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Modifications of Autonomic Activity and Baroreceptor Response on Posture Challenge in Patients with Vasovagal Syncope

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Background: Vasovagal syncope (VVS) is diagnosed by medical history and confirmed by a head-up tilt (HUT) test. The pathophysiology of VVS is controversial. **Methods:** In this study, we enrolled 30 VVS patients and compared normal study patients in Tri-Service General Hospital. We attempted to examine this controversy by evaluating heart rate variability and baroreceptor sensitivity of VVS in the upright posture. **Results:** The VVS patients had lower total peripheral vascular resistance, increased LF/HF (low frequency power / high frequency power) ratio, and decreased baroreceptor sensitivity in the HUT position. **Conclusion:** The VVS patients demonstrated postural vascular sympathetic dysfunction and cardiac sympathetic hyperactivity before syncope. The decreased baroreceptor sensitivity might be partly explained by the failure of the usual compensatory heart rate increase during orthostatic challenge.

Key words: vasovagal syncope, autonomic function test, baroreceptor response

INTRODUCTION

Syncope is a significant public health problem, accounting for 1% of hospital visits to emergency departments.[1] Vasovagal syncope (VVS), an important form of neutrally mediated syncope, is the most common cause of unexplained syncope.[2] VVS is usually a benign condition and rarely requires pharmacological treatment. The classic description of VVS includes a fall in blood pressure accompanied by a slowing of the heart rate. The result of this is a transient period of systemic hypotension leading to cerebral hypoperfusion with loss of consciousness and postural tone.

Patients susceptible to VVS can often be identified by head-up tilt (HUT) test. In healthy individuals, assumption of an upright posture from a recumbent position causes venous pooling in legs and an associated decrease in cardiac output, resulting in lower blood pressure and thus unloading of the baroreceptors, whereas patients with VVS fail to maintain adequate vascular tone during postural change. A tilt-table test was first applied to the assessment of syncope in 1980.[3] Syncope is hard to assess, and it produces abnormal results in 10 to 30 % of asymptomatic patients during HUT test. Accordingly, using drugs to promote specificity is not recommended.[4]

Patients with VVS tend to have relative reductions in central blood volume, which is further aggravated by an upright posture. A normal functioning baroreceptor system would be expected to compensate for the fall in systemic blood pressure by increasing the heart rate and initiating increased vasoconstriction through augmentation of sympathetic activity and withdrawal of parasympathetic activity. The recent study revealed cardioinhibition and mixed type VVS due to an increase in sympathetic drive followed by vagal reflex, causing bradycardia and hypotension.[5] In VVS patients, however, the baroreceptor feedback mechanism either fails entirely or is only partially effective. Factors contributing to the difference between normal baroreceptor response to upright posture, and the response during tilt-induced VVS are not clear.[6]

Through LF/HF and BRS changes in different stages of HUT, we attempt to understand the mechanism of cardiac autonomic hypersensitivity and reduced cardiopulmonary baroreceptor sensitivity associated with VVS

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during postural change.

PATIENTS AND METHODS

We retrospectively enrolled subjects who were referred to Tri-Service General Hospital from January 2005 to December 2010 for evaluating the cause of syncope, pre-syncope and unknown dizziness. Thirty subjects younger than 55 were classified as having VVS with the HUT test (mean age 27.2±11.6 year-old, 5 females, 25 males) and included in this study. Thirty age and gender matched subjects with normal response to HUT test (mean age 24.7±8.6 year-old, 4 females, 26 males) were enrolled as controls. All subjects were unremarkable after cardiological and neurological evaluation. All subjects took a light diet. A passive head up tilt-table test was performed between 9:00 and 12:00 or between 2:00 and 5:00 pm in a quiet and temperature controlled room (24-25 ^{o}C) with the lights dimmed. The patients were instrumented in supine position on a motorized tilt table with a footboard and knee and abdominal straps to prevent falling. The technician then set the blood pressure and heart rate monitor for at least 15 minutes with the patient in the supine position. The upright tilt test protocol begins with recording 10 minutes of supine rest period, followed by a second phase of 70^{o} upright for up to 45 minutes or until the onset of symptoms (mean around 17.4 minutes of HUT). During the test, patients underwent continuous electrocardiographic monitoring: beat-to-beat blood pressure was monitored noninvasively Task Force Monitor (CNSystems, Graz, Austria). If syncope or presyncope developed accompanied by an abrupt fall in blood pressure, the subject was returned to the supine position. The upright tilt test was considered positive on the reproduction of syncopal (loss of consciousness and postural tone) or near-syncopal (pallor, nausea, dizziness, lightheadedness, sensation of imminent syncope) symptoms associated with hypotension (drop in systolic blood pressure >60% from baseline values or an absolute value <80 mmHg) alone or combined to a bradycardia (drop in heart rate >30% from baseline value or an absolute value <40 bpm) or asystole. Positive responses were classified according to the Task Force on Syncope of the European Society of Cardiology.[7]

All cardiovascular assessments were carried out with continuous heart rate and beat-to-beat systolic arterial pressure (SAP) and impedance cardiography (ICG) measurement Task Force Monitor (CNSystems, Graz, Austria). Continuous SAP was obtained using the finger downloading technique and was automatically and continuously corrected to the oscillometric values obtained from the contralateral arm (brachial artery).[8] ICG is a noninvasive method of obtaining hemodynamics. Real-time beat-to-beat stroke volume was estimated using an improved method of transthoracic impedance cardiography. Afterload was calculated as total peripheral resistance index (TPRI)= (MAP-CVP) · 80/CI (CVP is around 4-10 mmH_2O and too low to be ignored) and cardiac contractility as Left Ventricular Work Index (LVWI). Left ventricular ejection time (LVET) is the interval of aortic valve opening to closure times the mean systolic time.[9]

The autonomic nervous system function was assessed at rest and during HUT using baroreflex sensitivity by the Task Force with the sequence method.[10] (to identify a series of at least three consecutive heart beats in which systolic pressure and the following RR-interval (RRI) either both increased or both decreased) and heart rate variability (HRV), using spectral analysis.[11] Frequency domain analysis of heart rate variability was performed for assessing autonomic activities. Traditional spectral analyses work with at least 256 samples (heart beats and diastolic blood pressure for blood pressure variability (BPV) and the time resolution correspondingly low (e.g. FFT - Fast Fourier Transformation). Therefore, we decided to take an adaptive auto-regressive (AAR) model to compute the time-varying spectral estimation. LF/HF ratio is a quantitative index for evaluating the sympathovagal balance and the short autonomic regulation.[12]

The SAP time series were scanned to identify ramps of four or more consecutive beats characterized by a progressive increase (up-ramp) or reduction (down-ramp) of at least 1 mmHg; spontaneous sequences were identified as SAP ramps followed by concomitant and concordant RRI lengthening/shortening of at least 5ms. The sequences were scanned with a lag order of 0, 1, and 2 including each sequence only once. The slope of the regression line between the RRI and SAP values was computed for each sequence, and taken as a measure of baroreflex sensitivity. (BRS; ms/mmHg).[9]

Baroreflex sensitivity was calculated as the slope of the linear regression line relating systolic blood pressure changes to RR interval changes. Regression lines with more than 20 data points and a correlation coefficient (r) greater than 0.8 were accepted for analysis.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or percent when appropriate. The between-group comparisons were made by Student's t test for continuous

Table 1. Variables determined by VVS-naïve and VVS-patients in the supine period.

	Naïve	Positive	*p*
Age	24.7±8.6	27.2±11.6	0.34
Gender	26M:4F	25M:5F	0.72
Height (cm)	171.4±8.9	170.5±7.3	0.65
Weight (kg)	68.9±10	62.9±11.3	0.036***
BMI (kg/m^2)	23.4±2.8	21.6±2.9	0.015***
HR (beat/min)	72.1±13.5	68.1±11.5	0.22
MBP (mmHg)	88.72±8.99	83.77±8.69	0.034***
TPRI (dyn · s · m^2/cm^5)	2037±409	1913±457	0.28
TFC (1/kOhm)	31.88±3.86	31.25±3.64	0.52
SI (ml/m^2)	51.47±8.24	52.29±8.26	0.7
CI (l/min · m^2)	3.54±0.75	3.53±0.65	0.93
EDI (ml/m^2)	79.39±12.9	81.61±11.99	0.49
IC (1000/sec)	63.65±14.93	66.67±14.07	0.42
LVWI (kg · m/m^2)	4.3±1.3	3.88±0.74	0.13
LVET (msec)	312.5±19.4	315.4±21.9	0.59
ET%	37.3±5.9	35.46±3.9	0.16
HRV LF/HF	1.38±0.83	1.06±0.57	0.08
BRS (ms/mmHg)	22.57±11.15	22.31±11.91	0.93
BPV ratio	4.76±2.5	5.63±4.07	0.32

Data are presented as the mean value ± SD, except for gender. BMI: body mass index; HR: heart rate; MAP: mean blood pressure; TPRI: total peripheral resistance index; TFC: total chest fluid content; SI: stroke volume index; CI: cardiac index; EDI: end-diastolic index; LVWI: left ventricular work index; LVET: left ventricular ejection time; ET%=left ventricular ejection time/RR interval; HRV LF/HF: low/high frequency; BRS: baroreceptor sensitivity; BPV ratio: blood pressure variability ratio.

variables, and the Chi-square test to compare categorical variables. The tests were considered statistically significant at $p< 0.05$. The data were analyzed by SPSS, version 18 for Windows (Chicago, Illinois).

RESULTS

There were no differences in baseline heart rate, age, and gender between the two groups. However, VVS subjects had significantly lower body weight, body mass index, and mean blood pressure at rest (Table 1). VVS subjects had a lower heart rate and mean blood pressure before tilt down (Table 2). Upon orthostatic challenge imposed by tilt up, VVS patients exhibited a high LF/HF ratio, and lower BRS that did not differ from the control group at rest (Table 3). Heart rate response increased significantly prior to syncope and then dropped during syncope in VVS subjects (Fig. 1). Postural HRV LF/HF ratio was significant different with 6.75±5.83 in the VVS group and 3.52±1.15 (p=0.003) in the control group.

Table 2 The heart rate and mean blood pressure at the end of HUT.

	Naïve	VVS	*p*
Heart rate	83.7±13.2	52.4±19.4	<0.001
Mean blood pressure	90.2±11.1	46.4±20.1	<0.001

Table 3 Presyncopal automonic function and hemo-dynamic data.

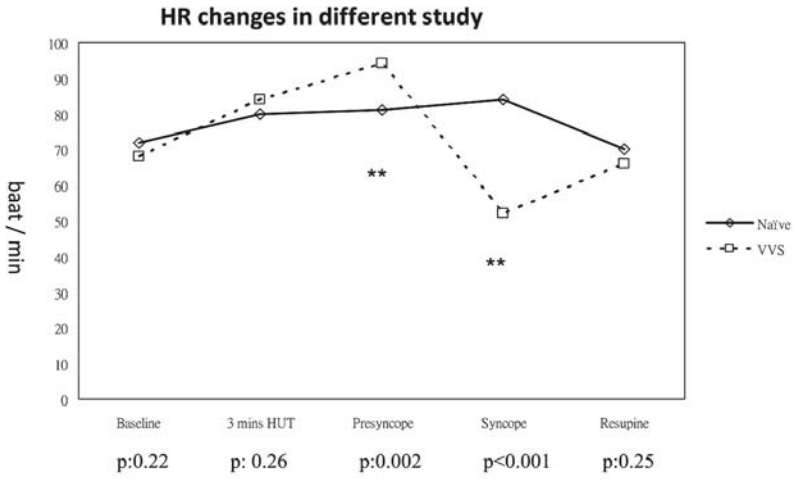
	Naïve	VVS	*p*
HR(beat/min)	81.3±13.6	93.9±15.8	0.002**
MBP(mmHg)	93.9±2	80.9±2.1	<0.001**
TPRI(dyn · sec · m^2/cm^5)	2800.17±641.59	2203.47±804.68	0.002**
TFC (1/kOhm)	29.57±3.36	28.88±3.45	0.44
SI (ml/m^2)	36.54±4.95	35.38±4.05	0.32
CI(l/min · m^2)	2.96±0.44	3.13±0.47	0.14
EDI (ml/m^2)	64.54±8.74	63.58±6.46	0.63
IC (1000/sec)	43.38±9.27	43.38±7.66	0.8
LVWI(kg · m/m^2)	4.15±1.15	3.71±1.11	0.13
LVET(msec)	271.97±22.6	257.57±46.55	0.13
ET%	40.02±3.29	35.94±7.33	0.008**
HRV LF/HF	3.52±1.15	6.75±5.83	0.003**
BRS (ms/mmHg)	11.1±3.82	8.7±4.88	0.038***

***p<0.05

**p<0.01

This study adopts a non-pharmacological HUT test to evaluate VVS and tries to explain its pathophysiological mechanism. Compared with the control, VVS subjects showed lower vascular resistance with poor sympathetic vascular activity under orthostatic stress. During postural change, frequency domain analysis of HRV data revealed an initial increase in sympathetic drive, presumably followed by the vagal reflex activation, causing bradycardia and hypotension.

VVS patients demonstrated a functional and presumably transient diminution of global baroreceptor response being below 10 ms/mmHg in association with head-up tilt-induced syncope. Compared with control subjects, VVS subjects had a statistically significant drop in



Presyncope means before syncope 5 mins

**p<0.01

Fig.1 HR changes to two groups, heart rate response increased prior to syncope and then dropped during syncope in VVS subjects.

baroreceptor sensitivity with the orthostatic challenge (VVS vs control: -61% vs -50.7%).The baroreflex dysfunction in modulating heart rate should also apply to baroreceptor control of peripheral sympathetic neural outflow. As expected, there was a mild increase of HR during tilt in control subjects. However, VVS subjects had a significantly higher increment of HR prior to the syncopal episode (37.8% vs 12.8 %).

DISCUSSION AND CONCLUSIONS

Slowing of the heart rate preceding syncope in VVS subjects could be due to increased parasympathetic or decrease sympathetic outflow to the sinus node, or both. Arguably, a sudden increase in parasympathetic outflow explains the acute bradycardia in vasovagal syncope. Although it is not possible to measure parasympathetic activity directly in humans, evidence for this is nevertheless compelling. In the period preceding vasovagal syncope, spectral analysis of R-R intervals showed higher spectral density in the high frequency band, a putative marker of increased vagal activity.[13] Tilt induced LF/HF ratio change in VVS patients was from 1.06±0.57 to 6.75±5.83 compared to control patients (from 1.38±0.83 to 3.52±1.15). Our results in patients with vasovagal syncope are very similar to those reported by Morillo et al. who found progressive R-R interval lengthening before syncope, a time when blood pressure was falling.[14]

The hemodynamic changes with decreased stroke volume before symptom onset may suggest excessive sympathovagal reactions as the cause of syncope in younger subjects.[15] However, there was no significant difference in the cardiac index between two groups during baseline or presyncopal period in this study (VVS:3.13±0.47 l/min · m^2 and Naïve: 2.96±0.44 l/min · m^2, p=0.14). The TPRI significantly increased in the group when the tilt was evoked (from 2037±409 to 2800±641 dyn · sec · m^2/cm^5), and postural TPRI in VVS patients showed less change (2203±805 dyn · sec · m^2/cm^5). The LVET is the time of ejection of the blood from the lef vnetriclet beginning with aortic valve opening and ending with aortic valve closure. The ET% equals the percentage of LVET/RRI · 100, reflecting the duration of ventricular ejection per second and meaning the systolic time of the heart.[16] ET% during tilt up of VVS patients being lower than the control group means blood volume and venous return reduced or systolic function impairment of VVS subjects following postural challenge occurred.

Jardine et al. reported increased low-frequency heart rate variability during early tilt and reduced arterial baroreceptor sensitivity in patients susceptible to tilt-induced syncope.[17] Folino et al. found tilt induced a significant increase in the LF as well as a decrease in the HF of HRV and reduction of atrial contractility. The reduced atrial work is associated with an increase in the sympathetic component of heart rate variability. This indicates distinct autonomic drives are responsible for the different part function of the heart, with sympathetic activity on the sinus node in the first and with vagal dominance on the atrial myocardium.[18] In the report by Vaddadi et al., baroreflex modulation of the vagal drive to the sinus node, as assessed by the sequence method, appears to be impaired when compared with what was found in a group of healthy controls. The final trigger for human orthostatic vasovagal reactions is sympathetic nervous system inhibition and systemic vasodilation, which are thought to underlie the blood pressure fall in VVS.[19] The report of Béchir et al. shows patients with vasovagal syncope, increased resting MSA (Muscle Sympathetic nerve activity) and blunted postural baroreflex regulation had impaired MSA adaptation.[20] The results of Wang *et al.* showed both reduction of cardiac output and withdrawal

of sympathetic vasoconstriction tone contribute to the development of hypotension in vasovagal syncope.[21]

The study showed tilt induced VVS increased the heart rate and increased fractional shortening as a percentage of LV shortening. Vasovagal syncope was associated with vigorous myocardial contraction.[22] Our study found a higher LF/HF ratio and impairment of BRS during presyncopal period in VVS patients, perhaps as a result of sinus node hypersympathetic activity followed by atrial hypoparasympathetic tone. One report revealed tilt-induced syncope had progressively marked increases in plasma epinephrine levels before syncope, which correlates with concurrent skeletal muscle vasodilation.[23] Vasovagal syncope patients have impaired forearm vasoconstriction or paradoxical forearm vasodilation during the application of subhypotensive lower body negative pressure. This suggests impaired cardiopulmonary baroreceptor inactivation or reduced cardiopulmonary baroreceptor sensitivity.[24] The lower total vascular resistance can be attributed to generalized vasodilator mechanism. Water ingestion decreases the cardiac index to compensate for the increase in the TPR through sympathetic vasoconstriction.[25,26]

There are several limitations to the present study. Because this study was retrospective in design, a prospective validation is suggested. The general syncopal population is female predominant, but this study was male predominant because we used military hospital data. The hemodynamic change in males is less than females in some studies.[27,28] The major limitation of this study is the small sample size. VVS has been classified into different subtypes according to hemodynamic changes. In addition, our subjects were relatively young. Whether our finding can be extended to different categories of VVS patients and older subjects needs further study with a larger cohort of diverse background.

In conclusion, this study found low postural total peripheral resistance in VVS subjects, suggesting vascular sympathetic impairment and inappropriate withdrawal of sympathetic neural constrictor tone might be the cause of VVS. In VVS subjects, there was overstimulation of the cardiac sympathetic pathway before syncope, as indicated by the increased heart rate and altered LF/HF ratio balance, followed by reflex vagal activation suggesting a slow heart rate. Whether sympathetic overstimulation is compensatory for low postural vascular tone awaits future study. The diminished BRS during evolving VVS may in part account for the failure of the baroreceptor system to initiate an adequate compensatory hemodynamic response with parasympathetic impairment. Therefore, the pathophysiologic mechanism for VVS involves not only peripheral sympathetic dysfunction, but also inadequate parasympathetic response to orthostatic stress such as tilt.

In summary, tilt induced altered sympathetic activity, as well as malfunction of cardiac baroreflex and parasympathetic dysregulation, were noted in VVS subjects. Then vagal activity might be induced by hypersympathetic tone followed by hypotension and bradycardia.

DISCLOSURE

The authors declare that this study has no conflict of interest.

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