Benchmarking Heart Rate Variability to Overcome Sex-Related Bias
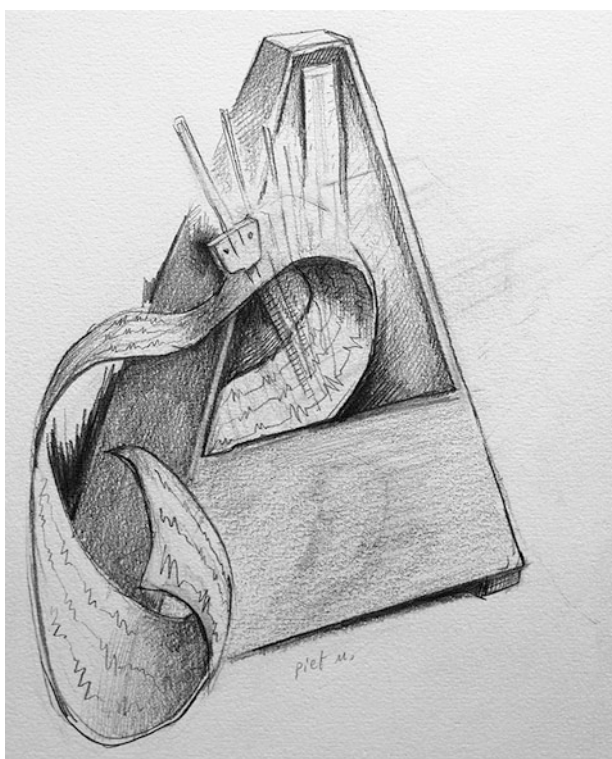
Massimo Pagani, Roberto Sala, Mara Malacarne, and Daniela Lucini

Heart rate variability. Illustration by Piet Michiels, Leuven, Belgium

Abstract

Since the seminal studies by Sayers (Ergonomics 16:17–32, 1973) and Akselrod et al. (Science 213:220–222, 1981) a few decades

ago, it became clear that beat-by-beat oscillations in RR interval length (i.e. heart-rate variability [HRV]) contain information on underlying neural-control mechanisms based on the instantaneous balance between para-sympathetic and sympathetic innervation.

M. Pagani (✉) · R. Sala · M. Malacarne · D. Lucini
BIOMETRA, University of Milan, Milan, Italy

Over the years, the number of studies addressing HRV has increased markedly and now outnumbers 23,000. Despite such a large interest, there is still a continuing debate about interpretation of indices produced by computer analysis of HRV.

The main part of studies relies on spectral techniques to extract parameters that are linked to hidden information. The general idea is that these proxies of autonomic regulation can be useful to clinical applications in various conditions in which autonomic dysregulation may play a role. There are, however, serious shortcomings related to algorithms, interpretation, and the hidden value of individual indices. In particular, it appears that specific training is necessary to interpret the hidden informational value of HRV. This technical complexity represents a severe barrier to large-scale clinical applications. Moreover, important differences in HRV separate the sexes, and age plays an additional confounding role.

We present here a preliminary application of a novel unitary index of RR variability (Autonomic Nervous System Index of cardiac regulation) capable of providing information on the *performance* of autonomic regulation using a percentile rank position as projected on a large benchmark population. A summary of the underlying sympatho-vagal model is also presented.

All affections of the soul are associated with the body

Aristotle, De Anima Book I

Conflicts are frequently over semantics, not substance

Dan Brown, Origin

Introduction

Novelties often arise from the fruitful combination of multiple epistemologies. Accordingly, the same word (say, "anchor") may carry a different meaning according to the context (nautical, construction, or even TV), or may take multiple meanings, thus potentially generating funny, at times comical, effects (*mistaking own wife for a hat*) [1]. Likewise, heart rate variability (HRV) may morph according to the context: In bioengineering it would lean on algorithms and computer programs; in information science it would refer to patterns and meaning; in cardiology it would be associated with arrhythmias, infarction, and mortality statistics; in neurophysiology it would be based on vagal or sympathetic efferent activity; in pharmacology it would be directed to the peripheral flows of autonomic transmitters (acetylcholine for parasympathetic control and norepinephrine [noradrenaline] for sympathetic control); and in medicine and psychology it would mostly be connected to the behavioral dynamics of arousal. Thus, to properly address HRV we must consider both the hard and soft sciences [2].

A Unitary Aim

In 1949, R. W. Hess was awarded the Nobel Prize for Physiology and Medicine for his studies on neural control of the activity of internal organs [3]. Here, again, semantics were implicated. At variance with English usage, dealing with the *autonomic* nervous system, Hess was interested in the "paired antagonistic innervation" (sympathetic and parasympathetic) of the *visceral* nervous system, grouped by various functional regions, "linked to the central nervous system" and therefore seen as a component of an integrated regulatory organization whereby multiple organs aim at a unitary function (*e pluribus unum*). He also conjectured that experimental studies of the neurovisceral system were rendered difficult by the "direct contiguity of functionally multivalent pathways and nuclei [confusing] the . . . elucidation of related symptoms." It was clear, however, that "the parts of the brain communicating directly with the spinal cord at the upper end –

the medulla oblongata, and the segment lying directly beneath the cerebrum, the so-called diencephalon – exert a decisive influence on the vegetative controlling mechanisms"—hence the major contradiction of an *autonomic* section of the nervous system that is (paradoxically) directly controlled by higher structures and communicates with them toward a unitary goal.

From "Autonomy" of Pharmacology to Innervated Medicine

Pharmacological experiments with catecholamines mimicking sympathetic stimulation, and physostigmine-simulating parasympathetic excitation, supported a monolithic view of "autonomic" innervation basically functioning as an overall efferent structure, consisting of two "fundamentally different systems" [4]. It was therefore an obligatory consequence to state that afferent fibers from visceral organs do not have a physiological function because "all autonomic nerves [are] motor" [4]. However, a physiological function was later attributed to visceral neural reflexes, organized like simple reflexes [5], of both negative and positive feedback sign [6] considering that "all parts of the nervous system are connected together" [5]. More specifically, the model underlying neural cardiac regulation considers a complex structure in which both efferent and afferent information travels through

visceral nerves: Cardiac innervation would therefore be characterized by a dual innervation (sympathetic and parasympathetic) made up of mixed (afferent and efferent) nerves.

The neural innervation of the cardiovascular system may remain a laboratory curiosity until new experimental needs suggest the appropriate technique of investigation [3] or new users' needs might suggest innovative applications (e.g., electroceuticals).

The Emergence of a New Paradigm: Bioengineering and Information

Importantly, a change of paradigm followed the introduction of bioengineering principles, shifting attention from pharmacology to biomathematics and devising electrophysiological techniques to investigate the complex dynamics of the (antagonistic) heart-rate response to electrical stimulation of the vagal and sympathetic nerves, whereby the vagus influence dominates the control of heart rate [7]. However, even if this model demonstrated an obligatory interaction between sympathetic and parasympathetic regulatory activity (Fig. 13.1), cardiovascular neural regulation is frequently (and simplistically) schematized as "autonomic" and either sympathetic or parasympathetic. The nonlinear interaction between these two components is frequently left out of the picture.
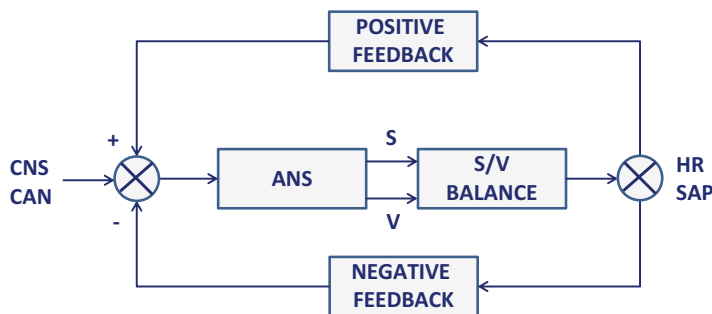

Fig. 13.1 Schematic representation of opposing feedback mechanisms that, in addition to central integration, sub-serve neural control of the cardiovascular system. Baroreceptive and vagal afferent fibers from the cardiopulmonary region mediate negative feedback mechanisms (exciting the vagal outflow and inhibiting the sympathetic outflow), whereas positive feedback mechanisms are mediated by sympathetic afferent fibers (exciting the sympathetic outflow and inhibiting the vagal outflow. (Redrawn from Ref. [6])

The progressive availability of growing computing power employed to study cardiovascular variables on a beat-by-beat basis, initially off line [8] then in real time, has opened the way to assess by proxy the *information* [9] about the dynamics of the balance [6] between sympathetic and parasympathetic regulatory activity.

Initial applications focused on HRV and on ergonomics [8] according to the hypothesis that information on physiological regulatory mechanisms could be coded in the oscillations hidden in the HRV (or rather RR variability) signal. The implications were therefore that a continuous series of symbols (RR intervals from the electrocardiogram [ECG]) could contain *information* [9] on cardiovascular regulation. What remained to be done was to crack the hidden code: We will not delve into the informational properties of scale (amplitude) and pattern because this is beyond the goal of this paper. However, allow us a brief detour to explore what information [9] might bring to our understanding of the physiology of autonomic regulation and HRV.

A Short Biased History of Findings

A seminal study by Akselrod et al. [10] formalized the idea that "sympathetic and parasympathetic nervous activity make frequency-specific contributions to the heart rate power spectrum," thus proposing a parallel between physiology and information. Accordingly, HR fluctuations could furnish a probe (i.e., proxy) of short-term neural cardiac regulation.

From our end, we reasoned that a key element in neural cardiac regulation was related to the obligatory neural interaction between the two branches of the autonomic nervous system, as shown, for example, by electrophysiological experiments on single cardiac vagal efferent fibers [11]. We thus suggested examining the relative powers of low- (LF) and high-frequency (HF) oscillations by shifting the attention beyond raw spectral data and computing normalized units ([nu] essentially focusing on spectral *patterns* as roughly synthesized by the LF/HF ratio) [12]. More importantly, we suggested to assess the excitatory responsiveness to upright stimulation (Fig. 13.2) as a key element of a dynamic protocol [12]. For clinical applications, this test can be simply performed by having subjects stand up for a few minutes.

The general underlying idea was that the key properties of neural structures revolve around dynamic activity, as epitomized by the time-varying spike sequence of nerve firing, which implicitly negates stationarity and implies a large repertoire of coding modalities [13]. Neural information can be hidden in various codes (such as digital or analog [14]), for example, *amplitude* (i.e., average number of spikes per unit time), *frequency* (i.e., instantaneous number of spikes as function of time), *gain* (i.e., a relationship between input and output), *phase* (i.e., a time relation between oscillations; relations between oscillators that we simplified with the ratio between LF and HF frequency oscillations of RR V), and so on, with increasing formality and complexity (such as the nonlinear properties) [15].

The model behind the LF/HF ratio can easily be considered inspired by the historical proposal of the unitary integration of two antagonistic control elements [2]. Numerically it could easily be obtained with a simple mathematical ratio of the LF and HF oscillations extracted from the variability signal. This approach has the advantage of describing changes in pattern [9], such as a power shifts toward the LF region (or vice versa) with a numerical increase (or decrease) of the LF/HF value.

Clinical Applications

Over the years, after a slow beginning and a Task Force Document [16], there was fast growth in the Medline database for HRV, now amounting to >23,000 hits and growing at >1000 hits/year. Surprisingly, however, there is still a need for shared standards of use in terms of underlying neural model and coding, data acquisition, algorithms of analysis, importance of given variables (time or frequency domain), and normative values for health or disease conditions. More importantly, reverse engineering of RR variability
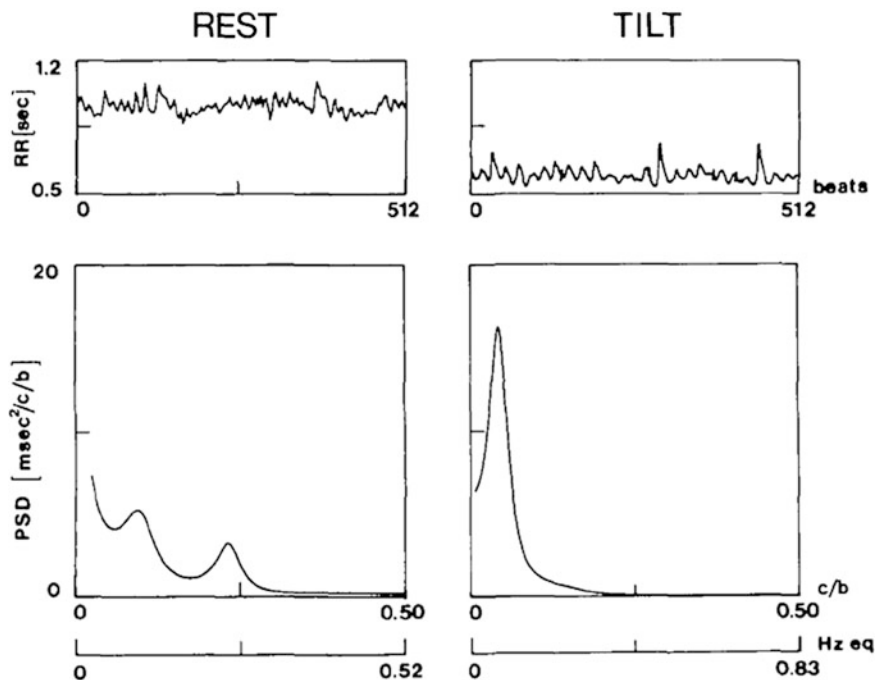
Fig. 13.2 RR interval series, that is, tachogram at rest and during passive upright 90° tilt. In the auto-spectra (bottom panels), two clearly separated LF and HF components are present at rest. During tilt, the low-frequency component becomes preponderant. Notice the change of *pattern*. (Taken from Ref. [12] with permission)

(RR V) should consider all elements together, aiming at reconstituting the unitary function that was broken into several indices by the process of analysis. Said otherwise: Does HRV provide a measure *of* physiology (hard science) or one of information *about* physiology (soft science) [2]?

To substantiate the hypothesis that (LF and HF) rhythms were the key elements carrying the information about a set level of the system, we performed a series of investigations in which we simultaneously recorded cardiovascular variables and electrophysiological signals of efferent sympathetic nerve fibers in human volunteers [17]. The level of sympathetic (and, by inference, parasympathetic) activity was increased or decreased by small infusions of vasoactive drugs, thus eliciting baroreflex-mediated changes (Fig. 13.3). We reported that during sympathetic activation in normal humans, there is a predominance in the LF oscillation of blood pressure, RR interval, and sympathetic nerve activity. During sympathetic inhibition, the HF component of cardiovascular variability predominates. This relationship is best seen when power spectral components are normalized for total power. The use of normalized units accounts in fact for the potentially diverging changes in total power (diminishing) and LF frequency oscillations increasing in relative but not absolute power, for example, with the volunteer standing up or performing light exercise. In any case, synchronous changes in the LF and HF rhythms of both the RR interval and muscle sympathetic nerve activity (MSNA) during different levels of sympathetic drive are suggestive of common central mechanisms governing both parasympathetic and sympathetic cardiovascular modulation. There is a similarity of patterns across different domains (activity of the central and peripheral nervous systems and cardiac rhythm [see Fig. 13.4]). Consequently we proposed [13] that RR V should be interpreted considering at least two different coding modalities: average amplitude (RR and RR variance) and dynamic oscillation (best
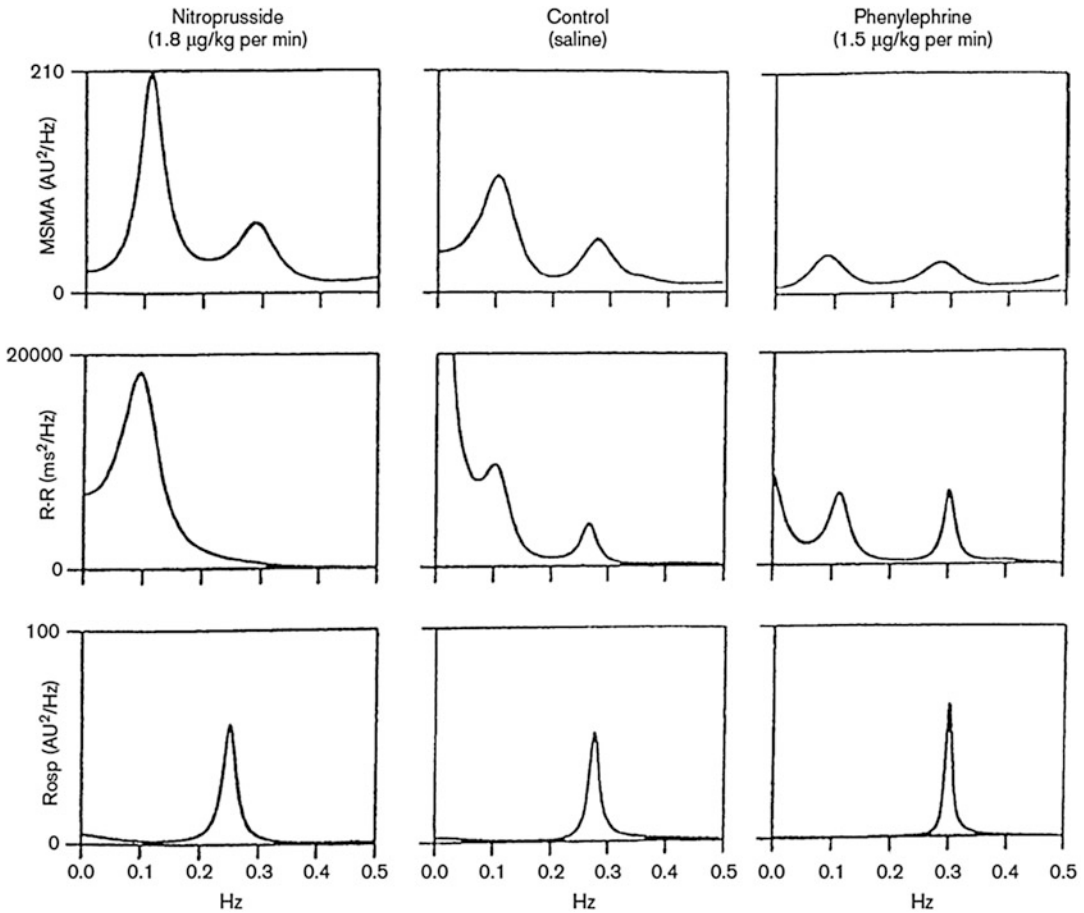
Fig. 13.3 Power spectra of MSNA, RR interval, and respiration (Resp) in a single subject during infusions of saline (Control), nitroprusside, and phenylephrine. During sympathetic activation induced by nitroprusside (left), the LF component of neural and cardiovascular variability signals predominates relative to the HF component. Conversely, during sympathetic inhibition and vagal activation induced by phenylephrine (right), there is an increase of the HF component relative to the LF component. a.u. indicates arbitrary units. Notice the change of patterns. (Taken from Ref. [17] with permission)

appreciated with LF and HF in normalized units). In this way, we avoid the implication of scaling and may easily focus on the change of pattern. As an example, Fig. 13.2 shows the change of pattern from a balanced LF and HF occurring at horizontal rest to a prevailing LF power of RR variability that follows a shift of autonomic balance (toward excitatory prevalence) accompanying the attainment of an upright posture. Similar shifts can be obtained by increasing (or decreasing) the excitatory (sympathetic) set level with manipulation of baroreflex activity using infusions of vasoactive substances. Importantly we should never forget that we are dealing with a complex integrated multi-domain structure.

Information about neurovisceral performance under various conditions might be useful to both physiological and pathophysiological applications. Initially one of the major applications regarded cardiac diseases, in particular, sudden coronary death and arrhythmias [16]. An additional area of potential bias for practical applications, even if not recognized, regards the difference related to sex [20]. It is in fact well recognized that men and women behave differently in terms of cardiovascular pathophysiology.
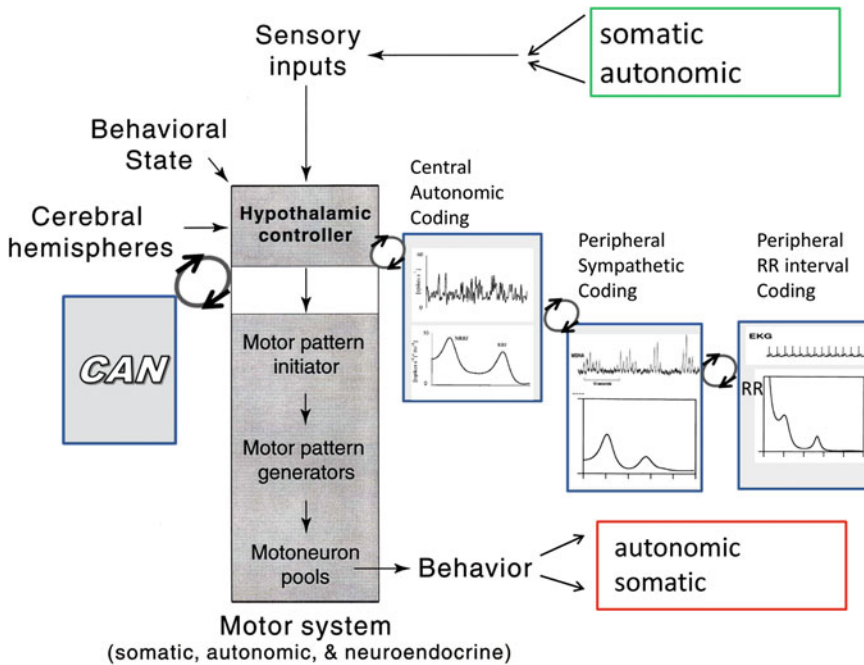
Fig. 13.4 Idealized, schematic representation of the circuitry responsible for generating simultaneous autonomic and somatic behavior as derived from motoneuron pools' activity. This activity is the outcome of the input from sensors (somatic and autonomic) after it has been processed by various controllers. The overall organization maintains an integrated performance of the motor system subdivided into somatic, autonomic and neuroendocrine. In parallel, it is possible to extract central, peripheral sympathetic and peripheral RR interval coding from related variability signals. Notice the similarity of patterns across different domains. (Inspired by Ref. [18], and data taken from Refs. [17, 19])

As an example, let us focus on the higher heart rate and lower arterial pressure observed in women as well as the different profile of cardiac diseases [21], such as the peculiar profile of coronary disease, the different hypertension history, and the emergence of conditions that appear easier to occur in women, such as the Takotsubo syndrome [22]. Approximately 10% of papers stored in the Medline database refer to "sex" or "gender" as a keyword. We will focus on some of the sex-related aspects of HRV, and we will present a novel unitary approach capable of superseding the sex (and age) bias of current autonomic evaluation [23].

Methodology in Practice

The practical value of HRV as a proxy of neural regulation of the heart (rate) depends on two factors referring to the importance of the underlying function (i.e., physiology) and ease of use (i.e., bioengineering).

It is important to point out that these factors, although related to the same aim (detect information on neural regulation), belong to different logical classes. Hence what pertains to physiology should be treated separately from what belongs to methodology. Said otherwise, HRV is *not* a measure of neural activity, although it might provide *information* [9] about neural regulation based on standard experiments employing classical stimulation and ablation protocols [10, 24]. In humans, stimulation of the system can easily be obtained by having the person stand up, thereby inducing a compensatory sympathetic increase and parasympathetic withdrawal (shorthand: "shift of the autonomic balance") [12].

The (metonymic) risk of equating RR V indices to "activity" of the nervous system (*ceci n'est pas un chapeau* [Magritte]) was probably

Fig. 13.5 Spectral analysis of RR interval (upper tracings in each panel) and systolic arterial pressure (SAP) (lower tracings in each panel) variabilities in conscious dogs at rest (CONTROL) and during experimental maneuvers leading to a sympathetic predominance (i.e., nitroglycerin infusion [NTG], treadmill exercise [Exercise], and transient acute coronary artery occlusion [Occlusion]). Note at control the presence of a single major HF component in the RR interval auto-spectrum; in SAP, a smaller LF component is also evident. During sympathetic activation, spectral distribution is altered in favor of low frequency; simultaneously, a drastic decrease in RR variance occurs (notice different scales on ordinates). PSD, power spectral density. (Reproduced from Ref. [6] with permission)
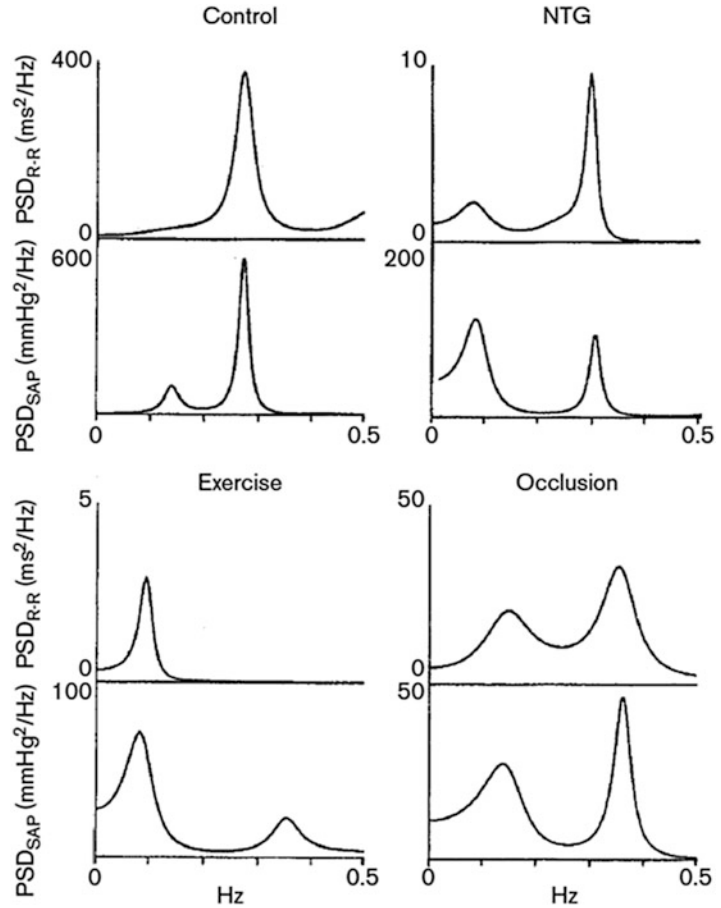
overlooked by a few investigators, and still now (over)interpretations might hover over ANS studies, for example, the interpretation of findings may be that at-rest LF oscillations (raw value) are mediated entirely by the vagus and that on standing by both the vagus and sympathetic arms; the respiratory (HF, raw values) oscillations are solely mediated by the vagus [24].

Based on a different model, acknowledging the obligatory nature of dual autonomic innervation—also derived from direct electrophysiological experiments in cats [11]—we looked at the effects of stimulation and ablation in both animals and humans, focusing not only on raw values of LF and HF but also on the relative power [12]. We saw, for example, that the shift in balance was particularly evident with nomalized-unit evaluation in both animals (using various stimuli

to increase the excitatory set of the system: nitroglycerine, mild exercise, or coronary occlusion) (Fig. 13.5) and humans [17]. In animals, by surgery we could selectively abolish cardiac sympathetic pathways (afferent and efferent). We also showed that other conditions (transient myocardial ischemia, moderate exercise) could increase normalized LF while decreasing RR variance and thus raw values of spectral components [6]. It was apparent that the relative power of spectral components had the capacity to follow more closely the changes in the sympathovagal (or sympathetic–parasympathetic) balance. Importantly the presence of oscillations at LF and HF frequency is found simultaneously in MSNA and vagal efferent activity. This suggests that the relative power of RR V oscillations could be used to seek information about the performance of

neurovisceral regulation [23]. A new unitary index, ANSI, is therefore proposed as a proxy of the performance of the entire system as a self-organizing [9] complex structure aiming at unitary goals [3].

Oscillations in HRV: Spectral Analysis

We will not delve into the technical aspects of methodologies that have been abundantly treated by several excellent reviews (starting with, e.g., [16]). We will only recall that the majority of studies employed parametric fast Fourier transformation algorithms to extract hidden oscillations; only a smaller fraction of studies employed non-parametric auto-regressive algorithms, which are less sensitive to the intrinsic nonlinearities and noise of the RR V signal [12]. The simplicity of obtaining the necessary signal with miniaturized instrumentation puts the use of HRV within everybody's reach. Hence, the importance of focusing on ECG rather than heart beats to obtain the tachogram for analysis, limiting analysis to sinus beat series, and avoiding slow breathing (i.e., entrainment) [25]. In brief, HRV measurement is easy to perform, non-invasive, and cost effective; however, it has several limitations, both methodological and practical.

First, according to specific algorithms, the number of extracted variables might vary. Furthermore, the rich data set might contain redundant variables [16], thus contributing to confound meaning and impairing usability. Finally, the interpretation of HRV indices varies according to the specific context (rest, standing, stress, drugs, etc.) and individual characteristics, such as age and sex or the presence of disease, such as diabetes.

In this context, the results of classical [3] and more recent studies [26] focusing on the hierarchical design of neural visceral regulation and providing evidence for common central mechanisms governing sympathetic and parasympathetic rhythmic activity [17] suggest the clinical usefulness of a unitary view of autonomic information, focusing on overall performance of regulation. We recently investigated whether a unitary Autonomic Nervous System Index of cardiac regulation (ANSI), as furnished by a radar plot [23] considering simultaneously the most informative spectral variables, could provide an easier appreciation of overall autonomic performance. We sought to verify whether a percentile rank transformation could allow the use of results from a large population as a benchmark of the information about autonomic regulation, against which individual autonomic performance could be tested. Hence, swapping physiology (and raw physical values) with information (and performance of process). A brief description of the methodology [12, 27] as in use in our laboratory follows.

Autonomic Evaluation

The day of autonomic evaluation, all subjects arrive in the clinic having avoided caffeinated beverages since waking as well as heavy physical exercise in the preceding 24 h. Recordings are performed between 09:00 am and 12:00 am in an air-conditioned, low-noise room. After a preliminary 10-min rest period in a supine position, ECG and respiratory activity are continuously recorded over a minimum 5-min period with the subject at rest and a 5-min period with the subject standing. Data are acquired with a PC, and a series of proxies of autonomic cardiac modulation are derived using an autoregressive spectral analysis tool [25]. In addition to RR interval (in msec) and RR-interval variability (assessed as total power [TP] in $msec^2$), the program automatically provides spectral components in both the LF (0.03–0.14 Hz) and HF (0.15–0.35 Hz) regions. The power of spectral components is assessed in both $msec^2$ and nu [12]. To include a simple evaluation of the effects of sympathetic activation as produced by active standing and the stand–rest difference, (Δ) in LFnu is computed.

Unbroken Nature of Neural Visceral Regulation: ANSI

Considering the fundamentally "unbroken" unitary nature of neural visceral regulation [16], we introduce a composite unitary autonomic nervous system index of cardiac regulation (ANSI) as a possible way to integrate the partial information spread across multiple autonomic variables (RR interval, TP, LF, and HF components [in both absolute and normalized units], LF/HF, and the stand–rest difference [in LFnu]) into a single comprehensive, heuristic parameter. ANSI is formally given by the areas of the octagon in the individual radar plots [28] that are built for each subject using eight HRV proxies, which are preliminarily scaled from 0 to 100 by the

percentile rank transformation to share a range of variation and unit of measurement. To account for age and sex effects, percentile rank transformation is computed within the groups defined by the combinations of sex and age classes (with thresholds at 30 and 49 years) using a simple routine. ANSI, expressed in percentiles instead of raw, physical values, allows to rank individuals' overall autonomic condition against the reference population.

To minimize redundancy, a second more parsimonious, clinically manageable, version of ANSI is constructed by employing a decreased number of proxies (Fig. 13.6). The minimum number of proxies is selected from among the HRV variables recognized as being substantial by the combination of factor analysis [29],
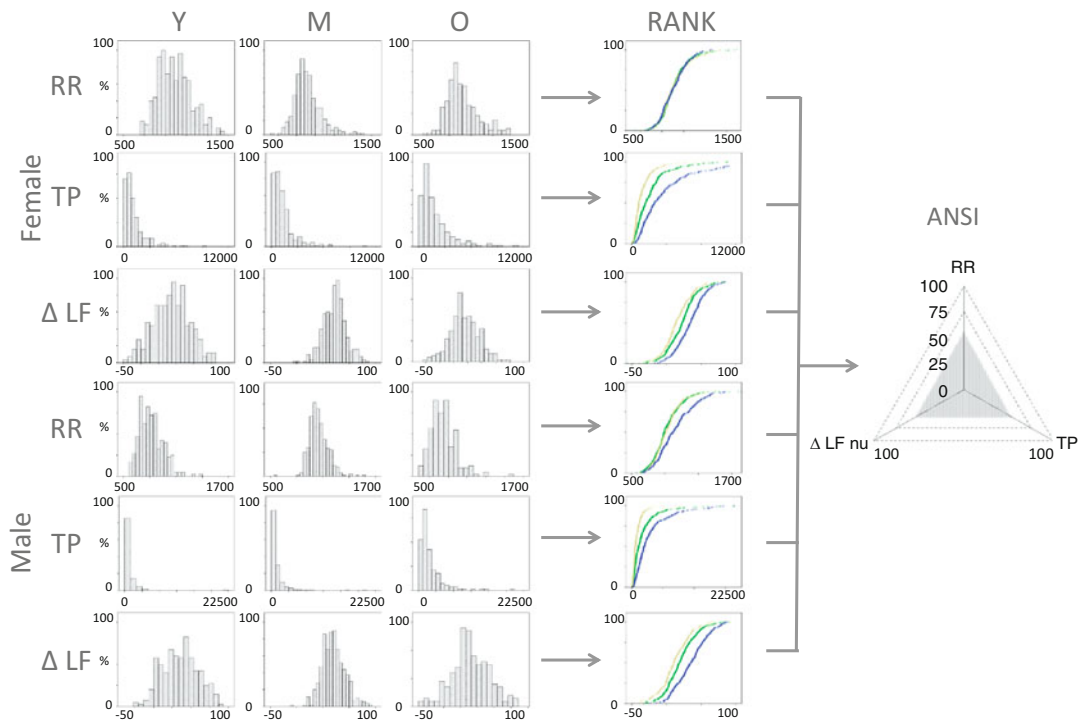

Fig. 13.6 The construction of $ANSI_3$ in its main steps. First, the procedure starts from the three selected HRV proxies (RR, RR power and ΔLFnu) and their distribution within sex and age classes jointly considered (left panels); then it proceeds through their within-group transformation according to the percentile rank (middle panels); and it ends by computing the indicator as the area of the triangle composing each individual radar plot, which is expressed

in percentile (right). Notice that in this procedure the sex (and age) bias is eliminated. Abbreviations: Age subgroups with thresholds at 30 and 49 years, Y = young, M = middle, O = old; RR = RR interval, TP = RR interval power; Δ LF = stand–rest difference in LF nu. X values for RR are in msec, TP are msec^2; Δ LF are in nu. (Taken from Ref. [23] with permission)

which is carried out with the principal factor extraction method and varimax rotation (considering meaningful only loadings >0.4), and physiological underpinnings. A reduced ANSI score is regarded as a good synthesis of autonomic information comparable with ANSI8 if the linear correlation coefficient between the two indices is significant and high (i.e., >0.8). Subsequently, groups approximating the clinical status of individuals were formed by combining together the categories of systolic arterial pressure (with thresholds at 120 and 140 mmHg), body mass index (with thresholds at 25 and 30 kg/m^2), and smoking (no/yes). In this way, the benchmark population is composed of only ambulant, not hospitalized, patients who are devoid of symptoms or acute conditions.

Results

We report herein a summary of a recent study [23] on a benchmark population ($n = 1593$, age 39 ± 13 years), resolving the implications of sex and age differences. Descriptive anthropometric and autonomic data for the reference population, subdivided into age and sex classes, are listed in Table 13.1. Significant within-sex differences between age classes are evident. Table 13.2 further focuses on the clear sex-related difference in the subgroup of normal healthy subjects (free from risk factors, such as hypertension, obesity, or stress). Notice that females have lower BMI, arterial pressure, and mean RR as well as RR TP and RR LF in raw values, whereas HF absolute (a) is similar in both sex groups. Conversely, normalized-unit RR HF is greater in females (RR LF is lower in both absolute and normalized values). The stand–rest difference in normalized-unit LF is similar in both sexes.

Factor analysis applied to the eight HRV proxies (Table 13.3) to extract the potential tendency of spectral indices to form clusters of homogeneous meaning demonstrates that the first three factors reproduce a high percentage (variance accounted for [VAF] = 82.7%) of the total information spread across variables. Analysis further shows that taken individually, the first factor

accounts for 44.0%, the second for 24.2%, and the third for 14.5% of the total variance. Moreover, factor loadings indicate aggregation of the HRV proxies into the following three clusters: normalized autonomic indices (LF nu, HF nu, LF/HF, and ΔLFnu [factor 1]), absolute indices (TP, LFa, and HFa [factor 2]), and RR interval (HR and RR [factor 3]). This suggests constructing the reduced ANSI with three selected proxies (ANSI$_3$), one for each factor.

In addition, binary logistic regression indicates that only the following variables carry significant information about sex prediction (71% correct prediction): RR ($p < 0.001$), RR LFnu ($p < 0.001$), RR HF nu ($p = 0.009$), and Δ stand–rest LFnu ($p < 0.001$). Interestingly, variance of RR—a major time domain index of HRV—does not add significantly to sex information. ANSI (Fig. 13.7), by design, is free from sex (and age) bias, and there is no difference between the sexes, for example, females 56.16 ± 27.79 versus males 54.43 ± 29.15 (not significant).

Discussion

Within the constraints of a complex system, neural visceral regulation can be depicted as the unitary result of a continuous dynamic balance between two opposing neural domains: an excitatory sympathetic one and an inhibitory parasympathetic one [6]. This is, on purpose, a simplified model because, for example, large nonlinearities are not addressed, and the opposing (excitatory–inhibitory) balance is not always appropriate (e.g., it does not consider possible parallel changes in either direction of the two autonomic arms).

However, this simplified model, as a first approximation, permits to argue about the (hypothetical) significance of the complex dynamics of HRV, for example, we can test experimentally whether increases in excitatory sympathetic drive are reflected in a change in spectral pattern: specifically a leftward shift of the spectral profile (Fig. 13.2). This implies that indices (or rather patterns [9]) from HRV can provide information about the underlying setting (prevailingly excitatory or inhibitory) of the entire system. The

Table 13.1 Descriptive anthropometric and autonomic data subdivided into sex and age sub-groups of the study population

		Young	Middle age	Old	
		Mean ± SD	Mean ± SD	Mean ± SD	Significance trend
Females					
		n = 225	n = 341	n = 205	
Age	Years	24.4 ± 3.4	40.2 ± 5.6	56.1 ± 5.5	p < .001
Weight	Kg	61.6 ± 13.6	69.3 ± 23.1	68.2 ± 17.0	p < .001
Height	Cm	165.0 ± 6.6	163.3 ± 6.5	160.7 ± 6.3	p < .001
BMI	Kg/m^2	22.6 ± 4.9	26.0 ± 8.3	26.4 ± 6.5	p < .001
HR	bpm	69.7 ± 12.2	69.5 ± 12.7	69.5 ± 13.3	p = .840
SAP	mmHg	109.1 ± 12.7	119.2 ± 18.8	134.5 ± 21.6	p < .001
DAP	mmHg	69.3 ± 9.6	76.3 ± 12.0	83.1 ± 12.4	p < .001
RR	ms	887.2 ± 155.0	893.7 ± 172.0	896.5 ± 178.1	p = .566
TP	ms^2	4073.7 ± 4195.7	2186.1 ± 2097.8	1250.4 ± 1180.9	p < .001
LFa	ms^2	1090.7 ± 1143.9	598.1 ± 732.2	365.7 ± 759.8	p < .001
HFa	ms^2	1586.8 ± 2157.5	558.4 ± 762.8	284.7 ± 510.0	p < .001
LF nu	nu	45.1 ± 20.6	50.8 ± 19.3	50.3 ± 20.5	p = .006
HF nu	nu	47.4 ± 21.2	41.0 ± 19.4	38.6 ± 20.2	p < .001
LF/HF	–	1.9 ± 3.5	2.4 ± 3.8	2.8 ± 5.3	p = .020
ΔLF nu	nu	34.0 ± 20.7	22.2 ± 21.7	15.7 ± 20.9	p < .001
Males					
		n = 265	n = 361	n = 196	
Age	Years	24.4 ± 3.6	40.1 ± 5.7	58.1 ± 7.4	p < .001
Weight	Kg	77.2 ± 13.3	81.0 ± 13.8	80.7 ± 17.2	p = .011
Height	Cm	179.8 ± 8.6	176.2 ± 7.7	171.7 ± 8.4	p < .001
BMI	Kg/m^2	23.8 ± 3.4	26.1 ± 4.1	27.4 ± 5.0	p < .001
HR	bpm	61.1 ± 13.0	67.2 ± 12.1	66.4 ± 11.3	p < .001
SAP	mmHg	122.2 ± 13.7	130.1 ± 18.3	138.7 ± 19.6	p < .001
DAP	mmHg	71.7 ± 9.4	82.6 ± 13.0	85.8 ± 11.9	p < .001
RR	ms	1028.9 ± 227.5	921.1 ± 181.8	931.8 ± 172.6	p < .001
TP	ms^2	4955.6 ± 8268.4	2959.0 ± 4690.2	1328.9 ± 1357.1	p < .001
LFa	ms^2	1332.4 ± 1830.5	893.2 ± 1302.3	406.3 ± 554.8	p < .001
HFa	ms^2	2003.6 ± 5403.5	727.8 ± 2239.4	177.2 ± 258.6	p < .001
LF nu	nu	49.0 ± 23.1	61.1 ± 22.0	58.1 ± 22.1	p < .001
HF nu	nu	46.1 ± 23.5	32.4 ± 21.4	32.4 ± 20.5	p < .001
LF/HF	–	2.1 ± 2.9	4.7 ± 7.4	4.2 ± 6.5	p < .001
ΔLF nu	nu	35.4 ± 23.7	20.1 ± 22.3	11.8 ± 22.6	p < .001

Abbreviations: *n* number of cases, *BMI* body mass index, *HR* heart rate, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *n* number of cases, *RR* RR interval, *TP* total power of RR variability, *LF* low-frequency component of RR variability, *a* absolute value, *HF* high-frequency component of RR variability, *nu* normalized unit, *Δ* stand–rest difference, *sig.* significance by trend test

autonomic nervous system becomes (or rather returns to being) connected to the central nervous system and to the sensory periphery in order to govern the various "bits" of unitary behavioral goals [30] that accompany everyday life from moment to moment. Early alterations in health status—such as hypertension, obesity, or stress—can thus be estimated from alterations in autonomic proxies. Obviously, the sex (and age) scalar difference in HRV indices might represent an important obstacle to simple clinical use of the methodology.

Table 13.2 Mean data for the study population of normal subjects ($n = 863$)

		Female		Male		
		Mean	SD	Mean	SD	p
Age	Years	34.70	11.67	33.39	11.88	
WEIGHT	kg	59.96	9.29	77.20	11.37	<0.001
HEIGHT	cm	163.97	6.61	178.00	8.85	<0.001
BMI	kg/m^2	22.30	3.14	24.32	2.67	<0.001
SAP	mmHg	110.55	12.74	121.06	12.70	<0.001
DAP	mmHg	70.47	8.62	73.12	8.91	<0.001
HR	b/min	68.43	11.26	62.81	12.61	<0.001
RRMean	msec	900.56	150.07	996.05	211.85	<0.001
RRTP	msec^2	3172.29	3453.82	4291.80	7326.63	0.006
RRLFa	msec^2	865.67	1031.88	1206.49	1752.07	0.001
RRHFa	msec^2	1136.65	1761.24	1593.64	4618.52	
RRLFnu	nu	46.16	19.36	51.96	22.78	<0.001
RRHFnu	nu	45.83	19.94	42.55	23.03	0.027
RRLFHF	–	1.88	3.31	2.53	3.54	0.006
RRLFHz	Hz	0.102	0.027	0.098	0.022	0.030
RRHFHz	Hz	0.27	0.06	0.26	0.06	0.044
ΔLFrrSTAND-REST	nu	30.14	20.00	29.82	24.48	

Abbreviations: *BMI* body mass index, *HR* heart rate, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *RR* RR interval, *TP* total power of RR variability, *LF* low-frequency component of RR variability, *a* absolute value, *HF* high-frequency component of RR variability, *nu* normalized unit, *Hz* Hertz, *Δ* stand–rest difference

Table 13.3 Factor analysis

Variance Accounted For (VAF) 82.7%			
Factor	1	2	3
VAF per factor	44.0%	24.2%	14.5%
	Loading		
HR			−.950
RR			.947
TP		.946	
LFa		.804	
HFa		.884	
LF nu	−.938		
HF nu	.923		
LF/HF	−.719		
ΔLF nu	.775		

Abbreviations: *RR* RR interval, *TP* total power of RR variability, *LF* low-frequency component of RR variability, *a* absolute value, *HF* high-frequency component of RR Variability, *nu* normalized unit, *Δ* stand–rest difference

Factor analysis is performed with principal factor extraction method and varimax rotation

With the emergence of personalized medicine, and the increasing availability of information technology for everybody, the value of indices capable of indicating the quality of control systems in maintaining health may grow, thus increasing their appeal to the market. In addition, it is conceivable that HRV will enjoy ever-increasing success. However, the methodological complexity involved is likely to act as a barrier to the acceptance of the necessary change of paradigm. We argue that a major facilitatory role might conversely be provided by using a single normalized (by rank) index (ANSI) [23], which can facilitate the practical use of the working of the autonomic nervous system. This approach permits to transcend the uncertainties of the physiological information carried by single indices. Thus, the focus might change from (scalar) measures of amplitude of sympathetic or parasympathetic activity, which are implicitly seen as separate (i.e., "autonomic"), to measures of performance of integrated neurovisceral regulation based on the dynamic interaction (pattern or "balance") of sympathetic and parasympathetic (oscillatory) control and the humoral milieu.

Irrespective of the specific methodology, age and sex are potent modifiers of (the amplitude) of

NORMAL vs.	p
FIT	< .001
OBESITY	< .001
HYPERTENSION	< .001
DM1	.202
DM2	< .001
CAD	< .001
ELITE ENDURANCE	< .001
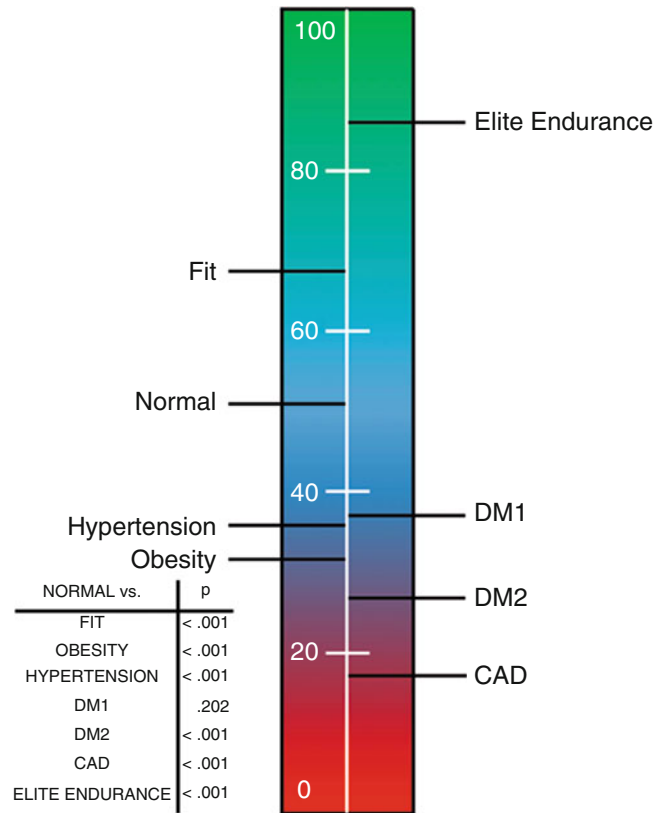
autonomic indices. The use of a unitary proxy (ANSI) permits to address directly the performance (with a 0–100 rank corresponding to the shift from poor to optimal) of overall autonomic regulation as defined against a benchmark of healthy, ambulatory population. Sex differences are recognized at the (scalar) level of raw individual indices, thus reinforcing the hypothesis that patterns and amplitudes provide a different kind of information [9].

We may regret the loss of the direct physiological information carried by the raw values of individual indices [31]. However, this may not be a limitation because mathematical manipulations might generate novel information [32] on the overall performance of the neural visceral regulation as the result of a unitary organization sub-serving complex behavioral dynamics. We might even argue that ANSI might supersede the previous view of the LF/HF ratio [12] as a comprehensive index of the balance between excitatory and inhibitory peripheral (sympathetic

and parasympathetic) nerve activities. ANSI [23] could thus furnish a proxy of the overall setting of the visceral regulation independent of age and sex. However, only large-scale applications will tell if this approach truly represents an advancement in the clinical use of autonomic (or visceral) nervous system assessment.

References

1. Sacks O. The man who mistook his wife for a hat. New York: Summit Books; 1985.
2. Editorial. The soft science of medicine. Lancet. 2004;363 (9417):1247.
3. Hess WR. Nobel Lecture: The Central Control of the Activity of "Internal Organs". Nobelprize.org.Nobel Media AB 2014. Web. 2016. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1949/hess-lecture.html
4. Langley JN. The autonomic nervous system (Pt. I). Cambridge: W. Heffer & Sons; 1921.
5. Burke RE. Sir Charles Sherrington's the integrative action of the nervous system: a centenary appreciation. Brain. 2007;130 (4):887–94.

6. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation. 1991;84(2):482–92.

7. Warner HR, Russell RO Jr. Effect of combined sympathetic and vagal stimulation on heart rate in the dog. Circ Res. 1969;24:567–73.

8. Sayers BM. Analysis of heart rate variability. Ergonomics. 1973;16(1):17–32.

9. Haken H. Synergetics: an introduction. Berlin: Springer Verlag; 1983.

10. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213(4504):220–2.

11. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. Circ Res. 1973;32(2):215–20.

12. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res. 1986;59(2):178–93.

13. Pagani M, Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. J Hypertens. 2000;18(s):1709–19.

14. Mochizuki Y, Shinomoto S. Analog and digital codes in the brain. Phys Rev E. 2014;89(2):022705.

15. Porta A, Guzzetti S, Montano N, et al. Entropy, entropy rate, and pattern classification as tools to typify complexity in short heart period variability series. IEEE Trans Biomed Eng. 2001;48(11):1282–91.

16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart-rate variability: standards of measurements, physiological interpretation and clinical use. Circulation. 1996;93 (5):1043–65.

17. Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation. 1997;95(6):1441–8.

18. Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 4th ed. New York: McGraw Hill; 2000.

19. Massimini M, Porta A, Mariotti M, Malliani A, Montano N. Heart rate variability is encoded in the spontaneous discharge of thalamic somatosensory neurones in cat. J Physiol. 2000;526:387–96.

20. Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-term heart rate variability—influence of gender and age in healthy subjects. PLoS One. 2015;10(3):e0118308.

21. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146–603.

22. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo syndrome. Circulation. 2017;135(24):2426–41.

23. Sala R, Malacarne M, Solaro N, Pagani M, Lucini D. A composite autonomic index as unitary metric for heart rate variability: a proof of concept. Eur J Clin Investig. 2017;47 (3):241–9.

24. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Phys. 1985;248(1 Pt 2):H151–3.

25. Lucini D, Marchetti I, Spataro A, et al. Heart rate variability to monitor performance in elite athletes: criticalities and avoidable pitfalls. Int J Cardiol. 2017;240:307–12.

26. Beissner F, Meissner K, Bar KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J Neurosci. 2013;33(25):10503–11.

27. Badilini F, Pagani M, Porta A. Heartscope: a software tool addressing autonomic nervous system regulation. Comput Cardiol. 2005;32:259–62.

28. Saary MJ. Radar plots: a useful way for presenting multivariate health care data. J Clin Epidemiol. 2008;61(4):311–7.

29. Sala R, Spataro A, Malacarne M, et al. Discriminating between two autonomic profiles related to posture in Olympic athletes. Eur J Appl Physiol. 2016;116(4):815–22.

30. Engel BT. Psychosomatic medicine, behavioral medicine, just plain medicine. Psychosom Med. 1986;48(7):466–79.

31. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation. 1997;96(9):3224–32.

32. Lucini D, Solaro N, Pagani M. Autonomic differentiation map: a novel statistical tool for interpretation of Heart Rate Variability. Frontiers Physiol. 2018;9:401