Impact of the posterior mitral leaflet anatomical variation on the efficacy of ValveClamp using three-dimensional transesophageal echocardiography

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March 31, 2022

Abstract

Background Multiple studies illustrated that mitral valve (MV) leaflet presented variations, and there is little known about the posterior mitral leaflet (PML) anatomical variation affecting residual MR in interventional mitral valve edge-to-edge repair (TEER) with the ValveClamp system in patients with degenerative mitral regurgitation (DMR) using three-dimensional transesophageal echocardiography (3D TEE). **Method** Fifty-five DMR patients treated with TEER were included and performed 3D TEE pre- and post-procedure immediately. 3D TEE images were proceeded to characterize the posterior mitral leaflet anatomy and investigate the relationship between variations and residual mitral regurgitation (MR). **Results** Variations in PML were found in 16 patients (32%) of this series, including 3 cases (6%) of one scallop, 8 cases (16%) of two scallops, and 5 cases (10%) of four scallops. Residual MR [?] 2+ were found in 3 patients with variant PML and 8 patients with classical PML post procedures, while other patients were all $<$ 2+. The Chi-square test results showed no correlation between residual MR and PML variants (18.8% vs. 23.5, ? ^{2} = 0, p = 0.988). Of the 5 patients with 4 scallops, 3 had poor clinical outcomes. Two patients were converted to surgical mitral valve repair and one died 1 month after implantation. **Conclusions** 3D TEE provides a novel and non-invasive method to characterize and classify PML variations. Variations in PML are relatively common and not associated with residual MR 2+.

Introduction

Mitral valve (MV) is always depicted with an anterior scallop and three evenly area posterior scallops in the textbooks.[1] However, researches about mitral valve anatomic variations in surgery have been carried out a lot since the 1950s[1-5]. A recent study firstly reported the various categories of the posterior mitral leaflet (PML) using three-dimensional transesophageal echocardiography (3D TEE)[6]. They found two main classification, including "Symmetrical PML (dominant P2 scallop, accessory P2 scallop, absent P2 scallop, and dichotomous P2 scallop) and the asymmetrical variations (fused P1-P2, fused P2-P3, commissural scallop, accessory scallops, dichotomous P1 or P3, and dominant P2 or P3)", which results were almost correspondence with the surgical study. Besides it, there is no significant association between mitral regurgitation (MR) and variations in PML.

Transcatheter mitral valve edge-to-edge repair (TEER) using the MitraClip system (Abbott Vascular, Menlo Park, California, USA) which approximates the mitral valve leaflets has been the typical treatment for symptomatic severe degenerative MR (DMR), and the RCT study has approved its efficacy and safety[7]. A challenge facing the device is post-procedure residual MR which results in high rates of rehospitalization and mortality[8, 9]. It is essential to determine the most available MV anatomy to avoid residual MR.

In this retrospective study, we investigated the correlation between variations in PML and residual MR after TEER with the ValveClamp system (Hanyu Medical Technology, Shanghai, China) among DMR patients.

Methods

Study population

Fifty-five consecutive patients with DMR undergone TEER using the ValveClamp system in Zhongshan Hospital of Fudan University from July 2018 to December 2019 were enrolled. Transthoracic echocardiography (TTE) was performed on admission, and intraprocedural transesophageal echocardiography (TEE) was performed by a multidisciplinary heart team pre- and post-procedure immediately. Eligible patients were with moderate to severe (3+) or severe (4+) MR and high risk for surgery according to the 2017 ESC/EACTS Guidelines for the management of valvular heart disease[10]. Primary regurgitant jet originated from malcoaptation of the A2 and P2 scallops are the most significant anatomic criteria. Patients were excluded with any of the following: (a) The pathogeny of MR is other than fibroelastic deficiency (FED) and Barlow disease (BD), (b) History of MV surgery or interventional treatment, (c) Untreated severe coronary artery stenosis requiring vascular reconstruction, (d) Stroke in the past 6 months[11-13]. 5 patients were excluded for the poor imaging quality, and therefore a total of 50 patients were enrolled in this study.

Procedures

Different from traditional surgery and minimally invasive video-assisted thoracoscopic surgery, ValveClamp is a novel interventional therapy based on "edge-to-edge" repair which is implanted through apical. The trans-apical step is performed with the patient under general anesthesia using 2D, 3D TEE and the TrueVue technology (Philips Medical Systems, Andover, MA) in the hybrid operation room. The implantation procedures were the same as formally described.[11-13] TEE can clearly demonstrated the micro MV structures and chordae tendineae connection, and is performed to guide the MV clamp devices and evaluate residual MR after implantation immediately[14, 15]. The clinical success was defined as MR reduced to $< 2+$ after procedures.

Data collection

Clinical and Echocardiographic data

Clinical data were acquired from the electrical medical record, including age, sex, height, weight, and concomitant diseases. TTE was routinely performed on admission, identifying the etiology, determining the severity of MR and evaluating the cardiac hemodynamic function and heart geometric characteristic. Under general anesthesia, TEE was performed to guide the ValveClamp system to the specific cardiac chamber position and evaluate the residual MR with advantages of real-time and high resolutions. TTE and TEE images were acquired using Epiq 7 echocardiography machines (Philips Medical Systems, Andover, MA) with the S5-1 and X8-2t probes respectively by a 3 level physician.

Transthoracic Echocardiography

The left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST), left ventricular posterior wall thickness (PWT), pulmonary artery systolic pressure (sPAP), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured according to the latest guidelines, in which LVEDV, LVESV and LVEF gained using biplane Simpson's method[16]. The severity of MR on TTE is determined combined quantitative and semi-quantitative parameters, including effective regurgitant orifice area (EROA), regurgitant volume (RVol), vena contracta width (VCW) and area (VCA). The severity of MR was classified into 0 (none or trace), 1+ (mild), 2+ (moderate), 3+ (moderate to severe), and 4+ (severe)[17, 18].

Transesophageal Echocardiography

TEE imaging datasets were offline analyzed by 3 senior echocardiographers blinded to each other using

Q-Lab software (Philips Medical Systems, Andover, MA). Multiplanar reconstruction planes were obtained from the mid-esophageal (ME) long-axis view (LAX) 3D Images in which can well identify the A2 and P2 segments in the mid-systole phase[14]. The anterior mitral leaflet (AML) length and PML length were measured before the device deployment, and the post-procedure leaflet length was measured from the origin of mitral annulus to the margin of the clamp after procedural immediately. We determined the AML/PML clamp rate as (PMLpre - PMLpost) / PMLpre or (AMLpre - AMLpost) /AMLpre. We identified PML anatomy according to the number and location of slits in the PML using 3D full volume images[19]. PML with 3 even-area scallops were deemed as classical MV, and 1, 2, 4 or more scallops were the variant.

Statistical Analysis

Statistical Analyses are done using SPSS software, version 25.0 (IBM Corp, Armonk, New York). Continuous variables are presented as the mean ± standard deviation (SD) or median (25th and 75th interquartile range) according to the data distribution (normal or non-normal distribution), and categorical data is expressed as proportion. The independent-sample t-test is performed to detect the difference of normal-distributed data, the Mann-Whitney test for non-normally distributed data, and the chi-square test for categorical data. $P < 0.05$ are considered as statistical significant.

Results

Demographic and clinical characteristics

A total of 50 DMR patients with MR 3+ or 4+ were analyzed in this study, and their demographic and clinical characteristics are displayed in Table 1. The mean age was 74.23 ± 6.53 years, and 52.9% were men. There is a high proportion of concomitant basic disease (median Society for Thoracic Surgeons risk score, 6.5%), and patients with hypertension (HBP) accounted for 73.5%, chronic obstructive pulmonary diseases (COPD) for 52.9, coronary atherosclerotic heart disease (CAD) for 38.2%, atrial fibrillation (AF) for 44.1%). Among 50 patients, 43 patients had a single clamp implanted, and 7 patients had bi-clamps implanted (4 in the classical group and 3 in the variant group).

Two-dimensional echocardiographic measurements

Table 2 displays the baseline of MV anatomic and hemodynamic characteristics. The variant group showed significantly larger LVESD (34.36 ± 4.5 vs. 31(30 - 34)mm, p = 0.034) and shorter AML length (22.2 ± 7.8 vs. 25.7 ± 3.2mm, p = 0.026) than the classical group. However, there were no significant differences in other parameters measured between the two groups. Besides it, the results of clamp rate of AML and PML between the two groups also presented no significantly differences.

PML anatomy and residual MR

According to Solomon Victor's study[19], we found that 34 patients were classical PML with 3 scallops, and 16 patients were variant PML.**Fig. 1** shows different types of PML variations. 7 and 3 patients were graded as residual MR [?] 2+ in the classical group and variant group respectively after ValveClamp implantation immediately, and there were no statistical differences between the two groups (18.8 vs. 23.5% , ?2 = 0, p = 0.988) (**Fig. 2**). However, the prognosis of patients with 4 scallops presented worse. Among these patients, 2 patients were turned to the surgical valvuloplasty because of the failed implantation of the clamp, and 1 patient died 1 month after TEER for the fall-of clamp due to high tension of AML.

Discussion

PML anatomical variation affecting residual MR after TEER in DMR patients remains a controversial field and is needed more relative researches to verify its true relationship. By comparing the classical and variant PML groups, our study yielded several notable findings: (a) variations in PML scallops are the common phenomenon, as defined by 3D TEE imaging, in which 1 scallop accounts for 6% (3/50) of enrolled patients, 2 scallops for 16 (8/50), 4 for 10% (5/50); (b) residual MR is not associated with PML variations; (c) the prognosis of patients with 4 scallops of PML is worse, requiring surgical valvuloplasty or died.

PML Variations

Studies in mitral leaflet variations are other than a novel topic. Harken and Rusted first reported variations in pathologic morphology of MV through the autopsy study of the MV[2, 4, 5]. They described that MV was constituted with aortic leaflet, ventricular leaflet and two additional triangular projections (anterior and posterior commissural leaflets), and the ventricular leaflet may be oblong, bifid, trifid or even indistinguishably other than triangular. Although their studies reported morphology variations of MV, they didn't carry more detailed research about scallop variations.

In 1970, Ranganathan et al reported the bi-scalloped without P2 and five-scalloped of PML at autopsy[20]. In 2017, Krawczyk-Ożóg et al performed the research about MV anatomy variability through studying 200 autopsied human hearts without heart valve diseases, and found that 29.5% of MV scallops presented variants[3]. Besides, they also reported that variations in PML are more common and associated with the presence of accessory scallops. However, the above studies are performed by surgical methods and are more invasive. Sweeney et al first studied the anatomic variations in the MV in a non-invasive manner using 3DTEE, which behaviors high resolution , real-time, and can well identify MV variants. They divided the scallops variation into dominant, accessory, absent, dichotomous, and single posterior scallops regarding the proportion of the scallop in the leaflet, making up 30% of the series[6]. Strikingly, our results are in line with the autopsy series and Sweeney's study (32%, 29.5% and 30%)[3, 6].

TEER and residual MR

Whether MitraClip or ValveClamp proved itself safe and efficacy, there is both challenge of residual MR after procedures[8, 9, 11]. EVEREST II registry study reported that 25% of patients with MitraClip suffered [?] 2+ residual MR, while ValveClamp was 20% in our former research[7]. The study had confirmed that immediate postoperative residual MR was the independent predictor of MR recurrence, heart failure rehospitalization, and mortality[21]. The results of the Italian team Alfieri indicated that surgical edge-to-edge mitral valve repair or the implantation of the MitraClip alone cannot achieve durable MR reduction in patients with DMR, especially in patients with residual MR [?] 2+ immediately after surgery[22]. Therefore, it is critical to clinically screen the appropriate MV anatomy to achieve the postoperative residual MR [?] 1+.

Residual MR and PML variations

A recent study demonstrated that there was no relationship between MR and mitral leaflet variations[6]. However, nearly 40% of the study population were graded as MR 3+ to 4+ which may contribute to the selection bias. In this study, patients referred for TEER were all MR 4+ and it was meaningless to discuss the role between MR and mitral leaflet variations. Further, we noted that residual MR also presented no significant association with the PML variant. Interestingly, patients with 4 scallops of PML had poorer outcomes. We attempted to interpret it by comparing different PML anatomical and procedural factors, but to no avail. In 2 patients referred for surgeries, both of them had part of P1 and P3 scallops involved and the MR was graded as more than MR 4+. In this way, it was difficult to clamp the prolapsed scallop and resulted in recurrent MR, requiring surgeries. And 1 patient died, because the fixed clamp slipped out of the scallops. However, such a small sample size cannot verify the reliability of the results.

Conclusions This study provides a novel method to study the relationship between TEER and MV anatomy. 3D TEE can well identify the PML anatomic classification, and PML variations are not associated with residual MR.

Limitations In our study, there are two main limitations: (a) This study is a single-center study with a small sample size. We need to extend the sample size and cooperate with other centers; (b) Our study has no autopsy study to verify the results of 3D TEE.

Funding This study was supported by grant 202140291 from Shanghai Municipal Health Commission, National Natural Science Foundation of China (81771837) , Clinical Research Plan of SHDC(SHDC2020CR4071)and Shanghai Rising Stars of Medical Talent Youth Development Program (SHWRS(2020)_087).

Conflict of interest All authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Table 1 Demographic and clinical baseline of 50 DMR patients

Parameters
Age (years)
Sex, male, n (%)
Height (cm)
Weight (kg)
BSA (m^2)
STS, n (%)
NYHA [?] III, n (%)
Creatinine (mg/dl)
NT-proBNP (pg/ml)
DM, n (%)
HBP, n (%)
COPD, n (%)
CAD, n (%)
AF, n (%)

BSA, body surface area; STS, Society for Thoracic Surgeons risk score; NYHA, New York heart association; DM, diabetes r

Table 2 Anatomic and hemodynamic echocardiographic characteristics

Parameters
LAD (mm)

LAarea (cm^2)
LVEDD (mm)
LVESD (mm)
LVEDVi (ml/m^2)
LVESVi (ml/m^2)
LVEF (%)
sPAP (mmHg)
AML length (mm)
PML length (mm)
MA diameter (mm)
MVA (cm^2)
MVPGmax (mmHg)
MVPGmean (mmHg)
VCW (mm)
VCA (cm^2)

LAD, left atrial diameter; LAarea, left atrial area; LVEDD/LVESD, left ventricular end-diastolic/systolic diameter; LVEDV

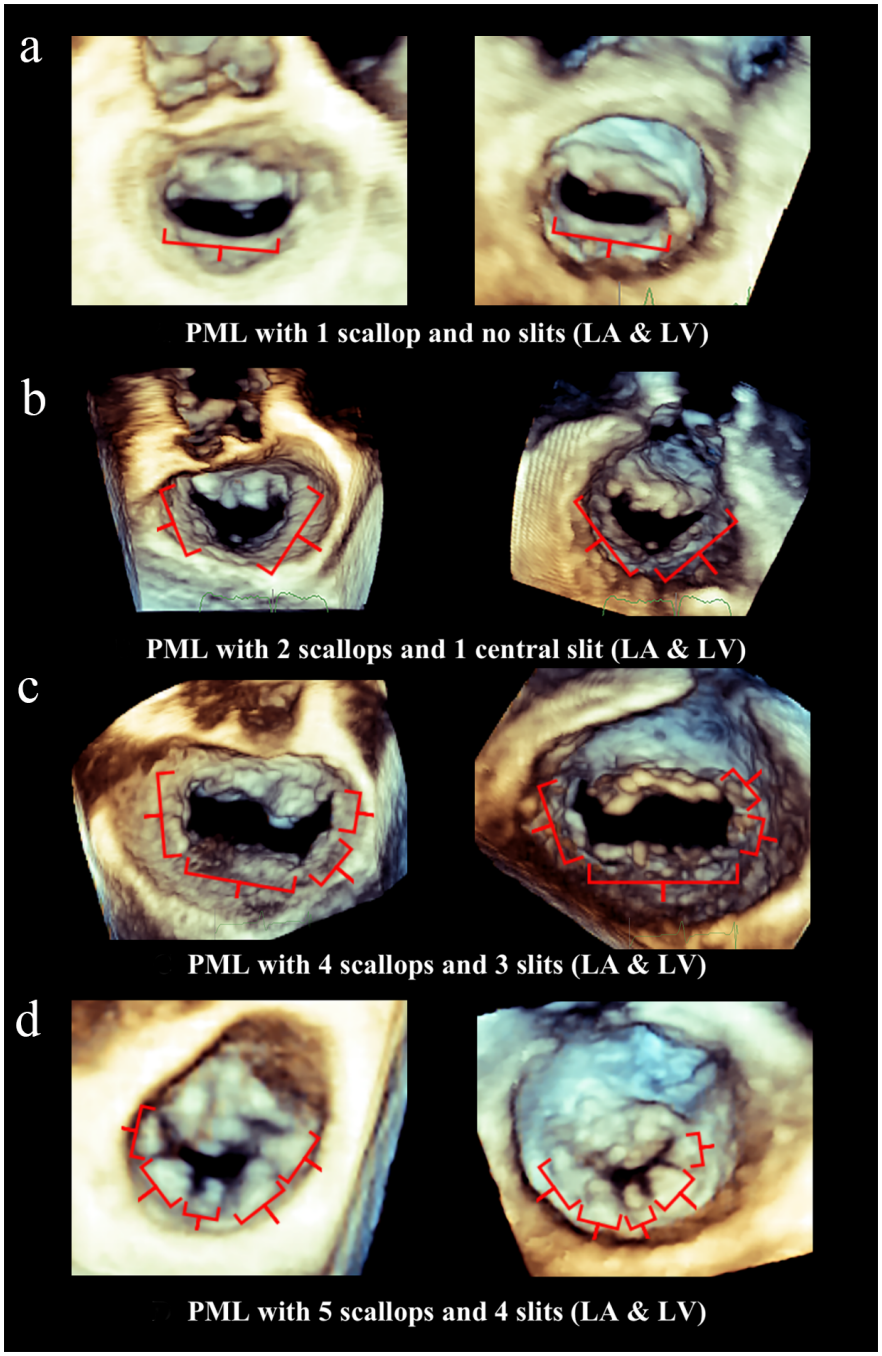

Fig. 1 Posterior mitral valve leaflet anatomical variants using 3D TEE.

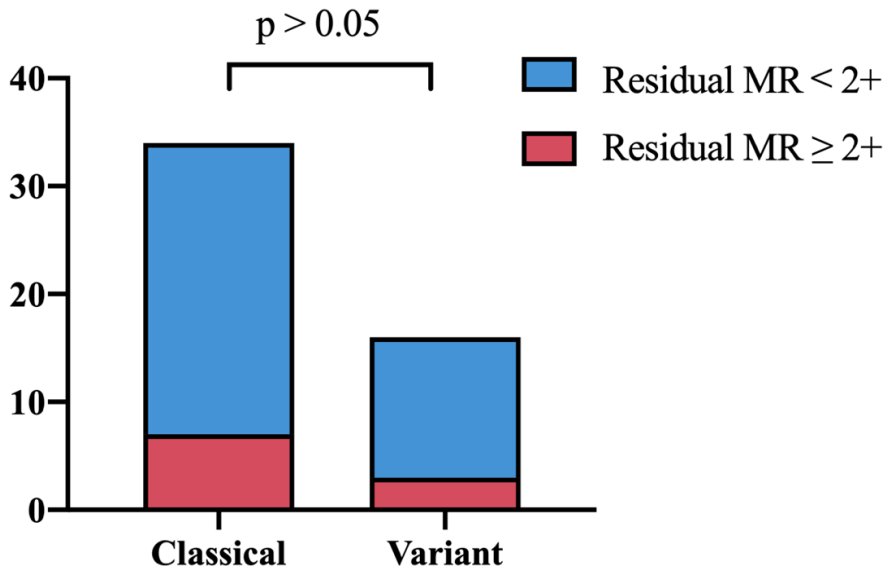

Fig. 2 Comparison of the residual MR between the classical group and variant group. Dot plot showing the relationship between the PML variations and the residual MR [?] 2+.