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ORIGINAL ARTICLE

Accuracy of Mitral Valve Leaflets Tips Separation Assessed by 3D Transthoracic Echocardiography in Predicting Rheumatic Mitral Valve Stenosis Severity

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Abstract

Background: ***A significant cause of cardiovascular load in developing nations is mitral stenosis (MS), which is primarily due to rheumatic fever.***

Aim and objectives: ***To assess the accuracy of mitral valve leaflets tips separation by 3DTTE in predicting the severity of rheumatic mitral valve stenosis and comparing MLS index by 3DTTE and MLS index by 2DTTE using planimetered MVA by 3DTEE as a reference method.***

Patients and methods: ***This analytic cross-sectional study was conducted at the Cardiology Department of Al-Azhar University (Bab El-Sheriya University Hospital) from September 2022 to October 2023. It included sixty consecutive patients candidates for TEE evaluation; thirty did not have rheumatic mitral valve stenosis, and thirty others had significant rheumatic mitral valve stenosis (mitral valve area ≤ 1.5 cm2 by 2D TTE).***

Results: ***According to our research, MLSI2D and MLSI3D have excellent predictive power for MS severity. Our findings also demonstrate that MLSI3D is an accurate, user-friendly, and readily accessible index that can be used as an alternative to other techniques for assessing the severity of MS, particularly by general cardiologists. This would lead to even more precise decision-making.***

Conclusion: ***Mitral leaflet separation assessed by 3D TTE has a reliable and unremarkable ability to predict the severity of rheumatic mitral stenosis. MLS assessed by 3D TTE is more accurate than MLS by 2D TTE in the prediction of the severity of mitral stenosis***

Keywords: Echocardiography; Rheumatic Mitral valve; Stenosis severity

1. Introduction

A significant cause of the cardiovascular load in developing nations is mitral stenosis (MS), which is primarily due to rheumatic fever. Although rheumatic heart disease is becoming less common in developed countries, MS remains a worry because of immigration from underdeveloped nations, along with a switch in aetiology from rheumatic disorders to degenerative valve disorders.[1]

Accurate Determination of the etiology and stage of MS is crucial for making decisions about medical and interventional treatment plans for the affected individuals. According to the most recent guidelines, the primary imaging modality for determining the severity of MS is echocardiography, which should be evaluated based on pulmonary pressures, Doppler gradients, and valve area.[2] Proximal iso-velocity surface area measurement (PISA), pressure half-time (PHT), transmitral gradient, continuity equation (CE), and planimetry are some of the techniques that have been proposed for evaluating mitral valvular orifice area (MVA). All techniques, however, have a few acknowledged potential drawbacks. Variations influence PHT in left ventricular compliance and preload and highly depend on hemodynamic factors. Trans-valvular flow, cardiac output, and concurrent mitral regurgitation (MR) have a significant impact on transmitral gradient and CE.[3]

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PISA takes multiple measurements, which could make it a complex and technically challenging procedure. Additionally, planimetry can be difficult to measure, particularly among less experienced cardiologists, and is highly operator-dependent despite having the best relevance with the anatomical MVA as determined by explanted valves.[4]

The most common modality available to cardiologists is two-dimensional transthoracic echocardiography (2DTTE). However, studies have shown that it overestimates the planimetered area of the MV when compared to three-dimensional transesophageal echocardiography (3DTEE).[5] Planimetered MVA using 3DTEE is arguably the most precise way of estimating MVA, but its semi-invasive nature and lack of accessibility make it unlikely to be used routinely.[6]

In the current study, we aimed to assess the accuracy of mitral valve leaflets tips separation by 3DTTE in predicting the severity of rheumatic mitral valve stenosis and comparing the MLS index by 3DTTE and MLS index by 2DTTE using planimeter MVA by 3DTEE as a reference method.

2. Patients and methods

This analytic cross-sectional study was conducted at the Cardiology Department of Al-Azhar University (Bab El-Sheriya University Hospital) from September 2022 to October 2023. The study included 60 patients who were candidates for TEE. They were subdivided into two groups: Thirty patients had had significant mitral valve stenosis (mitral valve area ≤ 1.5 cm2 by 2D TTE) of rheumatic aetiology. In contrast, the remaining thirty patients did not have this condition. They were enrolled in the study after obtaining their informed consent and after a full explanation of the purpose and nature of the study.

2.1.Inclusion criteria: Patients candidate for TEE with significant rheumatic MS (Area ≤ 1.5 cm2 by 2DTTE) and patients candidate for TEE without MS were included as a control group.

2.2.Exclusion criteria: Patients with prosthetic heart valves, sub-optimal and unfeasible imaging, a history of percutaneous mitral commissurotomy (PMC), and those who were rejected for the study.

2.3.Methods:

Detailed medical history taking with special emphasis on rheumatic fever (e.g., history of arthritis) and symptoms (dyspnea, especially in the Heart Association (NYHA), orthopnea, palpitation, cough, expectoration and hemoptysis). Detailed general and local clinical examination to detect predictors of severity of mitral stenosis according to ESC/EACTS Valvular Heart Disease Guidelines was obtained. A resting twelve-lead surface electrocardiogram (ECG) and a long strip were obtained to detect heart rhythm and rate in all patients.

2.4.Trans-thoracic Echocardiography:

A Philips® medical ultrasonogram machine (IE33, Philips® Medical Systems, USA) with S5-1 and X5-1 probes. The most current EACVI recommendations were followed while recording and calculating the ejection fraction and various cardiac chamber measurements. The maximal mitral valve leaflets tip separation at the inner edges was obtained by 2D echocardiography in the parasternal long-axis, parasternal short-axis, and apical four-chamber views with MVA. Then, MVA and mitral leaflet tip separation were measured in the parasternal short-axis view across the various mitral leaflet scallops (A1P1, A2P2, and A3P3) using X-plane 3D echocardiography. In patients with atrial fibrillation (AF), measurements were averaged over five cardiac beats and three subsequent cardiac cycles in patients with normal sinus rhythm . Figure 1

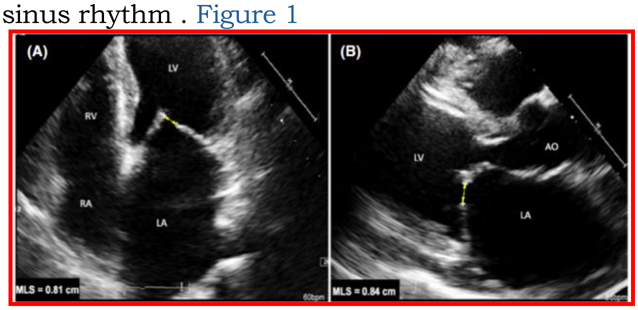

Figure 1. Using 2D transthoracic echocardiography, the mitral valve leaflet separation index (MLSI) is measured. By averaging the maximum distances at the leaflet tips in the parasternal long-axis (B) and apical four-chamber (A) views. RA is the right atrium, RV is the right ventricle, and LA is the left atrial (A) (B), after Bigdelu L, et al.[7]

Figure 2. Transthoracic three-dimensional quantitation of rheumatic mitral stenosis severity (parasternal window), after Bigdelu L, et al.[7]

2.5.Trans-esophageal echocardiography:

Trans-esophageal echocardiography under conscious sedation was performed at the same setting. A Philips® medical ultrasonogram machine (IE33, Philips® Medical Systems, USA) with the using of X7-2t probe to acquire both two-dimensional and three-dimensional trans-esophageal echocardiography. The process of acquiring images involved the bicommissural view in 2D, and then employing the 3D zoom mode to get real-time 3D "en face" views of the valve. Planimetry was carried out en face at an ideal cross section of the valve's annulus during its maximal early to mid-diastolic opening. Digitally stored photos were analyzed offline, and MVA3D was calculated using multi planar reconstruction using 3D images. According to figure 2, the most parallel viewpoint on the plane corresponding to the lowest mitral valve opening was the optimal cross section. In patients without atrial fibrillation (AF), measurements were averaged over three consecutive cardiac cycles, and in patients with AF, they were averaged over five.

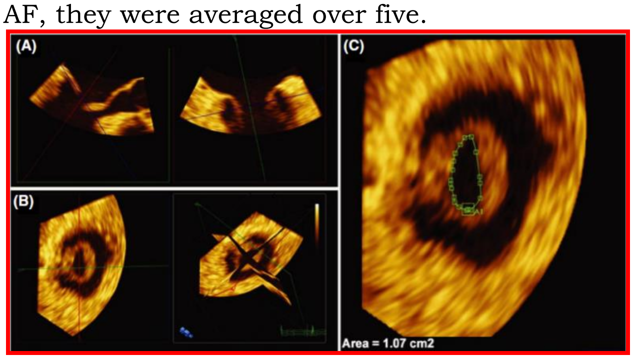

Figure 3. Mitral valve multiplanar reconstruction by trans-esophageal 3D echocardiography. An en face image for the measuring of mitral valve area (MVA) is provided by orthogonal cut planes produced using the narrowest mitral valves orifice at mid-diastole (A) and a perpendicular plane (B). Planimetry of the MVA using the short-axis view following multiplanar reconstruction at the tips of the mitral valve leaflets.

2.6.Statistical analysis

The data were inputted and analyzed using IBM SPSS software program version 25.0 (IBM Corp., 2017). IBM Corp. has released IBM SPSS Statistics for Windows, Version 25.0, in Armonk, NY. The qualitative data was characterized using both percentages and numerical values. The normality of the distribution was verified through the utilization of the Kolmogorov-Smirnov test. The quantitative data was described using the following metrics: mean, standard deviation, median, the interquartile range (IQR), and range (a minimum and maximum). A significance level of 5% was employed to evaluate the significance of the results. The chi-square test is employed to compare categorical variables within related samples and to compare dissimilar groups. The Student t-test is employed to compare related samples of normally spaced quantitative variables and to compare two examined groups. The Mann-Whitney test is employed to evaluate unevenly distributed quantitative variables between related samples, specifically to compare two examined groups. The paired student t-test is employed to compare related samples. Spearman's rank correlation coefficient (r) is employed to evaluate the magnitude of the relationship between non-parametric variables. The ICC is employed to evaluate the consistency or conformity of measurements conducted by different observers when measuring the same quantity. The Bland-Altman plot is a handy way to visually represent the relationship between two paired variables that are measured on the same scale. The ROC curve, which is a receiver operating characteristic, can be used to analyze the sensitivity and specificity of quantitative diagnostic measures that classify cases into two categories.

3. Results

The patients' age ranged between 34 years to 71 years with mean age was 49.43± 8.48 years. There were 25 (41.7%) males and 35 (58.3%) females with male to female ratio was 0.7:1. 24 (40%) cases were diabetics, 23 (38.3%) of them were hypertensive while 19 (31.7%) cases were smokers. The mean BMI and body surface area were 30.27± 3.08 Kg/m2 and 1.86± 0.14 m2 respectively, Table1.

Table 1. Demographic data and risk profile among the studied patients.

DESCRIPTION		STUDIED PATIENTS (N=60)	
		N	%
GENDER	Male	25	41.7%
	Female	35	58.3%
AGE (YEARS)	Mean±SD	49.43±8.48	
	Range	34.0-71.0	
DM	No	36	60.0%
	Yes	24	40.0%
HTN	No	37	61.7%
	Yes	23	38.3%
SMOKING	No	41	68.3%
	Yes	19	31.7%
BMI (KG/M^2)	Mean±SD	30.27±3.08	
	Range	21.9-37.3	
BODY SURFACE AREA (M^2)	Mean±SD	1.86±0.14	
	Range	1.56-2.20	

SD: standard deviation, DM: Diabetes Mellitus, HTN: Hypertension

According to 2D trans-thoracic Mitral leaflet separation measurements, PLAX, PSAX A1P1, PSAX A2P2, PSAX A3P3 and A4C were significantly lower in significant MS patients compared to controls (p<0.001), Table 2.

Table 2. Comparison between the two groups regarding 2D Mitral leaflet separation.

DESCRIPTION	CONTROLS (N= 30)					SIGNIFICANT MS (N= 30)					MANN-WHITNEY U TEST	
	Median	IQR		Range		Median	IQR		Range		Test value (Z_{MWU})	P-value
2D PLAX	3.18	3.01	-3.51	2.78	-3.73	0.88	0.70	-1.00	0.49	-1.2	6.395	<0.001
2D PSAX A1P1	2.79	2.64	-2.97	2.19	-3.32	0.58	0.48	-0.78	0.38	-0.95	6.262	<0.001
2D PSAX A2P2	3.25	3.09	-3.54	2.77	-3.82	0.81	0.69	-1.01	0.53	-1.2	6.373	<0.001
2D PSAX A3P3	2.81	2.67	-2.97	2.25	-3.22	0.60	0.48	-0.76	0.39	-0.89	6.314	<0.001
2D A4C	3.33	3.16	-3.62	2.91	-3.82	0.76	0.66	-1.02	0.55	-1.1	6.50	<0.001

p>0.05 is not significant, p≤0.05 is significant, p≤0.01 is highly significant, IQR: Interquartile range, PLAX: parasternal long axis view,

PSAX: Parasternal short axis, A4C: Apical 4 chamber * ZMWU Mann-Whitney U test

According to 3D trans-thoracic Mitral leaflet separation measurements (cm), PSAX A1P1, PSAX A2P2, and PSAX A3P3 were significantly lower in significant MS patients compared to controls (p<0.001), table 3.

Table 3. Comparison between the two groups regarding 3D Mitral leaflet separation.

	CONTROLS (N=30)					SIGNIFICANT MS (N=30)					MANN-WHITNEY U TEST	
	Median	IQR		Range		Median	IQR		Range		Test value (Z_{MWU})	P-value
3D PSAX A1P1	2.99	2.81	-3.19	2.47	-3.49	0.57	0.49	-0.80	0.42	-1.08	6.508	<0.001
3D PSAX A2P2	3.31	3.11	-3.57	2.89	-3.91	0.79	0.70	-0.92	0.50	- 1.3	6.507	<0.001
3D PSAX A3P3	2.98	2.87	-3.19	2.67	-3.59	0.62	0.49	-0.80	0.41	-1.1	6.568	<0.001

p>0.05 is not significant, p≤0.05 is significant, p≤0.01 is highly significant, IQR: Inter-quartile range, PSAX: Parasternal short axis view, * ZMWU Mann-Whitney U test

In patients with significant rheumatic MS there were:

Strongly positive and statistically significant Correlation (p-value<0.001) is seen between MVA & MLS3DTTE PSAX A1P1 (r=0.61). Positive and statistically significant correlation (p-value<0.001) is seen between MVA & MLS3DTTE PSAX A2P2 (r=0.81). Positive and statistically significant Correlation (p-value<0.001) is seen between MVA along with MLS3DTTE PSAX A3P3 (r=0.70). Positive and statistically significant correlation (p-value<0.001, r=0.73) is found between 2D PLAX and MVA. Positive and statistically significant Correlation (p-value<0.001, r=0.66) is seen between MVA & 2D PSAX A1P1. Positive and statistically significant correlation (p-value<0.001, r=0.76) is seen with 2D PSAX A2P2 and MVA. Positive and statistically significant correlation (p-value<0.001, r=0.70) is seen between MVA & 2D PSAX A3P3. Positive and statistically significant correlation (p-value<0.001, r=0.55) is found between MVA & 2D A4C view, table 4.

In patients without MS there were:

Control group had no MS "MVA was in normal range" and the MVA had no significant correlation with mitral leaflet separation in this group. Insignificant positive correlation is found (p-value=0.163, r=0.26) between 3D PSAX A1P1 and MVA. Insignificant positive correlation is found (p-value=0.324, r=0.18) between 3D PSAX A2P2 and MVA. Insignificant positive correlation is found (r=0.27, p-value=0.148) between 3D PSAX A3P3 and MVA. A positive but insignificant correlation (r=0.29, p-value=0.116) was found between 2D PLAX and MVA. There is a positive correlation between 2D PSAX A1P1 and MVA (P-value=0.174, r=0.25) indicating no statistical significance. There is a positive insignificant correlation (p-value=0.55, r=0.11) between 2D

PSAX A2P2 and MVA. There is a positive insignificant correlation found between 2D PSAX A3P3 and MVA (P-value=0.151, r=0.26) indicating no statistical significance. MVA and 2D A4C have a positive but also insignificant correlation (p-value=0.246, r=0.21), Table 4.

Table 4. Correlation study between 3D trans-esophageal MVA and mitral leaflet separation by 3D and 2D TTE in significant MS group.

		SIGNIFICANT MS		CONTROLS	
		r	p-value	r	p-value
3D	MVA vs PSAX A1P1	0.61	<0.001	0.26	0.163
	MVA vs PSAX A2P2	0.81	0.001	0.18	0.324
	MVA vs PSAX A3P3	0.70	<0.001	0.27	0.148
2D	MVA vs PLAX	0.73	<0.001	0.29	0.116
	MVA vs PSAX A1P1	0.66	<0.001	0.25	0.174
	MVA vs PSAX A2P2	0.76	<0.001	0.11	0.550
	MVA vs PSAX A3P3	0.70	<0.001	0.26	0.151
	MVA vs A4C	0.55	<0.001	0.21	0.246

(r): Pearson correlation coefficient. p-value<0.001 is considered highly significant.
p-value>0.05 is considered non-significant.

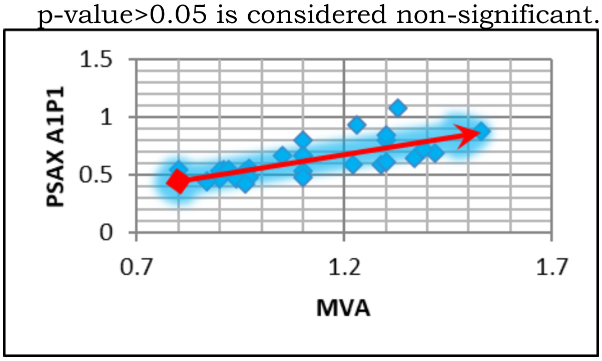

Figure 4. Positive correlation between MVA and PSAX A1P1 in patients with significant MS.

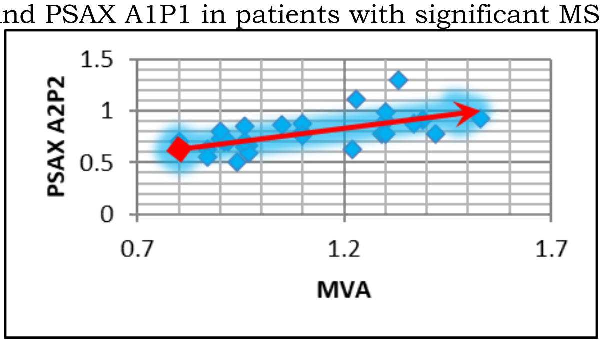

Figure 5. Positive correlation between MVA and PSAX A2P2 in patients with significant MS.

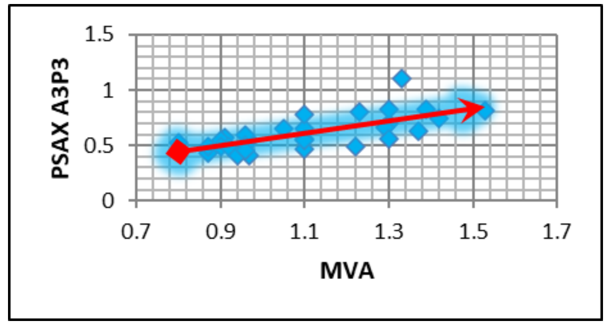

Figure 6. Positive correlation between MVA and PSAX A3P3 in patients with significant MS.

There is a strong and statistically significant positive correlation (r=0.900, p<0.001) was seen between MVA3D TEE and MVA2D TTE, as well as MVA3D TTE (r=0.932, p<0.001). Comparing MVA-2D TTE and MVA-3D TTE measures to MVA-3D TEE measurements (cm) revealed no discernible differences. When paired observations from different approaches were compared using Bland-Altman plots, MVA-3D TTE showed the best agreement (ICC=0.994, 95% CI=: 0.989-0.996), which was followed by MVA-2D TTE (ICC=0.987, 95% CI=: 0.978-0.992), Table 5.

Table 5. Correlation between MVA-3D TEE with MVA2D TEE and MVA3D TTE

	$MVA_{3D\ TEE}$	
	r	p-value
MVA_{2D} TEE	0.900	<0.001
MVA_{3D} TTE	0.932	<0.001

p>0.05 is not significant, p≤0.05 is significant, p≤0.01 is highly significant,
r: Spearman correlation coefficients

Table 6. Agreement between MVA-2D TTE and MVA-3D TTE compared to MVA-3D TEE as a reference standard method.

	ICC	95% CI		MEAN Δ	P-VALUE
		Lower limit	Upper limit		
MVA-2D TTE	0.987	0.978	0.992	-0.025	0.252
MVA-3D TTE	0.994	0.989	0.996	-0.048	0.188

p>0.05 is not significant, p≤0.05 is significant, p≤0.01 is highly significant,
ICC: Interclass correlation coefficient, mean Δ: mean difference compared with MVA3D-TEE

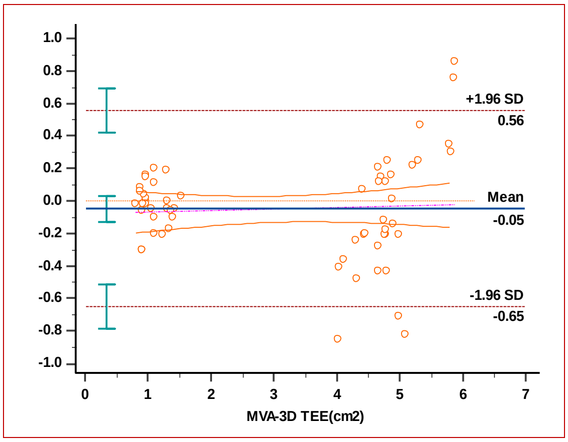

Figure 7. Bland-Altman plot for intra-observer variability for MVA3D MVA3D TTE.

In order to estimate the MS severity, the value of MVA2D TTE, MVA3D TTE, and MVA3D TEE were determined using a receiver operating characteristic (ROC) analysis. The highest AUC was found in MVA-3D TTE, followed by MVA-2D TTE, Table 7.

Table 7. Validity (AUC, sensitivity, specificity) for MVA2D TTE and MVA3D in prediction of MS severity.

	BEST CUT OFF	SENSITIVITY	SPECIFICITY	PPV	NPV	AUC	P-VALUE
MVA-2D TTE	1.47	90%	100%	100%	91%	0.961	<0.001
MVA-3D TTE	1.33	93.3%	100%	100%	93.7%	0.974	<0.001

AUC: Area Under a Curve, p value: Probability value, NPV: Negative predictive value,

PPV: Positive predictive value, *: Statistically significant at p ≤ 0.05

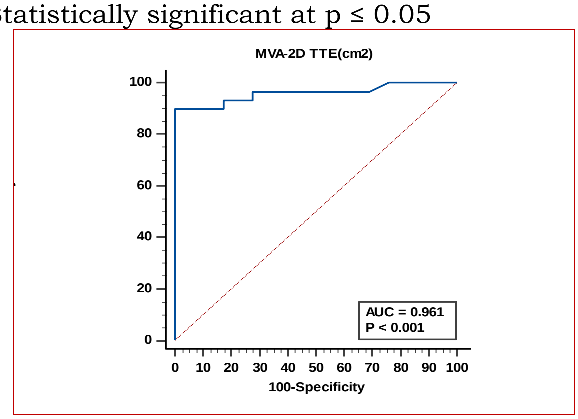

Figure 8. ROC curve of MVA2D TTE in prediction of MS severity.

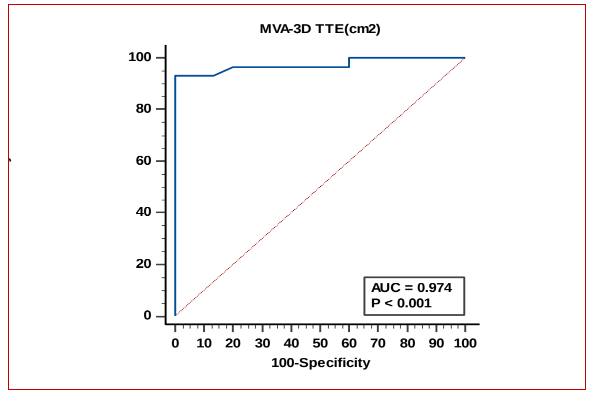

Figure 9. ROC curve of MVA3D in prediction of MS severity.

4. Discussion

Our research yielded a strong and statistically significant positive relationship between MVA3D TEE and MVA3D TTE (r=0.932, p<0.001). Additionally, a high and statistically significant positive correlation exists between the MVA3D TEE and MVA2D TTE (r=0.900, p<0.001). Utilizing 3D multiplanar reconstruction to generate a better image by cutting through leaflet tips is expected to result in more precise measurements. Our findings indicate that despite the excellent agreement between MVA measurements obtained using 2D planimetry and 3D TTE, the 2D planimetry method tends to overestimate MVA. There is a perception that MVA overestimation using 2D planimetry is more common than underestimating using 3D planimetry. Consequently, 3D imaging has been recognized as a more precise tool for MVA planimetry.

This was concordant with Bleakly et al., which studied Forty-one consecutive patients: the majority were 35 female (85.4%), with an average age of 55 (±17) years. The mean 2D planimetry MVA was 1.28 (±0.40) cm2, while the mean 3D planimetry MVA was 1.15 (±0.29) cm2.[8]

Also, the study was concordant with Min et al., which studied 87 individuals (sixty-seven men, mean age fifty-two±twelve years); they compared MVA by planimetry method measured by 2D TTE & 3D TEE who found that 3D TEE more accurate in MVA measurement & 2DTTE tend to overestimate MVA by (0.19±0.2 cm²), p-value <0.001.[9]

Also, the study was concordant with Dreyfus et al., which included eighty patients (fifty-eight±fifteen years of age, 86% female) referred for an MS examination and performed clinically recommended TTE and TEE. An experienced operator evaluated the 2D MVA and the 3D MVA (1.11±0.32 cm2) strongly correlated with the 2D MVA (1.10±0.34 cm2).[10]

In individuals with significant rheumatic MS, our data showed a strongly positive and statistically significant correlation between MLSI3D TTE and MVA3D TEE. A significant difference (p-value < 0.001) was observed.

Using Receiver operating characteristic curves, it was shown that 3D MLS measured in PSAX A1P1 can discriminate patients with significant MS at a cut-off level of<1.53, with 100% sensitivity and 100% specificity. PSAX A2P2 can be used at a cut-off level of<1.08, with 100% sensitivity and 100% specificity. PSAX A3P3 can be used at a cut-off level of<1.3, with 100% sensitivity and 100% specificity.

In individuals with significant MS, our data showed a strongly positive and statistically significant correlation between MLSI2D TTE and MVA3D TEE. A significant statistical difference (p-value<0.001) was observed.

We found that although MLS measurements using 2D and 3D TTE showed very high agreement, 3D measurements were more statistically significant according to the Spearman (r) Correlation statistical test. This led to the development of 3D imaging as a more precise technique, as cutting through the leaflet tips generated through 3D multiplanar reconstruction is thought to yield a more accurate measurement.

This aligned with Gokhroo et al., who examined 174 MS patients assessed for MVA estimation using several echocardiographic modalities. A unique 3D Xplane approach was used to measure the maximum leaflet separation and the accompanying planimetered MVA. A robust positive association (r=0.925, p < 0.001) was observed among planimetered MVA and MLS. The AUC for mild and severe MS was shown to be 0.966 and 0.995, respectively, on the receiver operating characteristic curves in MLS. With a sensitivity and specificity of 95.5% and 94.7% for severe MS and 93.2% and 91.4% for mild MS, respectively, MLS smaller than 8.62 mm and higher than 12.23 mm, respectively, indicated the two conditions.[11]

4. Conclusion

Mitral leaflet separation assessed by 3D TTE has a reliable and unremarkable ability in the prediction of the severity of rheumatic mitral stenosis. MLS assessed by 3D TTE is more accurate than MLS by 2D TTE in predicting the severity of rheumatic mitral stenosis. When assessing severity in individuals with mitral stenosis, 3D transthoracic echocardiography is a more precise approach than 2D TTE because the latter tends to overestimate the MVA.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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