Foundational concepts for cardiac neuromodulation

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“It is only through an improved mechanistic understanding of structure/function that rationale neuromodulation-based therapies of cardiac control will advance. The twofold objectives are: do no harm and develop a better understanding of the nuances governing structure/function of the cardiac control hierarchy; and, develop therapies that account for the biological complexity of the system.”

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Heart disease remains the primary cause of morbidity and mortality in the world with its impact cutting across all segments of the population [1]. The field of neurocardiology incorporates all aspects of cardiology with important elements of autonomic neuroscience to define cellular physiology/pathophysiology [2]. The fundamental premise of neurocardiology is that it is the dynamic interactions between autonomic control and the heart that ultimately determines how closed-loop control of cardiac function evolves in response to cardiovascular stressors including those leading to cardiac disease [2]. In the worst case scenario, imbalances in autonomic control coupled with regional variations in cardiac electrical/mechanical function set the stage for arrhythmias leading to sudden cardiac death or heart failure [3–5]. Through a mechanistic understanding of neurohumoral–cardiac processes, a rationale for therapies designed to maintain cardiovascular homeostasis [6] can be defined. Neuromodulation is at the forefront of novel therapies that are establishing new frontiers for effective treatments of cardiac disease. A conceptual framework for bioelectronic medicine, as related to cardiac disease, is presented via three key concepts of neurocardiology.

Concept 1: neural control of cardiac function involves a multitier hierarchy of interdependent reflexes

Cardiac control depends on interactions between intrathoracic and central aspects of the cardiac nervous system.

Peripheral neural networks for cardiac control include intrinsic cardiac and extracardiac–intrathoracic (e.g., stellate and middle cervical) ganglia. These ganglia contain all the necessary neural machinery for reflex control of the heart (afferent, efferent and local circuit interneurons for information processing) [2].

Centrally located neural networks involved in cardiac control include elements of the spinal cord, brainstem and higher centers up to and including the insular cortex [7–9]. These top-down contributions to control involve projections from preganglionic soma located in the brainstem (parasympathetic) and spinal cord (sympathetic) toward the heart with both regions (nucleus Ambiguus and intermediolateral cell column) impacted by interconnections with brainstem (e.g., nucleus tractus solitaries) and higher centers (e.g., hypothalamus, limbic system).

Bottom- and middle-level cardio-centric contributions to control include intrathoracic ganglia (intrinsic cardiac and stellate/middle cervical) receiving cardiac-related afferent projections and central neurons (spinal cord and brainstem) receiving cardiovascular-related afferent inputs via primary sensory ganglia (dorsal root, nodose and petrosal).

The integrated autonomic response to normal environmental stressors results from interactions between top, middle and bottom levels allowing for precise control of cardiac output, flow distribution and blood pressure. However, certain stressors, such as myocardial ischemia, can initiate a cascade of responses that can be catastrophic in a very short time [10].

Concept 2: there are inherent & acquired factors that impact the progression of cardiac disease

Remodeling of autonomic reflexes in response to cardiac pathology, while necessary to maintain homeostasis, can also accelerate the progression of disease [2,6]. A hyperdynamic sympathetic response is a key adverse effect which contributes to the increased risk of sudden cardiac death [4] and progression into heart failure [3,5]. Recent data suggest that these neural network adjustments are ‘free-floating’ with the interdependent control systems shifting to a new ‘normal’ for control based on network plasticity and memory [11]. Plasticity can involve loss of specific sub-populations of neurons [12] as well as alterations in the strength of interconnections within and between neurons in the various levels of control [13–15].

Concept 3: neuromodulation-based therapies impact multiple levels of control

Bioelectronic interventions have the potential to modulate activity on underlying axons of passage, associated neural networks (proximal and distal to site of stimulation) and critical aspects of end-organ function [16–20]. However, if endogenous control systems are modulated by bioelectronic interventions then the closed system tends to migrate toward a modified balance, or new normal, between control system components whose pathway and endpoint may be difficult to predict [21].

The biological response to bioelectronic interventions is determined by the characteristics of the stimulation protocol, the populations of neurons impacted and the current ‘active’ state of those neural networks [22]. In general, the preferred points of intervention are convergence/nexus points where afferent and efferent projections come together such as sympathetic ganglia and the vagus [16,22]. Open-loop assessment of intervention efficacy are less useful in the longer term since they disregard the closed-loop and interdependent nature of the control system components and their integrated response. The recent discouraging results of clinical studies can be partly explained by such simplistic assumptions of neurovisceral sciences. Therefore, the long-term objective of bioelectric medicine is to evolve sensing of appropriate biomarkers to integrate function into close-loop devices to maximize therapeutic efficacy.

As we contemplate new strategies for treatment of cardiac disease, it is critical to place the human suffering in context. According to recent data from the CDC (Health United States Report, 2016) 23.4% of all-cause mortality is attributed to heart disease. Recent trials involving bioelectronic medicine have yielded equivocal results [23–25]. These are likely due to sub-optimum applications of the therapy [22] based on an incomplete appreciation of control system component interdependencies. It is only through an improved mechanistic understanding of structure/function that rationale neuromodulation-based therapies of cardiac control will advance. The twofold objectives are: do no harm and develop a better understanding of the nuances governing structure/function of the cardiac control hierarchy; and, develop therapies that account for the biological complexity of the system.

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