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Editorial

Heart rate variability, autonomic regulation and myocardial ischemia

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At the beginning of all experimental work stands the choice of the appropriate technique of investigation

[(*R Hess, 1949*)]

Novelties often arise from the fruitful combination of multiple epistemologies, provided there is a (still unmet) need for what will emerge; and available technologies are capable to combine in a simple, robust outcome (all) the information distributed across multiple domains. Considering that heart diseases represent the leading cause of death and disability, and that coronary heart disease is the most common type of heart disease, the unequivocal observation that the autonomic nervous system has a powerful modulatory effect on clinical outcomes, particularly for myocardial ischemia, arrhythmias and sudden death, bears strong theoretical and practical relevance. In this context Heart Rate Variability (HRV), a relatively simple, non-invasive technique thought to provide an assessment of autonomic cardiac regulation, exceeds by now 45,000 hits in the Medline database. Interestingly in about 20,000 hits HRV is combined with heart disease and in about 5000 also with autonomic nervous system (ANS).

In an attempt to interpret the various indices derived from analysis of HRV we must consider that the technique is inherently multipronged, as it is based simultaneously on hard and soft aspects: from bioengineering (algorithms and computer programs) and information (patterns and meaning) to neurophysiology (vagal or sympathetic efferent activity, reticular arousal and Central Autonomic Network) and numerous clinical applications (e.g. arrhythmias, infarction and sudden death in cardiology; behavioral dynamics of arousal in functional diseases; pharmacology on the peripheral flows of autonomic transmitters). Accordingly studies on HRV as a proxy of neural control of the activity of the internal organs should consider this multitude of domains that collectively subserve the "paired antagonistic innervation" (sympathetic and parasympathetic) of the visceral nervous system [1], which being "linked to the central nervous system" is seen as a component of an integrated multi-level regulatory organization [2]. In this schema, a continuous flow of coded neural information reaches the central structures through vagal and sympathetic afferents that subserve important physiopathological functions, such as the sensory dynamics of ischemic pain that is changing according to the input pathway that is involved [3]. Beat by beat cardiac activity is continuously governed by the interaction of inhibitory (mostly vagally mediated, like the cardiac baroreflex) and excitatory (mostly sympathetically mediated, like the sympathetic pressor reflex from distention of the thoracic aorta [4]) reflexes which can be schematized cybernetically as the interaction of negative and positive feedback regulatory loops [5]. Here semantics rather than substance might represent serious barriers to advancement of knowledge.

Following traditional views [6] the implicit model subserving interpretations of HRV is based on an autonomic nervous system described as purely motor, i.e. efferent. According to this approach, it may be difficult to accept some data driven findings obtained with modern multivariate statistical tools [7], which show that the majority of (cardiac) autonomic information is divided in three major hidden variables. They correspond to three separate domains reflecting, respectively, pulse, amplitude and oscillations. They result from the continuous interplay of the complex network of autonomic neural structures, supporting functionally the dual antagonistic innervation [1]. This statistical approach, that requires large study populations, permits however to transform each variable of interest into equivalents that can be directly compared between them. Moreover the transformed variables can easily accommodate the complex nature of the underlying regulatory neural network whereby using multivariate statistics it becomes possible to make inferences about the underlying neural organization. Following a stepwise procedure simply concluded by a radar plot we could reduce the entire array of variables derived from autoregressive spectral analysis of HRV to a percent ranked unitary proxy of integrated autonomic nervous system performance (ANSI) (Fig. 1) [8], which reflects accordingly all the HRV information considering both static and oscillatory information embedded in HRV. This approach (which is by design insensitive to age and gender) permits, in addition, a direct comparison among different patients or among different conditions in the same patients, e.g. in longitudinal designs. Furthermore there is no need to select (usually arbitrarily) which variables utilize as proxies of specific autonomic functions. A typical uncertainty regards to focus on time

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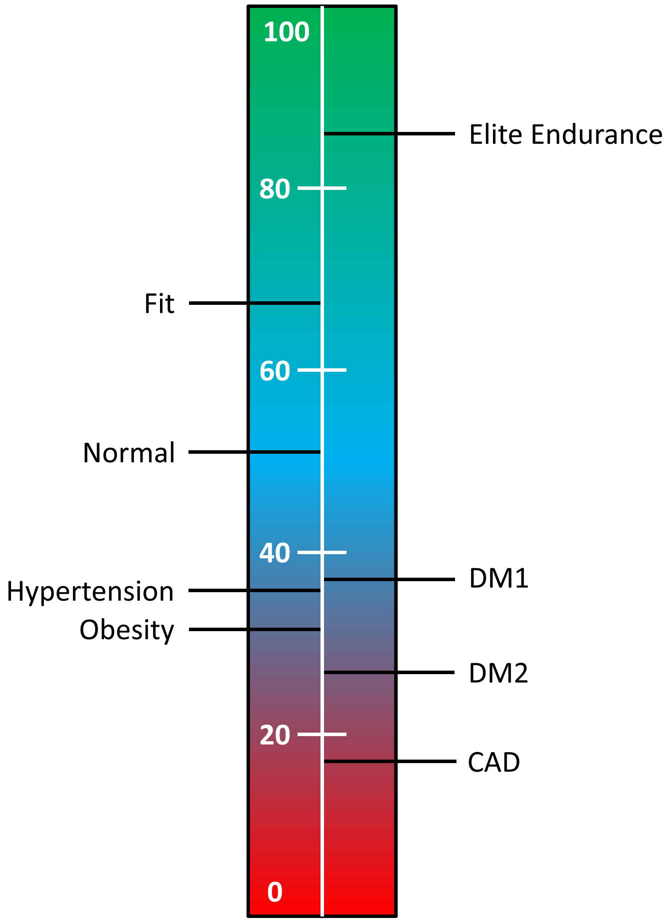

Fig. 1. Modified from [8]. Schematic representation of ANSI value of different subjects/patients groups. Notice that athletes and fit subjects present an ANSI value greater than normal subjects, while patients with chronic diseases present a lower ANSI value. Elite endurance = elite athletes; Fit = fit (but not athletes) subjects; Normal = healthy controls; DM1 = Type 1 diabetes; DM2 = Type 2 diabetes; CAD = coronary artery disease. A 0–100 reference scale (white) is provided in the bar.

domain indices (such as total variance) or on frequency domain indices (such as low, LF, or high, HF, frequency components), the extent to which either LF or HF can be used as metrics to assess sympathetic or vagal activity (or modulation), the different meaning between absolute and normalized power of LF and HF spectral components or the value of derived indices, such as LF/HF. In brief, ANSI reduces into a single parameter all the main aspects that an ANS investigator needs to consider in order to clinically define the ANS subject's profile.

The study by Shah et al. in this issue of the journal [9], addresses the application of HRV to the important task of *predicting* the timing of transient myocardial ischemia in a population of 246 patients, using a novel indicator of autonomic cardiac regulation. Authors faced the critical issue of addressing the validity of the new non-linear technique they use (derived from a specific version of Poincare's plot), as compared to current indices that are based on linearity.

Although the validity of the approach still requires additional work, findings definitely support the contention that "studying autonomic mechanisms …may yield insight into risk stratification and treatment". As a corollary, the growing success of cardiac wearables and availability of advanced IT applications are going to put short term HRV within nearly everybody's reach, maintaining elevated quality standards [10]. It is consequential to predict that the clinical importance of HRV as metrics of ANS in coronary blood flow regulation will find an unprecedented realization in everyday personalized cardiology.

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Declaration of competing interest

None.

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