Emotional Stress Triggered Severe Mitral Regurgitation: The Multifactorial Interplay of the Mitral Valve

Amir Aker, MD, Avinoam Shiran, MD, Basheer Karkabi, MD, Magdi Ghanayem, BSc, Hana Allo, BSc, Yuval Avidan, MD, and Salim Adawi, MD, *Haifa, Israel*

INTRODUCTION

Mitral regurgitation (MR) is a dynamic disease and is highly influenced by hemodynamic loading conditions and left ventricular (LV) geometry.[1,2] Rare entities of severe MR without evidence of mitral valve (MV) structural abnormalities and LV dysfunction have been reported.[3,4] The etiology and the pathogenesis in these cases remains unclear. We describe a case of an emotionally stressed patient who presented with severe MR with a structurally normal MV and LVfunction that rapidly subsided to mild MR once the patient became calmer. This case emphasizes the interplay between psychological factors and the MV, demonstrating how emotional stress and anxiety can lead to quick alteration in MV morphology and function due to increased sympathetic tone and abrupt changes in afterload.

CASE PRESENTATION

This case describes a 77-year-old woman referred to our echocardiography lab as part of a follow-up for severe MR detected in a prior echocardiogram. Comorbidities included systemic hypertension and dyslipidemia.

Six months prior to presentation, our patient was hospitalized due to pulmonary congestion and elevated blood pressure (BP). A transthoracic echocardiogram (TTE) at that time demonstrated normal LV global and regional systolic function with an ejection fraction (EF) of 65% with mild MR, left atrial volume index (LAVI) of 40 mL/m^2, and mild pulmonary hypertension (PH) of 45 mm Hg with evidence of a structurally normal MV. The electrocardiogram tracing was notable for sinus rhythm and a known left bundle branch block (LBBB) with a QRS duration of 120 ms (Figure 1A). A coronary angiography ruled out obstructive coronary artery disease (Figure 1B, 1C). During cardiac catheterization, LV end-diastolic pressure was 40 mm Hg (normal values <12 mm Hg), suggesting the presence of diastolic dysfunction.

During follow-up, some BP lowering medications were discontinued due to borderline symptomatic hypotension. Repeated TTE conducted during follow-up showed, exceptionally, severe MR assessed qualitatively by color-flow Doppler (CFD) with evidence of a large color-flow jet area (CFA) and a large vena contracta (VC) of 12 mm with normal LV global function and severe PH with a right ventricular systolic pressure (RVSP) of 70 mm Hg. Malcoaptation of MV leaflets was reported without any structural changes or evidence of regional wall motion abnormalities (RWMAs). Because of BP fluctuations, BP lowering medications were restarted, and a follow-up TTE was scheduled.

At presentation our patient denied any dyspnea, leg swelling, orthopnea, paroxysmal nocturnal dyspnea, or palpitations but reported feeling overwhelmed and emotionally distressed. Physical examination was unremarkable and without any signs of acute heart decompensation. No murmurs were detected by auscultation. During the TTE a regular heart rate of around 75 beats/min was noted.

The current TTE demonstrated normal LV global and regional systolic function (Figure 2, Videos 1 and 2) with an EF of 65% with normal LV chamber size consisting of an LV end-systolic diameter (LVESD) of 24 mm (indexed 1.2 mm/m^2) and LV end-diastolic diameter (LVEDD) of 41 mm (indexed 2.05 mm/m^2). The LV wall thickness was normal and there was no evidence of RWMAs. The right ventricle was of normal size and exhibited normal systolic function.

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, apical 3-chamber view without **(A)** and with **(B)** CFD obtained at presentation during emotional stress and anxiety, demonstrates normal global and regional LV systolic function, MV leaflet tethering, and malcoaptation with severe qualitative MR.

Video 2: Two-dimensional TTE, apical 4-chamber view without **(A)** and with **(B)** CFD obtained at presentation during emotional stress and anxiety, demonstrates normal global and regional LV systolic function, MV leaflet tethering, and malcoaptation with severe qualitative MR.

Video 3: Two-dimensional TTE, apical 3-chamber view without **(A)** and with **(B)** CFD obtained after calming, demonstrates normal global and regional LV systolic function and normal MV leaflet coaptation with mild qualitative MR.

Video 4: Two-dimensional TTE, apical 4-chamber view without **(A)** and with **(B)** CFD obtained after calming, demonstrates normal global and regional LV systolic function and normal leaflet coaptation with mild qualitative MR.

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From the Department of Cardiology, Lady Davis Carmel Medical Center, Haifa, Israel (A.A., A.S., B.K., M.G., H.A., Y.A., S.A.); and The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel (A.A., A.S., B.K., Y.A., S.A.).

Correspondence: Amir Aker, MD, Department of Cardiology, Lady Davis Carmel Medical Center, 7 Michal Street, Haifa 34362, Israel. (E-mail: *akeramir90@gmail.com*).

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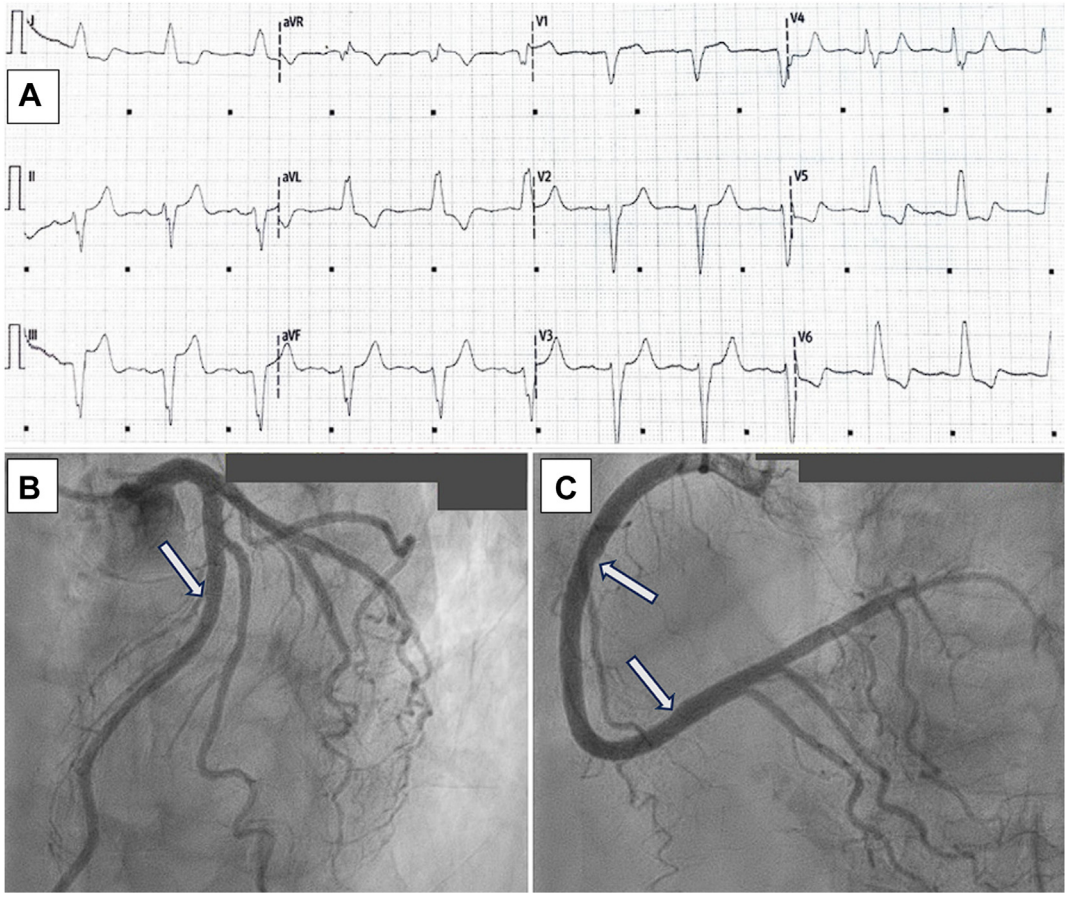

Figure 1 **(A)** Twelve-lead electrocardiogram demonstrates normal sinus rhythm with a (known) LBBB; **(B)** selective coronary angiography of the left **(B)** and right **(C)** coronary system demonstrates mild atherosclerosis (*arrows*) without evidence of obstructive coronary artery disease.

The MV appeared structurally normal with evidence of poor leaflet coaptation at end systole (Figure 2A). Assessment with CFD demonstrated a large jet of MR characterized by a CFA of >50% of the left atrial (LA) area (Figure 2C, Videos 1 and 2). Doppler interrogation of the MR showed a holosystolic flow (Figure 3A). Semiquantitative assessment was notable for a LAVI of 106 mL/m^2, a proximal isovelocity surface area (PISA) of 9.3 mm, VC of 12 mm, and a dominant E wave of 86 cm/sec, which further supported the presence of severe MR (Figures 2 and 3) in addition to severe PH with a RVSP of 72 mm Hg (Figure 3B). While we carried on with the examination, the patient was reassured and became calmer, leading to a prompt decrease of the MR severity to a mild degree within minutes. Repeated assessment during the index TTE demonstrated normal LV global and regional systolic function with EF of 65% and mild MR determined qualitatively by normal MV anatomy and leaflet coaptation alongside a reduction in PISA radius, VC diameter and in CFA to <10% of LA area. Moreover, a reduction in both, E wave to <50 cm/sec and RVSP to 40 mm Hg, was observed (Figure 4, Table 1). Worthy of note the bimodal shape of tricuspid regurgitant flow after the MR subsided to mild degree, indicating acute hemodynamic changes in the pulmonary circulation bed (Figure 3D). Quantitative assessment was not conducted due to the rapid resolution of the severe MR. Importantly, during the severe MR no RWMAs were observed. The LVESD was not altered, measuring 24 mm (indexed 1.2 mm/m^2) during both severe and mild MR, while LVEDD decreased minimally once the severe MR decreased to mild MR, from 41 mm (indexed 2.05 mm/m^2) to 38 mm (indexed 1.9 mm/m^2), respectively. In contrast, during severe MR, the LA diameter and LAVI were measured at 60 mm and 106 mL/m^2, respectively, and once the severe MR subsided to mild MR, these values quickly decreased to 34 mm and 43 mL/m^2, respectively. The MR was classified and reported as a class IIIb secondary MR evident by the dynamic and functional features, such as tethering and malcoaptation of the MV with no structural abnormalities (Figure 2, Videos 1 and 2). The BP measured 132/70 mm Hg. The electrocardiogram tracing on the TTE showed a reduction of the heart rate to 65 beats/min with the same pattern of LBBB. The patient remained asymptomatic without any further intervention and was discharged for an outpatient follow-up setting. An additional TTE was performed 2 months after presentation demonstrating mild MR.

DISCUSSION

Mitral regurgitation is a dynamic disease and is highly influenced by hemodynamic loading conditions and LV geometry[1,2] Emotional stress is known to be associated with autonomic disturbances.[5] It appears that enhanced sympathetic tone during emotional stress and anxiety, precipitated by excessive endogenous catecholamine stimulation, plays a key role in the pathogenesis of a wide range of cardiovascular disease. In fact, sympathetic activation represents a hallmark in anxiety and emotional stress, leading to increased cardiac output and afterload.[6] Nonetheless, the mechanisms behind cardiac

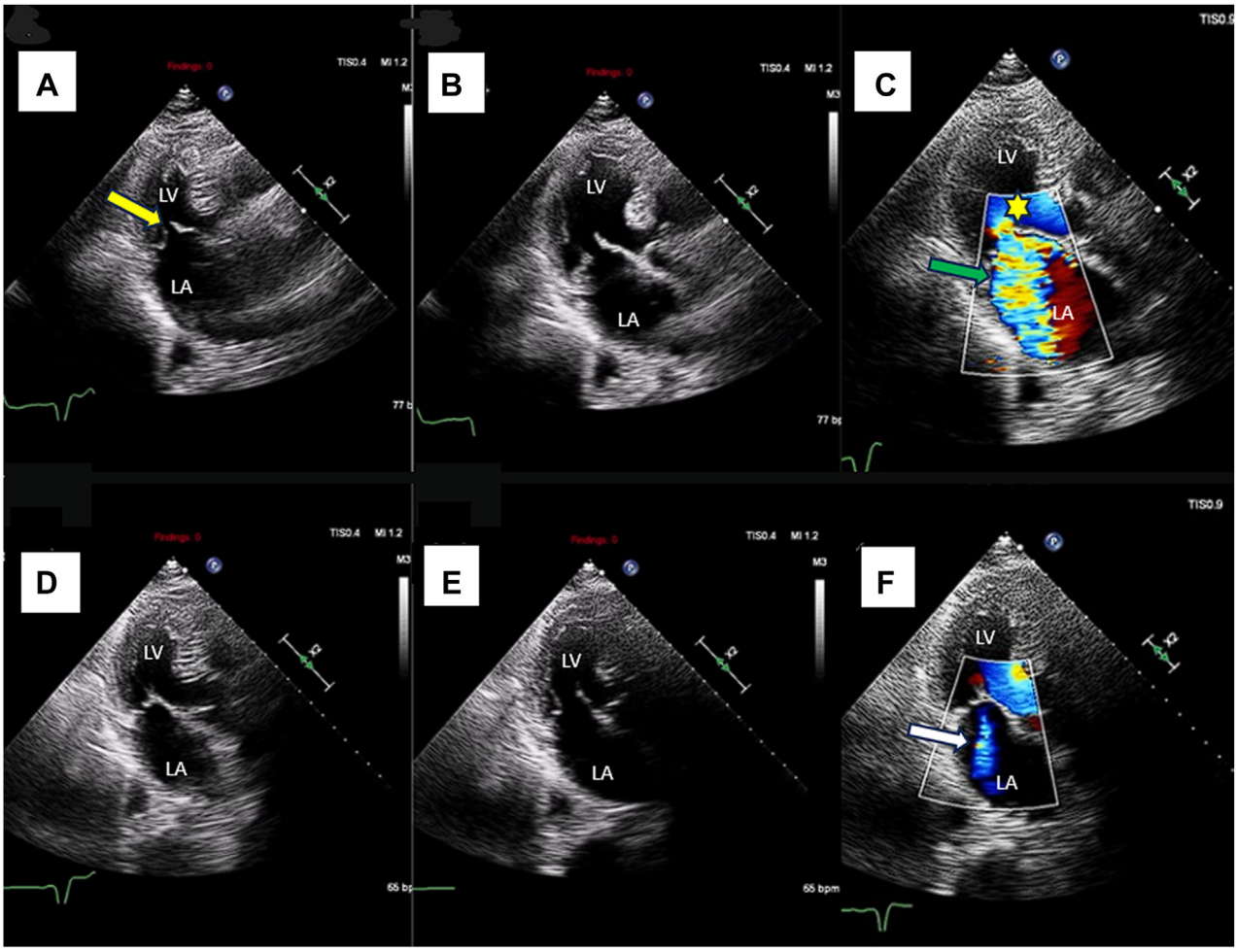

Figure 2 Two-dimensional TTE, apical 3-chamber systolic views, without **(A** and **D)** and with **(C** and **F)** CFD and diastolic **(B** and **E)** views during emotional stress *(upper panels)* and after calming *(lower panels)*, demonstrate malcoaptation of the MV leaflets *(yellow arrow)* with severe qualitative central MR and a CFA occupying >50% of the LA *(green arrow)* accompanied by a notable VC *(star)* that rapidly subsides to mild qualitative MR *(white arrow)*. *LA*, Left atrium; *LV*, left ventricle.

dysfunction induced by emotional stress remain unclear and require further investigation. Few data exist regarding dynamic MR exacerbated by emotional stress and anxiety. In the presence of a structurally normal MV and LV global function, the interaction between increased afterload and the MV represents the main contributing factor for acute MR deterioration.[1,2,6] In our case, the key factor contributing to the temporary worsening of MR is increased sympathetic tone during emotional stress, associated with an abrupt increase in afterload alongside valvular deformation with tethering of the MV leaflets resulting in leaflet malcoaptation (Figure 2A–C, Videos 1 and 2). This is evidenced by the rapid decrease in MR severity to a mild degree once the patient's mood is stabilized, along with a reduction in sympathetic tone as indicated by the decrease in heart rate and, presumably, in BP (Figure 2D-F, Videos 3 and 4). One striking hemodynamic finding is the drastic change in LAVI. Abrupt changes in mitral regurgitant volume may initially lead to a considerable chamber dilation in accordance with the Frank-Starling mechanism. With further MR worsening, the extent of atrial dilatation is diminished, resulting in an increase in LA pressure.[7] Nonetheless, ensuring accurate body surface area calculation and consistent LA volume measurements is essential for calculating precise LAVI values when comparing changes across multiple studies. In our case, these potential errors were eliminated, and the calculated LAVI values were validated by repeated measurements.

Systemic BP allows an indirect assessment of LV afterload, which is known to exacerbate MR severity. Afterload-dependent severe MR is well described in patients with LV dysfunction, coronary artery disease, and valve abnormalities, while it is relatively rare in the absence of these conditions.[8] One report described a case of transient MR due to increased afterload, which aligns with our case.[4] Yet, in our patient, BP measurement was not taken before the TTE. However, considering the history of imbalanced hypertension, we presume that the key element is increased afterload secondary to enhanced sympathetic tone during emotional stress. This is supported by the abrupt changes in MR jet maximal velocity and E-wave velocity, which reflect acute and rapid hemodynamic changes in LV afterload (Figure 3). Therefore, we suggest a routine preexamination BP measurement to more effectively identify patients with increased afterload in patients undergoing TTE for the assessment of MV disease. Of note, routine BP assessment prior to a clinically indicated TTE has not demonstrated a strong correlation with afterload throughout the whole TTE examination.[9] More specifically, this has not been

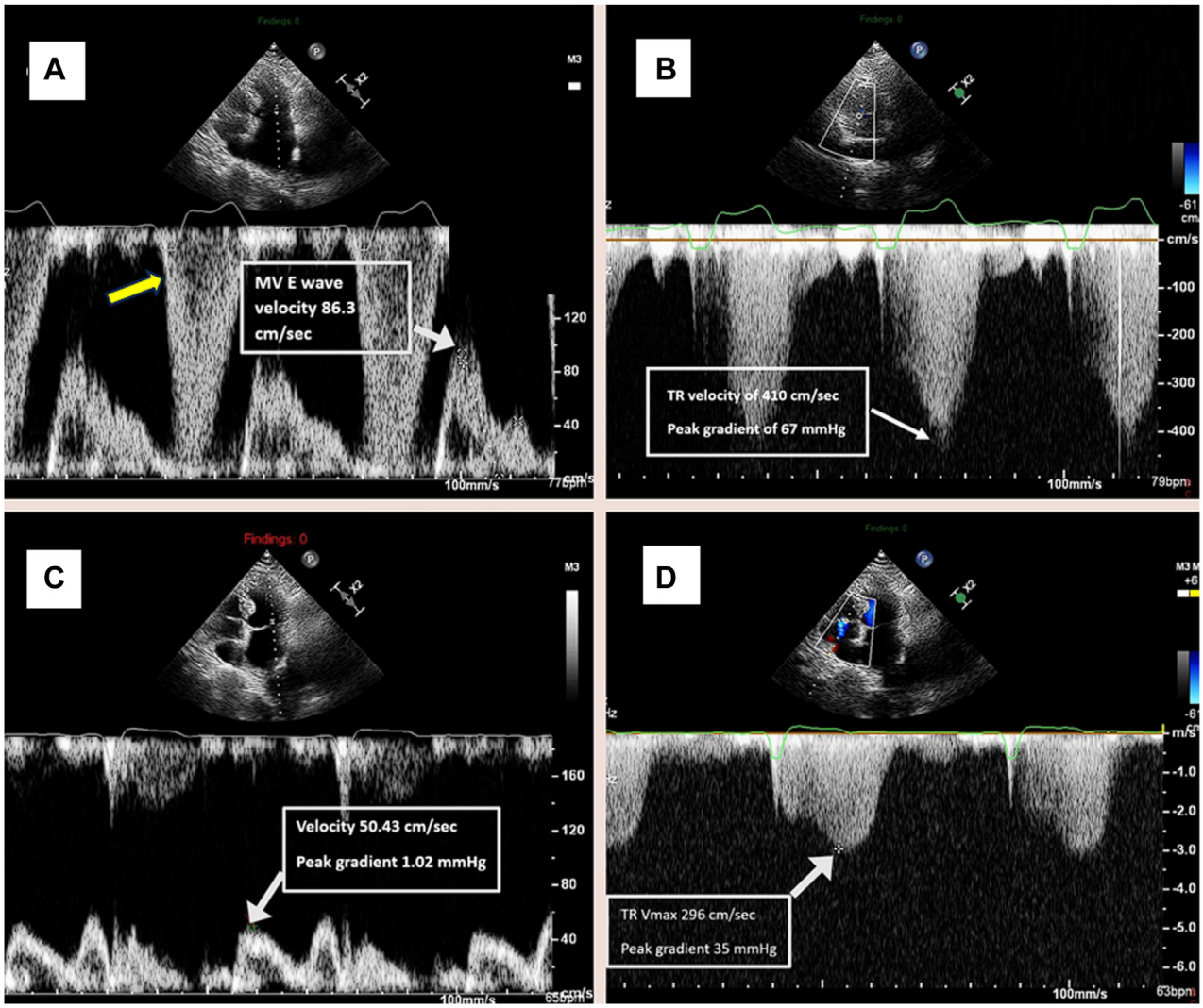

Figure 3 Two-dimensional TTE, apical 4-chamber views with PWD **(A** and **C)** and CWD **(B** and **D)** spectral displays during emotional stress *(upper panels)* and after calming *(lower panels)*, demonstrates the change in E-wave velocity (*white arrows*; 86 cm/sec to 50 cm/sec) and density of the holosystolic MR *(yellow arrow)* as well as the change in TR maximal velocity (*white arrows*; 410 cm/sec to 296 cm/sec). *PWD*, pulse-wave Doppler; *CWD*, continuous-wave Doppler; *TR*, Tricuspid regurgitation; *Vmax*, maximum velocity.

investigated in patients undergoing TTE for the evaluation of MV disease. Accurate assessment of the severity of MR is essential for appropriate selection of patients who may benefit from MV interventions. Thus, in cases of afterload-dependent MR, additional testing is required to confirm the diagnosis. This may be achieved through provocative testing by the use of vasoconstricting drugs or by stress testing. In one study, the use of intraoperative administration of phenylephrine and loading tests was useful to avoid MR severity underestimation induced by general anesthesia in patients with MR undergoing valve surgery.[2] It should be noted that patients with non-severe dynamic MR at rest increase MR severity in conditions of increased afterload, such as exercise. One study suggested handgrip exercise use to reclassify MR severity in patients presenting with non-severe MR at rest to severe MR during handgrip exercise.[10] Hence, physicians should be encouraged to use provocative stress testing when evaluating patients with dynamic MV disease. In the absence of structural abnormalities of the MV, signs of myocardial ischemia, or LV dysfunction, our case might represent a form of an entity, termed eclipsed MR, that is characterized by a reversible MR without major MV abnormalities or coronary artery disease potentially related to coronary artery vasospasm.[3] However, no indications of RWMAs were observed in our case, making this underlying pathophysiologic mechanism unlikely. Another potentially contributing factor to the deterioration of MR is the presence of LBBB, which is known to cause LV dyssynchrony.[11] This pathophysiologic mechanism is less prominent due to the chronic nature of LBBB in our case. Yet, the LV compensatory response to abrupt afterload increments may be inadequate in the presence of LV dyssynchrony. Supporting this, a study demonstrated worsening of LV dyssynchrony markers in response to increased afterload among patients with a hypertensive response during exercise.[12] Additionally, LBBB with normal LV global function might be associated with increased incidence of LV fibrosis, evaluated using cardiovascular magnetic resonance (CMR), as well as reduced myocardial strain, evaluated using speckle-tracking global longitudinal

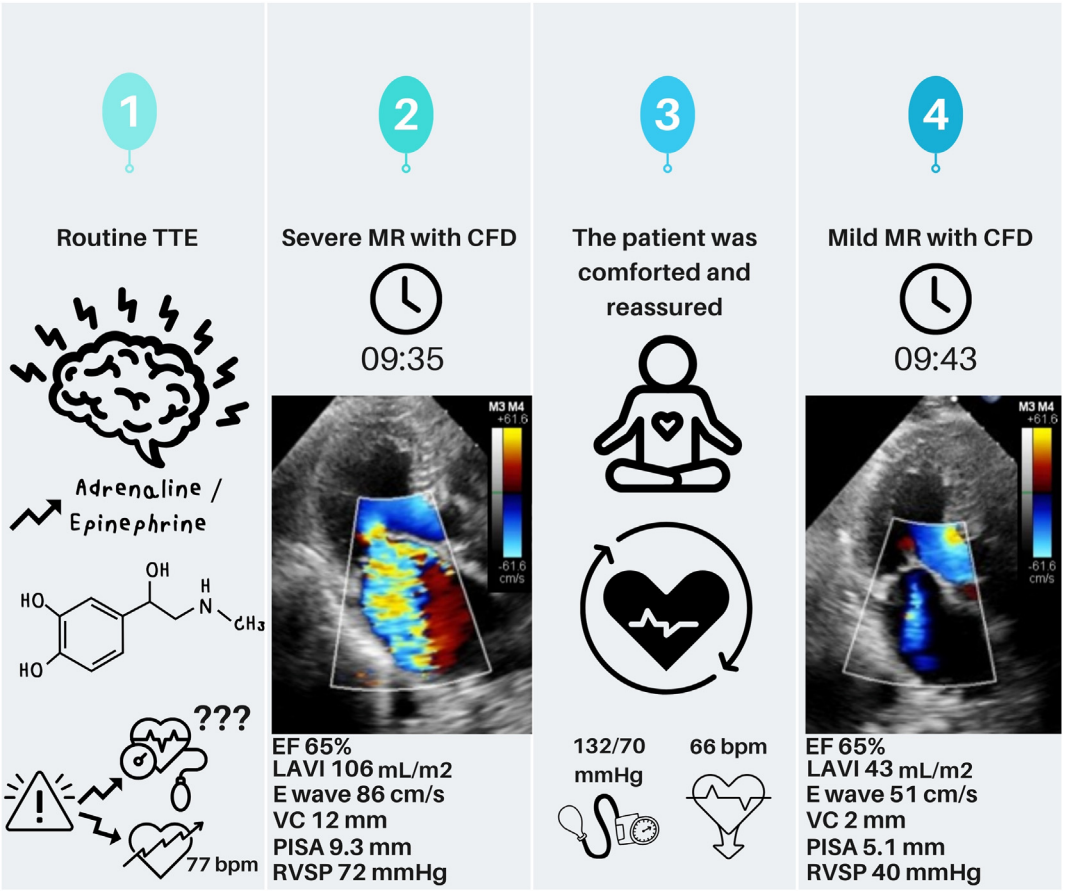

Figure 4 Case timeline. At presentation (1), severe MR was noted in the presence of emotional stress and anxiety (2). Once the patient was reassured and became calmer (3) the MR quickly subsided to mild MR (4).

Table 1 TTE parameters in presence of severe MR during emotional stress and mild MR after becoming calmer and the relative change in each parameter

	Severe MR	Mild MR	Change
EF, %	65	65	0
LVEDD (indexed), mm (mm/m^2)	4.1 (2.05)	3.8 (1.9)	–0.3 (–0.15)
LVESD (indexed), mm (mm/m^2)	2.4 (1.2)	2.4 (1.2)	0
LA diameter, cm	5.1	4.4	–0.7
LAVI, mL/m^2	106	43	–63
VC, mm	12	2	–10
PISA radius, mm	9.3	5.1	–4.2
PH (RVSP), mm Hg	72	40	–32
CFD jet area (%) to LA area	>50	<10	N/A
E wave, cm/sec	86	51	–35
TR velocity, cm/sec	410	296	–114

LA, left atrium; *LVEDD*, LV end-diastolic diameter; *LVESD*, LV end systolic diameter; *TR*, tricuspid regurgitation.

strain (GLS).[13,14] Therefore, implementing speckle-tracking GLS and CMR in evaluating patients with MV disease should be encouraged to detected subtle LV functional abnormalities despite normal traditional echocardiographic indices such as EF.

The prevalence, underlying mechanisms, and prognostic significance of dynamic MR have not been thoroughly investigated. This suggests a potential role for multimodality imaging application in patients with dynamic MR to identify patients at higher risk of MR progression. For instance, CMR may assist in evaluating the risk of MR progression and has been shown to be reliable in detecting subtle changes in cardiac chambers and mitral apparatus, through quantifying MR degree based on quantitative flow measurements and facilitating tissue characterization within the MV.[15]

Our case illustrates the dynamic interplay of the MV with a wide range of factors and highlights the potential impact of emotional stress and anxiety on cardiac function. It also underscores the importance of considering psychosocial factors and routine BP measurement when evaluating patients with MV disease to obtain an accurate diagnosis and identify patients with dynamic MV disease. Further studies are needed to assess the prognostic implications of dynamic MR and to expand our understanding of the pathophysiology of this entity.

CONCLUSION

Emotional stress and anxiety increase the sympathetic tone and may potentially lead to inaccurate MR assessment, mainly as a result of increased afterload. Physicians should be encouraged to consider psychological factors and routine preassessment of BP before and during echocardiography when evaluating patients for MV disease given the highly dynamic characteristics of the MV.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing deidentified data, informed consent was not required from the patient under an IRB exemption status.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2024.12.006.

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