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ORIGINAL ARTICLE

A composite autonomic index as unitary metric for heart rate variability: a proof of concept

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ABSTRACT

Background This study addresses whether a unitary cardiac autonomic nervous system index (ANSI), obtained combining multiple metrics from heart rate variability (HRV) into a radar plot could provide an easy appreciation of autonomic performance in a clinical setting.

Materials and Methods Data are standardized using percentile ranking of autonomic proxies from a relatively large reference population (n = 1593, age 39 ± 13 years).Autonomic indices are obtained from autoregressive spectral analysis of (ECG derived) HRV at rest and during standing up. A reduced ANSI (using RR, RR variance and rest–stand difference of LFnu) is then constructed as a radar plot, quantified according to its combined area and tested against different risk subgroups.

Results With growing risk profile, there is a marked reduction of the rank value of ANSI, quantified individually by the radar plot area.The practical usefulness of the approach was tested in small groups of additional subjects putatively characterized by elevated or poor autonomic performance. Data show that elite endurance athletes are characterized by elevated values of ANSI (80·6 ± 14·9, $P < 0·001$) while subjects with either Type 1 or Type 2 diabetes show lower values (DM1 = 37·0 ± 18·9 and DM2 = 26·8 ± 23·3, $P = 0·002$), and patients with coronary artery disease (CAD) represent a nadir (17 ± 20, $P < 0·001$).

Conclusions This observational study shows the feasibility of testing simpler metrics of cardiac autonomic regulation based on a multivariate unitary index in a preventive setting. This simple approach might foster a wider application of HRV in the clinical arena, and permit an easier appreciation of autonomic performance.

Keywords Autonomic nervous system, BMI, cardiometabolic risk, hypertension, personal prevention, smoke.

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Introduction

The autonomic nervous system (ANS) may be altered in several clinical conditions, ranging from chronic diseases (such as arterial hypertension, coronary artery disease (CAD), diabetes, obesity, cancer, functional syndromes) to unhealthy behaviour (such as cigarette smoking, sedentariness, stress) [1–4]. Conversely, autonomic improvement might contribute to the more favourable prognosis associated with cardiac rehabilitation [5,6] or in general to the beneficial effects of aerobic training, weight control programmes or stress management strategies [7].

Historically, clinical evaluation of the ANS focused on reflex changes of cardiovascular parameters [3].

In the last decades, the evolution of non-invasive techniques, like spectral analysis of heart rate variability (HRV), rendered the clinical use of indirect ANS evaluation widely available [8–11].

HRV is easy to perform, is totally non-invasive and cost-effective; however, it has several practical 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 [9,12], contributing to confound meaning and impair usability.

Finally, the interpretation of HRV indices varies according to the specific context (rest, stand, stress, drugs, etc.) and individual characteristics, such as age and gender or the presence of disease, such as diabetes [9,13,14] or CAD [15].

In this context, classical [16] and more recent studies [17] focusing on the hierarchical design of neural visceral regulation, and providing evidence for common central mechanisms governing sympathetic and parasympathetic rhythmic activity [18] suggest the clinical usefulness of a unitary view of autonomic *information*, focusing on overall quality of regulation [19].

Overall aim of this investigation is to assess whether a unitary autonomic nervous system index of cardiac regulation (ANSI), as furnished by a radar plot [20] considering simultaneously the most informative spectral variables could provide an easier appreciation of overall autonomic performance [21].

Specific object is to verify whether a percentile rank transformation [22], considering age and gender subgroups, could also allow easier and immediate benchmarking of patients against a large reference population [10] composed of individuals that are either healthy, or with various levels of putative ANS dysregulation. Additional object is to verify whether ANSI can track differences in quality of autonomic regulation as present in elite endurance athletes (improved regulation) or in patients with diabetes or CAD (impaired autonomic regulation).

Methods

The study is based on subsequent data from the short-term HRV database of the Exercise Medicine Unit of the University of Milan, referring to either healthy subjects or individuals with prehypertension or hypertension, as well as overweight or obesity (reference population, n = 1593, age 39 ± 13 years). Participants' health status is assessed by history and physical examination. Exclusion criteria comprise the following: age below 18 years; acute illness in prior 3 months; consumption of drugs for chronic conditions (hypertensive patients were either untreated or in 4 weeks wash-out) and presence of complications related to the hypertensive or obese status (stroke, arrhythmias, myocardial infarction or, respectively, diabetes or dysautonomia).

In addition, four small groups of subjects (elite endurance athletes, n = 25, age 27 ± 8; Type 1 diabetes, n = 15, age 19 ± 2; Type 2 diabetes, n = 19, age 62 ± 7, stable coronary artery disease-CAD, n = 13 age 62 ± 10) were employed as initial, feasibility, tests.

The study conforms to the standards set by the declaration of Helsinki on investigations regarding human subjects. Ethical approval was obtained from the local Ethics Committee.

Autonomic evaluation

The day of autonomic evaluation of all subjects arrive in the clinic, avoiding caffeinated beverages since waking and 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 supine position, ECG and respiratory activity are continuously recorded over minimum 5-min period at rest and 5 min during standing. Data are acquired with a PC, and as described previously [8], a series of proxies of autonomic cardiac modulation are derived using an autoregressive spectral analysis tool [23]. In addition to RR interval (in msec) and RR interval variability (assessed as total power, TP, in msec^2), the programme automatically provides spectral components both in the low-frequency (LF, 0·03–0·14 Hz) and in the high-frequency (HF, 0·15–0·35 Hz) regions. Power of spectral components is assessed in msec^2 and also in normalized units [8]. To include a simple evaluation of the effects of sympathetic activation as produced by active standing also the stand–rest difference (Δ) in LFnu is computed [2,8].

Statistics

In tables and text, data are presented as mean ± standard deviation (SD).

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 [20] that are built for each subject using the above eight HRV proxies, which are preliminarily scaled from 0 to 100 by the percentile rank transformation in order to share a range of variation and unit of measurement. To account for age and gender effects, percentile rank transformation is computed within the groups defined by the combinations of gender 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 reduced number of proxies (Fig. 1). The minimum number of proxies are selected from among the HRV variables recognized as substantial by the combination of factor analysis [24], which is carried out with the principal factor extraction method and varimax rotation (considering meaningful only loadings > 0·4), and physiological underpinnings. Reduced ANSI will be regarded as a good synthesis of autonomic information comparable to $ANSI_8$ if the linear correlation coefficient between the two indices is significant and high (i.e. > 0·8). Subsequently, groups of individuals approximating clinical status are formed by combining 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) together.

Attention is specifically put on comparisons between ANSI level of healthy individuals (i.e. non-smokers with SAP

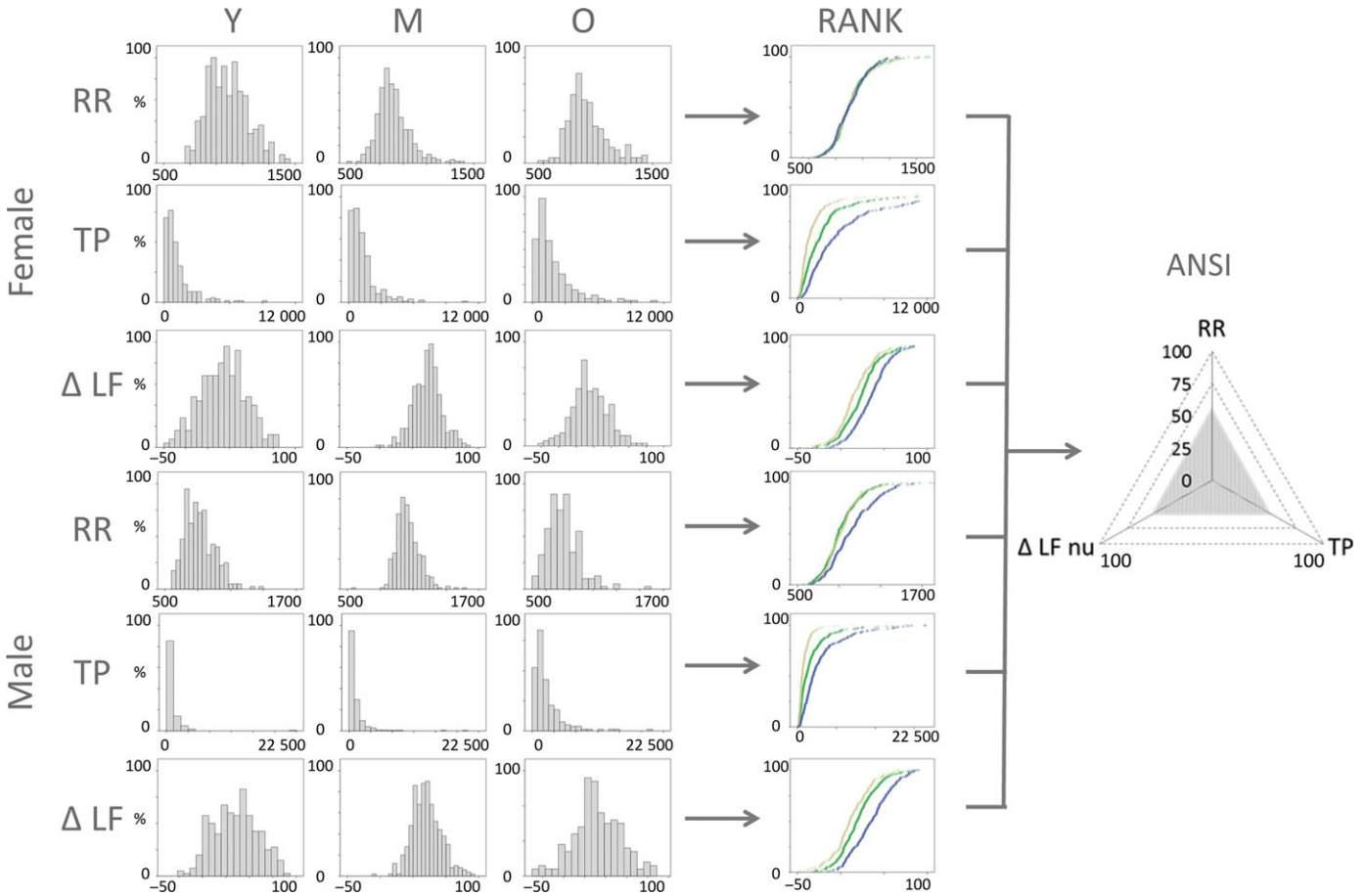

Figure 1 The construction of $ANSI_3$ in its main steps. First, the procedure starts from the three selected HRV proxies (RR, RR power and ΔLFnu), and their distribution within gender and age classes jointly considered (left panels), then proceeds through their within-group transformation according to the percentile rank (middle panels), and then ends by computing the indicator as the area of the triangle composing each individual radar plot, expressed in percentile (right). 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 $msec^2$; ΔLF are nu.

≤ 120 mmHg and BMI ≤ 25 Kg/m^2), treated as normal group, and ANSI levels of individuals in the other clinical status.

To verify the feasibility of testing this approach with other groups (athletes, DM1, DM2, CAD), ANSI is computed using ranking from the reference population, and projecting the relative value onto the reference scale.

Statistical analysis, considering 0·05 as a nominal level for significance, is performed using a commercial package (IBM SPSS 23).

Results

Descriptive anthropometric and autonomic data for the study population, subdivided in age and gender classes, are provided in Table 1. Significant within-gender differences between age classes are evident.

Factor analysis applied to the eight HRV proxies (Table 2) demonstrates that the first three factors reproduce a high percentage [Variance Accounted For (VAF) 82·7%] of the total information spread across variables, where individually the first factor accounts for 44·0% of total variance, the second 24·2% and the third 14·5%. Moreover, factor loadings indicate the following three clusters of the HRV proxies: 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 reduced ANSI with three selected proxies ($ANSI_3$), one for each factor.

Table 1 Descriptive anthropometric and autonomic data subdivided in gender and age subgroup of the study population

		Females			
		Young Mean ± SD *n* 225	**Middle age Mean ± SD *n* 341**	**Old Mean ± SD *n* 205**	**Significance trend**
Age	Years	24·4 ± 3·4	40·2 ± 5·6	56·1 ± 5·5	$P < 0·001$
Weight	kg	61·6 ± 13·6	69·3 ± 23·1	68·2 ± 17·0	$P < 0·001$
Height	cm	165·0 ± 6·6	163·3 ± 6·5	160·7 ± 6·3	$P < 0·001$
BMI	kg/m^2	22·6 ± 4·9	26·0 ± 8·3	26·4 ± 6·5	$P < 0·001$
HR	bpm	69·7 ± 12·2	69·5 ± 12·7	69·5 ± 13·3	$P = 0·840$
SAP	mmHg	109·1 ± 12·7	119·2 ± 18·8	134·5 ± 21·6	$P < 0·001$
DAP	mmHg	69·3 ± 9·6	76·3 ± 12·0	83·1 ± 12·4	$P < 0·001$
RR	ms	887·2 ± 155·0	893·7 ± 172·0	896·5 ± 178·1	$P = 0·566$
TP	ms^2	4073·7 ± 4195·7	2186·1 ± 2097·8	1250·4 ± 1180·9	$P < 0·001$
LF a	ms^2	1090·7 ± 1143·9	598·1 ± 732·2	365·7 ± 759·8	$P < 0·001$
HF a	ms^2	1586·8 ± 2157·5	558·4 ± 762·8	284·7 ± 510·0	$P < 0·001$
LF nu	nu	45·1 ± 20·6	50·8 ± 19·3	50·3 ± 20·5	$P = 0·006$
HF nu	nu	47·4 ± 21·2	41·0 ± 19·4	38·6 ± 20·2	$P < 0·001$
LF/HF	—	1·9 ± 3·5	2·4 ± 3·8	2·8 ± 5·3	$P = 0·020$
ΔLF nu	nu	34·0 ± 20·7	22·2 ± 21·7	15·7 ± 20·9	$P < 0·001$
		Males			
		***n* 265**	***n* 361**	***n* 196**	
Age	Years	24·4 ± 3·6	40·1 ± 5·7	58·1 ± 7·4	$P < 0·001$
Weight	kg	77·2 ± 13·3	81·0 ± 13·8	80·7 ± 17·2	$P = 0·011$
Height	cm	179·8 ± 8·6	176·2 ± 7·7	171·7 ± 8·4	$P < 0·001$
BMI	kg/m^2	23·8 ± 3·4	26·1 ± 4·1	27·4 ± 5·0	$P < 0·001$
HR	Bpm	61·1 ± 13·0	67·2 ± 12·1	66·4 ± 11·3	$P < 0·001$
SAP	mmHg	122·2 ± 13·7	130·1 ± 18·3	138·7 ± 19·6	$P < 0·001$
DAP	mmHg	71·7 ± 9·4	82·6 ± 13·0	85·8 ± 11·9	$P < 0·001$
RR	ms	1028·9 ± 227·5	921·1 ± 181·8	931·8 ± 172·6	$P < 0·001$
TP	ms^2	4955·6 ± 8268·4	2959·0 ± 4690·2	1328·9 ± 1357·1	$P < 0·001$
LF a	ms^2	1332·4 ± 1830·5	893·2 ± 1302·3	406·3 ± 554·8	$P < 0·001$
HF a	ms^2	2003·6 ± 5403·5	727·8 ± 2239·4	177·2 ± 258·6	$P < 0·001$
LF nu	nu	49·0 ± 23·1	61·1 ± 22·0	58·1 ± 22·1	$P < 0·001$
HF nu	nu	46·1 ± 23·5	32·4 ± 21·4	32·4 ± 20·5	$P < 0·001$
LF/HF	—	2·1 ± 2·9	4·7 ± 7·4	4·2 ± 6·5	$P < 0·001$
ΔLF nu	nu	35·4 ± 23·7	20·1 ± 22·3	11·8 ± 22·6	$P < 0·001$

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.

Table 2 Factor analysis

Variance Accounted For (VAF) 82·7%			
Factor	1	2	3
VAF per factor	44·0%	24·2%	14·5%
	Loading		
HR			−0·950
RR			0·947
TP		0·946	
LF a		0·804	
HF a		0·884	
LF nu	−0·938		
HF nu	0·923		
LF/HF	−0·719		
ΔLF nu	0·775		

Abbreviation: 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.

According to statistical evidence and physiological underpinnings, ΔLFnu for factor 1, RR variance (TP) for factor 2 and RR for factor 3 are singled out for the $ANSI_3$ set-up. Reduced $ANSI_3$ and $ANSI_8$ being strongly positively correlated (correlation coefficient = 0·940, $P < 0·001$), $ANSI_3$ is then preferred to $ANSI_8$ by the parsimony criterion.

Figure 1 sums up the construction of $ANSI_3$ in its main steps. The first step consists in building the distribution of the three selected ANS proxies (RR, RR variance and ΔLFnu) within each gender-by-age class (thresholds at 30 and 49 years; Fig. 1, left panels). Then, a within-classes percentile rank transformation is applied to each autonomic proxy (Fig. 1, middle panels) in order to obtain individual radar plots (Fig. 1, right panel), that is, a radar plot of triangular shape for each subject involved in the study. Individual $ANSI_3$ values are finally computed as percentile rank transformation of the areas of these triangular radar plots.

Practically, Fig. 2 demonstrates that reduced $ANSI_3$ values, indicative of impaired autonomic performance, are observed in groups with poor clinical profile, as approximated by clustering of elevated SAP, BMI and of smoking.

The potential usefulness of this approach is initially tested in small groups of additional subjects putatively characterized by

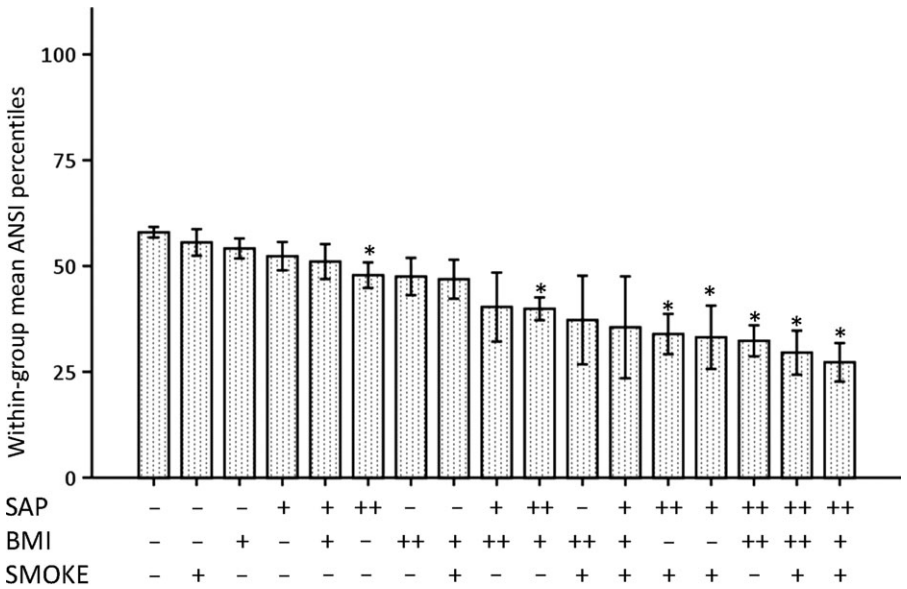

Figure 2 The bar plot of the means of $ANSI_3$ percentiles computed for each group formed by combinations of SAP, BMI and smoking categories. Overall, reduced ANSI values against reference normal group, indicative of impaired autonomic performance, are observed in groups with poor clinical profile, as approximated by clustering of elevated SAP and BMI, and of smoking. One-sided Dunnett's test to verify equality of within-group ANSI means against ANSI means lower than control group. Symbols for clinical conditions: SAP categories with thresholds at 120 and 140 mmHg are −, +, ++; BMI categories with thresholds at 25 and 30 kg/m^2 are −, +, ++; SMOKING is dichotomized into no/yes corresponding to − or +. A group with only 5 subjects (+,++,+) is not considered. *$P < 0·02$.

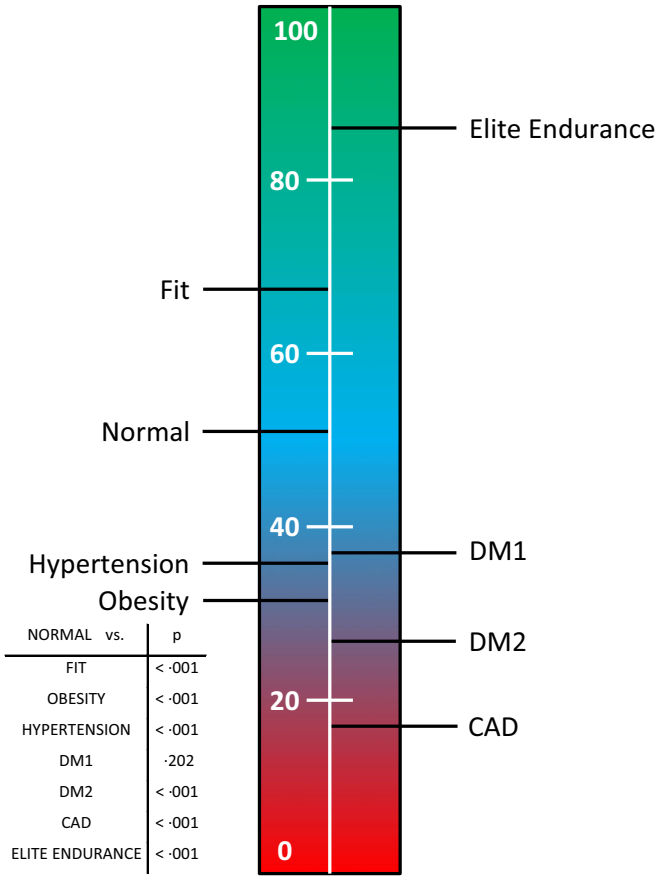

Figure 3 Schematic representation of the position of the mean value of percentile rank for the various groups (left) and projected mean values of tests groups (elite endurance, diabetes type 1, diabetes type 2, coronary artery disease, CAD). Significance of differences against normal (reference population of controls) is indicated in the bottom left panel (Dunnett's test). A 0–100 reference scale (white) is provided in the bar.

elevated or poor autonomic performance. Bar plot of $ANSI_3$ in Fig. 3 shows that elite endurance athletes are characterized by elevated values of ANSI (80·6 ± 14·9, $P < 0·001$) while subjects with either Type 1 or Type 2 diabetes show lower values (DM1 = 37·0 ± 18·9; DM2 = 26·8 ± 23·3, $P = 0·002$), and patients with CAD represent a nadir (17 ± 20, $P < 0·001$).

Discussion

This observational study suggests that a unitary composite autonomic nervous system index (ANSI), considering both static and oscillatory information embedded in HRV [25], is capable of detecting the graded changes in cardiac neural regulation occurring along the continuum from dysfunction in patients to improvement in endurance athletes.

Cardiac autonomic regulation and the unitary autonomic index (ANSI)

The fine tuning of the ANS underscores the beat-by-beat matching of hemodynamic performance with varying needs of the periphery. HRV reflects the attendant continuous variations in the combined activity of dual (sympathetic and parasympathetic) autonomic innervation [8]. The model of a unitary paired antagonistic organization [16] suggested ANSI as a simple practical proxy of the overall performance [19] of cardiac regulation. Translationally, the key issue is finding a balanced trade-off between technical simplicity and clinical value. The use of multiple signals (ECG, arterial pressure) [2] allows to predict with high accuracy the presence or absence of clinical conditions, such as normotensive or hypertensive status [13]. The simple ECG, still confers significant predictive accuracy [13], but with a far simpler methodology. In this case, ANSI, based on an integrated model of SA regulation, would be easier to manage in benchmarking specific populations (e.g. athletes, diabetics, CAD), free from the complexity of interpreting multiple autonomic indices and potential noise from redundancy.

A key, still unresolved issue regards which indices should be preferred for autonomic assessment [9,12]. This choice has obvious implications in building ANSI. We approach this issue with factor analysis showing that the large majority of information embedded into HRV is carried by only three separate factors: normalized oscillatory indices, absolute indices and RR (the inverse of HR). These findings are in agreement with previous studies, showing that amplitude and oscillations convey the bulk of information on autonomic cardiac regulation, and that few indices are sufficient to predict the horizontal from the upright position [24], or the hypertensive from normotensive state [13]. Furthermore, the strong correlation between ANSI obtained with three or eight proxies supports the parsimony criterion of using for the last part of analysis the simpler $ANSI_3$.

ANSI as clinical tool

ANSI does not evaluate underlying neural activity, but quantifies the ANS impairment associated with different clinical conditions (hypertension, obesity, smoking) [1,2,4], and the greater impact of their combination (see Fig. 2) if simultaneously present in the same subject. This approach may foster clinical applications. In fact, presently the clinical interpretation of HRV variables requires a level of expertise in ANS physiology, thus limiting a wider use of ANS evaluation in clinical settings. For a correct clinical interpretation, it is important to consider several interacting factors: the analysis algorithm (e.g. time or frequency domain, linear or non-linear [21]) and the specific protocol (rest, stand, exercise, etc.), the subject's or patient's clinical characteristics (health, disease, drug treatment, etc.). Moreover, some HRV variables may give more

reliable information on ANS function at baseline, while others are more useful during induced or spontaneous sympathetic predominance [24]. Time domain indices like total variance, are accepted as possible markers of increasing vagal modulation of moderate aerobic training [26]. This index might however be less reliable in detecting responses to excitatory stimuli [24].

Individual raw values may also be difficult to interpret because of variations in units or scales (linear, logarithmic) [9]. On the contrary, ANSI may easily provide information on ANS control that can be simpler to interpret. ANSI reduces into a single parameter all the main aspects that an expert ANS investigator needs to consider in order to clinically define the ANS subject's profile. To this end, each subject is simply gauged against the percentile rank of ANSI values from the reference population.

The possibility to easily obtain measures of integrated autonomic regulation could add value particularly in those conditions where:

-ANS may play a practical role in physical activity monitoring and training [26,27];
-ANS may play a significant role in development of diseases, such as hypertension [1,2], CAD [28], heart failure [14], diabetes [3];
-ANS may be altered before the onset of the disease, such as in arterial hypertension [2], diabetes [29], obesity [30];
-ANS profile may be ameliorated by lifestyle interventions, such as with weight reduction [31], stop smoking [32], cardiac rehabilitation [6,15], physical training in patients [33] or sport training in elite athletes [27];
-ANS profile may represent the only altered clinical parameters, such as in functional syndromes (e.g. stress syndrome, irritable bowel syndrome, fibromyalgia) [34,35], or in particular situations like overtraining or overreaching in sport [36], nowadays diagnosed usually by symptoms reports.

Here, we propose to use ANSI as a 'unitary' proxy of the fundamentally 'unitary' nature [16] of autonomic regulation of cardiovascular function.

Proofing the concept

To further test the potential clinical usefulness of ANSI, we examined a group of highly endurance trained athletes, expected to be characterized by a better autonomic regulation, as well as groups of patients expected to perform poorly (young type 1 and older type 2 diabetes, and CAD). We observe that athletes and CAD groups position themselves at the extremes of the range. Athletes have a greater ANSI value than observed in healthy (no risk factors) controls and fit individuals, further supporting the concept that intense endurance training might lead to further improvement [37]. Conversely, CAD and type 2 diabetes impair autonomic performance markedly, while metabolically controlled type 1 diabetes in young subjects appears less damaging (Fig. 3). Furthermore, the presence of other conditions, such as high blood pressure or elevated BMI, impairs ANSI to a significant extent. This finding brings further support to the model of a continuum of autonomic changes with the occurrence of initial heart rate dysregulation [38], easily to gauge because ANSI provides ranking (i.e. transformed) values in a 0–100 scale using as benchmark a large reference population (instead of raw values) [22].

Limitations

This is an observational study on data extracted from the database of an on-going lifestyle prevention project; an *ad hoc* intervention study would have offered more robust findings, however at the expense of immediacy of results and greater complexity and costs.

The model of a paired antagonistic organization of the visceral nervous system [16] may not always hold, as there are important instances of co-activation [39] in vagal and sympathetic activity, for example, with chemoreceptor stimulation.

ANSI is obtained with indirect techniques without any weighing of constitutive indices. More complex modelling based on larger populations with a longitudinal design associated with direct autonomic assessment might provide stronger findings. Also explicitly considering the influence of personal bias, such as the role of stress, could improve the analysis.

Conclusion

We conclude that our observational study shows the feasibility of testing simple metrics of cardiac autonomic regulation based on a unitary index. For its simplicity and low cost (use of only HRV for just few minutes), ANSI could thus be employed as a convenient proxy of the continuum of changes in quality of autonomic regulation, in all conditions where standardized autonomic assessment might be part of therapeutic or preventive programmes, such as in the emerging field of personalized medicine.

Authorship

RS contributed to design, data collection, analysis and discussion. MM contributed to data acquisition, analysis and discussion of findings. NS contributed to data analysis design and discussion. MP contributed to study design, data analysis, discussion and drafting of manuscript. DL contributed to study design, data analysis and drafting of manuscipt. All Authors contributed and approved the final version.

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References

1 Julius S. Autonomic nervous dysfunction in essential hypertension. *Diabetes Care* 1991;**14**:249–59.
2 Lucini D, Mela GS, Malliani A, Pagani M. Impairment in cardiac autonomic regulation preceding arterial hypertension in humans: insights from spectral analysis of beat-by-beat cardiovascular variability. *Circulation* 2002;**106**:2673–9.
3 Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007;**115**:387–97.
4 Grassi G, Seravalle G, Dell'Oro R, Turri C, Pasqualinotto L, Colombo M *et al*. Participation of the hypothalamus-hypophysis axis in the sympathetic activation of human obesity. *Hypertension* 2001;**38**:1316–20.
5 Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol* 2009;**587**:5551–8.
6 Lucini D, Milani RV, Costantino G, Lavie CJ, Porta A, Pagani M. Effects of cardiac rehabilitation and exercise training on autonomic regulation in patients with coronary artery disease. *Am Heart J* 2002;**143**:977–83.
7 Lucini D, Pagani M. From stress to functional syndromes: an internist's point of view. *Eur J Intern Med* 2012;**23**:295–301.
8 Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P *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**:178–93.
9 Task Force of the European Society of Cardiology, the North American Society of Pacing and Electrophysiology. Heart-rate variability: standards of measurements, physiological interpretation and clinical use. *Circulation* 1996;**93**:1043–65.
10 Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin Electrophysiol* 2010;**33**:1407–17.
11 Trimmel K, Sacha J, Huikuri HV. *Heart Rate Variability: Clinical Applications and Interaction between HRV and Heart Rate*. Frontiers in Physiology. Lausanne: CH; 2015.
12 Huikuri HV, Makikallio T, Airaksinen KE, Mitrani R, Castellanos A, Myerburg RJ. Measurement of heart rate variability: a clinical tool or a research toy? *J Am Coll Cardiol* 1999;**34**:1878–83.
13 Lucini D, Solaro N, Pagani M. May autonomic indices from cardiovascular variability help identify hypertension? *J Hypertens* 2014;**32**:363–73.
14 Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971;**285**:877–83.
15 La Rovere MT, Bersano C, Gnemmi M, Specchia G, Schwartz PJ. Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. *Circulation* 2002;**106**:945–9.
16 Hess WR. Nobel Lecture: The Central Control of the Activity of Internal Organs". Nobelprize.org.Nobel Media AB 2014. Web. 29 September 2016. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1949/hess-lecture.html.
17 Oppenheimer S, Cechetto D. The Insular Cortex and the Regulation of Cardiac Function. *Compr Physiol* 2016;**6**:1081–133.
18 Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C *et al*. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 1997;**95**:1441–8.
19 Moruzzi G. Sleep and instinctive behavior. *Arch Ital Biol* 1969;**107**:175–216.
20 Saary MJ. Radar plots: a useful way for presenting multivariate health care data. *J Clin Epidemiol* 2008;**61**:311–7.
21 Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng CK *et al*. Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace* 2015;**17**:1341–53.
22 Schoonjans F, De BD, Schmid P. Estimation of population percentiles. *Epidemiology* 2011;**22**:750–1.
23 Badilini F, Pagani M, Porta A. Heartscope: a software tool adressing autonomic nervous system regulation. *Comput Cardiol* 2005;**32**:259–62.
24 Sala R, Spataro A, Malacarne M, Vigo C, Tamorri S, Benzi M *et al*. Discriminating between two autonomic profiles related to posture in Olympic athletes. *Eur J Appl Physiol* 2016;**116**:815–22.
25 Pagani M, Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. *J Hypert* 2000;**18**:1709–19.
26 Sala R, Malacarne M, Pagani M, Lucini D. Evidence of increased cardiac parasympathetic drive in subjects meeting current physical activity recommendations. *Clin Auton Res* 2015;**25**:285–91.
27 Iellamo F, Legramante JM, Pigozzi F, Spataro A, Norbiato G, Lucini D *et al*. Conversion from vagal to sympathetic predominance with strenuous training in high-performance world class athletes. *Circulation* 2002;**105**:2719–24.
28 La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;**351**:478–84.
29 Lucini D, Zuccotti G, Malacarne M, Scaramuzza A, Riboni S, Palombo C *et al*. Early progression of the autonomic dysfunction observed in pediatric type 1 diabetes mellitus. *Hypertension* 2009;**54**:987–94.
30 Lucini D, Cusumano G, Bellia A, Kozakova M, Difede G, Lauro R *et al*. Is reduced baroreflex gain a component of the metabolic syndrome? Insights from the LINOSA study. *J Hypertens* 2006;**24**:361–70.
31 Grassi G, Seravalle G, Colombo M, Bolla G, Cattaneo BM, Cavagnini F *et al*. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation* 1998;**97**:2037–42.
32 Lucini D, Bertocchi F, Malliani A, Pagani M. Autonomic effects of nicotine patch administration in habitual cigarette smokers: a double-blind, placebo-controlled study using spectral analysis of RR interval and systolic arterial pressure variabilities. *J Cardiovasc Pharmacol* 1998;**31**:714–20.

33 Pagani M, Somers V, Furlan R, Dell'Orto S, Conway J, Baselli G *et al*. Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension* 1988;**12**:600–10.
34 Lucini D, Norbiato G, Clerici M, Pagani M. Hemodynamic and autonomic adjustments to real life stress conditions in humans. *Hypertension* 2002;**39**:184–8.
35 Lucini D, Riva S, Pizzinelli P, Pagani M. Stress management at the worksite: reversal of symptoms profile and cardiovascular dysregulation. *Hypertension* 2007;**49**:291–7.
36 Plews DJ, Laursen PB, Stanley J, Kilding AE, Buchheit M. Training adaptation and heart rate variability in elite endurance athletes: opening the door to effective monitoring. *Sports Med* 2013;**43**:773–81.
37 Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801.
38 Narkiewicz K, Somers VK. Chronic orthostatic intolerance: part of a spectrum of dysfunction in orthostatic cardiovascular homeostasis? *Circulation* 1998;**98**:2105–7.
39 Koizumi K, Kollai M. Multiple modes of operation of cardiac autonomic control: development of the ideas from Cannon and Brooks to the present. *J Auton Nerv Syst* 1992;**41**:19–29.