Gender differences in cardiovascular and cardiorespiratory coupling in healthy subjects during head-up tilt test by Joint Symbolic Dynamics

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Abstract—**Gender related-differences in the autonomic regulation of the cardiovascular and cardiorespiratory systems have been studied mainly by hemodynamic responses during different physical stressors. In this study, the influence of gender on the autonomic response to an orthostatic challenge was investigated by obtaining the cardiovascular and cardiorespiratory coupling using the nonlinear technique known as joint symbolic dynamics (JSD) representation. This study includes 24 healthy young subjects. Males (N=12) and age-matched females (N=12) were enrolled in a head-up tilt (HUT) test, breathing normally, including 5 minutes of supine position (baseline) and 25-40 minutes of 70° orthostatic phase. The cardiovascular and cardiorespiratory couplings were obtained at baseline, early and middle orthostatic phases. Although in baseline there were some gender differences, parameters from JSD showed highly significant (p=0.0004) differences in specific cardiovascular coupling patterns in the early tilt phase. Furthermore, JSD analysis revealed that in males, due to increased sympathetic activity, exist a lower degree of cardiovascular coupling accompanied with an increased occurrence of tachycardic patterns. On the other hand, the cardiorespiratory coupling revealed only very few slightly significant differences in all three phases.**

I. Introduction

In clinical practice evaluation of autonomic function during orthostatic challenge is routinely performed by means of the head-up tilt (HUT) test. An individual's tolerance to an orthostatic stress (OS) is dependent upon the degree of available vasoconstrictor reserve [1]. Short-term cardiovascular responses to OS are regulated by the autonomic nervous system (ANS) via the baroreflex. This results in a reflex response of increased sympathetic activity to increase both, heart rate (HR) and peripheral vasoconstriction to maintain blood pressure. With respect to gender, women have demonstrated more frequently an inability to maintain blood pressure upon upright posture (orthostatic intolerance) due to lower stroke volume than in men. This is associated with lower responsiveness of specific mechanisms of blood pressure regulation due to little sympathetic support and therefore reduced adequate vasoconstriction in young healthy females [1, 2]. The effect of gender during OS has been mostly investigated observing systemic and cerebral hemodynamic changes. Women are characterized by lower blood pressure, blood volume and stroke volume as a result of smaller overall heart size and subsequently less cardiac reserve during orthostasis [2, 3]. Investigators suggest that responses of muscle sympathetic nerve activity to OS are attenuated in women with no relationship to arterial pressure, total peripheral resistance or cardiac output [4, 5]. However, the acquisition of valid signals of hemodynamics, e.g. by ultrasound probes, can be accompanied with technical difficulties [6].

The increased predisposition of orthostatic intolerance in females may be, in part, due to the hormonal differences between men and women [6, 7]. Female sex hormones are supposed to cause greater vasodilatation and to influence baroreflex control mechanisms since a prominent role for cardiac baroreflex sensitivity (BRS) in responding to acute blood pressure (BP) changes do not exist in young women [8].

Studies on autonomic regulation analysis have been performed by linear and nonlinear univariate signal processing mainly applied to heart rate variability (HRV). Also, bivariate signal processing has been achieved to understand cardiovascular and cardiorespiratory systems coupling. Nevertheless, bivariate processing has been primarily performed by linear methods as in the case of cardiac baroreflex sensitivity (BRS) by analyzing few specific patterns of the cardiovascular coupling. However, nonlinear behavior may be present during OS. Consequently, in this study a nonlinear method known as joint symbolic dynamics (JSD) was used to analyze several types of short-term coupling patterns in a more detailed way [9] since JSD includes various patterns regulated by the baroreflex.

II. Materials and Methods

A. Subjects and experimental protocol

In this study, 12 healthy male (26 ± 4 years) and 12 age-matched healthy female (26 ± 5 years) subjects were enrolled. Tests were performed during the morning in an adequate laboratory with controlled environment in the National Institute of Cardiology at Mexico City. High-resolution ECG, non-invasive blood pressure and respiration were simultaneously and continuously recorded using a Task Force Monitor (CNSystems, Graz, Austria). Data recording

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started with a rest period of 5 minutes in the supine position (baseline - BL), after that the subject underwent a 70° head-up tilt [2]; the transition phase lasted one minute. The duration of the orthostatic phase (OP) varied between 25 and 40 minutes. None of the control subjects had any problems to complete the tilt test. After tilt back to supine within one minute recovery was recorded for up to 5 minutes. During OP the subjects were breathing normally.

B. *Pre-processing and data analysis*

Time series of successive beat-to-beat intervals (BBI, tachogram), respiratory phase (RESP, respirogram), systolic (SYS, systogram) and diastolic (DIA, diastogram) blood pressure were extracted from ECG, respiration and continuous non-invasive arterial blood pressure recorded by the Task Force Monitor. All extracted times series were manually reviewed and subsequently corrected for by interpolation of ventricular premature beats and artifacts using an adaptive filter [10] to obtain normal-to-normal beat time series (NN). For bivariate analyses, the time series were interpolated with a sampling frequency of 2Hz. For data analysis we used three 5-minutes windows referring to the stages of supine position (baseline - BL), early tilt (ET) starting 2 minutes after transition and middle tilt (MT) defined 8 minutes after transition. In each window, all JSD parameters were compared to establish statistical differences between men and women.

C. *Joint Symbolic Dynamics - JSD*

The JSD method, as an enhanced version of the univariate symbolic dynamics approach [11], quantifies the bivariate nonlinear behavior of short-term cardiovascular and cardiorespiratory coupling by means of symbols. Thereby, in the case of cardiovascular coupling JSD transforms the n beat-to-beat values of BBI and SYS time series (x^{BBI}, x^{SYS}) from a bivariate sample vector X, into a bivariate symbol vector S that consists of a sequence of symbols (s^{BBI}, s^{SYS}) using an alphabet A={0,1}, see Fig. 1. Symbol '1' represents increasing values and symbol '0' decreasing and unchanged values applying a threshold level l=0, as indicated in equations (1) and (2).

$$s_n^{BBI} = \begin{cases} 0 : (x_n^{BBI} - x_{n+1}^{BBI}) \le l^{BBI} \\ 1 : (x_n^{BBI} - x_{n+1}^{BBI}) > l^{BBI} \end{cases} \qquad (1)$$

$$s_n^{SYS} = \begin{cases} 0 : (x_n^{SYS} - x_{n+1}^{SYS}) \le l^{SYS} \\ 1 : (x_n^{SYS} - x_{n+1}^{SYS}) > l^{SYS} \end{cases} \qquad (2)$$

Afterwards, words (w) of symbol sequences with a length equal to three were formed. From all bivariate word type combinations the probability of occurrence $p(w_{i,j})$ was estimated using an 8x8 word distribution density matrix W (rows represent BBI, columns represent SYS, DIA or RESP) ranging from $(000, 000)^T$ to $(111, 111)^T$. From the W matrix the following indices were estimated:

- normalized probability occurrences of bivariate word type combinations (JSD1-JSD64) '*xxx*' of BBI time series and simultaneous '*yyy*' of SYS, DIA or RESP time series (e.g. BBI-100/RESP-101),
- sum of each row (combinations with equal BBI word: BBI*xxx*) and the sum of each column (combinations with equal SYS, DIA or RESP word: **yyy*),
- sums of diagonals within W: *SumSym* - symmetric word types and *SumDiam* - diametric word types,
- Shannon entropy of the word distribution density matrix as a measure of the overall degree of cardiovascular or cardiorespiratory coupling, i.e.,

$$JSD_{Shannon} = -\sum_{i,j=1}^{8} [p(w_{i,j}) \log_2 p(w_{i,j})] \qquad (3)$$

D. *Statistics*

The non-parametric Mann-Whitney U-test was applied for the statistical evaluation of all differences in JSD indices between men and women in each of the three windows (BL, ET and MT). Significance was set at three levels: slightly significant for p<0.05 (*), significant for p<0.01 (**) and highly significant for p<0.001 (***).

III. RESULTS AND DISCUSSION

Analysis by JSD showed that cardiovascular (BBI-SYS and BBI-DIA) as well as cardiorespiratory (BBI-RESP) couplings are significantly different between healthy young men and women in supine position. In BL, for BBI-SYS, mainly JSD parameters regarding the sum of respective rows and columns were significantly different between men and women, see Table 1. For BBI-DIA as well as for BBI-RESP, the statistical differences were on several word types. During ET phase the statistical differences between male and female were modified revealing higher significances, especially in the single word types, for cardiovascular coupling and lower significances for cardiorespiratory coupling. At the MT phase, there are significant JSD parameters and therefore, gender differences are still present in the cardiovascular and cardiorespiratory coupling, see Table 1. There were gender differences in cardiovascular couplings during ET and MT compared to BL.

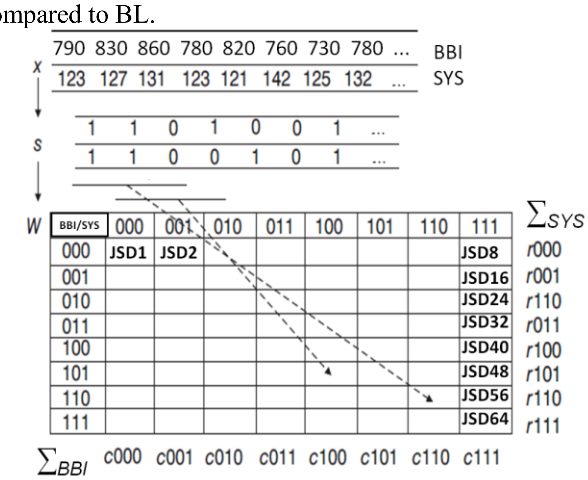

Figure 1: Transformation of vector x, bivariate beat-to-beat intervals and systolic blood pressure, into symbol vector s and word distribution matrix W, where in s the symbol 1implies increasing values while the symbol 0 indicates decreasing and equal values. Also, r_{BBI} = row sum; c_{SYS} = column sum.

TABLE 1. SIGNIFICANT JSD PARAMETERS FOR CARDIOVASCULAR (BBI-SYS AND BBI-DIA) AND CARDIORESPIRATORY (BBI-RESP) COUPLING DURING BASELINE (BL), EARLY TILT (ET) AND MIDDLE TILT (MT) PHASES BETWEEN MEN AND WOMEN; * P<0.05, **P<0.01, ***P<0.001.

COUPLING	PHASE BL	ET	MT
BBI-SYS	JSD46*	JSD5***	JSD5*
	JSD48**	JSD15*	JSD7*
	SYS001*	JSD20*	JSD8*
	SYS100*	JSD23**	JSD18**
	SYS111*	JSD29*	JSD21**
	BBI001*	JSD44*	BBI010**
	BBI010*	JSD47*	BBI100*
	BBI011*	BBI010*	JSDshannon*
	BBI100*	BBI100*	
		JSDshannon*	
BBI-DIA	JSD1*	JSD17*	JSD8*
	JSD15*	JSD24*	JSD22*
	JSD29*	JSD34*	JSD34**
	JSD41*	JSD45**	JSD41**
	JSD56*	JSD48*	BBI010**
	SumSym*		JSDshannon*
BBI-RESP		JSD4*	JSD4*
	JSD63*	JSD17*	JSD5*
	RESP000**	BBI000*	JSD17*
		BBI010*	JSD23*

A. Cardiovascular coupling

Analysis of cardiovascular coupling (BBI-SYS) by JSD revealed similar distributions of bivariate word types comparing men and women in baseline, see Fig. 2. For both genders dominant word types occurred along the symmetric diagonal reflecting unimpaired baroreflex activity. The transition from supine position to orthostatic phase caused a more pronounced redistribution of cardiovascular coupling patterns in male controls, see JSD matrix for ET phase in Fig. 2. This was characterized by an increased probability of occurrence of dominant ($p>0.03$) word types accompanied with a decreased probability of occurrence of seldom ($p<0.03$) word types in the early tilt phase, already two minutes after tilt up. Hereby, only seldom word types showed high significant gender differences. The probability of occurrence of one single bivariate word type, JSD5, was not significantly different between genders in baseline, but highly significantly increased in men in the early tilt phase, see Table 1. This index represents a short-term pattern of decreased BBI and simultaneously one beat delayed decreased SYS values reflecting tachycardic baroreflex and therefore, increased sympathetic activity in men in the early tilt phase. The measures for BRS (SumSym) and suppressed BRS (SumDiam) from cardiovascular coupling analysis of BBI and SYS time series were not significantly different between men and women in any of the three analyzed phases. However, they showed a trend of decreased SumSym and increased SumDiam in men pointing to reduced BRS in male controls during ET and MT phases. There was an agreement between decreased BRS indicated by SumSym and SumDiam and increased sympathetic activity in men revealed by JSD5. On the contrary, this parameter did not change in women, indicating no alterations in this specific tachycardic pattern due to orthostatic stress. Hence, in the early tilt phase specific word types of the JSD matrix were significantly higher altered in male than in female controls pointing out to different coupling characteristics. Furthermore, gender-related coupling differences remained in the middle tilt phase, see Table 1.

A global parameter for measuring the degree of cardiovascular coupling, JSDshannon [12, 13], showed no significant gender differences in baseline, but was significantly reduced in women compared to men in the early and middle tilt phases. Lower Shannon entropy of the JSD matrix reflected a higher degree of coupling between BBI and SYS time series in female subjects in the beginning of orthostatic phase, although BRS was not changed in women. Thus, men were able to remain an overall lower degree of cardiovascular coupling; however there was a redistribution of occurring bivariate word types due to increased sympathetic activity in male controls in the early tilt phase. In contrast, the significantly reduced Shannon entropy in women in the early tilt phase indicated an increased degree of cardiovascular coupling compared to men as well as in comparison to baseline conditions. In the middle tilt of the orthostatic phase the Shannon entropy of the JSD matrix from BBI and SYS time series remained significantly different between male and female subjects. Thus, in the middle tilt phase the degree of cardiovascular coupling was still different between gender groups. Also, in MT phase some single word types are still significantly different between men and women, see Table 1. The Shannon entropy from JSD analysis of BBI and DIA time series showed no significant differences between male and female controls in BL and ET phases. Furthermore, JSD analysis showed higher entropy values in the early and middle tilt phases compared

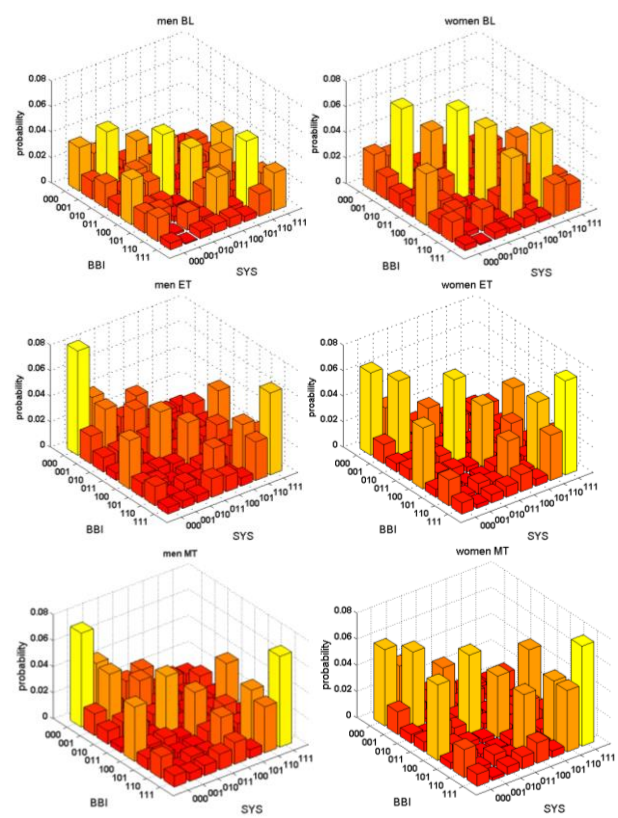

Figure 2: Averaged JSD matrices of cardiovascular coupling (BBI-SYS) during baseline (BL), early tilt (ET) and middle tilt (MT) phases in healthy young men (left) and women (right).

to baseline for both genders. This indicated less BBI-DIA coupling due to orthostatic stress in young controls independently from gender.

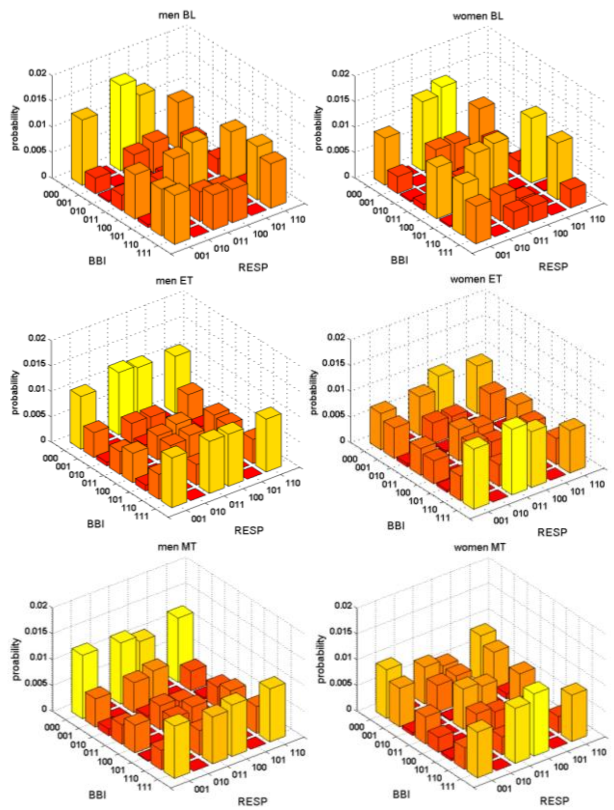

Figure 3: Averaged JSD matrices of cardiorespiratory coupling (BBI-RESP) during baseline (BL), early tilt (ET) and middle tilt (MT) phases in healthy young men (left) and women (right). The columns RESP000 and RESP111 are not shown due to high probabilities of occurrence.

B. *Cardiorespiratory coupling*

JSD analysis of cardiorespiratory coupling (BBI-RESP) revealed very few slightly significant differences between men and women in all three phases, see Table 1. Also, JSDshannon was not significantly different in any of the three phases, but showed a trend of lower Shannon entropy during orthostatic stress in female controls. This could indicate a tendency to higher degree of cardiorespiratory coupling in healthy women due to orthostatic stress. However, for both gender groups, the columns RESP000 and RESP111 had the highest probabilities in all three phases independently from BBI word types. These two RESP columns represent three consecutive RESP decreases and increases, respectively, which were mostly occurring (≈80%) within RESP time series. RESP000 and RESP111 were excluded from graphical representations of cardiorespiratory couplings, see Fig. 3, to compare visually the averaged distribution of seldom word types in more detail. Considering the averages of seldom word types, orthostatic stress caused dominant rows in the JSD matrix including BBI000 and BBI111, representing similarly consecutive BBI decreases and increases, respectively. Hereby, the JSD index BBI000 was significantly increased in men in the early tilt phase, indicating increased tachycardic BBI patterns in combination with RESP patterns of low variability [001, 011, 100 and 110] due to increased sympathetic activity in male controls caused by orthostatic stress.

IV. Conclusion

Orthostatic stress caused already in the early tilt phase gender dependent different alterations in cardiovascular and cardiorespiratory couplings. JSD analysis revealed clearly that in male, due to increased sympathetic activity, existed a lower degree of cardiovascular coupling accompanied with an increased occurrence of tachycardic patterns. Therefore, gender influences need to be considered when performing future studies of orthostatic challenges.

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