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The Role of the Baroreflex in Tilt Table Testing

Outcome and Type of Response

Ashish Chaddha, MD, Kevin E. Wenzke, MD, Michele Brignole, MD, Stephen L. Wasmund, PhD, Richard L. Page, MD, Mohamed H. Hamdan, MD, MBA

ABSTRACT

OBJECTIVES The purpose of this study was to better understand the role of the baroreflex in tilt-induced vasovagal syncope (VVS).

BACKGROUND The role of the baroreflex in tilt-induced VVS remains controversial. The authors hypothesized that: 1) patients with positive tilt table test (TTT) results have greater baroreflex gain (BRG) compared with patients with negative TTT results; and 2) patients with tilt-induced asystole have greater BRG compared with patients without asystole.

METHODS Using the sequence method, BRG measurements were obtained in 438 consecutive patients undergoing TTT. Two hundred sixty-eight patients (61%) had positive TTT results (mean age 50 ± 21 years; 34% men), and 170 patients (39%) had negative TTT results (mean age 48 ± 21 years; 35% men).

RESULTS Mean BRG was significantly higher in patients with positive TTT results compared with those with negative TTT results (12.9 ± 6.0 ms/mm Hg vs. 11.5 ± 6.0 ms/mm Hg; $p = 0.01$). Among the 268 patients with positive TTT results, 23 (9%) had more than 3 s of asystole (mean age 37 ± 17; 30% men), and 245 patients had a mixed vasodepressor or cardioinhibitory response without asystole (mean age 51 ± 17 years; 34% men). Mean BRG was greater in patients with tilt-induced asystole (>3 s) compared with patients without asystole (15.3 ± 5.9 ms/mm Hg vs. 12.7 ± 5.9 ms/mm Hg; $p = 0.03$).

CONCLUSIONS The results of this study demonstrate that baseline BRG was higher in patients with positive TTT results compared with those with negative TTT results, with greater values noted in patients with tilt-induced asystole (>3 s) compared with those without asystole. (J Am Coll Cardiol EP 2016;2:812–7) © 2016 by the American College of Cardiology Foundation.

Syncope is a common clinical problem affecting up to 3.5% of the population (1). Vasovagal syncope (VVS) is one of the most frequent types of syncope, accounting for 30% of all cases (1). Clinically, VVS is characterized by the development of autonomic symptoms such as warmth and nausea when exposed to a known trigger, followed by lightheadedness and loss of consciousness. Despite its high prevalence, the pathophysiology and treatment of VVS are poorly understood.

Several studies have suggested a role for the cardiovascular reflexes in the pathophysiology of VVS, leading to increased vagal tone and/or peripheral sympathetic withdrawal (2). Some studies have shown impairment in the baroreflex, whereas others have shown an increase or no change in baroreflex function in patients with VVS (3–8). Furthermore, in patients with positive tilt table test (TTT) results, the role of the baroreflex in predicting the type of response remains poorly understood.

From the Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin. This work was supported in part by funds provided from the Mildred and Marv Conney Chair in Cardiology. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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The purpose of this study was to better understand the role of the baroreflex in tilt-induced VVS. We hypothesized that: 1) patients with positive TTT results have greater baroreflex gain (BRG) compared with those with negative TTT results; and 2) patients with a significant tilt-induced cardioinhibitory response (i.e., >3 s of asystole) have greater BRG compared with those with a mixed vasodepressor or cardioinhibitory response without asystole.

METHODS

This was a retrospective study performed on patients presenting to a specialized "faint and fall clinic" at the University of Wisconsin. The study was approved by the Institutional Review Board. We examined the records of 482 consecutive patients referred for TTTs between March 2013 and February 2015 for further evaluation of syncope. Inclusion criteria included referral for TTT for further evaluation of syncope. Exclusion criteria included patients with positive TTT results for delayed orthostatic hypotension as defined by the Heart Rhythm Society and European Society of Cardiology (9,10) (n = 15) and the presence of cardiac pacing or atrial arrhythmias prior to tilt testing (n = 29). Four hundred thirty-eight patients met the inclusion criteria and none of the exclusion criteria and formed the cohort for this study.

DATA COLLECTION AND ANALYSIS. The medical record was reviewed to collect patients' baseline characteristics, including age, sex, and cardiac history. BRG was measured prior to the TTT in the supine position using the sequence method. The analysis involved the identification of spontaneous changes in blood pressure (BP) and heart rate (HR) that are mediated by the arterial baroreflex. Specifically, the computer identifies spontaneously occurring sequences of consecutive beats in which progressive increases in systolic BP of at least 1 mm Hg/beat for at least 3 consecutive heartbeats are followed by a progressive lengthening in RR intervals of at least 4 ms/beat. Similarly, the computer seeks to identify progressive decreases in systolic BP followed by progressive shortening in RR intervals (11,12). The slope of the relationship between systolic BP and RR changes for all identified sequences is averaged and used as an index of the sensitivity of arterial baroreflex modulation of HR. HR decreases and increases following spontaneous increases and decreases in BP have been shown to be the result of vagal activation and withdrawal, respectively, thus making BRG a reliable measure of vagal control of HR. Beat-to-beat noninvasive BP and HR monitoring and subsequent BRG calculations were performed using the Task Force Monitor (CNSystems, Graz, Austria). The investigator analyzing the data was not blinded to tilt results, but the process used in the data acquisition was automated through the Task Force Monitor.

TILT TEST PROTOCOL. Tilt table testing took place in a dedicated procedure room that is staffed by a clinical nurse and an advanced practice provider. Patients were asked to lie down in the supine position for the placement of the chest electrodes, BP monitoring system, and intravenous access. After ensuring the proper function of the monitoring equipment, patients rested for another 10 to 15 min before the acquisition of the BRG measurements. Once the BRG measurements were completed, the table was tilted to 70°. If VVS did not occur after 20 min, patients received 0.3 mg of sublingual nitroglycerin. The test was then continued for another 10 min. The type of response was determined using the modified VASIS (Vasovagal Syncope International Study) classification, which consists of type 1 (mixed), type 2A (cardioinhibitory without >3 s of asystole), type 2B (cardioinhibitory with >3 s of asystole), or type 3 (vasodepressive) (13).

STATISTICAL ANALYSIS. The study data were analyzed using basic Student *t* tests or rank sum tests, as appropriate on the basis of normality, to determine if there was a statistically significant difference in BRG values between subjects who had positive and negative TTT results. Among subjects who had positive tilt test results, Student *t* tests or rank sum tests were used to determine if there was a significant difference in BRG values between those who had a cardioinhibitory response with >3 s of asystole (i.e., VASIS type 2B) and those with a mixed vasodepressor or cardioinhibitory response without asystole. Chi-square tests were used to determine if proportions in the various categories were different. Multiple logistic regression analyses with stepwise selection were performed to assess the independent roles of age, BRG, diabetes mellitus (DM), and hypertension (HTN) in predicting tilt outcomes. A p value <0.05 was considered to indicate statistical significance. All study data are expressed as mean ± SD. Analyses were performed using SigmaPlot (Systat Software, San Jose, California).

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
BRG = baroreflex gain
DM = diabetes mellitus
HR = heart rate
HTN = hypertension
LBNP = lower-body negative pressure
TTT = tilt table test
VVS = vasovagal syncope

TABLE 1 Patient Characteristics

	Negative TTT Result (n = 170)	Positive TTT Result (n = 268)
Mean age (yrs)	48 ± 21	50 ± 21
Male/female	59/111	90/178
Mean EF (%)	65 ± 7	64 ± 7
Diabetes	19 (11)*	14 (5)
Hypertension	39 (23)	69 (26)
Heart failure	0 (0)	4 (1)
Prodromes present	107 (63)	172 (64)
Multiple events	44 (26)	85 (32)
Autonomic symptoms	82 (48)	117 (44)
Medications		
Beta-blockers	45 (26)	55 (21)
Ca^{++}-channel blockers	8 (5)	4 (1)
Antiarrhythmic drugs	0 (0)	3 (1)

Values are mean ± SD or n (%). *p < 0.05 versus positive TTT result.
EF = ejection fraction; TTT = tilt table test.

RESULTS

PATIENT CHARACTERISTICS. The mean age was 49 ± 20 years, and 34% of patients were men. Two hundred sixty-eight patients (61%) had positive TTT results (mean age 50 ± 21 years; 34% men), and 170 patients (39%) had negative TTT results (mean age 48 ± 21 years; 35% men). The clinical characteristics of patients with positive TTT results were not significantly different from those of patients with negative TTT results, except for a lower prevalence of DM (5% vs. 11%; p < 0.05). A summary of selected patient characteristics is provided in Table 1.

Among the 268 patients with positive TTT results for VVS, 23 (9%) had >3 s of asystole (type 2B), and 245 patients (91%) had a mixed (type 1; n = 156) cardioinhibitory without asystole (type 2A; n = 9) or vasodepressor response (type 3; n = 80). Patients with type 2B response were younger (37 ± 17 years vs. 51 ± 17 years; p < 0.01), with a lower prevalence of HTN compared with the other groups, albeit not significant. Furthermore, none were on beta-blockers, compared with 17%, 33%, and 31% of patients with types 1, 2A, and 3 responses, respectively. A summary of patients' clinical characteristics among these subgroups is shown in Table 2.

TABLE 2 Patient Characteristics: Positive TTT Results

	Type 2B (n = 23)	Type 2A (n = 9)	Type 1 (n = 156)	Type 3 (n = 80)	Types 2A, 1, and 3 Combined (n = 245)	p Value, Type 2B vs. Types 2A, 1, and 3 Combined
Mean age (yrs)	37 ± 17*	49 ± 17	47 ± 19*	58 ± 22	51 ± 17	<0.01
Male/female	7/16	3/6	53/103	27/53	83/162	0.92
Mean EF (%)	65 ± 3	65 ± 3	64 ± 3	64 ± 6	64 ± 3	0.16
Diabetes	0%	0%	5%	8%	5%	0.49
Hypertension	9%	22%	23%	36%	26%	0.09
Heart failure	0%	0%	1%	3%	1%	0.78
Medications						
Beta-blockers	0%	33%	17%	31%	21%	0.02
Ca^{++}-channel blockers	0%	0%	1%	4%	1%	0.78
Antiarrhythmic drugs	0%	0%	0%	4%	1%	0.62

Values are mean ± SD, n, or %. P values are provided comparing type 2B response with all non-type 2B responses. *Dunn's post hoc comparison differs from type 3 response.
Abbreviations as in Table 1.

BRG AND TILT-INDUCED VVS. Mean BRG was significantly higher in patients with positive TTT results compared with those with negative TTT results (12.9 ± 6.0 ms/mm Hg vs. 11.5 ± 6.0 ms/mm Hg; p = 0.01). The median values were 11.8 ms/mm Hg (range: 3.0 to 34.7 ms/mm Hg) in the tilt-positive group and 10.2 ms/mm Hg (range 1.5 to 30.4 ms/mm Hg) in the tilt-negative group. In patients with a significant cardioinhibitory response (i.e., type 2B), mean BRG was higher compared with those with positive TTT results but no asystole (i.e., types 1, 2A, and 3 combined) (15.3 ± 5.9 ms/mm Hg vs. 12.7 ± 5.9 ms/mm Hg; p = 0.03). The median values were 14.8 ms/mm Hg (range 6.0 to 27.3 ms/mm Hg) and 11.5 ms/mm Hg (range 3.0 to 34.7 ms/mm Hg), respectively. A summary of the BRG measurements in all groups is provided in Table 3.

Subgroup analysis including only patients with drug-free induced syncope (i.e., tilt positive without nitroglycerin) revealed even greater differences that remained statistically significant. Mean BRG in the drug-free tilt-positive patients (n = 61) was 14.6 ms/mm Hg compared with 11.5 ms/mm Hg in the tilt-negative group (n = 170) (p = 0.001). In the type 2B group (n = 11), mean BRG was 18.6 ms/mm Hg compared with 13.7 ms/mm Hg in patients with positive TTT but no asystole (n = 50) (p = 0.01).

Because drugs can have an impact on BRG measurements, we also performed subgroup analysis after the exclusion of all patients taking medications (i.e., 57 patients from the tilt-positive group and 51 patients from the tilt-negative group). Mean BRG was 13.5 ms/mm Hg in the tilt-positive group (n = 211) and 11.7 ms/mm Hg in the tilt-negative group (n = 119) (p = 0.005). In the type 2B group (n = 23), mean BRG was 15.3 ms/mm Hg compared with 13.2 ms/mm Hg in patients with positive TTT results but no asystole (n = 188) (p = 0.11).

AGE, BRG, AND TILT RESPONSE. Patients with an asystolic response had a lower mean age compared with those with a vasodepressor response (37 ± 17

TABLE 3 BRG Values Among All TTT Groups

	All TTTs (n = 438)			Positive TTT Results (n = 268)					
	Negative TTT Results (n = 170)	Positive TTT Results (n = 268)	p Value	Type 2B (n = 23)	Type 2A (n = 9)	Type 1 (n = 156)	Type 3 (n = 80)	Types 2A, 1, and 3 Combined (n = 245)	p Value, Type 2B vs. Types 2A, 1, and 3 Combined
BRG	11.5 ± 6	12.9 ± 6	0.01	15.3 ± 5.9*	14 ± 5.3	13 ± 5.8	11.8 ± 6.1	12.7 ± 5.9	0.03

*Dunn's post-hoc comparison differs from type 3 response (p = 0.04).
BRG = baroreflex gain; TTT = tilt table test.

years in type 2B vs. 58 ± 22 years in type 3; $p < 0.05$). Furthermore, patients with a mixed response were also younger than patients with a vasodepressor response (47 ± 19 years in type 1 vs. 58 ± 22 years in type 3; $p < 0.05$). Therefore, it appears that there is a relationship between age and type of response, with a decrease in the prevalence of tilt-induced asystole and an increase in the prevalence of mixed and vasodepressor responses in older patients.

A similar relationship was also noted between BRG and type of tilt response. Patients with an asystolic response had higher BRG than patients with a vasodepressor response (15.3 ± 5.9 ms/mm Hg in type 2B vs. 11.8 ± 6.1 ms/mm Hg in type 3; $p < 0.05$). In addition, patients with a mixed response had a higher BRG than patients with a vasodepressor response, albeit not statistically significant (13 ± 5.8 ms/mm Hg in type 1 vs. 11.8 ± 6.1 ms/mm Hg in type 3; $p = 0.06$). Therefore, it appears that there is also a relationship between BRG and type of tilt response, with greater BRG values noted in patients with tilt-induced asystole and lower BRG values noted in patients with mixed and vasodepressor responses.

To better understand the relationship among age, BRG, and other variables such as DM and HTN in predicting tilt outcome, we performed a multiple logistic regression analysis including age, BRG, DM, and HTN. The results showed that BRG ($p = 0.03$) and DM ($p = 0.04$) were independent predictors of tilt outcome and that age ($p = 0.002$) was an independent predictor of the type of response (i.e., type 2B vs. positive TTT result without asystole).

DISCUSSION

The main findings of our study are that: 1) patients with positive TTT results for VVS have higher BRG compared with those with negative TTT results; 2) patients with tilt-induced asystole have higher BRG compared with those with positive TTT results but without asystole; and 3) BRG and age are independent predictors of tilt outcome and type of response, respectively, with a higher prevalence of mixed and vasodepressor responses and lower BRG values noted in older patients compared with younger patients. To our knowledge, this is the largest study to assess the role of BRG in determining tilt outcome and type of response in patients with syncope.

THE ROLE OF THE BAROREFLEX IN VVS. The role of the baroreflex in tilt-induced VVS remains controversial (2,6,14–22). Some studies have suggested reduced baroreflex function (6,17,22), whereas others have shown an increase (14,19,20) or no change in BRG in patients with VVS (15,16,18,21).

Using the sequence method, Iacoviello et al. (6) noted a decrease in BRG immediately before syncope in patients who received nitroglycerin compared with those with negative TTT results, suggesting impairment in the arterial baroreflex as a contributing factor. Mitro et al. (23) measured baroreflex sensitivity during tilt table testing in 51 patients with histories of syncope. Similar to the study by Iacoviello et al., the investigators found no differences in baseline values and during passive head-up tilt before syncope. At the time of syncope, however, baroreflex sensitivity was lower in tilt-positive patients compared with tilt-negative patients. Although the absolute values were not statistically significant, the baroreflex sensitivity ratio, defined as the ratio of the actual value to the baseline value, was significantly lower at the time of syncope in tilt-positive patients compared with tilt-negative patients (0.54 ± 0.27 vs. 0.72 ± 0.35, $p = 0.03$). This decrease coincided with lower cardiac output, suggesting inability to vasoconstrict as a contributing factor to the observed hypotension. Interestingly, the investigators found no difference in BRG in the absence of pharmacological challenge. Our group previously evaluated the sympathetic response in subjects with and without lower-body negative pressure (LBNP)-induced pre-syncope. We found attenuation in reflex sympathoexcitation in patients with pre-syncope during low-level LBNP (−10 mm Hg), with no difference during high-level LBNP (−60 mm Hg), suggesting possible impairment of the cardiopulmonary baroreflex in the setting of a preserved arterial baroreflex (8). Similarly, Bechir

et al. (3) showed that patients with histories of VVS had a blunted sympathetic response during LBNP and reduced baroreceptor sensitivity both at rest and during orthostatic stress.

Sneddon et al. (21) found no difference in baroreflex sensitivity in patients with VVS compared with a control group. The investigators noted that baroreflex sensitivity in patients with a cardioinhibitory response was not significantly different than in those with a vasodepressor response. In another study including patients with syncope, the same group found that patients with positive TTT results had an augmented cardiopulmonary baroreflex. During low-level LBNP (−5, −10, and −20 mm Hg), patients with positive TTT results had a significantly greater increase in forearm vascular resistance compared with those with negative tilt test results ($p < 0.001$) (24).

There are several potential reasons for the conflicting findings regarding the role of the baroreflex in VVS, including the methods used to induce orthostatic stress (i.e., tilt table testing vs. LBNP) and the methods used to measure baroreflex sensitivity, such as the Oxford technique (25), the sequence method, or direct measurements of sympathetic nerve activity using microneurography. In addition, the subjects enrolled varied among the studies, including healthy subjects and patients with atypical and typical histories of VVS.

PRESENT STUDY. In the present study, we used the sequence method to assess BRG because it is easily available and does not require vasoactive agents. Our findings of increased BRG in patients with positive TTT results compared with patients with negative TTT results suggest the presence of an exaggerated HR response for given change in BP. In addition, we found that patients with tilt-induced asystole had a higher gain compared with those with positive TTT results but without asystole. This finding suggests that there might be a role for the baroreflex in predicting asystole in patients with suspected VVS. This hypothesis, however, remains to be proved.

We have also made the observation of a relationship between age, BRG, and tilt outcome, including the type of response. It appears that as we get older, we are more likely to have a mixed or vasodepressor response compared with younger patients, who are more prone to tilt-induced asystole. We also found a similar relationship between BRG and the type of tilt response, with higher BRG values noted in patients with cardioinhibitory responses and lower BRG values noted in patients with mixed and vasodepressor responses, suggesting a shift from cardioinhibition to a mixed or vasodepressor response as BRG decreases. Gribbin et al. (26) showed decades ago that increased age was associated with reduction in baroreflex sensitivity. Our findings of the relationship between BRG and tilt outcome highlight the importance of performing additional work in this area to better understand the pathophysiology of VVS, particularly in older patients, and the clinical implications vis-à-vis cardiac pacing.

STUDY LIMITATIONS. First, this was a retrospective study with all the intrinsic limitations associated with such analysis. Second, we compared BRG in patients with positive and negative TTT results for VVS. Our results may not apply to patients with spontaneous VVS, as tilt-induced events might be different from clinical events. Third, we did not have a control group including patients without histories of syncope. However, it was not the intent of this study to assess BRG in patients with VVS compared with those with no histories of syncope. Our goal was to assess differences in BRG in patients with positive TTT results compared with those with negative TTT results, recognizing the limitations of this test. Fourth, some patients were taking medications that could have an effect on BRG measurements. Subgroup analysis, however, revealed an even greater difference in tilt-positive patients compared with tilt-negative patients after the exclusion of patients taking medications. Fifth, our findings represent the experience of a single academic medical center. Even though this study consisted of a large number of patients, our experience may differ from others.

CONCLUSIONS

Our results demonstrate that patients with positive TTT results have greater BRG compared with those with negative TTT results, with higher values noted in patients with a significant cardioinhibitory response compared with those without asystole. Furthermore, we found a relationship between age, BRG, and tilt response, with a greater propensity for a vasodepressor response noted in older subjects that seems to be linked to a decrease in BRG.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Mohamed H. Hamdan, Division of Cardiovascular Medicine, University of Wisconsin, H4/534 Clinical Science Center, 600 Highland Avenue, Madison, Wisconsin 53792-3248. E-mail: mhamdan@medicine.wisc.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: BRG plays a role in determining TTT results, including the type of response. Older patients have lower BRG and a greater propensity for a vasodepressor response.

TRANSLATIONAL OUTLOOK: Additional studies are needed to determine the role of BRG in predicting spontaneous asystole and the need for pacing in patients with VVS.

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