threshold polymodal receptors and the peripheral chemoreceptors [15].

The cardiovascular effect of SNS is mediated by the release of two catecholamines (CAs): norepinephrine (NE or noradrenaline) and epinephrine (EPI or adrenaline). CAs act through several mechanisms: NE, released by cardiac sympathetic nerve terminals (only a minimal rate ~~derived~~ from adrenal medulla), increases heart rate, reduces atrioventricular conduction and increases contractile strength and blood pressure; EPI, released into the circulation by the adrenal medulla, has effects on the myocardium and peripheral vessels; finally, both CAs can be locally released by various peripheral adrenergic nervous systems via autocrine/paracrine and are located in blood vessels and in cardiac myocytes themselves [15, 16]. The parasympathetic activity is mediated by acetylcholine, that activating specific receptors, decreases sinoatrial node depolarization rate and atrioventricular node conduction velocity, thus resulting in reduced heart rate with minimal or no effect on cardiac contractility.

Alterations in autonomic function are involved in the pathogenesis of several cardiovascular diseases, including HF, hypertension, cardiac arrhythmias, myocardial ischemia, and sudden cardiac death [17]. Importantly, SNS hyperactivity is one of the most important neuro-hormonal mechanisms underlying heart failure pathogenesis and progression [18].

## Adrenoceptors in the Cardiovascular System

The adrenergic receptors belong to the G proteins- coupled receptors (GPCRs) superfamily consisting of a seven-transmembrane-spanning receptor domain and an intracellular heterotrimeric G-protein complex (Gαβγ) domain. In the inactive form the G protein binds the nucleotide GDP ensuring the subunit α attached to the complex. When the receptor is activated by agonist, the subunits βγ remain anchored to plasma membrane, while the subunit α hydrolyzes GTP and dissociates from the complex. The α subunit can stimulate (Gαs) or inhibit (Gαi) adenylate cyclase, or activate phospholipase C (Gαq). The adrenoceptors are classified in α and β receptors based on their responses to drugs, the endogenous ligands, their distribution in tissues and structural characteristics [19]. The α-adrenergic receptors (αAR) are divided into three $\alpha_1$-receptors ($\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$) and three $\alpha_2$-receptor ($\alpha_{2A}$, $\alpha_{2B}$ and $\alpha_{2C}$). The $\alpha_1$-AR recognizes EPI as the main agonist and couples to the Gq protein, thus activating phospholipase C. Phospholipase C cleaves phosphatidylinositol 4, 5 bisphosphate, which in turn increases inositol triphosphate and diacylglycerol. Inositol triphosphate interacts with calcium channels of endoplasmic and sarcoplasmic reticulum increasing intracellular calcium store, whereas diacylglycerol activates protein kinase C and transient receptor potential channels. $\alpha_1$-ARs are mainly localized in vascular smooth muscle and, following activation, induce blood vessel vasoconstriction (i.e. aorta, pulmonary arteries, mesenteric vessels). $\alpha_2$- AR is a presynaptic receptor placed in the nerve fiber endings and coupled to the Gi protein. Its activation causes a negative feedback on NE release from the presynaptic neurons. Furthermore, $\alpha_2$-AR activation causes a decrease in cAMP activity resulting in smooth muscle contraction. These receptors are mainly localized in central nervous system and in vascular pre-junctional terminals. The βARs include three subtypes: $\beta_1$, $\beta_2$, $\beta_3$. All signal through Gs proteins, although $\beta_2$AR also couples to Gi. The human heart contains all three βAR subtypes, with $\beta_1$AR represent-

ing 75-80% of all cardiac adrenergic receptors and with expression levels that are ~4 times higher compared to $\beta_2$ARs. $\beta_2$ ARs and $\beta_3$ARs receptors are less represented in the heart (15-18% and 2-3% of total cardiac βARs, respectively). β ARs are activated following binding by sympathetic neurotransmitters (NE and EPI) and, upon activation, they increase heart rate (chronotropy), contraction force (inotropy) and hearth relaxation (lusotropy) [20]. Gs protein signaling stimulates the adenylate cyclase, causing an increase in AMPc synthesis and activation of Protein Kinase A (PKA). This latter kinase phosphorylates several substrates inducing an elevation in intracellular calcium that is the most important regulator of cardiac contractility. PKA can phosphorylate $\beta_2$AR reducing receptor affinity for Gs and increasing its affinity for Gi. The activation of $\beta_2$AR Gi-dependent signaling triggers a pro-survival, pro-angiogenic and anti-apoptotic pathway, while the stimulation of $\beta_1$AR acts via Gs and has a pro-apoptotic effect in cardiomyocyte [21, 22]. Finally, $\beta_3$AR has a marginal role in physiological conditions, but it is upregulated in HF. Its activation seems to produce a negative inotropic effect, balancing $\beta_1$AR and $\beta_2$AR signaling, through a pathway mediated by Gi/o and endothelial type-3 NO synthase [23]. Importantly, alteration in cardiac βAR signaling and function are of great relevance in the pathogenesis of cardiovascular diseases, including HF [24].

## Adrenoceptors in Brain

The major source of NE in brain is the locus coeruleus (LC), located in the dorsal pontine tegmentum and connected to several brain regions including brainstem, cerebellum and neocortex. The LC plays an important role in the regulation of vigilance and sleep-wake cycles as well as in attention, synaptic plasticity and memory formation and retrieval [25].

The NE exerts its effects in the CNS through three classes of adrenergic receptors: $\alpha_1$AR, $\alpha_2$AR and βAR, the latter divided into the $\beta_1$, $\beta_2$ and $\beta_3$ subtypes. While the α1AR and βAR are post-synaptic receptors, the $\alpha_2$AR is presynaptic and, when stimulated, it inhibits further NE release in the synaptic cleft [26, 27].

Several studies have investigated the role of AR in the CNS and, in particular, in the regulation of cognitive functions. It seems that activation of the $\alpha_1$AR improves learning and the use of α1AR antagonists like prazosin decrease spatial learning [28, 29]. Genetic studies have also shown that both $\alpha_{1A}$-AR and $\alpha_{1B}$-AR knockout mice exhibit impaired cognitive functions, especially in spatial learning and memory [30]. As for the $\alpha_2$AR, it has been reported that antagonism of these receptors improves cognition. In particular, preclinical studies with the $\alpha_2$AR blocker yohimbine have demonstrated beneficial effects on spatial memory assessed by Morris water maze test in rodents [31]; other researchers have demonstrated that dexefaroxan, another α2AR antagonist, is able to ameliorate learning and memory in treated mice [28]. On the contrary, $\alpha_2$AR agonist clonidine impairs fear memory reconsolidation but, interestingly, it improves working memory in the prefrontal cortex [32]. Working memory deficits have also been observed in knockout mice for $\alpha_{2A}$-AR [33].

Also the βAR exert important functions is the CNS, as demonstrated by several pharmacological studies. The βAR agonist isoproterenol has been shown to improve memory consolidation and long term potentiation in the mouse hippocampus [34]; intra-amygdalar injection of the $\beta_2$AR agonist clenbuterol enhances retention of the inhibitory avoidance in mice [35]. Conversely, recent data indicate that the βAR blocker propranolol is able to improve performance during cognitive flexibility tasks in rodent [36] while xamoterol, a partial $\beta_1$AR agonist, impairs hippocampus-dependent emotional memory retrieval in mice [37]. Mirbolooki *et al.* have demonstrated that intracranial administration of $\beta_3$AR antagonists induces amnesia in chicks, while memory loss is rescued by $\beta_3$AR antagonists [38].

## Regulatory Mechanisms of Adrenoceptor Signaling and Function

Adrenergic receptor signaling is highly regulated, undergoing processes known as desensitization and down-regulation. In this scenario, a prominent role is played by the family of G protein-coupled receptor kinases (GRKs), and in particular by GRK2 that represents the predominant isoform in the heart. GRK2 is a serine/threonine cytosolic kinase and, within its well-conserved structure, contains a central catalytic domain, an amino-terminal domain and a carboxyl-terminal domain that includes specific regulatory sites [39]. GRK2 is primarily a cytosolic protein, but once GPCRs, including cardiac βARs, are activated by agonists, it translocates to the plasma membrane where it is able to come in contact and phosphorylate agonist-occupied βARs, initiating the processes of receptor desensitization [40]. It is well known that in order to move to the plasma membrane GRK2 binds the Gβγ subunits of the heterotrimeric G-proteins through binding sites within its carboxyl-terminal domain. Following receptor phosphorylation by GRK2, β-arrestins bind this complex preventing further G-protein-mediated signaling [41]. Thus, β-arrestins have been originally described as a terminator of GRCR signaling. More recently, it has been described that β-arrestins are able to activate through scaffolding functions an alternative signal, known as G protein independent signaling [42, 43]. Under physiological conditions, signal through βARs is the result of receptor activation by agonists and receptor phosphorylation by GRK2 which initiates processes of receptor desensitization/downregulation. However, there are several demonstrations available of the therapeutic effects of GRK2 inhibition in the heart via the peptide βARKct, which competes with endogenous GRK2 for Gβγ binding at the plasma membrane [44-46]. Moreover, preclinical studies have shown that long-term administration of βAR agonists increases cardiac GRK2 activity, while β-blocker decreases GRK2 levels in the heart [39]. Thus, it is nowadays widely accepted that up-regulation of cardiac GRK2 levels/activity, despite protective in the short term with the attempt to defend the heart from the toxic effects of excessive βAR activation, it becomes maladaptive over time blunting βAR signaling that become unresponsive to SNS activation.

## Assessment of SNS Hyperactivity

The sympathetic and parasympathetic nervous system regulates several physiological functions, including cardiovascular (blood pressure and heart rate modulation), respiratory, gastrointestinal and urinary ones.

The dysfunction of the autonomic nervous system can be evaluated by a number of feasible tests, especially aiming at the assessment of cardiovascular autonomic modulation [47].

### *Heart Rate Interval Variability*

It is calculated on a continuous electrocardiogram (ECG), recorded for 5 minutes while the patient is resting supine. Both time-domain indexes and frequency-domain indexes are calculated. Time-domain indexes are based on a statistical calculation of consecutive R-R intervals, while frequency-domain indexes derive from a spectral method that analyses the fluctuations in the frequency domain. A specific algorithm is used to convert R-R intervals on ECG in spectral density, and the ratio between low frequency/high frequency bands represents a marker of sympathovagal balance [48].

### *Ewing's Battery Tests*

This battery is composed of five cardiovascular reflex tests originally developed to evaluate autonomic function in diabetic patients [47]. They involve the recording of continuous ECG and include the following: 1) Valsalva ratio, which is calculated dividing the maximal R-R interval by the minimal R-R interval during the Valsalva maneuver; 2) Heart rate response to standing, calculated by the 30:15 ratio. The ratio is the maximum R-R interval at the 30th beat after standing divided by the minimum R-R interval at the 15th beat after standing. 3) R-R interval variation (RRIV) during rest and deep breathing which is calculated while the patient performs forced deep breaths at a rate of 6 per minute. The mean R-R is calculated as the mean value of the longest and shortest R-R and the average R-R is calculated as the difference between the longest and shortest R-R intervals. The RRIV is the ratio between mean/average R-R. 4) Blood pressure variation (BP), which can be measured according to several methods. Classically, orthostatic hypotension is evaluated by monitoring BP in supine position after 10 minutes of rest and then after 3 minutes of active standing position. However, BP variation can be evaluated during Valsalva maneuver, as the difference between the peak systolic BP during the maneuver and the mean systolic BP prior to the maneuver, or during isometric exercise, calculated as difference between the mean diastolic BP prior to sitting position and just before the end of sitting exercise, or after a cold presser test, as diastolic BP variation after the participant submerges his left hand in cold water at 4°C. According to the Ewing's classification and depending on how many tests are normal, borderline or abnormal, cardiovascular autonomic function can be classified as normal, early impaired, definitely impaired, severely impaired or atypical, with the heart rate tests providing information on the parasympathetic function and the BP tests better evaluating sympathetic function [49].

### *Baroreflex (BR) Estimation*

As BR is the mechanism responsible for BP and HR control, BR estimation consists of simultaneous ECG recording and BP assessment. Indeed, The BR provides a rapid negative feedback loop when abrupt changes in BP cause a modulation of the HR in order to restore the BP, as a result of sympathovagal activation [50].

### *Carotid Sinus (CS) Massage*

After 5 seconds of CS massage, a fall in HR can be noticed and after 20 seconds, a fall in BP is usually found. This response is a measure of CS reflex sensitivity but should be avoided in patients with cerebrovascular events or recent myocardial infarction [51].

### *Plasma Epinephrine and Norepinephrine Measurement*

The levels of plasma cathecolamines should be evaluated after both 30 minutes in resting supine position and after 5 minutes of orthostatic standing. Blood samples should be kept in ice and processed within 1 hour of collection [47].

### *123I-MIBG Scintigraphy*

The iodine-123 metaiodobenzylguanidine (123I-MIBG) imaging is a noninvasive scintigraphy assessing adrenergic neuronal efferent in the heart, as the MIBG is a noradrenaline analogue competing for the noradrenaline transporter. A reduced MIBG uptake has been correlated to sympathetic dysfunction in heart failure and diabetic neuropathy [52]. Interestingly, myocardial MIBG scintigraphy helps to differentiate between Parkinson's disease and other parkinsonian syndromes, as well as to differentiate between dementia with Lewy body and AD [53].

## Heart Failure Pathophysiology

Any cardiac structural or functional disorder, that compromises ventricular filling or emptying, may lead to the development of HF. About half of patients with HF have a reduction of the ejection fraction. In these patients, the most frequent cause of systolic HF is coronary artery disease, often associated with the presence of diabetes and hypertension. HF with preserved ejection fraction is a growing problem, but is associated with a better prognosis compared to heart failure with impaired systolic function. It seems to be more frequent in older adults and women, and is often secondary to arterial hypertension and left ventricular hypertrophy, rather than coronary artery disease [5, 14, 15].

The failing heart activates several compensatory mechanisms, such as the Frank-Starling mechanism, ventricular remodeling and neurohormonal activation, in order to maintain adequate tissue perfusion. In particular, Frank-Starling mechanism establishes that cardiac muscle contraction increases in response to a rise in the volume of blood filling the heart. Accordingly, left ventricular stroke volume is directly proportional to the amount of blood present in the ventricle at the end of diastole. Augmentation in ventricular preload causes an elongation of the sarcomere, and so an immediate increase in the force of contraction. This phenomenon appears to be due mainly to a greater cardiomyocyte calcium sensitivity elicitated by stretching.

Cardiac remodeling consists of a series of structural and functional alterations, in response to pressure overload, volume overload or cellular damage. Several alterations are reported at cellular level, such as cardiomyocytes hypertrophy, necrosis and apoptosis, accumulation of pro-inflammatory mediators, fibroblast proliferation and extracellular matrix rearrangement. Macroscopically, it is characterized by the presence of ventricular hypertrophy and dilatation due to cardiomyocyte elongation and reorganiza-

tion. These changes lead to a variation in ventricular geometry in the attempt to maintain an adequate stroke volume and cardiac output in response to the reduced ejection fraction. Cardiac remodeling process is progressive and in the long term harmful: it increases myocardial oxygen demand and reduce myocardial contractility, leading to less effective pumping.

Neurohumoral activation includes the renin–angiotensin–aldosterone system (RAAS) and hyperactivation of the sympathetic nervous system. RAAS is overactive in HF and contributes to disease progression through impairment of pressure stability and fluid volume homeostasis. RAAS, through the activation of angiotensin II receptor type 1 (AT1), causes systemic and renal vasoconstriction, renal blood flow reduction and an increase in glomerular filtration and proximal sodium and fluid reabsorption. In addition, AT1 activation induces oxidative stress, inflammatory cytokines production, fibroblasts activation, vascular smooth muscle growth and endothelial dysfunction [54]. These effects lead to progressive renal and heart injury. AT1 activation also stimulates aldosterone secretion, resulting in sodium and water retention [55]. Aldosterone receptors are located in several tissues (i.e. heart, blood vessels and brain) and, together with angiotensin, contribute to the development of cardiac fibrosis and remodeling [56, 57]. Due to its central role in HF pathophysiology, RAAS is currently an important pharmacological target in HF management. Other neurohormones are hyperctivated in HF, such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), released in response to atrial and ventricular stretching, and C-type natriuretic peptide (CNP) found predominantly in the central nervous system. They determine vasodilation, increase sodium and water secretion, and also inhibit the release of renin, aldosterone and vasopressin [58].

Although all these mechanisms are initially beneficial, attempting to support cardiac function, overtime they become maladaptive, leading to reduction of cardiac contractility and facilitating HF progression [5].

## Role of SNS Hyperactivity in HF (Regulation of SNS Activity and Effects of SNS Hyperactivity on Cardiac Adrenoceptors)

SNS activation is one of the first adaptive responses to reduced cardiac function, primarily resulting from decreased blood pressure. Sympathetic hyperactivation is characterized by increased NE release and decreased NE reuptake from sympathetic nerve endings, resulting in increased NE spillover [14, 15]. Physiologically, SNS activation is under the control of pressure-sensitive receptors, known as baroreceptors that can be divided into two categories based on the type of blood vessel in which they are located: high-pressure baroreceptors placed in the carotid sinus and aortic arch, and low-pressure baroreceptors, located in the right atrium and in the wall of major veins. These receptors are involved in the control of SNS activity, specifically activating a negative-feedback. Their actions are opposite to activation of peripheral chemoreceptors that stimulate SNS. During HF, this equilibrium is shifted towards increased activation of SNS, with decreased sympatho-inhibitory and increased sympatho-excitatory reflexes, leading to altered heart rate variability, increased peripheral resistance, blood pressure, ventricular contractility and heart rate, in order to maintain the cardiac output. Recently, a new molecular mechanism controlling SNS outflow in HF has been described [59, 60]. Briefly, GRK2 up-regulation in the adrenal medullary chromaffin cells leads to down-regulation of the sympatho-inhibitory $\alpha_2$AR. The loss of this negative feedback to catecholamine release results in uncontrolled NE and EPI production, with a relevant role both under physiological conditions and in the patho-physiology of sympathetic hyperactivation observed in HF [60, 61]. Importantly, this mechanism seems to be involved also in the increased NE release from cardiac nerve endings [62]. *In vivo* GRK2 inhibition in the chromaffin cells of HF rats results in reduced SNS activity and ameliorated cardiac function. Therapeutic modalities known to positively modulate sympathetic activity in HF are able to reduce circulating catecholamine via restoration of adrenal $\alpha_2$AR signaling [63, 64].

Similarly to other neurohormonal systems, also adrenergic hyperactivity exerts detrimental effects on cardiac function and structure in the long-term [14, 15]. In fact, circulating catecholamine levels, as well as other parameter of SNS activity, are directly correlated with HF severity and mortality, suggesting plasma NE as a guide to prognosis in patients with congestive HF [58]. As already mentioned, sustained SNS activation causes cardiac βAR desensitization and downregulation via increased GRK2 activity, resulting in impaired chronotropic and inotropic responses [65]. The $\beta_1$AR is primarily involved in this mechanism, leading to cardiomyocyte apoptosis, necrosis and hypertrophy and increased oxidative stress [66, 67]. Differently, $\beta_2$AR is exclusively desensitized in HF, suggesting that this receptor may be relevant for the inotropic support of the failing heart ~~HF~~. In addition, $\beta_2$AR exerts anti-apoptotic effects in contrast to the pro-apoptotic action of $\beta_1$AR stimulation. Of note, *in vivo* gene therapy experiments, aiming at cardiac GRK2 inhibition, resulted in improved cardiac function, ameliorated $\beta_1$AR and $\beta_2$AR, activation of alternative receptors signaling and reduced SNS outflow [68-74].

The pivotal role of GRK2-mediated βAR down-regulation in HF pathophysiology prompted researchers to investigate a potential role of this kinase as a biomarker in patients with chronic HF [64]. Importantly, cardiac GRK2 levels depend on the degree of βAR stimulation by CAs, thus reflecting the status of adrenergic activation of the failing heart [65]. Cardiac GRK2 levels are mirrored by circulating lymphocytes, tracking with the degree of HF severity and cardiac dysfunction [75]. It has been shown that lymphocyte GRK2 protein levels independently predict prognosis among patients with HF [76] and blood GRK2 levels can change in response to specific HF therapies [77, 78].

## β-Blockers in HF

Over the past three decades, HF therapeutic armamentarium has been enriched with several drugs that have been shown not only to curb symptoms in these patients, but also to significantly reduce HF-related mortality [5]. Among these new therapeutic opportunities, the introduction of β-blocker represents a milestone in HF therapy. The success of β-adrenergic blocking agents use in patients with mild-to-

moderate chronic heart failure has been widely demonstrated in clinical trials over the past 20 years and their use is widely recommended in guidelines [5]. β-Blockers are usually classified into three generations: a) the first generation includes blockers that unselectively bind both β1 and β2AR subtypes, examples of this class are propanol and timolol; b) the second generation, includes β-blockers with higher affinity for the β1AR than for the β2AR, examples of this class are metoprolol and bisoprolol); and c) the third generation, which includes both subtype-selective (nebivolol) or subtype-nonselective (carvedilol) blockers, that can also block α1ARs, thereby causing peripheral vasodilation (i.e. bucindolol, carvedilol). Nebivolol can also induce nitric oxide production. All β-adrenergic antagonists exert negative chronotropic and inotropic effects, but β1AR-selective agents less frequently cause bronchoconstriction and vasoconstriction. The reduction in cardiac inotropism and heart rate results in decreased oxygen/energy demand of the failing heart, thus, improving cardiac function in the long-term. However, there are several other mechanisms reported for the beneficial effects of β-blocker therapy in HF, including: reverse ventricular remodeling, reduced risk of arrhythmias, increased cardiac angiogenesis and coronary blood flow [79], protection of the heart from the cardiotoxic effects of catecholamine, restoration of cardiac βAR signaling [80], improved cardiac inotropic reserve, reduction of SNS hyperactivity [81].

## Cognitive Impairment Pathophysiology

Alzheimer's disease is a neurodegenerative condition and the most common cause of dementia, accounting for 60-80% of cases. It is clinically characterized by a progressive decline in memory, language, problem solving abilities and deficits in other cognitive domains that ultimately result in the loss of the patients' ability to perform activities of everyday life.

Evidence from clinical and preclinical studies conducted in the last decades have shown that the brain changes associated with AD begin 20 or more years before the disease manifests clinically with cognitive symptoms. This time from the initial brain changes to the symptoms onset has been defined as the "AD continuum" and, also thanks to this new concept, the diagnostic criteria for AD have been revisited in 2011 by the National Institute on Aging (NIA) and the Alzheimer's Association [82]. While the 1984 diagnostic criteria were based on the presence of memory loss and cognitive deficits for the AD diagnosis to be made, the 2011 criteria identify three stages of AD (preclinical, mild cognitive impairment and dementia), with the first occurring before symptoms development, and introduce biomarkers tests. These criteria and guidelines identify two biomarker categories: a) markers of beta-amyloid accumulation in the brain and b) markers of neurodegeneration. Indeed, AD is characterized, from the neuropathological point of view, by the formation of extracellular amyloid β (Aβ) plaques and intraneuronal deposits of neurofibrillary tangles (NFTs). NFTs are helical filaments constituted by hyperphosphorylated tau protein, while Aβ plaques are formed of aggregated amyloid β peptide [83]. The NFT in AD are found in the amygdala, hippocampus and temporal association cortex while Aβ plaques are distributed throughout the association neocortex and in the striatum. Apart from these two well-known pathophysiological mechanisms, other factors contribute to AD onset and progression. Neuroinflammation (the inflammatory response in the central nervous system secondary to neuronal insult) is one of these and its cellular players are microglia and astrocytes. Despite being described as protective in the early phases and aimed at the removal of toxic Aβ, in the long term neuroinflammation results detrimental, contributing to brain damage with the release of cytokines and neurotoxic agents from activated glial cells [84]. In addition to that, vascular pathological alterations have an important role in AD pathogenesis, as demonstrated by several studies [85]. Vascular injury induces toxic accumulation of Aβ and capillary hypoperfusion, leading to early neuronal dysfunction while Aβ accumulation in the perivascular region leads to cerebral amyloid angiopathy; moreover, cardiovascular diseases are an important causal or contributing factor in AD, with hypertension regarded as the most powerful vascular risk factor for AD [86]. Additionally, it is well established that both early-onset and late-onset AD have a genetic component. In the late-onset form, apolipoprotein E (APOE) has been established as the most important susceptibility gene; recent evidence from genome-wide association studies (GWAS) has identified other new loci for AD risk but all their effect is much smaller compared to those of APOE [87, 88].

From the therapeutic point of view, drug development for AD has proven to be very difficult, with only four drugs currently approved for the treatment of AD including three cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate (NMDA) receptor AD antagonist (memantine). In the decade 2002-2012, over 400 interventional trials have been conducted in AD, with an overall success rate of 0.4% (99.6% failure), thus there is an urgent need for new therapies in AD [89]. Moreover, along with the search for therapies that can modify the course of AD, there is a need to identify reliable biomarkers to help in diagnosis and monitoring progression, with neuroimaging markers being among the most valuable tools for this purpose. Indeed, structural brain MRI and fluoro-deoxy-D-glucose (FDG)-PET already have a role in evaluating brain atrophy and metabolism respectively but, in recent years, other PET tracer have been developed to specifically assess AD neuropathology *in vivo*; among them, amyloid imaging, microglial activation and neuroinflammation, cholinergic pathways, and, more recently, imaging tau and neurofibrillary tangles have an invaluable role [90-96].

## Potential Involvement of SNS Dysfunction on Cognitive Function: The New Adrenergic Hypothesis? (Should this question mark come?)

Alterations in autonomic function are found in AD patients and they are due, at least in part, to the deficit in central cholinergic function observed in these patients. Several recent lines of evidence indicate a potential involvement of βAR system also in AD pathogenesis, with interesting implications on the clinical management of subjects with CI. This is relevant since the current therapeutic armamentarium available to treat dementia, only allows symptomatic improvement without any effect on disease progression. The central noradrenergic system undergoes extensive modifications in the course of AD.

Different lines of evidence have shown that in AD there is a significant decrease in the total concentration of βARs in many brain regions. Importantly, β1ARs concentration is significantly reduced in the hippocampus while β2ARs are decreased in the thalamus, cerebellum and in the nucleus basal of Meynert, highlighting many βARs changes in AD dementia [97]. Importantly β2ARs stimulation by NE causes increase of cAMP that results in an overexpression in AβPP by enhancing γ secretase activity [98].

Moreover, Aβ is implicated in β2 AR internalization and degradation mediated by phosphorylation of GRKs and arrestins resulting in a decrease in noradrenergic activity [99].

Indeed, LC degeneration occurs early in AD pathogenesis and reduction in cortical NE concentration and in NE transporter correlate with the severity of CI [100-102].

LC degeneration is caused by the early occurrence of abnormal hyperphosphorilated tau proteins in a few neurons of the LC that can aggregate into neurofibrillary tangles. Other studies indicate that NE is increased in the cerebrospinal fluid of AD patients [103], probably as a compensatory effects occurring in the remaining noradrenergic brain areas [104]. Importantly, also βARs seem to play a role in CI, with implications not only on amyloid production and precipitation, but also in amyloid-dependent neurotoxicity [105-107]. These observations are supported by recent evidence indicating a possible role of β-blocker therapy in AD onset and progression [27]. Finally, it is important to underline that post-receptor components of βAR system, and in particular GRK2, might be involved in AD pathogenesis. Lymphocyte GRK2 levels are increased in patients with AD, tracking the degree of CI [108]. Deeper knowledge on the role of the adrenergic system in AD pathogenesis is of great clinical interest for the development of novel prognostic and therapeutic strategies.

### SNS Dysfunction as a Link between Heart Failure and Cognitive Decline

Both HF and AD represent growing healthcare and social problems, especially in the elderly population; they often occur together, increasing the cost of healthcare. Several non-cardiac conditions might indeed impact on HF-related mortality and CI is among those [109-110]. This underlines the importance of investigating the relationship between these conditions, and SNS dysfunction might play a role in that.

It is known that appropriate treatment of cardiovascular conditions can reduce the prevalence of AD and that heart disease and AD share similar risk factors and genetic susceptibility genes, such as ApoE polymorphisms. Moreover, the relationship between HF and cognitive impairment is further confirmed by the fact that the "cardiogenic dementia" was identified in the 1970's and since then several studies have shown that HF contributes to cognitive decline and that its severity correlates with cognitive performance. One of the factors possibly linking the two conditions is the inadequate blood supply due to reduced cardiac output in HF, as it has been confirmed by data indicating that reduced left ventricular ejection fraction is associated with impaired cognition and that low cardiac index is associated with low brain volume [111]. Moreover, it has been demonstrated that patients with HF present with more white matter hyperintensities, lacunar infarcts and medial temporal lobe atrophy, compared to healthy controls and that patients with AD have a reduced regional and total cerebral blood flow resulting in brain hypoperfusion, compared to cognitively normal controls [112, 113]. A chronic reduction in cerebral blood flow might result in cellular hypoxemia and acidosis, followed by oxidative stress, ultimately aggravating both Aβ and tau pathologies.

As discussed above, impaired cardiac function activates neurohormonal systems, as the SNS and the renin-angiotensin-aldosterone system, further contributing to HF progression. Altered neurohormonal signals also activate the CNS, which in turns regulates cardiac function; however, the exact mechanisms of this regulation are still unknown. Preclinical evidence indicates that brain administration of β-blockers in an animal model of myocardial ischemia reduced mortality more effectively than peripheral administration [46].

In addition to that, several studies indicate that an impairment of autonomic function is present both in HF and AD and more importantly, modifications of the cardiac sympathovagal balance towards a higher sympathetic and lower parasympathetic modulation are highly prevalent in the elderly and might contribute to disrupted homeostatic adaptive capacity in both conditions [114].

Thus, it is likely that the relationship between HF and AD might reflect neurohormonal activation and its systemic consequences, rather than perfusion alone.

In summary, data from the studies reviewed here globally indicate that:

- HF and AD represent growing healthcare problems in the elderly population that can often occur simultaneously
- Improved medical treatment of cardiovascular conditions can reduce the prevalence of AD
- HF patients show brain abnormalities that are observed in AD patients (white matter hyperintiensities, regional atrophy)
- AD patients present with reduced cerebral blood flow resulting in hypoperfusion
- Altered neurohormonal signals (including the adrenergic system) activate the CNS, which in turns regulates cardiac function
- an impairment of autonomic function is present both in HF and AD and might be a link between the two pathologies

## CURRENT & FUTURE DEVELOPMENTS

Given the enormous impact of both HF and AD on elderly health status, it is not surprising that several studies are ongoing, in the search for appropriate and effective treatments for both conditions; moreover, increasing interest is growing in understanding the relationship between cardiovascular disease and cognitive impairment. In the present manuscript, we have reviewed how SNS dysfunction might be a link between heart failure and neurodegeneration.

Recently, patents have been developed proposing AR modulation as a target for both conditions [115], and other AR targeted-drugs are being developed in pharmacological research [116]. New compounds modulating guanilate cyclase have been recently patented as a treatment for HF [117] and polymorphisms and haplotypes of the alpha2c AR gene are being investigated as a risk factor for HF [118]. In cognitive impairment, few compounds have been patented in the last few years for the treatment of this condition [119, 120], thus more research studies need to be undertaken, aiming at the discovery of effective therapeutic tools.

## CONFLICT OF INTEREST

The authors confirm that this article has no conflict of interest.

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