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Automated quantification of mitral valve tenting volume in functional mitral regurgitation by three-dimensional echocardiography

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Abstract

Background: Tenting of the mitral leaflets is a major pathophysiological factor contributing to functional mitral regurgitation (FMR). A novel software tool allows automated quantification of the tenting volume (TnV) by 3D transesophageal echocardiography (TEE). The aims of this study are to investigate the correlations of biometric patient characteristics with the TnV and whether a threshold value for the diagnosis of a moderate or severe FMR can be calculated for the TnV.

Methods: This explorative and hypothesis-generating study analyzed the TnV of the mitral valve obtained by clinically indicated TEE. The mid-systolic, threefold calculated and averaged TnV from 80 patients with no or mild FMR and 27 patients with moderate or severe FMR was determined using the TomTec 4D MV Assessment tool.

Results: The TnV correlated significantly with the body size (r = 0.341), the weight (r = 0.272), and the body surface area (r = 0.320). After the adjustment to the body size, a threshold value of 1.25 cm^3/m was determined for the TnV by using a receiver-operating characteristic curve. This value distinguished moderate to severe from none to mild FMR with a sensitivity of 85% and a specificity of 71%. The intra-observer variability and inter-observer variability were determined to be 0.96 and 0.85, respectively.

Conclusions: Automated assessment of TnV has the potential to support the diagnostic evaluation of FMR. Further studies are needed to validate this result, detect additional factors influencing the size of the TnV, and determine further thresholds for any degree of FMR.

KEYWORDS

mitral regurgitation, three-dimensional echocardiography

Henryk Dreger and Fabian Knebel contributed equally to this study and would therefore like to share the last-authorship

1 | INTRODUCTION

Prevalence of mitral regurgitation (MR) increases with age and reaches 9.3% in over 75-year-old patients.[1] Therefore, it is an important public health problem.[1] Functional mitral regurgitation (FMR) is defined as regurgitation caused by deformation of the mitral valve (MV) system due to remodeling of the left ventricle (LV).[2]

Due to its complex anatomy and dynamic behavior, grading of FMR can be challenging.[2] The diagnosis is performed using echocardiography, but only the comprehensive use of several qualitative as well as quantitative parameters enables an accurate grading of FMR.[2] However, established parameters have several limitations.[2] Therefore, additional grading parameters would be desirable.

Because of the tethering that occurs during LV dilatation, the MV leaflets are tightened like a tent, resulting in the echocardiographic phenomenon of tenting.[3] The volume stretched between the MV leaflets and the annulus can be calculated as the tenting volume (TnV) (Figure 1), which is investigated exploratively in this paper as a quantitative measurement of FMR.

The automated calculation of the TnV represents a novel tool to assess FMR with several advantages.[4] As a three-dimensional parameter of all components of tethering and tenting, such as the area and height of the tenting and the MV annulus, the TnV provides comprehensive information about the MV.[5]

The TnV is at its peak after MV closure, that is, in early systole, and progressively decreases during midsystole to finally increase again slowly in late systole.[6] Several studies have already been able to assess a statistically significant higher TnV for both patients with FMR[5–10] and with ischemic MR[11–16] compared to patients without MR.

However, there are sex differences with a significantly lower TnV for women.[6] Furthermore, correlations of TnV with body size and body surface area (BSA) have been reported.[17] It was shown that the TnV has excellent intra-observer and inter-observer variability.[5-8,16,18–20]

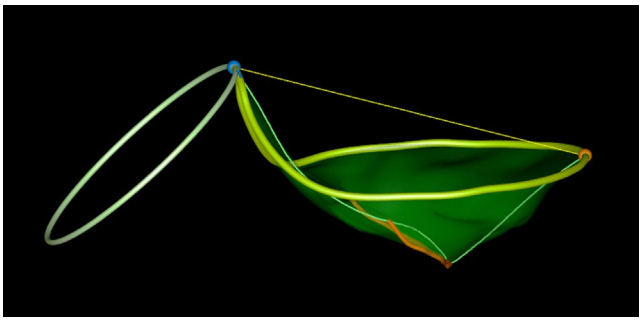

FIGURE 1 Illustration of the TnV. The figure shows a 3D image of the MV, which was created with the help of the software TomTec 4D MV Assessment. The TnV is illustrated by the green highlighted volume. TnV = tenting volume

With the exception of Song et al,[5] no study has yet investigated a threshold for the FMR to diagnose a significant FMR. However, only 31 patients were considered in this study, whereby only 4 healthy control subjects were present. Furthermore, in this study the 3D images of transthoracic echocardiography were used and the TnV was not specified for an exact time, instead the minimum and maximum TnV of the systole was given. In addition, the TnV was not evaluated in terms of biometric patient data. Therefore, the aims of the study were to use 3D transesophageal echocardiography (TEE) to identify correlations between biometric patient characteristics and the TnV and to determine a threshold value to diagnose moderate or severe FMR.

2 | METHODS

2.1 | Study population

From August 2017 to March 2019, 135 patients who underwent routine TEE were enrolled into the study. Inclusion criteria were an age over 18 years and a suitable image quality. 28 patients were excluded due to structural abnormalities of the mitral apparatus, a history of MV annuloplasty or replacement. The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Charité-Universitätsmedizin (Berlin, Germany).

Patients were divided into two groups: Group A included patients with none or mild FMR, and patients in group B had moderate or severe FMR.

2.2 | Echocardiographic examination

The TEE was performed using commercially available ultrasound system (General Electric Vivid E95 or Philips Epiq 7) with Philips X7-2t Live 3D TEE xMATRIX array transducer and the probe 6VT-D from Electric Vivid E95. Additional to our conventional TEE protocol, electrocardiographically gated, full-volume datasets were obtained during apnea and simultaneous avoidance of patient or probe movements. Sedatives were only used when necessary. It was ensured that the MV apparatus was shown for the entire acquisition of the 3D image. Grading of FMR was based on the current guidelines of the European Association of Cardiovascular Imaging[21] and the American Society of Echocardiography[2]—whereby with a narrow angle in patients with sinus rhythm there were used multibeats and in patients with atrial fibrillation (AF) single beat images, respectively.

2.3 | Image analysis

The analysis of mid-systolic TnV was performed using the commercially available TomTec Image Arena software with the 4D MV

Assessment 4.6 tool (TomTec Imaging Systems GmbH). After selecting the mid-systolic 3D volume, several anatomic landmarks, that is, the mitral annulus, the coaptation point, and the aortic valve position, are placed in several views. Subsequently, the software tracks the MV landmarks and areas during the systole. After adaptations of the leaflets in static and dynamical models, the calculation of the TnV is done. The data export and analysis take, on average, <3 minutes.

2.4 | Statistics

Statistical analysis was performed using SPSS version 25.0 (SPSS Inc). The BSA was calculated by the DuBois formula.[22] Normal distribution of variables was checked using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. The data are expressed as mean ± standard deviation and median [25th percentile-75th percentile] for continuous variables and as frequencies (%) for categorical variables. Group comparison of continuous variables was performed using the unpaired *t* test. For non-normally distributed data, the Mann-Whitney *U* test was deployed. Correlations between variables were assessed by the Pearson correlation coefficient.

TnV is presented as a box plot with the boundaries of the box as the 25th and 75th percentiles with a line representing the median. The whiskers above and below the box marked the maximum and minimum values.

A receiver-operating characteristic (ROC) curve and the Youden's Index were performed to determine the discriminatory characteristic of the TnV and to define the best threshold for identifying an at least moderate FMR.

Reproducibility of the evaluation was assessed in a random sample of 10 patients by examining the inter-observer and intra-observer variability for the TnV using the Pearson correlation coefficient. A *P* value < .05 was considered as significant.

3 | RESULTS

3.1 | Study population

80 patients of group A and 27 patients of group B were evaluated in this study. Patient characteristics and hemodynamic data of all patients are listed in Table 1. With regard to body size, sex, and body mass index (BMI), there were no significant differences in baseline characteristics between the two groups. However, the groups differed in age, body weight, and BSA. The patients of the group B suffered more frequently from coronary artery disease (CAD), a lower left ventricular ejection fraction (LVEF), and myocardial infarction (MI). Furthermore, they had a higher left atrial volume index (LAVI) and left ventricular end-diastolic diameter (LVEDD). In addition, the patients of the group B showed more often LV dilatation. No differences between the groups were detected regarding the prevalence of AF.

TABLE 1 Patient characteristics of patients with none or mild FMR (group A) and patients with moderate or severe FMR (group B)

Variable	A	B	*P* value
n	80	27	
Age (y)	67.7 ± 14.4 71.0 [60.03–79.0]	73.44 ± 12.35 77.0 [67.0–81.0]	.045
Female (%)	37 (46.3)	8 (29.6)	.132
Body size (cm)	171.5 ± 10.3 170.0 [163.3–179.5]	173.6 ± 7.0 173.0 [168.0–180.0]	.334
Weight (kg)	78.6 ± 19.3 76.5 [63.3–87.0]	83.6 ± 14.2 86.0 [73.0–95.0]	.028
BMI (kg/m^2)	26.5 ± 4.7 25.6 [23.5–30.1]	27.7 ± 4.0 28.1 [25.5–30.1]	.259
BSA (m^2)	1.91 ± 0.26 1.84 [1.72–2.06]	1.98 ± 0.19 1.99 [1.85–2.15]	.042
LVEF (%)	54.4 ± 11.6 60.0 [56.3–60.0]	39.1 ± 16.7 38.0 [27.0–55.0]	<.001
LAVI (mL/m^2)	33.44 ± 10.97 32.23 [25.63–40.58]	41.30 ± 10.71 41.39 [31.99–49.81]	.002
LVEDD (mm)	44.98 ± 6.46 45.00 [40.00–50.00]	52.19 ± 8.79 50.00 [45.00–59.00]	<.001
AF (%)	53 (66.3)	15 (55.6)	.320
LV dilatation	6 (7.5)	10 (37.0)	<.001
CAD (%)	21 (26.3)	16 (59.3)	.002
MI (%)	4 (5)	6 (22.2)	.008
TnV (cm^3)	1.94 ± 1.11 1.61 [1.17–2.34]	3.59 ± 1.54 3.30 [2.30–4.80]	<.001

All values are expressed as mean ± SD and median [25th percentile-75th percentile] or n (%).

Abbreviations: BMI = body mass index; CAD = coronary artery disease; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

3.2 | Intra-observer and inter-observer variability

The intra- and inter-observer variabilities for the measurement of the TnV were excellent with correlation coefficients of 0.96 and 0.85, respectively (*P* < .001).

3.3 | Correlations

For the TnV, statistically significant correlations with body size, weight, and BSA could be determined, as shown in Table 2. The highest correlation was found for body size; therefore, the TnV was adjusted to

the body size of each patient. For this, the TnV was divided by the body size. The resulting mean TnV is shown in the box plot in Figure 2.

3.4 | ROC

Figure 3 shows the ROC analysis of the TnV. The threshold value of 1.25 cm^3/m distinguished group A from group B with a sensitivity of 85.2% and a specificity of 71.2%. The area under the curve was 0.825 ($P < .001$) with the corresponding 95% confidence interval 0.738–0.911.

4 | DISCUSSION

In this study, a significantly different TnV could be determined depending on the severity of FMR, which was higher in patients with a moderate or severe FMR.

The TnV correlated in decreasing order with body size ($r = 0.341$), BSA ($r = 0.320$), and weight ($r = 0.272$). With correlation coefficients of $r = 0.41$ for the BSA and of $r = 0.31$ for the body size, lower correlations for the body size, but higher for the BSA, were demonstrated by the study from Sonne el al.[17] However, the acquisition of the data was done by transthoracic echocardiography and different software. In addition, the control cohort comprised healthy subjects.

Due to the highest correlation with body size, the TnV was adjusted to the individual body size of the patient. As a result of the ROC analysis, a threshold value of 1.25 cm^3/m, which distinguished the groups, was determined. This deviates from the calculated TnV of Song et al with a value of 6.02 mL, whereby this value was the highest value during systole. The same sensitivity (86%) and specificity (100%) for the minimal TnV was achieved in the study from Song et al with a value of 3.09 mL. But these values are not normalized to the body size, the images were obtained transthoracically and the MR was evaluated only via the proximal isovelocity surface area method.[5] Although it has already been determined that the TnV is dynamic—with a maximum in early systole, a decrease in midsystole and an increase again in late systole [5–7,18,19]—the study by Song et al did not report the precise time when the evaluation was performed.[5]

Our data further corroborate previous studies that demonstrated that TnV is a reliable method for the evaluation of FMR.[6–10] In these studies, a TnV of 0.45-2.4 cm^3 was calculated for the control group and a TnV in the range of 2.6-4.8 cm^3 was measured for patients with FMR. Thus, the mean values measured in these studies were in the range of our values, but our measured TnV was adjusted for the body size. However, the patients of the individual cohorts were very heterogeneous regarding the group size, the time and method of measurement, the underlying diseases, and the cause of FMR. This results in a limited comparability.

In various studies, similar results could be determined regarding the intra-observer and inter-observer variability.[5–9,16,18–20] The mean intra-observer variability observed in these studies ($r = 0.94$) corresponds to the value measured here ($r = 0.96$). Similar results are seen

TABLE 2 Correlation of TnV with body size, weight, BMI, and BSA

Variable	Correlation with TnV	*P* value
Body size (cm)	0.341	<.001
Weight (kg)	0.272	.005
BMI (kg/m^2)	0.138	.157
BSA (m^2)	0.320	.001

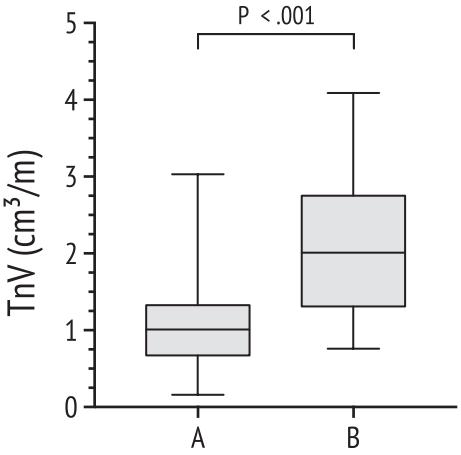

FIGURE 2 Box plot of the TnV (cm^3/m) of patients with none or mild FMR (group A) and patients with moderate or severe FMR (group B). TnV = tenting volume

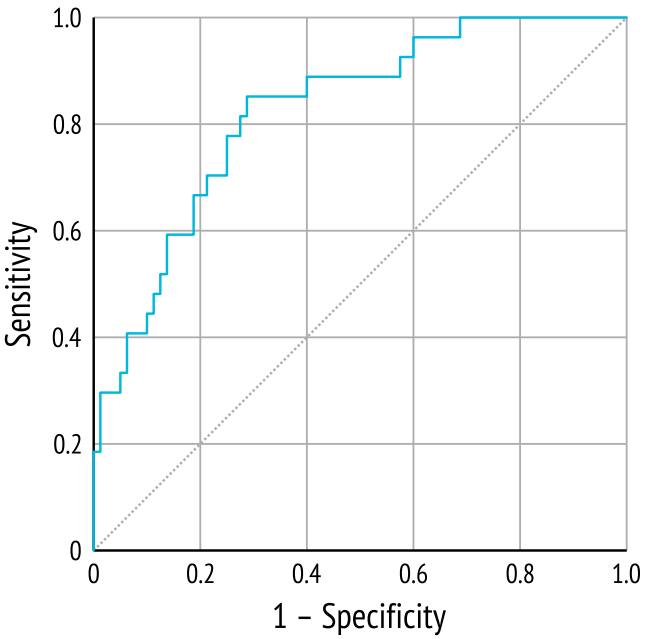

FIGURE 3 ROC curve for TnV distinguishing between patients with none or mild FMR (group A) and patients with moderate or severe FMR (group B). ROC = receiver-operating characteristic; TnV = tenting volume

for the inter-observer variability with a value of $r = 0.85$, whereby a range from $r = 0.78–0.97$ with the mean value $r = 0.87$ was found in the other studies. In summary, the automated quantification of TnV is time efficient at the same time as being very reproducible.

4.1 | Limitations

Due to our sample size, we opted to divide our population in only two groups. With only 11 patients having a severe MR, no statistically significant difference could be calculated between patients with moderate and patients with severe MR. Consequently, these patients were summarized and compared with patients with a maximum mild MR. Further studies with larger cohorts are needed to investigate whether TnV is also able to distinguish patients with moderate and severe FMR. Because this study was designed retrospectively, possible influences, such as selection bias, could not be determined or changed. Furthermore, this cohort does not represent a normal population, because the patients had a clinical indication for the TEE.

Another potential restrictive parameter was the influence of sedatives on FMR during TEE, which affects the assessment of the severity of the FMR.[2] Although sedatives were used as rarely as possible, this influencing aspect could not be avoided with absolute certainty.

5 | CONCLUSIONS

In summary, this was the first study to examine TnV, indexed for body size, in relation to the severity of FMR. While we could demonstrate the ability of TnV to distinguish between none or mild to moderate or severe FMR, further studies are needed to investigate whether estimation of TnV helps to differentiate all FMR grades. Additional studies are necessary to validate this result and to evaluate the influence of etiology as well as other cardiac diseases on the size of TnV. This could increase the clinical applicability and help establish it in routine diagnostics.

IMPACT ON DAILY PRACTICE

Quantification of TnV has the potential to support the diagnostic evaluation of FMR. However, further studies are needed to verify additional thresholds and influencing variables.

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