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Heart Rate and Blood Pressure Variability as Predictors for the Attacks in Patients with Neurocardiogenic Syncope

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ABSTRACT

Background: For a long time, researchers have employed head-up tilt to analyze how the heart and blood pressure react to different positions. The vasovagal reflex is responsible for the most prevalent type of reflex syncope, known as vasovagal syncope (VVS) or neurocardiogenic syncope.

Objective: The goal of teaching patients to notice prodromal symptoms and doing suitable physical counter-maneuvers (PCMs) to increase blood pressure in order to prevent or postpone attacks is to reduce the likelihood of future attacks.

Patients and methods: In a case-control study, fifty-seven subjects were enrolled in the study. Thirty-five patients were in 1st case group with recurrent history of presyncope or syncope and positive tilt test. Twenty-two age matched healthy subjects were in 2nd control group. All underwent head up tilt testing (HUTT).

Results: there was a statistical significance increase in LF power during P2 in cases compared to controls and also significant increase in LF/HF ration in P1 and P2 reflecting the high sympathetic predominance just preceding the episode of syncope**.** The magnitude of effect of LFP2, LF/HF at rest and Δ LF between P2 and P1, Δ LF/HF between P1 and R was high denoting the rapid autonomic alteration resulting from postural and stressful conditions preceding the occurrence of syncope. **Conclusion:** Variability in heart rate provides information about the autonomic nervous system's health (ANS). How much the heart rate (HR) varies tells us about how well the nervous system regulates the heart rate and how quickly the heart can react to external stimuli.

Key words: Heart Rate, Blood Pressure, Variability, Neurocardiogenic Syncope.

INTRODUCTION

The overall lifetime prevalence of syncope in the population is close to 20%, making it a prevalent clinical condition. Syncope becomes more common as people get older, with a noticeable spike beyond age 70**(1).**

Extreme lightheadedness, visual disturbances like "tunnel vision" or "greying out," and varying degrees of altered consciousness without total loss of consciousness are all indications of presyncope, which occurs before syncope. You may experience syncope, or it may end before that happens**(1).**

Cardiac, orthostatic, and neurogenic syncope are the most common types, however other causes, such as carotid sinus hypersensitivity, situations, and vasovagal collapse, are also considered causes of syncope. Those over the age of 65 are more likely to experience orthostatic, carotid sinus hypersensitivity, or cardiac syncope, whereas those under the age of 35 are more likely to experience vasovagal syncope. Besides neurally mediated and orthostatic syncope, patients who report with syncope have an elevated risk of death **(2).**

Recognizing prodromal symptoms and learning how to use physical counter-maneuvers (PCMs) that raise blood pressure (such crossing legs, sitting, crouching, hand gripping, and arm tensing) to prevent or postpone attacks is the focus of education. Physical activity (lower body isometrics, rowing), as well as standing training, may reduce vulnerability over the long run. Patients should also be informed of factors that put them at higher risk for an adverse outcome **(3).**

Studies of how the heart and blood pressure react to shifts in position have long made use of head-up tilt (HUT). As a side effect of the testing, some participants lost consciousness completely or nearly completely for a short period of time, and in other cases, hypotension was accompanied by a sudden, profound bradycardia consistent with a vasovagal syncope (VVS) reaction**(4).**

Only in cases where patient hydration and physical interventions have failed can pharmaceutical management of reflex syncope (and especially vasovagal syncope) be considered. Midodrine and fludrocortisone, a mineralocorticoid that retains salt, are the only treatments that have shown any promise **(5).**

The purpose of this research was to teach patients how to recognize prodromal symptoms and how to do physical counter-maneuvers (PCMs) to raise blood pressure, which can prevent or postpone attacks.

PATIENTS AND METHODS

We performed our study in Zagazig University Hospitals Autonomic Laboratory. during the period from February 2019 to February 2020. Fifty-seven subjects were enrolled in the study:

The studied population was classified into two groups:

Group 1 (Cases): This included 35 patients with recurrent history of presyncope or syncope and positive tilt test.

Group 2 (controls): Twenty-two age matched healthy subjects.

Inclusion Criteria: Patients who had: (1) Having experienced syncope twice before. (2) One syncopal episode and four or more presyncopal episodes. (3) Single occurrence of syncope leading to catastrophic harm.

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Exclusion criteria: (1) Patients suffering from heart failure or structural heart disease. (2) Evidence of bifascicular block or ventricular tachycardia. (3) Adrenoceptor-blocking medications, disopyramide, and anticholinergics were contraindicated in patients. (4) Individuals suffering from liver or kidney failure. (5) Patients with severe anemia. (6) Patients with diabetes and peripheral neuropathy. (7) Patients with recent stroke (within 7 days). (8) Patents with metabolic acidosis or electrolyte imbalance.

Methods:

All individuals signed a written consent and were subjected to:

1) **Complete thorough history taking and physical examination.**
2) **Scoring using Calgary Score.**

   For the diagnosis of vasovagal syncope (VVS) in younger populations without evidence of structural cardiac disease, a simple point score of history features, the Calgary Syncope Symptom Score (CSSS), has been validated as having high sensitivity and specificity. The Calgary Score is a set of seven diagnostic questions about transient loss of consciousness (TLoC)-related factors, including patient history, triggers, circumstances, and symptoms. A yes or no answer is given to every inquiry. Points are awarded or deducted based on whether a yes answer decreases or increases the risk of VVS. The final score (from -6 points to +6 points) is calculated by adding up the scores from each question. A Calgary Score diagnosis of VVS is obtained if the total score is -2 or above.
3) **Laboratory parameters:** Complete blood count, liver and kidney function, serum electrolytes, and thyroid function tests.
4) **ECG:** Twelve lead standard surface ECG was done to exclude channelopathies, ectopic beats, ischemia, chamber enlargement.
5) **Echocardiography**: 2D, M mode and Doppler echo data was done to look for and exclude cardiomyopathies, ischemic heart disease and complications, significant valvular heart disease as well as adult congenital heart disease, LV dimensions and both systolic and diastolic functions were assessed.
6) **Head up tilt table test with Holter monitor device** attached to the patient (VX3 Digital ECG Recorder, USA 2007).

   Preparation prior to tilt testing:

   Ensure the patient is dressed in a hospital gown that does not have any tight bindings at the patient's waist or legs. Secure the patient in a supine position on the tilt table using the safety straps. Perform a series of baseline measurements, including blood pressure, heart rate, oxygen saturation, and rhythm. Set up your Holter monitor and begin recording. The patient should lie down in a supine position for 5 minutes. Make sure the space is calm, dim, and warm enough. Tilt the table all the way up to a maximum of 80 degrees. Take readings of vitals including blood pressure, heart rate, and oxygen saturations continuously for an hour. For 20 minutes, the table should be propped up. If there are any changes in rhythm, write them down on the ECG chart. After 20 minutes of tilt, decide if pharmacologic stimulation with nitroglycerine is required to elicit a reaction. In the next 20 minutes, make a note of any symptoms or indicators we notice. When the systolic blood pressure drops below 70 mmHg, even in the absence of symptoms, the tilt must be stopped. If the patient starts to feel dizzy, stop the tilt and lay them back down. If the patient's blood pressure does not stabilize, the reverse Trendelenburg position should be used. In cases of hypotension, a 250-mL bolus of 0.9% NaCl should be given. Keep track of your heart rate and blood pressure until they return to normal. You should unplug the patients and let them relax on the chair for five minutes.
7) **Reading the Holter recordings:**

   Data recorded were imported, with special concerns for the heart rate variability parameters during rest (R) and 20 minutes of upright passive tilt period 1 (P1) and the last 10 minutes just before termination of the test; period 2 (P2).

I- ***Time Domain parameters:*** Standard deviation of the IBI of normal sinus beats SDNN: measured in msec. PNN50: percentage of adjacent NN intervals that differ from each other by more than 50 msec. RMSSD: root mean square of successive differences between normal heart beat.

II- ***Frequency Domain parameters:*** Low frequency band (LF). High frequency band (HF). LF/HF ration. Total power: which is the sum of VLF, LF and HF in short term recordings.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

IBM's SPSS program (IBM Corp., Armonk, NY), version 20.0, was used to analyse the data submitted into the computer. To ensure a normally distributed sample, the Kolmogorov-Smirnov test was used. Quantitative data were presented as mean, standard deviation (SD), and range. Qualitative data were presented as frequency and percentage. P <5% was considered significant.

RESULTS

There were no statistically significant differences existed in demographics (age, sex makeup, HR, SBP, and DBP) across the groups **(Table 1).**

Table (1): Demographic and vital data of the studied groups

Variable		Group I (Cases) (n=35)	Group II (Control) (n=22)	P
Age: (year)	Mean ± SD Range	32 ± 7.6 20 - 45	31.5 ± 8.03 20 - 45	0.83
Sex:	Female N (%) Male N (%)	20 (57.1%) 15 (42.9%)	12 (54.5%) 10 (45.5%)	0.85
Supine HR (beat/min)	Mean ± SD Range	76.5± 12.17 55 - 96	71.9± 12.75 55 - 95	0.18
Supine SBP (mmHg)	Mean ± SD Range	115.9± 12.16 90 - 137	111.5± 14.25 91 - 136	0.21
Supine DBP (mmHg)	Mean ± SD Range	73.1± 12.02 50 - 97	67.7± 8.68 54 - 86	0.07

The clinical data of the studied cases are shown in table 2.

Table (2): Clinical data of the studied cases group

Variable		Group I (Cases) (n=35)
Time of symptoms: (months)	Mean ± SD Range	27.7 ± 6.43 4 – 48
Time since last episode: (weeks)	Mean ± SD Range	9.91 ± 2.11 1 – 20
Number of episodes:	Mean ± SD Range	8.74 ± 1.51 2 – 15
Calgary score:	Mean ± SD Range	1.91 ±0.42 -2 – 6
Prodrome:	No	0 (0%)
	Yes	35 (100%)
Trauma:	No	31 (88.6%)
	Yes	4 (11.4%)
Trigger:	Long standing	18 (51.4%)
	Crowded	10 (28.6%)
	Hot	6 (17.1%)
	Stress	1 (2.9%)
Response:	Mixed	27 (77.1%)
	Cardio-inhibitory	4 (11.4%)
	Vasodepressor	4 (11.4%)
Time to symptoms (minutes)	Mean ± SD Range	8.8 ± 1.62 3 – 15
Time to syncope (minutes)	Mean ± SD Range	10.6 ± 2.57 4.5 – 16.5
Time to syncope-time to symptoms (minutes)	Mean ± SD Range	1.9 ± 0.32 0.5 – 3

In P2, the cases had significantly lower SDNN and PNN50 than the controls did. In all other respects, there was no discernible difference between the cases and the controls **(Table 3).**

Table (3): Heart rate variability (Time domain parameters) of both groups

Variable	Group I (Cases) (n=35)	Group II (Control) (n=22)	P
	Mean ± SD	Mean ± SD	
SDNNR	160.1± 31.73	158.8± 32.41	0.881
SDNN p1	147.2± 25.66	140.6± 24.24	0.336
SDNN p2	120.6± 31.02	138.9± 33.17	**0.04***
RMSSDR	39.3± 11.78	40.3± 10.89	0.759
RMSSDP1	30.6± 17.29	28.8± 17.61	0.713
RMSSDP2	23.7± 9.84	26.9± 13.34	0.306
PN50R	21.7± 13.6	24.2± 16.12	0.53
PN50P1	15.5± 8.92	15.5± 8.03	0.989
PN50P2	5.8± 4.11	9± 4.45	**0.008***

(R) coincided with the first phase of the tilt test. (P1) just following the passive tilt and (P2) the last five minutes preceding the occurrence of syncope or the last five minutes before the end in controls. *: Significant

In this table, we can see that the LF power was much statistically higher during P2 compared to controls and also significant increase in LF/HF ration in P1 and P2 reflecting the high sympathetic predominance just preceding the episode of syncope **(Table 4).**

Table (4): Heart rate variability (frequency domain parameters) of both groups

Variable	Group I (Cases) (n=35)	Group II (Control) (n=22)	P
	Mean ± SD	Mean ± SD	
LF R	1141.9± 284.69	1241.3± 326.79	0.231
LF P1	1638.2± 402.43	1560.4± 349.86	0.50
LF P2	1827.8± 386.01	1375.3± 216.69	**0.001****
HFR	907.8± 216.31	891.7± 211.75	0.853
HF P1	683.9± 167.06	778.8± 180.86	0.048*
HF P2	578.1± 132.79	669.2± 155.59	0.022*
LF/HF_R	1.3± 0.22	1.4± 0.17	0.075
LF/HF_P1	2.6± 0.41	2.1± 0.36	**0.001****
LF/HF_P2	4± 0.91	2.2± 0.59	**0.021***
Total power R	3618.1± 889.6	3652.3± 870.84	0.908
Total power P1	3862.3± 955.29	3630± 880.32	0.450
Total power P2	3096.6± 694.45	3630.8± 860.43	0.013*

*: Significant. **: Highly significant

This table shows that there were statistical significance differences between the two groups TP and LF at all times and differences between R and PI of HF **(Table 5)**.

Table (5): Differences in heart rate variability (frequency domain parameters) at different times of both groups

Variable	Group I (Cases) (n=35)	Group II (Control) (n=22)	Test	P
	Mean ± SD	**Mean ± SD**		
TP_P1-R	244.3± 58.1	22.4± 4.53		<0.001**
TP_P2-P1	765.7± 170.79	0.9± 0.21		<0.001**
LF_P1-R	496.3± 98.07	319.1± 87.56		<0.001**
LF_P2-P1	189.6± 42.61	185.1± 18.15		<0.001**
HF_P1-R	223.9± 59.91	112.9± 66.26		<0.001**
HF_P2-P1	105.8± 65.53	109.6± 78.52		0.844

**: Highly significant

This table shows that the magnitude of effect of LFP2, LF/HF at rest and Δ LF between P2 and P1, Δ LF/HF between P1 and R was high denoting the rapid autonomic alteration resulting from postural and stressful conditions preceding the occurrence of syncope **(Table 6).**

Table (6): Linear regression analysis of Factors in the model

Factors	Wilks' Lambda	Tests of Equality of Group Means				Magnitude of effect table	Equation Components
		F	df1	df2	P		
SDNNp2	0.926	4.425	1	55	0.04	0.407	0.013
pnn50P2	0.879	7.556	1	55	0.008	-0.947	-0.223
LFP2	0.825	11.658	1	55	0.001	-2.262	-0.005
LF/HF_R	0.919	4.82	1	55	0.032	2.313	11.599
LF/HF_P1	0.828	11.408	1	55	0.001	-0.635	-1.374
LF/HF_P2	0.907	5.67	1	55	0.021	0.006	0.002
LF_P1-R	0.723	21.053	1	55	<0.001	2.823	0.02
TP_P1-R	0.697	23.954	1	55	<0.001	0.03	0
TP_P2-P1	0.327	113.273	1	55	<0.001	-0.375	-0.001
LF_P2-P1	0.318	117.916	1	55	<0.001	1.98	0.016
HF_P1-R	0.563	42.718	1	55	<0.001	-1.426	-0.023

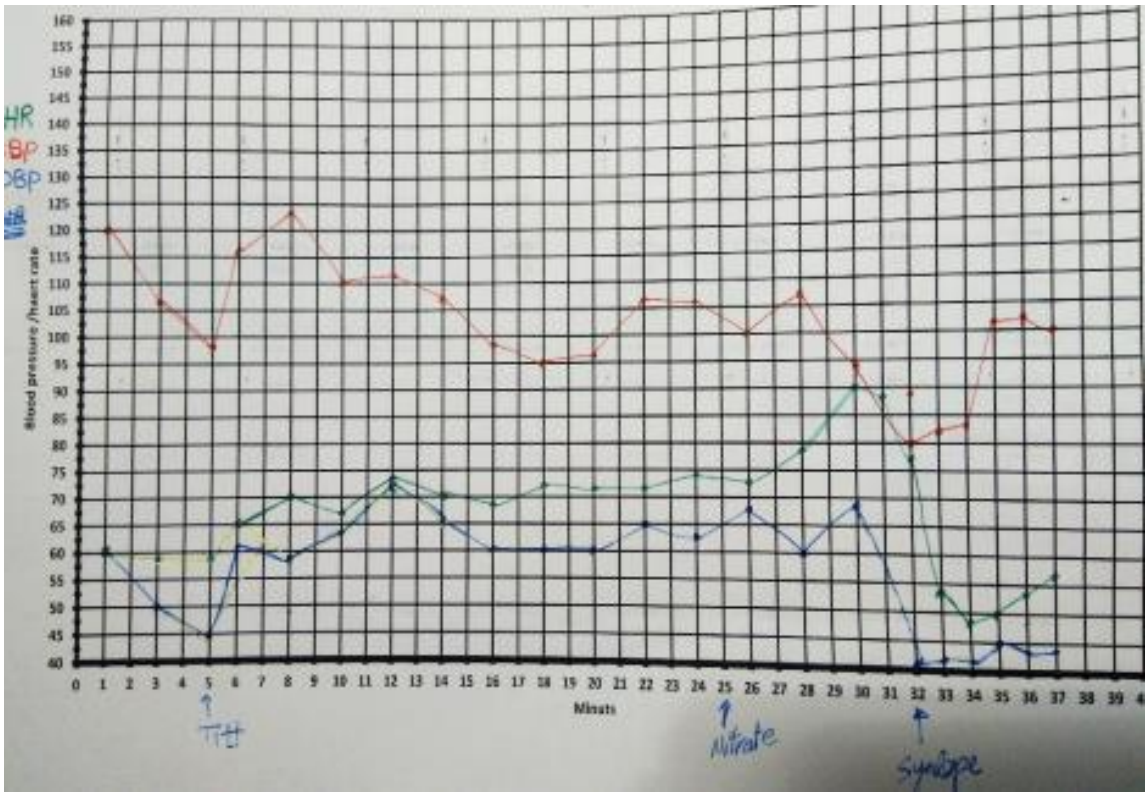

Fig. (1): Male patient, 36 years old, nonsmoker, not diabetic nor hypertensive, no history of any cardiovascular disease, complained of recurrent episode of syncope, ECG: within normal, Echo cardiography: Normal echo study, Calgary score: 0, Tilt table test: positive for vasovagal syncope.

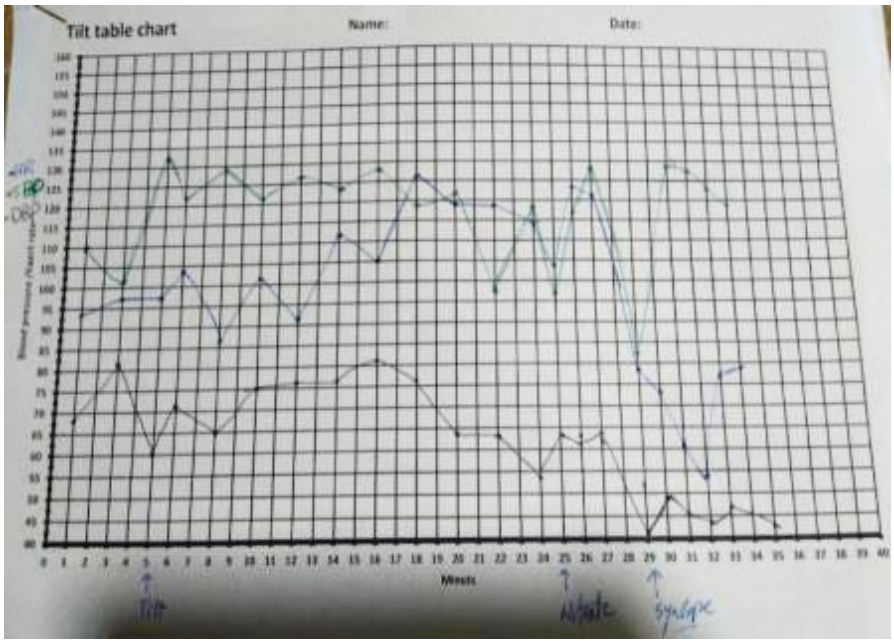

Fig. (2): Female patient, 20 years old, not diabetic, not hypertensive, no history of cardiovascular disease, complained of recurrent episode of syncope, ECG: within normal, Echo cardiography: Normal echo study, Calgary score: 1, Tilt table test: positive for vasovagal syncope.

DISCUSSION

Syncope, or brief loss of consciousness, is a sudden loss of awareness that lasts only a few seconds and is followed by a full recovery with no lasting neurological effects. Loss of consciousness often occurs with a systolic blood pressure of less than 70 mmHg or a mean arterial pressure of less than 40 mmHg **(6).**

Variability in heart rate is a way to assess the severity of an illness or investigate its pathophysiological significance because it is thought to be a measure of autonomic nervous system (ANS) activity **(7).** In cases of vasovagal syncope, the pattern of change in ANS activity is quite different. Most cases show delayed increase in sympathetic activity just before syncope with increase in left ventricular end systolic dimension together with increased contractility upon an almost empty chamber thus triggering ventricular mechanoreceptors with resultant reflex bradycardia and vasodilation **(8).**

In our study, we determined and assessed changes in heart rate variability, which can predict the pathophysiology as well as the occurrence of syncope and so giving the patient enough time to prevent its occurrence. We found that, Heart rate variability parameters can help in prediction of syncope mainly the time domain SDNN and the spectral domain LF, LF/HF ratio. Our study is strongly in agreement with **Virag *et al.*** **(9)** during the tilt test, they suggested an algorithm to predict VVS. It is based on a comparison of low-frequency power (LF) between rising RR intervals (RRIs) and rising systolic blood pressure (SBP). That algorithm predicts syncope two minutes before it really happens. The ability to foresee syncope episodes even moments before they occur would have profound implications for the wellbeing of patients. Modifications in autonomic function during tilting were compared between young and elderly patients with vasovagal syncope using spectral analysis of heart rate variability. All groups' LF and HF frequency bands, as well as the LF/HF ratio, were measured in the frequency domain by analysing Holter recordings taken at 4-minute intervals before, during, and after the tilting. When tested on normal participants, tilting significantly increased LF band power ($P < 0.001$) and the LF:HF ($P < 0.0001$) whereas the spectral power in the HF range dropped. Tilting also decreased the HF spectral strength in syncopal patients ($P < 0.001$). While the LF:HF ratio was stable, the LF power was significantly reduced ($P < 0.001$) in comparison to the controls **(10).** This study was concordant with our study with the significant increase of LF values in cases group and decrease of HF and disagree with that LF: HF ratio remains constant, as in our study significantly it increased in cases group.

In our study, we found not only significant decrease in PNN50 P2 but also SDNN P2 in cases group than in control group.

The most important discovery of the current study was that patients with vasodepressive syncope had a considerably lower SDANN than all the other groups of participants (with negative or cardioinhibitory). Significantly decreased levels of RMSSD and the disappearance of the circadian LF/HF rhythm also suggested a sympathetic predominance in patients with vasodepressive syncope **(11)**.

We disagree with this study as we found significant decrease in SDNN and PNN50 and lower values of RMSSD in cases group, not only this but increase in LF value and LF/HF ratio reflecting the high sympathetic predominance just preceding the episode of syncope.

Mallat *et al.* [12] reported outstanding positive and negative accuracy using HR alone; but, highlighting the potential that a single measured parameter would fail to address all conditions, we opted to analyse HR, BP, and HRV parameters instead.

Our results are discordant with **Budrejko *et al.* [6]** who found that conventional hemodynamic monitoring might be improved without the use of HRV parameters. In particular, they did not distinguish between individuals who had a positive or negative reaction to TT, and any effort to incorporate additional factors to predict TT response prior to syncope itself appears to be worthless.

Our results show significant value of HRV parameters especially PNN50, SDNN, LF and LH/HF ratio in positive tilt test for syncopal (cases) group than controlled one.

Our study disagrees with **Arslan *et al.* [13]** when looked at 33 patients with a typical VVS history and HUTT, those who did well on the test had higher NN50, pNN50, RMSSD, and SDNN index values than the control group. Patients with syncope were found to have a higher likelihood of a positive HUTT if they had stronger parasympathetic tonus, as measured by HRV parameters. Our study reflected the high sympathetic predominance just preceding the episode of syncope as their increased values of LF and LF/HF ratio.

Lippman [14] found that subjects who did not experience tilt-induced syncope had a reduction in parasympathetic tone (as shown by a lower RMSSD), whereas subjects who did have a positive tilt response had no such uniform change. There was a comparable increase in heart rate between the two groups. Patients with a positive tilt response, in whom the increase in heart rate may be attributed (to a much greater extent) to parasympathetic withdrawal, would require a greater increase in sympathetic tone to achieve this increase in heart rate than patients with a negative tilt response.

CONCLUSION

Over half of patients who have had syncopal episodes repeatedly in the year or two before evaluation do not have syncopal recurrences in the year or two after evaluation, and the burden of syncope lowers by more than 70 percent in those who do. Most likely, the decline in syncope occurrences can be attributed to the impact of education and reassurance.

The HUT has been shown to be a useful, accessible, and safe technique for identifying sensitivity to vasovagal syncope, and can be performed drug-free or with pharmacological provocation (often nitroglycerin) as necessary (VVS). HRV can be a reliable indicator of autonomic nervous system (ANS) health. How much the HR varies tells us about how well the nervous system regulates the heart rate and how quickly the heart can react to external stimuli.

Heart rate variability parameters can help in prediction of syncope; mainly the time domain SDNN and the spectral domain LF, LF/HF ratio.

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Author contribution: Authors contributed equally in the study.

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