Cardiovascular physiology, emotions, and clinical applications: are we ready for prime time?

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The linkage between health and emotions is as old as mankind. The account of Anania’s death for fear of God’s punishment in the Act of the Apostles is but an example. Little was known then of mechanisms, although the Aristotelian view that all affections of the soul are associated with the body, implying that given emotions are also capable of producing specific somatic effects (2), may look farsighted.

In recent years, the molecular and technological revolutions have drastically reshaped medical thinking, now driven almost solely by a mechanistic view of medicine governed by the hard sciences (29a). However, although it is clear that it is not all in the genes (16), to address the soft part of medicine and to consider the individual, as opposed to the group, prevention as opposed to therapy requires a change of paradigm and a return to physiology as the basis of medicine as an “art with a view to the health” (13).

The issue is quite complex since it touches simultaneously on different domains (physiology, psychology, and information) that are addressed separately. Clinical applications must consider both the diseases of organs (parts of the body) and processes (functions of systems) in a synergistic fashion (1), since this synergy is regulated by the neurovegetative and other systems (such as hormonal and immunological). In addition, the (sociocultural) context can no longer be overlooked, particularly in the realm of cardiovascular medicine (29).

The Autonomic Nervous System: Measures and Models

Because the autonomic nervous system (ANS) is still modeled by some as a pure outflow, the role of abnormal sensory influences from the organs at the periphery, as from a diseased heart, is not a typical component of our clinical thinking.

In the last decades, cardiac ischemic pain provided a paradigm shift. Experiments showed that cardiac pain could be initiated by an abnormal stimulation of the normal sympathetic afferent innervation of the heart (22), leading to a complex pattern of temporospatial activation of spinal, subcortical, and cortical structures (4). As a corollary, the ischemic event could be associated to pain, or not, according to the specific neural substratum or environmental frame that would be involved. It is also of importance to recall that the activation of this sensory channel is not an isolated event but is likely to be part of the normal, beat-by-beat autonomic regulation of the cardiovascular system, in a positive feedback organization (23), that could be initiated by chemical stimuli to the heart (28) or mechanical stretch of the thoracic aorta (27). A number of laboratories (3, 19) have further clarified the role of various metabolites, which are produced during cardiac ischemia and may stimulate sympathetic afferents, presumably responsible for pain. In this context, endogenous bradykinin production (30) might be a key player, although several metabolites may operate interactively (19). A key limitation of this type of research derives from the techniques that are available to provide physiological measures with sufficient confidence. Direct measures, in fact, can be obtained in humans only intermittently or with invasive methods in the case of the sympathetic innervation (muscle sympathetic nerve activity and catecholamines), but there is no available technique to directly assess vagal drive. Clinical applications, particularly aiming at individualized diagnosis and treatment (31), require instead techniques that are friendly, noninvasive, and easy to use and that can be employed repeatedly if not continuously. In this context, physiology could facilitate clinical medicine to address the individual in a flow of measures and observations, potentially leading to action for (tailored) therapy or prevention. To this end mathematical modeling, as in the case of cardiovascular beat-by-beat variability (23, 25), is a tool capable to provide information (26) useful to guide action (21), even if still debated in its underlying physiology (7, 24).

The ANS: Multiplicity of Variables and Observations

The paper by Henze et al. (12) in this issue strikes a hit in favor of rising the level of complexity of multiple measures from beat-by-beat cardiovascular variability, combining them with behavioral observations to better illuminate the link between the ANS and the failing heart, at least in rodents. The key points of these investigations are that ANS responses are inferred from the analysis of beat-by-beat fluctuations of one variable (R-R interval, analyzed with mathematical models in the time or frequency domain), combined with a more complex analysis of R-R and systolic arterial pressure, with bivariate and oscillatory interaction, i.e., coherence function.

ANS indexes are combined with a further level of data, observing behavior induced by the model of elevated plus maze and allowing inferences on anxiety. In these rats, multiple levels of physiological and behavioral data might be concurrently used to “make unbiased estimates . . . in agreement with all the possible knowledge available about the system” (11). The resulting information supports the hypothesis that a major abnormality of the ANS state could be the peripheral trigger for an abnormal behavior of anxiety: “increased incidence of panic disorder with heart failure may be the result of, rather than the cause of, ventricular dysfunction” (12).

Notably, the strength of the study is furthered by the use of telemetry of measures, thus avoiding the confounding effects of anesthesia and recent surgery, and by a strict protocol to obtain unequivocal conditions of congestive heart failure (CHF) by a prior coronary artery ligation. Results of this procedure were documented by quantitative assessment through ultrasound imaging during the study and terminal congestive assess-
ment, at the expense of eliminating a sizable fraction of animals that did not meet the CHF criteria.

The abnormal sensory input from the failing heart to the central structures would thus produce an abnormal cardiovascular ANS regulation and abnormal anxiety behavior. How should therapeutic actions take into consideration this novel view?

The ANS: Inferences and Actions

A practical issue in cardiovascular medicine regards the likelihood that the knowledge of being affected by a heart disease (hypertension, myocardial infarction, and CHF) might worsen, per se, the condition and cause anxiety (from within). Because of the fact that rodents cannot have knowledge that they are affected by CHF, Henze et al.’s study (12) strikes the balance in favor of the opposite view that abnormal sensory messages from the periphery might favor the abnormally anxious behavior so frequently encountered in this condition (9, 29).

In humans with severe CHF, orthotopic cardiac transplant reverses to normality not only the hemodynamic dysfunction but also the sympathetic oscillatory profile (32), in addition to improving symptoms such as dyspnea and quality of life (10). Cardiovascular rehabilitation improves autonomic profile (increasing high-frequency R-R variability) in patients with CHF (6). In patients with coronary artery disease, cardiac rehab improves baroreflex gain (15, 20) with potential beneficial effects on survival (17). A reduction of baroreflex gain and a shift toward sympathetic predominance [as assessed from heart rate variability (HRV)] are also a hallmark of conditions of real-life stress, which can be ameliorated with specific outpatient training (21).

An additional mechanism not explored by Henze et al. (12), by which the autonomic profile could be altered in postinfarction CHF, is by way of a different responsiveness of cardiac afferents to the continuous flow of chemical mediators and their interaction, contingent upon a different interplay (18) between mechanoreflexes, metaboreflexes, and cardiogenic reflexes in a very complex system. This peripheral abnormality might be improved by gene therapy, as shown by gene transfer of NGF in streptozocin-induced diabetic mice (14).


REFERENCES


