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Echocardiographic parameters in patients with positive head up tilt test

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ABSTRACT

Background: *syncope, defined as a sudden transient loss of consciousness with complete neurologic recovery**.** The reduction in cardiac output is a result of decreased stroke volume due to decreased venous return from blood pooling in the lower limbs venous and splanchnic circulation secondary to impaired splanchnic vasoconstriction**.** The aim of the study was to determine the predictors of positive head-up Tilt Test in patients with vasovagal syncope using echocardiography.**Methods:** The current study is a cross-sectional study involving 180 patients with acute myocardial infarction undergoing primary percutaneous coronary intervention, admitted to the Coronary Care Unit in Zagazig University Hospitals in the period between January 2019 and January 2020. They were classified into two groups: Group 1 (Low thrombus burden of culprit vessel). Group 2 (High thrombus burden culprit vessel).**Results:***The demographic data of the studied patients, the mean age was 27.7 years ranged from 18 to 40 years and 54.8% of them were males. Their body surface area ranged from 1.1 up to 2.1 m^2. 64.3% o the studied group showed positive results of head tilt up test and gave the response within time range from 5 min. up to 29 min., the commonest response type was mixed response among 51.9% of HTT positive group. shows that both LAVI and IVC either supine or standing position was significantly lower among HTT positive group than negative group, while no significant difference regarding other ECHO parameters. shows that after multivariate logistic analysis, both LAVI on standing position and IVC supine and standing were significant predictors of positive HTT results.* ***Conclusion:*** *Small LA volume in standing position and IVC diameter in supine and standing position in addition to their percentage of change between supine and standing position are independent predictors of HTT-induced VVS.*

Key words: *predictors- positive head-up Tilt Test- vasovagal syncope- echocardiography*

I. Introduction:

syncope, defined as a sudden transient loss of consciousness with complete neurologic recovery[(1)]Although the final common pathway is global reduction of cerebral blood flow, various mechanisms may induce it, including reduced cardiac output from increased parasympathetic effect, reduced arterial tone, vasodilatation, and

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orthostasis.[2]Increased venous compliance has been postulated as the pathophysiology of syncope in young adults[3]with orthostatic venous pooling leading to paradoxical activation of the cardioneural inhibitory reflexes[3].

The reduction in cardiac output is a result of decreased stroke volume due to decreased venous return from blood pooling in the lower limbs venous and splanchnic circulation secondary to impaired splanchnic vasoconstriction[4]

A study in young adult patients has shown bigger diameters of the inferior vena cava (IVC) in patients with vasovagal syncope compared with controls, and the study suggested that increased venous compliance manifests as IVC dilation, which in turn leads to exaggerated abdominal venous pooling of the blood during standing, with resultant orthostaticmanifestations.[5]

LA acts as a "reservoir" during systole, a "conduit" and a "booster pump" in early and late diastolic period, respectively [6] , progressive decline of LA volume by venous blood pooling and transient LA hypocontractility by parasympathetic activity were mentioned to be contributory factors in VVS during HTT [7]**.** Therefore, subjects with small LA volume reserve may show a significant decrease of cardiac output, leading to syncope during orthostatic stress.

Small LA and LV volume were related with HTT results. Furthermore, the smaller LA the subject had, the faster was the time to faint during HTT. On the other hand, patients with large LA size (LAVI≥36 ml/m2) did not faint during HTT and this finding suggests that VVS is unlikely to be the reason of unexplained syncope in patients with significantly enlarged LA[8]

Early diastolic mitral annular velocity (E′) was higher in HTT+ group than in HTT− group[8]**.**E′ has been known to reflect myocardial relaxation characteristic**.** Therefore, they supposed that higher E′ is related with better ventricular diastolic function and smaller LAVI or more likely fainting during HTT. However, further studiesanalysing the role of myocardial function and VVS is needed.

The aim of the study was to determine the predictors of positive head-up Tilt Test in patients with vasovagal syncope using echocardiography.

II. Patients and methods

Patients:

The study enrolled 42 subjects, 27 of them had two or more episodes of syncope or pre syncope, and 15 normal controls. They were recruited in 6 months from august 2019 to January 2020. The study was conducted in cardiac EPS unit, Cardiology department, Zagazig University hospitals.

Inclusion criteria:

patients less than 40 years old with, two or more episodes of syncope or presyncope within 6 months(a transient self-limited loss of consciousness, the onset of which was relatively rapid, and the subsequent recovery spontaneous, complete, and prompt), and normal LV systolic function (LV ejection fraction [EF]≥50%) on echocardiographic evaluation

Exclusion criteria:

- **<u>Presence of definitive structural heart disease including</u>** :

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.

- **<u>ECG abnormality suggestive of arrhythmic syncope including</u>**:

a) Persistent sinus bradycardia< 40 bpm in awake or repetitive sinoatrial block or sinus pauses ≥ 3 s.

b) Mobitz II second or third degree AV block.

c) Alternating left and right bundle branch block.

d) Ventricular tachycardia or rapid paroxysmal supraventricular tachycardia.

e) Non-sustained episodes of polymorphic ventricular tachycardia and long or short QT interval.

f) Pacemaker or ICD implantation.

g) Bifascicular block.

h) Other intraventricular conduction abnormalities.

i) Pre-excited QRS complexes.

j) Brugada Syndrome.

k) Q waves suggesting MI.

l) Atrial fibrillation

- Family history of sudden cardiac death.
- **<u>Features suggestive of epilepsy</u>**:

a) Tonic clonic activity persisting for >15s from onset of attack

b) Prolonged unconsciousness for more than a few minutes

c) Prolonged recovery with disorientation and drowsiness

- Acute myocardial infarction.
- Acute massive pulmonary embolism.
- Persistent focal neurological deficit.
- Severe anaemia.
- Congenital heart diseases.

Methods:

All patients were subjected to the following:

1) Thorough history taking with special emphasis on important features:

Questioner(filled by the patient whenever possible or by the attending physician)

A- Questions about circumstances just prior to the attack:

- Position (supine, sitting or standing).
- Activity (rest, change in posture, during or after exertion, during or immediately after urination, defecation, cough, or swallowing).
- Predisposing factors (e.g. crowded or warm places, prolonged standing, and post-prandial period) and of precipitating events (e.g. fears, intense pain, neck movements).

B- Questions about onset of the attack:

- Nausea, vomiting, abdominal discomfort, feeling of cold, sweating, aura, pain in neck or shoulder, blurred vision, dizziness.
- Palpitations.

C- Questions about the end of the attack:

- Nausea, vomiting, sweating, feeling of cold, confusion, muscle aches, skin color, injury, chest pain, palpitations, urinary or fecal incontinence.

D- Questions about the attack (eyewitness) if present:

- Way of falling (slumping or kneeling over),skin color (pallor, cyanosis ,flushing),duration of loss of consciousness, breathing pattern (snoring), movement (tonic, clonic,tonic-clonic,minimal myoclonus or automatism),duration of movments,onset of movement in relation to fall ,tongue biting.

D- Questions about the background:

- Family history of sudden death, congenital arrhythmogenic heart disease or fainting.
- Previous cardiac disease.
- Neurological history (parkinsonism,epilepsy,narcolepsy).
- Metabolic disorders (DM, etc.).
- Medications (antihypertensive, antianginal, antidepressant agent, anti- arrhythmic, diuretics, and QT-prolonged agents) or other drugs including alcohol.
- In the case of recurrent syncope, information on recurrences such as the time from the first syncopal episode and on the number of spells.

1) Physical examination: as regard

- Blood pressure obtained in supine, sitting and erect position
- Heart rate
- Measuring weight, height and calculation of body surface area
- Complete Cardiac examination

2) Blood tests (taken within one week prior to tilt table test):

- Complete blood count

3) Standard 12 lead ECG(paper speed 25 mms with 10 MV calibration if appropriate) : for evidence of abnormalities suggestive of arrhythmic syncope.

4) Conventional transthoracic echocardiography(using SIEMENS ACUSON X300,Korea):to measure LVESD ,LVEDD, EF, RWMA by eye balling, LV septal thickness (for confirmation of exclusion criteria) and to measure

- **LAV and LAVI** by biplane area method by the following equation

LAV=0.85*A1*A2/L.

LAVI=LAV/BSA .

- **Early mitral inflow peak velocity (E)** :was measured using the pulsed wave Doppler method by placing a sample volume at the opening level of the mitral valve leaflet tips.
- **The IVC diameter** was measured in longitudinal plane from the subcostal view. Maximal end expiratory diameter (during normal breathing) from the distal 2.5 cm of IVC near the cavo-atrial junction .

All the previous echo parameters were measured in supine and standing position.

5) Head-up tilt- table testing :for the included subjects:

Basic Technology and Protocols for Head-Up Tilt Table Testing:

Laboratory environment:

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 5 minutes before beginning the test.

Patient condition:

- All non-essential drugs withheld for a period exceeding 3 drug half –lives.
- Patients were instructed to fast for 6 hours.
- Saline was infused in a volume equal to 75 ml for each hour of fasting.

Recordings:

- One electrocardiographic (ECG) lead was recorded continuously throughout the study.
- Indirect blood pressure monitoring by automated blood pressure cuff inflated every 1 min.

Tilting procedure:

The table used during the study (Medeco, model EL-12D, Shanghai, China). Recordings was achieved using PHILIPS V24/26 monitor, Germany.

- The patient was secured to the table using 2 strappings.
- The patient feet were allowed to rest securely in the foot board of the table.
- The patient was monitored for 5 minutes in supine position.
- The transition from supine to standing position was achieved smoothly and relatively rapid up to 70^{o}.

- The patient was monitored for 30 minutes at 70º.
- If no symptoms appeared the patient was given 5mg isosorbidedinitrate sublingual and monitored for another 30 min.

Chronobiologic factors:

The time of day in which testing is undertaken was relatively constant for each patient

Test results:

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 asystole of less than 3 s.
- Blood pressure falls before the heart rate falls.

Type 2A Cardioinhibitor without asystole

- Heart rate falls to a ventricular rate less than 40 b/ min for more than 10 s but asystole of more than 3 s does not occur.
- Blood pressure falls before the heart rate falls.

Type 2B Cardioinhibitor with asystole

- Asystole occurs for more than 3 s.
- Blood pressure fall coincides with or occurs before the heart rate falls.

Type 3 Vasodepressor

- Blood pressure falls to systolic value less than 60 mmHg
- Heart rate does not fall more than 10% from its peak at the time of syncope
- **Exception :**Chronotropic incompetence: No heart rate rise during the tilt testing (i.e., less than 10% from the pre-tilt rate)

Statistical analysis

Statistical analysis for the collected data was performed using statistical package for the social sciences (SPSS) version 23. Normally distributed numerical data was described as mean ± standard deviation (SD), non-normally distributed numerical data was described as median and range, while categorical data was described as number and percentage. The correlation between tilt test result and other numerical variables was assessed by Spearman's rank correlation. Stepwise multiple regression analysis was then performed to detect the associated independent variables for positive results. The differences between both tilt positive and negative groups regarding categorical data was assessed using Chi-square (X2) test. Differences between subjectsregarding numerical variables were assessed using the Mann- Whitney U test, then odds ratio for the statistically significant independent variables were assessed using binary logistic regression analysis. A receiver operating

characteristic (ROC) curve was then performed to assess a cut-off value for percentage of change of LAVI and IVC diameter between supine and standing position to predict the positive results with the best available sensitivity and specificity. Area under the curve was assessed, criteria to qualify for AUC were as follows: 0.9-1 = excellent, 0.8-0.9 = good, 0.7-0.8 = fair, 0.6-0.7 = poor, and 0.5-0.6 = fail. All tests of significance were two-tailed and a p-value < 0.05 was considered statistically significant.

III. Result:

- **The demographic data of the studied subjects**: The study included 42 subjects 27 were symptomatic tilt positive and 15 asymptomatic were tilt negative. The mean age was 27.7 ± 5.38years ranged from 18 to 40 years and 54.8% of them were males. Their body surface area ranged from 1.1 up to 2.1 m^2**(Table 1)**.
- Regarding the past history of the studied group 64.2% of them had positive history of syncope during the last 6 months and only 11.9% of them gave positive drug history,9.5% usedpropranolol(Inderal™)as treatment and 2.4% used BetahistineDihydrochloride(Betacerc™) **(Table 2)**.
- Regarding the Results of head up tilt test among the studied group 64.3% of studied group showed positive results of head tilt up test and gave the response within time range from 5 min. up to 29 min. following tilt , the commonest response type was mixed response among 51.9% of HTT positive group **(Table 3)**.
- The studied population was divided into two groups: HTT positive group and HTT negative group (control). HTT positive group were significantly younger than negative group and 63% of them were males in contrast to the negative group in which males represented only 40% while no significant difference regarding BSA as shown in table 10 **(Table 4)**.
- The study showthat both LAVI and IVC either supine or standing position was significantly lower among HTT positive group than negative group, while no significant difference regarding echocardiographic parameters **(Table 5)**.
- It shows that no statistical significant difference among HTT positive group and negative group regarding E\A value or diastolic functions **(Table 6)**.
- It shows that both LAVI on standing and supine position was in high significantly positive correlation with time needed to appearance of symptoms of HTT. Also there was positive correlation with basal SBP, hemoglobin, IVC supine and standing, E\A value and ECG rate but not reach significant level, while there was negative correlation with LVEF, basal SBP, E and A values of ECHO **(Table 7)**.
- By studying the difference between LAVI and IVC diameter in supine and standing position ,we found significant reduction in LAVI as it decreased by 22±6% in syncope group and decreased by 14±5% in control group and significant increase in IVC diameter as it increased by 30±10% in syncope group and 15± 10% in control group **(Table 8)**.
- By performing ROC analysis for our parameters we found that the percentage of change between supine and standing position can predict a positive HTT with very high accuracy **(Table 9)**.

Table (1): Demographic data of the studied patients:

Demographic data	**Studied sample(n=42)**	
	Mean ± SD	
Age (years)	27.7 ± 5.38	
(Range)	(18 - 40)	
BSA (m^2)	1.67 ± 0.17	
(Range)	(1.1 - 2.1)	
Variable	**Frequency (42)**	**%**
Sex		
Male	23	54.8
Female	19	45.2

Table (2): Past history among the studied subjects:

Variables	**Case group (n=42)**	
	Frequency	**%**
Past history of syncope in last 6 months		
Yes	27	64.2
No	15	35.7
Drug history		
Yes	5	11.9
No	37	88.1
Drugs used:	(n=5)	
propranolol	4	9.5
BetahistineDihydrochloride	1	2.4

Table (3): Results of head up tilt test among the studied group

Variables	**Study sample(n=42)**	**%**
Positive test	27	64.3
Negative test	15	35.7
Type of response among positive test results:	N =27	
Inhibitory tilt response	4	14.8
Vaso-depressant tilt response	9	33.3
Mixed response	14	51.9
Time to response:	10.1 ± 8.92	
Mean ± SD (Range)	(5 – 29)	

Table (4): Comparison between patients with positive and negative tilt test results regarding demographic characters.

Variable	**Positive test (N=27)** mean ± SD	**Negative test(N=15)** mean ± SD	**-test**	**P**
Age (years)	25.6 ± 5.1	31.6 ± 3.6	.53	**<0. 001 HS**
BSA	1.66±0.19	1.69± 0.13	.62	0.54 NS
Variable	**F %**	**F %**	**²**	**P**
Sex				
Male	1763.0	6 40.0	.1	0.15 2 NS
Female	10 37.0	9 60.0		

NS: P-value>0.05 is not significant HS: P-value <0.001 is high significant

Table (5): Comparison between patients with positive and negative tilt test results regarding ECHO changes.

Variable	**Positive test (N=27) mean ± SD**	**Negative test(N=15) mean ± SD**	**t-test**	**P**
LVEF	64.8 ± 2.96	64.9 ± 2.7	0.056	0.98 NS
LAVI supine position	22.9 ± 6.03	40.6 ± 4.9	**9.38**	**<0.001 HS**
LAVI standing position	18.6 ± 4.34	35 ± 3.76	**12.3**	**<0.001 HS**
IVC supine position	1.45 ± 0.27	1.93± 0.29	**5.41**	**<0.001 HS**
IVC standing position	1.85 ±0.27	2.21 ± 0.23	**4.39**	**<0.001 HS**
E supine position	81.5± 12.1	81.4 ± 12.5	0.03	0.95 NS
E standing position	66.8 ±10.13	66 ± 9.94	0.26	0.803 NS
A supine position	60.2 ± 10.6	61.2 ± 12.4	0.29	0.78 NS
A standing position	50.4± 10.1	50.7± 10.79	0.089	0.92 NS

Table (6): Comparison between patients with positive and negative tilt test results regarding E\A value and functions.

Variable	**Positive test (N=27)** mean ± SD	**Negative test(N=15)** mean ± SD	**t-test**	**P**
E\A value	1.34 ± 0.24	1.36 ± 0.32	0.24	0.81 NS
	F %	**F %**	**χ^2**	**P**
Diastolic functions				

Normal	25	92.6	12	80.0	1.45	0.231
Impaired	2	7.4	3	20.0		NS

NS: P-value>0.05 is not significant

Table (7): Correlation between time to symptoms after HTT and clinical data of the studied group.

Variable	**Time to symptoms**	
	r	**P**
Basal SBP	-0.181	0.556 NS
Basal DBP	0.161	0.422 NS
Hemoglobin	0.351	0.072 NS
LVEF	-0.216	0.28 NS
LAVI supine position	0.883	**<0.001 HS**
LAVI standing position	0.914	**<0.001 HS**
IVC supine position	0.096	0.663 NS
IVC standing position	0.220	0.240 NS
E supine position	-0.168	0.402 NS
E standing position	-0.280	0.153 NS
A supine position	-0.199	0.320 NS
A standing position	-0.203	0.302NS
E\A value	0.069	0.733 NS
ECG rate	0.339	0.082 NS

Table(8): comparison of percentage of change in LAVI and IVC diameter in supine and standing position for both groups.

	HTT +ve (n=27)	HTT -ve (n=15)	T	p
LAVIsup	23.7±5.68	40.6±4.9	-9.6	<0.001
LAVIstan	18.5±4.51	35±3.76	-11.8	<0.001
IVCsup	1.4±0.27	1.9±0.29	-5.5	<0.001
IVCstan	1.8±0.27	2.2±0.23	-4.33	<0.001
LAVI%CHA	0.22±0.06	0.14±0.05	4.7	<0.001
IVC%CHA	0.3±0.1	0.15±0.1	4.3	<0.001

sup (supine), stan (standing),%CHA (percentage of change)

Table (9) :showing area under the curve and 95% confidence of ROC analysis of our parameters.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LAVICHA	.912	.062	.000	.790	1.034
IVCCHA	.844	.065	.000	.717	.971

The test result variable(s): LAVICHA, IVCCHA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

IV. Discussion

In our study we have demonstrated that small LAVI and small IVC diameter in addition to their percentage of change between supine and standing position as indicators of volume status are good predictors of positive results in head up tilt test.

According to***Moon et al.,*** [8] Small LA and LV volume were related with HTT results. Furthermore, the smaller LA the subject had, the faster was the time to faint during HTT. On the other hand, patients with large LA size (LAVI≥36 ml/m2) did not faint during HTT and this finding suggests that VVS is unlikely to be the reason of unexplained syncope in patients with significantly enlarged LA

According to***Shivaram et al.,*** [5]study in young adult patients has shown bigger diameters of the inferior vena cava (IVC) in patients with vasovagal syncope compared with controls, and the study suggested that increased venous compliance manifests as IVC dilation, which in turn leading to exaggerated abdominal venous pooling of the blood during standing, with resultant orthostatic manifestations.

According to our study the HTT positive group were significantly younger in age the same as***Moon et al.,*** [8]and have higher systolic blood pressure than negative group , while there is no significant difference regarding BSA , sex ,basal diastolic blood pressure and basal resting heart rate which is different from ***Moon et al.,*** [8]which shows HTT+ patients more likely to be female , had smaller BSA and had higher basal HR and this can be explained by different sample size and the study population.

From the statistical analysis from our study , both LAVI and IVC either supine or standing position was significantly lower among HTT positive group than negative group. which were the same result of***Moon et al.,*** [8]regarding LAVI and could be explained by:

firstLA acts as a “reservoir” during systole, a “conduit” and a “booster pump” in early and late diastolic period, respectively , progressive decline of LA volume by venous blood pooling and transient LA hypocontractility by parasympathetic activity were mentioned to be contributory factors in VVS during HTT . Therefore, subjects with small LA volume reserve may show a significant decline of cardiac output, leading to syncope during orthostatic stress.

Second, lower stroke volume in the condition of orthostatic stress needs higher heart rate responsiveness.However, an increase in heart rate alone may not besufficient to maintain cardiac output and cerebral perfusion in patientssusceptible to VVS with limited heart rate response and LA volumereserve and there is no significantly different in basal HR of both groups.

And against***Shivaram et al.,*** [5]and explained it by young adults with syncope showing relative increases in splanchnic blood volume during the tilt test ***(9)*** Other studies have demonstrated that abdominal compression is more effective than lower extremity compression in preventing orthostatic symptoms and have suggested that abdominal venous blood pooling plays a role in pathogenesis of this type of syncope [10]and his findings lend further support to the concept that in adolescents with syncope, IVC enlargement may serve as a surrogate clinical marker of elevated systemic venous compliance, which contributes to their tendency to faint.

But according to the result of our study which shows that the IVC diameter is significantly lower in HTT positive group and we explain it the IVC diameter in normal individuals is an indicator to the whole body volume status not only for elevated systemic venous compliance.

Our results shows that both LAVI on standing and supine position was in high significantly positive correlation with time needed to appearance of symptoms of HTT which are the same result of ***(8)***

Our results shows that there is no statistical significant difference among HTT positive group and negative group regarding E\A value or diastolic functions which needs further studies to be evaluated .

Our results shows that the percentage of change between supine and standing position can predict the occurrence of syncope with

Cutoff value for LAVI % of change was if the individual has a % of change in his LAVI over 16.2 % he will develop syncope with a sensitivity of 96% and a specificity of 80% and if he has % of change in diameter of IVC of 18.2 % or more he will develop syncope with a sensitivity of 88% and a specificity of 60%.

V. Conclusion

Small LA volume in standing position and IVC diameter in supine and standing position in addition to their percentage of change between supine and standing position are independent predictors of HTT-induced VVS.

Limited intracardiac volume reserve might play an important role in the mechanism of VVS.

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