

EVALUATION OF THE CAUSE OF CARDIOVASCULAR SYNCOPE IN FEMALES VERSUS MALES IN A SAMPLE OF YOUNG EGYPTIAN POPULATION

By

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ABSTRACT

Background: Vasovagal syncope (VVS) occurs in > 40% of individuals at least once in their lifetime. Sex-dependent differences in presentation and outcomes are not understood.

Objective: To study the cause of syncope in young Egyptian Population with inconclusive holter monitoring results.

Patients and Methods: The present study enrolled 60 patients with unexplained syncope presenting at Cardiology Department, Alexandria Main, University Hospital, either as outpatients or during hospitalization. We excluded patients with cardiac or neurologic syncope. All patients were subjected to thorough history taking with special emphasis on important features, physical examination (blood pressure, pulse and complete cardiac examination), standard 12 lead emergency electrocardiography (ECG) for evidence of abnormalities suggestive of arrhythmic syncope, calculations of OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) risk score (ORS), conventional transthoracic echocardiography for confirmation of exclusion of definitive structural heart diseases, Holter 24 hours for exclude any arrhythmic syncope, and Head-up tilt- table testing.

Results: There was a statistically significant difference between the 2 studied groups regarding true syncope (p-value 0.001), frequency of attacks (p-value 0.001), prodromal symptoms (p-value 0.001), duration (p-value 0.006), resting pulse (p-value 0.013), and resting systolic pressure (p-value 0.001). There was no difference regarding recovery (P value = 1), resting diastolic pressure (p-value 0.317) and mean age (Value = 0.264). There were statistically significant differences between the 2 studied groups regarding the negative results of head up tilt testing (HUT) test (p-value 0.001), drug free phase (p-value 0.002), pharmacological provocation (p-value 0.001), and the vasodepressor response III (p-value 0.038). The mixed response I was not statistically significant between the 2 groups (p-value 0.754) as well as the cardio inhibition response with Iib or without Iia a systole (p-value 0.612).

Conclusion: Female patients were experiencing syncopal episodes for longer periods of their lives, and more episodes of syncope than male patients

Keywords: Neurocardiogenic syncope, Head up tilt testing (HUT), Gender difference in vasovagal syncope

INTRODUCTION

Syncope is defined by rapid onset of transient loss of consciousness and postural tone attributed to cerebral hypo perfusion with spontaneous recovery (*Moya et al., 2011*). The majority of syncope is attributed to simple faint, denoted vasovagal syncope (VVS), and often triggered by upright posture. Upright posture causes sub diaphragmatic gravitational blood pooling, primarily within the venous system that reduces central blood volume (*Sheldon et al., 2015*).

In the absence of skeletal muscle pump activity, this reduces venous return and cardiac output (CO). Blood pressure is maintained by baroreceptor-mediated increases in systemic vascular resistance (SVR), passive elastic recoil of venous blood, active splanchnic vasoconstriction, and an increase in heart rate (HR). Splanchnic vaso- and vasoconstriction are integral to maintaining upright blood pressure (*Wieling et al., 2016*).

Syncope may be caused by inadequate regulation of the heart and vessels function by the autonomic nervous and neuroendocrine systems. A tilt table test is a diagnostic procedure for patients with syncope of unknown origin. During the test, the patient is exposed to orthostatic stress, which may be exaggerated during the negative-passive phase of the test by nitroglycerine, clomipramine, and isoprenaline administration. A negative result tilt table test is characterized by a moderate increase in heart rate and the maintaining of the systolic blood pressure above 90 mmHg without symptoms during the planned duration of the study. The tilt table test may provoke a

neurocardiogenic reflex with its vasodepressor and cardio inhibitory components. However, some other positive responses may be distinguished, for example, initial orthostatic hypotension, orthostatic hypotension, delayed orthostatic hypotension, postural orthostatic tachycardia. The patient may present chronotropic incompetence when their heart rate does not increase more than 5/min above baseline values. The neurocardiogenic reflex may occur suddenly or may be preceded by orthostatic hypotension or delayed orthostatic hypotension. Today, a tilt table test is believed to reveal susceptibility to reflex hypotension rather than the cause of the syncope. During the test, the patient may present pseudo-syncope often manifested by a sudden silence, head dropping, and closed eyes, which cannot be opened, even with force. In such a case, the patient can maintain an upright position, and blood pressure and heart rate are within normal limits (*Zysko et al., 2012*).

Syncope is a frequently observed symptom, and the prevalence in the general population is 3.0 percent in men and 3.5 percent in women. Neurally mediated syncope is the most common cause of syncope, which account for 28.7 percent in all episodes of syncope. It often occurs in response to orthostatic stimulus (prolonged standing), other nonorthostatic stimuli (fear, emotional stress, pain), and a variety of activities (micturition, defecation, coughing, swallowing, postprandial, and pressure on the carotid sinus). These stimuli transiently cause a sudden failure of the autonomic nervous system resulting in hypotension and

bradycardia, which eventually cause syncope (*Goyal and Maurer, 2016*).

The present work aimed to study the cause of syncope in young Egyptian Population with inconclusive Holter monitoring results, and compare male versus female gender.

PATIENTS AND METHODS

The present study enrolled 60 patients with unexplained syncope presenting at Cardiology Department Alexandria Main University Hospital, either as outpatients or during hospitalization.

The design of this observational study was in two phases:

Phase (A): A retrospective analysis of their clinical management in the 6 months prior to the first presentation to the hospital.

Phase (B): Their subsequent clinical management at the Cardiology Department.

Inclusion criteria:

1. Young Egyptian population < 30 years old.
2. Patients presenting with a transient self-limited loss of consciousness, the onset of which was relatively rapid, and the subsequent recovery spontaneous, complete, and prompt.

Exclusion criteria:

- Presence of definitive structural heart disease including:
 - a. Hypertrophic obstructive cardiomyopathy.
 - b. Obstructive cardiac tumors or thrombi.

- c. Severe aortic stenosis.
- d. Pericardial tamponade.
- e. Aortic Dissection.
- f. Significantly reduced ejection fraction.

- ECG abnormality suggestive of arrhythmic syncope.
- Family history of sudden death.
- Syncope associated with palpitations.
- Syncope while supine.
- Features suggestive of epilepsy.
- Acute myocardial infarction.
- Acute massive pulmonary embolism.
- Persisting focal neurological deficit.

All patients were subjected to the following:

- Thorough history taking with special emphasis on important features.
- Physical examination as regard blood pressure obtained in supine, sitting and erects position, heart rate, complete cardiac examination.
- Blood tests (taken within one week prior to tilt table test): Complete blood count, Serum electrolytes and blood glucose.
- Standard 12 lead ECG for evidence of abnormalities suggestive of arrhythmic syncope.
- Calculations of OESIL risk score (ORS) which was based on four parameters: Age > 65 years, abnormal ECG, lack of prodromes and history of previous cardiovascular diseases (including hypertension).

- Conventional transthoracic echocardiography for confirmation of exclusion criteria.
- Holter 24 hours for excluding any arrhythmic syncope.
- Head-up tilt- table testing.

The laboratory environment in which tilt testing undertaken was important. The room was quiet, at a comfortable temperature and as nonthreatening as possible. The lighting was dim, and the patient permitted to rest in the supine position for 20 to 45 min before beginning the test. Patients were instructed to fast overnight in preparation for early morning studies or for several hours before tilt table testing in the case of studies scheduled later in the day. As a consequence, susceptibility to gravitationally induced hypotension may be increased. To diminish the possibility of "false positive" tests, it was reasonable to consider provision of parenteral fluid replacement before initiating the procedure by infusing normal saline in a volume approximately equivalent to 75 ml for each hour of the fasting period. For initial diagnostic studies, all nonessential drugs should be withheld for a period exceeding several drug half-lives.

Recordings: A minimum of three electrocardiographic (ECG) leads were recorded simultaneously and continuously throughout the study. Beat-to-beat blood pressure recordings, using the least intrusive method possible, were obtained and recorded continuously during the entire study. In principle, intermittent sphygmomanometer pressure recordings had limited number of blood pressure recordings that can be obtained during the course of the procedure. Nonetheless, the

sphygmomanometer continues to be widely used in clinical practice.

Table design: An appropriate tilt table permitted calibrated upright tilt angles at 70°. Typically, the transition from supine to upright position was achieved smoothly and relatively rapidly (e.g. 10 to 15 s). The table permitted the patient to be gently secured to prevent falling, and was sufficiently robust to avoid wavering or losing position during the test. The table was able to be reset quickly to the supine position (10 to 15 s) when the test was complete or should supervising personnel wish to interrupt testing. The table may be either manually or electronically operated. Only tilt tables of the foot-board support type were appropriate for syncope evaluations. To maximize passive gravitational stress, patients were instructed to avoid flexing ankles, knees or lower extremity muscles.

Tilt angle: We tilted our inclusion subjects at 70°. Available evidence suggested that the physiologic effects of passive upright posture were comparable for tilt angles 70°. Less severe angles (i.e. 30° to 45°) did not seem to provide sufficient orthostatic stress, and resulted in a lower yield of positive test responses in patients with syncope.

Chronobiology factors: The time of day in which testing undertaken was relatively constant for each patient. It seemed likely given the tendency for spontaneous vasovagal events within individual patients to cluster in time, that chronobiology factors played a role in the emergence of the condition. Similarly, they expected to contribute to the occurrence of vasovagal symptoms under provocative tilt table testing conditions.

Classification of positive responses to tilt testing:

Type I Mixed: Heart rate falls at the time of syncope but the ventricular rate does not fall to less than 40 b/ min or falls to less than 40 b/ min for less than 10 s with or without a systole of less than 3 s. Blood pressure falls before the heart rate falls.

Type 2A Cardio inhibition without a systole: Heart rate falls to a ventricular rate less than 40 b/ min for more than 10 s but a systole of more than 3 s does not occur. Blood pressure falls before the heart rate falls.

Type 2B Cardio inhibition with a systole: A systole occurs for more than 3 s. Blood pressure falls coincides with or occurs before the heart rate falls.

Type 3 Vasodepressor: Heart rate does not fall more than 10% from its peak at the time of syncope.

Exception 1: Chronotropic incompetence: No heart rate rise during

the tilt testing (i.e., less than 10% from the pre-tilt rate)

Exception 2: Excessive heart rate rise: An excessive heart rate rise both at the onset of the upright position and throughout its duration before syncope (i.e., greater than 130 b/ min).

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level. P value < 0.05 was considered significant.

RESULTS

There was a statistically significant difference between the 2 studied groups regarding true syncope (p-value 0.001), frequency of attacks (p-value 0.001), prodromal symptoms (p-value 0.001), duration (p-value 0.006), resting pulse (p-value 0.013), and resting systolic pressure (p-value 0.001). There was no difference regarding recovery (P value = 1), resting diastolic pressure (p-value 0.317) and mean age (Value =0.264).

In our study there was a statistically significant difference between the 2 studied groups regarding the negative results of HUT test (p-value 0.001), drug free phase (p-value 0.002) and pharmacological provocation (p-value

0.001), also regarding the vasodepressor response III as the (p-value 0.038). The mixed response I was not statistically significant between the 2 groups (p-value 0.754) as well as the cardio inhibition response with IIb or without IIa a systole (p-value 0.612) (**Table 1**).

The results of our study concluded that vasodepressor response was more frequent in females. Also, women have a higher symptom burden, different triggers and suffer from more recurrent syncopal episodes than men. We also concluded that men were more susceptible to induction of VVS without nitroglycerin (drug free phase) and women after it (pharmacological provocation).

Table (1): Comparison between the two studied groups according to different parameters

Parameters	Groups	Females (n = 30)	Males (n = 30)	p
Age (years)				
<20		10 (33.3%)	7 (23.3%)	MC p= 0.236
20 –<25		5 (16.7%)	5 (16.7%)	
25 –<30		15 (50%)	14 (46.7%)	
≥30		0 (0%)	4 (13.3%)	
Mean ± SD.		22.7 ± 5.55	24.4 ± 5.7	0.264
Median (Min. – Max.)		25 (12 – 29)	25.5 (10 – 35)	
Syncope				
True syncope		30 (100%)	20 (66.7%)	0.001
Other T-LOC diagnosis		0 (0%)	10 (33.3%)	
Frequency of attacks				
Infrequent		0 (0%)	20 (66.7%)	<0.001
Frequent		30 (100%)	10 (33.3%)	
Prodromal		30 (100%)	20 (66.7%)	0.001
Duration				
10 – 30		9 (30%)	1 (3.3%)	0.006
Minutes		21 (70%)	29 (96.7%)	
Recovery				
Spontaneous (Complete prompt)		27 (90%)	28 (93.3%)	FE p= 1.000
Intervention		3 (10%)	2 (6.7%)	
Resting pulse				
≤60		0 (0%)	4 (13.3%)	MC p= 0.013
60 – 100		26 (86.7%)	26 (86.7%)	
>100		4 (13.3%)	0 (0%)	
Blood pressure				
Resting systolic <90		20 (66.7%)	2 (6.7%)	<0.001
Resting diastolic <60		7 (23.3%)	4 (13.3%)	0.317
HUT results				
Type of response				
Negative (Control)		0 (0%)	10 (33.3%)	0.001
I (Mixed)		7 (23.3%)	6 (20%)	0.754
IIa (Cardioinhibition without asystole)		3 (10%)	1 (3.3%)	FE p=0.612
IIb (Cardioinhibition with asystole)		0 (0%)	1 (3.3%)	FE p=1.000
III (Vasodepressor)		20 (66.7%)	12 (40%)	0.038
Drug free phase		2 (6.7%)	12 (40%)	0.002
Pharmacological provocation		30 (100%)	20 (66.7%)	0.001

SD: Standard deviation, t: Student t-test, χ^2 : Chi square test

FE: Fisher Exact test, MC: Monte Carlo

DISCUSSION

Detailed history and physical examination are both central to the diagnosis of neurally mediated syncope. Head-up tilt test (HUT) was used to

confirm the diagnosis of neurally mediated syncope in suspected case. Previous studies reported the clinical features of neurally mediated syncope. Neurally mediated syncope is widely believed to be more common in females

than in males. However, the gender difference of recurrent neurally mediated syncope has not well been evaluated in a large patient population (*Sheldon et al., 2016*).

Our findings suggested that female patient may be prone to experience syncopal episodes more easily than male patients (P. value 0.001). Our finding was also supported by previous several studies, which showed gender differences in orthostatic tolerance and response to lower negative body pressure in healthy normal subjects (*Fu et al., 2010* and *Zysko et al., 2012*).

We also concluded that male gender experienced more syncopal episodes in the drug free phase than female gender. Females had more syncopal episodes during pharmacological provocation.

Differences in body composition between men and women might in part account for differences in tilt table testing (TTT) sensitivity in the absence or presence of nitroglycerin (NTG), and thereby tie in with current ideas regarding the pathophysiology of vasovagal syncope (VVS). Specifically, current concepts point to excessive venous pooling with diminished venous return to the heart causing reduced stroke volume as the step ending in a marked reduction of arterial blood pressure (*Jardine et al., 2018*). One possible cause of excessive venous pooling in women might be the relative dose-to-body size effect of NTG. We used a fixed dose which amounts to a relatively greater concentration in women, who typically have smaller body mass than do men. However, the NTG effect can only contribute to a high rate of VVS in women after NTG. It cannot explain the higher

rate of men fainting before NTG. Another potential explanation resides in men having a relatively greater muscle mass than women (*Bootsma et al., 2010*). If, in VVS-susceptible males, muscles act as a low-compliance vascular bed in which venous blood may pool, then a relatively larger muscle mass allows more pooling. There is an evidence to support the idea that men have a higher rate of venous pooling in the legs than women: in healthy subjects, leg volume increased more in the first 5 min of TTT in men than in women (*Thijs et al., 2012*).

Unfortunately, there appear to be no data for longer periods of head-up tilt. If men indeed have a higher rate of venous pooling, they may be expected to reach a critical level of excessive pooling earlier than women, i.e. before NTG administration. However, if pooling in muscle mass is to explain their tendency to faint, then this mechanism should also be active after NTG. So, men should also faint more readily than women in that phase, the opposite of what we found. Similar reasoning might be added for other vascular beds: either a differential sensitivity of the splanchnic and muscular beds to pooling, or a different size of these beds, or a combination of sensitivity and size, might explain sex differences. Emotional triggers might explain sex differences. Unfortunately, the number of observations was limited, so these data can only be regarded as exploratory. Our findings did not demonstrate sex differences as regards emotional triggers. However, there are reports that emotional triggers for VVS differ between men and women.

Our observations also suggested that the better blood pressure response to HUT of women makes them more resistant to VVS in the early phases of TTT than men. More women than men fainted after the application of NTG. NTG is a potent vasodilator that can provoke not only vasovagal syncope but also migraine attacks. Of note, migraine affects more women than men (*Thomsen et al., 2010*), and VVS is more prevalent in those with migraine, especially in women with migraine. This suggests that female sex hormones might interact with NTG effects on vasodilation. More pathophysiological studies are warranted to study this phenomenon (*Thijs et al., 2013*).

CONCLUSION

Upright tilt table test was performed for the evaluation of syncope although the test has limited specificity, sensitivity, and reproducibility. Gender had relevance for the clinical evaluation, rate of recurrence, and subsequent specific treatment. Women have a higher symptom burden, different triggers and suffer from more recurrent syncopal episodes than men. Sex-specific diagnostic and therapeutic strategies may be warranted to target the differing mechanisms of vasovagal syncope between men and women. Female patients were experiencing syncopal episodes for longer periods of their lives and more episodes of syncope than male patients. Men were more susceptible to induction of VVS without nitroglycerin (drug free phase) and women after it (pharmacological provocation). The vasodepressor response was more frequent in females.

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تقييم اسباب فقدان الوعي المؤقت في عينة من الشباب (الذكور مقابل الاناث) في المجتمع المصرى

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خلفية البحث: يحدث الإغماء الوعائي المبهيمي أكثر من 40% من الأفراد مرة واحدة على الأقل في حياتهم. و الاختلافات المعتمدة على الجنس في العرض والنتائج ليست مفهومة.

الهدف من البحث: دراسة سبب فقدان الوعي المؤقت الوعائي عند الشباب المصري مع نتائج رصد هولتر غير حاسمة، ومقارنة التقييم بين الجنسين.

المرضى وطرق البحث: شملت الدراسة الحالية 60 مريضاً يعانون من إغماء غير مفسر قدموا إلي قسم القلب مستشفى جامعة الإسكندرية الرئيسي، إما كمرضى خارجيين أو أثناء الاستشفاء. واستبعد المرضى الذين يعانون من إغماء قلبي أو عصبي. وتم إخضاع جميع المرضى من خلال التاريخ مع التركيز بشكل خاص على الميزات الهامة، والفحص البدني (ضغط الدم والنبض والفحص الكامل للقلب)، والمعيار 12 لتخطيط القلب الكهربائي في حالات الطوارئ للحصول على دليل على وجود تشوهات توحى بإغماء عدم إنتظام ضربات القلب، وحسابات درجة مخاطر (المرصد الوبائي للإغماء فيلاتسيو)، وتخطيط صدى القلب التقليدي عبر الصدر لتأكيد إستبعاد أمراض القلب الهيكلية النهائية، وهولتر 24 ساعة لاستبعاد أي إغماء غير منتظم وإختبار إمالة الرأس.

نتائج البحث: كان هناك فروقاً ذات دلالة إحصائية بين المجموعتين المدروستين فيما يتعلق بالإغماء الحقيقي، و تكرار النوبات، و الأعراض البادرية، والمدة، والنبض أثناء الراحة، والضغط الانقباضي أثناء الراحة. ولم يكن هناك فرق فيما يتعلق بالشفاء والراحة والضغط الانبساطي ومتوسط العمر. وكانت هناك فروقاً ذات دلالة إحصائية بين المجموعتين المدروسة فيما يتعلق بالنتائج السلبية لاختبار

إمالة الرأس لمرحلة خالية من العقار والاستفزاز الدوائي، وكذلك فيما يتعلق باستجابة الاكتئاب الوعائي III. ولم تكن الاستجابة المختلطة I ذات دلالة إحصائية بين المجموعتين وكذلك استجابة تثبيط القلب مع IIb أو بدون توقف الانقباض IIa.

الاستنتاج: كانت النساء يعانين من نوبات إغماء لفترات أطول منحياتهن و نوبات إغماء أكثر من المرضى الذكور.

الكلمات الدالة: إغماء القلب العصبي، اختبار إمالة الرأس، الفرق بين الجنسين في الإغماء الوعائي المبهمي.

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