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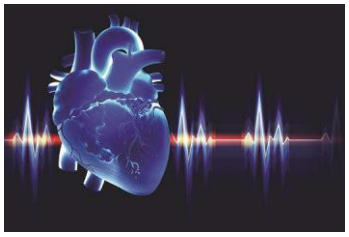
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗ ΑΠΟΚΑΤΑΣΤΑΣΗ»

(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)



Μεταπτυχιακή Διπλωματική Εργασία

«Διαταραχές του αυτονόμου νευρικού συστήματος στην καρδιακή ανεπάρκεια: Η θεραπευτική σημασία της διέγερσης του παρασυμπαθητικού»

Του φοιτητή

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Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Καρδιακή ανεπάρκεια – Καρδιο-ογκολογία – Καρδιαγγειακή αποκατάσταση»

Λάρισα, Μάιος 2023

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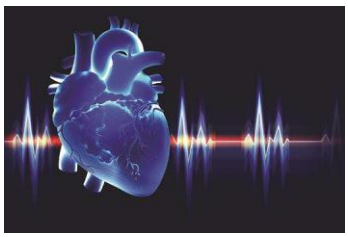

"Autonomic imbalance in heart failure: Therapeutic significance of parasympathetic stimulation."

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΛΕΒΕΝΤΗΣ ΙΩΑΝΝΗΣ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2023

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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Τίτλος εργασίας στα αγγλικά: ***"Autonomic imbalance in heart failure: Therapeutic significance of parasympathetic stimulation.***

Ευχαριστίες

Με την ολοκλήρωση της εκπόνησης της παρούσας διπλωματικής εργασίας αισθάνομαι την επιθυμία αλλά και την υποχρέωση να ευχαριστήσω τους καθοδηγητές μου σε αυτήν την προσπάθεια.

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CONTENTS

Abbreviations-Acronyms

HFpEF: Heart failure, preserved ejection fraction

HFmrEF: Heart failure, mildly reduced ejection fraction

HFrEF: Heart failure, reduced ejection fraction

HFimpEF: Heart failure, improved ejection fraction

RAAS: Renin-Angiotensin-Aldosteron system

ACEinh: Angiotensin convering enzyme inhibitors

SNS: Sympathetic nervous system

MRA: Mineralocorticoid receptor antagonist

ANS: Autonomic nervous system

AR: Adrenergic receptor

BAT: Baroreflex Activation Therapy

PIP_2: Phosphatidylinositol biphosphate

IP_3: Inositol triphosphate

DAG: Diacylglycerol

cAMP: cyclic Adenosine monophosphate

PKA: Protein kinase A

PNS: Parasympathetic nervous system

CNS: Central nervous system

VNS: Vagus nerve stimulation

HRV: Heart rate variability

LV: Left ventricle

LVESV: Left ventricle end-systolic volume

LVEDV: Left ventricle end-diastolic volume

MMP: Matrix metalloproteinase

VF: Ventricular fibrillation

TIMP: Tissue inhibitor of metalloproteinase

NO: Nitric oxide

TNF: Tumor necrosis factor

TNFR: Tumor necrosis factor receptor

CRP: C-reactive protein

NYHA: New York Heart Association

MLHFQ: Minnesota Living with Heart Failure questionairre

LVESD: Left ventricle end-systolic diameter

LVEDD: Left ventricle end-diastolic diameter

AE: Adrverse event

RCT: Randomized controlled trial

LVESVi: Left ventricle end-systolic volume index

SAE: Serious adverse event

TWA: T-wave alternans

TWH: T-wave hetrogeneity

Hs-CRP: High-sensitivity C-reactive protein

NSVT: Non-sustained ventricullar tachycardia

6MWT: 6-minute walk test

NT-proBNP: N-terminal pro brain natriuretic peptide

GDMT: Guidelines directed medical treatment

KCCQ: Kansas City Cardiomyopathy Questionnaire

CRT: Cardiac Resynchronization Therapy

Περίληψη

Η καρδιακή ανεπάρκεια αποτελεί ένα πολυπαραγοντικό σύνδρομο με συνεχώς αυξανόμενη νοσηρότητα και θνητότητα παγκοσμίως, αποτελώντας ουσιαστικά μια σύχρονη πανδημία. Ανάμεσα στους παθοφυσιολογικούς μηχανισμούς της καρδιακής ανεπάρκειας η νευροορμονική διέγερση κατέχει θεμελιώδη ρόλο με το σύστημα ρενίνης-αγγειοτενσίνης-αλδοστερόνης και το συνμπαθητικό νευρικό σύστημα να αποτελούν βασικούς πυλώνες. Η θεωρία με βάση την οποία η καρδιακή ανεπάρκεια χαρακτηρίζεται από υπερδραστικότητα του συμπαθητικού και ταυτόχρονα απόσυρση του παρασυμπαθητικού αποτελεί παγιωμένη γνώση. Σχετικά με το κομμάτι της θεραπείας η άμβλυνση της δραστιριότητας του συμπαθητικού έχει αποτελέσει αντικείμενο μεγάλου όγκου έρευνας, ενώ παράλληλα η τροποποίηση του τόνου του παρασυμπαθητικού ανεκπλήρωτη ανάγκη/στόχο.

Η ρύθμιση του αυτονόμου νευρικού συστήματος μέσω της διέγερσης του πνευμονογαστρικού αποτελεί μια αναδυόμενη θεραπευτική δυνατότητα και μεγάλος όγκος έρευνας διεξάγεται στην προσπάθεια να αποσαφηνιστούν τα οφέλη της στην καρδιακή ανεπάρκεια.

Σκοπός της παρούσας εργασίας είναι η αναλυτική περιγραφή του ρόλου του αυτόνομου νευρικού συστήματος στην καρδιακή ανεπάρκεια καθώς και η συστηματική ανασκόπηση της υπάρχουσας βιβλιογραφίας που αφορά στη διέγερση του παρασυμπαθητικού στην ομάδα αυτών των ασθενών.

Μια πληθώρα μελετών σε ζωικά μοντέλα συσχέτισε τη διέγερση του πνευμονογαστρικού με μεταβολές της καρδιακής λειτουργίας καταδεικνύοντας το ρόλο της στην ανάστροφη διαμόρφωση του μυοκαρδίου καθώς και τις αντιοξειδωτικές, αντιαρρυθμικές και αντιφλεγμονώδεις ιδιότητές της. Παράλληλα, ποικίλες κλινικές μελέτες εξετάζουν αυτή την υπόθεση με διφουρούμενα αποτελέσματα. Περαιτέρω κλινικές δοκιμές απαιτούνται ώστε να φωτιστεί το εν λόγω πεδίο ενώ τα αποτελέσματα εν εξελίξει μελετών αναμένονται με μεγάλο ενδιαφέρον.

Abstract

Heart failure is a multifactorial and considerably prevalent syndrome with continuously increasing rates of mortality, comprising a worldwide pandemic. The neurohormonal concept holds a pivotal role in heart failure pathophysiology and progression, with renin-angiotensin-aldosterone and sympathetic nervous system comprising its two pilars. Sympathetic overactivity along with parasympathetic withdrawal in heart failure are well-established. In the therapeutic context, most efforts have been put on mitigating sympathetic activity whilst modifying parasympathetic tone remains, in some degree, an unmet need.

Autonomic regulation therapy by vagus nerve stimulation is an upcoming therapeutic potential and intensive investigation is conducted to delineate its possible benefits in heart failure.

The purpose of this paper is to describe and analyze the autonomic involment in heart failure and systematically review current literature about vagal stimulation in this patient population.

Plenty of studies in animal models associated vagal stimulation with altered cardiac function, demonstrating reverse myocardial remodeling, antioxidative, antiarrhythmic and antiinflammatory properties. Various clinical trials also tested this hypothesis with promising but simultaneously inconclusive results. Further trials are warranted to shed light in this field, while ongoing trial results are also awaited with great interest.

Introduction

Heart failure (HF) is a complex and multiphenotypic syndrome, characterized by the presence of elevated filling pressures or impaired cardiac output at rest or during exercise and activity. These alterations are attributed to structural and/or functional abnormalitites of the cardiac muscle (1). HF has a large aetiological heterogeneity; coronary artery disease holds the lion's share followed by hypertension, valvular, disease cardiomyopathies, arrhytmias and an extended group of more rare conditions including congenital heart disease, drug toxicity, systematic disease and others (1). Within the past decades, many methods to stratify HF patients have been proposed. To date, the most commonly used classification is based on the parameter of left ventricular ejection fraction (LVEF) including HF with preserved ejection fraction (HFpEF: EF≥50%), with mildly reduced EF (HFmrEF: 40-49%) and with reduced EF (HFrEF: <40%) (1). Recently releashed guidelines from American Heart Asociation/American College of Cardiology propose an additional category referred to patients with a history of HFrEF and systolic improvement in follow-up evaluation (LVEF≥40%), namely HFimpEF (2). In total, HF is a considerably common situation with an anticipated prevalence of 3% in the United States by 2030 (3) and sporadic prevalence over the world approaching 4-5% (4) (**Figure 1**).

Discussing the pathogenesis and mostly the mechanisms of maintanance and progression of HF, the notion that it is not merely a cause or/and a result of hemodynamic alterations had been proposed over than two decades (5). Instead, a theory involving neurohormonal pathophysiological pathways was been introduced, which could potentially augment hemodynamic compromise or target directly the cardiomyocytes and derange their physiology. This theory is represented by the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) activation. It has to be mentioned that this statement refers primarily but not only to HFrEF. About the role of RAAS first evidence came years ago by clinical trials which demonstrated reduced mortality rates in patients with severe systolic HF treated with the angiotensin converting enzyme inhibitors (ACE-i) enalapril and captopril (6-8) and this effect was attributed to modifications in subjects' neurohormonal status. To date, the cardioprotective properties of RAAS inhibition are well established, with sacubitril valsartan, ACE-i as long as minerallocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, holding a strong recommendation in HFrEF and a less dominant, yet considerable role in HFpEF current guidelines (1, 2). With regard to the sympathetic nervous system, the long-term beneficial effect of its inhibition by b-blockers in HF emerged from trials conducted years ago and were endorsed by subsequent large randomized trials (9-13). As such, beta-blockers are also a first-line therapy for patients with HF, particularly with reduced ejection fraction (1, 2).

Apart from pharmacological interventions a lot of effort has been put on device based regulation of sympathetic nervous system (14). Sympathetic influence on the heart is affected by reflex stimuli originating in specific parts of human body and which reflect the hemodynamic state and assist in maintaining homeostasis (15) including the aortic and carotid baroreceptors, cardiopulmonary baroreceptors and others, pulmonary reflexes,

peripheral chemoreceptor reflexes and feedback from skeletal muscles (16). HF is associated with impaired baroreflex reactivity both upon activation and deactivation (17, 18) with concurrent evidence indicating a negative prognostic property of this effect (19). In this context, baroreflex activation therapy (BAT) was evaluated as a potential new therapeutic choice in systolic HF with experimental (20, 21) and clinical (22-24) studies eliciting benefits in both myocardial remodeling and function parameters as well as symptoms amelioration. Spinal cord stimulation is another interesting proposal for SNS modulation. However, despite promising results in some of the available trials in humans, discrepancies attributed to methodological reasons warrant further evaluation.

All the above evidence emphasize in restain SNS overeaction. Nonetheless, it is now an accepted theory that sympathetic hyperactivity is accompanied by parasympathetic withdrawal (25-27). Given the fact that HF is considered a pandemic, since the absolute numbers and associated mortality have importanlty increased within the last decades (28, 29) with enormous economical burden for health systems and continuously increasing rates (3), intervention in the parasympathetic status seems a promising field for novel therapeutic choices and better prognosis. The most popular and well-studied type of such intervention is cervical vagous nerve stimulation.

In this review, current knowledge about the role of autonomic nervous system in progression of HF is discussed with a specific focus to up to date literature for cervical vagal stimulation therapy.

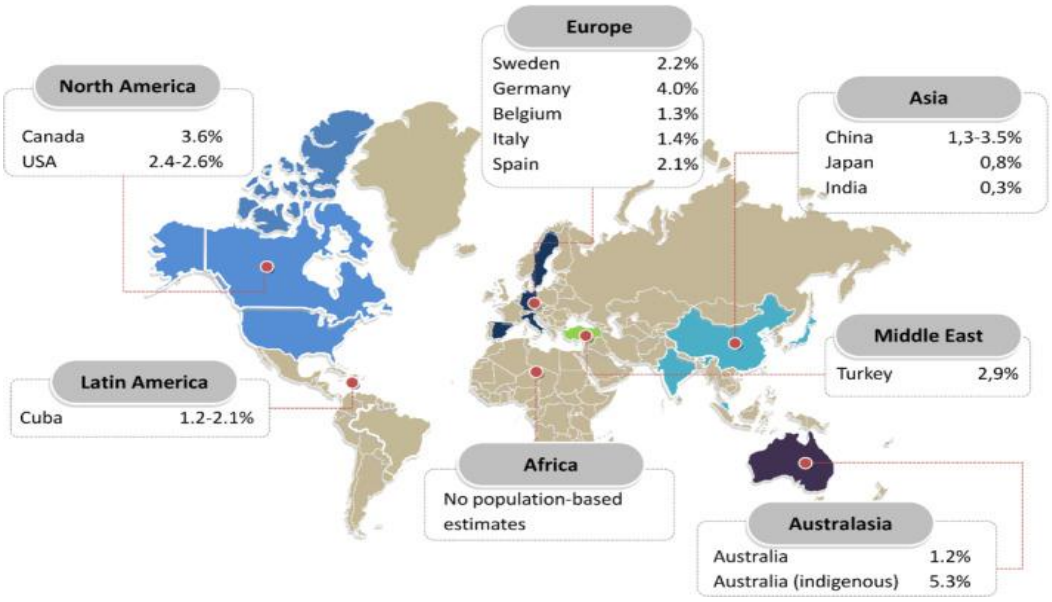

Figure 1: The prevalence of heart failure around different regions in the world.
(Adapted from: Groenewegen A, et al. *Eur J Heart Fail* 2020; 22:1342–1356)

1. Autonomic nervous system

1.1 Anatomy & Physiology

In this fisrt unit, basic anatomic parts of ANS are mentioned along with nessesary physiology knowledge which will help in better comprehending next parts. The autonomic nervous system has a fundamental role in the innervation and physiology of all human organs. It is separated in two major components, the sympathetic and parasympathetic nervous system, which coexist in a fine and mutable balance. Temporary changes in this balance happen with a direct respondance to various stimuli in order to maintain homeostasis. Anatomically, both sympathetic and parasympathetic neurons formate intermediate signalling stations named ganglia, which are encountered bilaterally of the spinal cord and in spatial affinity with all internal organs (15, 30, 31). Both branches are organized in afferent and efferent fibres. With a superficial approach, efferent fibers relay messages to intermediate points of the ANS (i.e. ganglia) and on target organs whilst the afferent ones provide feeback of the systematic physiological conditions and reflexes to the upper control centers. Sympathetic ganglia are mainly located in the paravertebral area of the thoracic, the lumbar segment of the spine and on the end of the cervical including the right and left stellate ganlgion. Signals originating from spinal cord are transmitted to these ganlia through pre-ganglionic fibers and thereafter post-ganglionic fibers innervate target tissues and adrenal medula for the production of catecholamines (epinephrine, norepinephrine). Schematically, the structure of SNS is depicted in **Figure 2**. Inversly, parasympathetic ganglia are mainly distributed in cervical and sacral part (15, 30, 31). Right and left vagus nerve, originating in their core in medulla oblongata, is the main representative of parasympathetic (15, 32) and its peripheral brances innervate and regulate the function of heart, lungs, abdominal organs e.t.c. In both limbs upper neuronal stations in medulla and hypothalamus act as coordinators.

Neuronal communication is carried out with the assistance of specific peptides named neurotransmitters. Since many years ago it is known that sympathetic signaling is mainly performed by acetylocholine in the pre-ganglionc part and by norepinephrine in the post-ganlgionic part (15, 31). When released in the synaptic cleft and after playing its role, a significant proportion (about 80%) of norepinephrine is reabsorbed in the neuron's terminal and then cleaved by monoaminoxidase while the rest is channeled in systematic circulation. Acetylocholine is though, the sole neurotransmitter of the parasympathetic (31, 32) Those molecules act by their linkage to particular protein receptor residing in cell membrane incuding adrenergic receptors for parasympathetic and nicotinic and muscaring receptors for parasympathetic. Adrenergic receptors (AR) are classified as alpha and beta AR with rhe first being divided in alpha-1, subdivided in alpha-1A, alpha-1B and alpha-1D and alpha-2 adrenoceptors which also are subcategorized in alpha-1A, alpha-1B and alpha-1C. Three types of beta AR have been described namely the beta-1, beta-2 and beta-3 receptors (15). The binding of a neurotansmitter to an aplha-1 receptor initiates a complex and multi-staged physiological pathway starting with activation of G_q protein which in turn hydrolyzes phosphatidylinositol biphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG) with a further phosphorylations of various endocellular molecules

that lead in increased cell membrane permeability and intracellular Ca^{2+} and contractility increase (15) (**Figure 3**).

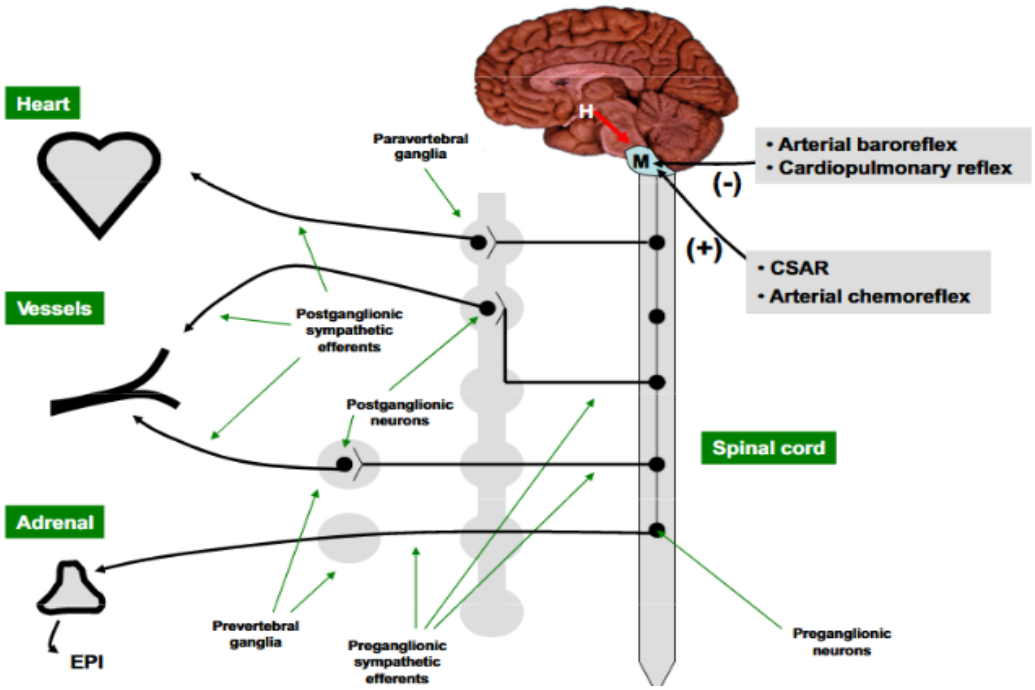

Figure 2. Anatomical formation of the sympathetic nervous system.
(Adapted from Triposkiadis et al. *J Am Coll Cardiol.* 2009 Nov 3;54(19):1747-62.

Activation of beta ARS promotes the formation of 3'-5' cyclic monophosphate (cAMP) augmenting the activity of protein kinase A (PKA) and triggering a group of phosphorylations which in cardiac cells, in particular, comprise the physiological background of increased contractility and elecrical conductivity (**Figure 4**).

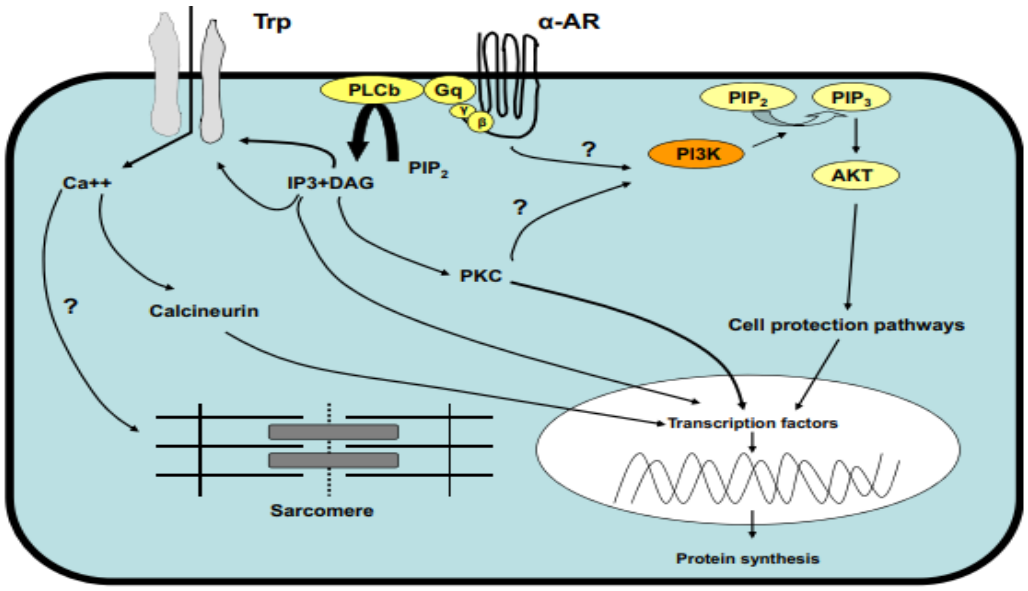

Figure 3. Alpa AR activation.
(Adapted from Triposkiadis et al. *J Am Coll Cardiol.* 2009 Nov 3;54(19):1747-62.

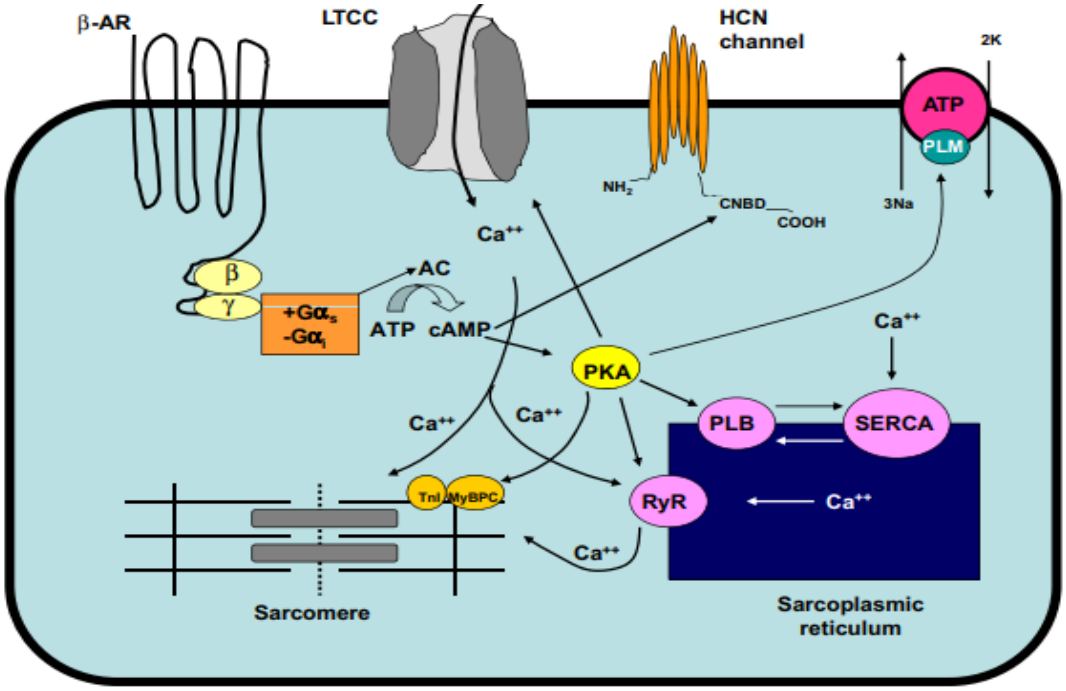

Figure 4. Beta AR activation.
(Adapted from Triposkiadis et al. *J Am Coll Cardiol.* 2009 Nov 3;54(19):1747-62.

Alpha-2 receptors participate in neurotransmition providing a negative feedback in norepinephrive secretion, when stimulated by the peptide itself. In this way, an

inappropriate sympathetic activation is hampered and its harmful consequences are prevented (15, 30).

Parasympathetic neurotransmition is achieved via muscarinic and nicotinic receptors. Five types of muscarinic receptors have been identified the M1, M_2, M_3, M_4, and M_5 receptors. M_1 -M_3 participate in autonomic transmition(31). M_2 and M_3 present a wide distribution over human tissues, with the first being the predominant receptor in cardiac cells and the latter being encountered mainly in the gastrointestinal and urinary tract(31). Autonomic ganglia carry M_1 receptors. When activated all of them trigger a MAP kinase mediated by a G protein which differs among them as M_1 and M_3 bind to G_q to activate phospholipase C and promote DAG and IP3 to increase intracellular Ca^{2+} levels and M_2 activate adenylyl cyclase by connecting to protein G_i and G_o ro conclude on cAMP inhibition. Finally, nicotinic receptors are separated in N_M receptors, found in neuromuscular synapse and N_N receptors, answered in autonimic ganglia and adrenal medula(31). The information above consists a first step description of autonomic nervus system. Further information regarding its physiology are beyond the targets of this paper.

2. Autonomic nervous system and the heart.

2.1. Anatomy and physiology

Both sympathetic and parasympathetic efferent fibers are responsible for heart innervation. Post-ganglionic neurons from each branch follow a distinct path as sympathetic neurons head in the epicardium while parasympathetic ones follow a subendocardial route (15, 30). In a more detailed manner, efferent fibers of both branches reach to ganglia located within the fat tissue surrounding the epicardium and with this the two limbs connect and interact with each other forming the so called " cardiac plexus" (27, 30). Moreover, vagal fibers mainly dwell in the atria, the pulmonary veins and near the sinoatrial node cardiac tissue, with a less dense presence in ventricular myocardium. On the contrary sympathetic fibers have an abundant role in ventricles (15).

Human heart is mainly characterized by the presence of beta adrenergic receptors, in approximately 90% and with a beta-1 predominance (70-30% versus beta-2 receptors) and a small proportion of alpha-1 receptors (about 10%) (15, 30). Beta-3 adrenoceptors are also found on the myocardiac cells' membrane, albeit with a different function as mentrioned below. Beta-1 and beta-2 receptors' activation plays a pivotal role in cardiac contractility, cardiac frequency elevation as well as atrioventricular conduction. On the other hand beta-3 receptors seem to exist in an inactive state in the absence of myocardial disease induced stimuli and convey a negative inotropic effect which has been discribed as a possible counterbalancing mechanism of beta1-2 overactivity in continuously increased sympathetic tone(33). Furthermore, as mentioned above, the cardioinhibitory properties of parasymptahtetic take place by M_2 muscarinic receptors. M_2 receptors are mainly expressed at the endocardial territory as well as the coronary artery and arteriole wall and the atrial and nodal area to regulate heart rate(32).

Additionally, the degree of SNS activity is modyfied by specifing reflexes coming from receptor systems and circuits whose existance aims to help SNS adapt through the evaluation of mechanical and chemical stimuli (15, 16). Such reflexes include i) the arterial baroreflex, with special baroreceptors residing on aortic arch and carotid sinuses and regulate SNS drive based on arterial blood pressure (BP). Rises in BP lead to SNS suppresion while BP falls activate SNS to maintain tissue perfusion. ii)Cardioplulmonary reflexes which, according to most recent literature tend to increase sympathetic activation when cardiac filling pressures rise, iii)Pulmonary reflexes with receptors on the respiratory tract which exert excitatory effects on the sympathetic in case of fluid overload, among others (34), iv)Arterial chemoreceptors inducing sympathetic activation in hypoxia, v)Reflexes from skeletal muscle and kidneys.

Overall, SNS is labeled by a cardioexcitatory effect, as a homeostatic reflex in normal circumstances while PNS comes to maintain balance by antagonizing SNS's effects. Still, this is only the headline of an extremely complicated and remarkable neuronal circuit as it has been proposed that ANS cardiac regulation is carried out by a three leveled neuronal model described as the "cardiac hierarchy" (Figure 4) (35). These stations include the central nervous system, the intrathoracic extracardiac ganglia and the intrinsic cardiac ganglia which belong to the cardiac plexus. Efferent neuronal fibers allow the regulation of all levels by the CNS while afferent fibers from all levels provide feedback to the upper cores at the same time. Sympathetic and parasympathetic fibers also interact in each level, rendering them, in some ways, independent centers of regulation.

Keeping this information in mind, in the next field the role of both sympathetic and parasympathetic in heart failure is described as well as the alterations caused by the disease itself in both parts.

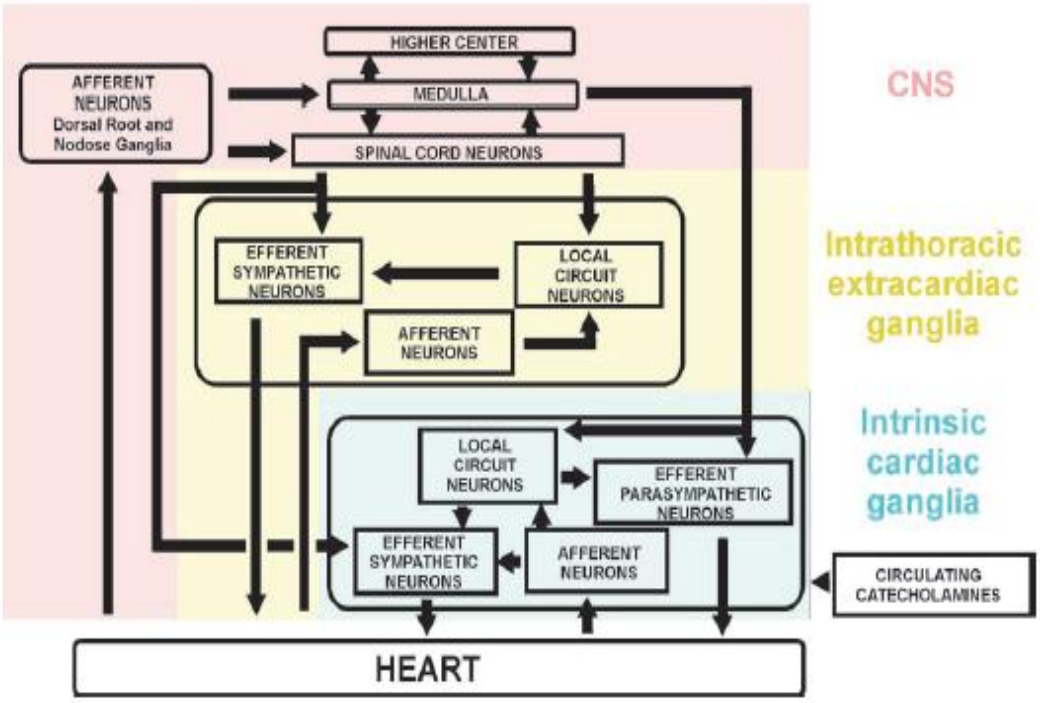

Figure 5. The "cardiac hierarchy".
Adapted from Armour et al. *Am J Physiol Regul Integr Comp Physiol* 287: R262–R271, 2004

2.2. Autonomic nervous system and heart failure

Autonomic dysfunction has been strongly associated with the progression of heart failure as a leading pathophysiological mechanism with the general principle of sympathetic hyperactivity and parasympathetic withdrawal. Herein, a detailed description of current knoweledge is presented.

2.2.1. Sympathetic nervous system and heart failure

HFrEF

In patients with systolic dysfynction, increased sympathetic activity in early stages if the disease is a compensatory reflex in order to maintain hemodynamic balance and peripheral tissue perfussion (30). In the chronic context, this sympathetic overactivation loses its temporary compensatory character and becomes a harmful factor for myocardial structure, physiology and fuction. Mechanisms of sympathetic overactivity in systolic heart failure are discussed below:

i) Regulatory reflexes' impairment: As analyzed before, sympathetic tone is regulated by a group of reflexes which present altered sensitivity in HF. At firtst, arterial baroreflex seems to desensitized being unable to counterbalance sympathetic overactivity. Interestingly, this has been demonstrated both in patients with marked (17) and moderate

systolic dysfunction (18) and in the study of La Revere et al. impaired barorelex sensitivity was associated with an increase in cardiovascular events on follow-uo arguing an independent prognostic significance, except for being a simple pathophysiologic mechanism. However, controversial evidence tend to underrate the degree of arterial baroreflex malfunction in heart failure (16). Cardiopulmonary reflexes have also been proposed as an important alternative mechanism. In fact, old evidence showed a preferance in cardiopulmonary over baroreflex impairement in sympathetic activation pathogenesis (36). Other afferent reflexes such as pulmonary, peripheral chemoreceptor reflexes and stimuli from skeletal muscles and kidney in renal disease have also been proposed to augment sympathetic activity (16). Summarizing the aforemention data, J. Floras in his narrative analysis of this issue introduced a new model according to which modified and deranged afferent reflexes from various systems preserve sympathetic overactivity and supress parasympathetic. These result in heart rate increase, peripheral vascular resistance elevation, fluid and sodium retention via peripheral vasoconstriction including afferent renal arteriole. This model is illustrated in **Figure 6**.

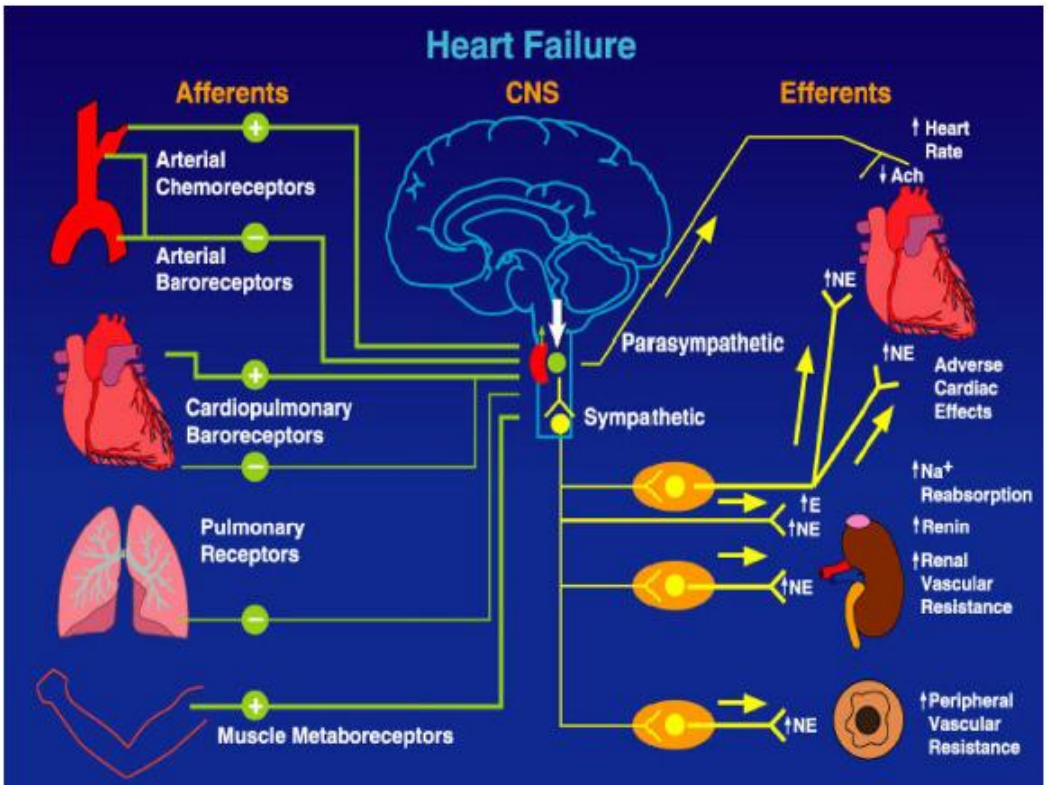

Figure 6: A model of pathophysiologic mechanisms involved in sympathetic overractivity in heart failure.
Adapted from Floras JS. *J Am Coll Cardiol* 2009 Jul 28;54(5):375-85

ii) Central mechanisms: The chronic and sustained activation of RAAS in heart failure leads to elevated levels of angiotensin II and aldosterone in blood stream. These elevations

are also apparent in the brain parenchyma, where RAAS derivatives are formed locally and trigger a nitric oxide de-activating pathway which, in turn, through reduced levels of nicotinamide adenine dinucleotidephosphate oxidase (NADPH) favor the formation of oxygen free radicals which have been associated with sympathoexcitatory effects (16, 37). Another mechanisms involves the triggering of a cytokine catarract following myocardial infarction, which enhances the brain production of cycloxygenase 2 (COX-2) which intensifies sympathetic activation (38).

iii) Cardiac hierarcy derangement: A dysregulation of the cardiac neuronic-signalling circuit in heart failure patients has been mentioned as a potential sympathoexcitatory mechanism (15).

HFpEF

Similarly with HFrEF, the hypothesis of altered autonomic function and the participation of these alterations in HFpEF pathogenisis and progression has been investigated in various studies (39). Current evidence, despite contradictory, in summary point towards sympathetic hyperactivation, represented by noradrenaline spillover in synaptic clefts, muscle sympathetic nerve activity and other indices of SNS activation as well as parasympathetic supression, in accordance with HFrEF. Still, all authors addressing this issue concluded that further clinical investigation is required to enlighten this topic (30, 39).

2.2.2. Cardiac effects of sympathetic hyperactivity

i) Adrenoreceptors: Heart failure is characterized by alterations in adrenoreceptors expression, morphology and associated signaling (15, 30). Many years ago Bristow et al. showed evidence that indicated a reduced density of beta-1 adrenoreceptors in failing human hearts (40) and few years later, Engelhardt et al imlied the same by discovering reduced beta-1 receptors' mRNA in histological study of cardiac tissue from patients with heart failure (41). On the contrary, beta-2 adrenoreceptors are upregulated as demonstrated in another experimental study by Bristow et al. with a reversal in the beta-1/beta-2 receptor ratio in heart (42). Moreover, derarangements in beta AR G-protein signalling have been presented in heart failure (15, 30). In accordance with beta-2, beta-3 adrenoceptors present increased density in failing myocardium with controversial studies about the nature of the effect of their stimulation on the heart contractility (43-45).

ii) Cateholamine myocardial toxicity: Heart failure is accompanied by elevated cateholamine levels in blood stream and increased noradrenaline spillover in the synaptic cleft (15). Cateholamines have pleiotropic deleterious effects on myocardial cells and myocardial structure. These include calcium overload, direct damage through toxic metabolites and reactive oxygen species, cytoskeleton alterations including fibrosis and

dilation. Cateholamines also promote cardiomyocytes' apoptosis through various pathways as cAMP elevation, beta-1 adrenoreceptors overstimulation, TNF and caspases route(15).

2.2.3 Parasympathetic nervous system and heart failure.

A considerable amount of literature endorses the parasympathetic attenuation in patients with systolic HF, although robust evidence is still lacking. First implications of impaired PNS drive in heart disease came over fourty years ago by Eckberg et al. who showed impaired baroreflex in patients with heart disease attributed mainly to parasympathetic lowerd activity (26). Attempting to delineate which level of parasympathetic route is responsible for this alteration Dunlap et al. gave implications of an intact parasympathetic postganglionic pathway and increased muskarinic receptor density on dogs with induced HF (46). Similar results came from the experiment of Bibevski et al. supporting the idea that parasympathetic impairment is localized on the preganglionic part or the ganglia(47). In addition, parasympathetic undrerreactivity has been obvious in the results of another study from Dunlap, who discovered attenuated cardiopulmonary baroreceptor reflexes in HF dogs and suggested the involment of vagus afferent fibers in this process (48).

Various mediators of altered parasympathetic activity in heart failure have been derscribed. Nitric oxide seems to take part in parasympathetic tone in heart failure as increased levels of neural and inducible NO synthase have been discussed (32). The inflammation pathways also seem to be associated involving interleukin-1β, interleukin-6, tumor necrosis factor-α, lipopolysachaccharides and others. Finally, several individual molecules have been mentioned as potential modulators of parasympathetic activity including bradykinin, histamine, free radicals, cyclooxygenase and others.

3. Methods-materials

A systematic search in the scientific database “PUBMED” was conducted for publications addresing the role of vagal stimulation in heart failure and current knowledge on this field. The following search terms were used: “vagal stimulation” OR “autonomic nervous system regulation” AND “heart failure”. Each individual publication was screened in an abstract-based manner for potential relevance with the aforementioned topic and non-relevant publications were automatically excluded. Full-text examination was performed in articles and clinical trials with relevant content. In addition, referrences from publications emerged from the basic searched were also screened as a potential pool of related information. EndNote X6 was used as a citation manager.

4. Results

The initial search revealed 1,079 publications and 945 were adjudicated as irrelevant in the screening process. The reuslts of the primary evaluation of remaining articles are depicted in the flow diagram (**Figure 7**).

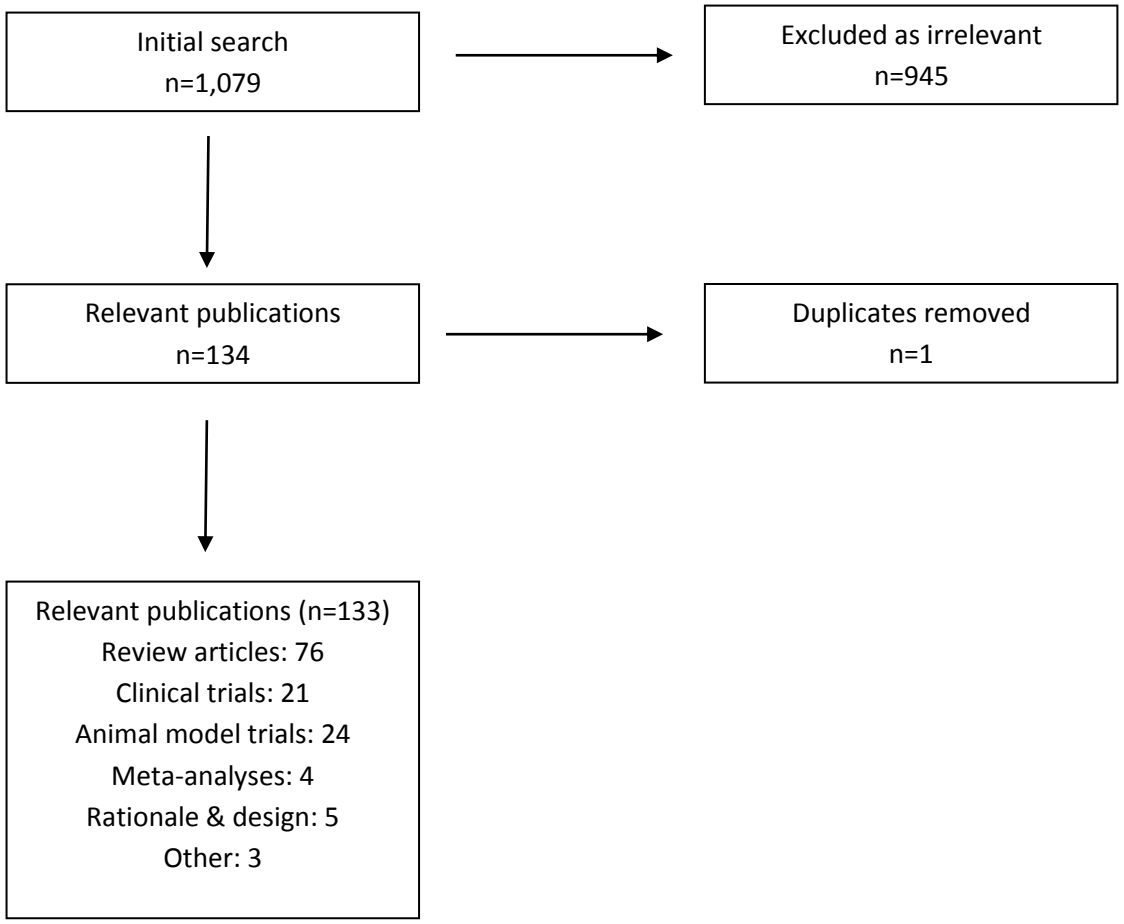

Figure 7: Flow diagram of systematic search and publication evaluation for relevance with the review topic.

5. Vagus Nerve Stimulation in Heart Failure

5.1. Experimental evidence

The notion that parasympathetic nervous system through vagus nerve stimulation (VNS) might be a potential target of therapeutic maneuvres in heart disease, has been proposed decades ago and a considerable amount of studies, mostly experimental, have been conducted in this context (14). A wide variety of underlying mechanisms and pathophysiologic pathways have been associated. The most investigated are discussed below:

i) Autonomic balance-Sympathetic nervous system supression: As described above, autonomic imbalance with SNS prevailing over parasympathetic, substantially participates in the pathogenesis and progression of heart failure. When applied to sample of rats with congestive heart failure, vagal stimulation achieved to reduced mean heart rate compared to control group (sham-stimulation) (49). In an experimental study by Zhang et al (50) 15 dogs with induced heart failure by ventricular pacing in high rates, were divided in either to receive VNS or not. Among other parameters heart rate variability on month 4 and 8 was estimated. The results presented increased HRV in the intervention group, indicating an enhanced autonomic balance. In addition, baroreceptor reflex sensitivity was tested, by the administration of phenylephrine. VNS was associated with a higher degree of baroreflex sensitivity in both time points (4 and 8 weeks, **Figure 8**). Circulating norepinephrine levels were measured in all three time points and VNS was related to significant decreases in the cateholamine levels. Similar results were also shown by Li et al showing a significant decrease in plasma norepinephrine levels after 6 weeks of mechanical vagal stimulation in rats with LV systolic dysfunction compared to control heart failure rats (49).

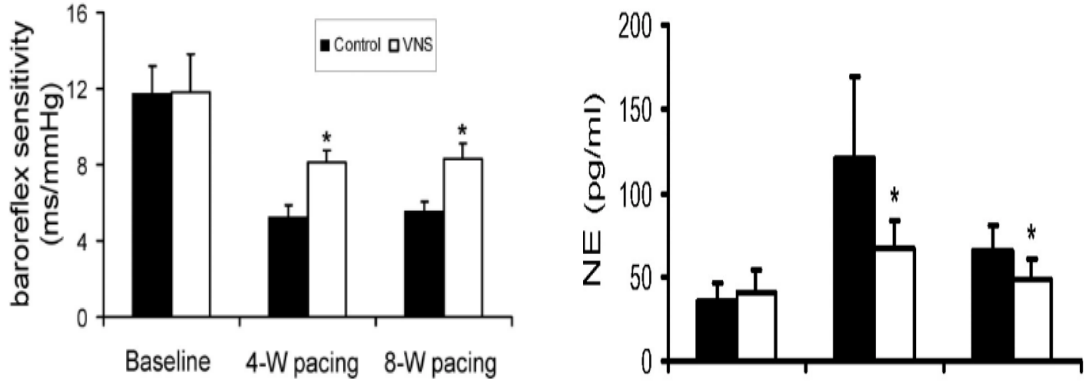

Figure 8. Baroreflex sensitivity and norepinephrine levels in high-rate ventricular paced canine models with VNS vs control.
(Zhang et al. *Circ Heart Fail* 2009 Nov;2(6):692-9).

ii) Left ventricular remodeling/Left ventricular function: In the experimental study mentioned above by Li et al (49), VNS was associated with beneficial effects in left ventricular diastolic function as end-diastoling pressure was lower in the VNS receiving rats compared to the sham-stimulation rats. Accordingly, LV dp/dtmax was increased, indicating improved diastolic function. Furthermore, in the study of Zhang et al. VNS enhanced LV contractility as LVEF was higher after 4 and 8 weeks of the therapeutic maneuvre with a concurrent reduction in LVESV and LVEDV, indicative of reverse myocardial remodeling (50). One pathophysiological pathway related to these alterations is interfering in the matrix metalloproteinases (MMP) and their inhibitory enzymes' production, namely the tissue inhibitors of metalloproteinases (TIMPs). Webb et al. revealed an increase in MPP-9 and MMP-8 after myocardial infarction (MI) in humans, also suggesting temporal patterns in these enzymes' rise and falls (51). In specific, MMP-9 showed an early increase post MI and preserved high levels over the first month, whilst MMP-8 consistelnty rose early and returned to normal range within the 5th day. On the contrary, TIMP-4, the inhibitor with specificity for cardiac tissue was constanty reduced over the follow-uo period. The fact that LVEDV was elevated in the MI patient group compared to control groups argues an association between the MMP/TIMPs status and myocardial remodeling. On that basis, Uemura et al. investigated the effects of VNS in the levels of MMP and TIMPs in rabbits which previously had undergone an iatrogenic myocardial infarction (52). Interestingly, MMP-9 was underproduced in the VNS rabbits compared to control and TIMP-1 was significanly overexpressed in the intervention group.

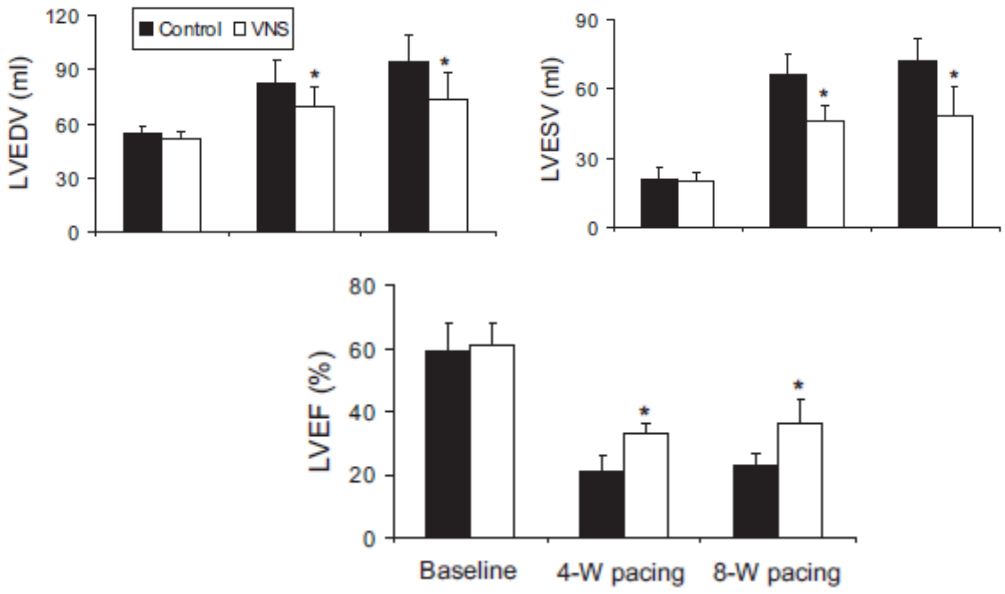

Figure 9. Left ventricular end-systolic/end-diastolic volume and LVEF in rats 4-week and 8-week VNS versus control.
(Zhang et al. *Circ Heart Fail* 2009 Nov;2(6):692-9).

iii) Oxidative stress protection: Tsutsumi et al. implemented in vivo and in vitro techniques demonstrating that VNS can ameliorate redox status, and reduce free oxygen

radicals in cadiomyocyte cultures (53). These results raise implications for a possible an extra beneficial effect of VNS in heart failure through via this pathway.

iv) Antiarrhytmic effects. Antiarrhythmic effects of vagal stimulation were initially proposed by Kent et al. who showed that amplified vagal effect significanlty decreased predisposition to ventricular fibrillation in dog heart, while in ischemic condition (54). Similar results presented by Myers et al. showing an association of vagal stimulation-induced bradycardia, with delays in the occurrence of ventricular fibrillation (VF). Additionally, an association with VNS intensity, VF prevention and short-term survival was shown (55) (**Figure 10**).

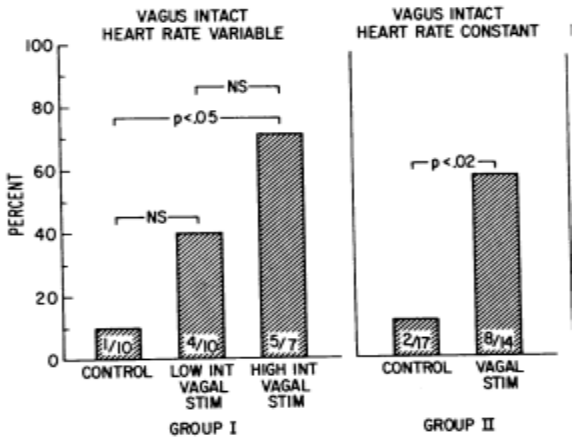

Figure 10. Antiarrhythmic effects of vagal stimulation.
Adapted drom Myers et. al. Circulation. 1974;49:943–947

Another study by Yoon et al. failed to confirm the preventive role of vagal stimulation in lethal arrhytmias in hypoperfused canine myocardium (56). Interstingly, this association was apparent when the hypothesis was tested under normal conditions. Years later, the same was tested in non anesthitized animal models, and particularly dogs which had undergone an myocardial infarction befory thirty days. After a second occlussion of the circumflex artery, the presence of a VNS device was associated with significant reduction in the probability of VF occurrence (57). Finally, the antiarrhytihmic properties of vagus activity were evident in the study of Prystowsky et al, in which pharacological vagal stimulation with atropine, along with propranolol administration, significantly reduced the duration of both effective and functional refractory period of ventricular myocardial cells (58). The same mechanism is considered to be involved in nitric oxide mediated benefit of vagal stimulation to prevent ventricular arrhythmia (59).

v) NO-related Vasodilation: Extended literature points to a mitigating role of brain and peripheral nitric oxide (NO) in excessive sympathetic outflow (60). Vagal stimulation has been associated with elevated neural NO synthase exrpression (61). Experimental evidence

from prior decades as well as more recent imlied that vagus nerve stimulation conveys vasodilatory effects, carried by NO, which also apply to coronary vessels (62, 63).

vi) Systemic inflammation: Tumor necrosis factor (TNF) is considered to play an important role in the pathogenesis and progression of heart failure. Still, existing evidence suggsest a biphasic behaviour with regard to the binding receptor. Activation of TNFR-1 mediates myocardial cell death, and consequently heart failure and opposingly TNFR-2 has been suggested by Higuchi et al as a factor that alleviates myocardial damage under hypoperfusion conditions (64). VNS was found to be a potential modifier of this pathway as both in vivo and in vitro experiments in mice was associated with promotion of TNFR-2 expression and suppression of TNFR-1 (65). Serum C reactive protein (CRP) levels were also shown to be significantly reduced after VNS in dogs, the study of Zhang et al (50).

5.2. Devices, impantation technique and stimulation principles

The general concept of cervical vagus nerve stimulation devices consists of a pulse generator and a lead cuff which is attached to cervical vagus. Differences among devices exist as, for instance, the CardioFit® device also includes a sense electrode, driven inside the right ventricle (R-wave synchronous stimulation, see below) (66).

The procedure of implantation typically requires to be familiar with neck anatomy and vascular structures. After a small incision in the neck the cervical part of the vagus is unvealed, with extremely cautious manouevre to protect the carotid artery. Then the lead cuff is put arround the nerve from its posterior side to avoid excessive dislocation of the nerve fibers and potential complications. Furthermore, the lead should be attcached in not tight and simultaneously not loose manner to prevent neural damage or poor function of the stimulator. Finally, the lead is anchored with sutures with preferance to local fascia which prevents from excessive mobility of the lead-nerve unity. Most frequently the operation is performed by vascular surgeons, neurosurgeons, head and neck surgeons or cardiothoracic surgeons.

With regard to the philosophy and the mechanisms of electrical vagal stimulation, one categorization is to open-loop and close-loop stimuation (14). In the first case the generator behaves as an autonomous unit, irrespectively of the stimulation effects, while in a close-loop system the stimulation is temporarily and quantitatively adjusted to a prespecified marker, most commonly the electrocardiogram. Another distinction is between continuous-cycled and synchronous stimulation. The fisrt model is comprised of stimulation “ON” and “OFF” periods of standarized duration, with longer duration for the latter, while in the second electrical pulses are syncronized to the R wave or respiration. Finally, current related parameters are the amplitude (mA, frequency (Hz) and pulse width (μsec).

5.3. Clinical trials

The first attempt to evaluate the possible beneficial effects of vagal stimulation in the clinical setting was held more that 15 years ago. **Scwartz et al.** assessed whether CVS with the implantation of the CardioFit® device could alter the clinical condition and symptomatically improve patients with HFrEF with a satisfactory safety profile (67). Eight patients with an LVEF≤35% were included and underwent a heart rate-synchronized vagal stimulation with gradual up-titration as per study protocol. After 6 months of follow-up notable alterations were observed with transition from NYHA III to NYHA II in most of the patients, quality of live (qoL) improvement according to the Minnesota Living with Heart Failure® questionnarie (MLHFQ), slight increase in 6-minute walk test distance and significant reduction in left ventricular end-systolic and end-diastolic volume. These results were reproduced when this concept was extended in a second patient group (24 patients) with an additional significant increase in LVEF at 12-month follow-up (68). Small number of serious adverse events occurred with the majority of them considered irrelevant with the device implantation.
Evidence from larger and controlled trials fisrt came up in 2014 with the completion of the **NECTAR-HF** trial (69). INOVATE-HF (70) followed and was the fisrt trial to include "hard" clinical endpoints. It has to be underlined that almost all trials were conducted on HFrEF population with the exceptipn of ANTHEM-HFpEF trial. The ANTHEM-HFrEF (71) is an ongoing, controlled with larger population magnitude trial, which will reasssess the effects of chronic VNS in heart failure patients, including major efficacy clinical outcomes. Studies' characteristics and results are separately summarized below:

i) NECTAR-HF (72): Eighty-seven patients with HFrEF and dilated left ventricle (≥55mm), according to the study's protocol, were implanted with the "Precision" device from Boston Scientific, which was subsequently activated or not (treatment/placebo arm) in a 2:1 ratio. Efficacy endpoints included possible alteration in LVESD/LVESV, LVEDD, LVEF, as well as patients' functionality assessed with MLHFQ and SF-36 questionairre, NT-proBNP and peak VO_2. Safety was assessed by the occurrence of adverse events. Analyses showed non-significant changes in LV remodeling indices, whilst with a statistically significant number of NYHA class improvement and MLHFQ reduction. The proportion of AEs including death, hospitalization and non-cardiovascular ones was higher in the control arm with a slightly higher percentage of device related complications in the therapy group.

ii) **INOVATE-HF (70):** In this large, open-label RCT, with the participation of many different centers, 707 patients with HFrEF were allocated (in a 3:2 alllocation ratio) to receive the CardioFit® VNS system or to control group. A progressive increase in the stimulation amplitude was performed and participants were followed at 3, 6 and 12 months. For the fisrt time mortality and morbidity endpoints were assessed as the primary efficacy endpoint included death and hospitaization attributed to heart failure deterioration.

Secondarily, functionality endpoints were also assessed as long as left venstricular end systolic volume index (LVESVi) as a marker of myocardial histological alteration. Notably, VNS failed to reduced mortality rates or to induce myocardial remodeling reversal since LVESVi were similar between study groups. However, in the intervention group significant increase in the 6-min walk distance were observed along with NYHA class and self estimated qol improvement. With regard to safety the composite endpoint of all-casuse death and complications was assessed, with similar rates between patient groups.

iii) **ANTHEM-HF (73)**: In this trial, conducted in India, 60 patients with symptomatic heart failure (NYHA Class II-III) with reduced ejection fraction (EF≤40%) were implanted with the Cyberonics VNS device (Demi-pulse Model 103 pulse generator-PerenniaFLEX 304 lead), on top of best tolerated medical treatment. Half of the participants had the device set on the right vagus while the left vagus was stimulated on the rest. Titration of the output amplitude was performed periodically during the 6-month follow up. Safety was evaluated by the occurrence of implantation-related adverse events. Efficacy parameters included possible alterations in left ventricle size and systolic performance as well as patients' symptomatology. Several adverse events occurred during the follow up period, the majority of which were non-clinically significant and short-lasting. One case of ischemic stroke, attributed to the implantation precedure was occurred, in a patients subsequently diagnosed with ipsilateral critical carotid atherosclerotis. Two deaths during within the follow-up period were primarly adjudicated due to worsening of heart failure. With regard to efficacy outcomes, no differences between right and left vagus stimulation were observed. In the pooled patient population an improvement in LVEF approaching 5%, along with a reduction in LVESD was noticed. Difference in LVESV were no significant. Mean heart rate, was reduced and heart rate variability increased. Functionallity parameters were augmented, i.e NYHA class, 6MWD and MLHFQ. Finally, slight but significant reductions in hs-CRP were apparent.

iv) ANTHEM-HFpEF (74): This is the unique trial to date that addressed the hypothesis of possible favourable outcomes with vagal stimulation in HFpEF and HFmrEF. Fifty-two patients with LVEF≥40% (HFpEF: 77%) were implanted with the LivaNova vagus nerve stimulation device (Demipulse® Model 103 pulse generator and PerenniaFLEX® Model 304 lead, LivaNova, Houston, TX, USA). There was not control group or sham-implantation group. Right side was chosen in all patients according to the study's protocol and VNS was titraded during study to achive a top amplitude of 2.0 ± 0.5mA and frequency of 5Hz. Similarly with previous trials in HFrEF, safety was assessed by serious adverse events associated with the procedure. Two operation-related SAEs were noted, both non-fatal, including an infection at the site of the device and an episode of low heart rate with temporary clinical deteriotation. Efficacy evaluation included LV structrural and performance parameters, symptomatic and functional status while special focus was given to arrhythmic events and arrhytmic predisposition. Pre-arrhytmic parameters assessed included T-wave alternans (TWA), T-wave heterogeneity (TWH) and electrocardiogram presence of non-sustained ventricular tachycardia (NSVT) with more than four QRS complexes.

With the completion of the 1-year follow-up period no differences were noticed in LVEF, filling pressures (estimated by E/e' ratio) and LVESD, LVESVi, LV mass index. More than half of the patients presented an improvement in NYHA class, mean distance at 6MWT was slightly, yet significantly increased. Quality of life was also improved based on MLHFQ. Baseline mean TWA and TWH indicated excessive pre-arrhythmic risk and chrinic vagal stimulation considerable reduced these markers (**Figure 11**). Hs-CRP and NT-proBNP levels were not significantly affected by therapy intervention.

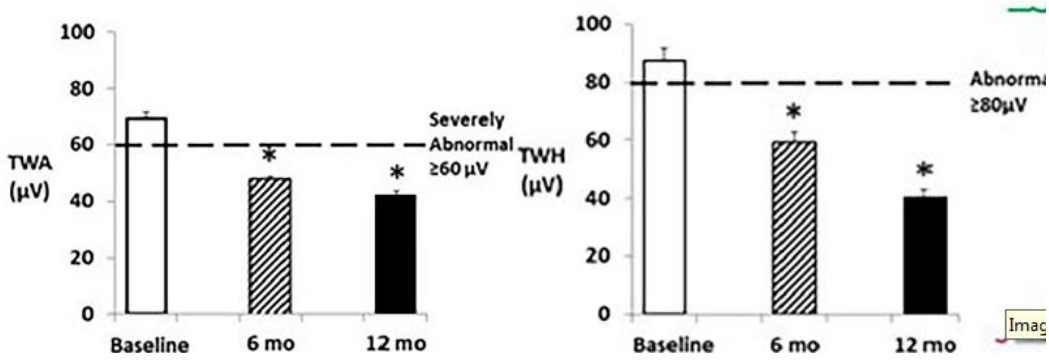

Figure 11. Baseline and 6- and 12-month values of TWA and TWH in ANTHEM-HFpEF. Adapted from Kumar et al. *International Journal of Cardiology* 381 (2023) 37–44

v) **ANTHEM-HFrEF** (71): This is an ongoing, international, open-label, randomized controlled trial, anticipating to enroll hundreds of patients with HFrEF. Participants are randomized, in a 2:1 ratio, to be implanted with the VITARIA® vagal stimulation system, designed by LivaNova, TX, Houston, US or to control group. As in ANTHEM-HF study, right cervical vagus stimulation was selected. Prerequisites for the trial are the presence of NYHA class III heart failure, or NYHA class II with heart failure decompenasation requiring hospital care within the previous year, a LVEF≤35%, under maximal torelated guideline-directed medical therapy (GDMT) for at least one month. In addition, elevated natriuretic peptides are demanded (i.e. NT-proBNP≥800pg/ml) and the capability to fulfill a 6MWD of 150-450 meters. Patients with diabetes mellitus with HbA1c ≥8%, permanent atrial fibrillation, of ablation therapy with the past 90 days, CRT/CRT-D carriers for the past 6 months and device-based ART patients were not candidates for the trial according to protocol. For the first time in clinical trials with VNS in humans "hard" endopoints were assessed since the composite major efficacy outcome included cardiovascular death or hospitalization for heart failure. Safety was mainly evaluated based on the rates of patients without implantation-related asverse events within the first 3 months. Independent committees, blinded to the treatment allocation are to adjudicate outcome events. Secondary outcomes include all-cause mortality, rates of mean changes in LVEF, 6MWD, LVEDD, LVESD, LVESVi, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, percentage of patients with NYHA class improvement and rates of hospitalization-free days from baseline. First data are awaited to emerge from an interim analysis when 400 subjects are enrolled.

	CardioFit, *Biocontrol, 2011*	**ANTHEM-HF** *Cyberonics, 2014*	**NECTAR-HF** *Boston Scientific, 2014*	**INOVATE-HF** *Biocontrol-MDT, 2016*	**ANTHEM-HFpEF** *LivaNova, 2023*	**ANTHEM-HFrEF** *LivaNova-VITARIA, ongoing*
Baseline characteristics						
Patient Population	NYHA Class III EF ≤ 35%	NYHA Class II-III EF ≤ 40%	NYHA Class II-III EF ≤ 35%	NYHA Class III EF ≤ 40%	NYHA Class III EF >40%	NYHA Class III EF ≤ 35%
Randomized/Controlled	-/-	-/-	-/+	+/+	-/-	+/+
Population number (male, %)	32 (94)	60 (87)	95 (86)	707 (79)	52 (31)	Recruiting (over 400)
Mean LVEF ±SD(%)	23±8	32±7	30±6	25±7	60.4±12.5	NA
Ischemic heart failure (HF) (%)	62	75	67	60	14*	NA
Stimulation side	Right	Right vs left	Right	Right	Right	Right
ICD/CRT/None (%)	59/0/41	0/0/100	76/10/14	48/34/28	0/NA/NA	NA
Stimulation parameters						
Pulse Width	1000 μsec nonprogrammable	250 μsec programmable	300 μsec nonprogrammable	1000 μsec nonprogrammable	250 μsec programmable	250 μsec programmable
Stimulation Frequency	1-3 Hz R-wave linked, nonprogrammable	10 Hz Open-loop, programmable	20 Hz Open- loop, nonprogrammable	<1 Hz R-wave linked, nonprogrammable	5 Hz Open-loop, Programmable	5-10Hz Open-loop, Programmable
Stimulation Amplitude	**4.1 ± 1.2 mA**	**2.0 ± 0.6 mA**	1.2 ± 0.7 mA	3.9 ± 1.0 mA	2.4 ± 0.5 mA	2.5- 3.0 mA
Stimulation Time	10 s on 15 s off Cycled	14 s on, 66 s off Continuous	10 s on 50 sec off Continuous	5 s on 7 s off Cycled	14 s on, 66 s off Cycled	14 s on, 66 s off Cycled
Results						
Primary results	**Safe** Improvement in cardiac function and HF symptoms	**Safe** Improvement in cardiac function and HF symptoms	**Safe** No change in cardiac function (dosing issue)	**Safe** Stopped for futility (pt selection, study design, & dosing issues)	**Safe** No changes in cardiac remodeling and function parameters Improved symptoms and qoL. Implications for	NA

					antiarrhythmic properties	
Results						
	CardioFit, *Biocontrol, 2011*	**ANTHEM-HF** *Cyberonics, 2014*	**NECTAR-HF** *Boston Scientific, 2014*	**INOVATE-HF** *Biocontrol-MDT, 2016*	**ANTHEM-HFpEF** *LivaNova, 2023*	**ANTHEM-HFrEF** *LivaNova-VITARIA, ongoing*
Therapy-related SAEs	7 (22%)	1 (2%)	13 (14%)	46 (9.4%)	2 (8.6%)	NA

*Refers to history of coronary artery disease.

Table 1. Baseline characteristics and primary results of clinical trials with cervical vagus nerve stimulation therapy in heart failure paitients.

6. Discussion - Conclusions

In this narattive review current knowledge regarding the role of autonomic nervous system in heart physiology and heart failure pathophysiology are discussed and a detailed description of experimental and clinical data of the cervical vagal stimulation in heart failure is made. The cardiac ANS presents an extreme anatomical and physiological complexity which facilitates its regulative role and hemodynamic balance (15, 16, 27, 30). The fundamental role of ANS in heart failure is also documented by the fact that fisrt-line medical agents in heart failure treatment, such as beta-blockers, target the sympathetic activity and improve survival. Accumulating data over the past decade proposed parasympathetic activity as an alternative or complementary therapy target in heart failure and vagal stimulation is an upcomming and promising choice to cover this unmet need (14, 27, 75).

Following a large amount of experimental studies clinical trials assessed the effects of cervical vagal stimulation in heart failure patients, with interesting and variant results. In summary, vagal stimulation was associated with improvement in symptoms, quality of life and functionallity. However, considerable discrepancies were observed between trials in the effect on cardiac remodeling and perfomance markers as well as ANS activity markers which were primarily attributed to methodological differencies by authors. In particular, stimulation intensity is considered to be substantially involved. In the NECTAR-AF study a high frequency (20Hz) stimulation protocol was chosen, which according to the investigators' judgement, restrained the up-titraition of stimulation amplitude by provoking irritating symptoms (76, 77). This might explain the lack of improvement in structural and functional markers. Conversely, in the INOVATE-HF trial, a low-frequency protocol was associated with no modifications in LVESVi as a representative marker or, especially, the primary efficacy endpoint of survival and HF hospitalization. A lower magnitude stimaulation delivery due to low frequencies was presumed to have causality with the trial's results (70, 76, 77). Still, in the CardioFit phase II trial similar stimulation parameters were associated with improved LVEF in the end of follow-up. As in both trials the same VNS device was implanted, with a closed-loop delivery system (R-wave linked stimulation, intracardiac lead implantated) this disagreement may be attributed to the population number gap or other reasons. In the pilot ANTHEM-HF trial a moderate stimulation frequency, similar to indigenous parasympathetic freequency (78) allowed the accomplishment of a greater current amplitude and conferred both symptomatic benefits and LVEF, LVESD and HRV improvement (73). These results speculate that stimulation freequency plays a decicive role in VNS efficacy. Moreover, HRV was increase increased in ANTHEM-HF in contrast to the rest studies raising thoughts that HRV as a marker of sympathetic suppression could be considered a prognostic marker of LV response to VNS. Still, all the above remain hypotheses as extraction of safe results is limited by the methodological heterogeneity among studies. Finally, the consistency in symptomatic aleviation in all VNS is encouraging but is also limited by the non controlled or non blinded manner of trials' conduction.

With regard to the safety of cervical VNS, device or procedure related adverse event were not substantially high in the aforementioned trials with comparable rates to other ART methods as baroreflex activation therapy (79) as well as with cardiac resynchronization therapy (CRT) device implantation (80). Furthermore, in the extended follow-up results from the ANTHEM-HF and NECTAR-HF trial, VNS was not related with different rates of adverse events (81, 82). Notably, the safety of VNS is also strenghtened as it is including in the therapeutic arsenal of depression and epilepsy (83, 84). Concerning potential VNS related arrhytmiogenesis, available evidence from clinical trials by participants' ICD shocks, show no clear association of VNS with ventricular tachyarrhytmias (68, 72). In line, current knowledge about VNS and atrial tachyarrhytmias does not pose a causal association (85). It has to be pointed out, nonetheless that data about possible atrial fibrillation induction related to VNS are absent in available trials.

The ANTHEM-HFpEF trial results emphasize in an antiarrhythmic benefit of VNS in patients with HFpEF which is of large importance since as summarized by Triposkiadis et al, elevated sudden cardiac death rates extend across the whole ejection fraction spectrum (86). Despite this and the consistency in improving quality of life and symptoms, VNS was not associated with structural and performance changes. Of course, these facts underline the gap in knowledge about HFpEF pathophysiology with systemic inflammation also holding a significant role (87) and comprising a new therapeutic target with monoclonal antibody in the upcomming HERMES trial (NCT05636176, *ClinicalTrials.gov*). In ANTHEM-HFpEF though, inflammation markers such as hs-CRP did not alter by VNS. Finally, a new interventional ART approach with aortic vagal afferent fibers is being evaluated in the ENDO-HF trial (NCT02633644, *ClinicalTrials.gov*). Preliminary results seem encouraging (88).

In conclusion, the autonomic nervous system plays a key role in heart failure physiology, pathophysiology and progression, representing a target for established heart failure therapies and a potential target for new pharmaceutical agents such as SGLT2 inhibitors (89). Extended investigational studies showed beneficial effects of VNS in heart failure, mediated by multiple mechanisms with a quite satisfactory safety profile. Accumulating trials investigating the potential role of vagus nerve stimulation in covering the unmet need to face parasympathetic withdrawal provided promising but not quite strong results, especially in "hard" endpoints. Methodological reasons seem to be the leading cause of these discrepancies. The results of the ANTHEM-HFrEF trial are awaited to fill this gap or turn the research in other potential targets.

7. Bibliography

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ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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