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Small left atrial volume is an independent predictor for fainting during head-up tilt test: The impact of intracardiac volume reserve in vasovagal syncope

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ABSTRACT

Background: Vigorous left ventricular (LV) contraction with progressive ventricular emptying during orthostatic stress may induce hyper-responsiveness of cardiac mechanoreceptor and vasovagal syncope (VVS). We hypothesized that intracardiac volume reserve estimated by the left atrial (LA) volume index (LAVI) plays an important role in the mechanism of VVS.
Methods: A total of 234 patients (115 male, 44 ± 18 years) who underwent head-up tilt test (HTT) and transthoracic echocardiography for unexplained syncope were consecutively enrolled. Patients with a positive HTT result (HTT+; n = 152) were compared with those with negative HTT response (HTT−; n = 82).
Results: 1. Compared to HTT− patients, HTT+ patients were younger (41 ± 17 vs. 48 ± 17 years, p = 0.005), included a higher number of females (56% vs. 50%, p = 0.009) and showed higher basal heart rate (67 ± 12 vs. 63 ± 11 bpm, p = 0.047). 2. LAVI (20 ± 5 vs. 26 ± 13 ml/m^2, p < 0.001), LV end-diastolic dimension (47.4 ± 3.7 vs. 49.0 ± 4.1 mm, p = 0.015), and the proportion of LV hypertrophy (13% vs. 24%, p = 0.027) were smaller and early diastolic mitral annulus velocity was higher (9.7 ± 3.0 vs. 8.5 ± 2.6 cm/s, p = 0.004) in HTT+ patients than those in HTT− group. 3. LAVI (OR 0.917 (0.860–0.977), p = 0.007) was the only independent predictor of HTT induced VVS, and LAVI had a linear correlation with time to syncope during HTT (r = 0.39, p = 0.034). In addition, patients with LAVI ≥ 36 ml/m^2 did not faint during HTT.
Conclusion: Small LA volume is an independent predictor of HTT-induced VVS. Limited intracardiac volume reserve might play an important role in the mechanism of VVS.

1. Introduction

Vasovagal syncope (VVS) is a common problem in clinical practice, but its mechanism has not yet been clearly elucidated. Fainting due to VVS is generally attributed to the activation of left ventricular (LV) mechanoreceptors which mediate the Bezold–Jarish reflex and consequently decrease the cardiac output or blood pressure [1]. However, the pathophysiologic concept and therapies in VVS patients are, by and large, on the basis of logical deductions or assumptions without sufficient data [2]. The Bezold–Jarish reflex is believed to be triggered by venous pooling, compensatory activation of the sympathetic nervous system, and/or reflex hypercontractility of the LV which is relatively underfilled [3–6]. Meanwhile, Yamanouchi et al. [7] reported that the rate of intracardiac volume depletion in the upright position was faster in patients with VVS than that in control group, and the distribution of blood volume was a more important determinant of VVS than the total blood volume. It is noteworthy that the left atrium (LA) is located between the pulmonary veins and LV and functions as a "reservoir" [8]. Previously, progressively decreasing LA volume during orthostatic stress has been documented in several interesting studies performed in subjects who underwent head-up tilt test (HTT) [9,10]. Because LA size varies from patient to patient, we hypothesized that intracardiac volume reserve estimated by LA volume plays an important role in the mechanism of VVS. We investigated the interrelationship between LA volume and the occurrence of HTT-induced VVS in patients with unexplained syncope.

2. Methods

2.1. Study population

The study protocol was approved by the Institutional Review Board of Severance Cardiovascular Hospital, Yonsei University Health System, and complied with the Declaration of Helsinki. Informed consents were obtained from every patient. A total of 234 patients with unexplained syncope were consecutively enrolled in this retrospective study. The selection criteria were as follows: (1) two or more episodes of syncope in recent 6 months, (2) no symptomatic heart disease except syncope and normal neurologic evaluations at the time of enrollment, (3) no significant valvular heart disease or cardiomyopathy, and normal LV systolic function (LV ejection fraction [EF] ≥ 50%) on echocardiographic evaluation and (4) no atrial fibrillation or symptomatic

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bradycardia. We included the patients with hypertension or LV hypertrophy (LVH). No patient had any clinical contraindication to the isoproterenol administration. We divided the study population into two groups according to the results of HTT: patients with documented syncope or significant hemodynamic compromise during HTT (HTT+ group) and those who showed negative response to HTT (HTT− group).

2.2. Head-up tilt test (HTT)

After a 4-hour fast, study subjects were placed in the supine position on a tilt table, and an intravenous catheter was inserted into an accessible peripheral arm vein. Continuous electrocardiographic monitoring was initiated, and blood pressure was recorded with an automatic cuff sphygmomanometer. At baseline, patients were in the supine position for 10 min, and their hemodynamic parameters were monitored, including blood pressure and heart rates (HR) every minute. After that, the subjects were tilted to an 80-degree head-up position for 30 min with their feet resting on the footboard for support. Then, blood pressure, HR, and subjective symptoms were monitored and recorded every 2 min. If results of the baseline tilting were negative, the patients were then returned to the supine position. After 5 min of rest, intravenous isoproterenol was administered at 1 μg/min. The dosage was increased by 1 μg/min every 3 min until a HR of 120/min or a maximum dosage of 5 μg/min was reached. Then, head-up tilt to 80° was repeated for 10 min. A positive result (with or without concomitant isoproterenol infusion) was defined as follows: 1) syncope or 2) the development of presyncope in association with an abrupt fall in systolic BP to <70 mm Hg or bradycardia (HR<40/min) and reproduction of the patient's relevant clinical symptoms. We determined the type of positive response to HTT as vasodepressor type, cardioinhibitory type and mixed type, as previously described [11].

2.3. Echocardiography

All 234 patients included in this study underwent echocardiographic evaluation. Comprehensive transthoracic echocardiography was performed using commercially available devices (Sonos 5500, Philips Medical System, Andover, MA, USA or Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Standard M-mode, 2-dimensional and Doppler images were acquired in parasternal and apical views. Measurements from five cardiac cycles were averaged for analysis. LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), and LVEF were calculated from 2-dimensional images using the modified Quinones method as previously described [12]. LV mass was calculated using a formula shown below.

$$0.8 \times \left[1.04(SWTd + LVEDD + PWTd)^3 - LVEDD^3\right] + 0.6(\mathrm{g})$$

In this formula, PWTd is the posterior wall thickness at the end diastole, and SWTd is the septal wall thickness at the end diastole [13]. LV mass was indexed to the body surface area (LV mass index [LVMI]). LVH was defined as LVMI larger than 95 g/m^2 in female patients and 105 g/m^2 in male patients [13]. LA volume was determined at LV end systole by the prolate ellipsoid formula and was indexed to the body surface area (BSA) (LA volume index [LAVI]) [13]. Early mitral inflow peak velocity (E) was measured using the pulsed wave Doppler method by placing a sample volume at the opening level of the mitral valve leaflet tips. The tissue Doppler-derived diastolic mitral annular velocity (E′) and peak systolic mitral annular velocity (S′) were measured from the septal corner of the mitral annulus in the apical four-chamber view. The echocardiographic data were gathered and analyzed by two echocardiographers who were unaware of patients' clinical data and the HTT results.

2.4. Heart rate variability (HRV) analysis

Among the study subjects, 92 patients (39%) underwent 24-hr ambulatory Holter monitoring additionally for HRV analysis. The records were analyzed with a commercially available system (MARS®, GE Healthcare Inc., Milwaukee, WI, USA). Artifacts or arrhythmias were excluded from the analysis through a careful manual review by two experienced technicians who were supervised by a cardiologist. Mean HR including minimal and maximal HR were calculated and analyzed. The following time domain indexes were determined: mean of all normal R–R interval (MeanNN), the standard deviation (SD) of all normal R–R interval (SDNN), the SD of the 5-minute averages of normal R–R interval (SDANN), the root mean square of the difference between successive normal intervals (rMSSD) and the proportion of adjacent R–R intervals differing by greater than 50 ms (pNN50 [%]). Spectral indexes of HRV were calculated by fast Fourier transform on each two minute segment of the recording using a Hanning window to minimize spectral leakage. The spectral powers were quantitatively assessed and expressed as ln X (ms^2/Hz), where ln is the natural logarithm of the quotient after measuring the areas of 2 frequency ranges: low frequency (LF [0.06–0.15 Hz]) and high frequency (HF [0.15–0.4 Hz]). The ratio of LF/HF band was calculated.

Table 1
Patient demographics and baseline echocardiographic parameters (HTT+: patients with positive head-up tile test result, HTT−: patients with negative response to head-up tilt test).

	All subjects (n = 234)	HTT+ (n = 152)	HTT− (n = 82)	p value*
Age (years)	44 ± 18	41 ± 17	48 ± 17	0.005
Male, n (%)	115 (49)	65 (44)	50 (60)	0.009
Hypertension, n (%)	48 (19)	25 (16)	23 (25)	0.107
Diabetic, n (%)	7 (3)	5 (3)	2 (2)	0.757
BSA (m^2)	1.69 ± 0.19	1.66 ± 0.18	1.73 ± 0.19	0.006
Basal systolic BP (mm Hg)	118 ± 16	117 ± 16	118 ± 17	0.837
Basal diastolic BP (mm Hg)	73 ± 10	74 ± 10	72 ± 10	0.501
Basal HR (/min)	65 ± 12	67 ± 12	63 ± 11	0.047
LVEF (%)	67 ± 5	67 ± 6	67 ± 5	0.946
LAVI (ml/m^2), [range]	22 ± 9 [8–103]	20 ± 5 [8–35]	26 ± 13 [13–103]	<0.001
LAAPD/height (mm/m)	20.4 ± 3.3	19.7 ± 2.9	21.8 ± 3.7	<0.001
LVEDD (mm)	47.9 ± 3.9	47.4 ± 3.7	49.0 ± 4.1	0.015
LVESD (mm)	31.3 ± 3.9	30.9 ± 4.1	32.0 ± 3.6	0.052
LVH, n (%)	40 (17)	20 (13)	20 (24)	0.027
Diastolic function, n (%)				0.008
Normal	135 (58)	97 (64)	38 (46)	
Relaxation abnormality	86 (37)	52 (34)	34 (41)	
Pseudonormal	4 (2)	2 (1)	2 (2)	
Restrictive	0 (0)	0 (0)	0 (0)	
Indeterminate	9 (4)	1(1)	10 (12)	
E (m/s)	0.68 ± 0.17	0.69 ± 0.16	0.67 ± 0.18	0.241
A (m/s)	0.56 ± 0.17	0.54 ± 0.17	0.58 ± 0.15	0.532
DT (ms)	198.8 ± 34.2	196.0 ± 35.3	204.4 ± 31.4	0.078
RVSP (mm Hg)	22.9 ± 5.1	22.5 ± 4.8	23.8 ± 5.5	0.069
S′ (cm/s)	7.7 ± 1.6	7.7 ± 1.7	7.7 ± 1.4	0.997
E′ (cm/s)	9.3 ± 3.0	9.7 ± 3.0	8.5 ± 2.6	0.004
A′ (cm/s)	8.1 ± 2.0	7.9 ± 1.8	8.5 ± 2.1	0.208
E/E′	8.1 ± 2.8	8.0 ± 2.9	8.3 ± 2.6	0.343

BSA: body surface area, BP: blood pressure, HR: heart rate, LVEF: left ventricular ejection fraction, LAVI: left atrial volume index, LAAPD: left atrial anterior–posterior diameter, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, LVH: left ventricular hypertrophy, E: peak velocity of early diastolic filling, A: peak velocity of late diastolic filling, DT: deceleration time of E wave, RVSP: right ventricular systolic pressure, E′: early diastolic mitral annular velocity, A′: late diastolic mitral annular velocity, E/E′: early mitral inflow velocity to early diastolic mitral annular velocity ratio.
* $p<0.05$ indicates significance.