# Is There a Structural Basis for Vasovagal Syncope? Cardiac Functions in Patients with Vasovagal Syncope

Erkan Alpaslan[1], Ummu Tas[2] Sedat Tas[*3], Ebru Ozpelit[4]

1 Department of Cardiology, İzmir Gazi Hospital, İzmir, Türkiye
2 Department of Cardiology, İzmir Demokrasi University, İzmir, Türkiye
3 Department of Cardiology, Manisa Celal Bayar University, Manisa, Türkiye
4 Department of Cardiology, İzmir Dokuz Eylül University, İzmir, Türkiye

Abstract

**Aim:** The pathophysiology of vasovagal syncope (VVS) is not completely understood. Some echocardiographic parameters have been defined to contribute to its pathophysiology. However. whether right atrial (RA) and right ventricular (RV) functions have any impact on development of VVS is not well known. In this study we aimed to evaluate the baseline echocardiographic parameters in patients with VVS with special focus on right ventricle and atrium functions.

**Material and methods:** We evaluated the medical records of 42 patients with VVS and 41 age and sex matched healthy subjects. Patients with at least two syncopal attack and positive head-up-tilt test were enrolled in the study. All medical records of echocardiography and head-up-tilt test were obtained.

**Results:** Among left ventricular function parameters, there were no significant difference between the groups. Right ventricle myocardial performance index (p= 0.003) and maximal pulmoner systolic flow velocity (PVmax) (p=0.03) were significantly differ between the groups. RAA was significantly larger (p=0.04) and the ratio of tricuspid filling velocities (E/A), (p=0.01) was significantly lower in VVS group.

**Conclusions**: The findings of the present study indicate a subtle RA diastolic dysfunction in patients with VVS. Decreased RA contribution to RV filling may cause a lower RV stroke volume which explains the lower PVmax values in our VVS group. All together, those findings may serve for a tendency to low output states and hypotension as in VVS.

***Keywords:*** *vasovagal syncope, right ventricle, right atrium, head-up-tilt test*

## 1. Introduction

Syncope is a frequent clinical issue, with an occurrence rate of 1.3 to 2.7 per thousand population[1]. Vasovagal syncope (VVS) is the most frequent source of syncope and is also the most recurrent type. From a clinical perspective, these episodes can be either a single incident with an identifiable cause or a series of multiple episodes that needs thorough analysis. VVS is the most common reflex syncope in young patients. Clinical investigations demonstrate that the highest number of cases occur between the ages of 10 and 30[2,3]. Age-dependent differences in syncope epidemiology exist: neural-mediated mechanisms are more prevalent among the young, while cardiovascular causes are more common in the elderly. Elderly people tend to have cardiac issues, orthostatic and postprandial hypotension, and medication side effects as a cause of syncope, whereas VVS is less likely to be seen in this age group [4]. The diagnostic process is more convoluted in elderly patients and the prognosis is poor while in younger patients, VVS is more prevalent and the treatment is uncertain.

The pathophysiology of VVS is not fully understood. Basically, it is related to a drop in cerebral perfusion pressure that results in a syncope episode caused by a failure in the autoregulation of blood pressure and, ultimately, a transient loss of consciousness. Many complex and interrelated mechanisms are responsible. However, the most frequently emphasized mechanism is related to the reflex arc in the afferent and efferent nerve pathways of the autonomic nervous system, which is activated by an external stimulus. Increased cardiac contractility due to hypovolemia stimulates the vagal system, resulting in a decrease in heart rate, cardiac output, vascular resistance and a decrease in central blood pressure[5] .

Echocardiographic evaluation is an important part of the assessment of patients with syncope, but its use in the evaluation of patients with VVS is not common. Some echocardiographic parameters have been described to contribute to the pathophysio-

* Corresponding Author: Sedat Tas
e-mail: sedattas2000@yahoo.com
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logy of VVS, such as reduced left atrial contribution to left ventricular filling, small left atrial size, small left ventricular size and increased left ventricular contractility[6,7]. There are limited studies in the literature on whether RA and right ventricular function influence the development of VVS[8] . There are limited demographic and clinical factors identified to predict VVS[9,10] . We used echocardiography as one of the predictive factors because it is simple and easily accessible. In our opinion, there are no studies investigating the relationship between VVS and cardiovascular function and evaluating this relationship as a predictive factor for right heart echocardiographic parameters. Therefore, in this study, we aimed to evaluate basic echocardiographic parameters in patients with VVS, with a particular focus on RV and RA function.

## 2. Materials and methods

### 2.1. Patient population

This retrospective study was designed and conducted in accordance with the Declaration of Helsinki and approved by an institutional ethics committee of Dokuz Eylül University (Date and decision number: 2023/14-29). Forty-two patients who had at least two syncope episodes without an apparent cause and who were admitted to our clinic between 2012 and 2015 and 41 age- and sex-matched healthy individuals as the control group were retrospectively evaluated. Personal information and medical history of the patients were obtained from medical records.

Subjects underwent routine cardiologic evaluation and complete physical examination, including evaluation for orthostatic hypotension and carotid hypersensitivity, followed by 12-lead electrocardiography and data recorded. Subjects underwent echocardiographic examination before the procedure. In all subjects, laboratory samples were taken after a 12-hour overnight fast to exclude metabolic abnormalities for syncope. In addition, neurological and psychiatric evaluations were performed by relevant departmental experts to exclude psychological/ neurological etiologies of syncope. Data were collected from all patients who met the criteria, had no proven cause of syncope and underwent the tilt table test. The data were then compared between the two groups

### 2.2. Exclusion criteria

Exclusion criteria (1) presence of structural heart disease, diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, anemia, hyperthyroidism, hypothyroidism, goiter and other thyroid diseases; (2) Using drugs with potential chronotropic effects

### 2.3. Head-up Tilt Test

The protocol of the head-up tilt-test[11] applied to the patients was as follows: The patients were put in a supine position on the tilt table, and an intravenous catheter was inserted into the peripheral vein following a 6-hour fast. An electrocardiography was used for continual monitoring and BP readings were taken non-invasively with an automated cuff sphygmomanometer at 2-minute intervals. Initially, patients were lying down for 10 minutes and their vital signs including blood pressure and pulse rate (PR) were monitored at one-minute intervals. The table was slanted to the horizontal plane and subjects were angled in a 70-degree head-up position for 20 minutes, with their feet held in place by the foot board for assistance. Blood pressure, PR, and subjective symptoms were observed every 2 minutes to look for potential signs of hypotension or bradycardia. If a positive response was obtained during upright tilt, the protocol was terminated by returning patients to the supine position. If no positive response happened after this phase, patients were put back in supine position and 1 µg/min isoproterenol infusion was initiated. Subsequently, the head-up tilt of 70 degrees was repeated for 10 minutes. If a positive reaction was recorded, the subjects were laid down and the protocol was completed. A positive response (with or without concurrent isoproterenol infusion) was defined as follows: A sudden drop in systolic blood pressure to < 70 mm Hg or the development of syncope or presyncope with bradycardia (PR < 40/min), as well as the presence of relevant clinical symptoms in the patient.

### 2.4. Echocardiography

Transthoracic echocardiogram was executed with the Philips HD11XE and frequencies of 2.5 or 3.5 mHZ transducers with tissue velocity imaging according to the patient's age. The systolic pulmonary artery pressure was calculated by combining the estimated RA pressure with the maximum speed of tricuspid regurgitation. Ejection fraction was computed by means of M-mode echocardiography and the Teichholz technique[12]. Pulsed Doppler method was used for blood flow measurements through the heart valves (mitral, aortic, tricuspid and pulmonary): flow velocity (E) during early filling, flow velocity (A) during atrial contraction, and ejection time (ET) were measured, and then E/A was calculated. Tissue doppler imaging (TVI) measurements were measured from the basal segments of the lateral LV wall, septal wall and RV free walls. Mitral annular early (Em) and late (Am) diastolic velocity and tricuspid annular early (Et) and late (At) diastolic velocity were measured. The ratio between early mitral flow velocity and mitral annular early diastolic velocity (E/Em) and the ratio between early tricuspid flow velocity and tricuspid annular early diastolic velocity (E/Et) were calculated. RV myocardial performance index (RV MPI index) was calculated according to the following formula[13] (Figure 1).

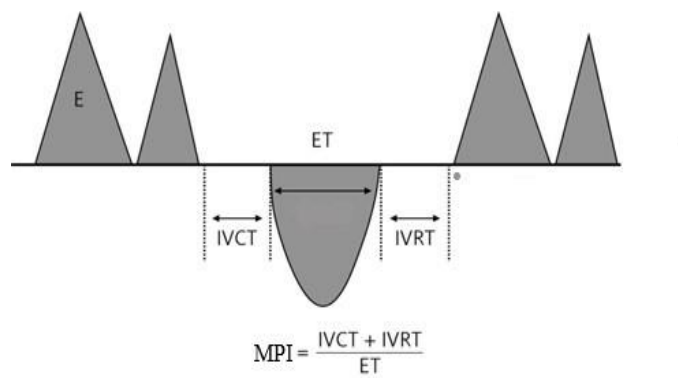


**Figure 1**

Method of MPI measurement. IVCT – isovolumetric contraction time, IVRT – isovolumetric relaxation time, ET – ejection time, AoVF – flow through aortic valve

### 2.5. Statistical analysis

Statistical Package for Social Sciences 22.0 software was used to carry out statistical analyses. (SPSS, Chicago, Illinois, United States of America). The Kolmogorov-Smirnov test was used to confirm whether the distribution of continuous variables was normal. According to the distribution pattern of continuous variables, the choice of independent sample t-test or Mann-Whitney U-test was made. Mean and standard deviation were utilized to express continuous variables while number and percentage were employed to express categorical variables, in accordance with the distribution pattern. Chi-square test was performed to analyze categorical variables. P value below 0.05 was taken as significant.

## 3. Results

The mean age of the patient group and the control group were 39.1±13.8 and 36.8±7.4 years, respectively. The patient group had a greater BMI than the control group, without any significant difference. The main clinical characteristics of the patients are presented in Table 1. Among the left ventricular function parameters, only two parameters differed between the groups: mitral early filling rate (E) (p= 0.007) was significantly lower and deseleration time (DT) (0.003) was significantly higher in the VVS group compared to the control group (Table 2). Right atrium area was significantly larger in the VVS group compared to the control group (p= 0.04). Similarly, RV MPI was significantly higher in patients with VVS compared to controls (p= 0.003). In addition, the ratio of maximal pulmonary systolic flow velocity (PVmax) (p= 0.004) and tricuspid filling velocities (E/A) (p= 0.01) were significantly lower in the VVS group. Except for the variables mentioned above, the right ventricular function parameters showed no significant difference between the two groups (Table 3).

**Table 1**

The baseline characteristics of the participants

| | patient | control | P value |
|---|---|---|---|
| Age | 39,1±13,8 | 36,8±7,4 | 0.126* |
| Sex (M, %) | 12 (%28.6) | 15 (%36.6) | 0.43¥ |
| Smoking (n,%) | 11 (%26.2) | 7 (%17.1) | 0.31¥ |
| BMI | 25,3±3,1 | 24,5±3,7 | 0.13* |

¥ Chi-square test, *Independent t-test, M: Men, BMI: Body mass index

## 4. Discussion

The primary findings of our study were as follows: (i) A slight degree of RV diastolic dysfunction and decreased RV outflow was common in in VVS patients and was associated with HRV, LV E/A ratio and RV MPI. (ii) Lower PVmax and higher RV MPI values were observed among the VVS group. (iii). There were no significant differences evaluating in terms of LV functions

Vasovagal syncope occurs as a reflection of decreased blood distribution to the brain. Different theories have been suggested to account for the hemodynamic transformations leading to syncope, such as ventricular theory, baroreflex malfunction theory, low blood volume theory, and neurohumoral theories, but the mechanism of VVS has not been clearly elucidated[14,15] . Echocardiographic examination has a great role in explaining the "ventricular theorem" which is considered to be the most common pathophysiologic cause of neurogenic syncope. Shaley et al. demonstrated a significant decrease in left ventricular systolic diameters and a significant increase in myocardial contractility in patients who experienced syncope with passive or isoproterenol provocation in the oblique table test compared to non-syncope or control group[16] . In the study by Moon et al.[17], echocardiography was performed during tilt table testing and left ventricular hypercontractility was observed immediately after passive tilting in patients who developed neurogenic syncope due to tilt table testing. In another study, patients were evaluated by strain echocardiography 6 months after tilt table testing. They found a decrease in myocardial strain as a predictor of positive tilt test[18]. In our study, echocardiography was performed at rest before the procedure. In line with the findings of Goel et al., we also found decreased RV function in patients with VVS compared to healthy controls. It is possible that VVS-prone individuals show a decreased myocardial tension at rest, but increased tension and contractility with provoking stimuli[8]. Based on the above mechanisms, the common approach to the treatment of VVS in syncope clinics is to increase dietary salt and water intake. On the other hand, there is not much proof to corroborate this strategy. Bellard et al.[19] suggested that this strategy may be explanatory in the short term, but increased hydration alone does not improve orthostatic intolerance. The other approach that may help VVS is various physical therapies and maneuvers. One of these is exercise training. The evidence for the effectiveness of exercise training in the prevention of syncope is inconclusive, yet its ability to increase blood volume and change baroreceptor function is evident [20,21] .

**Table 2**

The comparation of LV functions between the groups

| | Patient | Control | P value |
|---|---|---|---|
| LVESD | 27 ± 6 | 26 ± 5 | 0.07* |
| LVEDD | 44 ± 7 | 44 ± 6 | 0.59* |
| LAA | 15.5 ± 2.8 | 15.0 ± 2.5 | 0.41* |
| Mitral E/A | 1.2 ± 0.34 | 1.6 ± 1.1 | 0.20* |
| LV Em | 7.2 ± 2.8 | 7.0 ± 1.7 | 0.67* |
| LV Sm | 9.0 ± 3.0 | 9.6 ± 3.9 | 0.39* |
| Mitral E | 82.2 ± 21.2 | 93.2 ± 13.6 | 0.007* |
| Mitral DT | 150.8 ± 28.3 | 129.2 ± 33.3 | 0.003* |

*Independent t-test, DT: Decelaration time, E: Transmitral early diastolic wave velocity, E/A: The ratio of transmitral early and late diastolic wave velocity. Em: Mitral annular early diastolic wave velocity, LAA: Left atrium area, LV: Left ventricle, LVESD: Left ventricular end systolic diameter, LVEDD: Left ventricular end diastolic diameter, Sm: Systolic motion, VVS: Vasovagal syncope

**Table 3**

The comparation of RV functions between the groups

| | patient | control | P value |
|---|---|---|---|
| RV E/A | 1.1 ± 0.44 | 1.4 ± 0.35 | 0.01* |
| RAA | 13.9 ± 3.3 | 12.6 ± 2.5 | 0.04* |
| PVmax | 0.9 (0.2) | 1.0 (0.2) | 0.004# |
| TAPSE | 22.4 ±2.8 | 23.3 ± 2.5 | 0.13* |
| RV Sm | 14.6 ± 3.6 | 14.0 ± 3.2 | 0.46* |
| RV Em | 4.7 ± 1.02 | 4.4 ± 1.2 | 0.32* |
| RV MPI | 0.50 ± 0.13 | 0.42 ± 0.03 | 0.003* |

*Independent t-test, #Mann Whitney-U test, Em: Tricuspid annular early diastolic wave velocity, E/A: The ratio of transtricuspid early and late diastolic wave velocity, MPI: Myocardial performans index, RAA: Right atrium area, PVmax: Maximum pulmonary flow velocity, TAPSE: Tricuspid Annular Plane Systolic Excursion, RV: Right ventricle, Sm: Tissue Doppler systolic motion, VVS: Vasovagal syncope

Isometric exercise has been shown to improve arterial blood pressure and cardiac output[22-24] . The basis of these therapeutic approaches is to increase blood flow to the heart and blood flow to the end organs. When the above-mentioned therapeutic approaches are considered together, one of the main problems is RV diastolic function, RA size and function, which can lead to decreased venous return and cardiac output. In this study, we found that the RAA was significantly larger than in the control group. Besides atrial fibrillation, any change in right ventricular function can cause volume overload, increased pressure and enlargement of the RA. We found that the ratio of tricuspid filling rates (Et/At), which is an indicator of right ventricular diastolic function, was lower in patients with VVS. Sotiriadou et al.[25] suggested that the contribution of the atria to ventricular filling is higher in young people and atrial function is better than in older people. In contrast to Sotiriadou et al, we found differences in RV function between similar age groups in our study. We found that the RV MPI value, an indicator of global right ventricular function, was higher in patients with syncope than in controls. This result suggests that right heart function is worse in patients with positive oblique table test. This results in a much stronger preload reduction, probably due to any reduction in mechanical function, and hence syncope. During the tilt-table test, LV contractility is already increased and diameters are shortened. In patients with RV dysfunction, volume overload and increased pressure in the atria worsen this condition and increase the tendency to syncope. We also found that Et/At and PVmax, indicators of RV function, were significantly lower in patients with VVS. The enlargement of RA in patients with VVS compared to controls may be explained by decreased RV function. Inconsistent findings regarding the response to blood volume expansion in patients with VVS have been reported in the literature. These inconsistent findings support the suspicion that there may be another pathophysiologic mechanism rather than volume deficit.

Our study has some limitations. Most importantly, it included a small number of patients and was single centered. Secondly, echocardiography was performed before the procedure. Since echocardiography was not performed during the tilt table test, we do not have data on cardiac function during the procedure.

## 5. Conclusions

This research points to a slight degree of RV diastolic dysfunction in VVS patients, which likely reduces the RV stroke volume due to the lesser RA contribution to RV filling, thus elucidating the lower PVmax values observed among the VVS group. Taken as a whole, these results may lead to conditions of reduced cardiac output and hypotension, such as in VVS. Further research is required to gain a better understanding.

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## Statement of ethics

The study was approved from Dokuz Eylul University Ethics Committee (2023-14-29) and was conducted in accordance with the Declaration of Helsinki.

## Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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## Author contributions

EA, data collection, literature review, writing of the study, UT, hypothesis, data collection and statistics, writing of the study, ST, data collection, writing of the study, literature review, hypothesis.

All authors reviewed and accepted the final version of the study.

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