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Review Article

Autonomic Nervous System Assessment: A Novel Window on Clinical Stress

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Abstract

Stress is one of the most used, or abused, word in the world because of its ubiquitary involvement in health and disease. Both direct (involving bodily control systems, such as the Autonomic Nervous System, ANS) and indirect mechanisms underlay the relationship between stress and important conditions, like ischemic heart disease, hypertension, metabolic syndrome, cancer and functional syndromes. Stress management may also be important as a component of new strategies to better prevent/treat these conditions.

Historically reliable evaluation of ANS was usually performed with invasive and intrusive techniques like MSNA or catecholamine's spillover, relegating it preferentially to specific research settings. In the last decades the evolution of non-invasive techniques, like spectral analysis of heart rate variability (HRV), rendered the clinical use of ANS evaluation widely available offering a new window for the study of stress and functional syndromes, and in general of patients who report medically unexplained symptoms. HRV is a non-invasive, non-intrusive technique, based on indices derived from beat by beat RR variability, which furnishes markers of sympathetic and vagal modulation of the SA node, represented respectively by low frequency and by high frequency component of RR interval variability, possibly complemented by baroreflex gain assessment (which requires the simultaneous recording of ECG and arterial pressure waveforms).

Recently we showed the feasibility of testing simpler metrics of cardiac autonomic regulation based on a multivariate unitary index particularly in clinical setting providing a composite unitary Autonomic Nervous System Index of cardiac regulation (ANSI). This index (expressed in percentile rank) integrates the partial information spread across multiple autonomic variables and represents a proxy of quality of autonomic regulation, assessed against a benchmark population. [n = 1593, age 39 ± 13 yrs]. This integrated approach minimizes the major drawback of RR variability that derives from the multiplicity of indices that are produced by analysis and lack of consensus on which index to select as autonomic proxy.

ANSI might thus furnish a simple proxy of the quality of autonomic regulation, and be employed in a variety of clinical fields, such as in functional syndromes or in the management of stress, fostering a wider application of autonomic evaluation in the clinical arena.

Keywords: *Autonomic Nervous System; Stress; Health; Disease; Functional Syndrome*

Abbreviations

A.U.: Arbitrary Units; 4SQ: Somatic Stress Perception Questionnaire; ANSI: Autonomic Nervous System Index (Light Bars Denote: Before Intervention; Dark Bars Denote: After Intervention)

Importance of stress in chronic non-communicable diseases

Stress is one of the most used, or abused, word in the world, at least in the western part. There are many meanings attached to the concept of stress, reflecting its psychological, physiological, behavioral or social aspects [1-3]. The definition to which we will refer [4], in the full awareness that it might be improved, is: "stress may be considered as the psychological, behavioral and physiological (or pathophysiological) consequence of the interaction between a subject and a stressor; considering as "stressor" everything (acute or chronic) present in the environment or in the subject's mind that could be perceived as important, dangerous or potentially capable to modify, both negatively or positively, the subject's life [5]. Stress per se [6] is a physiological, useful, response [2,7] to re-establish homeostasis through a complex process. This implies regulatory systems (hypothalamic-pituitary-adrenocortical, autonomic nervous system and immunity) [8-14] modulated by subjective perception of stress, individual (genetic, biological, psychological) differences and behavior [13]. The negative nature of stress appears when the final result is not adaptation, homeostasis, but when bodily (somatic symptoms or diseases such as coronary artery diseases, and functional syndromes [3,12,15,16]) or psychosocial effects (change of the mood, unwillingness to change, isolation [17,18]) appear.

Negative consequences of stress on health are so important that nowadays stress, modulated by genetic predisposition [2,4,12], may be considered a risk factor for coronary artery disease and a growing number of studies show its association with other conditions such as hypertension, metabolic syndrome, arrhythmias, depression, cancer, immunological, infective or gastrointestinal disorders [3,12,19-25]. Moreover it may foster clinical condition characterized by somatic symptoms not explained by the presence of "traditional" medical disease [26], like irritable bowel syndrome, fibromyalgia, psoriasis, chronic fatigue syndrome and chronic stress syndrome [27-32], conditions which are nowadays identified as Functional Syndromes. In the past, these clinical entities were often considered as psychiatric disorders, due to the lack of possibility to find attendant biological alterations and to the frequently present association with anxiety and depression. Nowadays a growing number of scientific studies and clinical evidence suggests that biological factors, such as mitochondrial dysfunction [33], genetic predisposition [34], reversible functional disturbances of the nervous system or immune system [16,22,27,35-38], central nervous system alterations [39], are important in many functional syndromes. Depression and anxiety frequently characterizing functional patients may be more the consequence, rather than the cause, of the symptom/s and of the lack of support/treatment [40].

Mechanisms underlying the relationship between stress and diseases are multifarious, being both direct (involving bodily control system) and indirect [5]. These latter ones are mostly associated to negative behavioral responses related both to choices of unhealthy life styles (such as smoking, incorrect nutrition, sedentary life, abuse of alcohol or drugs) [2-4,8,12], and to psycho-social/relational changes like isolation [41] or reduced compliance to medical prescriptions [4,12].

Among direct mechanisms, hypothalamic-pituitary-adrenocortical axis and their inter-relationship with immune system and consequently inflammation [7,9,11,21] are well described in the literature. In this paper, we mostly focus on the role of autonomic nervous system (ANS) as important mediator of stress response. In case of acute stressors the autonomic nervous system provides the most immediate responses which provoke rapid alterations in physiological states through neural innervation of end organs, aiming to maintain physiological integrity [10], while chronic stress conditions may induce chronic autonomic nervous system dysfunctions [19,42], generally characterized by sympathetic overactivity [4,19,22,42]. Moreover, ANS is strictly linked both with Hypothalamic-pituitary-adrenocortical axis [7] and with immune system [10,21].

From a clinical point of view, the increasing interest in stress is not only due to the importance to better understand the great number of factor implied in the pathophysiology of some important conditions like ischemic heart disease, hypertension, metabolic syndrome, cancer and functional syndromes, but also to the possibility to define new strategies to better prevent/treat these conditions [19,30,41]. Applying a multidimensional approach that considers, further to drugs or surgery, also psychological strategies primarily based on cognitive behavioral therapy in order to foster lifestyle change and relaxation techniques may improve their prognosis.

In this context, there is abundant evidences showing that stress management is a valuable tool in clinic [30,41] and that the modulation of ANS by stress management technique [19,43] may be of particular practical interest.

Autonomic Nervous System and Stress

The tight link between behavior and diseases has historical roots in the concepts of disease as God's punishment for human sin, such as Ananias's and Sapphiras' death because of their lies regarding the sale of their field, as reported in the Acts of Apostles. More recently the scientific interest focused the interaction between heart and brain [44], such as in the models of homeostasis and in the fight-or-flight response, essentially governed by the antagonistic interaction between parasympathetic and sympathetic arms of the visceral (otherwise known as "autonomic") nervous systems [45].

Classically depicted as a pure effector system, based on the vagal and sympathetic dyad innervating all organs, more recently attention has been brought to a cybernetic model, where vagal and sympathetic afferents subserve multiple feedback loops (organized as continuous interaction between negative and positive circuits) [46]. Very recent studies show that the overall system is governed by a central cluster of nuclei that behave as veritable governor [44] of the dynamics of visceral ("autonomic") nervous system in parallel with motor, or emotional behavior. In this context stress represents a valuable proxy of all behavioral inputs to the system [1], capable of inducing measurable changes in autonomic performance, usually characterized by increased sympathetic excitatory drive (and parallel reduction of vagal parasympathetic activity) [4]. It should be noted that, also pathological inputs (e.g. acute myocardial ischemia) may be seen as stress (attempt to disrupt homeostasis) by the system.

Historically reliable evaluation of ANS was usually performed with invasive and intrusive techniques like MSNA or catecholamine's spillover, relegating it preferentially to specific research settings and requiring specific expertise. In the last decades the evolution of non-invasive techniques, like spectral analysis of heart rate variability (HRV), rendered the clinical use of ANS evaluation widely available [47-50] offering a new window for the study of stress and functional syndromes, and in general of patients who report medically unexplained symptoms [4,19,22,36,37,42,51].

It may be worth recalling that this non-invasive, non-intrusive technique, based on indices derived from beat by beat RR variability, furnishes markers of sympathetic and vagal modulation of the SA node, represented respectively by low frequency and by high frequency component of RR interval variability [4,47]. Moreover, if a continuous arterial pressure signal is also simultaneously available, a marker of sympathetic modulation to the vasculature may be obtained by the low frequency component of systolic arterial pressure variability, and an overall marker of baroreflex sensitivity is furnished by the frequency domain alpha index (or by the baroreflex slope) [52,53]. This technique showed that acute stress, like mental arithmetic or computer tasks, is associated to increased markers of sympathetic activity both in healthy [54] subjects as well as in cardiac [55] and hypertensive [56] patients. It also shows that chronic stress condition, as in work restructuring [4,19], induces in healthy subjects an increase of the marker of sympathetic activity. Subjects lamenting functional symptoms and experiencing psychosocial stress [22], like caregivers of cancer patients [57], are characterized by signs of autonomic nervous system impairment. Patients with chronic fatigue syndromes [36,37] or symptoms related to irritable bowel syndrome [27] show a significant increase of the marker of sympathetic, and a reduction of marker of vagal modulation as compared to controls [36,37]. Interestingly markers of these autonomic nervous system alterations significantly correlate with psychological scores related to stress, tiredness and somatic symptoms perception derived by simple questionnaires [4,19,22,43]. Of potential clinical importance is that this technique was capable of revealing a significant improvement of autonomic nervous system alterations after a period of treatment employing cognitive restructuring and mental relaxation [19,43,58]; moreover, it showed that these treatments implying the active involvement of patients are superior to passive ones, like oriental massage [43].

On the other hand, we may not disregard that HRV is however far from being the optimal technique to assess ANS, in particular because it furnishes only indirect markers of autonomic control of the circulation. Yet, to the best of our knowledge, it is the only non-

invasive, easy to perform and cost saving methodology that can be employed in a real clinical setting on large populations. What actually might contribute to limit the clinical use of this technique, is the difficulty to derive consistent information of practical usage from the large set of potentially redundant variables furnished by the analysis [48,59]. Moreover, HRV variables may not only depend numerically from the specific algorithm employed [60], but some of them reflect prevalent sympathetic or prevalent parasympathetic modulation, and the interpretation of their clinical meaning varies also according to the specific context (rest, stand, stress, drugs, etc…) and individual characteristics, such as age and gender or the presence of disease [48,61-63] or stress conditions [4].

In addition, classical [15] and more recent studies [45,64] focusing on the hierarchical design of neural visceral regulation, and providing evidence for common central mechanisms governing sympathetic and parasympathetic rhythmic activity [65] suggest the clinical usefulness of a unitary autonomic index.

Recently we showed the feasibility of testing simpler metrics of cardiac autonomic regulation based on a multivariate unitary index in clinics [66]. A composite unitary Autonomic Nervous System Index of cardiac regulation (ANSI) (expressed in percentile rank [reference population, n = 1593, age 39 ± 13 yrs]) [66] is a possible way to integrate the partial information spread across multiple autonomic variables and represents a proxy of quality of autonomic regulation against a benchmark population. This approach, considering both static and oscillatory information embedded in HRV, is capable of detecting the graded changes in cardiac neural regulation occurring along the continuum from dysfunction in patients to improvement in endurance athletes, detecting the expected graded impairment in baseline cardiac neural regulation mediated by clustering of hypertension, obesity or smoking in otherwise healthy subjects. This simple approach might foster a wider application of HRV in the clinical arena, and permit an easier appreciation of autonomic performance. This possibility may be particularly useful when studying the effects of exercise [67] or stress and/or stress management in clinical setting.

Autonomic Nervous System Index and stress management

In this context, we tested the hypothesis that this new Index, proxy of quality of autonomic regulation, may easily employed to reveal the benefic effect of a stress management intervention program, based on mental relaxation and lifestyle interventions, on the autonomic dysregulation induced by stress in a group of 25 white collar workers (age 43 ± 1.5 yrs) of a major multinational corporation undergoing an unexpected reorganization. No-one was under medical treatment or affected by acute or chronic diseases and Informed consent was obtained by all participants.

Subjective stress levels were assessed in all subjects by a structured questionnaire, which had been validated before [19,22,51,57,68]. The questionnaire explores cognitive and somatic components, using a numerical scale from 0 to 10 (cognitive component: perception of stress or tiredness) or 0 to 180 (somatic component, 4SQ: sum of scores related to symptoms referred to organs or functions, like, e.g. feeling fidgety or perception of palpitation). In previous studies on the autonomic effects of stress, these values were found useful as proxy of the domains of stress, tiredness or stress related somatic symptoms, correlating with hemodynamic and autonomic nervous system parameters [19,22].

The intervention was multidimensional and based on cognitive behavioral elements, associated to a breathing focused relaxation training, in addition to a general medical supervision. The intervention lasted 12 months and was administered on site in a dedicated room under weekly supervision by a physical therapist.

As shown in figure 1 proxies of stress after intervention (dark bars) were reduced for all explored domains (stress perception, tiredness perception as well as 4SQ) as compared before the intervention (light bars).

The simultaneous effects on cardiac autonomic regulation were explore by a novel unitary autonomic nervous system index (ANSI) that provides a single proxy of quality of autonomic performance as projected onto a large benchmark population. The major advantage of this approach derives from its capacity to integrate in a single rank value all the meaningful information embedded in time and frequency

domain markers of autonomic regulation. This integrated approach therefore minimizes the major drawback of RR variability that derives from the multiplicity of indices that are produced by analysis and lack of consensus on which index to select as autonomic proxy.

Figure 1 clearly shows that ANSI levels are increased after intervention suggesting an overall improvement of autonomic quality.

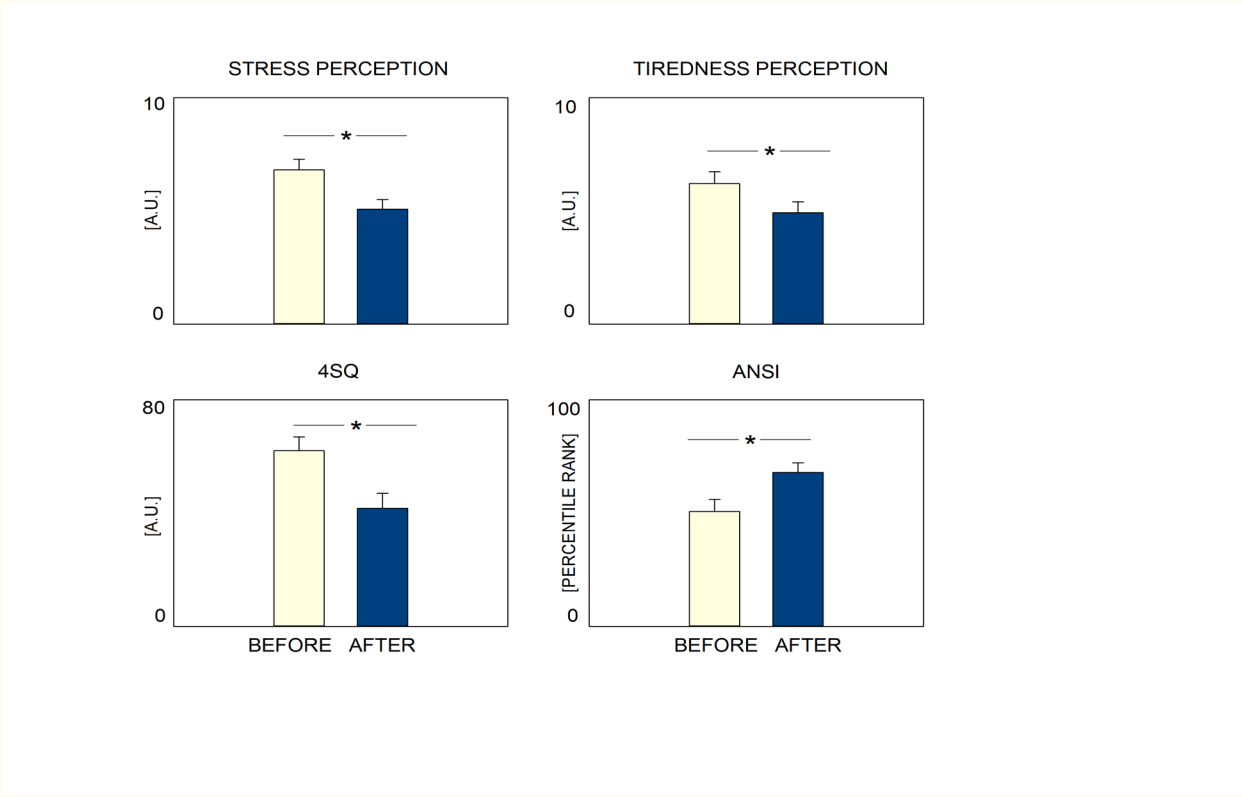

Figure 1: *Beneficial effects of a stress management intervention on a white collar population. Notice the improvement in markers of stress (stress perception, top left; tiredness perception, top right; and 4SQ, bottom left) and a corresponding increase in ANSI (bottom right).*

Conclusions

Stress is a ubiquitous concept that is difficult to adapt to usual clinical practice. Recent findings highlighting the heart-brain interaction as a unitary system [45] reinforce the historical view of Rudolf Hess [45] depicting the visceral ("autonomic") nervous system as the essential neural structure underlying the intrinsic unitary nature of the multitude of parts constituting every living individual. ANSI [66] might furnish a simple proxy of the quality of autonomic regulation, and be employed in a variety of clinical fields, such as in functional syndromes or in the management of stress, fostering a wider application of autonomic evaluation in the clinical arena.

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