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HRV in an Integrated Hardware/ Software System Using Artificial Intelligence to Provide Assessment, Intervention and Performance Optimization

Robert L. Drury

Abstract

Heart rate variability (HRV) is increasingly recognized as a central variable of interest in health maintenance, disease prevention and performance optimization. It is also a sensitive biomarker of health status, disease presence and functional abilities, acquiring and processing high fidelity inter beat interval data, along with other psychophysiological parameters that can assist in clinical assessment and intervention, population health studies/digital epidemiology and positive performance optimization. We describe a system using high-throughput artificial intelligence based on the KUBIOS platform to combine time, frequency and nonlinear data domains acquired by wearable or implanted biosensors to guide in clinical assessment, decision support and intervention, population health monitoring and individual self-regulation and performance enhancement, including the use of HRV biofeedback. This approach follows the iP4 health model which emphasizes an integral, personalized, predictive, preventive and participatory approach to human health and well-being. It therefore includes psychological, biological, genomic, sociocultural, evolutionary and spiritual variables as mutually interactive elements in embodying complex systems adaptation.

Keywords: heart rate variability, HRV, health, well-being, health biomarker, high fidelity data acquisition, digital epidemiology, KUBIOS platform, high-throughput artificial intelligence, implantable biosensors, iP4 health model, complexity theory, complex adaptive systems

1. Introduction

The history of science shows clearly that the development of new techniques and tools of observation lead to improved scientific understanding and the development of more adequate theories. The development of the telescope and microscope made for conceptual breakthroughs in both the physical and biological sciences, facilitating empirical observations that allowed astute observers to create new and more powerful conceptual approaches.

This chapter will describe the development of heart rate variability (HRV) as a meaningful variable to monitor, interrogate and intervene in the functioning of the human nervous system and the psychophysiological systems it communicates with [1, 2]. It will provide a context for understanding HRV's role in the assessment, maintenance and enhancement of human health, well-being and performance. Further, appropriate techniques for studying HRV will be explored and a variety of applications will be described. Finally, iP4, a systems-based model of human health and optimal performance will be described, and several HRV-based integrated hardware/software systems will be described that exemplify that model.

2. HRV and the nervous system

Since the development of the original neuron approximately 600 billion years ago in worm-like creatures, the nervous system has emerged into increasingly complex and multifunctional neural networks that have vastly increased the adaptive capabilities of those organisms so endowed. This typifies the evolutionary process that has been studied as complexity theory within the systems view life [3]. Recently, the understanding of complex adaptive systems has been aided by the application of non-linear systems dynamics, as a supplement to more traditional linear modes of exploration and understanding. Increasingly complex entities emerge through processes of self-organization in interaction with environments demanding fitness to form adaptive systems which consist of multiple interactive and interdependent coevolving components. In the case of humans, the nervous system has played a decisive role in the increasingly dominant position currently occupied in the planetary ecosystem.

The central nervous system (CNS), composed of the brain and spinal cord has been historically identified as the most important part of the nervous system for conventional scientific study [4], with Kandel devoting only one chapter out of 64 to the autonomic nervous system (ANS). It is becoming increasingly clear that the peripheral nervous system (PNS) plays a crucial part in the remarkable abilities of humans. In particular, the ANS is known to mediate the sophisticated homeostatic dynamics that allow organisms to maintain a relatively stable interior environment needed to carryout complex adaptive tasks and supports the affective elements that comprise the significant motivational features characteristic of humans. The two major subdivisions of the ANS are the sympathetic and parasympathetic nervous systems [5]. The sympathetic nervous system is associated with energizing the organism during times of threat or challenge. Such activities have been described as "fight or flight" responses. The parasympathetic nervous system has been found to exert calming, stabilizing or reparative effects described as "tend and befriend" responses. A key structural and functional component which modulates the dynamic homeostatic balance is the vagus nerve complex, which originates in the brain stem and is widely connected with major organs such as the heart, lungs, stomach, genitals, pharynx, larynx, facial musculature, and middle ear muscles [1]. In addition to the stress "fight or flight" and calming "tend and befriend" responses, the vagus mediates the equally important "freeze" or immobilization response which is associated with death feigning in many species possessing the vagal nerve complex. These three response elements are integral to HRV, which is defined as the amount of variance in R-R wave intervals, also called the interbeat interval (IBI). The IBI is used to calculate the moment by moment variations in heart rate which constitutes HRV.

In addition to the systems described above, other neural network systems play significant roles in the overall integrated functioning of the human organism.

A key example is the enteric nervous system (ENS) which is an integral part of the enteric region and bidirectionally communicates with the CNS and ANS [6]. It has been described by some investigators as a "second brain" and functions largely independently, generating significant amounts of the neurotransmitter serotonin, important in proper neurobehavioral functioning. It also may be a key participant in the functioning of the immune system and mediate the role of the enteric microbiome. It is proposed here that the increasing empirical understanding of the vagal nerve complex warrants the use of the term cardio-vagal nervous system (CVNS). Notably, the role of the vagus nerve and its role in determining HRV, which has been studied for over 150 years [7], have been expanding rapidly with over 26,000 citations resulting from a recent PubMed search of the terms "HRV" and "heart rate variability."

3. Heart rate variability and the vagal nerve complex

The term vagus derives from the Latin term for "traveler." As described above, this is apt as the vagal nerve complex is widely distributed throughout the body. Its origins in the subcortical region of the CNS have been identified by Porges [1] as the nucleus ambiguus, the dorsomedial medulla and the nucleus tractus solitarius. These three neural structures represent the primary central regulatory components of the vagal complex and are responsible for three significant functions. The sympathetic mobilization for fight or flight has been recognized for some time, while the dorsal vagal response is a vestigial immobilization/death feigning system and the ventral vagal complex mediates the social engagement system for adaptive motion, emotion and communication. This is perhaps its most important feature to social organisms such as humans, where communication and mutual support have been identified as crucial aspects of evolutionary fitness, contributing to both biological and cultural evolution. This conceptual approach has been called the polyvagal theory by Porges [1] and the neuro-visceral integration model by Thayer and Lane [2].

While these functions are not currently subject to isomorphic assessment, it has been demonstrated empirically that HRV is an accurate and sensitive measure of the actions of these three subsystems. HRV is defined as the instantaneous variability found when continuous R-R intervals in the EKG are recorded [8]. These intervals are easily recorded using both standard 12 lead EKG protocols and a wide variety of freestanding equipment whose quality ranges from adequate to poor. It is impossible to obtain reliable HRV data when the equipment used to acquire the R-R intervals is either lacking reliability or is poor fidelity. If high fidelity quality data are obtained, there are three primary approaches to data analysis that have been found valuable: frequency domain measures, time domain measures and nonlinear measures [9]. Each of these approaches have demonstrated utility, although it has also been shown that some measures are less sensitive to salient phenomena and therefore, selection of the most robust analytic strategy is an important area of ongoing investigation and will be discussed further in the section of algorithmic analysis, artificial intelligence and related issues.

The research literature on HRV indicates that it can be a sensitive biomarker for a wide variety of disorders and conditions [10]. This includes medical disorders such as all-cause mortality, sudden cardiac death, sepsis, myocardial infarction, diabetic neuropathy, transplantation issues, myocardial dysfunction/heart failure and noncardiovascular diseases such as Alzheimer's dementia, epilepsy, diabetes, tetraplegia and liver cirrhosis [11]. It is important to note that in some conditions such as sepsis, the onset of subjective symptoms is often delayed and makes

effective intervention difficult or impossible. However, HRV is frequently suppressed before these subjective reports occur, giving a crucial advanced warning of serious developments. HRV has also been shown to be sensitive to psychosocial disorders and dysfunctions such as depression, anxiety, bipolar disorder, attention deficit/hyperactivity disorder, substance abuse/craving disorder and post-traumatic stress disorder. HRV has also been used as a sensitive monitoring strategy in pacing physical training and determining when rest and recovery are indicated to avoid overtraining. Similarly, HRV has been shown to be an indicator of the level of executive functioning and resilience, both positive psychological phenomena. Another positive adaptive measure is the respiratory sinus arrhythmia (RSA), which is observed when HR increases during inhalation and decreases during exhalation. Notably, when a person is near death, the RSA, and therefore, HRV, are diminished or nonexistent. It should be noted that while HRV fulfills the epidemiological virtue of relatively high sensitivity, it does not possess high specificity, and therefore a careful consideration of contextual factors is necessary to make HRV a useful biomarker of health [12, 13]. In general, reduced HRV indicates impairment or dysfunction, while increased HRV shows improved functional or health status.

4. Methodological and technical issues

Accompanying the explosive growth of interest and research on HRV (12) have come a number of significant issues and problems that can impede progress. While the standard 12 lead EKG protocol is widely used in conventional medicine to produce high quality data, it is cumbersome, obtrusive and expensive. It also lacks the necessary data analytic software capable of recording and interpreting multiple HRV domains. These issues limit accessibility and more widespread use. A number of devices are available for research and clinical applications, some of which use hardwired photoplethysmography and occasionally wireless photoplethysmography accomplished by Bluetooth, relieving the individual from being physically connected to the equipment. Research studies have shown that implanted sensors may acquire interbeat interval data from which HRV can be derived. The interbeat interval data is either stored for later analysis or processed onboard with some type of feedback "HRV" score generated. The actual details regarding the meaning of some composite "HRV" scores is not always clear.

Similar devices are offered on the consumer market, targeting customers wishing to enhance or "fine tune" their physical training regimens. These devices most often use either ring or watch based sensors to obtain interbeat data and reliability data are not generally available, but it is likely that these modes of data collection and analysis contain significant artifacts and other data flaws more accurate chest straps and photoplethysmography sensors are seldom used. A transparent approach to the operation of such devices is desirable to examine both the reliability and validity of such devices, although manufacturers sometimes proclaim proprietary interests which shield them from this type of accountability. A technically feasible approach for interbeat data collection is to use implanted sensor systems which combine high fidelity data acquisition with Bluetooth data transmission and wireless capacitive battery charging so that the device could remain in place for a significant period, even indefinitely. This method would allow collection of more longitudinal data and make data collection in the natural environment relatively simple. Such data would be invaluable in determining a person's baseline state, a feature that is often missing in brief "snapshot" assessments. With such baseline data, a much more meaningful "vital sign" could be available, not only during office visits, but at any other time deemed relevant. It would also popularize the use of

HRV, since one of the drawbacks cited by many individuals is the cumbersome and inconvenient nature of currently available devices. Using the Bluetooth protocol to transmit data to a smart phone would also make data collection and analysis much more accessible, since smart phones are very widely used globally, including in areas with no other communication resources. With appropriate machine learning algorithms, the smart phone could also mediate actionable patient prompting or intervention, including HRV biofeedback. Using the digital epidemiological approach of population surveillance, ongoing monitoring could be available to distant healthcare facilities to prompt more detailed assessment and/or intervention at the individual or group level. Since this approach could involve an implanted device and longitudinal assessment, it might be perceived as more "invasive" and raise privacy and confidentiality issues, especially as used in healthcare contexts. Such concerns are legitimate and would need to be carefully addressed, although data collected by other means is equally worthy of such consideration, especially at this time when individual's data are regularly "harvested" or "scraped" surreptitiously by commercial ventures and monetized.

Until our understanding of HRV improves through machine learning and other artificial intelligence approaches, any one metric amongst the more than a dozen available, is somewhat incomplete. Currently, the SDNN time domain measure (standard deviation of interbeat intervals) is most frequently used and has value. A very comprehensive systemic software suite has been developed by Tarvainen and colleagues [14] called KUBIOS. It is available for analysis of HRV in multiple modes of time domain, frequency domain and nonlinear modes using a batching approach. A current limitation, however, is that KUBIOS does not conduct its analyses in real time, but that limitation is being addressed and a real time version of KUBIOS is in development for purposes of both scientific clarity and consumer use [15]. The KUBIOS platform offers many benefits such as multi-method analytic strategies and clear documentation, making it ideal for increasingly popular big data approaches such as artificial intelligence, machine learning, and high-throughput and cloud computing. Such approaches are especially applicable to the large number of data points that can be collected in longitudinal HR data.

5. Innovative applications of HRV

Given the popularity and "sizzle" of developments in the big data areas of artificial intelligence, machine learning and high-throughput cloud computing, a recent report by Liu and colleagues [16] illustrates an area of high potential value. Building on the work of King and associates [17] on the use of HRV in decision support for trauma patients being transported by helicopter to a trauma center, Liu used machine learning to create predictive models that could detect the need for lifesaving interventions. Their results were near perfect predictions with receiver operating characteristics under the curve = 0.99. While their preliminary report suffered from issues such a relatively small sample size and difficulty extracting high fidelity HRV data, it is still proof of concept that such a systems approach is feasible and relevant.

Another important model described by the National Institute of Standards and Technology as the Analysis as a Service (AaaS) has been developed and exemplified by IBM's Watson Analytics (WA), which is a cloud based AaaS that claims to "carry out a number of significant data analysis and display approaches in a user friendly manner" [18]. The Explore and Predict modalities use a variety of data clustering and machine learning approaches that can go far beyond single variable linear prediction, while the Assemble modality develops effective data display and infographics.

The use of WA by Guidi and colleagues [19] demonstrates proof of concept for a cloud-based data acquisition and analysis system which can make accurate clinical diagnostic decisions differentiating patients with heart failure from normal individuals on the basis of HRV. The process developed by Guidi involves data acquisition using the PhysioBank and PhysioNet to obtain and categorize ECG data into the appropriate format of R to R intervals using the PhysioNet HRV Toolkit [20]. This data consisted of 15 subjects with severe heart failure, 29 subjects with moderate heart failure and 54 healthy subjects with normal respiratory sinus arrhythmia. All subject data was initially collected using standard ECG protocols. The resulting data set was examined by WA and a variety of commonly used HRV statistics were derived. These statistics were compared to the data available in the current literature. This shows the results concerning accuracy of prediction using the Total Power HRV (TOT_PWR) statistic with a 90% predictive accuracy.

The use of such tools in critical care is exemplary and similar approaches have been suggested by Drury [21] in the areas of more routine clinical care and digital epidemiology. As noted by Topol [22], while the use of the terms artificial intelligence and machine learning has tended to be overblown, the use of existing big data sets and extensive longitudinal data as proposed here is ideal for such an approach and can assist in the laborious and sometimes obscure task of empirical investigation. I have previously suggested [10] using a wireless implantable high fidelity data acquisition device, networked by Bluetooth to a suitable machine learning version of the functionalities possessed by KUBIOS could interrogate the data sets for the creation of the most suitable predictive models for making not only clinical decisions based on changes in patient status, but monitor patients regarding the emergence of new conditions. This type of monitoring could also realize the concept of digital epidemiology, including the use of self-monitoring prompts to aid individuals in appropriate help seeking and self-regulation strategies. See **Figures 1** and **2** to visualize the use of such a system and its ability to discriminate rest, activity and recovery periods [23]. As is indicated by the development of groups such as the quantitative self and biohackers, there is a social demand to assist individuals in optimizing their health and well-being and enhancing their performance in a wide variety of areas. As proposed here, these groups have sometimes used

Figure 1.
ReThink wireless biosensor with capability to acquire HR, three-dimension accelerometry and respiration data. These data are then transferred to a Bluetooth enhanced personal device, as well as stored there. Quarter is shown for size comparison, with dimensions of 7.5 mm width, 4 mm height, and 1.4 mm depth (used with permission).
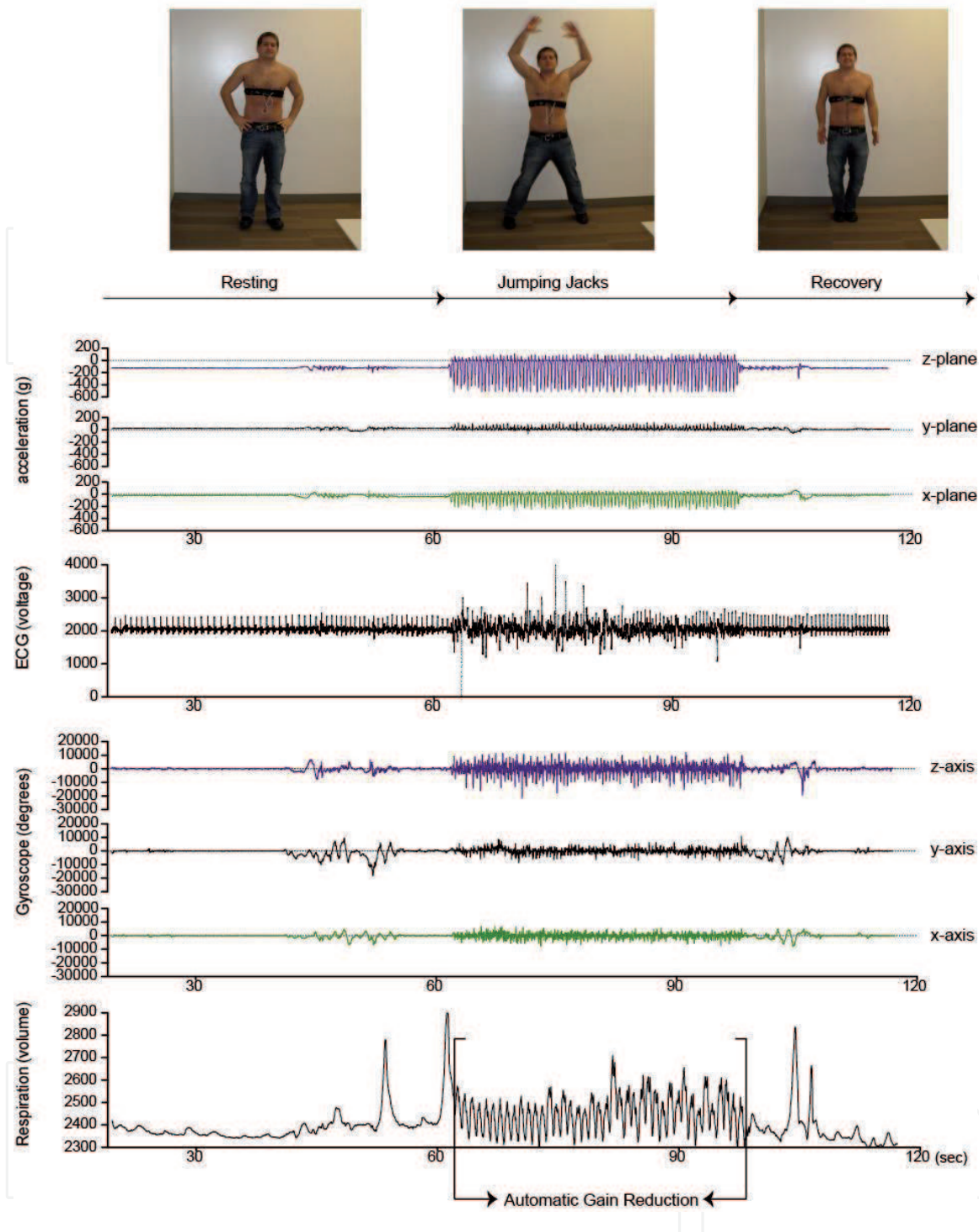
Figure 2.
A subject using the ReThink wireless biosensor during rest, activity and recovery periods. Note that multiple physiological data channels (HR, respiration and accelerometry) are displayed on a laptop computer (used with permission).

implanted devices to monitor their physiological status. The professional community has perennially spoken through the Institute of Medicine, the National Science Foundation, the National Institutes of Health, the World Health Organization and other organizations of the need for accessible, safe and effective healthcare.

The development and utilization of predictive models derived from artificial intelligence approaches such as machine learning could be beneficial in many aspects of care provided by the current healthcare industry. If clinicians had highly specific empirically based decision support data readily available, their interactions with patients might be more timely, less stressful and "more human," to use Topol's

phrase, with less time with the care provider on the computer and more face to face interaction. If ongoing HRV monitoring was used to track clinical status of patients, the need for routine exams, especially of the "worried well" would likely decrease. Prompt intervention for patients whose ongoing status was being monitored would be more likely, thus addressing the serious problems of both under and overutilization of medical services. This would accomplish a transition away from the expensive intensive care model to a less expensive, more extensive model. As is the case with the work of Liu's proof of concept, this approach is currently feasible and the elements of such a hardware-software system exist. Using the rubric of artificial intelligence could complete the development of such an approach by creating the necessary predictive models, as I have advocated elsewhere [10].

6. Conclusion: health, well-being and HRV

It is an oversimplification to suggest that the adoption of the HRV software/ hardware integrated system proposed would resolve the many serious issues that plague the current healthcare environment in the United States. Similarly, Topol of the Scripps Transformational Research Institute observes in his recent Deep Medicine [22] that the increasing use of artificial intelligence (AI) is not a panacea and can only contribute to improving the status quo. In particular, machine learning may make significant progress possible by using the relatively large number of data points generated by HRV and other psychophysiological parameters. It is a truism that both data quality and quantity are crucial in producing the most valuable predictive algorithmic equations. In addition to Topol's astute observations, other physicians such as Agus in the End of Illness [24] and Emanuel in Prescription for the Future [25] have also voiced more nuanced critiques of the healthcare venture in the US, identifying multiple domains of concern. The use of innovations such as machine learning and integrated HRV systems, however, may contribute to the achievement of a reformulated model of health, well-being and healthcare that is both more comprehensive and more tailored to the care of specific individuals. This approach was initially introduced as the human genome was being sequenced as personalized or precision medicine, the implication being that knowledge of the details of the individual's genetic makeup would make for highly specific treatment recommendations perhaps involving genetic engineering. A more multidimensional approach has emerged which addressed the many individual characteristics that each individual possesses; not just genetic, but biochemical, anatomical/physiological, cognitive/affective, social, cultural and spiritual. One of the major limitations of the majority of AI initiatives is the relative neglect of the affective domain of functioning that most distinctively characterizes humans. These multiple domains of individual variability require not only a highly personalized approach, but an integral view of the caring relationship that is participatory, predictive and preventive, as well. I have described this approach as the iP4 health model [10]. The emphasis on an *integral* perspective [26] highlights that each person is a complex adaptive system and that no aspect of their condition is independent from other details of their internal characteristics and external environmental conditions. The focus on *predictive* understanding acknowledges that a variety of risk and resilience factors exist and that any effort to maintain optimal health and well-being must note and plan to deal with such factors. Similarly, a *preventive* approach focuses on identification and early intervention to minimize or eliminate the onset and/ or severity of disease states and promote health. Perhaps most important, we hope to partner with informed individuals and support their decisions that will maximize their *participation* in the care process, making it not only more efficient and

effective, but also actually demonstrating care for the individual. It is only through a detailed integration of such important issues that a truly *personalized* health care is possible. Since we do not see this as a continuation of the existing approach to patient care, we prefer to designate the individual not as a patient, but a Pioneer.

The role which HRV may play in actualizing this model is expanding rapidly and, together with Drs. Steven Porges, Julian Thayer and Jay Ginsberg, I have edited a Research Topic that has jointly appeared in the journals Frontiers in Medicine and Frontiers in Public Health entitled "Heart Rate Variability, Health and Wellbeing: A Systems Perspective" [27]. This series of research papers and reviews summarizes current empirical findings and conceptual bases for applying our understanding of HRV to a wide variety of problems, diseases and issues. Thus, our efforts will not only monitor the various human nervous systems but help to assist and optimize them in their important task of shepherding each individual's health and well-being. Through both scientific and technological investigation using advanced AI tools such as machine learning, and appropriate provider education, a common interactional language must evolve that allows the evaluation of HRV and other relevant parameters to generate actionable feedback, whether decision support for physicians and other healthcare personnel or personal behavioral prompts or interventions for individuals. Though the current state of our understanding is relatively primitive, there is reason to be optimistic that such an evolution is possible.

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Conflict of interest

The author declares no conflict of interest.

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