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Assessing Correlation between Heart Rate Variability Markers Based on Laguerre Expansion and Direct Measures of Sympathetic Activity during Incremental Head-up Tilt

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***Abstract*— Traditional frequency domain analysis of heart period (HP) variability allows the estimation of the parasympathetic modulation directed to the heart but the sympathetic one remains largely unknown. Recently, sympathetic and parasympathetic activity indexes (SAI and PAI) have been proposed to address this issue. SAI and PAI were derived from HP variability via the application of an orthonormal Laguerre expansion allowing the separation of HP variations driven by sympathetic and parasympathetic outflows. In this study, SAI and PAI were validated against tonic and variability measures of muscle sympathetic nerve activity (MSNA) and more traditional markers derived from HP variability. Indexes were calculated in 12 healthy subjects (9 females, age from 20 to 36 years, median 22.5 years) undergoing incremental head-up tilt. Results showed that traditional HP and MSNA variability markers as well as SAI and PAI were modified in proportion to the magnitude of the postural challenge. However, SAI was not correlated with any MSNA markers and PAI was not linked to respiratory sinus arrhythmia. SAI and PAI can capture modifications of cardiac control induced by the orthostatic challenge but they might be weak surrogates of vagal and sympathetic activities and/or modulations.**

***Clinical Relevance*— SAI and PAI markers are useful to characterize cardiac control but poorly linked with autonomic nervous system state.**

I. Introduction

Autonomic nervous system (ANS) is fundamental for maintaining physiological homeostasis and its state is traditionally inferred noninvasively and indirectly from heart period (HP) variability [1]. The low frequency (LF, from 0.04 to 0.15 Hz) power of HP series expressed in absolute units is linked to both sympathetic and vagal controls, while the high frequency (HF, from 0.15 to 0.4 Hz) power of HP variability expressed in absolute units is exclusively associated to vagal modulation [2]. The consequence is that the LF power marker is less specific than the HF power marker: as a matter of fact, the LF power of HP series expressed in absolute units remains constant during graded head-up tilt maneuver due to the simultaneous vagal withdrawal and sympathetic activation, while the HF power index of HP variability progressively decreases with the magnitude of the postural challenge [3]. Frequency domain markers of ANS state were validated against variability markers computed from direct recordings of muscle sympathetic nerve activity (MSNA) acquired via microneurographic techniques from the peroneal nerve [4-9].

Recently, Valenza et al. [10] have proposed two new HP variability indexes, labelled sympathetic activity index (SAI) and parasympathetic activity index (PAI). SAI and PAI are computed according to a Laguerre expansion of HP variability [10] and a Kalman filtering method able to extract the values of SAI and PAI on a beat-to-beat basis [11]. The main feature of this approach is the less rigid association between the HP variability markers and the set of frequencies of HP oscillations compared to the frequency domain technique. This attitude should be helpful to attribute to PAI even contributions of the vagal control occurring the LF band and should prevent the dependence of SAI from contributions of the vagal control occurring along time scales typical of the LF band.

The aim of this study was to validate the SAI and PAI indexes versus more traditional frequency domain HP variability markers and indexes derived from MSNA recorded in healthy young subjects during incremental head-up tilt inducing sympathetic activation and vagal withdrawal according to tilt table inclination [12,13].

II. Methods

A. SAI and PAI Estimation Procedure

SAI and PAI indexes were extracted via orthonormal Laguerre expansion able to separate the contributions of vagal and sympathetic branches to HP control [10,11]. Briefly, HP

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series is modelled as a linear combination of orthonormal Laguerre functions weighting the original HP values. This classical linear problem can be easily solved via traditional least squares method. The Laguerre function selection procedure to achieve SAI and PAI estimates was reported in [10]. Two separate identification procedures were applied to extract sympathetic and vagal contributions to HP dynamics. This choice favors the relative independence of SAI and PAI markers. SAI and PAI were dimensionless. The final model was turned out into the predictive form using a Kalman filter representation, thus providing SAI and PAI overtime [10,11]. Any HP variability series can be uploaded in a suitable format to http://www.saipai-hrv.com/ and the final beat-to-beat estimates of SAI and PAI can be automatically obtained.

III. Experimental Protocol and Data Analysis

A. Experimental Protocol

Twelve healthy subjects (9 females, age from 20 to 36 years, median 22.5 yrs) were enrolled and underwent an incremental head-up tilt test as previously described [12,13]. The table was tilted at 0°, 20°, 30°, 40° and 60° (T0, T20, T30, T40, and T60) with subjects kept in each position for 10 minutes without returning to T0 until the end of the protocol and incrementing each time the inclination angle. Subjects signed an informed consent before participating. The protocol was approved by the Alfred Hospital Ethics Review Committee (no. 144/06) and was conformed to the Declaration of Helsinki for studies involving human subjects and to the relevant guidelines of the National Health and Medical Research Council of Australia.

Electrocardiogram (ECG) acquired via a bioamplifier (ADInstruents, Castle Hill, NSW, Australia) from lead III and MSNA (IOWA Nerve Traffic Analyzer, model 662C-3, The University of Iowa, Iowa, IA, USA) were recorded for the overall duration of the study. Microneurography was performed with a tungsten microelectrode percutaneously inserted in the peroneal nerve to record the multiunit postganglionic sympathetic nerve discharge. The raw MSNA signal was band-pass filtered between 700 and 2000 Hz and then amplified, rectified and integrated with a time constant of 0.1 s. The integrated MSNA and ECG were sampled at 1000 Hz. Recordings of 2 subjects in T20, of 1 subject in T30 and T40 and of 5 subjects in T60 were excluded for bad signal quality or because the subjects did not complete the protocol.

B. Variability Series Extraction and Data Analysis

HP was extracted as the temporal distance between two consecutive R-wave apexes. The calibrated MSNA variability was derived from integrated MSNA as described in [7]. First, MSNA bursts were detected in a window from 0.9 to 1.7 s after the R-wave peak to account for sympathetic baroreflex latency. Then, MSNA bursts were counted in a moving time window of 5 s advancing with steps of 1 ms. The obtained step-wise signal was low-pass filtered at 0.5 Hz and then sampled at the occurrence of the first R-wave peak of the HP. Thus, the MSNA value was divided by the time window duration (i.e. 5 s) to obtain a calibrated series expressed in burst$\cdot s^{-1}$. Mean and variance were extracted from HP and MSNA variability series of 256 consecutive values in each experimental condition, labeled μ_{HP}, σ^2_{HP}, μ_{MSNA}, and σ^2_{MSNA} and expressed respectively in ms, ms^2, burst$\cdot s^{-1}$, and burst$^2\cdot s^{-2}$. Power spectral density was computed after modeling the series according to an autoregressive model with optimal order chosen via the Akaike figure of merit in the range from 8 to 14. Power spectral density was then factorized into spectral components. LF power of MSNA variability (LF_{MSNA}) and HF power of HP series (HF_{HP}) were calculated as the sum of the powers of all spectral components whose central frequencies dropped in the assigned bands. LF_{MSNA} and HF_{HP} were expressed in absolute units (i.e. burst$^2\cdot s^{-2}$ and ms^2) [1]. LF_{MSNA} and HF_{HP} were taken as a direct measure of sympathetic modulation directed to vessels and as indirect measure of parasympathetic modulation directed to the heart respectively. The ratio of LF to HF power computed over HP series (LF/HF_{HP}) was assessed as well and taken as a marker of sympatho-vagal balance [4]. The median value of the beat-to-beat SAI and PAI series was calculated for each subject in each experimental condition and taken as representative of the entire series [10,11].

C. Statistical Analysis

One-way analysis of variance (Dunnett's test for multiple comparisons), or Kruskal–Wallis one-way analysis of variance on ranks when appropriate (Dunn's test for multiple comparisons), was applied to check the differences of values in each experimental session (i.e. T20, T30, T40 and T60) compared to T0. Spearman's rank correlation coefficient ρ and type I error probability p were computed between any variability indexes and SAI or PAI. Analyses were carried out with a commercial software (Sigmaplot 14.0, Systat Software Inc., San Jose, CA, USA). A $p<0.05$ was always deemed as

TABLE I. Time and Frequency Domain Parameters of HP and MSNA Series.

Index	T0	T20	T30	T40	T60
μ_{HP} [ms]	1003.37±147.240	926.793±136.555	884.741±129.437	805.867±112.608*	688.152±119.874*
σ^2_{HP} [ms^2]	5442.558±3439.995	4553.214±3651.593	4346.397±2605.237	3004.888±1816.474	2498.300±939.257*
HF_{HP} [ms^2]	1356.608±743.537	733.430±341.530	581.949±593.938	211.212±134.264*	83.449±76.666*
LF/HF_{HP}	2.116±2.059	1.811±1.184	2.110±1.985	6.173±7.280	34.468±41.754
μ_{MSNA} [burst$\cdot s^{-1}$]	0.331±0.091	0.371±0.078	0.467±0.132*	0.496±0.126*	0.451±0.162
σ^2_{MSNA} [burst$^2\cdot s^{-2}$]	0.033±0.010	0.043±0.015	0.044±0.008	0.057±0.018*	0.056±0.021*
LF_{MSNA} [burst$^2\cdot s^{-2}$]	0.022±0.010	0.027±0.012	0.026±0.013	0.043±0.022*	0.043±0.029
SAI	32.087±8.384	40.081±11.690	46.533±12.010*	59.475±13.325*	89.694±24.867*
PAI	73.557±11.436	66.929±15.376	57.720±11.624	51.404±8.826*	41.985±8.673*
Number of subjects	12	10	11	11	7

μ_{HP} = HP mean; σ^2_{HP} = HP variance; μ_{MSNA} = MSNA mean; σ^2_{MSNA} = MSNA variance; LF = low frequency; HF = high frequency; HF_{HP} = HF power of HP series; LF/HF_{HP} = ratio of the LF to HF powers on HP series; LF_{MSNA} = LF power of MSNA series; SAI = sympathetic activity index; T0, T20, T30, T40, T60 = head-up tilt at 0°, 20°, 30°, 40°, 60° respectively. Results are reported as mean±standard deviation. The symbol * indicates $p<0.05$ versus T0.

TABLE II. CORRELATION ANALYSIS BETWEEN VARIABILITY INDEXES AND SAI.

marker	T0		T20		T30		T40		T60	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
μ_{HP}	-0.848	2.00×10^{-7}*	-0.952	2.00×10^{-7}*	-0.827	2.00×10^{-7}*	-0.891	2.00×10^{-7}*	-0.964	2.00×10^{-7}*
σ^2_{HP}	-0.329	2.84×10^{-1}	0.030	9.19×10^{-1}	-0.500	1.09×10^{-1}	-0.455	1.49×10^{-1}	-0.857	6.00×10^{-3}*
HF_{HP}	-0.629	2.60×10^{-2}*	-0.370	2.75×10^{-1}	-0.382	2.33×10^{-1}	-0.236	4.67×10^{-1}	0.393	3.41×10^{-1}
LF/HF_{HP}	0.427	1.57×10^{-1}	0.297	3.84×10^{-1}	0.282	3.84×10^{-1}	0.023	9.24×10^{-1}	0.036	9.05×10^{-1}
μ_{MSNA}	0.168	5.88×10^{-1}	0.225	5.12×10^{-1}	0.000	9.89×10^{-1}	-0.009	9.68×10^{-1}	0.500	2.17×10^{-1}
σ^2_{MSNA}	0.056	8.52×10^{-1}	0.539	9.80×10^{-2}	0.509	1.02×10^{-1}	-0.036	9.03×10^{-1}	0.179	6.60×10^{-1}
LF_{MSNA}	-0.140	6.51×10^{-1}	0.006	9.73×10^{-1}	0.236	4.67×10^{-1}	0.118	7.14×10^{-1}	0.250	5.45×10^{-1}

μ_{HP} = HP mean; σ^2_{HP} = HP variance; μ_{MSNA} = MSNA mean; σ^2_{MSNA} = MSNA variance; LF = low frequency; HF = high frequency; HF_{HP} = HF power of HP series; LF/HF_{HP} = ratio of the LF to HF powers on HP series; LF_{MSNA} = LF power of MSNA series; SAI = sympathetic activity index; T0, T20, T30, T40, T60 = head-up tilt at 0°, 20°, 30°, 40°, 60° respectively. ρ = Spearman's rank correlation coefficient; p = type I error probability. The symbol * indicates $p<0.05$.

significant.

IV. RESULTS

Table I shows HP and MSNA time and frequency domain indexes. As expected, μ_{HP}, σ^2_{HP} and HF_{HP} decreased with tilt table angle. In particular, during T40 and T60 μ_{HP} and HF_{HP} were significantly lower than T0, while σ^2_{HP} only during T60. LF/HF_{HP} increased but its rise was not significant due to limited statistical power of this index. μ_{MSNA}, σ^2_{MSNA} and LF_{MSNA} increased with the tilt angle: μ_{MSNA} was significantly higher during T30 and T40, σ^2_{MSNA} during T40 and T60, and LF_{MSNA} during T40 compared to T0. SAI raised during T30, T40 and T60 with respect to T0, while PAI decreased during T40 and T60 with respect to T0.

Table II shows results of correlation analysis between variability indexes derived from HP and MSNA variability and SAI as a function of tilt angle. μ_{HP} was negatively correlated with SAI at any inclination of the tilt table. σ^2_{HP} and HF_{HP} was significantly and negatively correlated with SAI during T60 and T0 respectively. MSNA indexes and LF/HF_{HP} were never significantly correlated with SAI.

Table III is analogous to Table II but shows results of correlation between variability indexes and PAI. μ_{HP} and PAI were significantly and positively correlated at any degree of tilt. σ^2_{HP} was significantly and positively correlated with PAI during T60, while HF_{HP} and LF/HF_{HP} were never significantly correlated with PAI. σ^2_{MSNA} was the sole MSNA marker that was found significantly and negatively correlated with PAI and this finding was observed during T20.

V. DISCUSSION

The main results of this study can be summarized as follows: i) indexes derived from HP and MSNA variability suggest the presence of a progressive sympathetic activation and vagal withdrawal during incremental head-up tilt; ii) the same conclusion can be drawn using SAI and PAI markers computed exclusively from HP variability; iii) SAI was uncorrelated with both markers of tonic sympathetic activity (i.e. μ_{MSNA}) and modulation (i.e. σ^2_{MSNA} and LF_{MSNA}); iv) PAI is not significantly correlated with HF_{HP} power.

A. Incremental Head-up Tilt and its Effects on Sympathetic and Vagal Controls

Incremental [12,13] or graded [5,14] head-up tilt is traditionally exploited to probe ANS state. Indeed, orthostatic challenge causes a tonic increase of sympathetic activity and vagal withdrawal necessary to cope with the decrease of venous return proportional to the magnitude of the challenge. The progressive increase of μ_{MSNA} with tilt table inclination confirmed the tonic increase of sympathetic activity during postural challenge. The modification of the tonic sympathetic activity was accompanied by the decrease of the magnitude of the respiratory sinus arrhythmia and an increase of the MSNA variability. This result indicates a gradual modification of the magnitude of the variations of the neural outflow about its mean value (i.e. modulation). The increase of tonic sympathetic activity and modulation and the decrease of vagal modulation are likely to contribute to the decrease of cardiorespiratory coupling [15], the increase of the information transfer along cardiac baroreflex [15], the diminished sensitivity of the cardiac arm of the baroreflex [5,16], the stable information transfer along sympathetic baroreflex [17] and the limited increment of the gain along the sympathetic arm of baroreflex [8] observed during postural challenge.

B. SAI and PAI during Incremental Head-up Tilt

SAI and PAI markers has been proposed to overcome limitations of more traditional LF and HF power indexes derived from HP variability series [1]. These limitations are mainly the effect of the contribution of the sympathetic and vagal controls in the LF band that make the LF power marker to be a weak indicator of sympathetic control when expressed in absolute units [2]. Normalization by σ^2_{HP} leading to percent or normalized units contribute to limit this caveat [4] but did not exclude that percent or normalized LF markers could be affected by vagal control. The less strict link between SAI and PAI with time scales of the HP variations compared to frequency domain markers could be helpful at this regard [10,11]. Also the separate computation of SAI and PAI indexes from HP series [10,11] could contribute to their uncorrelation and to make them suitable for describing co-activation or co-inhibition of vagal and sympathetic controls [14]. In the present study we observed that SAI and PAI were significantly associated with the magnitude of the orthostatic challenge and this result suggests a certain ability in describing regulatory mechanisms operating during posture modification.

C. SAI is not Significantly Associated with MSNA Variability Markers and PAI is not Linked to Respiratory Sinus Arrhythmia

SAI exhibited no significant association with direct markers of neither tonic sympathetic activity (i.e. μ_{MSNA}) nor

TABLE III. CORRELATION ANALYSIS BETWEEN VARIABILITY INDEXES AND PAI.

marker	T0 (n=12)		T20 (n=11)		T30		T40		T60	
	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
μ_{HP}	0.750	3.98×10^{-3}*	0.867	2.00×10^{-7}*	0.855	2.00×10^{-7}*	0.755	6.00×10^{-3}*	0.857	6.00×10^{-3}*
σ^2_{HP}	0.140	6.51×10^{-1}	-0.248	4.68×10^{-1}	0.536	8.20×10^{-2}	0.264	4.16×10^{-1}	0.857	6.00×10^{-3}*
HF_{HP}	0.441	1.43×10^{-1}	0.164	6.31×10^{-1}	0.418	1.88×10^{-1}	-0.082	7.97×10^{-1}	0.393	3.41×10^{-1}
LF/HF_{HP}	-0.280	3.64×10^{-1}	-0.345	3.09×10^{-1}	-0.136	6.73×10^{-1}	0.205	5.20×10^{-1}	-0.036	9.05×10^{-1}
μ_{MSNA}	0.028	9.21×10^{-1}	-0.097	7.59×10^{-1}	-0.064	8.39×10^{-1}	-0.091	7.76×10^{-1}	-0.179	6.60×10^{-1}
σ^2_{MSNA}	-0.203	5.13×10^{-1}	-0.648	3.80×10^{-2}*	-0.409	1.99×10^{-1}	0.173	5.95×10^{-1}	-0.143	7.20×10^{-1}
LF_{MSNA}	-0.179	5.57×10^{-1}	-0.103	7.59×10^{-1}	-0.209	5.20×10^{-1}	-0.091	7.76×10^{-1}	-0.179	6.60×10^{-1}

μ_{HP} = HP mean; σ^2_{HP} = HP variance; μ_{MSNA} = MSNA mean; σ^2_{MSNA} = MSNA variance; LF = low frequency; HF = high frequency; HF_{HP} = HF po$\times10^{-1}$er of HP series; LF/HF_{HP} = ratio of the LF to HF powers on HP series; LF_{MSNA} = LF power of MSNA series; PAI = parasympathetic activity index; T0, T20, T30, T40, T60 = head-up tilt at 0°, 20°, 30°, 40°, 60° respectively. ρ = Spearman's rank correlation coefficient; p = type I error probability. The symbol * indicates $p<0.05$.

modulation (i.e. σ^2_{MSNA} and LF_{MSNA}). PAI exhibited no significant association with one of the most widely accepted marker of vagal modulation (i.e. HF_{HP}). We conclude that SAI and PAI might represent weak proxies of sympathetic and vagal activities and/or modulations as derived from HP variability. The link with tilt table angle might suggest that SAI and PAI can represent interesting markers of cardiovascular control complementary to more traditional frequency domain indexes (e.g. HF_{HP}). SAI and PAI might describe regulatory mechanisms that are not fully under neural control or whose activity does not reflect completely neural outflows directed to the sinus node and its changes. Another possibility is that these findings could be the mere consequence of the small number of subjects enrolled in this study.

VI. CONCLUSIONS

This study tested two recently proposed HP variability markers, i.e. SAI and PAI [10,11], during an incremental head-up tilt protocol featuring the direct assessment of sympathetic activity. Results suggested that both indexes can capture the cardiac control modifications induced by orthostatic challenge. However, uncorrelation of PAI with respiratory sinus arrhythmia and that of SAI with direct indexes of sympathetic activity and/or modulation indicates that SAI and PAI are more likely to describe cardiac regulatory mechanisms that are not entirely governed by vagal and sympathetic branches of the ANS. Further studies testing correlation of SAI and PAI with baroreflex sensitivity, cardiorespiratory coupling and alternative direct measurements of sympathetic activity such as catecholamine concentration are need to elucidate their link with cardiovascular control mechanisms.

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