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Valsalva Maneuver Impact on Both Ventricular Systolic and Diastolic Echocardiographic Parameters in Subjects with Normal Versus High Ventricular Filling Pressures: A Double Blinded Study

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Abstract

Introduction: Echocardiography is used as a useful and common method to assess Left Ventricular and Right Ventricular (LV and RV) systolic and diastolic functions. Valsalva Maneuver (VM) with the increase in the intra-thoracic and intra-abdominal pressure is often used as an uncomplicated, cost-effective and non-invasive technique for diagnosing clinical conditions such as heart murmurs. However, in terms of echocardiography, the use of VM has been limited to only a few parameters for many years. In contrast, blood level of N-Terminal Pro-B-Type Natriuretic Peptide (NT Pro-BNP) indirectly discriminates normal or high ventricular Filling Pressure (FP). This study aimed at providing a comprehensive review of the technique as well as comparing the VM effect in ACS patients; with and without elevated FP on either RV or LV diastolic and systolic echocardiographic parameters.

Methods: Thirty-eight patients, who were diagnosed with possible ACS; unstable angina pectoris, NSTEMI and STEMI, underwent coronary angiography enrolled in this double-blinded clinical trial study. The mild Coronary Artery Disease (CAD) with normal NT Pro-BNP levels were included in study group one and cases with significant CAD and high level of NT Pro-BNP who underwent PCI were included in study group two. All the systolic and diastolic indicators of both ventricles, totaling twenty-four parameters which have been previously mentioned in the academic literature, have been evaluated; once before valsalva and once during second stage of the maneuver. Echocardiography is performed by an advanced echo machine and by an expert cardiologist-echocardiographer; the recorded images were reviewed by the second echocardiographer separately.

Results: Between the two groups, LV parameter analysis showed significant difference in LV EF pre and post VM. However, there was a statistically insignificant difference regarding other systolic as well as diastolic parameters. Between the two groups, RV parameters analysis indicated no significant difference regarding systolic and diastolic parameters pre and post VM.

Conclusion: This research for the first time assessed post VM changes in four chambers as well as mitral and tricuspid valves parameters in ACS patients with normal *versus* high level of FP. Previously, LV diastolic dysfunction and Doppler mitral inflow pattern correlation with VM were verified. In the present study, in addition to those known findings from before-except the LV Ejection Fraction (LVEF) that showed there was statistically significant difference in pre-and post-VM-other systolic parameters, as well as diastolic indicators in either RV and LV, were identical. Therefore, we do not recommend conducting valsalva maneuver on the rest of the other parameters to diagnose systolic and diastolic dysfunction in ACS patients with mild *versus* significant CAD who were assumed to have normal or elevated filling pressures.

Keywords: Valsalva maneuver • Echocardiographic parameters • Ventricular systolic function • Ventricular diastolic function

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Introduction

Echocardiography is used as a useful and common method to assay the left ventricular function [1]. Assessing the Left Ventricular (LV) diastolic function is an integral component of a regular examination, especially among cases suffering from ischemic heart disease and cases with acute coronary syndrome; ST Segment Elevation Myocardial Infarction (STEMI) *vs*. Non-ST Segment Elevation MI (NSTEMI) [2]. Some of the patients with MI would suffer Heart Failure (HF) [3]. LV diastolic function evaluation and filling pressures is helpful in discriminating the HF from many disorders, such as pulmonary disease leading to dyspnea; assessing the prognosis and identifying the underlying HF and is considered as the most effective therapy [4]. Mitral inflow examination by doppler echocardiography has been extensively applied for assessing the LV diastolic function [5]. Evaluation of alterations in the mitral inflow due to a Valsalva maneuver has been proposed to differentiate between normal and pseudo-normal LV filling models [6].

Valsalva maneuver by the increase in the intrathoracic and intraabdominal pressure is often used as an uncomplicated, cost-effective, non-invasive technique for diagnosing some clinical conditions such as heart murmurs, patent foramen ovale or septal defects [7]. NT-Pro-BNP, as a neuro-hormone that is mainly yielded in the heart, increases the HF as well as exacerbates the valve disease and Coronary Artery Disease (CAD) [8].

Echocardiography has been widely used to evaluate LV diastolic function over the last 20 years [9]. This research aimed at providing a comprehensive review on the methods and also diastolic and systolic factors importance [10]. Also, we aimed to determine the effect of Valsalva maneuver, a well-known technique for several years to discriminate different diastolic grades; in other words, we attempted to help unmask grade II from grade I and also grade IIIa from grade IIIb diastolic dysfunction. However, we aimed at evaluating the maneuver impact on both ventricular systolic and diastolic functions as well as concomitant measurement of NT-pro BNP as a marker for cardiac disease status [11].

Materials and Methods

Patients

The current double-blinded, clinical trial was carried out in three medical university hospitals, Alzahra cardiac hospital, Faghihi hospital and Namazi hospital, affiliated to Shiraz university of medical sciences from October 2018 to February 2019 [12]. The institutional review board and the medical ethics committee of Shiraz University of medical sciences confirmed the research protocol [13]. All the participants presented their written informed consents prior to the study. This clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT20141218020364N11) [14]. All patients who were diagnosed with possible primary Acute Coronary Syndrome (ACS), unstable angina pectoris, STEMI and NSTEMI and had undergone coronary angiography were enrolled in the study [15]. All ACS patients who were over 18, were able to cooperate for Valsalva's maneuver and whose echocardiography could be done with proper technique were enrolled [16].

Cases with previous history of HF, cardiac resynchronization therapy devices or implantable cardioverter defibrillator, multiple history of heart attack, coronary artery bypass grafts requiring catheterization or emergency bypass surgery, chronic respiratory problems or asthma and persistent ischemia were excluded [17].

In total, 38 cases were diagnosed with ACS at the hospital by coronary angiography [18]. The participants were informed about the research procedure and the written informed consents were obtained [19].

The subjects were assigned into two groups according to the angiography reports; those with mild Coronary Artery Disease (CAD) were assigned into study group one and the significant CAD cases who had undergone stent angioplasty were enrolled in study group two [20]. Nine mild CAD patients were detected to have severe CAD by the second opinion and were excluded [21].

Two severe CAD patients did not participate in the study and were excluded [22]. Twelve patients with mild CAD and fifteen with severe CAD who had undergone stent angioplasty were enrolled in the study [23]. The acute phase of CAD was improved in both groups and patients were in stable condition [24].

Serum NT-proBNP levels were assessed just before doing echocardiography in both groups [25]. Studies were conducted through the second stage of Valsalva maneuver [26]. Patients blew on a narrow serum tube (forceful expiration) attached to the mercuric barometric device to 40 mm Hg pressure for 10 seconds [27].

Systolic and diastolic indicators were measured once before Valsalva and once during stage 2 of the maneuver [28]. Echocardiography is performed by an echo device and by one cardiologist [29].

In this double-blind research, the subjects were familiar with Valsalva maneuver method and echocardiography. In addition, the observer (who answered the questionnaire) and the analyst were blinded to the groups.

The main researcher (cardiologist) was informed about the groups and all echocardiographies were conducted by a different cardiologist. The study groups were not blinded to the safety and data monitoring committee.

Standard echocardiographic measurements

The left atrium end-systolic volume was measured by the modified biplane simpson technique from four-chamber and two-chamber images. The left atrial volume index was calculated by the volume of the left atrium to body surface ratio. The right atrium end-systolic area was measured from apical 4-chamber images.

The right ventricle end-systolic and end-diastolic dimensions, in addition to Fractional Area Changes (FAC), were assessed from the apical right chamber focus view. The LV Ejection Fraction (LVEF) was evaluated by using a modified biplane Simpson approach. The peak flow velocity in early diastole (E-wave) as well as through the atrial contraction (A-wave) and also the E/A ratio and the Deceleration Time (DT) of the E-wave of the left and right ventricles were calculated.

The LV and LV systolic function was measured using Mitral and Tricuspid Annular Plane Systolic Excursion (MAPSE and TAPSE) respectively at the septal direction by M-mode echocardiography from an apical four-chamber vision and defined as an alternate to the total systolic longitudinal function of the lateral annulus of either valve. In fact, the e amount of the septal and lateral ventricle wall of the LV and RV were assessed with Doppler Tissue Imaging (DTI).

Through the four-chamber vision, extraction of the doppler trace was done from the septal as well as lateral mitral annulus. Then, the mean of the two early diastolic tissue velocities (E) and E/e ratio were calculated.

Reference range for N-terminal proBNP

Natriuretic peptides are mostly used for establishing the HF diagnosis in patients needing emergency care for an uncertain diagnosis.

The reference amounts of BNP and NT-proBNP act differently in excluding or confirming HF diagnosis. NT-proBNP based reference laboratory was as follows: At age less than 75; more than 125 pg/ml; in favor of HF diagnosis. At equal or more than 75 years of age; more than 450 pg/ml; in favor of high ventricular filling pressures.

Statistical methods

Quantitative data were reported as mean and standard deviation. Qualitative variables were presented as a number.

A student t-test was applied to compare the two groups. If the data were not normal, the mann-whitney test was employed.

The paired sample t-test was applied for comparing the parameters before and after the intervention; if the data were not normal, the Wilcoxon singed ranks test was used.

Data analysis was performed by SPSS 16. The P values of smaller than 0.05 were regarded significant (Figure 1).

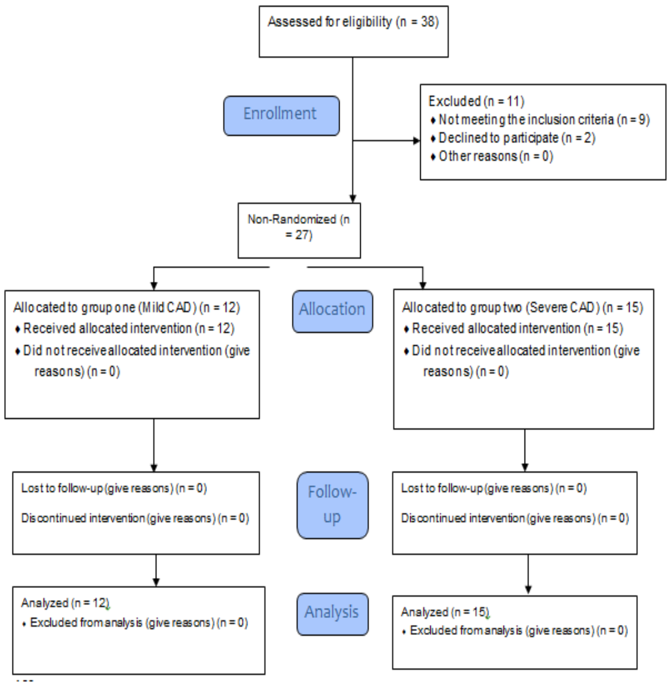

Figure 1. The consort diagram showing the allocation process throughout the trial.

Results

In this pre-and post-semi-experimental double-blind clinical trial study, 38 patients aged 37 years-78 years with the average age of 55.66 ± 10 years were included. The individual characteristics, anthropometric indicators, as well as the history of cardiovascular risk factors. The results of the four-chamber parameters are presented in and the comparison of the mitral and tricuspid valves parameters is presented in Tables 1-3.

Table 1. Participants characteristics, distribution of anthropometric indices and cardiovascular risk factors past medical history.

		Mean ± SD number (%)
Age		55.66 ± 10.00
Gender	Male	23 (60.5)
	Female	15 (39.5)
Weight		68.55 ± 12.65
Height		167.55 ± 9.76
BMI		24.5 ± 4.59
DM		15 (39.5)
Smoke		18 (47.4)
HTN		13 (34.2)
HLP		21 (55.3)

Table 2. Comparison of mean pre-and post-Valsalva maneuver parameters between groups and inter-groups.

Variable	Echocardiography parameters	Mean ± SD		P-value
		Group one	Group two	
LV diastolic	Baseline	105.76 ± 21.89	128.96 ± 33.38	0.079
	During Valsalva maneuver	87.02 ± 27.96	102.97 ± 36.93	0.251
	P-value	0.004	0.007	
LV systolic	Baseline	43.81 ± 1394	71.89 ± 25.98	0.002
	During Valsalva maneuver	39.75 ± 12.78	63.73 ± 31.74	0.015
	P-value	0.193	0.395	
EF%	Baseline	59.4 ± 8.40	42.54 ± 11.54	<0.001
	During Valsalva maneuver	55.56 ± 6.20	42.05 ± 11.39	<0.001
	P-value	0.076	0.85	
LAVI	Baseline	23.37 ± 5.79	23.81 ± 6.59	0.859
	During Valsalva maneuver	14.59 ± 4.97	15.36 ± 6.19	0.728
	P-value	<0.001	0.002	
RV diastolic area	Baseline	30.22 ± 10.63	24.47 ± 11.04	0.184
	During Valsalva maneuver	24.30 ± 10.21	19.60 ± 8.48	0.202
	P-value	0.078	0.078	
RV systolic area	Baseline	10.72 ± 2.85	9.90 ± 5.21	0.631
	During Valsalva maneuver	10.17 ± 4.43	8.04 ± 3.58	0.179
	P-value	0.641	0.225	
RV FAC%	Baseline	46.90 ± 10.46	43.32 ± 9.58	0.363
	During Valsalva maneuver	42.63 ± 8.51	42.93 ± 11.63	0.941
	P-valu	0.223	0.922	
RA area	Baseline	62.16 ± 14.92	70.73 ± 25.22	0.309
	During Valsalva maneuver	52.75 ± 19.95	52.06 ± 24.03	0.938
	P-value	0.074	<0.001	

Table 3. Comparison of mean pre- and post-Valsalva maneuver mitral and tricuspid valves parameters between groups and inter groups.

Variable	Echocardiography parameters	Mean ± SD		P-valve
		Group one	Group two	
Mitral E	Baseline	62.16 ± 14.92	70.73 ± 25.22	0.309
	During Valsalva maneuver	52.75 ± 19.95	52.06 ± 24.03	0.938
	P-value	0.074	<0.001	
Mitral A	Baseline	73 ± 9.50	76.13 ± 21.16	0.614
	During Valsalva maneuver	62.58 ± 11.57	64 ± 24.28	0.854
	P-value	0.346	0.244	

Mitral E/A	Baseline	5.22 ± 15.04	0.9 ± 0.55	0.427
	During Valsalva maneuver	8.59 ± 26.89	0.82 ± 0.42	0.347
	P-value	0.346	0.244	
Mitral DT	Baseline	222.85 ± 71.68	185.86 ± 33	0.12
	During Valsalva maneuver	250.75 ± 79.00	196.53 ± 102.27	0.144
	P-value	0.423	0.685	
Mitral septal e	Baseline	7.57 ± 1.91	7.49 ± 2.17	0.92
	During Valsalva maneuver	11.56 ± 20	9.74 ± 17.51	0.806
	P-value	0.488	0.62	
Mitral lateral e	Baseline	10.14 ± 2.92	8.60 ± 3.23	0.213
	During Valsalva maneuver	8.15 ± 2.05	7.26 ± 2.46	0.322
	P-value	0.083	0.067	
Mitral E/e	Baseline	7.27 ± 1.32	8.39 ± 2.07	0.116
	During Valsalva maneuver	6.74 ± 3.02	8.46 ± 3.2	0.161
	P-value	0.495	0.945	
Tricuspid E	Baseline	40.91 ± 9.56	42.91 ± 14.09	0.679
	During Valsalva maneuver	38.08 ± 7.44	41.78 ± 9.31	0.273
	P-value	0.195	0.667	
Tricuspid A	Baseline	44.33 ± 15.11	46.34 ± 20.85	0.782
	During Valsalva maneuver	37.16 ± 11.71	49.58 ± 25.13	0.128
	P-value	0.039	0.578	
Tricuspid E/A	Baseline	1.00 ± 0.41	1.49 ± 1.96	0.408
	During Valsalva maneuver	1.08 ± 0.33	1.11 ± 1.83	0.83
	P-value	0.486	0.441	
Tricuspid septal e	Baseline	7.57 ± 1.91	7.49 ± 2.17	0.92
	During Valsalva maneuver	5.94 ± 1.14	5.36 ± 0.87	0.151
	P-value	0.008	0.001	
Tricuspid Lateral e	Baseline	10.40 ± 3.01	10.40 ± 2.45	0.999
	During Valsalva maneuver	6.96 ± 2.41	7.18 ± 3.64	0.859
	P-value	0.005	0.009	
Tricuspid E/e	Baseline	4.69 ± 1.40	4.68 ± 2.04	0.991
	During Valsalva maneuver	6.07 ± 1.60	6.52 ± 2.20	0.557
	P-value	0.001	0.006	
Mitral lateral S	Baseline	8.78 ± 1.52	8.26 ± 3.42	0.631
	During Valsalva maneuver	10.58 ± 2.27	8.70 ± 3.32	0.997
	P-value	0.02	0.732	
Mitral septal S	Baseline	7.69 ± 1.42	7.00 ± 1.84	0.339
	During Valsalva maneuver	9.55 ± 4.06	7.20 ± 2.35	0.108
	P-value	0.11	0.723	

Tricuspid lateral S	Baseline	13.02 ± 2.64	12.14 ± 2.02	0.071
	During Valsalva maneuver	11.82 ± 5.60	8.60 ± 3.10	0.07
	P-value	0.436	0.001	

Between the two groups, analysis of the LV parameters showed a significant difference in pre-post Valsalva maneuver EF and LV systolic parameters. This results showed no significant difference in LV diastolic, LAVI, Mitral E velocity, Mitral A velocity, Mitral E/A, Mitral DT, Mitral Septal e, Mitral Lateral e, Mitral E/e, Mitral Lateral S and Mitral Septal S parameters between groups one and two. Inter-group (group one) analysis of LV parameters showed significant difference in pre-post valsalva maneuver LV diastolic and Mitral Septal and lateral S parameters. These results showed no significant difference in LV systolic, LAVI, EF, Mitral E, Mitral A, Mitral E/A, Mitral D/T, Mitral Septal e, Mitral Lateral e, Mitral E/e and Mitral Septal S parameters in group one in pre- post Valsalva maneuver. Inter-group (group two) LV parameters analysis showed a significant difference in pre-post Valsalva maneuver LV diastolic and Mitral E parameters. This result showed no significant difference in LV systolic, LAVI, EF, Mitral A, Mitral E/A, Mitral D/T, Mitral Septal e, Mitral Lateral e, Mitral E/e, Mitral Septal S and Mitral Lateral S parameters in group two in pre-post Valsalva maneuver. RV parameters analysis showed no significant difference in pre-post Valsalva maneuver including RV diastolic area, RV systolic area, RV FAC, RA area, Tricuspid E velocity, tricuspid A velocity, tricuspid E/A, tricuspid septal e, tricuspid lateral e, tricuspid E/e and tricuspid septal and lateral S parameters between groups one and two. Within group one, RV parameters analysis showed a significant difference in pre-post Valsalva maneuver Tricuspid A velocity, tricuspid septal e, tricuspid lateral e and tricuspid E/e parameters. Within group two, RV parameters analysis showed a significant difference in pre-post Valsalva maneuver tricuspid lateral S, tricuspid septal e, tricuspid lateral e and tricuspid E/e parameters. No significant difference was found in pre and post-Valsalva maneuver TAPSE and MAPSE parameters by through intra and inter-groups analysis (Figures 2 and 3).

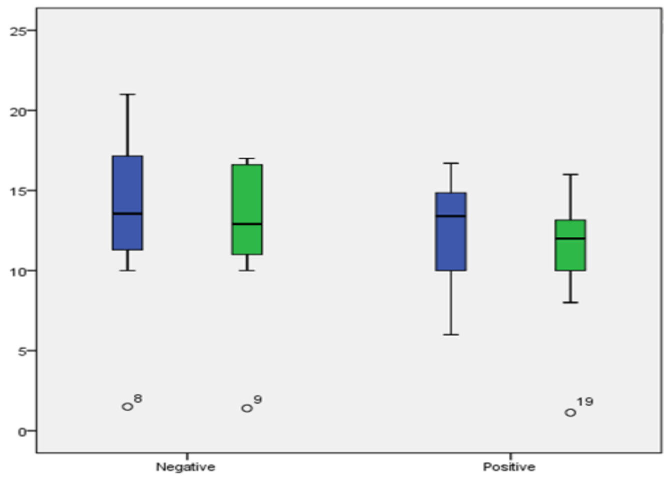

Figure 2. Mitral annular plane systolic excursion comparison with M-mode echocardiography from an apical 4-chamber view, pre and post-Valsalva Maneuver in both positive and negative NT-proBNP groups. **Note:** ■-MABSE baseline ■-MABSE during

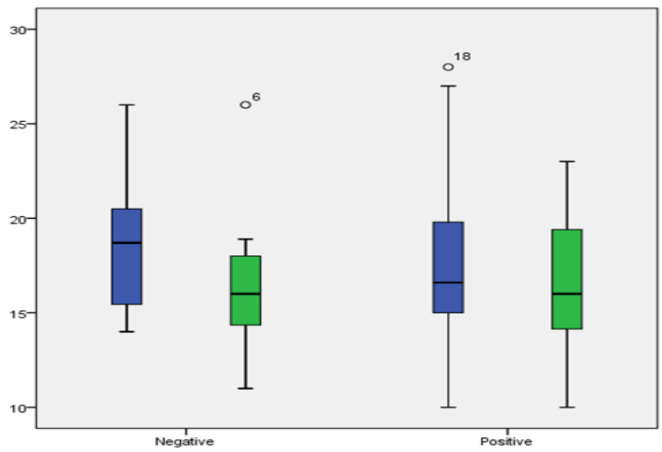

Figure 3. Tricuspid annular plane systolic excursion comparison with M-mode echocardiography from an apical 4-chamber view, pre-and post-Valsalva maneuver in both positive and negative NT-proBNP groups. **Note:** ■ -TAPSE baseline ■ -TAPSE during

Discussion

Antonio Maria Valsalva is famous for describing the maneuver that bears his name. In the original 1704 reporting, the use of the maneuver, essentially a strong expiration to a closed mouth and nose, was beneficial in rapid expulsion of pus from the middle ear. Subsequent investigation of the Valsalva maneuver has focused on its cardiovascular and autonomic nervous properties. When the Valsalva maneuver is performed in a medical environment (e.g. hospital, clinic, etc), all patients should have vital signs monitored before and after the maneuver. Although seldom used in current practice, the Valsalva maneuver has been evaluated among cases with heart failure and/or LV dysfunction. Patients using Valsalva maneuver for diagnostic purposes in this setting should have continuous blood pressure monitoring along with continuous heart rate monitoring (single-lead telemetry is adequate here) during the maneuver.

The Valsalva maneuver can be conducted by forceful expiration (nearly 40 mmHg) to a closed nose and mouth, resulting in an intricate hemodynamic process of 4 stages. LV preload is decreased in the strain stage (stage II) and mitral inflow alterations are monitored for distinguishing normal from PNF (pseudo normal LV filling) figures. An adequate elevation should be generated by the patient in intrathoracic pressure. The echocardiographer needed to maintain the accurate specimen volume location between the mitral leaflet tips through the maneuver. A reduction of 20 cm/s in the mitral peak E velocity is commonly regarded as a proper attempt in cases with no restrictive filling.

Valsalva maneuver includes four stages. Stage one is known as the beginning of straining with enhanced intrathoracic pressure in which the heart rate is the same, however, blood pressure increases.

Stage two is characterized with reduced venous return resulting in reducing the stroke volume as well as pulse pressure continuously straining. There is an increase in heart rate and blood pressure is decreased. In stage three there is straining with reduced intrathoracic pressure and pulmonary blood flow normalization. Stage four features an increase in blood pressure (regarding the healthy heart) and the heart rate is returned to its baseline. Although information on the impact of Valsalva's maneuver on echocardiographic parameters is limited, reports indicate that the Valsalva maneuver is capable of modifying echocardiographic findings in cardiac patients.

A pseudo-normal mitral inflow figure can be occurred with a mild-to-moderate elevation in LA pressure in postponed myocardial relaxation. Valsalva maneuver reduces the preload through the strain stage and, therefore, pseudonormal mitral inflow alters the impaired relaxation figure.

Regarding the E/A ratio and Valsalva, the absolute a velocity (peak A minus the E height at the beginning of A) is essential. Among cardiac cases, a reduction of Δ50% in the E/A ratio has shown greatly instrumental for enhanced LV filling pressures; however, lower changes do not always represent normal diastolic performance. Moreover, there is an incomplete irreversible Valsalva, which is used as an index for the diastolic filling figure irreversibility.

The second phase of Valsalva maneuver changes the amplitude as well as some waves time and distances in the electrocardiogram. In this context, this is one of the famous effects is Brody theory. Valsalva maneuver's effect on the difference between the highest and lowest QT-intervals and levels below the T-wave curve have been reported to not be significant.

Recently reported that the hemodynamic effect of Valsalva consists of four initial steps, which is applicable in echocardiography for a precise diagnosis. Valsalva can be utilized for reducing the preload and stimulating the LV Output Region (LVOT) gradient in the LOVT obstruction. Additionally, the E/A proportion decrease in the mitral inflow of over 50% with Valsalva is closely linked to an enhanced LV filling pressure as well as diastolic dysfunction. Valsalva maneuver can also increase the temporary RA pressure. Studied the impact of Valsalva maneuver on cardiac hemodynamics and right-to-left shunting among cases with patent foreman oval. They have argued that the Valsalva maneuver increases a pressure felt inside the chest. It also prevents the intravenous return, which results in limitation of the LV filling and reduction of E and A peaks. They also stated that in the Valsalva maneuver, the LV End Diastolic Volume (LVEDV) reduced meaningfully.

In the study, the preload reduction impact on the transmitral flow velocity with Valsalva maneuver among cases with hypertension was compared with normal patients. They found that after the Valsalva maneuver in these patients, one percent of patients had hypertension, LV relaxation dysfunction and diastolic disorders, along with a reduction in coronary reserve. An interesting study by Jensen and colleagues comparing Valsalva maneuver as well as exercise echocardiography in subjects with LVOT in obstructive cardiomyopathy was conducted in 2010. They have argued that the Valsalva maneuver and exercise echocardiography produce similar degrees of LVOT gradient. They have indicated that the effects of Valsalva's maneuvers on the echocardiography results were significant. Therefore, Valsalva's maneuvers should be considered as the first choice of stress modality in hypertrophic cardiomyopathy patients.

Our results showed that EF and LV systolic parameters (LV Parameters) in pre-post Valsalva maneuver showed a significant difference among both groups. LV parameters assessment of group one (negative NT-proBNP) showed a significant difference in pre-post Valsalva maneuver LV diastolic, Valsalva Mitral S parameters. Analysis of the LV parameters of group 2 (Positive NT-proBNP) showed a significant difference in pre-post Valsalva maneuver, r LV diastolic and Mitral E parameters.

Conclusion

Analysis of RV parameters between the groups showed no significant difference in pre-post Valsalva maneuver RV diastolic area, RV systolic area, RV FAC, RA area, tricuspid E velocity, tricuspid A velocity, tricuspid E/A, tricuspid septal e, tricuspid lateral e, tricuspid E/e and tricuspid septal and lateral S parameters. Analysis of the RV parameters of group one showed a significant difference in pre-post Valsalva maneuver tricuspid A, tricuspid septal e, tricuspid lateral e and tricuspid E/e parameters. Also, the analysis of RV parameters of group two showed a significant difference in pre-post Valsalva maneuver Valsalva tricuspid S, tricuspid septal e, tricuspid lateral e and tricuspid E/e parameters. This research for the first time assessed four-chamber, mitral and tricuspid valves post-Valsalva's maneuvers changes in ACS patients. Previously, the correlation of LV diastolic dysfunction and doppler mitral inflow pattern with Valsalva's maneuver was validated. No statistically significant difference was found in pre- and post-Valsalva maneuver TAPSE and MAPSE parameters by within and between the groups. LV diastolic dysfunction was approved using Valsalva's maneuver in both groups, too. Currently, we do not recommend conducting Valsalva maneuver on the test of the other parameters to diagnose diastolic dysfunction. One limitation of the study to note was the small sample size.

Conflict of Interest

None

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