



A case report of transcatheter repair of severe functional mitral regurgitation in cardiac amyloidosis

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Background

Transcatheter therapy has become an alternative for functional mitral regurgitation (FMR) in patients at high surgical risk. However, the intervention of FMR in cardiac amyloidosis (CA) with transcatheter edge-to-edge repair (TEER) is controversial due to the potential risk of left atrial pressure (LAP) elevation.

Case summary

An 83-year-old woman with repeated heart failure (HF) and severe mitral regurgitation (MR) was referred to our centre for TEER. Pre-procedural transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) confirmed the degree of MR and a functional aetiology. A peculiar LAP increase in this patient occurred immediately after successful TEER clip implantation and her *n*-terminal prohormone of brain natriuretic peptide significantly increased post-operatively. The diagnosis of CA was suspected and was subsequently established through endomyocardial biopsy. Aggressive anti-HF therapy was initiated and the patient was discharged after her HF symptoms were relieved. At 6-month follow-up, the patient was still alive and no episode of acute HF was experienced.

Discussion

Severe functional MR in CA treated with TEER has the potential risk of increasing LAP. During the short-term follow-up, TEER appears beneficial for left heart function (reduction of MR) but harmful for right heart function (increase of LAP). CA patients with severe FMR should be carefully evaluated about the benefits and potential harm of TEER intervention.

Keywords

Cardiac amyloidosis • Mitral regurgitation • Transcatheter edge-to-edge repair • Case report

ESC Curriculum

2.2 Echocardiography • 4.3 Mitral regurgitation • 6.2 Heart failure with reduced ejection fraction • 5.3 Atrial fibrillation • 6.5 Cardiomyopathy

Learning points

- We report the first case of a patient with severe functional mitral regurgitation in the context of cardiac amyloidosis successfully managed with implantation of the ValveClamp system.
- The observation of left atrial pressure elevation intraoperatively after deployment of transcatheter edge-to-edge systems should alert clinicians to the possibility of an underlying restrictive cardiomyopathy.
- Transcatheter edge-to-edge repair may be beneficial for left heart function but harmful for right heart function

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Introduction

Cardiac amyloidosis (CA) is a restrictive cardiomyopathy (RCM) with a poor prognosis. It presents with a variety of clinical manifestations, such as heart failure and arrhythmias while mitral regurgitation (MR) is usually a rare finding. More than 98% of currently diagnosed CA results from the two main forms of amyloidosis: monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its hereditary or acquired (ATTRwt-CA) forms.¹ One study showed that ATTRwt-CA patients had a high prevalence of atrial fibrillation (88%), among whom only a modest number of patients develop moderate or above MR (4.4%).² Whether to treat MR with transcatheter edge-to-edge repair (TEER) in CA patients is under continuing debate. Patients with RCM have a rigid, non-compliant left ventricle with impaired diastolic filling and high left atrial pressure (LAP).³ TEER is affected by the intrinsic limitation that while MR is treated, the effective orifice area is reduced, thereby increasing the risk of inducing transmitral gradients.⁴ Patients with poor chamber compliance might be more susceptible to LAP elevation, which is prognostic for survival after TEER.⁵ The concomitant presence of amyloid may come with potential anatomic challenges for TEER therapy in primary MR.⁶ The presence of pure functional mitral regurgitation (FMR) caused by cardiac dilatation in CA patients would add to the complexity of the clinical decision.

We describe herein a CA patient with severe FMR who was successfully treated using a TEER system (ValveClamp system, Hanyu, Medical Technology, Shanghai, China). The ValveClamp is a novel user-friendly transapical (TA) TEER device composed of a front clamp, a rear clamp, and a closed ring and it is designed to mimic the surgical 'edge-to-edge' technique^{7,8} (see [Supplementary material online, Figure S6](#) and [Supplementary material online, Video S1](#)). FMR patients with baseline New York Heart Association functional Class III/IV (100%) showed improvement of at least 1 class after TEER with the ValveClamp system at the 3-month follow-up.⁹

Timeline

Time	Events
3 months before procedure	Patient was hospitalized with symptoms of heart failure (breathlessness, oedema in lower extremities) in another hospital. During hospitalization, patient had been diagnosed with severe mitral regurgitation (MR).
25 days before procedure	Transthoracic echocardiography (TTE) showed that MR effective regurgitation orifice area was 0.37 cm ² , and the MR volume was 37 mL (Figure 1) and the MR remained severe (see Supplementary material online, Video S2).
6 days before procedure	Transoesophageal echocardiography (TOE) further demonstrated severe MR and mitral valve tethering (see Supplementary material online, Video S3).
5 days before procedure	The result of coronary computed tomography angiography was that there were no thickening and calcification of the mitral

Continued

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Time	Events
1 day before procedure	annulus (see Supplementary material online, Figure S3). N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) was 7671.0 pg/mL; troponin T was 0.052 ng/mL; international normalized ratio was 2.51.
TEER procedure	The procedure was successful. However, the mean left atrial pressure (LAmP) was increased from 16 mmHg preoperatively to 19 mmHg immediately after the procedure. NT-pro BNP was significantly increased (Figure 3).
Post-procedural 3 days	Lyophilized recombinant human brain natriuretic peptide was delivered. NT-pro BNP then began to decline (Figure 3).
Post-procedural 7 days	Coronary angiography and endomyocardial biopsy were performed. Coronary angiography revealed a 50–60% stenoses in the proximal left anterior descending artery.
Post-procedural 21 days	Discharge.
Post-procedural 39 days	The result of endomyocardial biopsy was that Congo red staining showed amyloid deposition in myocardial tissue.
Post-procedural 3 months	TTE showed left heart function became better (mild MR and left ventricular ejection fraction was 40%), while right heart function became worse (see Supplementary material online, Figure S4).
Post-procedural 6 months	The patient was still alive and her symptoms of heart failure were alleviated.

Case presentation

An 83-year-old woman with severe MR was admitted to the department of cardiac surgery of our institute to receive TEER of MV. Her past medical history included heart failure (HF), hypertension, atrial fibrillation (AF), and coronary artery disease (CAD). Three months ago, she was hospitalized in another hospital because of shortness of breath and oedema in lower extremities. During hospitalization, severe MR was diagnosed with transthoracic echocardiography (TTE) and diuretics (torsemide, spironolactone) were used to relieve her symptoms. Other important medicines history included warfarin, carvedilol, isosorbide mononitrate and sacubitril/valsartan. Though she was receiving optimized medical therapy, breathlessness and oedema relapsed and prompted her transportation to our centre. A comprehensive TTE was performed and showed that MR effective regurgitation orifice area was 0.37 cm² and MR volume was 37 mL ([Figure 1](#)) and MR remained severe (see [Supplementary material online, Video S2](#)).

Transoesophageal echocardiography (TOE) demonstrated that the posterior valve was tethering at an angle of 63° and the anterior valve was overriding (see [Supplementary material online, Video S3](#)). Colour doppler flow imaging displayed that the vena contracta width was

7 mm and the MR area was 17.7 cm². Coronary computed tomography angiography revealed that there were multiple coronary plaques with varying degrees of lumen stenosis and no thickening and calcification of the mitral annulus (see [Supplementary material online, Figure S3](#)). Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM) score was 9.09% and the possibility of a transcatheter procedure was considered. MV anatomy was assessed and the choice of transcatheter mitral valve intervention devices was discussed. The option of replacement was discouraged (the anterior valve length was 2.5 cm, and the septal bulge was 14 mm) and durable repair was expected (no annular calcification, the anterior-posterior diameter was 3.6 cm, MV area was 5.56 cm²).¹⁰ An edge-to-edge repair device rather than an annuloplasty one was chosen given her non-dilated annulus and ‘functionally prolapsed’ valve (annulus area index was 6.41 cm²/m², the posterior valve was tethering at an angle of 63°, the anterior valve was overriding).¹¹ For the choice of the TA or transfemoral (TF) approach, the decision was made based on both the experience of our centre and the patient’s willingness. Cardiologists in our centre were more experienced in ValveClamp (performed on more than 50 patients, the clinical trial started in 2018 in China) than in MitraClip (performed on six patients, Chinese Food & Drug Agency clearance in 2020). The possibility of a TF approach in other referral centres with more experience in MitraClip was discussed with the patient, and she refused to be referred to other centres. So, the transapical ValveClamp system was selected.

One day before procedure, laboratory test results showed that N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) was 7671.0 pg/mL (normal range is 0–300 pg/mL); troponin T was 0.052 ng/mL (normal range is less than 0.03 ng/mL); international normalized ratio was 2.51. TEER was performed the day after admission using the ValveClamp system. Intraoperative TOE revealed a significant reduction in MR severity from severe to mild (see [Supplementary material online, Video S4](#) and [Supplementary material online, Video S5](#)) and a postoperative mitral valve orifice area of 2.7 cm² by direct planimetry ([Figure 2](#)). The mean transmitral pressure gradient increased from 1 mmHg preoperatively to 2 mmHg (see [Supplementary material online, Figure S5](#)). The procedure was successful. However, the left atrial V-wave pressure (LAvP) increased from 24 mmHg preoperatively to 28 mmHg immediately with the left atrial mean pressure (LAmP) elevated from 16 to 19 mmHg after the procedure. In the next few days, her heart failure became worse ([Figure 3](#)). Aggressive treatment for heart failure was used to reduce symptoms (Lyophilized recombinant human brain natriuretic peptide was delivered in the post-procedural 3 days) and NT-pro BNP then began to decline ([Figure 3](#)). After a careful review of the patient’s medical history, combined with echocardiographic findings, cardiologists were prompted that she might suffer from a RCM (retrospective analysis using speckle-tracking echocardiography found a significant decrease in global longitudinal strain and apical sparing pattern) (see [Supplementary material online, Figure S1](#)). Her serum kappa and lambda free light chain ratio were 0.667(normal range is 0.310–1.560). Both urine and serum protein

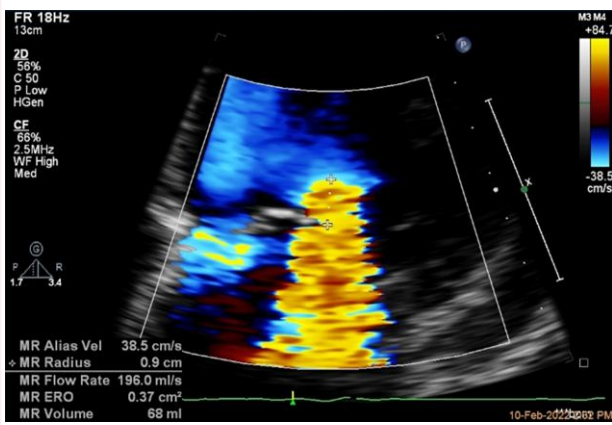


Figure 1 Pre-procedural TTE showed severe MR (image size: 693px × 496px).

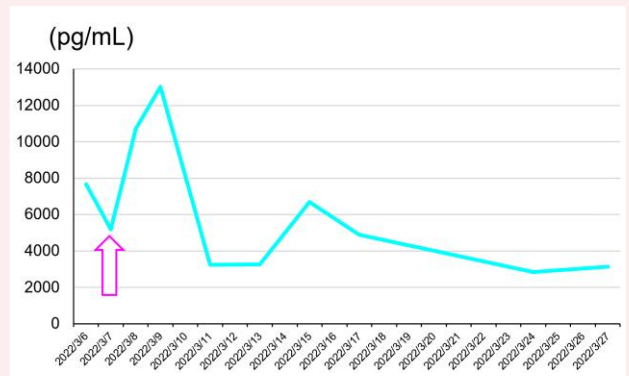


Figure 3 Changes in NT-pro BNP during hospitalization (the arrow points the day of procedure) (image size: 1653px × 986px).

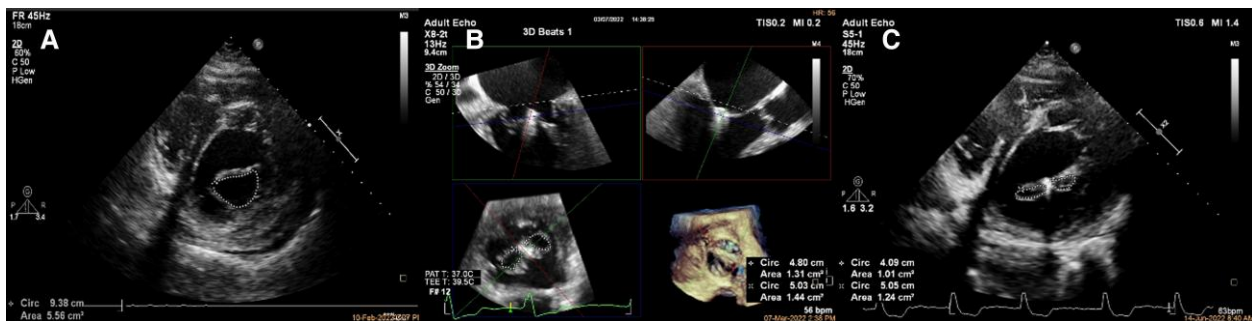


Figure 2 Pre-procedural and post-procedural mitral orifice area (image size: 1269px × 319px). (A) Pre-procedural mitral orifice area was 5.56 cm². (B) Intraoperative TOE showed the mitral orifice area was 2.75 cm². (C) Post-procedural 3 months mitral orifice area was 2.25 cm².

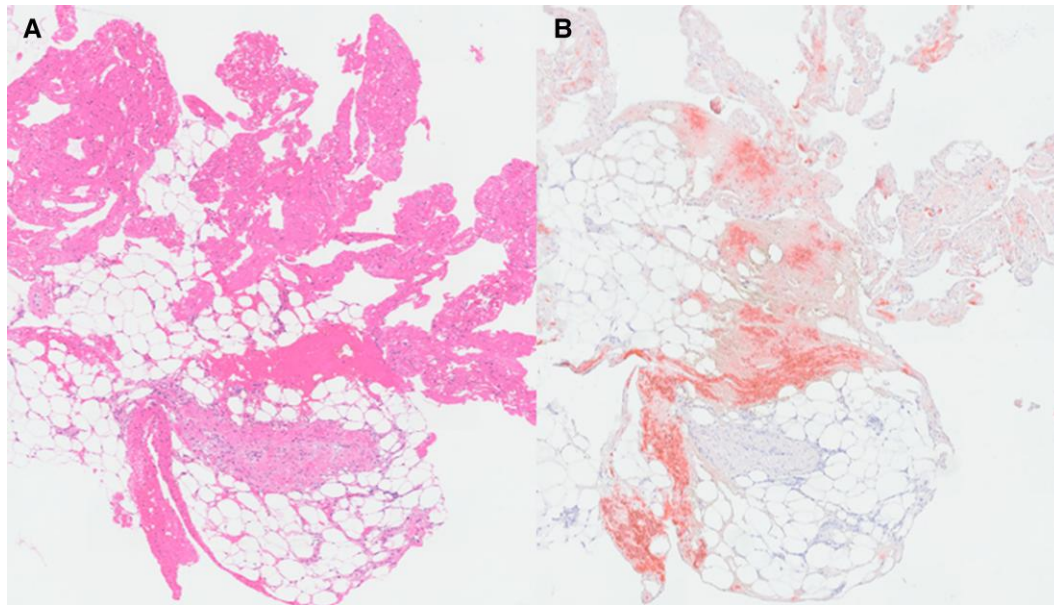


Figure 4 Histological staining of endomyocardial biopsy (image size: 865px × 492px). (A) H&E-stained myocardial tissue (HE 10×). (B) Congo red-stained myocardial tissue (Congo red 10×).

Table 1 Echocardiographic parameters changes during the past 12 years

	2010/8/13	2012/12/7	2022/2/10	2022/3/16	2022/6/14	Normal ranges
Left atrial front-rear diameter (mm)	54	58	67	68	67	19–40
LVEDD (mm)	62	62	68	65	63	35–56
LVESD (mm)	50	45	57	58	55	23–35
LV wall thickness (mm)	11	13	14	14	13	6–11
SPAP (mmHg)	38	32	50	51	75	< 40
LVEF (%)	41	44	33	29	40	> 54
MR	Mild	Mild	Severe	Mild	Mild	
Pericardial effusion	Mild	Mild	Moderate	Very small amount	Very small amount	

LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; LV = left ventricular; SPAP = systolic pulmonary artery pressure; LVEF = left ventricular ejection fraction; MR = mitral regurgitation

immunofixation electrophoresis were negative. Post-procedural 7 days, coronary angiography and endomyocardial biopsy were performed. Coronary angiography showed a 50–60% stenoses in the proximal left anterior descending artery. The result of endomyocardial biopsy was that Congo red staining showed amyloid deposition in myocardial tissue (Figure 4). The diagnosis of CA was confirmed. Six-month after procedural, the patient was still alive and her symptoms of HF were alleviated.

Discussion

Few cases have been reported with mitral valve infiltrated by the amyloid to cause thickening of the leaflets and severe MR^{12–14} and treated with either transcatheter or surgical procedure as per guideline recommendation. A patient with primary (AL) amyloidosis was successfully treated using the MitraClip,¹³ but another case who was treated with

transcatheter mitral valve replacement (TMVR) unfortunately died on postoperative day 5.¹⁵ TMVR is a possible alternative therapy for treating FMR.¹⁰ Valve-in-mitral annular calcification is not possible as there is no mitral annular calcification in this patient. There are also some risks (left ventricular wall is 14 mm, anterior valve length is 25 mm) of left ventricular outflow tract obstruction, so TMVR may not be a valid choice for this patient. A heart transplant may be the ultimate option. On the choice of TA or TF devices, the left ventricular apex has proved to be a safe and valid alternative access for various other structural heart procedures.¹⁶ The comparison of the TA and TF approach has been extensively discussed in the transcatheter aortic valve implantation.^{16–18} Although the transapical approach is more invasive compared with the TF approach, the outcome difference between TA and TE became acceptable because the device is constantly updated and the accumulated experience.¹⁹

The diagnosis of CA is challenging. In this case, the diagnosis of CA was made post-TEER, which may be not ideal if this case is meant to be a

didactic one. The patient is a female with a long history of heart failure. Echocardiography signs in this patient were not typical enough to alert clinicians to the possibility of CA before intervention (Table 1). Increased left ventricular wall thickness (14 mm) can be explained by the history of hypertension. Left atrial enlargement can be attributed to AF. QRS voltage is normal in electrocardiogram (see [Supplementary material online, Figure S2](#)). The immediate increase of LAP after TEER indicated the diagnosis of CA. Reduction in global longitudinal strain with relative apical sparing, namely 'cherry on the top' phenomenon, provided another powerful evidence in this patient's diagnosis. Speckle-tracking echocardiography plays an important role in early non-invasive screening.

Whether or not to treat severe FMR in CA patients seems to a dilemma. In this case, TEER reduces mitral regurgitation while also reducing MV orifice. A mitral orifice area of 2.75 cm² is reasonable for patients without diastolic dysfunction but not for those with restrictive changes (Figure 2). The non-compliant ventricular wall adds to the difficulty of driving blood flow from the left atrium into the ventricle in addition to the relatively small mitral valve opening area, resulting in markedly increased LAP. An increase in LAmP during TEER was an independent predictive of worse clinical outcomes at short-term follow-up, the benefit from MR reduction can be counter-balanced by the induction of increased LAmP⁴. Reduction in MR and guideline-directed medical therapy increase left ventricular ejection fraction (LVEF) and reverse left atrial remodelling. The patient's LVEF recovers from 29% to 40% and the left atrial volume index declines from 101.19 mL/m² to 80.36 mL/m². However, echocardiographic results seem to imply that the TEER may be harmful to right heart function. The elevated LAP propagates into the pulmonary vasculature and makes the systolic pulmonary artery pressure increase. SPAP is elevated from 50 mmHg preoperatively to 75 mmHg and tricuspid annular plane systolic excursion declines from 2.13 cm to 1.12 cm (see [Supplementary material online, Figure S4](#)).

Conclusions

Benefits and cost should be well balanced in CA patients with severe FMR when receiving TEER, as it reduces MR but may worsen HF and make LAmP increased immediately. FMR requires careful identification of the pathogenesis before the TEER procedure to help exclude patients with limited benefit from TEER.

Lead author biography



Meng Fangmin, 24 years old, is a graduate student of Shanghai Institute of Medical Imaging, Fudan University, intending to pursue a doctor's degree.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal – Case Reports*.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidelines.

Conflict of interest: None declared.

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