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ORIGINAL ARTICLE

Vasovagal syncope is associated with poor prognosis in patients with left ventricular dysfunction

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Abstract Vasovagal syncope (VVS) is known to have a benign prognosis and be associated with enhanced contraction and activation of the left ventricular (LV) mechanoreceptors. However, a little is known about VVS in patients with LV dysfunction. The present study aimed to investigate the prevalence and prognosis of VVS in patients with LV dysfunction. We enrolled 368 patients with unexplained syncope. In 7 of these patients, LV ejection fraction was lower than 40%. The results of a head-up tilt test (HUT) and the recurrence of syncope were compared between these 7 patients with LV dysfunction and the remaining patients. Positive HUT was obtained in the 6 patients (86%) with LV dysfunction; this rate tended to be higher as compared with normal cardiac function (192/361, 53%, $P = 0.069$). In patients with LV dysfunction, response in HUT was mostly vasodepressor type (62%); however, most of HUT responses were mixed type in patients with normal LV function (67%). Among patients with positive HUT, the recurrent rate of syncope after HUT was higher in those with LV dysfunction than in those with normal LV function (67 vs. 21%, $P = 0.008$). VVS in patients with LV dysfunction may be refractory to treatment and could be associated with poor prognosis.

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Introduction

Vasovagal syncope (VVS) is the most frequent cause of unexplained syncope, especially in patients without apparent structural cardiovascular diseases [1–3]. VVS is mediated by activation of the left ventricular (LV) mechanoreceptors mostly through enhanced LV contraction caused by increased sympathetic nervous activity. Additionally, decrease of venous return due to dehydration or vasodilator drugs could be involved in the pathogenesis of VVS. Since an enhanced LV contraction is required to initiate this mechanism, VVS is considered to be uncommon in patients with LV dysfunction [4]. However, recent studies suggested that other mechanisms could be involved in the pathogenesis of VVS in patients with clinically significant LV dysfunction [5]. A head-up tilt test (HUT) has been recognized as a useful tool for diagnosis of unexplained syncope [2, 3, 6, 7]. Several observations suggest that hypotension/bradycardia induced by HUT is essentially equivalent to the spontaneous episodes of VVS in patients without structural cardiovascular disease [2, 3, 6, 7]. However, the role of HUT in patients with syncope and LV dysfunction has not been elucidated thoroughly yet. Stanton et al. showed that VVS occurred in patients with clinically significant LV dysfunction [5]. Although prognosis of VVS appears benign, a little is known about the risk and prognosis of VVS in patients with LV dysfunction, who have decreased LV contraction. The present study aimed to investigate the results of HUT and recurrence rates of syncope in patients with LV dysfunction in comparison with those with normal LV function.

Materials and methods

Subjects

This study included 368 patients who were referred to our Hospital for detailed evaluation of unexplained syncope from May 1989 to March 2013. The subjects consisted of 7 patients with low LV ejection fraction [LV ejection fraction (LVEF) < 40%; low LVEF group] and 361 with normal LVEF (≥ 40%). Of the 361 patients with normal LVEF, 89 patients who had been followed for at least 1 year constituted the normal LVEF group. The present study protocol was approved by the review board of our institution and carried out in accordance with the Declaration of Helsinki. All patients gave their informed consent prior to their inclusion in the study.

Head-up tilt test

To investigate the cause of unexplained syncope, all the subjects underwent head-up tilt (HUT) testing, which started after a 10-min rest in the supine position. Each patient was tilted to a 60° upright position for 30 min with a footboard with monitoring of blood pressure and heart rate. A positive response was defined as a decrease in mean blood pressure ≥ 20 mmHg from the value at 1 min of tilt or a trough systolic blood pressure < 70 mmHg associated with syncope or presyncopal symptoms. Positive responses were classified according to the VASIS classification [7]: mixed (heart rate falls at the time of syncope, but not below 40 beats/min for 10 s or more); cardioinhibitory (heart rate falls below 40 beats/min for 10 s or more, or asystole over 3 s occurs); and vasodepressor (heart rate does not fall more than 10% from the peak). In all subjects with a negative response to baseline HUT, isoproterenol was intravenously infused at rates of 0.01–0.03 μg/kg/min and/or 0.3 mg nitroglycerine was given sublingually, and the test was repeated as in our previous study [6].

Statistical analysis

Numerical data are expressed as mean ± standard deviation (SD). The 2-tailed unpaired *t* test was used to examine statistical differences between the two groups, when the data had a normal distribution (Shapiro–Wilk test). The Wilcoxon rank sum test was used when the data groups did not have normal distributions. Difference in the type of response to HUT was examined using Pearson's Chi-square test. Recurrence-free probability was analyzed using Kaplan–Meier method and the statistical difference was examined by the log-rank test. Statistical significance was set at $P < 0.05$.

Results

Results of head-up tilt test

Clinical characteristics of patients in low and normal LVEF groups are given in Table 1. Detailed characteristics of patients in low LVEF group are summarized in Table 2. Six patients in the low LVEF group were diagnosed with dilated cardiomyopathy and one, myocardial infarction. The rate of positive HUT result tended to be higher in low LVEF group (6/7, 86%) than in normal LVEF group (192/361, 53%, $P = 0.069$; Fig. 1). The type of response to HUT tended to be different between the two groups ($P = 0.078$). Most of the positive responses were vasodepressor type in low LVEF group ($n = 4$, 66.7%) and mixed type in normal LVEF group ($n = 30$, 63.8%).

Although the 6 patients with a positive HUT in low LVEF group performed lifestyle modification and reduced dosage of vasodilators and diuretics, 4 patients had recurrent syncope and two of these 4 (Patient 1 and 2, Table 2) died of other causes than lethal ventricular arrhythmias or heart failure. On the other hand, no patients in normal LVEF group died during the follow up period. The recurrence rate of syncope was higher in low LVEF group than in normal LVEF group (57 vs. 10%, $P < 0.001$; Fig. 2a). Among patients with a positive HUT, the recurrence rate was also higher in low LVEF group than in normal LVEF group (67 vs. 21%, $P < 0.001$; Fig. 2b). Although the interval from HUT to the recurrence of syncope was not different between low (3.3 ± 2.2 months) and normal (14.9 ± 21.0 months) LVEF groups ($P = 0.116$), the recurrence-free probability was significantly lower in low LVEF group than in normal LVEF group ($P < 0.001$; Fig. 3).

Table 1 Patient characteristics in the low and normal LVEF groups

	Low LVEF group (LVEF < 40) ($n = 7$)	Normal LVEF group (LVEF ≥ 40) ($n = 89$)	*P* value
Male/female	3/4	57/32	$P = 0.274$
Age (years)	48.9 ± 19.3	36.2 ± 16.9	$P = 0.137$
LVEF (%)	33.9 ± 5.9	65.2 ± 9.9	$P < 0.001$
Types of positive response to HUT			$P = 0.078$
Mixed	2 (33.3%)	30 (63.8%)	
Cardioinhibitory	0 (0%)	6 (12.7%)	
Vasodepressor	4 (66.7%)	11 (23.4%)	

HUT head-up tilt, *LVEF* left ventricular ejection fraction

Table 2 Detailed characteristics in the low LVEF group

Patient	Age (years)	Sex	Diagnosis	LVEF (%)	Response to HUT	Outcome
1	50	Female	DCM, VT	28	VD	Recurrence (4 months), death (4 years)
2	69	Male	DCM, VT	36	VD	Recurrence (6 months), death (1 year)
3	64	Male	OMI	33	Mix	Death (2 months) due to HF
4	15	Male	DCM	39	Mix	No recurrence
5	38	Female	DCM, VT	39	VD	Recurrence (1 month)
6	65	Female	DCM, AF	38	VD	No recurrence
7	41	Female	DCM	24	Negative	No recurrence

LVEF left ventricular ejection fraction, *DCM* dilated cardiomyopathy, *HF* heart failure, *VT* ventricular tachycardia, *OMI* old myocardial infarction, *AF* atrial fibrillation, *VD* vasodepressor type, *Mix* mixed type

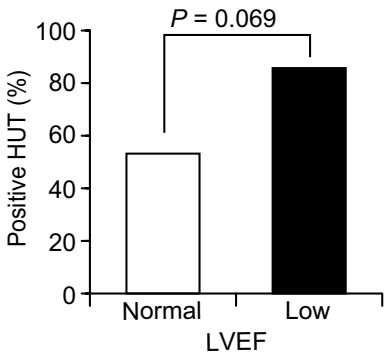

Fig. 1 Comparison of positive rate of HUT testing between normal (normal) and low LVEF (low) groups. *HUT* head-up tilt, *LVEF* left ventricular ejection fraction

A representative case

A 50-year-old woman (Patient 1, Table 2) was admitted to our hospital for the treatment of recurrent episodes of syncope. She had experienced the first episode of syncope in her 20s. She was diagnosed with dilated cardiomyopathy and a pacemaker was implanted for sick sinus syndrome at the age of 47 years. Even after the implantation, she had recurrent episode of syncope and frequency of syncopal attacks increased along with an increase in dosage of diuretics and vasodilators for the treatment of heart failure. On admission, blood pressure was 114/86 mmHg and heart rate was 60 beats/min. A 12-lead electrocardiogram showed atrial pacing rhythm and LV hypertrophy (Fig. 4a). Two-dimensional transthoracic echocardiography revealed LV dilatation (LV end-diastolic dimension = 55 mm) and decreased systolic function (LVEF = 28%, Fig. 4b). Presyncopal symptoms developed in association with abrupt hypotension (68/38 mmHg) at 8 min of HUT with a 0.3 mg nitroglycerin provocation (Fig. 4c), and VVS was diagnosed as the cause of syncope. Lifestyle guidance and modification were performed and doses of vasodilators were reduced. However, syncopal episodes were increased in frequency along with an increase in dosage of vasodilators and diuretics for the treatment of worsening cardiac failure during ambulatory care. One day, she experienced a cold sweat and nausea with defecation leading to syncope with hypotension (60/42 mmHg) and subsequently cardiac arrest. Despite cardiopulmonary resuscitation with bolus infusion of atropine sulfate and rapid fluid infusion, she died without ventricular tachycardia/fibrillation during the continuous bedside ECG monitoring.

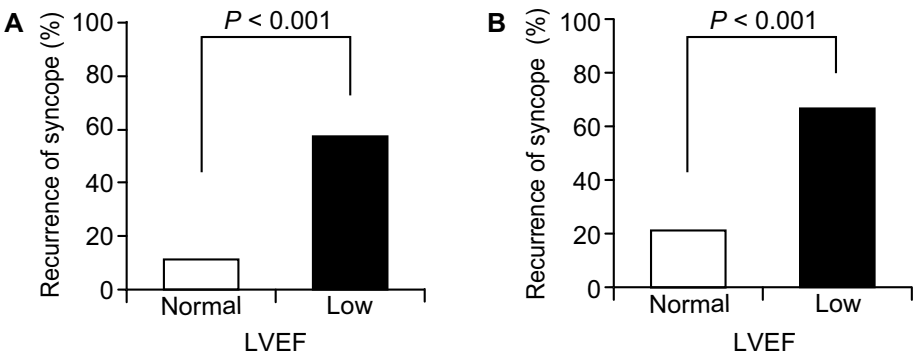

Fig. 2 Comparison of recurrence rate of syncope after head-up tilt testing between all the patients (**a**) and patients with a positive head-up tilt testing (**b**) in normal and low LVEF groups. LVEF, left ventricular ejection fraction

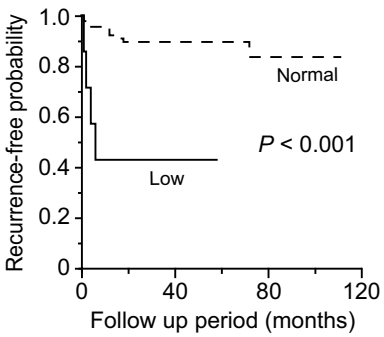

Fig. 3 Recurrence-free probability after head-up tilt testing in the normal and low left ventricular ejection fraction groups

Discussion

The major findings of the present study are as follows. First, in patients with LV dysfunction, VVS was common as a cause of syncope and often caused by drug therapy for heart failure including vasodilators and diuretics. Second, VVS was refractory and recurred frequently, and could be sometimes associated with poor prognosis in patients with LV dysfunction.

VVS is the most common cause of syncope in patients without structural heart diseases [1–3]. The Bezold–Jarisch reflex, which was originally described as enhanced contraction and activation of LV mechanoreceptors, has been regarded as the most common pathophysiological mechanism of VVS [8]. However, this mechanism could not be implemented in patients with LV dysfunction because LV

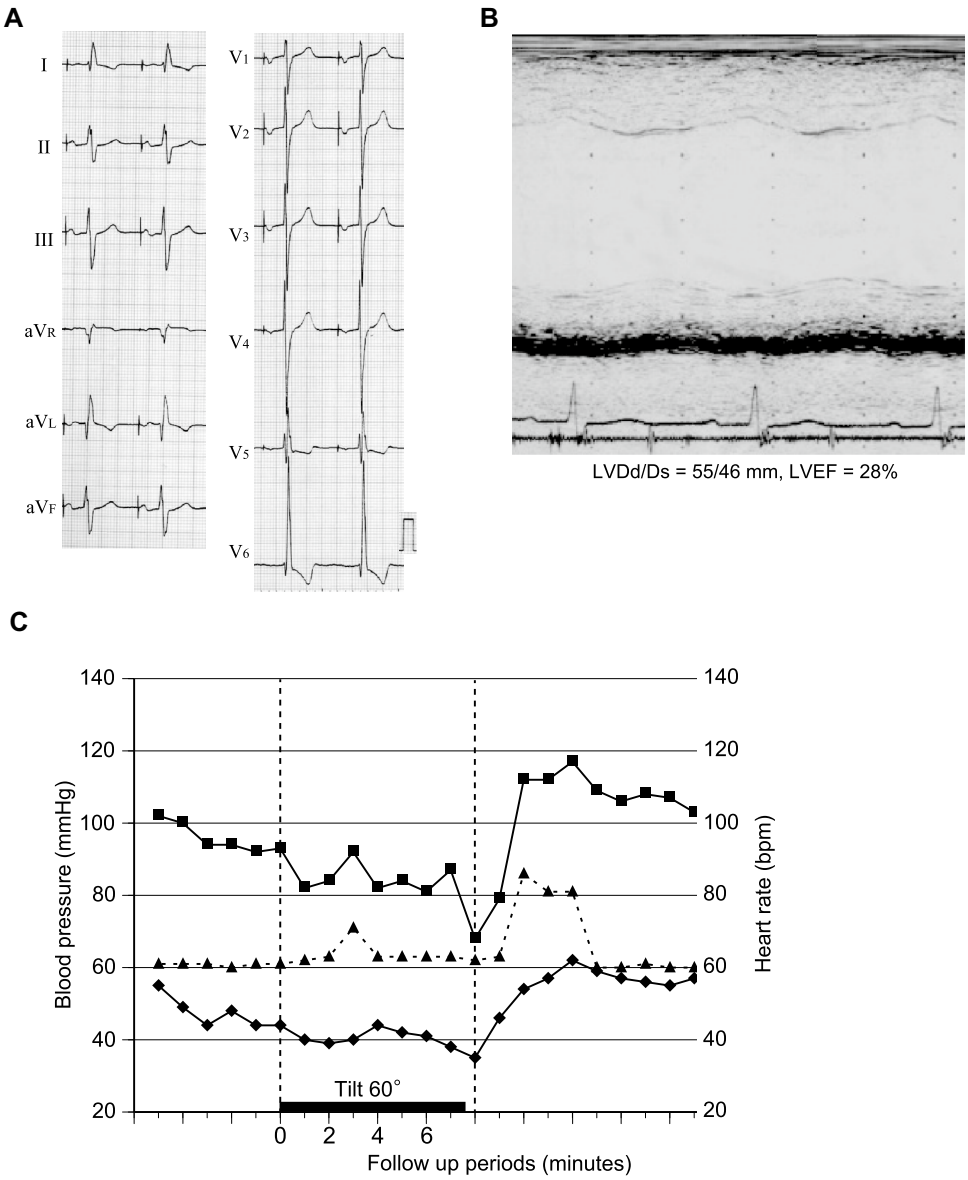

Fig. 4 A representative 12-lead electrocardiogram (**a**), M-mode echocardiography (**b**) and blood pressure and heart rate recording during head-up tilt testing (**c**) of a 50-year-old woman with left ventricular dysfunction due to dilated cardiomyopathy (patient 1, Table 2). Closed squares show data of systolic (*square*) and diastolic (*diamond*) blood pressures and closed triangles indicate heart rate

does not contract vigorously. Therefore, neurohumoral factors which are regulated mainly by the central nervous system are involved in the pathophysiology of VVS in patients with LV dysfunction [9–14]. Serotonin and serotoninergic receptors have a significant role in blood pressure regulation and in the pathogenesis of VVS [9–12]. In addition, a link between the central nervous system monoaminergic transmitters and peripheral sympathetic nervous stimulation was evident in patients with heart failure [12]. Moreover, in patients with heart failure, plasma adenosine levels increased [13], and could increase sympathetic nerve activity, thereby serving as a modulator for VVS [14].

Sympathetic nerve activity could be increased persistently in LV dysfunction due to various reasons, including pulmonary congestion, low cardiac output and drug therapy for heart failure [15], such as vasodilators and diuretics which decrease in venous return. Based on these conditions, further decrease in the cardiac venous return in the standing posture could lead to a further rise in sympathetic nerve activity via the baroreceptor reflex. Causative mechanism of this enhanced sympathetic nervous activity in the pathogenesis of VVS through activation of LV mechanoreceptors or peripheral vasodilatation may not be entirely excluded in patients with LV dysfunction.

The prognosis of VVS in patients with normal LV function is usually benign [16]. Although a previous report [12] suggested that prognosis was not different between patients with cardiac syncope and with non-cardiac syncope among patients with advanced heart failure, and VVS in patients with LV dysfunction could be potentially associated with poor prognosis. In the present study, the recurrence rate of syncope was higher in patients with LV dysfunction than in those without LV dysfunction. Moreover, 2 of 7 patients with LV dysfunction died without any evidence of fatal arrhythmias during the follow-up period after positive HUT. These results suggest that recurrent VVS in patients with LV dysfunction could be an ominous sign of poor prognosis [17]. Hypotension and bradycardia caused by vasovagal reflex may lead to a vicious circle of low cardiac output and hypotension through myocardial hypoperfusion and ischemia, especially in patients with LV dysfunction. In the representative case (Patient 1, Table 2), there was no evident sign of cardiogenic shock or lethal ventricular arrhythmias before syncope, and therefore, defecation-induced vasovagal reflex could lead to the above mentioned vicious cycle resulting in a cardiac arrest. Additionally, impairment of baroreflex-mediated vasoconstrictor responses[4] could play a role in the vicious circle in patients with LV dysfunction. However, the causal relationship between recurrent VVS and poor prognosis in our study cohort has not been clarified in the present study. After careful investigation of the cause of syncope, most of the syncopal patients with low LVEF were diagnosed as a cardiogenic syncope. Therefore, very small number of patients with low LVEF was candidate for HUT. Further investigation with a larger study population is needed to elucidate the more detailed mechanism of VVS and its relation to prognosis in patients with LV dysfunction and VVS.

Conclusions

In patients with LV dysfunction, VVS was common and often exacerbated by drug therapy for heart failure including vasodilators and diuretics. VVS was refractory, recurred frequently, and could be an ominous sign of poor prognosis in these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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