

AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

## *Editorial*

It is for me a great pleasure to host on this issue of AMPS QT Prof. Massimo Pagani, a personal friend and an inspiring figure from the very early days of my career when I was working on my thesis at the Politecnico of Milan. Since then, we built a creative research relationship that continued through the years and that is still productive, with direct impact on all AMPS technology that relates to some degree to the assessment of the autonomic nervous system.

From a scientific perspective, Prof. Pagani does not need many introductions. His 1986 Circulation Research original study on conscious dogs is one of the trademarks and (still today) one of most referenced articles in the literature [1]. He and his group introduced (and named!!) the sympatho-vagal balance and, most importantly, a way to assess and quantify it from the surface ECG.

Everybody who has ventured into the quest to discern the clinical understanding of heart rate variability knows Pagani and his papers and I am truly honored to host an historical and valuable critical review on the subject in our newsletter. I am positive that all of you will enjoy it as much as I did!

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AMPS LLC

[1] Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, 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 Aug; 59(2):178-93.

## *A Noteworthy Contribution:*

### **The Sympatho-vagal Balance: a Biased History**

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#### *Foreword*

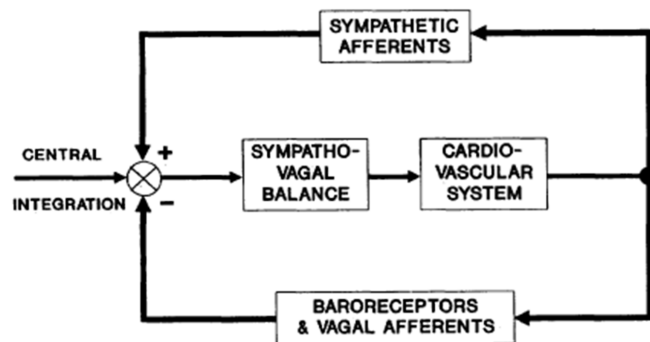
To address the topic of this short story we must first venture into a world of multiple epistemologies: computer science, neurophysiology, behavior, and medicine, considering both hard and soft sciences [1]. Such an endeavor carries an unpredictable risk. After playing croquet, Alice would tell us to beware of the flamingos that might bend their necks, or the ball might run away, leaving us in a muddle [2]. If we are not scared to proceed along these lines we may ask ourselves the key question: why should we care about an index of sympatho-vagal balance? Our response must consider the goal of estimating the dynamics of central arousal from an easily obtainable peripheral signal: the continuous ECG-derived tachogram. This goal needs the balanced collaboration of computer science (and bioengineering) and neurophysiology to produce a proxy of the workings of the visceral nervous system, describing visceral behavior [3] and providing quantitative indices of the elusive topic of subjective stress, functional syndromes and lifestyle related disease risk. The overall goal might be that of

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contributing to Hippocrates' ideal of a "medicine that has been discovered with a view to health, and saving of men, avoiding the life styles from which pain and suffering might come" [4].

### ***A matter of semantics***

It is not rare for a word (say: anchor) to change of meaning according to the context (nautical, construction, or even TV programs). Likewise, Heart Rate Variability may be morphing according to the context. In bioengineering it would lean on algorithms and computer programs; in cardiology on arrhythmias, infarction and mortality statistics; in neurophysiology on vagal or sympathetic activity; in pharmacology on the peripheral action of autonomic transmitters (acetylcholine for parasympathetic and nor-adrenaline for sympathetic control); in lifestyle medicine mostly on behavioral dynamics of arousal. From this particular point of view, the integrated idea of sympatho-vagal balance may be useful.



*Figure 1: Schematic representation of opposing feedback mechanisms that, in addition to central integration, subserve 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).*

A few decades ago the dawn of computers into the medical arena permitted to tackle novel, unthinkable objectives [5]. Accordingly, few seminal papers addressed the potential capacity of adapting FFT algorithms, a powerful computer tool, to the analysis of RR variability as a means to discretely evaluate the elementary components of work-related stress [6] or

vagal and sympathetic influences on heart rate regulation [7]. Both studies highlighted the possibility to extract indices related to underlying mechanisms at specific oscillatory patterns; of relevance, those centered at about 0.1 Hz (low-frequency or LF) and at those associated with respiration (high-frequency or HF). Subsequently, in a preliminary report from our group on hypertensive patients, spectral analysis of heart rate variability was proposed as an index of sympatho-vagal interaction [8]. Since then, the numbers of hits with HRV as a keyword reached more than 20.000, with those referring to the specific issue of the interaction between the two autonomic branches reaching 1.100.

Various groups from different fields were already exploring the usefulness of RR variability in areas ranging from sleep in children [9], aging and respiration [10] or more in general hemodynamic regulation [11, 12]. The value of parametric spectral analysis techniques more resilient to critical aspects of the near stochastic RR variability signal was also addressed [13].

We were however joined in publishing studies dealing specifically with the hypothesis that the dynamic regulatory balance of the two autonomic branches could be explored with analysis of hidden rhythms in the RR variability balance in 1989 [14, 15].

We could luckily stand on the shoulder of giants. In his Speech for the 1949 Nobel prize for physiology or medicine, WR Hess made two far-reaching statements [16]:

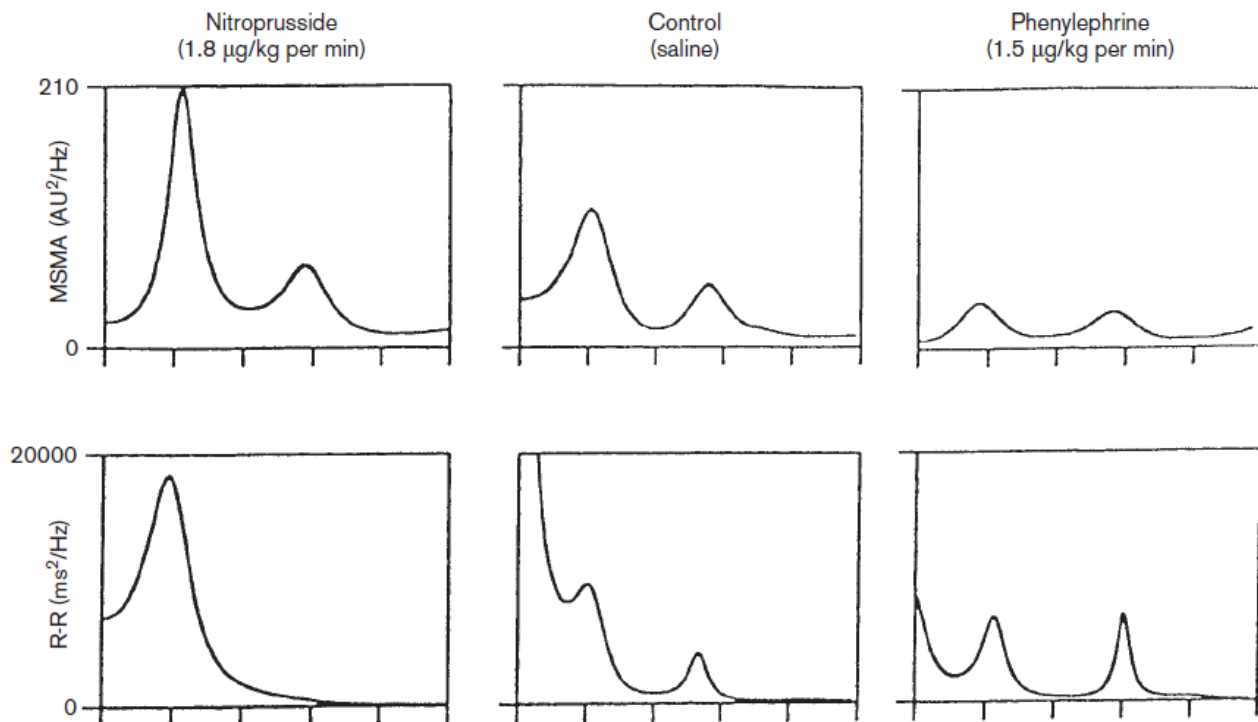
1. "every living organism is not the sum of a multitude of unitary processes, but is, by virtue of interrelationships of higher and lower levels of control, an unbroken unity".
2. This integration depends upon a "paired antagonistic innervation (sympathetic and parasympathetic) of the internal organs".

On the other hand, Moruzzi [17] had proposed an application of the inverted U model of cue function [18] to explain the relation between levels of reticular activation and behavior.

In addition, Hess (who worked in Zurich) observed that the morphological and physical structure of the so-called vegetative nervous system becomes “autonomic” in English usage. *Nomen omen*. This semantical mismatch may lead to a possible implicit contradiction between *ideas* of a complex neurovegetative system, as a dynamic bridge between centers and periphery as opposed to an autonomic (i.e. independent from the centers) effector system. In the last few years, several investigators seem to

start exploring the potential role of a functional integration of central with peripheral neurovisceral structures [19].

In summary, bioengineering may provide tools (i.e. computer analysis of RR variability) for applying physiology to psychology and behavior in medicine [20]. It should be kept in mind that the goal of advantages and criticisms should be always made context-dependent.



*Figure 2: Spectral profiles of RR and MSNA (a direct nerve-related measurement of sympathetic activity) variability in a volunteer, at control (center panel), during reflexly increased (nitroprusside, left panels) and reduced sympathetic activity (Phenylephrine, right panels). Notice the shift in variability profiles towards Low Frequency during sympathetic activation and the reverse during inhibition, as a mirror of a shifting sympatho-vagal balance.*

### Sympathetic reflexes and positive feed back

Malliani’s seminal studies on cardio-cardiac reflexes [21] and subsequent investigations [22] led to the proposal of a neurovegetative model of cardiac regulation based on the continuous interplay of negative and positive feedback systems, integrated with central command, and governing a continuous, instantaneous balance of sympathetic and vagal activity to the SA node [23].

In 1986, we sought to “assess the relative role of vagal and sympathetic activities in determining the

variability in heart rate and arterial pressure at rest and during induced changes of autonomic regulation” analyzing conditions of normal and altered (either increased or decreased sympathetic activity) [24]. We also proposed the use of a dynamic protocol, as with a rest-stand model, in order to explore the capacity of the system to respond to an (excitatory) stimulus. We concluded that the ratio between LF and HF powers could furnish a convenient index of the physiological balance between sympathetic and vagal regulatory activity. More detailed information can be gleaned from simultaneous recordings of neural activity, such as the muscle sympathetic nerve activity (MSNA), and

RR variability signals (see Figure 2). An investigation addressing the changes in absolute (i.e. average) and oscillatory (i.e. phasic) changes in sympathetic activity in response to variations in pressure intended to alter the (central) balance between excitatory and inhibitory regulation showed a compelling evidence for a relationship between changes in autonomic drive and cardiovascular LF and HF oscillations [25]. The coherence between HF and LF fluctuations in MSNA and RR interval (see Figure 3) and the persistence of this synchrony of rhythms across a range of pressure changes (in line with previous models), supports the idea of common central mechanisms governing sympathetic and parasympathetic rhythmic activity. Within this design, it should be mentioned that there is a difference of meaning between modalities of autonomic activity (i.e. coding of nerve impulses) such as average and oscillatory neural codes [26].

The intrinsic nature of sympatho-vagal balance had a clear antecedent in historical experiments on anesthetized dogs showing that electrical stimulation of either autonomic branch (parasympathetic or sympathetic) demonstrated a strong interaction at the SA node[27]: HR changes were indeed faster with vagal as opposed to sympathetic stimulation; and greater if vagal stimulation was combined with sympathetic stimulation. Selective information on either vagal or sympathetic regulation could thus be hidden in the speed (hence frequency) of RR changes.

In 1997, a critique to the use of sympatho-vagal balance was published [28]. The sympatho-vagal concept was considered mostly as a simple mathematical manipulation of HRV and that as such it imposes attributes on physiological regulatory mechanisms that they do not possess. Nerve traffic, and its effects on RR variability, could be likened to the ocean: it is the depth (i.e. intensity of firing) rather than its variations (“ripples on the sea”) that are important. These critical remarks however disregard the role of indices of dynamic LF/HF interaction as proxy of sympatho-vagal balance, implying that RR variability and MSNA variability might follow different coding modalities [29].

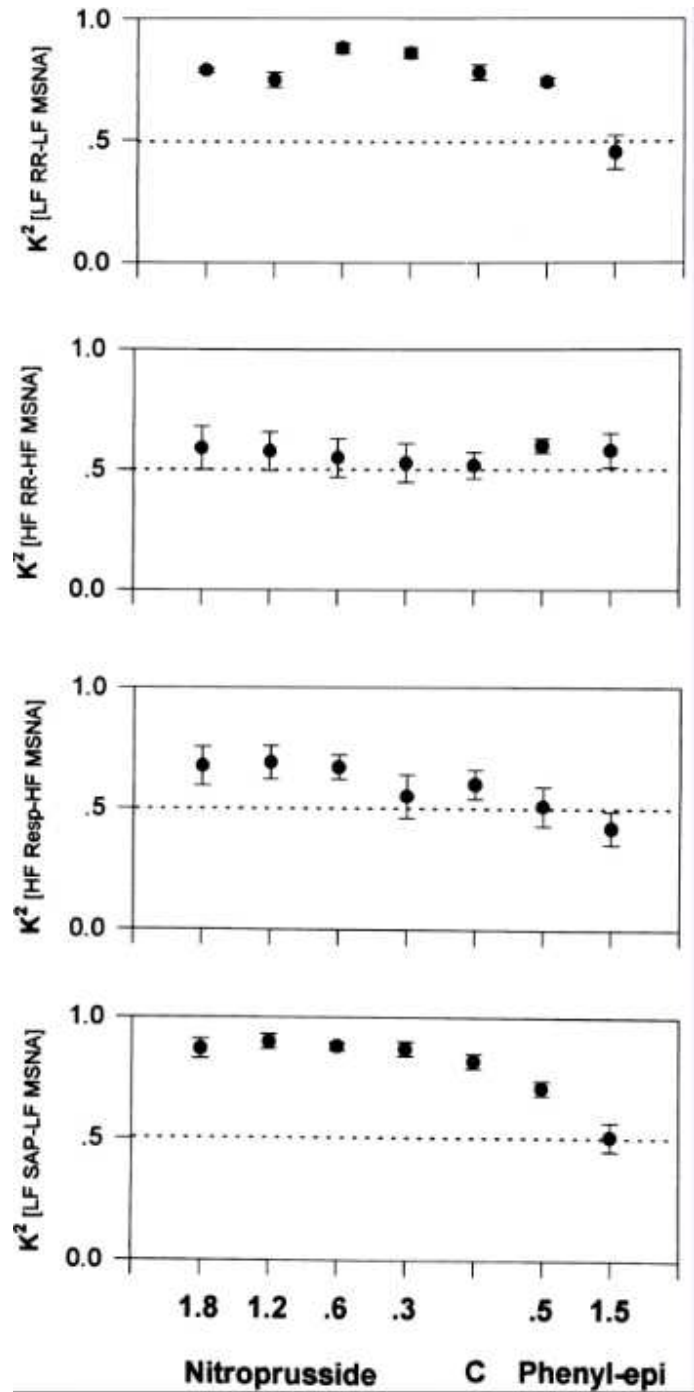


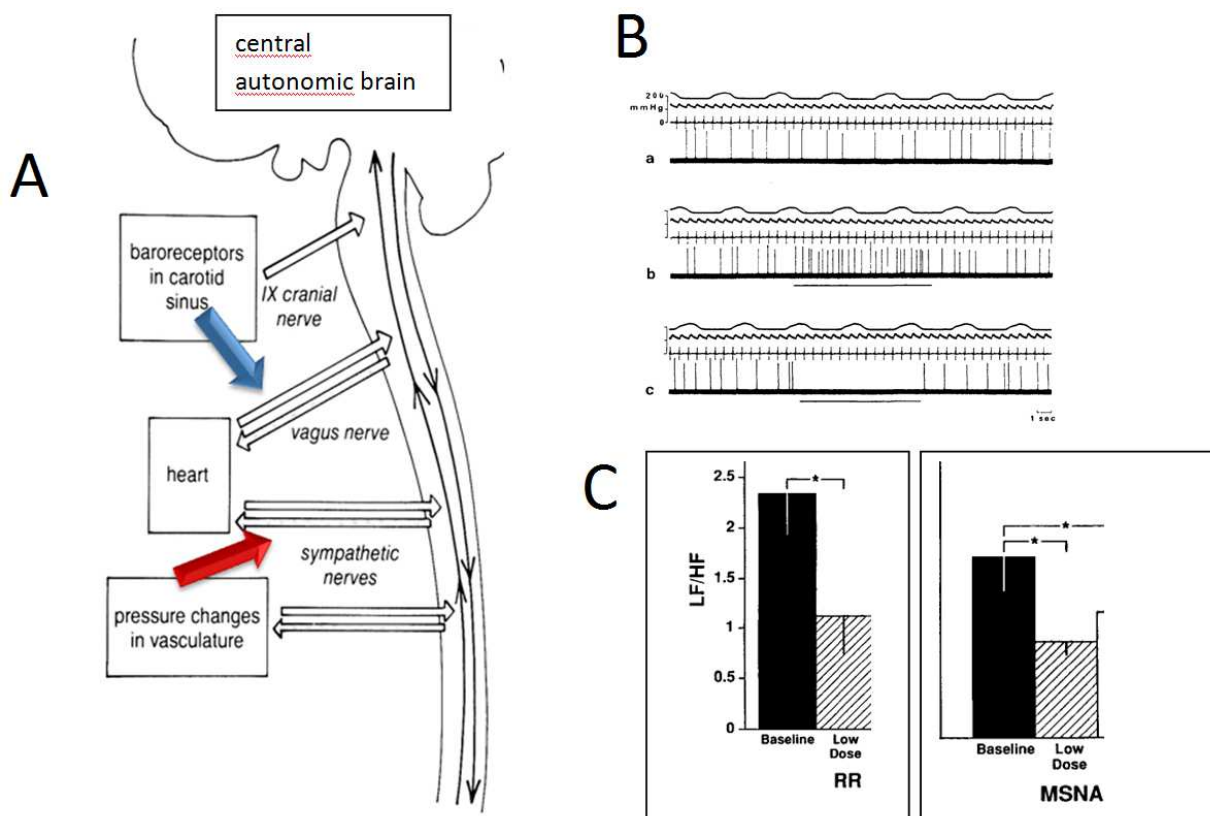
Figure 3: Average coherence values ( $K^2$ ) between (from top to bottom) LF components of RR interval and MSNA, HF components of RR interval and MSNA, HF components of respiration (Resp) and MSNA, and LF components of SAP and MSNA. The dotted lines indicate the threshold value (0.5) above which there is a significant correlation between oscillations in different variables. C indicates control; Phenyl-epi, phenylephrine.



An interesting and constructive debate followed for some time [30] and, among various suggestions, the simple RR variability was indicated as the most suitable signal [31]. Challenge to the sympatho-vagal model usually disregards the fundamental difference between absolute and normalized units [32]. Accordingly, the complexity of codes in neural autonomic regulation cannot be utilized in the clinical assessment. Given the importance of baroreflex, it is worth mentioning that there is a disconnection between the normalized LF component (in normalized units) and the baroreflex sensitivity (the so-called  $\alpha$  index). Indeed, from a series of 191 subjects ( $43 \pm 13$  years old), we found a strong correlation between the absolute LF RR (in msec<sup>2</sup>) and  $\alpha$  LF ( $r = 0.608, P << 0.001$ ), but no correlation between LF RR in normalized units and  $\alpha$  LF ( $r = 0.093, P = 0.209$ ) [33].

A more detailed discussion of the conditions in which LF RR increases independently of the baroreflex is provided elsewhere (e.g. see Figure 1 of [26]).

We may summarize our position stating that in closed-loop conditions, 2 main rhythms, 1 marker of excitation and linked to sympathetic excitation (LF) and 1 marker of inhibition and quiet and linked to vagal predominance (HF), would be organized, in physiological conditions, in a reciprocal manner (akin to Hess's dual antagonistic innervation). These rhythms underscore the heuristic value of sympatho-vagal balance as a proxy, not of neural activity at the periphery, but of the balance between central inhibitory and excitatory set (i.e. arousal in Moruzzi's terms) [17], which is correlated with an increased sympathetic drive [25, 34].



**Figure 4:** Schematic representation of the circuitry underlying sympatho-vagal regulation of the heart (left panel, A). Notice that vagal and sympathetic circuits contain both efferent and afferent (sensory) fibers. Changes in efferent activity might result from altered inputs from the periphery (right panel, B) or altered signals from the central structures (right panel, C). In panel B, efferent vagal activity to the SA node (control in a, anesthetized cat) is exquisitely sensitive to inputs from the periphery: increased input from the contralateral vagal afferents initiates a vagal reflex activation (b), while sympathetic afferent stimulation initiates an inhibitory reflex (c)[37]. In panel C, effects of increased central parasympathetic activity with low doses of atropine (2mg/kg) on LF/HF ratio are represented for both RR and MSNA variability. Notice the reduction of the LF/HF ratio in both cases[36].

Finally, it should be recalled that the interaction between vagal and sympathetic mechanisms may manifest itself also as the reduced vagal RR response to increased circulating catecholamines, which may obscure the underlying neural rhythms [35].

Increasing central parasympathetic activity with low dose atropine is associated to a shift from LF towards HF oscillations in both RR variability and MSNA, reiterating the concept of common oscillatory properties of cardiac and sympathetic regulatory signals [35, 36]

### ***From keyboard to real life***

In order to apply the concept of sympho-vagal balance to practical, real life conditions, we must reiterate that we are dealing with nothing more than a concept. However, this concept is critical to understand the complexity of medicine as an innervated entity [38].

We do not dwell into the individual cases (from hypertension, to myocardial infarction, or even cancer caregiving, or elite sports training) where the use of spectral analysis of RR variability might be helpful. Nevertheless, a critical component of the overall process is represented by the software applications that are employed. In this sense, we feel that

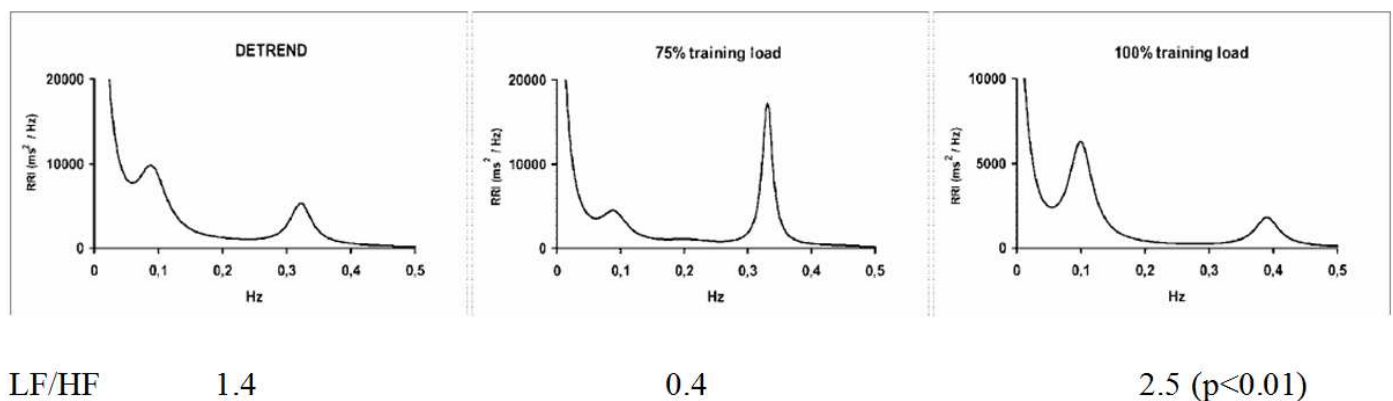
employing parametric techniques (such as the autoregressive or AR modeling approach) paired with user-friendly tools for an adequate analysis review (as with Heartscope) is of paramount importance [39].

We would also add that differences in techniques might matter. Indeed, parametric and nonparametric spectral analyses provide indices that cannot be treated as interchangeable, even if they give similar results [40].

Key to the correct interpretation is therefore also the choice of methods, and on top of that the correct setting (e.g. the model order in case of AR algorithms).

### ***Sympho-vagal balance in the age of personalized medicine***

The mass application of individual data and the explosive development of molecular biology and in particular genetics, permits to plan the detailed titration of medical interventions, up to the extreme level of individualized medicine: restoring the tradition of the personal physician of times past. Precision in medicine may be an extension of this novel paradigm, facilitated by the large scale use of computers and Internet applications.



*Figure 5: Representative example of the progressive shift of LF and HF balance of RR variability spectra in a young rower from control detrended condition (left), to mid season, moderat load training (after 6 months, middle) and (right) at peak, precompetition, training load. Notice the swing in LF/HF balance throughout.*

The use of bio markers may thus be applied not only to molecules but also to functions, whereby altered autonomic regulation, as exemplified by sympatho-vagal balance (using LF/HF as metrics) may become a metric of deranged function. LF/HF could thus furnish interesting targets for functional therapy or preventive intervention.

An area of growing interest refers to the quantification of the autonomic regulation as a consequence of planned physical training.

If you followed this biased narrative, you may also like the representative example shown in Figure 5, showing the capacity of autonomic indices to disclose the shift from (putative) vagal to (putative) sympathetic predominance in a young rower throughout a year of intense training, until the junior rowing world cup [41].

A similar approach could be used in population studies to assess the potential beneficial role of regular physical activity or in general of lifestyle optimization on autonomic regulation.

Trying to balance old and new, we believe, however, that the major part of the story still needs to be told.

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## *News: AMPS, CiPA and the FDA open-source library*

On December 6th, during the CSRC annual meeting which focused on the CiPA advancements, the FDA team announced the release of the open source code with the algorithms used for the computation of the ECG parameters (JT<sub>p</sub>, TpTe) recently published.

AMPS is particularly focused on this initiative and we've already started to work on its implementation, which will be made available to customers, primarily in an upgraded version of CalECG. Timing of these releases will be known during the early part of January and will be adequately and promptly announced. During the first quarter 2017 we also plan to organize a public webinar to review the nuts and bolts of our technologies and its regulatory implications, also including the state of the art with respect to the digital submission of 10-seconds and continuous ECGs in the FDA warehouse. Finally, the next issue of AMPS QT newsletter, due at the end of March 2017, will be entirely dedicated to this topic. Stay tuned!

## *Products News*

### **Looking forward**

In early Q1 we will release a new version of CER-S, including the following revised platforms:

- Continuous ECG beat detection and classification
- ECG beat editor
- Arrhythmia detection and Arrhythmia editor

Later in Q1/Q2 2017 AMPS is planning to release:

- A new version of Fat-QT and TrialPerfect with the latest version of BRAVO algorithm, released in Q1.
- A new version of CER-S, including the following revised platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor (including fully renewed algorithm)
  - Arrhythmia detection and Arrhythmia editor

And with the addition of measuring capability both on beat-to-beat basis and averaged time-templates.



*On Sunday October 16th AMPS teams and families attended the Brescia "Race for the Cure", an initiative organized by Susan G Komen (the international organization fighting breast cancer) in association with the Poliambulanza di Brescia, our partner hospital in the Italian telecardiology project. This picture was taken just before the start time of the race. Of note, the AMPS team (at least a couple of its members) provided an outstanding performance!*