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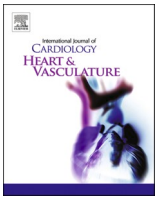

Neurocardiac Axis Physiology and Clinical Applications

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ABSTRACT

The neurocardiac axis constitutes the neuronal circuits between the arteries, heart, brain, and immune organs (including thymus, spleen, lymph nodes, and mucosal associated lymphoid tissue) that together form the cardiovascular brain circuit. This network allows the individual to maintain homeostasis in a variety of environmental situations. However, in dysfunctional states, such as exposure to environments with chronic stressors and sympathetic activation, this axis can also contribute to the development of atherosclerotic vascular disease as well as other cardiovascular pathologies and it is increasingly being recognized as an integral part of the pathogenesis of cardiovascular disease. This review article focuses on 1) the normal functioning of the neurocardiac axis; 2) pathophysiology of the neurocardiac axis; 3) clinical implications of this axis in hypertension, atherosclerotic disease, and heart failure with an update on treatments under investigation; and 4) quantification methods in research and clinical practice to measure components of the axis and future research areas.

1. Composition and normal function of the neurocardiac axis

1.1. Nerve – artery- immune interface

One of the main goals of vascular control by the nervous system is to ensure that the peripheral tissues and organs are perfused appropriately. This is achieved through an interplay between systemic vasculature and peripheral organs via both afferent and efferent nerve pathways that sense signals from the environment to allow the body to quickly adapt to changing environmental conditions. [1] The autonomic nervous system (ANS) comprises the sympathetic (Fig. 1, Fig. 2) and parasympathetic nervous systems (Fig. 3, Fig. 4). [2] The ANS communicates with arteries via preganglionic nerves initiating in the central nervous system (CNS) brainstem or spinal cord and proceed to synapse on autonomic ganglia in the periphery. [2] These post synaptic neurons innervate the lamina adventitia of arteries. [2 3] The organs and cells of the immune system also interact with the artery adventita and nerve endings, this three-part unit is also referred to as the neuroimmune cardiovascular interface (NICI). [3] The NICI primarily arises in disease states, triggered by the presence of an atherosclerotic plaque which will be discussed later.

Most of the major immune organs are innervated by the nervous system, including the thymus, bone marrow, spleen, and mucosa associated lymphoid tissue. [4] The thymus is innervated predominately sympathetically, receiving signals from the spinal cord, paraventricular nucleus, rostral ventrolateral medulla, and medulla oblongata in animal studies. [5] Lymph nodes have afferent innervation through the dorsal root ganglion, allowing for the collection of central information relevant to peripheral immune activities. [6] The spleen is innervated by the splenic nerve via the celiac ganglion. [7] Mucosa associated lymphoid tissue (MALT) has both sympathetic innervation as well as neurotransmitter mediated signaling with peptides such as the vasoactive intestinal peptide and substance P. [1] This allows for sensation of peripheral inflammation and mounting of an immune response. [8] Additionally, the vagus nerve is implicated in adulthood development of tertiary lymphoid organs in states of chronic inflammation colitis models. [9] Peripheral nerves and immune cells assist in guiding arterial differentiation and branching in arteriogenesis by release of signaling molecules from the nerves such as vascular endothelial growth factor A (VEGF-A). [10–12] The co-localization of nerves and arteries allows for the nerves to obtain necessary nutrients, as well as the arteries to receive sympathetic innervation. [12] The innate immune system also assists with tissue healing after damage such as after an ischemic cardiac insult, and plays a key role in cardiac remodeling. [10,13].

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1.2. Cortical and subcortical mechanisms of cardiac modulation

Many cortical and subcortical brain regions work in concert to modulate the cardiovascular system (Fig. 1). [14] Within the brain, the lamina terminalis has several sensory circumventricular organs (CVOs) whose effects on the cardiovascular system has been well documented. [15–20] These brain regions are involved in communication with peripheral tissues and in sensing and responding to volume perturbations. [15,18] The CVOs include the subfornical organ (SFO) and organum vasculosum (OVLT) and area postrema (AP). [15] One of the unique characteristics of the SFO and OVLT is that there is no blood brain barrier, allowing for communication between the periphery and the CNS. [18].

The SFO connects to the OVLT and median preoptic nucleus (MnPO) via afferent neurons. [21] The OVLT has osmoreceptors that are sensitive to blood sodium levels as well as angiotensin I and II and subsequently activate neuronal pathways that stimulate the individual to intake water and solutes to achieve homeostasis. [15,21] The OVLT also modulates volume status by neural projections to the hypothalamus that result in vasopressin and oxytocin release with subsequent downstream effects. [15] It also has sensory receptors for angiotensin and salt balance. Further, activation of OVLT neurons leads to elevated blood pressure through sympathetic activation. [16] The SFO also senses angiotensin II via angiotensin II type 1 receptor subtypes (AT1). [22] Activation of AT1 receptors is associated with increased firing and sympathetic activation, and if activated chronically, can contribute to hypertension. [23,24] AT1 receptor stimulation can also lead to increased reactive oxygen species production via increase in expression of the AT1 receptor, with subsequent activation of the sympathetic nervous system including elevated blood pressure. [22,24].

Additionally, the SFO has projections to the hypothalamus where it leads to activation of vasopressin and oxytocin secreting neurons resulting in the release of these hormones. [16,18] The MnPO on the other hand serves as a coordination center, integrating signals from the OVLT and SFO, as well as medullary afferents from the vagal nerve and carotid baroreceptor to regulate blood osmolarity through mechanisms including the thirst and vasopressin pathway. [17,25] The MnPO itself may also be directly involved in osmotic sensation and subsequent vasopressin release based on MnPO ablation experiments in animal models, which resulted in loss of the vasopressin secretion response to osmotic changes. [19] The MnPO is also involved in modulating activity of renal sympathetic afferent nerves, inhibiting sympathetic activity in hypernatremic states. [17,20] Firing rates of neurons in the MnPO are increased in hypertensive, compared to normotensive, animals. [17,26] Of note, it can be difficult to discern the roles that the various CNS nuclei play in individual physiological processes, as it is challenging experimentally to isolate nuclei and nerve projections. [17].

1.3. Neurogenic cardiac interface

The heart itself is innervated with afferent and efferent neurons, sympathetic and parasympathetic nerves, which make up the intracardiac nervous system (ICNS). [27] Afferent nerves sense information from the heart and send signals centrally where the information is processed. Subsequently the CNS incorporates this information with other central and peripheral signals to project efferent signals to cardiac myocytes and the ICNS to modulate several components of cardiac function including heart rate, inotropy, conduction, and diastolic

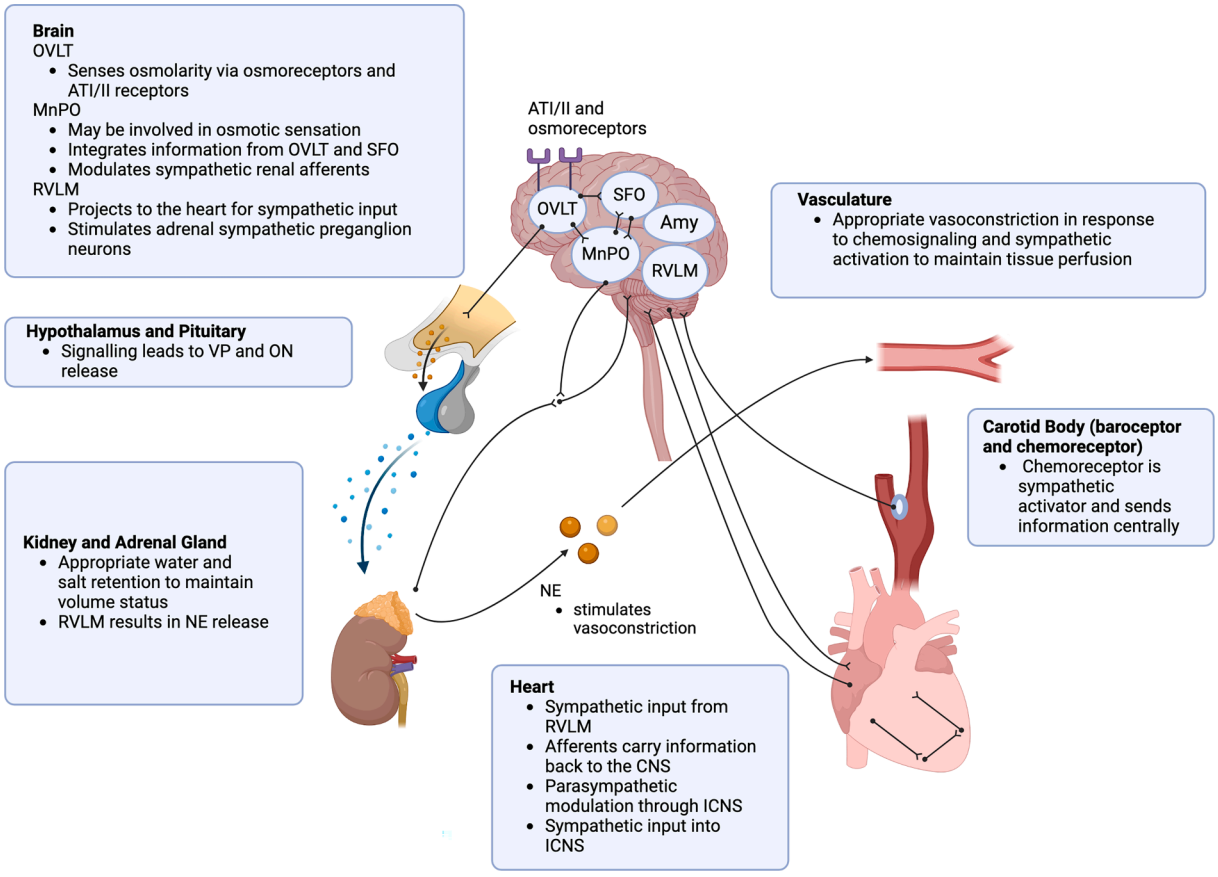

Fig. 1. Sympathetic mechanisms of the neurocardiac axis in healthy states. OVLT – organ vasculosum of lamina termainalis; SFO – subfornical organ; MnPO – median preoptic nucleus; RVLM – rostral ventrolateral medulla; NE – norepinephrine; VP – vasopressin; VIP – vasoactive intestinal peptide; ICNS – intracardiac nervous system; MALT – mucosal associated lymphoid tissue; NICI – neuro immune cardiovascular interface; ON – oxytocin; ATI – angiotensin I; ATII – angiotensin II; CNS – central nervous system; Amy – amygdala.

function in response. [28] Efferent neurons originating centrally also transmit information from the CNS to the myocardium, cardiac conduction system and pacemaker cells. [28].

The heart receives most of its sympathetic effectors projecting from the rostral ventrolateral medulla (RVLM) (Fig. 1). [29] This group of neurons is also involved in blood pressure control and also interacts with parasympathetic neural pathways through direct projections (Fig. 3). [29] Sympathetic inputs may either directly innervate the cardiac myocytes via efferent sympathetic neurons or interface with parasympathetic nerves through the ICNS. [30,31] Additionally, the RVLM, when activated, stimulates adrenal sympathetic preganglionic neurons resulting in release of norepinephrine which increases heart rate, inotropy, systemic vascular resistance, and venous return (Fig. 1). [32,33]

Parasympathetic effectors to the heart project from the rostral ventromedial medulla (RVMM), pons and hypothalamus and travel via the paravertebral ganglia. [29] Parasympathetic inputs are also initiated in the nucleus ambiguous and brainstem within the dorsal motor nucleus and travel through the vagus nerve. The vagus nerve itself has both afferent and efferent components, and while predominately parasympathetic, also carries some sympathetic fibers. [30] Activation of the vagal nerve by electrical stimulation initially results in decreased central afferent parasympathetic signaling, and at higher activation levels stimulates efferent fibers. [30] These neurons further cluster into integrated intracardiac ganglia (ICG). [31] Additionally, the cardiac ganglia have interneurons that communicate between ganglia which allows for further connectivity. [27] In disease states, cardiac interneurons overactivity may have a role in the development of atrial fibrillation. [34] Spinal cord stimulation may protect against atrial tachyarrhythmias in a canine model by changing the ICNS connectivity circuits. [35] There is significant neural reorganization in disease states, including heart failure, myocardial infarction, and hypertension (Fig. 3). [28,36,37]

The myocardium and arteries also produce neurotrophic signaling molecules that influence parasympathetic and sympathetic nervous system activation. [38–41] Additionally, neurons with cell bodies in the dorsal root ganglia of the spine and cardiac ganglia serve as information conduits from the heart by releasing signaling peptides such as substance P and calcitonin gene related peptide (CGRP). [38,39] Substance P in normal states acts as a vasodilator to assist with modulation of hemodynamic parameters. [38] CGRP is associated with angiogenesis promotion and is cardioprotective against post-myocardial infarction reperfusion injury (Fig. 3). [39]

1.4. Carotid baroreceptor

Carotid body baroreceptors and chemoreceptors are intricately involved in modulating sympathetic tone. [42] The chemoreceptors communicate with the sympathetic nervous system via direct innervation and relay responses to multiple arterial blood parameters including oxygen levels, carbon dioxide levels, and pH, and is primarily a sympathetic activator. [43] The carotid baroreceptor on the other hand primarily attenuates the sympathetic response. [44].

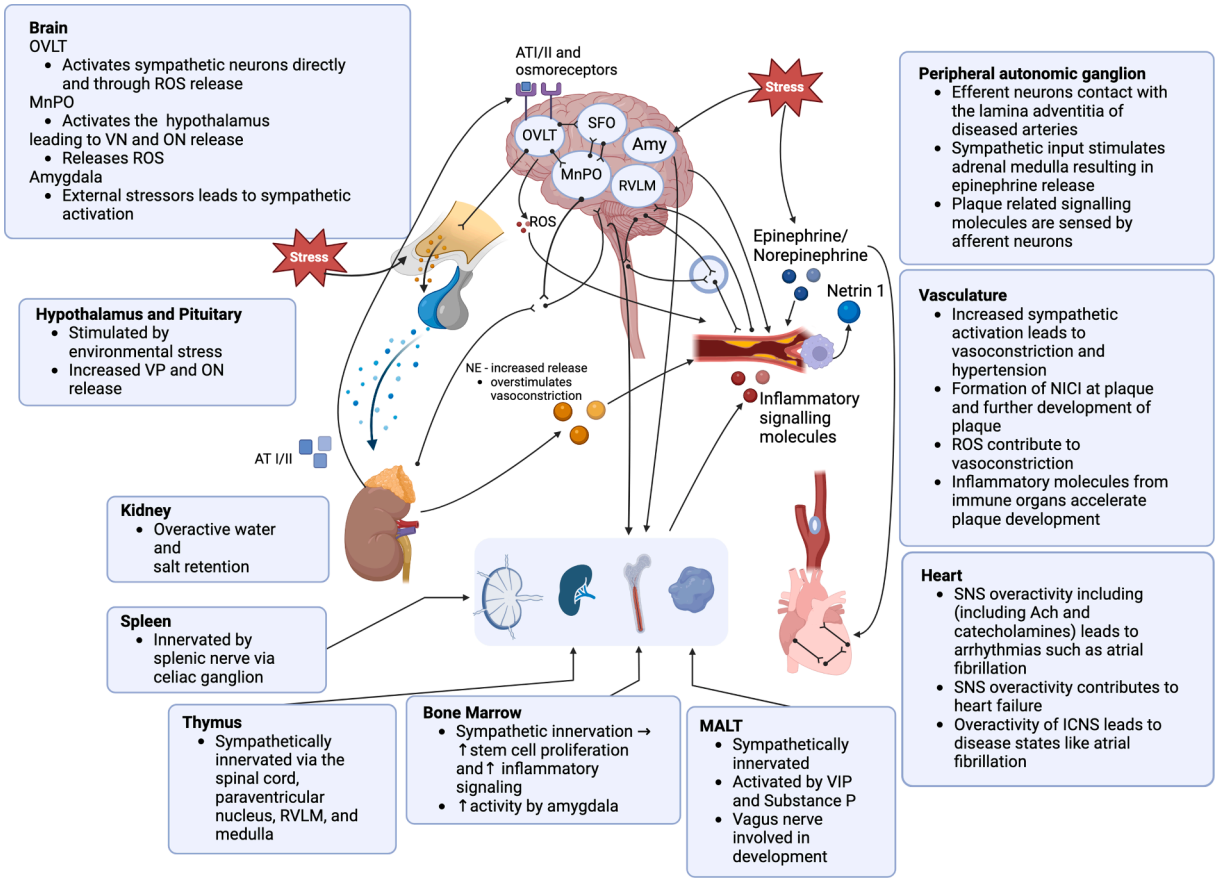

Fig. 2. Sympathetic mechanisms of the neurocardiac axis in states of disease. OVLT – organ vasculosum of lamina termainalis; SFO – subfornical organ; MnPO – median preoptic nucleus; RVLM – rostral ventrolateral medulla; NE – norepinephrine; VP – vasopressin; VIP – vasoactive intestinal peptide; ICNS – intracardiac nervous system; MALT – mucosal associated lymphoid tissue; NICI – neuro immune cardiovascular interface; ON – oxytocin; ROS – reactive oxygen species; ATI – angiotensin I; ATII – angiotensin II; Ach – acetylcholine; SNS – sympathetic nervous system; Amy – amygdala.

2. Pathophysiology

2.1. Hypertension pathophysiology

Hypertension is influenced by multiple nervous system processes. First, blood pressure is under autonomic nervous system control, which includes the sympathetic and parasympathetic systems. [45] Development of hypertension is associated with increased sympathetic tone. [46,47] Increased sympathetic tone is also responsible for a greater hypertensive response in stress states, such as during exercise or with elevated salt intake, through increased activity of the RVLM. [48,49] It is also shown in human microneurographic studies with increased intensity and frequency of sympathetic bursts in hypertensive and borderline hypertensive, compared to normotensive, patients. [50,51] Patients with white coat hypertension exhibited less significant microneurographic signal changes that were more similar to those of normotensive patients, suggesting that other mechanisms may be driving this disease process. [51].

In physiological states, the afferent arterial baroreflex activation signals to the nucleus tractus solitarii and leads to suppression of sympathetic nerve activity, which ultimately results in a decrease in heart rate through parasympathetic signaling, blood pressure through vasodilation, reduced vasopressin release and reduced renal renin release. [52–54] Conversely, the baroreceptor has efferent sympathetic nerves which result in norepinephrine release with sensation of decreased pressures, which results in appropriate compensatory vasoconstriction. [55] Arterial baroreceptors are located in the aortic arch, carotid sinuses, thoracic artery and heart. [55] In afferent baroreflex failure, such as from vagal or glossopharyngeal nerve damage or baroreceptor overstretching, individuals are prone to hypertension and tachycardia, sometimes with a component of orthostatic hypotension as well due to inability to suppress sympathetic activity. [55] In efferent sympathetic baroreflex failure, such as from diabetes or infiltrative disease, the clinical presentation is primarily orthostatic hypotension due to lack of vasoconstriction. [55] However supine hypertension can also develop due to inappropriate activation of the remaining sympathetic fibers. [52,55] with the dysregulated adaptive response. [55] The severity of the clinical presentation is dependent on whether the lesion predominately effects the preganglionic or postganglionic efferent nerve. [55] (Fig. 2).

2.2. Treatments for hypertension targeting neurologic mechanisms

2.2.1. Carotid baroreceptor modulation

Multiple neurologically mediated mechanisms are under investigation as targets to address hypertension. Individuals with resistant hypertension are defined as those with hypertension despite treatment with at least three or four antihypertensive medications, one of which is a diuretic(the exact number of antihypertensives depends on the defining group). [42,56] These individuals are thought to have a form of hypertension that is more strongly mediated by the sympathetic nervous system and adrenergic overdrive than non-resistant hypertension. [42] This has been established through comparison of sympathetic drive between normotensive, hypertensive, and resistant hypertensive patients using microneurography. [42] See Table 1 for a review of treatment modalities targeting the neurocardiac axis.

One treatment that targets the carotid baroreflex is the Rheos implantable device. [57] The Rheos device works by stimulating the carotid sinus wall through direct electrical impulses, activating the carotid baroreflex. [58] There are three main studies examining the outcomes of using this device for patients with resistant hypertension – the US Rheos Feasibility Trial (non-randomized, prospective), the DEBuT-

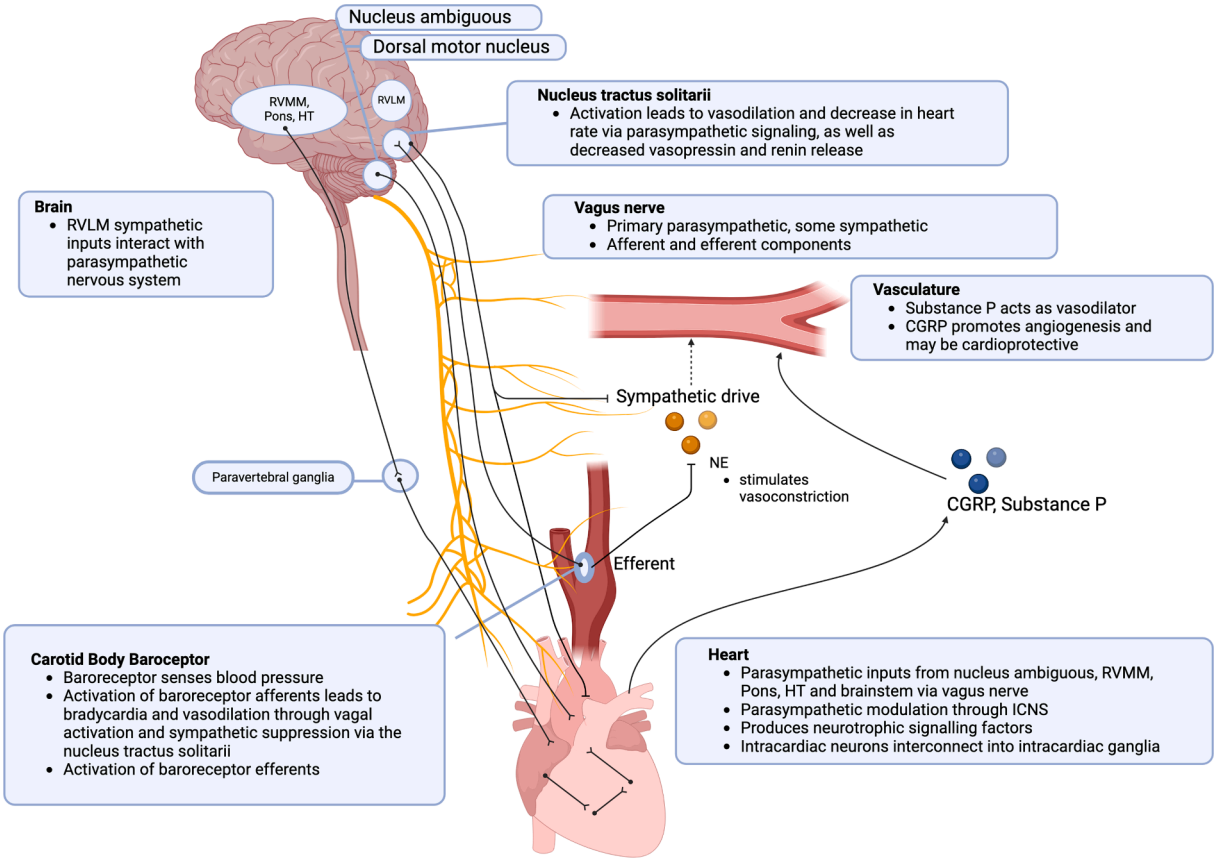

Fig. 3. C. Parasympathetic mechanisms of the neurocardiac axis in healthy states. RVMM – rostral ventromedial medulla; HT – hypothalamus; CGRP – calcitonin gene related peptide; ICNS – intracardiac nervous system.

HT Rheos Trial (non-randomized, prospective), and the Rheos Pivotal Trial (double blind with sham arm). [57,59–61] A longitudinal analysis of data collected over the six years following study enrollment from patients enrolled in at least one of these trials showed a significant decrease in systolic blood pressure (from 179 mmHg to 144 mmHg, $p < 0.0001$) and a significant decrease in diastolic blood pressure (from 103 mmHg to 85 mmHg, $p < 0.0001$). [57] At six years out, there were 136 patients still on active treatment, and 111 patients reported a total of 335 all comer serious adverse events. Of these events, only 26 were thought to be directly resultant to the device or the implantation surgery. [57] These directly attributable adverse outcomes ranged from issues with the device, such as lead or device migration, to cardiovascular problems like hypotension or hypertension to stroke. [57] Adverse effects remain a barrier to widespread use of this technology. [57].

2.3. Renal denervation

Another approach to address neurogenically mediated hypertension under investigation is renal denervation. [62,63] Several studies have investigated this treatment, with mixed results depending on the severity of hypertension and study design. [62,63] The SYMPLICITY HTN-3 study in 2014 was a randomized, single-blind trial with a sham control. [62] While the renal denervation procedure reduced blood pressure, the decrease was not significantly greater than that observed in the sham group, which also experienced a postoperative blood pressure decrease. [62] However, the following year, the SPYRAL HTN-ON MED trial, which had a similar, randomized sham-controlled design, and enrolled people with moderate hypertension on fewer blood pressure medications compared to SYMPLICITY showed a significant, moderate, blood pressure benefit favoring the renal denervation procedure. [63].

2.4. Renin angiotensin aldosterone system (RAAS) modulation

The RAAS system leads to production of Angiotensin II which stimulates AT1 receptors as described previously. [64] Dysregulation of the RAAS system results in renally mediated sympathetic overdrive which can contribute to hypertension via release of norepinephrine. [65] Overactivation of this system is also associated with atrial fibrillation and heart failure. [65,66] Medications such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) reduce hypertension by decreasing sympathetic drive as measured by muscle sympathetic nerve activity (Table 1). [67]

2.5. Sympathetic Activation, and atherosclerotic cardiovascular disease (ASCVD)

As described earlier in this review, the neurological component of ASCVD development centers on the interaction between the artery adventitia, nerves, and immune system called the NICI. [3] The NICI is essentially only present in ASCVD affected arteries, and arises in response to signaling from the peripheral nervous system in response to inflammatory changes at the site of atherosclerosis. [3,68] Once plaques form within arteries, the adventitia is invaded by inflammatory immune cells. [68] The signaling molecules produced by plaque are detected by receptors including the nociceptor transient receptor potential vanilloid 1 (TRPV1) which allows for the NICI to transmit atherosclerotic plaque inflammation centrally. [3,68] Further, the sympathetic nervous system has efferent neural projections to the plaque from the medulla and

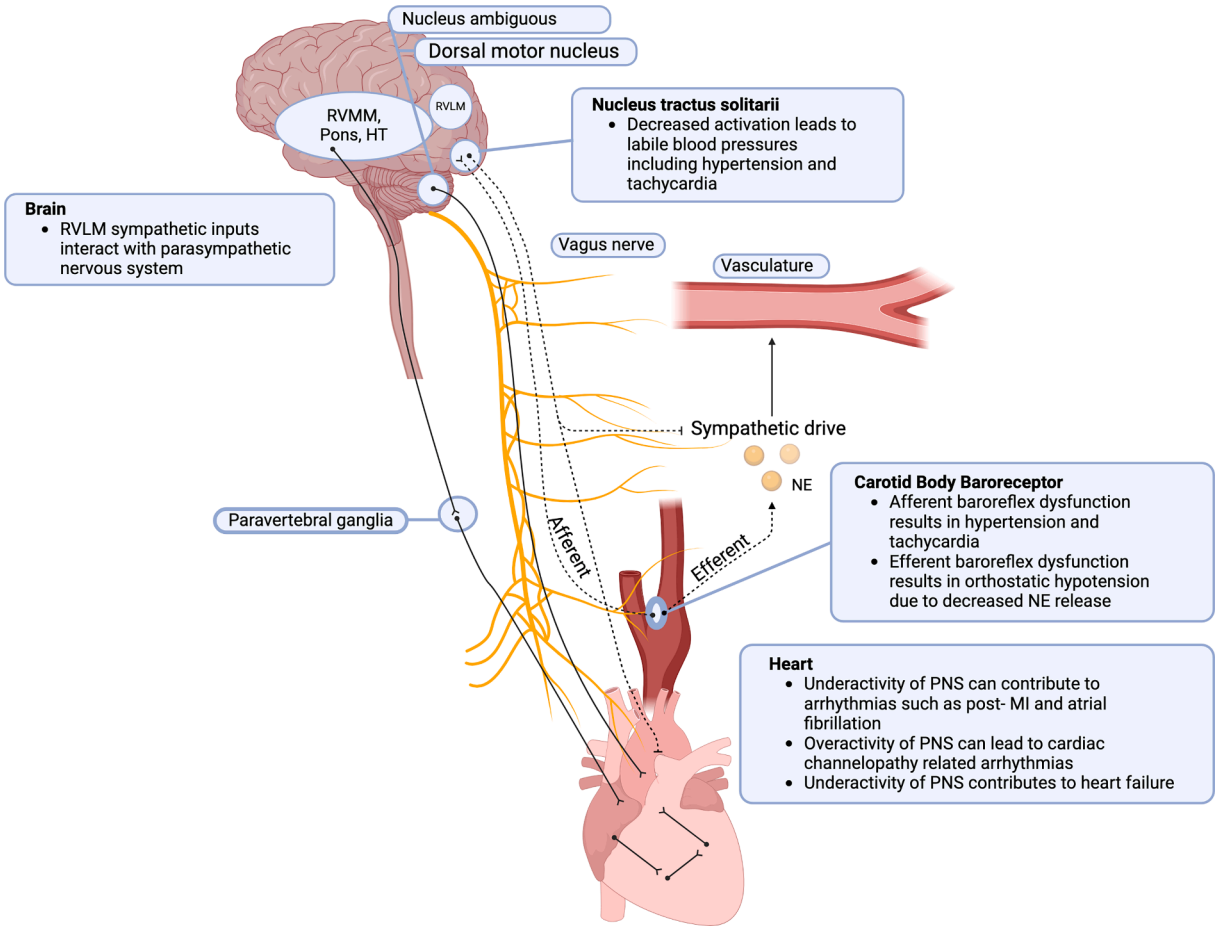

Fig. 4. D. Parasympathetic mechanisms of the neurocardiac axis in states of disease RVMM – rostral ventromedial medulla; HT – hypothalamus; CGRP – calcitonin gene related peptide; ICNS – intracardiac nervous system, MI – myocardial infarction. Created with Biorender.

Table 1
Summary of interventions targeting the neurocardiac axis discussed in this review article organized by category.

Neurocardiac Axis Targets	
Adrenergic Receptors	
Beta-1 adrenergic receptor antagonist (predominately sympathetic)	• Ulleryd MA, Bernberg E, Yang LJ, Bergström GML, Johansson ME. Metoprolol reduces proinflammatory cytokines and atherosclerosis in ApoE-/- mice. *Biomed Res Int.* 2014;2014:548783. https://doi.org/10.1155/2014/548783.Vrablik M, Corsini A, Tůmová E. Beta-blockers for atherosclerosis prevention: A missed opportunity? Curr Atheroscler Rep. 2022;24(3):161–169. https://doi.org/10.1007/s11883-022–00983-2. https://doi.org/10.1007/s11883-022–00983-2.
Beta-3 adrenergic receptor agonist (predominately sympathetic)	• O'Mara AE, Johnson JW, Linderman JD, et al. Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. *J Clin Invest.* 2020;130(5):2209–2219. https://doi.org/10.1172/JCI131126. Cypess AM, Weiner LS, Roberts-Toler C, et al. Activation of human brown adipose tissue by a β3-adrenergic receptor agonist. *Cell Metab.* 2015;21(1):33–38. https://doi.org/10.1016/j.cmet.2014.12.009.
Autonomic Nervous System Targets	
Renal denervation (predominately sympathetic)	• Nawar K, Mohammad A, Johns EJ, Abdulla MH. Renal denervation for atrial fibrillation: A comprehensive updated systematic review and *meta*-analysis. *J Hum Hypertens.* 2022;36(10):887–897. https://doi.org/10.1038/s41371-022–00658-0.https://doi.org/10.1038/s41371-022–00658-0. Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: The CABANA randomized clinical trial. *JAMA.* 2019;321(13):1275–1285. https://doi.org/10.1001/jama.2019.0692. Steinberg JS, Shabanov V, Ponomarev D, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: The ERADICATE-AF randomized clinical trial. *JAMA.* 2020;323(3):248–255. https://doi.org/10.1001/jama.2019.21187.Accessed 6/16/2024. https://doi.org/10.1001/jama.2019.21187. Mauri L, Cohen SA, Liu M, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370(15):1393–1401. https://doi.org/10.1056/NEJMoa1402670. https://doi.org/10.1056/NEJMoa1402670. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet.* 2018;391(10137):2346–2355. https://doi.org/10.1016/S0140-6736(18)30951–6.
Vagus nerve stimulation (predominately parasympathetic)	• Ardell JL, Rajendran PS, Nier HA, KenKnight BH, Andrew Armour J. Central-peripheral neural network interactions evoked by vagus nerve stimulation: Functional consequences on control of cardiac function. *American Journal of Physiology-Heart and Circulatory Physiology.*;309(10):H1740-H1752. https://doi.org/10.1152/ajpheart.00557.2015.doi: https://doi.org/10.1152/ajpheart.00557.2015.
Pulmonary vein ablation (predominately sympathetic)	• Mark DB, Anstrom KJ, Sheng S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: The CABANA randomized clinical trial. *JAMA.* 2019;321(13):1275–1285. https://doi.org/10.1001/jama.2019.0692. Nawar K, Mohammad A, Johns EJ, Abdulla MH. Renal denervation for atrial fibrillation: A comprehensive updated systematic review and *meta*-analysis. *J Hum Hypertens.* 2022;36(10):887–897. https://doi.org/10.1038/s41371-022–00658-0.https://doi.org/10.1038/s41371-022–00658-0.
Baroreceptor stimulation (predominately sympathetic)	• de Leeuw PW, Bisognano JD, Bakris GL, Nadim MK, Haller H, Kroon AA. Sustained reduction of blood pressure with baroreceptor activation therapy. *Hypertension.* 2017;69(5):836–843. https://doi.org/10.1161/HYPERTENSIONAHA.117.09086.doi: https://doi.org/10.1161/HYPERTENSIONAHA.117.09086. Ng MM, Sica DA, Frishman WH. Rheos: An implantable carotid sinus stimulation device for the nonpharmacologic treatment of resistant hypertension. *Cardiol Rev.* 2011;19(2):52–57. https://doi.org/10.1097/CRD.0b013e3181f87921. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol.* 2011;58(7):765–773. Scheffers IJ, Kroon AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: Results of a european multi-center feasibility study. *J Am Coll Cardiol.* 2010;56(15):1254–1258. Illig KA, Levy M, Sanchez L, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II rheos feasibility trial. *Journal of vascular surgery.* 2006;44(6):1213–1218. e1.
RAAS Targets Angiotensin II receptor blockade	• Iravanian S, Dudley Jr SC. The renin-angiotensin-aldosterone system (RAAS) and cardiac arrhythmias. Heart rhythm. 2008;5(6):S12-S17.Nap A, Balt JC, Mathy MJ, Van Zwieten PA. AT1-receptor blockade and sympathetic neurotransmission in cardiovascular disease. Autonomic and Autacoid Pharmacology. 2003;23(5–6):285–296. https://doi.org/10.1111/j.1474–8673.2004.00301.x. https://doi.org/10.1111/j.1474–8673.2004.00301.x.
Environmental Exposures	
Stress	• Tawakol A, Osborne MT, Wang Y, et al. Stress-associated neurobiological pathway linking socioeconomic disparities to cardiovascular disease. *J Am Coll Cardiol.* 2019;73(25):3243–3255. https://doi.org/10.1016/j.jacc.2019.04.042. Tawakol A, Ishai A, Takx RA, et al. Relation between resting amygdalar activity and cardiovascular events: A longitudinal and cohort study. *Lancet.* 2017;389(10071):834–845. https://doi.org/10.1016/S0140-6736(16)31714–7. Dai N, Tang X, Weng X, et al. Stress-related neural activity associates with coronary plaque vulnerability and subsequent cardiovascular events. *JACC: Cardiovascular Imaging.* 2023;16(11):1404–1415. https://www.sciencedirect.com/science/article/pii/S1936878X23001912. https://doi.org/10.1016/j.jcmg.2023.04.004.

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Table 1 (*continued*)

Neurocardiac Axis Targets	
	Batty GD, Russ TC, Stamatakis E, Kivimäki M. Psychological distress and risk of peripheral vascular disease, abdominal aortic aneurysm, and heart failure: Pooling of sixteen cohort studies. *Atherosclerosis*. 2014;236(2):385–388. https://doi.org/10.1016/j.atherosclerosis.2014.06.025. Nabi H, Kivimäki M, Batty GD, et al. Increased risk of coronary heart disease among individuals reporting adverse impact of stress on their health: The whitehall II prospective cohort study. *Eur Heart J*. 2013;34(34):2697–2705. https://doi.org/10.1093/eurheartj/eht216. Radfar A, Abohashem S, Osborne MT, et al. Stress-associated neurobiological activity associates with the risk for and timing of subsequent takotsubo syndrome. *Eur Heart J*. 2021;42(19):1898–1908. https://doi.org/10.1093/eurheartj/ehab029. https://doi.org/10.1093/eurheartj/ehab029.
Exercise	• Hadil Z, Osborne Michael T, Shady A, et al. Effect of stress-related neural pathways on the cardiovascular benefit of physical activity. *J Am Coll Cardiol*. 2024;83(16):1543–1553. https://doi.org/10.1016/j.jacc.2024.02.029. https://doi.org/10.1016/j.jacc.2024.02.029.

hypothalamus to transmit signals peripherally. [3] This sympathetic input results in the release of local signaling molecules such as epinephrine that contribute to further evolution of the plaque. [3] The sympathetic activation also produces changes to proliferation rates of stem cells in the bone marrow and subsequent activation of inflammatory immune cells and signaling pathways. [3].

Mouse studies have shown that there is a higher density of axons in the adventitia near atherosclerotic plaques, which is also seen in post mortem tissue samples. [3] These axons also expressed axon associated growth and maintenance associated proteins, indicating that they were proliferating and stabilizing nerves in the area. [3] Further, this study observed increased inflammatory cells in the nerves around the plaques, indicating that the immune system is also communicating with the periarterial nerves in addition to the vessel itself. [3] The proposed mechanism is that inflammatory immune cells localize to the adventitia of the artery which leads to the development of tertiary lymphoid organs near the artery which further drives inflammation. [69,70] Subsequently, the pro inflammatory immune response around the plaque and nerves promotes the development of ASCVD in the intimal layer of the affected segment as well as PNS innervation of the plaque adventitia. [69] Other signaling processes lead to innervation of the adventitia of the plaque. For example, macrophages in atherosclerotic plaques express a laminin related secretion protein thought to be involved in axon guidance and arterial innervation called netrin 1. [71 72] In an experiment with netrin-1 and LDL receptor null mice, atherosclerotic plaques were smaller, indicating that netrin-1 promotes plaque development. [73] Further work needs to be done to elucidate whether this netrin mediated mechanism of arterial innervation is distinct from the NICI complex adventitial innervation described previously.

2.6. Therapeutic targets for neurological mechanisms impacting ASCVD

Research on the neurological underpinnings of ASCVD identified several potential therapeutic targets (Table 1). A cross-sectional study of participants demonstrated an inverse correlation between stress related amygdala activation and exercise. [74] Further, multivariate modelling indicates that this exercise mediated decrease in amygdala activation partially accounts for the benefit of exercise suggesting that exercise has a protective role against cardiovascular disease via a neural-related mechanism. [74] Additionally, the effect was even greater for individuals with a diagnosis of depression, implying that specific patient groups may derive an even greater benefit from such an intervention. [74].

Another approach under investigation is to impact the NICI. In one animal study, investigators performed a celiac ganglionectomy on mice which resulted in decreased size of NICI, decreased ASCVD burden, and stabilized the atherosclerotic plaques. [3] Unfortunately, there are several anticipated challenges with this therapeutic approach for human use. First, severing the celiac ganglion also denervates the splenic nerve, impairing the spleen's ability to modulate the immune system. This disruption affects immune functions involved in cardiac healing after a myocardial infarction. [75 68] This intervention also severs the innervation of the gastrointestinal tract. [68].

Additionally, some investigators have studied the role of beta blockade in preventing atherosclerotic plaque progression. In one study in mice, Beta 1 (B1) receptor blockade reduced inflammatory signaling molecules in circulation, specifically tumor necrosis factor alpha (TNFa) and chemokine CXC motif ligand 1 (CXCL). [76] The treatment also reduced the number of macrophages in atherosclerotic lesions and resulted in smaller plaque sizes compared to controls. [76] B1 blocker receptors are present in multiple locations, including the coronary arteries of the heart, the myocardium, and kidneys. [77] Nonselective beta blockers are associated with a decrease in pro-inflammatory immune cells. Unfortunately, both nonselective and selective B1 blockers are associated with reduced HDL levels and increased VLDL and TG levels, so they are not recommended for atherosclerotic disease risk reduction. [77].

Newer beta 3 (B3) agonists that are under investigation for their use in modulating atherosclerotic risk. In mouse models they were shown to have favorable effects on fat metabolism but do not impact atherosclerotic plaque size or characteristics. [78] A clinical trial studied the impact of B3 receptor agonism in humans with Mirabegron. [78] There was an increase in fat lipolysis and oxidation, including brown fat metabolism. [78,79] Unfortunately the doses studied also resulted in adverse cardiac outcomes including increased heart rate, blood pressure, and oxygen consumption which could limit therapeutic use. [78] More work needs to be done in this area to understand the intricacies of beta receptor modulation to limit atherosclerosis, while avoiding unfavorable cardiac side effects.

2.7. Neurocardiac axis and arrythmias

Most arrhythmias arise in the state of sympathetic overactivity and parasympathetic underactivity. Specifically, atrial fibrillation and post myocardial infarction associated arrhythmias have been associated with neurologic underpinnings. [80] In atrial fibrillation, both sympathetic and parasympathetic activation of intracardiac nerves near the pulmonary vein can promote paroxysmal atrial fibrillation. [81,82] Thus, pulmonary vein ablation, which targets innervation of this area is an effective treatment for atrial fibrillation, associated with higher rates of remission of atrial fibrillation and higher quality of life scores compared to medical therapy alone. [83] Additionally, renal denervation is being investigated as another way to treat atrial fibrillation in patients with atrial fibrillation and hypertension. [84] Additionally, a recent prospective analysis of 197 patients with heart failure with reduced ejection fraction (HFrEF) demonstrates an association between alterations in brain metabolic activity and risk of arrythmias using fluorodeoxyglucose F 18 positron emission testing (FDG PET) imaging. [85] Specifically, in patients with decreased intracranial metabolic activity (particularly in subcortical regions) is associated with a higher risk of subsequent arrythmias including ventricular tachycardia, implantable cardioverter – defibrillator (ICD) therapy administration and cardiac arrests.[85] This increased risk is attributed to an imbalance in sympathetic and parasympathetic systems and prolongation of the QTc interval. [85].

The ERADICATE-AF trial studied patients who had both hypertension and paroxysmal atrial fibrillation and found that those randomized to the dual catheter ablation and renal denervation group had significantly lower rates of atrial fibrillation at 12 months (72.1 % free of atrial fibrillation) compared to the catheter ablation only group (56.5 % free of atrial fibrillation). [86] The goal is to decrease sympathetic drive to the heart by interrupting renal sympathetic pathways communicating with the central nervous system and the heart. [84] There is also a significantly higher risk of arrhythmias including ventricular fibrillation and tachycardia after a stroke. [87 88] The etiology of this response is also thought to be sympathetically driven. [81] On the other hand, cardiac channelopathy related arrhythmias can arise when there is parasympathetic overactivity. [80] However, in most disease states the parasympathetic nervous system is largely protective against arrhythmias. [80] (Fig. 4).

2.8. Environmental stressor activation of CNS

Environmental stressors can activate the CNS, leading to increased downstream risk of atherosclerosis. [89] There are innumerable clinical studies that show an association between stress and development of atherosclerotic disease. For example, the INTERHEART study is a cross-sectional study that included individuals from 52 countries with a history of myocardial infarction and a healthy control group with no history of coronary atherosclerotic disease. [90] It reveals that exposure to stress, as measured by a composite self-report score, independently increased the risk of a myocardial infarction. [90] An observational study of a population exposed to an earthquake showed there are higher rates of myocardial infarction after the event which could be a result of environmental sympathetic stimulation. [91] In another study, individuals exposed to higher levels of noise pollution at home have an increased risk of ischemic cardiovascular events. [92] Additionally, patient reported stress levels are correlated with increased risk of peripheral vascular disease and heart failure. [93,94].

Stress contributes to atherosclerosis through several mechanisms – activation of the hypothalamic-pituitary axis, activation of the sympathetic nervous system, and activation of the amygdala. [89,95–97] (Fig. 2) These three mechanisms lead to at times overlapping downstream effects. Activation of the HPA axis starts with an initial stressful event leads to hypothalamic activation, which then triggers release of corticotrophin-releasing hormone (CRH) and vasopressin. [96] CRH leads to adrenocorticotropic hormone (ACTH) release which stimulates release of cortisol and other glucocorticoid hormones from the adrenal cortex. [89,96,98] Chronic exposure to corticosteroids has several well studied effects on the vascular system including inhibition of angiogenesis, insulin resistance from excess cortisol exposure, and hypertension, all of which can contribute to development and progression of cardiovascular disease. [99,100] The second mechanism, activation of the sympathetic nervous system, operates predominately through activation of spinal cord sympathetic neurons which ultimately lead to sympathetic activation of the heart and adrenal medulla. [89] A surge in sympathetic signaling to the heart and vascular system leads to a multitude of effects including increased blood pressure, tachycardia, and vasoconstriction of peripheral vessels. [97] Sympathetic activation of the adrenal medulla also leads to release of norepinephrine and adrenaline which also contribute to similar effects. [101] Hypertension and peripheral vasoconstriction contribute to development of atherosclerotic disease over time, and can contribute to other cardiac morbidities like arrythmias and heart failure. [97,102,103] Third, amygdalar activation correlates with increased arterial inflammation which is likely predominately mediated through increased bone marrow as measured through image derived SUV and 18F-FDG uptake in PET-CT scans.[95] Indeed, amygdalar activity is associated with the presence of high-risk coronary plaque and future risk of cardiovascular disease end point events in longitudinal studies. [95,104] In addition to the contribution to atherosclerotic disease, higher levels of amygdalar activity are associated with elevated risk of future development of stress cardiomyopathy, also known as Takotsubo cardiomyopathy, implicating the amygdala as a central player in the disease process. [105].

On a broader level, the impact of stress on cardiovascular risk is being studied as one of the mechanisms to explain the well-established link between socioeconomic factors and cardiovascular outcomes. For example, lower income is inversely associated with amygdalar activity as measured by FDG- PET and positively associated with major adverse cardiac events. [106] As stress contributes to cardiac disease thought the three mechanisms outlined above, targeting these pathways could be a fertile ground for therapeutic intervention. Indeed, several different programs have been developed to reduce sympathetic drive through improving patient self-regulation of stress responses with mixed clinical impacts. One systematic review found that patients with a history of myocardial ischemia who participate in more intensive forms of relaxation training have decreased rates of arrythmias, cardiac related death and increased rates of being able to resume their occupations. [107] Another systematic review of patients with coronary artery demonstrated a slight reduction in cardiac related mortality in subgroup analysis, however did not show reduction in the rates of all-cause mortality, myocardial infarctions or the need for revascularization. [108] A third *meta*-analysis of stress management programs for patients after a cardiac event showed that the main groups that had decreased mortality rates after the intervention were male patients as well as when the intervention was started two months or later after the initial event. [109] While it is unclear why men benefited more than women in this analysis, it could point to the importance of tailoring programs to patient's individual needs and background. [109].

3. Quantification techniques

The complexity of circuits and interorgan communications makes the neurocardiac axis both an exciting and challenging area to study. Brain activity and stressor exposure is usually measured through FDG-PET, cardiac magnetic resonance imaging (cMRI) or patient report of stress. Amygdalar activity is often quantified through 18F-fluorodeoxyglucose positron emission tomography. [110] This technique is beneficial because it allows for a direct quantitative measurement without reporter bias. However, it is primarily used in research contexts as the clinical implications of the findings are not well defined, and the imaging itself can be time and resource intensive. Some studies have utilized patient report of stress levels; however this technique is limited by reporter bias. [95] Plaque burden in the coronary arteries is well characterized by coronary computed tomographic angiography (cCTA), a technique that is already used widely in clinical practice. Additionally, some studies utilize *peri*-coronary fat attenuation index which adds additional information about the extent of coronary artery inflammation. [111 110] Neuronal connections between cardiovascular structures and the CNS or PNS can be characterized by retrograde viral tracing experiments. [112].

Additionally, there is ongoing research on developing biomarkers to quantify individual susceptibility to cardiovascular disease and events. Brain derived neurotrophic factor (BDNF) is a protein that is synthesized in neurons and glial cells, especially astrocytes. In normal physiological states, BDNF is neuroprotective, declines over the course of life, and levels are impacted by a spectrum of insults from disease states to environmental exposures. [113].

4. Future areas of research

There are ample topics to continue work on the neurocardiac axis in the future. First, there is an opportunity to further elucidate the neurological pathways through which physical activity modulates cardiovascular outcomes. Second, more investigation into the sequence of events that lead to immune organ activation could allow for better targeting of therapeutic intervention to limit the progression of ASCVD. In regard to targeting the neurologic underpinnings of hypertension, more

work can be done on selective ablative targeting of areas of pathological innervation while retaining nerve structures that are necessary for the individual to retain normal physiologic functioning, cMRI and FDG-PET are powerful tools for understanding real time brain region involvement in neurocardiac pathways, however their use for this purpose is primarily limited to research settings. It will be interesting to study how these technologies could be incorporated into clinical practice to improve treatment decisions.

CRediT authorship contribution statement

Caroline Plott: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Tarek Harb:** Writing – review & editing, Data curation, Conceptualization. **Marios Arvanitis:** Writing – review & editing, Supervision, Conceptualization. **Gary Gerstenblith:** Writing – review & editing, Supervision, Conceptualization. **Roger Blumenthal:** Writing – review & editing, Supervision, Conceptualization. **Thorsten Leucker:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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