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RESEARCH ARTICLE

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Vasovagal syncope in patients with reduced left ventricular function

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Abstract Vasovagal syncope (VVS) is mediated by arterial mechanoreceptors, resulting in reflexive changes in heart rate and vascular tone. The Bezold–Jarisch reflex was originally described as enhanced contraction and activation of left ventricular mechanoreceptors, but later studies implicated other triggers, including coronary, carotid, and cerebral arterial mechanoreceptors. VVS is uncommon in patients with left ventricular dysfunction. We hypothesized that VVS could occur in this subset and examined patient characteristics and hemodynamic responses during tilt table testing. From 1996 through 1998, 128 consecutive patients with ejection fraction <40% underwent tilt table testing (70°, 45 min). A total of 15 patients (11.7%) had a positive neurocardiogenic response thought to be the cause of syncope. Clinical data and hemodynamic responses were reviewed. Mean patient age (±SEM) was 70.1 ± 12.2 years. Nine patients were male. Mean ejection fraction was 27.7% ± 7.1%. Thirteen had electrophysiologic studies with normal findings or abnormal findings insufficient to account for syncope. Hemodynamic analysis of 14 patients who had a vasovagal response during passive tilt table testing showed a mean time to positive response of 17.6 ± 12.7 min. Cardioinhibitory responses (pauses >3 sec or heart rate < 40 beats/min for ≥10 sec) were not observed. Five responses were classified as mixed type (>10% decrease in heart rate without a cardioinhibitory response) and 9 as vasodepressor type (≤10% decrease in heart rate). VVS occurs in patients who have clinically significant left ventricular dysfunction. Although this study had a small cohort size, the predominantly vasodepressor response without a cardioinhibitory component warrants further investigation into mechanisms of VVS in these patients.

Key words autonomic nervous system · heart failure · hemodynamics · reflexes · syncope

Background

The Bezold–Jarisch reflex is the most commonly cited model used to describe vasovagal syncope (VVS) [1, 9, 11, 17, 23, 25–27]. Preload reduction (from various causes) results in decreased ventricular volume, thereby stimulating enhanced inotropy, which activates left ventricular mechanoreceptors. Activation of the mechanoreceptors causes reflexively increased parasympathetic activity and decreased sympathetic activity, resulting in marked vasodilatation, varying degrees of bradycardia, and, ultimately, syncope. Since a vigorous ventricular response is prerequisite to initiation of this mechanism, VVS is considered to be uncommon in patients with left ventricular dysfunction. However, several more recent studies suggest that other triggers and mechanisms of the reflex are also present [3, 7, 10, 14, 18, 22]. One such study suggests that increased sympathetic activation is not the sole initiating factor in patients who have recurrent VVS [15]. Another study examining sympathetic and vagal modulations to the sinoatrial node in patients experiencing VVS suggests that discrete autonomic patterns exist in this patient population [8]. Studies performed on anesthetized dogs placed on cardiopulmonary bypass suggest that coronary arterial mechanoreceptors may be very active in regulating vascular tone [28]. These suggestions of extraventricular and neurohormonal mechanisms, along with case reports describing these reflexes in heart transplant patients [20], indicate that VVS is possible in this cohort.

We hypothesized that the vasovagal response does occur in patients with severe cardiac dysfunction and can be induced during tilt table testing. Specific goals were (1) to determine the prevalence of a positive vasovagal response during tilt table testing in patients with clinically significant cardiac dysfunction undergoing evaluation for syncope, (2) to characterize their hemodynamic parameters during the vasovagal response, and (3) to assess clinical outcomes of these patients during follow-up.

Methods

Patient selection

From 1996 through 1998, 128 consecutive patients with ejection fraction <40% underwent head-up tilt table testing as part of their evaluation for syncope or near syncope of unknown origin. Patients with a positive vasovagal response thought to be the cause of their syncope were included in this study.

Data collection and patient follow-up

The included patients had undergone head-up tilt table testing (70°, 45 min) with continuous, beat-to-beat blood pressure and heart rate monitoring using photoclamp-plethysmography or direct measurement through femoral artery catheterization when the tilt table testing was done in conjunction with an electrophysiologic study. Results were entered into a longitudinal syncope database. Charts and tilt reports of included patients were reviewed. Up to 2 letters were mailed to patients requesting permission to contact them by telephone for follow-up information, in accordance with the Health Insurance Portability and Accountability Act of 1996 and institutional policy. After patients gave permission, they were contacted by telephone for follow-up information using an institutional review board—approved telephone script, and results were entered into a database. Statistical analysis was performed with the help of a statistician.

Statistical analysis

Baseline and tilt data were analyzed using a Wilcoxon signed rank test. Significance was defined as $P < 0.05$.

Results

Patient demographics

In total, 15 patients had a positive vasovagal response that was thought to be the cause of syncope. Their baseline characteristics are summarized in Table 1.

Hemodynamic responses to tilt table testing

In total, 15 patients underwent tilt table testing (Table 2). Thirteen patients underwent electrophysiologic studies that yielded either normal findings or abnormal findings insufficient to account for syncope (Table 3). One patient was excluded from hemodynamic analysis because the diagnosis was made using an isoproterenol challenge rather than passive tilt. Hemodynamic responses of the remaining 14 during tilt table testing are summarized in Table 4. Mean duration to positive response was 17.6 ± 12.7 min. Cardioinhibitory responses (pauses >3 sec or heart rate <40 beats/min for ≥10 sec) were not observed in this patient subset. Five patients were classified as having a mixed type of response (>10% decrease in heart rate without a cardioinhibitory response), and nine were classified as having a vasodepressor type of response (≤10% decrease in heart rate). Tracings of these types of vasovagal responses are provided in Fig. 1.

Therapy and other associated clinical observations

Owing to the clinical complexities of these patients and their multiple comorbidities, most patients were treated conservatively with adjustment and titration of medication dosages (in 1 patient, use of isosorbide

Table 1 Clinical characteristics of study patients ($N = 15$)

Characteristic	Value*
Age, years	70.1 ± 12.2
Sex	
Male	9 (60%)
Female	6 (40%)
Ejection fraction (%)	27.7 ± 7.1
Cardiac comorbidities	
Coronary artery disease	8 (53%)
Dilated cardiomyopathy	3 (20%)
Coronary artery bypass graft	1 (7%)
Restrictive heart disease	1 (7%)
Chronic obstructive pulmonary disease	1 (7%)
Medications	
β-Blockers	4 (27%)
Digoxin	3 (20%)
Nitrates	2 (13%)
Diuretics	8 (53%)

*Continuous data are presented as mean ± SEM; categorical data as number and percentage of patients

dinitrate was discontinued after subsequent episodes of syncope) and use of compression stockings. Since they already had poor cardiac function, few patients were encouraged to increase fluid and salt intake and no patients were prescribed α-agonists (i.e., midodrine). Permanent pacemakers were subsequently implanted in 2 patients after atrioventricular nodal ablation procedures and in 2 patients for a suspected propensity for bradyarrhythmias. Implantable cardioverter-defibrillators were not used in any of these patients, because the inducible ventricular arrhythmias during the electrophysiologic study were not thought to be responsible for the clinical syncope.

Follow-up

Two patients were deceased at the time of follow-up. Of the remaining 13 patients, 5 did not respond to letters requesting a follow-up telephone interview. Follow-up analysis was performed on information from the 8 patients who participated in the telephone interview (Table 5).

Discussion

In a longitudinal epidemiologic study, syncopal episodes occurred in approximately 3% of men and 3.5% of women [19]; at initial presentation, the mean age was 52 years for men and 50 for women. In another study, recurrent syncopal episodes of any type were noted in approximately 35% of patients at 3-year follow-up [12]. Sheldon et al. [21] observed that the probability of remaining free of VVS recurrences decreased over time, such that only 51% were free of recurrences at 3 years. Although recurrences were common in VVS patients, mortality was very low, approaching 0% at the time of follow-up [22].

The patients' clinical characteristics and the outcomes described in the present study differ from those in previous investigations. First, the patients in our study were substantially older at initial presentation, with a mean age >70 years, and were predominantly male. Second, these patients had more cardiovascular comorbidities than patients in previous studies. Third, clearly documented recurrences were noted in only 2 of 8 patients (25%) in whom follow-up data were obtained, yet mortality was greater (12%). A permanent pacemaker was implanted in 1 patient following a recurrent syncopal episode.

Diagnosis and management of VVS are challenging in this group of patients. First, the advanced age and multiple comorbidities make primary cardiac or alternative and additional vascular causes for syncope likely. Second, the historical elements in this age group are frequently lacking, inconsistent, or insufficient to diagnose VVS. A recent study suggests that diagnosis based on history alone was possible in only 5% of patients older than 65 years, compared with 26% of younger syncope patients [6]. This frequently necessitates the use of aggressive diagnostic testing (electrophysiologic studies in addition to tilt table testing). Third, common treatments used for younger, healthier patients with VVS are frequently contraindicated in this subset. Specifically, increased consumption of water and liberalization of salt intake are not recommended owing to the risk of decompensated heart failure. Fourth, the role of cardiac pacing in VVS is an area of active research and discussion [2, 4, 5, 24]. At this time, however, it is not recommended as first-line therapy and should be reserved for severe and refractory cases in patients with documented bradycardia. Our approach centers around robust patient education (understanding and avoiding triggers, recognition of prodrome, and rapid patient response to prevent syncope and associated trauma), compression stockings, and, in some patients, orthostatic training.

The main limitations of this study are the relatively small cohort size and the limitations inherent to a retrospective review of clinical information. Also, because the cause of syncope in the elderly is often multifactorial, causality is difficult to establish (although it is striking that a vasovagal response was induced in more than 10% of this study cohort). Additionally, many patients were using vasodilators and other cardiac medications, and a drug-provoked vasovagal reaction or response to ischemia induced by tilt cannot be excluded. It should be noted that although drug-induced orthostatic intolerance is

Table 2 Results from tilt table testing

Patient	Indication	Response to CSM	Vasodepressor syncope
1	Near syncope/syncope	Normal	+
2	Syncope/NSVT	Vasodepressor	+
3	Syncope	Mixed CI, vasodepressor	+
4	Syncope	Normal	+
5	Syncope/NSVT	...	+
6	Near syncope	Vasodepressor	+
7	Syncope	...	+
8	Syncope	Normal	+
9	Syncope	Normal	+
10	Syncope	Normal	+
11	Near syncope	Normal	+
12	Syncope	...	+
13	Near syncope/syncope/conduction disease	Normal	+
14	Near syncope/syncope	...	+
15	Syncope	Normal	+

CI, cardioinhibitory; CSM, carotid sinus massage; NSVT, non-sustained ventricular tachycardia; +, yes

Table 3 Results from electrophysiologic testing in 13 patients

Patient	Indication	Antiarrhythmics	Sinus node function	AV node function	His-Purkinje system function	Inducible supraventricular arrhythmia	Inducible ventricular arrhythmia
1	Near syncope/syncope	0	Normal	Normal	Normal	0	0
2	Syncope/NSVT	0	Normal	Normal	Moderately abnormal	Sustained atrial flutter	0
3	Syncope	0	Normal	Normal	Normal	0	Polymorphic VT (poorly tolerated)
5	Syncope/NSVT	0	Normal	Abnormal	Mildly abnormal	Sustained AF	Polymorphic VT (poorly tolerated)
6	Near syncope	β-Blocker, digoxin	Normal	Normal	Normal	0	0
7	Syncope	β-Blocker	Normal	Normal	Normal	0	0
8	Syncope	Amiodarone	Normal	Abnormal	Moderately abnormal	0	0
9	Syncope	Digoxin	Normal	Normal	Mildly abnormal	...	Monomorphic VT (well tolerated)
10	Syncope	0	Normal	Normal	Mildly abnormal	0 (dual AV physiology)	VF
11	Near syncope	0	Normal	Normal	Normal	0	Polymorphic VT (poorly tolerated)
12	Syncope	0	Abnormal	Abnormal	...	...	0
13	Near syncope/ syncope/conduction disease	0	Normal	Normal	Normal	0	Polymorphic VF (poorly tolerated)
15	Syncope	0	Normal	Abnormal	Normal	0	0

AF, Atrial fibrillation; AV, atrioventricular; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; 0, no

Table 4 Hemodynamic responses of 14 patients during tilt table testing

Variable	Baseline supine	Vasovagal response during tilt	*P*-value
Cycle length, mean ± SEM (msec)	828.5 ± 146	1,001.1 ± 254.5	0.04
Blood pressure, mean ± SEM (mm Hg)			
Systolic	131 ± 15.5	60.7 ± 9.5	<0.001
Diastolic	62.9 ± 6.9	31.4 ± 5	<0.001

Table 5 Follow-up data

Patient	Number of follow-up calls	Number of syncopal episodes	Number of presyncopal episodes	Palpitations or other symptoms*	Pacemaker placed*	Cardiac surgery*
1	3	0	0	0	0	0
2	3	0	0	+	+	0
3	7	0	0	+	+	+
4	7	1	1	+	+	0
5	3	0	0	0	+	+
6	5	0	0	0	0	0
7	3	0	11	+	0	0
8	2	0	0	0	0	0

*Plus sign indicates ''yes''; Zero indicates ''no''

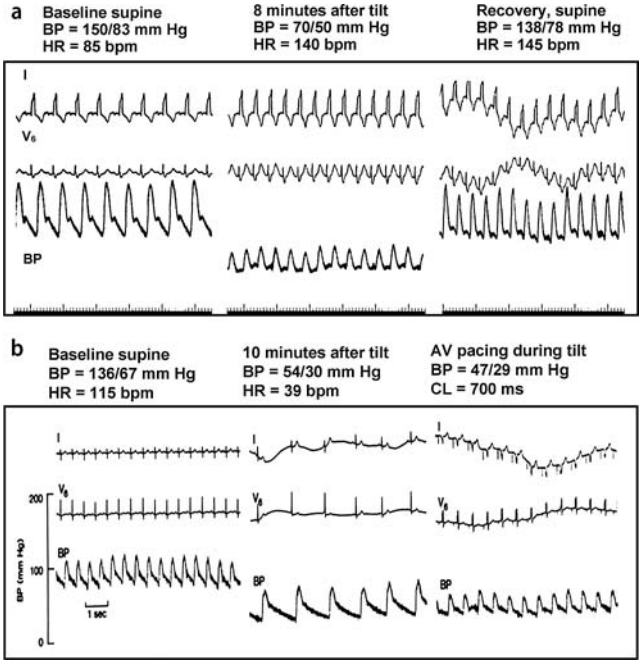

Fig. 1 Examples of tracings from tilt table testing. *A*, Vasodepressor type of response. *B*, Mixed type of response. AV, atrioventricular; BP, blood pressure; bpm, beats per minute; CL, cycle length; HR heart rate. (From Chen LY, Shen W-K. Neurocardiogenic syncope: latest pharmacological therapies. Expert Opin Pharmacother. 2006; 7:1151–1162. Used with permission.)

common in the elderly, the vasovagal responses seen in this study are quite distinct (mean duration from tilt to positive symptoms was >15 min).

Despite these limitations, this study provides evidence that a vasovagal response is inducible in patients with severe cardiac dysfunction. Although the precise explanation for the absence of a clinically significant cardioinhibitory response in this population is unknown, further investigation into the sympathovagal interaction may provide a mechanistic explanation of this interesting observation, especially because sympathovagal imbalance is so common in elderly patients and those with severe cardiac dysfunction. The pathophysiology of the vasovagal response is complex and incompletely described by the Bezold–Jarisch reflex. It is possible that other mechanisms, including coronary baroreceptors and alternative neurohormonal pathways [16], predominate in this population. Further investigation is needed to elucidate the specific mechanism(s) of VVS in this complex group of patients.

Conclusions

Despite previous suggestions to the contrary, vasovagal responses can be induced by tilt table testing in patients with severe cardiac dysfunction. Thus, VVS should be considered in the differential diagnosis of such patients undergoing evaluation for unexplained syncope. In this group, the most common type of mechanism of VVS is vasodepressor, followed by mixed. Cardioinhibitory responses were not observed. Outcomes were almost uniformly poor for this cohort.

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