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Cardiovascular pathophysiology from the cardioneural perspective and its clinical applications ☆,☆☆

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ABSTRACT

Coronary heart disease and psychological stress factors such as depression are prevalent and associated with high morbidity/mortality; they are also challenging to manage, especially when treated in isolation of each other. Recent advances support an integrated approach to their management that is built on a foundation of an extensive, multi-component network of neurological structures. In this review, we describe this extensive cardioneural network that encompasses the heart, brain, spinal cord, and ganglia throughout the body, and then discuss ambulatory and laboratory-based non-invasive measures of this network that both measure psychological stress and heart disease severity. Lastly, we discuss their potential transformative clinical and public health applications, and also possible cardioneural interventions such as exercise and biofeedback.

Introduction

Coronary heart disease (CHD) is the number one killer worldwide. Although recent progress has been made at decreasing its public health burden, specific gender and race disparities are growing and suggest new approaches are needed [1]. Psychological conditions that are associated with increased CHD risk such as depression are increasing in prevalence [2], and the lack of integration of these stress factors in cardiac risk assessments may be contributing to our diminished progress in CHD prevention [3]. Previous studies have largely focused on patient-reported outcomes, which may be subject to recall bias [4]. Physiologic autonomic biomarkers may enable more rigorous and objective investigations between psychological stress and CHD and facilitate a breakthrough in CHD risk assessment and prevention. The use of such biomarkers in clinical settings may help inspire more aggressive psychological and behavioral interventions that not only reduce CHD risk but also sudden cardiac death (SCD), which may manifest as the first clinical manifestation of CHD [5].

Previous studies have shown that psychological stress can manifest in several forms and influence a large proportion of CHD events. The landmark INTERHEART study, an international multisite study of nearly 25,000 individuals with and without recent myocardial infarction (MI) [6], estimated that 33% of CHD events are attributable to exposures or mood states related to psychological stress. Examples include work stress, home stress, financial stress, exposure to traumatic life events, reduced locus of control, and depressive symptoms. Unlike other traditional risk factors like diabetes, hypertension, and hyperlipidemia, clinicians lack validated clinical decision support tools to screen for and address these stress-related risk factors for CHD. Heart-brain biomarkers may help to collectively capture the effects of heterogeneous stress-related influences on CHD susceptibility or CHD outcomes in a way that avoids stigma, and then be used in certain therapies such as neuromodulation [7].

This review describes the relationship of psychological stress with CHD and SCD with an integrated cardioneural network that includes the heart, brain, and autonomic nervous system [8]. We review the anatomy and physiology of this network as it relates to cardiovascular disease and psychological stress, as well as potential ways of measuring the bidirectional communications between the heart and brain through autonomic and cardiac-specific mea-

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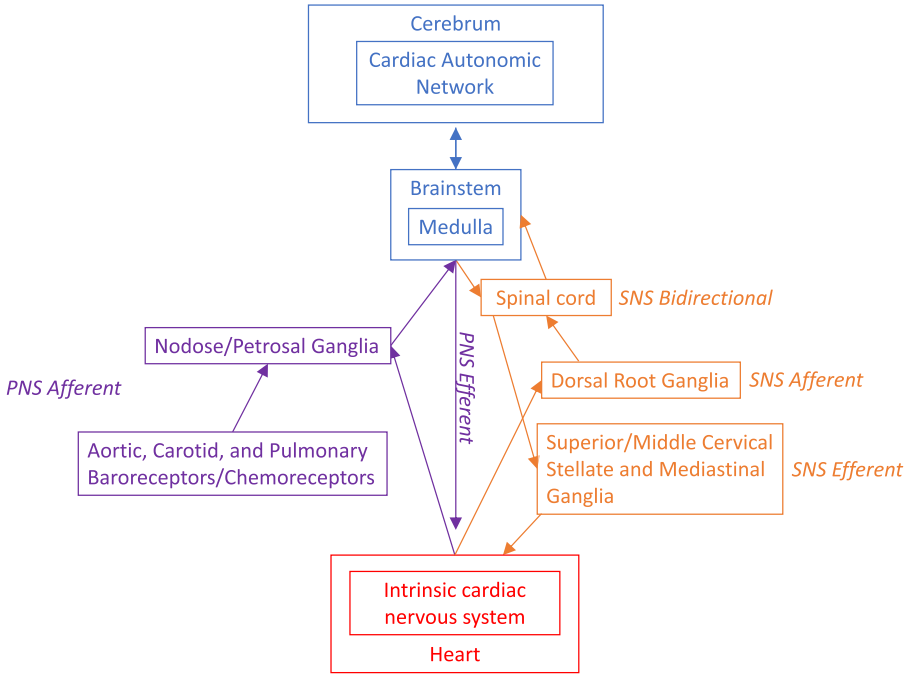

Fig. 1. Overview of Cardioneural Network from the Perspective of the Heart. This describes in detail the cardiac and thoracic structures that relay information between the heart and brain. The role of these structures in stress perception and physiology are described in italics. Afferent, efferent, and bidirectional pathways are described.

sures. We then discuss applications in the management of both psychological and cardiac conditions. Although we present evidence mostly from experimental studies of individuals with CHD, the core concepts are likely generalizable beyond this population.

Anatomical basis for the cardioneural network from the cardiac perspective

The brain and heart are closely linked through several interdependent neurologic networks, as illustrated in Fig. 1 [9]. Chemosensory and mechanosensory neurites in the heart communicate with the intrinsic cardiac nervous system (ICNS), a "little brain" comprised of intracardiac ganglia [10]. Cardiac afferent neurologic activity also routes through synaptic connections in the dorsal root ganglia and nodose ganglia, which subsequently reach the brain through the spinal cord and brainstem, respectively [11]. Disruption of this homeostatic mechanism due to an acute myocardial infarction may impair the ICNS and disrupt afferent neurological activity that is vital for homeostasis [12].

Neurological structures in the thoracic cavity may influence the heart-brain relationship and impact both psychological and cardiovascular disease risk. Important intrathoracic extracardiac ganglia include stellate ganglion, the pulmonary stretch receptors, and the aortic/carotid baroreceptor, which regulate respiration and blood pressure through autonomic mechanisms [13]. In addition, the dorsal root ganglia transmit afferent sympathetic nervous system (SNS) signals from the ICNS to the brain [13]. Several other extrathoracic extracardiac ganglia also facilitate afferent communication between the cardiovascular system and the brain, including the superior and middle cervical ganglia, which transmit efferent sympathetic activity to the heart. The nodose and petrosal ganglia are extrathoracic, extracardiac ganglia that receive chemosensor and mechanosensor input from the vagus, baroreceptors, and the heart.

These anatomical relationships help to understand potential mechanisms linking incident cardiac events with heart-brain disorders. Ischemia in the anterior or posterior wall of the left ventricle may influence brain activity through afferent nerve activity traveling from the heart through the dorsal root ganglia and spinal cord, where it synapses, to the brain [14,15]. This may influence efferent outflows at the level of the heart, sympathetic thoracic ganglia, brainstem, and higher brain centers that involve the stress response [16].

This extensive network plays a vital role in emotional regulation and the perception of feelings from the body's visceral organs, such as sensations in the chest during stress episodes. Although the psychological impact of ICNS dysregulation is not well understood, the increase in suicide rates and high depression prevalence after acute myocardial infarctions warrant further research into its effects [17]. Cardiac autonomic structures may also be involved in interoception, or a heightened sensation of the visceral organs, that form the foundation for panic disorder and other psychopathologies [18]. Another clinical example is idiopathic pure autonomic failure, a condition characterized by the autonomic ganglia's selective cell death due to the accumulation of Lewy bodies [19], and can cause blunted physiologic and emotional responses to mental stress [20]. The vagus nerve, which courses through the neck [21], is easily accessible by non-invasive and implanted neuromodulation therapies, and may be effective in treating depression and other stress-related conditions [22].

Cardioneural pathways of stress from the brain vantage point

The central autonomic network (CAN) describes a cluster of regions in the cerebral cortex and brainstem (Fig. 2) that jointly regulates several physiological and psychological autonomic processes implicated in CHD pathogenesis [23]. External threats are processed in certain regions in the medial prefrontal cortex and the amygdala. These regions are central to the fear-based "fight or flight" adaptive response that includes sympathetic arousal and parasympathetic inhibition [24]. The amygdala works closely with the insular cortex, which is involved in autonomic regulation, and has bidirectional connections with the heart and other visceral organs. The amygdala inhibits several brainstem PNS nuclei, including the nucleus ambiguous, dorsal motor nucleus, and nucleus tractus solitarius [25]. The amygdala also inhibits the caudal ven-

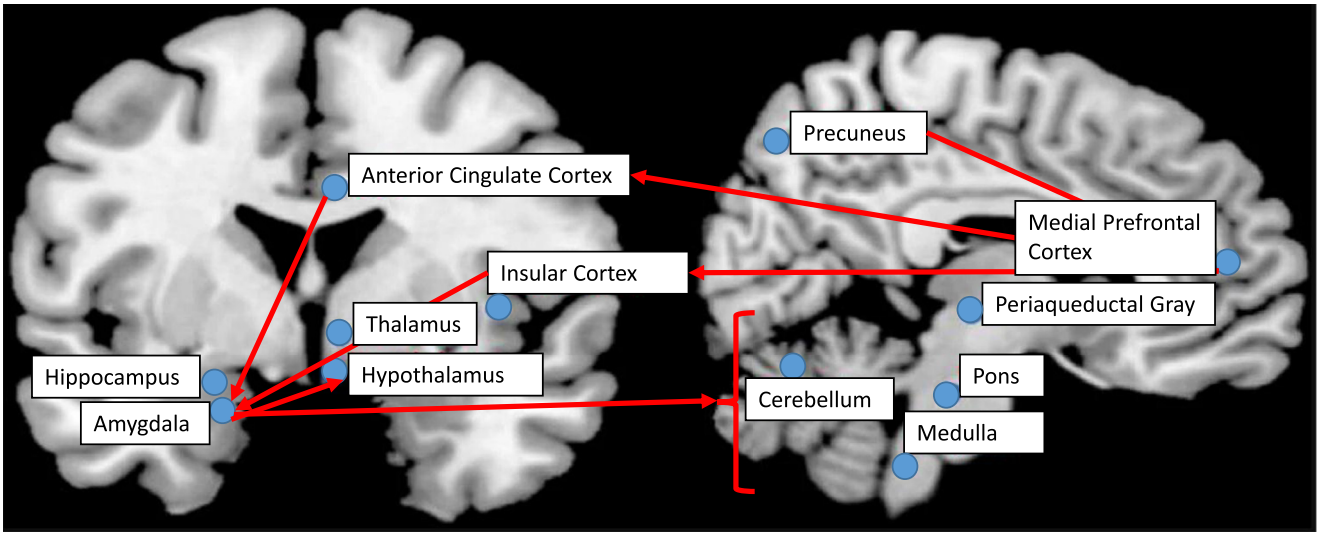

Fig. 2. Overview of the Cardioneural Network from the Perspective of the Brain, with a Focus on the Central Autonomic Network. This figure summarizes the key brain rations in the cardiac autonomic network, and the relationship of forebrain, midbrain, and brainstem structures with the arrows. This figure was adapted from Sklerov M. et al., Clinical Autonomic Research 2019 (29:555-566). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

trolateral medulla (CVLM), which results in increased SNS activity by activating the rostral ventrolateral medulla (RVLM) [26]. The pons, which projects autonomic fibers throughout the brain, contains the locus coeruleus and other important nuclei involved in the autonomic regulation of psychological stress, sleep, respiration, and cognition. The amygdala also regulates the hypothalamus, which, in turn, controls temperature, thyroid function, cortisol production, circadian rhythms, and sex hormones [23].

Recent studies highlight the potential importance of these brain regions in cardiovascular disease pathogenesis. Tawakol et al. examined whole-body positron emission tomography scans in 293 people without CHD (mean age 55 years, 58% women). They found that higher resting amygdala activity was associated with increased arterial inflammation and risk of adverse cardiovascular events [27]. Bremner et al. studied 170 individuals with known CHD in a laboratory setting and examined changes in brain perfusion with O-15 water positron emission tomography during stressful (versus neutral) tasks using a whole-brain analysis. They found an association ($p<0.005$) between the stress reactivity of several CAN structures (minimum size 11 voxels) and mental stress-induced myocardial ischemia (MSIMI) [28], including the insula and anterior cingulate cortex. Other important regions of stress activation that related to MSIMI were the inferior frontal gyrus and parietal cortex. In the same cohort, Moazzami et al. found that stress reactivity in the rostromedial subregion of the medial prefrontal cortex was associated with reduced high frequency heart rate variability during stress, higher interleukin-6 levels 90 min after stress, and increased risk of cardiovascular events or death [29]. Still in the same cohort, inferior frontal lobe activation during mental stress was found to associate with angina. Most notably, this association was stronger than the association of angina with traditional myocardial ischemia [14], suggesting the need to reconsider angina as a neurocardiac symptom, rather than strictly a condition of impaired myocardial perfusion.

The increased CHD risk due to psychological stress may involve physiologic mechanisms arising from activation in the CAN and its relationship with baroreflex sensitivity [30]. For example, early life trauma can affect neurological responses to stress and associates with worsened blood pressure trajectories in children and young adults [31,32]. The cardiac effects of the CAN may be further elucidated by studies in individuals with cardiac transplantation, whose hearts are denervated from the brain. One study of 20 cardiac transplant individuals found significantly attenuated heart-rate responses to stress compared to controls age-matched to both the donor and the recipient [33]. As such, it demonstrated the effects of disrupted communications from the CAN to the heart during stress provocation that may also influence their vulnerability to acute stress.

Summary of bidirectional communication between the heart and brain

A complex network of structures supports the bidirectional communication between the heart and the brain. CHD affects neurological networks/ganglia outside of the heart in the cervical/thoracic regions and spine. It also activates several autonomic structures in the brain and brainstem that process psychological stress. From the brain perspective, psychological stress processing involves the cardiac autonomic network, which has efferent effects on the heart and can increase CHD risk through hypertension, for example. Core structures like the vagus nerve transmit bidirectional communications between the heart and brain, and may be the target for neuromodulation therapies. These connections, which are summarized in Fig. 3, form the anatomical basis for a new paradigm that considers ischemic heart disease and psychological conditions as interrelated, interdependent conditions.

Assessment of the cardioneural network with non-invasive ambulatory and laboratory measures

Integration of cardioneural metrics into clinical settings can help with risk stratification and monitoring of behavioral interventions that include, for example, exercise training, psychotherapy, and meditation. Many cardioneural measures are derived from the electrocardiogram (ECG), which allows for cost-effective and portable assessments in both laboratory and home settings. Additional non-invasive cardiovascular assessment strategies include impedance cardiography and photoplethysmography, which can measure the effects of mental stress on myocardial contractility and vasomotor tone, respectively. Long-term ambulatory monitoring can potentially help assess everyday stress physiology and behavior in the home setting, although more data are needed to sup-

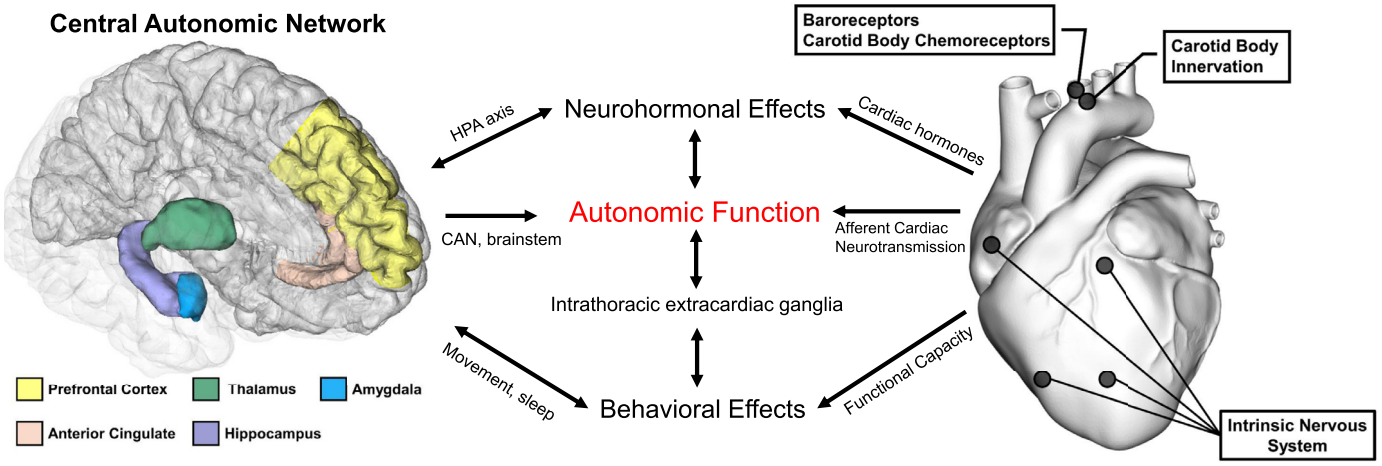

Fig. 3. Overview of Cardioneural Network that Arise from the Brain and Heart. Several neurological structures in both the brain and heart contribute to autonomic measurements that can be measured non-invasively. The neuroendocrine and immune systems are also closely involved, both as a result of direct input from both the brain and heart, as well as the mechanisms involving the peripheral autonomic nervous system. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

port this approach. On the other hand, laboratory testing can be useful for more rigorous, controlled assessments of stress reactivity with mental stress challenges [28].

One of the most commonly used cardioneural metrics is heart rate variability (HRV), an ambulatory, ECG-based measure of the dynamic heart rate changes that are attributable primarily to fluctuations in ANS activity. It can be useful in detecting dysfunction in the CAN, ICNS, or specific autonomic reflex ganglia and can be influenced by acute psychological stress and myocardial ischemia [8]. There are different ways to index HRV; among these, frequency domains are most commonly used, followed by time domain and non-linear methods. Frequency domain HRV measures heart rate oscillations coupled with other rhythmic physiologic processes at different frequency bands. Psychosocial stress and CHD both reduce the amplitudes of these oscillations to varying degrees. High frequency (HF) HRV (0.15 – 0.40 Hz) describes parasympathetic activity modulation with respiration but also reflects activity levels and connectivity within the CAN, and is lower during exposure to stress and in persons with CHD [34]. Low frequency (LF) HRV (0.04 – 0.15 Hz) reflects a combination of sympathetic and parasympathetic function that is mostly controlled by the baroreflex and the anterior cingulate region of the CAN, and is reduced by nearly 50% in posttraumatic stress disorder (PTSD) [35]. HRV can also predict the future risk of depression and PTSD in trauma-exposed individuals [36]. Non-linear HRV metrics, such as multiscale entropy, measure the amount of disorder in the system and indicate a breakdown in homeostasis due to either cardiovascular disease or psychological and mental health disturbances. Non-linear metrics from the Poincare plot may uniquely capture irregularities caused by periodic, disordered ANS activity bursts that occur with myocardial ischemia [37].

In addition to HRV, repolarization and myocardial contractility measurements can help evaluate the effects of psychological stress on ventricular sympathetic activation [38]. T-peak to T-end interval reflects SNS stimulation through stellate activation (Fig. 1) and predicts ventricular tachyarrhythmias [39]. Pre-ejection period estimates cardiac inotropic effort from the interval between ventricular depolarization and the mechanical ejection of blood. This metric is a useful SNS measure in laboratory settings to assess the beta-1 effects of acute mental stress challenges [40].

Baroreceptor sensitivity (BRS), which measures the ability to regulate blood pressure through autonomic modulation, is another cardioneural measure that helps understand the connections between stress and CHD because of the brainstem influence on BRS (Fig. 1) [26, 41]. Low BRS predicts sudden cardiac death after myocardial infarction and is decreased in both depression and posttraumatic stress disorder; it may also exacerbate hemodynamic reactivity to acute stress [42–44]. Heart rate turbulence is another PNS measure of heart rate changes after premature ventricular contractions. It reflects baroreflex dysfunction, decreases after acute myocardial infarction, and predicts adverse cardiovascular events [45].

Several other laboratory measures can be important indicators of disruption in cardioneural networks, which can be important in risk prediction and provide a deeper understanding of cardioneural mechanisms underlying CHD pathogenesis. MSIMI, for example, is a phenomenon due, at least in part, to microvascular dysfunction during acute laboratory mental stress challenge. It has been associated with over a 2-fold increased risk of adverse events [46]. SNS stimulation during mental stress causes the initiation of the inflammatory cascade, which results in the release of cytokines, including interleukin-6, monocyte chemoattractant protein-1, and matrix metallopeptidase 9 [47]. SNS activation during acute mental stress also causes peripheral microvascular vasoconstriction and reduced brachial artery flow-mediated dilation [48, 49]. These represent relatively low-cost methods that may index SNS activation and are also predictive of future CHD events [49, 50].

Applications of cardioneural measures in clinical diagnosis and treatment

Further research into the measurement of the cardioneural network can help set the stage for a new clinical paradigm of *behavioral preventive cardiology* that includes an increased focus on autonomic health and intensive behavioral interventions. While ambulatory ECG-based assessment strategies are currently the most well-studied and easy to translate into clinical practice using Holter monitors or ECG monitoring patches, other methods that involve laboratory-based mental stress challenges provide more rigorous assessments of stress physiology. Individuals with high CHD risk who may be amenable to cardioneural assessments and interventions may include those with psychiatric diagnoses such as depression and PTSD, those reporting high levels of general stress, and potentially also those with abnormal stress reactivity- for example, patients with white coat hypertension. More research in this area is needed however, to develop and test clinical decision-

making programs in order to translate research findings into preventive action. Randomized controlled trials of behavioral and neuromodulation therapies in high-risk individuals, with cardioneural outcomes to assess treatment response, are especially needed. Examples include behavioral and stress management programs during cardiac rehabilitation and sleep hygiene education. Therapies such as HRV biofeedback, yoga, and vagal nerve stimulation target specific autonomic mechanisms, including the baroreceptor and PNS [51]. In these cases, cardioneural outcomes may be vital for monitoring treatment efficacy [7].

Overall, CHD and mental health problems are the largest contributors to morbidity and mortality in the world. Their collective high prevalence underscores the need for future research on the cardioneural network as a common mechanism in both conditions that could shed light on synergistic treatment pathways. Metrics such as HRV and vascular and ischemic responses to mental stress may someday become incorporated with other traditional measures for the risk assessment of CHD patients. These metrics may facilitate identifying individual patients who would benefit the most from biobehavioral and neuromodulatory interventions based on their autonomic activations at home or during laboratory stress. More research is needed on large and diverse populations to create robust clinical standards for cardioneural metrics and accompanying mind-body and neurmodulating interventions.

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