Modifications of Autonomic Activity and Baroreceptor Response during Tilt-induced Vasovagal Syncope

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Abstract

Vasovagal syncope (VVS) is diagnosed by medical history and confirmed by head-up tilt (HUT) test. In this study, we attempted to examine this controversy by evaluating heart rate variability and baroreceptor sensitivity in VVS during upright posture.

The VVS subjects had lower total peripheral vascular resistance at baseline supine and HUT position. During HUT test, the VVS subjects had increased LF/HF ratio and decreased baroreceptor sensitivity.

In conclusion, VVS subjects demonstrated vascular sympathetic dysfunction and postural cardiac sympathetic hyperactivity. The decreased baroreceptor sensitivity may explain in part the failure of the usual compensatory heart rate increase during orthostatic challenge.

1. Introduction

Syncope is a significant public health problem, accounting for 1% of visits to the Emergency Department of a general hospital. Vasovagal syncope (VVS), an important form of neutrally mediated syncope, is the most common cause of unexplained syncope. Vasovagal syncope is usually a benign condition and rarely requires pharmacological treatment. Classic description of vasovagal syncope was that of a fall in blood pressure accompanied by slowing of the heart rate. The result 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 means of Head-up tilt (HUT) test.

In healthy individuals, assumption of 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 baroreceptors. Patients considered to have VVS tend to have relative reductions in central blood volume, which is further aggravated by upright posture. A normally functioning baroreceptor system would be expected to compensate for decreasing systemic pressure by increasing the heart rate and initiating increased vasoconstriction through augmentation of sympathetic activity and parasympathetic withdrawal. 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. The recent study revealed the cardioinhibition and mixed type VVS is based on the fact that an increase of sympathetic drive comes first and induces the final vagal reflex, causing bradycardia and hypotension [1].

2. Patients and methods

We enrolled retrospectively subjects who were referred to Tri-Service General Hospital to evaluate the cause of syncope or pre-syncope from 2005 to 2009. Twenty subjects classified as having VVS with HUT test (mean age 29±14 yrs, range 17–68 yrs; 4 females, 16 males) were included in the study. Twenty age and gender matched subjects with normal response to HUT test (mean age 25±10 yrs, range 16–52 yrs; 4 females, 16 males) were enrolled as controls. All subjects were unremarkable after cardiological and neurological evaluation.

Passive head up tilt-table test was performed between 2:00 and 5:00 pm in a quiet and temperature controlled room (24–25 ◦C) with light dimmed. The patients were instrumented in supine position on a motorized tilt table with footboard and knee and abdominal straps to prevent fall. The upright tilt test protocol began with 10 minutes of supine rest period, followed by a second phase of 70° upright for up to 45 minutes or until onset of symptom (mean around 15 minutes of HUT)(Fig.1). During the test, patients underwent continuous electrocardiographic monitoring: beat-to-beat blood pressure was monitored noninvasively (Task Force Monitor, CNSystems, Graz, Austria). 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 to a 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.

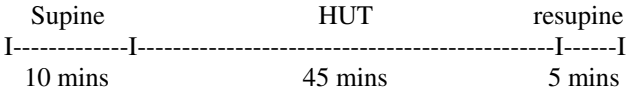

Figure 1. HUT protocol. Rest supine period for 10 minutes, and 70° head tilt up for 45 minutes, then tilt down and resupine for 5 minutes.

2.1. Cardiovascular parameters

All cardiovascular assessments 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 [2], and was automatically and continuously corrected to the oscillometric values obtained from the contralateral arm (brachial artery). 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 and cardiac contractility as Left Ventricular Work Index (LVWI).

2.2. Assessment of autonomic parameters

The autonomic nervous system was assessed at rest and during HUT using baroreflex sensitivity by the Task Force with the sequence method (to identify a series of at least three consecutive heart beats in which systolic pressure and the following RR-interval either both increased or both decreased) and heart rate variability (HRV), using spectral analysis.

2.3. Arterial baroreflex sensitivity (BRS)

The SAP time series were scanned in order 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 a s a measure of baroreflex sensitivity. 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. (BRS; ms/mmHg) [2].

2.4. Tilt down baroreflex response

We used the moment of tilt down (i.e., when the electrical tilt table began to move down from the 70 degree up position) as benchmarks for the periods during which blood pressure and R-R intervals were compared. The time of tilt down was defined operationally as syncope/near syncope, as it was the time the physician performing the test determined that the patient was experiencing or was about to experience syncope as a result of low blood pressure. Baroreflex sensitivity measured by the downward tilting method was calculated as the slope of the linear regression line relating systolic blood pressure changes to RR interval changes during downward tilting. Regression lines with more than 12 data points and r greater than 0.8 were accepted for analysis [3].

2.5. Heart rate variability (HRV)

Frequency domain analysis of heart rate variability was performed for assessment of autonomic activities. Traditional spectral analyses work with at least 256 samples (heart beats) and the time resolution is 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 quantitative indices to the sympathovagal balance and the short autonomic regulation.

2.6. Statistical analysis

Data are presented as mean ± standard deviation (SD) or percent when appropriate. The between-group comparisons were made by means of Student's t test for continuous variables, and the Chi-square test to compare categorical variables. The tests were considered statistically significant at $p<0.05$.

3. Results

VVS subjects had lower body mass index compared with controls. There were no difference in baseline heart rate, mean blood pressure between the two groups. However, VVS subjects had significantly lower total peripheral resistance index at rest (Table 1). With orthostatic challenge imposed by tilt up, VVS patients revealed high LF/HF ratio, and low BRS which were not different from control group at rest (Table 2). Heart rate response increased prior to syncope and then dropped during syncope in VVS subjects (Fig. 2).

Table 1. Clinical Characteristics and Hemodynamic Data of the VVS group and Control Group during rest period.

	Control±SD	VVS±SD
Clinical data		
Age(years-old)	25±10	29±14
Gender(% male)	80%(16M/4F)	80%(16M/4F)
BMI(kg/m^2)	23.36±2.90	21.62±2.18*
Hemodynamic data		
HR(beats/min)	70.1±14.11	70.35±11.89
MAP(mmHg)	87.24±8.34	85.15±9.39
LF/HF ratio	1.35±0.94	1.26±1.37
BRS(ms/mmHg)	24.04±11.13	22.17±13.59
SV(ml)	90.7±17.07	87.95±20.65
TPRI(dyn · s · m^2/cm^5)	2092±393.64	1876±398.44*
CI(l/min · m^2)	3.34±0.67	3.63±0.60
LVWI(kg · m/m^2)	3.89±0.99	4.07±0.72

Data are presented as the mean value ± SD, except for gender. BMI = body mass index; HR = heart rate; MAP=mean blood pressure; LF/HF = low/high frequency; BRS = baroreceptor sensitivity; SV=stroke volume; TPRI = total peripheral resistance index; CI = cardiac index; LVWI = left ventricular work index.*P<0.05.

Table 2 Hemodynamic Data of the VVS group and Control group during Tilt up period

	Control±SD	VVS±SD
LF/HF ratio	3.45±1.21	7.86±6.20**
BRS (ms/mmHg)	11.88±3.34	7.99±2.34***
HR (beats/min) before syncope	79.57±14.13	89.93±12.80*
SV(ml)	63.9±10.55	59.9±9.75
TPRI(dyn · s · m^2/cm^5)	2947.5±651.32	2306.75±827.94*
CI (l/min · m^2)	2.90±0.47	3.12 ±0.49
LVWI(kg · m/m^2)	4.16 ±1.04	3.92±1.26
DT-BRR(ms/mmHg)	16.49±13.6	5.68±11.25**

*P<0.05;**P<0.01;***P<0.001

This study adopts a non-pharmacological HUT test to evaluate VVS and tries to explain its pathophysiological mechanism. Compared with control, VVS subjects showed low vascular resistance with poor sympathetic vascular activity both at baseline resting condition and under orthostatic stress. During postural change, frequency domain analysis of HRV data revealed initial increase of sympathetic drive (Fig. 3), presumably followed by the vagal reflex activation, causing bradycardia and hypotension (Table 3).

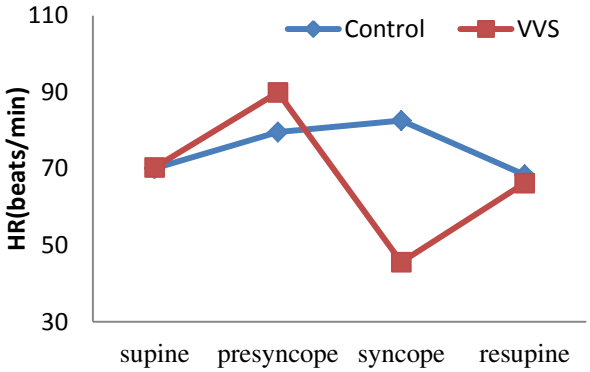

Figure 2. Heart rate change between control and VVS subjects during HUT study.

VVS prone patients demonstrated a functional and presumably transient diminution of global baroreceptor response below 10 ms/mmHg in association with head-up tilt-induced syncope (Fig. 4). Compared with control subjects, VVS subjects had statistically significant drop of baroreceptor sensitivity with orthostatic challenge (VVS vs control: -64% vs -50%).Tilt-down BRR was lower in VVS group. The baroreflex dysfunction in modulating heart rate should also apply to baroreceptor control of peripheral sympathetic neural outflow.

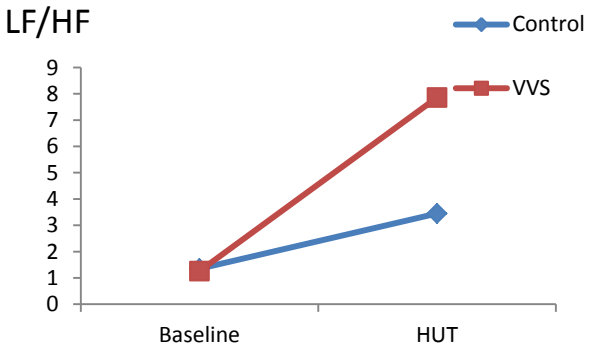

Figure 3. LF/HF atio change in VVS and control subjects during HUT test.

Table 3 Heart rate and mean blood pressure during syncope of VVS and end of HUT of control subjects

	Control ±SD	VVS±SD
HR (beats/min)	82.59±13.95	45.58±16.36*
MAP (mmHg)	88.82±11.24	52.23±20.1*

*P<0.001

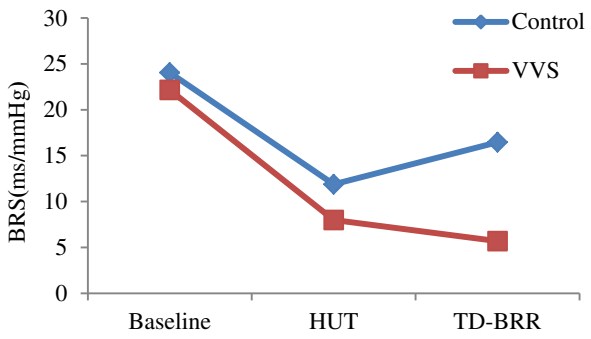

Figure 4. BRS change in both groups during baseline, HUT and tilt down period.

As expected, there was mild increase of HR during tilt in control subjects. However, VVS subjects had significant higher increment of HR prior to syncopal episode (27.8% vs 13.5%; p=0.02).

4. Discussion and conclusions

Slowing of the heart rate preceding syncope in VVS subjects could be due to increase 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. Because it is not possible to measure parasympathetic activity directly in humans, however, the evidence for this is indirect but 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 [4]. Our results in patients with vasovagal syncope are very similar to those reported by Morillo et al. who found that progressive R-R interval lengthening before syncope, a time when blood pressure was falling [5].

The hemodynamic changes with decreased stroke volume before symptom onset can indicate syncope that results from excessive sympathovagal reactions in younger subjects [6]. However in this study, there was no significant difference in cardiac index between two groups. The general syncopal population is female predominant, but male predominant is in this study because of military hospital characteristic. The hemodynamic change in male is less than female in some study[7,8].The major limitation of this study is small sample size. VVS has been classified into different subtypes according to hemodynamic changes. Our subjects are relatively young. Whether our finding can extend to different categories of VVS patients and older subjects need future study with larger cohort of diverse background.

In conclusion, this study confirmed low baseline and postural total peripheral resistance in VVS subjects, suggesting vascular sympathetic impairment, inappropriate withdrawal of sympathetic neural constrictor tone . In VVS subjects, there is overstimulation of the cardiac sympathetic pathway before syncope as indicated by increased heart rate and shifted LF/HF ratio balance, followed by reflex vagal activation suggested by slowed heart rate. Whether sympathetic overstimulation is compensatory for low baseline vascular tone awaits future study. The diminished BRS during evolving VVS may in part account for 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.

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