

Contribution of left atrial volume and function in neurocardiogenic syncope

Vasovagal senkop gelişimine sol atrium fonksiyonu ve hacminin katkısı

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ABSTRACT

Objective: In this study, we aimed to investigate the presence of atrial volume and decrease in contraction force by measuring left atrial volume and contraction with the head-up tilt table (HUTT) test in patients who were diagnosed with neurocardiogenic syncope (NCS).

Methods: Overall, 45 patients (26 females/19 males, mean age: 26.4±9.2 years) who experienced vasovagal syncope in HUTT (HUTT+) and 40 healthy controls (17 females/23 males, mean age:28.8±10.5 years; HUTT-) were included in the study.

Results: When comparing the groups in terms of left atrial ejection force, there was a significant difference between the HUTT+ and HUTT-vasovagal syncope groups (p=0.05). In both groups, there was a positive correlation between atrial ejection force and left atrial volume (r=0.287, p=0.016) and left atrial volume index (r=0.261, p=0.029).

Conclusion: We showed that the left atrial ejection force and the left atrial volume index were significantly lower in positive vasovagal syncope patients than those in the negative vasovagal syncope patients.

Keywords: Syncope, echocardiography, left atrium

ÖZ

Amaç: Vasovagal Senkop (VVS) sık görülen klinik bir durum olmakla birlikte altta yatan mekanizmalar henüz tam olarak anlaşılama- mıştır.Bu çalışma, eğik masa testi pozitif olan VVS'lu hastalarda, sol atrial sistolik fonksiyonun VVS gelişimindeki rolünü araştırmak amacıyla yapılmıştır.

Yöntemler: Açıklanamayan senkop nedeniyle eğik masa testi ve ekokardiyografi uygulanan toplam 95 hasta çalışmaya alındı. Eğik masa testi pozitif olan 45 hasta (n=45), eğik masa testi negatif olan 40 hasta (n=40) ile karşılaştırıldı.

Bulgular: Yaş ve cinsiyet dağılımı açısından gruplar arasında fark gözlenmedi (sırasıyla p=0,27 ve 0,11). Ekokardiyografik değerlendirmede sol atrium hacmi, sol atrium hacim indeksi ve sol atrial ejeksiyon kuvveti eğik masa testi pozitif olan grupta anlamlı olarak daha düşük bulundu (sırasıyla p=0,03, 0,05 ve 0,05). Mitral kapak anulusünden kaydedilen Doppler akımları açısından gruplar arasında fark saptanmadı fakat E/A oranı eğik masa testi pozitif olan grupta anlamlı olarak daha düşük bulundu (p=0,02).

Sonuç: olarak bu çalışma bazalde daha düşük atrial hacim ve kontraksiyon kuvvetine sahip bireylerin ortastatik stres esnasında ventriküler doluşun devamını sağlamada yetersiz kalabileceklerini düşündürmektedir.

Anahtar kelimeler: Vasovagal senkop, sol atrium, ekokardiyografi

INTRODUCTION

Syncope is frequent among the normal population, and neurally mediated syncope is the nearly usual cause. Neurocardiogenic syncope (NCS) is clinically defined as the sudden onset and very short (usually 1 or 2 minutes) duration of loss of consciousness due to global cerebral hypoperfusion, which is quite disturbing particularly when repetitive. NCS can cause impaired quality of life and significant injury in some cases, but its exact mechanism has not been clearly understood yet (1). Several theories have been recommended to provide an explanation for the pathophysiology concerning NCS. Left atrium (LA) contraction contributes to maintaining left ventricular end-diastolic (LVED) pressure and cardiac output. We hypothesized that left atrial volume and systolic function may be a contributing component of the NCS.

The present study is intended to evaluate the relation between the left atrial systolic function using left atrial ejection force (LAEF) in patients with head-up tilt test (HUTT)-induced NCS.

METHODS

We enrolled consecutive patients who had been admitted to our clinic because of unexplained syncope between January 2013 and August 2014. The selection criteria were age 18-70 years, ≥2 episodes of syncope, normal neurologic evaluations, no significant valvular heart diseases, normal ejection fraction(>50%) on echocardiography, and absence of any significant arrhythmia. We excluded patients with no technically optimal echocardiographic images, hypertension, thyroid diseases, impaired renal function, and structural heart diseases. Patients were divided

into two groups based on HUTT results: patients experiencing syncope or significant hypotension and/or bradycardia at some point of the test were assigned to HUTT-positive (+) group and those without syncope, bradycardia, and hypotension were assigned to HUTT-negative (-) group. The ethics committee approved the study protocol and informed consent was obtained from every patient.

Echocardiography: All participants underwent a detailed transthoracic echocardiographic evaluation. Transthoracic echocardiography was performed using a Vivid 7 Echocardiography machine (GE Ultrasound, Horten, Norway). Two-dimensional and tissue Doppler's images were acquired in parasternal and apical views. The values of all echocardiographic parameters from three cardiac cycles were averaged for data analysis. The two-dimensional apical four-chamber view was used to calculate left ventricular (LV) ejection fraction (LVEF) according to biplane modified Simpson's rule. LA anteroposterior dimension (LAAPD) was measured in the parasternal long axis view, and LA volume was measured using the biplane disk summation method in the apical four and two chamber views at the end of the LV systole. LA volume was indexed to the body surface area (BSA) as an LA volume index (LAVI). Mitral inflow velocities included peak early (E), peak late(A), and the E/A ratio were assessed using the pulsed wave Doppler method by putting a sample volume at the opening level of mitral valve leaflet tips in the apical four-chamber view. Tissue Doppler-derived velocities of the mitral annulus were obtained from the apical four-chamber view at the lateral and medial mitral annular corners. Peak systolic velocity (S'), early diastolic velocity (E'), and late diastolic velocity (A') were measured. The velocities were recorded at a sweep speed of 100mm/s (2). LAEF was calculated according to the method provided by Manning (3). The formula is as follows: $LAEF = 1/2 * MOA * A^{2q}$, where MOA: mitral orifice area (cm²), A: peak late diastolic transmitral flow velocity (cm/sec), q: blood density (1.06 g/cm³). The mitral annulus was assumed to be circular, and its diameter (d) was measured from the apical four-chamber view. MOA was calculated as $\pm * d^2/4$. The peak velocity was obtained at the level of the mitral annulus (3). All measurements were performed by a cardiologist blinded to the study.

Head-up Tilt Table Test: The HUTT protocol began with 5 minutes in the supine position for the first phase, then the subject tilted passively to 70 degrees upright position for 20 minutes in the second period, if the second p was negative, 0.4 mg sublingual nitroglycerine spray was administered, and head-up tilt to 70 degrees was repeated for 10 minutes. During the test, subjects had electrocardiographic monitoring, and blood pressure was measured by an automatic cuff sphygmomanometer at intervals of every minute. The test was definitely positive if syncope occurs or if presyncope developed in association with an abrupt fall in systolic blood pressure to below 70 mm Hg or bradycardia (heart rate below 40 bpm) (4).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA). Continuous variables were presented as mean±standard deviation

(SD) and categorical variables were expressed as percentages. Patients were grouped according to the positive or negative HUTT. Differences between groups were analyzed using unpaired samples Student's t-tests and analysis of covariance for continuous variables and χ^2 analysis for discrete variables. Two-tailed p values less than 0.05 were considered significant for all tests.

RESULTS

From a total of 95 screened subjects, a positive response was induced in 45 patients (mean age: 26.4±8.8 years, 19 men, and 26 women) and negative response in 40 patients (mean age: 28.8±10.5 years, 23 men, and 17 women). Age and gender were similar between groups (p=0.27 vs p=0.11, respectively). In the echocardiographic evaluation, LVED volumes, ejection fractions, and LAAPD were found similar between groups. The statistical significance of LAVI and LAEF were p=0.05 vs p=0.05, respectively, but LAV was significantly smaller in the HUTT+ group compared to the

Table 1. The patient characteristics and intergroup comparison between HUTT+ group and HUTT- group of clinical and echocardiographic parameters

| | HUTT(+) (n=45) | HUTT(-) (n=40) | p |
|-------------------------------|-------------------|-------------------|------|
| Age | 26.4±9.2 | 28.8±10.5 | 0.27 |
| Gender (male/female) | 26/19 | 17/23 | 0.11 |
| BMI (kg/m ²) | 23.1±3.1 | 24.6±4.5 | 0.08 |
| BSA (m ²) | 1.73±0.14 | 1.78±0.16 | 0.12 |
| LVEDV (mL) | 68.4±25.2 | 72.2±18.3 | 0.58 |
| LAV (mL) | 35.9±8.9 | 42.7±15.1 | 0.03 |
| LAVI (mL/m ²) | 20.1±5.1 | 23.7±8.0 | 0.05 |
| LAEF (kdynes/m ²) | 11.0±6.0 | 13.8±6.6 | 0.05 |
| LAAPD (mm) | 30.6±5.8 | 31.2±4.4 | 0.68 |
| E | 0.89±1.9 | 0.84±1.8 | 0.26 |
| A | 0.57±1.2 | 0.60±1.3 | 0.33 |
| E/A | 1.6±0.4 | 1.4±0.3 | 0.02 |
| E/E' | 5.6±2.1 | 5.3±1.7 | 0.47 |
| S lateral | 12.1±3.1 | 11.9±2.4 | 0.76 |
| E' lateral | 16.4±4.0 | 16.0±3.5 | 0.66 |
| A' lateral | 8.9±2.1 | 9.5±3.1 | 0.37 |
| S septal | 9.7±1.6 | 9.4±1.9 | 0.39 |
| E' septal | 13.1±3.1 | 12.6±3.3 | 0.52 |
| A' septal | 9.0±2.8 | 9.5±2.8 | 0.45 |

BMI: body mass index; BSA: body surface area; HUTT: head-up tilt table; LVEDV: left ventricular end-diastolic volume; LAV: left atrial volume; LAVI: left atrial volume index; LAEF: left atrial ejection force; LAAPD: left atrial anterior-posterior diameter; E: peak velocity of early diastolic filling; A: peak velocity of late diastolic filling; E/A: early mitral inflow velocity to late mitral inflow velocity ratio; S: systolic mitral annular velocity; 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

HUTT- group ($p=0.03$). The Doppler flow velocities recorded from mitral annulus did not differ significantly, except for a significantly higher E/A ratio in the HUTT+ group ($p=0.02$). Also, (TDI) parameters were similar in the two groups. Demographic characteristics and echocardiographic findings of the HUTT+ and HUTT- groups are detailed in Table 1. A correlation analysis revealed that LAEF was significantly correlated with age ($r=0.237$, $p=0.036$), body mass index (BMI; $r=0.481$, $p=0.001$), left atrial volume ($r=0.287$, $p=0.016$), LAVI ($p=0.029$), and E/E ($r=0.394$, $p=0.001$), while there was a negative correlation with mitral E/A ratio ($r=-0.519$, $p=0.001$).

DISCUSSION

This study showed that LAEF was decreased in patients with vasovagal syncope. LAEF is defined as the force generated by the LA to expel the blood through the mitral valve during atrial systole (5). The contribution of the left atrial contraction to the LV filling becomes more significant, particularly in patients with diastolic dysfunction (6). In this study, it was associated with decreased LAEF volume and decreased LAVI in the HUTT results. Our knowledge about the NCS pathophysiology still remains unclear. The mechanism of NCS has thought to be triggered by ventricular mechanoreceptor's discharge induced by venous blood, pooling those results from orthostatic. The reflex increase in sympathetic stimulation to maintain cardiac output and peripheral vascular resistance leads to a baroreceptor-mediated sudden surge in vagal tone and retraction of the sympathetic tone, resulting in vasodilation and/or bradycardia; the consequence is a rapid decline in systolic blood pressure (7). Vaddadi et al. (8) demonstrated that efferent sympathetic activity was maintained during vasovagal syncope episodes, and they speculated that activation of vasodilator mechanisms may be responsible for vasovagal syncope. In addition, Cooke et al. (9) showed that withdrawal of muscle sympathetic activity is not mandatory for presyncope. Some studies have shown that without decrease in peripheral vascular resistance, decrease in cardiac output alone can cause presyncope (1, 10). LA systole is responsible for nearly 20% of the diastolic LV filling (11, 12). Therefore, atrial mechanical and volumetric contribution to cardiac output can be substantial in some circumstances, such as orthostatic stress. There are few studies on the contribution of LA function to the vasovagal syncope mechanism. In the present study, we used LAEF to determine atrial mechanical function and found that LAEF were moderately lower in HUTT+ group than in the HUTT- group ($p=0.05$). LAEF is the pressure applied by LA to drive blood through the mitral valve to the LV throughout atrial systole and has been proposed as a surrogate marker of atrial mechanical function (3). Chinali et al. (13) revealed that the left atrial systolic force was independently associated with stroke volume and cardiac output. Also, LAEF can be used as a surrogate marker for restoration of the mechanical functions of LA after successful cardioversion for atrial fibrillation (14, 15). Similar to our study, Folino et al. (16) reported that a gradual decline in LA volume due to venous pooling and brief LA hypocontractility by vagal reflexes was known to contribute to NCS during HUTT. In our study, tissue doppler echocardiography showed significant reductions in atrial velocities only in patients with positive HUTT test, while a decrease in early diastolic filling waves were similar and ventricular contractility remained almost unchanged in both positive and negative groups (16, 17). These

findings can be explained by rich a vagal innervation of atriums, which may cause a reduction of atrial performance during vagal discharge in these patients. However, we measured echocardiographic parameters at rest just before the HUTT protocol because of technical difficulties. Therefore, we could not show atrial function changes preceding the vasovagal reaction. We also found that LAV was significantly lower in the HUTT+ group than that in HUTT- group ($p=0.03$). Patients with limited LA volume might be more susceptible to NCS. Moon et al showed that a small LA volume is an independent factor of HUTT-induced NCS, and patients with large LA size ($LAVI > 36 \text{ mL/m}^2$) did not faint during HUTT (18). Additionally, in the present study, the E/A ratio was significantly higher in the HUTT+ group. We may speculate that despite the better early diastolic filling in the HUTT+ patients than in the HUTT- patients, the decrease of cardiac output can be attributed to the low contribution of atrial filling in these patients.

Taken together, these findings suggest that reduced active ventricular filling during atrial systole plays an important role in the pathogenesis of vasovagal syncope. This reduction is not caused by reducing ventricular filling. The finding of a similar decrease in the LAV and LAVI in the HUTT+ group further clarifies that this reduction is not caused by diminished ventricular filling and signifies deteriorated atrial mechanical function. Folino et al. (16) found similar results and hypothesized that the rich vagal innervation of the atria is responsible for diminished atrial mechanical functions. This reduced atrial function seems to be the major contributor of reduced cardiac output resulting in syncope. In the Strong Heart Study, LAEF was found to correlate with age and BMI, and we found a strong association between LAEF and age and BMI in our study (13).

Study Limitations

We did not evaluate changes in the left atrial volume and LAEF just before syncope because of technical difficulties; therefore, we could not have assessed the contribution of atrial mechanical and volumetric changes to syncope. We enrolled only patients with mixed-type NCS and thus the findings are only pertinent to this type of syncope.

CONCLUSION

We conclude that the baseline capacity of atrial volume and contractile function may determine the atrial performance during orthostatic stress. Patients with small atrial volume and contractile function may tend to fail in sufficient atrial performance to maintain ventricular filling during NCS. However, more studies investigating that the relative contribution of atrial mechanical functions to the NCS episodes are regarding the role of atrial function and NCS are needed.

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