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Original Article

Evaluation of Myocardial Function in Children with Vasovagal Syncope Using Speckle-Tracking Echocardiography

Vazovagal Senkoplu Çocuklarda Miyokard Fonksiyonunun Speckle-Tracking Ekokardiyografi ile Değerlendirilmesi

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ABSTRACT

Objective: Syncope is a transient, sudden and reversible loss of consciousness caused by cerebral hypoperfusion. The most common type of childhood syncope is neurally mediated syncope, with more than 50% of cases suffer from vasovagal syncope (VVS). Although VVS is commonly seen during both childhood and adulthood, its underlying pathogenesis and prognosis are still unclear. We have aimed to evaluate both left ventricular (LV) and left atrial myocardial function in children with VVS using two-dimensional speckle-tracking echocardiography (2D-STE) during the non-syncopal period.

Method: The study population included patients under the age of 18 years diagnosed with VVS based on patient history and physical examination findings. Cases with structural heart disease, arrhythmia, or syncope due to metabolic or neurological causes were excluded. The control group consisted of healthy children without systemic diseases.

Results: A total of 36 children with VVS and 36 healthy controls were included. No significant differences were found between the groups regarding age, gender, body mass index, systolic/diastolic blood pressure and heart rate. Conventional echocardiographic measurements showed no differences between both groups in terms of LV volume, systolic and diastolic functions. However, LV global longitudinal and circumferential strain, left atrial peak strain values were lower in the VVS group. LV global longitudinal strain, circumferential strain, and left atrial strain were significantly associated with the presence of syncope.

Conclusion: The study demonstrated that myocardial performance parameters are affected in children with VVS. In addition to conventional echocardiography, evaluation of cardiac functions with 2D-STE imaging will provide important information for these patients.

Keywords: Neurally mediated syncope, vasovagal syncope, two-dimensional speckle-tracking echocardiography, atrial function, ventricular function

ÖZ

Amaç: Senkop, serebral hipoperfüzyon nedeni ile ortaya çıkan geçici, ani ve geri döndürülebilir bilinç kaybıdır. Çocukluk çağında senkopun en yaygın nedeni nöral iletişim aracılı senkop olup, olguların %50'sinden fazlası vazovagal senkop (VVS)'dir. VVS hem çocukluk hem de yetişkinlikte yaygın olarak görülse de altta yatan patogenez ve prognoz hâlâ belirsizdir. Çalışmamızda VVS'li çocuklarda hem sol ventrikül hem de sol atriyal miyokardiyal fonksiyonları senkop olmayan dönemde iki boyutlu speckle-tracking ekokardiyografi (2D-STE) kullanarak değerlendirmeyi amaçladık.

Yöntem: Çalışmamıza 18 yaş altı hastalar dahil edildi ve hasta öyküsü ile fiziksel muayeneye dayanarak VVS teşhisi kondu. Metabolik veya nörolojik nedenlere bağlı, senkop, yapısal kalp hastalığı, aritmi nedenli senkop gelişen olgular hariç tutuldu. Kontrol grubu, sistemik hastalığı olmayan sağlıklı çocuklardan oluşturuldu.

Bulgular: VVS tanılı 36 çocuk ve adölesan, 36 sağlıklı çocuk dahil edildi. Gruplar arasında yaş, cinsiyet, vücut kütle indeksi, sistolik/diyastolik kan basıncı ve kalp atış hızı açısından anlamlı farklar bulunmadı. Geleneksel ekokardiyografik ölçümler, sol ventrikül (LV) hacminde, sistolik ve diyastolik fonksiyonlarda herhangi bir fark göstermedi. Ancak, LV global longitudinal strain, circumferential strain ve sol atriyal strain değerleri VVS grubunda daha düşüktü. Ek olarak LV global longitudinal, circumferential strain ve sol atriyal strain değerleri, senkopun bağımsız öngörücüleri olarak bulundu.

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Sonuç: Çalışmamız, VVS'li çocuklarda miyokard performans parametrelerinin etkilendiğini göstermiştir. Geleneksel ekokardiyografiye ek olarak, 2D-STE görüntüleme ile kardiyak fonksiyonun değerlendirilmesi bu hastalar için klinik tanı aşamasında önemli bilgiler sağlayacaktır.

Anahtar kelimeler: Nöral aracılı senkop, vazovagal senkop, speckle-tracking ekokardiyografi, atriyal fonksiyon, ventriküler fonksiyon

INTRODUCTION

Syncope can be defined as transient, sudden, completely reversible loss of consciousness accompanying with a loss of posture due to cerebral hypoperfusion[1].

Neural-mediated syncope (NMS) or orthostatic intolerance is the leading underlying disorder of pediatric syncope, frequently involving vasovagal syncope (VVS), postural tachycardia syndrome (POTS) and situational syncope. VVS is one of the common hemodynamic type of neurally mediated syncope accounting for more than 50% of cases in childhood[2,3] Although VVS is commonly seen in both childhood and adulthood, the underlying pathogenesis and prognosis are still unclear and relevant studies are still ongoing. Autonomic nervous dysfunction, reflex vasodilation, vasomotor dysfunction, and genetic factors are considered as potential pathogenic mechanisms for VVS[4]. Another pathophysiologic cause that has been investigated is related to the function of the cardiac chambers. Some evidence now suggests that changes in cardiac chamber volume and function may be a determinant factor in recurrent episodes of syncope. However, further studies are needed to elucidate the precise roles of heart chamber functions in its pathogenesis.

Nowadays, advanced echocardiographic modalities such as two-dimensional speckle-tracking echocardiography (2D-STE) have made it possible to qualitatively assess myocardial performance in real-time. Compared with other echocardiographic methods, 2D-STE is an angle-independent method capable of direct myocardial function evaluation during the cardiac cycle by measuring related deformation markers. The systematic use of these modalities could contribute to the evaluation of the atrial and ventricular performance leading to further insights into the mechanism of VVS.

In the literature, we have not encountered a study that investigated atrial and ventricular myocardial performance in combination and evaluated cardiac function in childhood with VVS. In this study, we aimed to evaluate both left ventricular (LV) and left atrial (LA) myocardial function in children with VVS using 2D-STE during non-syncopal period.

MATERIALS and METHODS

This retrospective cross-sectional study was conducted between January 2023 and December 2023 at the department of pediatric cardiology. Medical records of patients who met the inclusion criteria during the study period were reviewed. Patients under the age of 18 diagnosed with NMS syncope were included in our study. Medical history and physical examinations of the study participants were reviewed as the first step in the diagnosis of NMS syncope. Episodes of syncope and the presence of predisposing factors were questioned. Patients who experienced at least two syncopal episodes within the last year were included in the study. Predisposing factors were considered to be: prolonged standing or sudden changes in body position (rapid change of body position from supine or sitting or squatting to upright), exposure to emotional stress, pain or occurrence of syncope during medical procedures. Concomitant prodromal symptoms including dizziness, nausea, weakness, paleness, and sweating were questioned. After history taking and physical examination, other diseases in the differential diagnosis of syncope were investigated. Patients with structural heart disease, arrhythmia detected by electrocardiographic examination and 24-hour Holter monitoring received the diagnosis of cardiac syncope and excluded from the study. In addition, patients diagnosed with syncope due to neurologic and metabolic causes were also excluded from the study.

Active standing and active sitting test were applied to patients with a preliminary diagnosis of NMS[5]. Based on the results of these tests, patients diagnosed with POTS, and patients with situational syncope were not included in the study. The diagnosis of VVS was made after excluding all other causes of syncope.

The control group included healthy children who presented to the pediatric cardiology clinic with complaints of chest pain or heart murmur but without any systemic diseases.

Complete medical history taking and physical examination were performed for all study participants. The age, weight, height, systolic blood pressure, and diastolic blood pressure (DBP) measurements and body mass index (BMI) of the study participants were recorded. BMI were calculated as follows: body weight (kg) divided by square of height (m^2). All patients underwent comprehensive transthoracic echocardiographic examinations. The echocardiographic examinations (described below) and all relevant data were recorded on data collection forms.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Participants, and approved by the Institutional Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital (decision no: 2023/183, date: 25.10.2023). Informed consent was obtained from all patients and their families.

Conventional Echocardiography

We performed echocardiographic study in all included children according to the current guidelines of the American Society of Echocardiography[6]. Echocardiographic assessments were performed by using simultaneous electrocardiographic recordings with the help of the Philips Affiniti 50C ultrasound system by using appropriate transducers.

Images were obtained from parasternal and apical windows using 2D, M-mode, and Doppler echocardiography. M-mode echocardiography in parasternal long and short axis views were used to assess left ventricular (LV) systolic functions: LV end-diastolic diameter and end-systolic diameter, left ventricle end-diastolic volume and end-systolic volume (LVESV), fractional shortening (FS) and ejection fraction values were measured.

To determine LV diastolic functions; the mitral inflow signal was evaluated in the apical four-chamber view. Doppler echocardiography was used to measure the early (E) and late (A) diastolic flow velocities of the mitral valve, which were used to calculate the E/A ratio.

From the apical four- and two-chamber views, the maximum LA volume (LAV) was calculated using the area-length method according to the guidelines of the American Society of Echocardiography[6] .The LAV index (LAVI) was calculated as LAV divided by body surface area.

Speckle-Tracking Echocardiography

The 2D-STE examinations were performed with study participants in both patient and control groups. Standard grey-scale 2D images were obtained and frame rate was adjusted to 60-90 frames/second and three to five consecutive cardiac cycles synchronized to a continuous electrocardiogram were recorded. Post-processing of the digitally stored image data was performed offline using QLAB software.

LV longitudinal strain peak S values were measured by using the apical 4,3,2 chamber images and followed by averaging the three chambers and the determination of the global longitudinal strain value. Circumferential strain was measured in the standard parasternal short-axis at the papillary muscle plane.

For the left atrium 2D-STE analysis, images from the apical four and two chamber views was obtained. In order to calculate the LA strain (LAS), the atrial endocardial border was outlined manually in the end-systolic frame and the epicardial surface was calculated automatically[7].

Statistical Analysis

All data were analysed using SPSS Statistics version 23.0 for Windows software. Frequency and percentile values were noted for categorical variables. The chi-square test was used for the comparison of categorical variables.

Normality tests were conducted, and then for comparative analyses between the syncopal and non-syncopal groups, the Student's t-test was used in cases of normal distribution, and the Mann-Whitney U test was employed in cases of non-normal distribution. If the continuous variables were normally distributed, they were expressed as mean ± SD and median values (min, max). P-value of <0.05 was considered statistically significant.

The predictive value of the variables for the occurrence of the study endpoints was assessed using regression analyses. Univariate logistic regression analysis was initially performed to evaluate the association between clinical, echocardiographic, and strain parameters and syncope. Variables with $p<0.05$ were subsequently entered into multivariate logistic regression models adjusted for age and sex. Receiver operating characteristic (ROC) curve analysis was subsequently performed to assess the discriminatory ability of significant echocardiographic and strain parameters for identifying patients with syncope. The optimal cut-off values were determined using the Youden index.

A post-hoc power analysis was performed for the primary comparison of LV global longitudinal strain between the syncope and control groups.

RESULTS

Thirty-six patients with VVS and 36 healthy children in the control group were included in the study. There were 10 male (27.8%) and 26 female (72.2%) patients in the syncope and 17 male (47.2%) and 19 female (52.8%) participants in the control group. There was no difference in age, sex, BMI, systolic and DBP parameters between syncope and control groups. There was no significant difference between heart rates during echocardiographic

examination in the non-syncope period. The demographic characteristics and clinical features of the study population are presented in Table 1.

The conventional echocardiographic parameters, including LV end-diastolic, end-systolic diameters, LV end-diastolic volume, LVESV were not different between the study groups. LV systolic functions did not show any statistically significant difference between the patient and control groups in terms of EF, FS values.

In the evaluation of LV diastolic function, The E/A ratio was lower -though not statistically significant- in patients with VVS.

LAVI was 24.77±1.55 mL/m^2, 24.16±1.53 mL/m^2 in syncope and control group respectively. There was no difference in the measurement in both groups. The conventional echocardiographic findings are presented in Table 2.

LV strain parameters, including LV global longitudinal strain (-17.86±1.88 vs -19.49±2.22) and circumferential strain (-18.68±1.00 vs -21.25±2.28) were observed to be lower in the patient group compared to the control group. LA peak strain was observed to be lower in patients with syncope compared to the control group (35.67±4.18 vs 44.13±7.08). The 2D- STE data are presented in Table 3.

In the univariate logistic regression analysis, demographic, echocardiographic and clinical variables potentially associated with the presence of syncope were evaluated individually. Among these variables, LV longitudinal strain, LV circumferential strain, and LAS measurements were found to have statistically significant potential predictive value for the development of syncope. The results of the univariate regression analysis are presented in Table 4. Due to potential collinearity between strain parameters, each strain variable was tested in a separate logistic regression model adjusted for age and sex. In separate logistic regression models adjusted for age and sex, LV longitudinal strain, LV circumferential strain, LAS measurements were each significantly associated with the presence of syncope. The results of the multivariable logistic regression model are presented in Table 5. ROC curve analysis demonstrated that LV global longitudinal strain had a moderate ability to discriminate patients with syncope from controls [area under the curve (AUC)=0.73], cutoff value of -18.5%, predicted syncope with 72.2% sensitivity and 70% specificity and LA peak strain showed a higher discriminatory performance (AUC=0.85) cutoff value of 39.2%, predicted syncope with 77.8 % sensitivity and 80.6% specificity. Post-hoc power analysis for the primary comparison demonstrated a statistical power of 91%.

Table 1. Demographic characteristics and clinical features of the study population

Variables	Syncope group (n=36)	Control group (n=36)	p-value
Age (years)	13.33±3.16	12.41±3.45	0.24
Sex (male:female)	10:26	17:19	0.08
BMI (kg/m^2)	21.3±0.79	19.21±3.83	0.11
Heart rate (bpm)	74.5±10.8	78.58±11.35	0.12
SBP (mmhg)	110.77±9.46	110.41±15.60	0.67
DBP (mmhg)	71.66±6.21	70.27±6.54	0.28

BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

Table 2. Conventional echocardiographic findings of the study population

Variables	Syncope group	Control group	p-value
Ejection fraction (%)	72.86±2.93	73.25±3.67	0.62
Fractional shortening (%)	42.44±2.84	42.30±3.14	0.84
LVEDD (cm)	4.16±0.39	4.26±0.44	0.29
LVESD (cm)	2.35±0.19	2.46±0.31	0.06
LVEDV (mL)	68.69±3.56	69.36±3.51	0.42
LVESV (mL)	15.69±2.67	16.77±2.40	0.075
E-wave/A-wave	1.91±0.24	2.01±0.20	0.06
LAVI (mL/m^2)	24.77±1.55	24.16±1.53	0.09

LV: Left ventricular, EDD: End diastolic diameter, ESD: End systolic diameter, EDV: End-diastolic volume, ESV: End-systolic volume, E/A: Transmitral flow velocity ratio, LAVI: Left atrial volume index

Table 3. 2D-speckle tracking derived peak systolic LA and LV strain results					
Variables	**Syncope group**	**Control group**	**Mean difference**	**95% CI**	**p-value**
Left ventricle global longitudinal strain (%)	-17.86±1.88	-19.49±2.22	1.63	0.66-2.60	0.001*
Left ventricle circumferential strain (%)	-18.68±1.00	-21.25±2.28	2.56	1.72-3.40	0.001*
Left atrial peak systolic strain (%)	35.67±4.18	44.13±7.08	8.46	5.71-11.21	<0.001*
*p<0.05 CI: Confidence interval, LA: Left atrial LV: Left ventricular					

Table 4. Univariate Regression Model results of echocardiographic parameters for the presence of syncope			
	Univariate analysis results		
	Statistics	**OR (95% CI)**	**p-value**
E-wave/A-wave	0.13	0.01-1.14	0.066
Left ventricle global longitudinal strain (%)	0.66	0.50-0.87	0.004
Left ventricle circumferential strain (%)	0.19	0.09-0.43	0.000
LAVI (mL/m^2)	1.3	0.95-1.78	0.102
Left atrial peak systolic strain (%)	0.75	0.66-0.86	0.000
Result variable: Presence of syncope. Exposure variables: Echocardiographic parameters Adjust variables: None, LAVI: Left atrial volume index, CI: Confidence interval, OR: Odds ratio			

Table 5. The relationship between strain parameters and syncope in different models					
LV global longitudinal strain		**LV circumferential strain**		**Left atrial peak systolic strain**	
Model 1		**Model 2**		**Model 3**	
OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**	**OR (95% CI)**	**p-value**
0.64 (0.47-0.85)	0.003	0.18 (0.08-0.41)	0.000	0.76 (0.66-0.87)	0.000
Model 1, 2, 3 was adjusted for age and sex. The Hosmer-Lemeshow test was used to assess the goodness of fit of the discriminant model. Hosmer-Lemeshow testi p>0.05. OR: Odds ratio, LV: Left ventricular, CI: Confidence interval					

DISCUSSION

Our study is the first to evaluate both LA and LV myocardial performance in patients with VVS in the pediatric age group. The relationship between cardiac chamber functions and syncope in these patients with syncope is not yet clear. Although there are different studies on this subject in both pediatric and adult patients, to our knowledge, there is no study in which both atrial and ventricular cardiac strain parameters were investigated using 2D-STE method in the pediatric age group.

The left atrium provides a critical relationship in ensuring LV performance through reservoir, conduit, and booster pump functions during the cardiac cycle. LAV measurements are strongly correlated with the assessment of cardiovascular diseases and the prediction of outcomes, but increasely accumulating data shows that the evaluation of LA functions provides more prognostic information[8-10]. At this point, the evaluation of LA functions has gained increasing importance, especially with the growing use of 2D-STE, which has allowed for earlier assessment and recognition of changes in LA functions, because it provides more reliable and accurate measurements compared to other measurement methods[11,12]. In a study evaluating LAV in adult patients with VVS, maximal and minimal LAV were found to be lower in VVS patients compared to the healthy control group[13]. In another study in adults, it was reported that patients with VVS under 35 years of age had better atrial contractility than patients with VVS over 35 years of age, but both LA and right atrial volumes were lower. As a result, it has been argued that in patients with syncope at an early age, the reduction of preload is more prominent and the recurrence of syncope is more frequent[14]. In our study, unlike them, both patients in the childhood age group were evaluated, and

there was no significant difference in LAV measurements between patients with syncope and the healthy group. Başanalan et al.[15] measured the LA ejection force using the mitral valve orifice area and a wave as a reference and reported that in patients with VVS who were head-up tilt test (HUTT) positive, the force was lower compared to those who were HUTT negative. Additionally, when they evaluated LA phasic functions[10] with tissue Doppler imaging, they did not observe a difference between the two groups. However, their measurements are more angle-dependent measurements, while we directly measured LA deformation in our study. We found that in the measurement of LA deformation parameters during the non-syncopal period, patients with VVS had lower LA systolic functions compared to the control group.

It is accepted that increased sympathetic activity occurs with the increase of blood catecholamine (epinephrine and norepinephrine) levels in the initial stage of NMS. Younger patients with HUTT-positivity have been shown to have higher epinephrine release in the pre-syncope period compared to older patients. This result led to the conclusion that there are fluctuations in epinephrine/norepinephrine levels that change with age[16]. As a result of all this, it has been reported that the decrease in preload and the accompanying atrial functions are less effective in the etiology of syncope[17,18]. Our study was conducted during periods without syncope in children with syncope recurrence. It was observed that atrial contraction were fewer in patients at rest. Based on this result, we can say that due to the relatively fewer atrial contractions at baseline, patients are unable to provide sufficient systolic power at the onset of syncope.

Another possible reason playing a role in pathophysiology is the ventricular theory. According to the ventricular theory, it is thought that syncope occurs due to an increase in cardiac contractility caused by high catecholamine levels during syncope, resulting in activation of mechanoreceptors subsequent withdrawal of the sympathetic system and an increase in vagal tone[4,18]. It is still being investigated because, in some adult studies, the opposite results have been reported, and it has been argued that strong contraction of the LV is less responsible for the decrease in LV volume[19,20]. Liu et al.[21] reported a decrease in end- systolic stress, cardiac index, and LV end-diastolic volume predicting a positive tilt test.

The "ventricular theory" in patients with VVS was questioned by Goel et al.[22] in 2013 and reported that paradoxical reduction in LV strain was observed in patients with VVS and HUTT(+). Although the results seem to be contrary to the excessive contractility advocated in the ventricular theory, they reported that they obtained different results due to the fact that the evaluations were performed at rest and direct myocardial deformation was measured. Similarly, in our study, when we evaluated myocardial deformity in patients with VVS, we found that LV strain was lower. Similar results were reported by Hensel et al.[3] indicating that the LV resting longitudinal strain rate at rest in patients with VVS was lower than in the control group which was more pronounced during HUTT.

Additionally, in the present study, LV global longitudinal strain, circumferential strain, and LAS were significantly associated with syncope. These findings suggest that subclinical alterations in myocardial mechanics may be associated with syncope, even in the absence of overt structural cardiac abnormalities. ROC analysis showed that LV global longitudinal strain had a moderate discriminatory ability, whereas LA peak strain demonstrated a stronger ability to differentiate patients with syncope from controls.

Study Limitations

The primary limitation of our study is that it was conducted as a single-center study with a cross-sectional design and a limited sample size. Another limiting factor was that we were not able to perform the HUTT, which would have allowed us to determine the subtypes of VVS in patients initially diagnosed with neurally mediated syncope and evaluated as VVS. This was due to the unavailability of this test at our center. However, there are studies in the literature that recommend performing this test only in cases where differential diagnosis cannot be achieved through a typical clinical history and physical examination, given the challenges associated with its application[23,24]. Consistent with these findings, another study has indicated that the presence of syncope episodes in the clinical history is a strong predictor of HUTT positivity[25].

CONCLUSIONS

In this study, we observed that myocardial strain parameters were affected in patients with VVS in childhood compared to the healthy group. However, it is fair to say that it is not possible to explain the etiology with cardiac chamber function alone. In addition to conventional echocardiography, evaluation of cardiac functions with 2D-STE imaging will provide important information for these patients. However, given the relatively small

sample size and the absence of longitudinal follow-up, these findings should be interpreted with caution. In the follow-up of patients with syncope in childhood is to reduce recurrences and improve quality of life. Further large-scale prospective studies are needed to clarify the potential diagnostic and prognostic role of 2D-STE in this patient population.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Participants, and approved by the Institutional Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital (decision no: 2023/183, date: 25.10.2023).

Informed Consent: This is a retrospective study.

Footnotes

Conflict of Interest: The author disclose no potential conflicts of interest.

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