ESC European Society of Cardiology
European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytab150

CASE REPORT
Cardiac imaging

Dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis with concomitant severe functional mitral regurgitation: a case report

Kenichi Ishizu *, Akihiro Isotani , Shinichi Shirai, and Kenji Ando

Department of Cardiovascular Medicine, Kokura Memorial Hospital, 3-2-1 Asano, Kokurakita-ku, Kitakyushu, Fukuoka 802-8555, Japan

Received 13 September 2020; first decision 3 November 2020; accepted 9 April 2021

Background Dobutamine stress echocardiography (DSE) in classical low-flow, low-gradient (LFLG) aortic stenosis (AS) is recommended in recent guidelines to differentiate true-severe AS from pseudo-severe AS. However, DSE for patients with concomitant significant mitral regurgitation (MR) is often inaccurate or inconclusive.

Case summary A 73-year-old man with a history of coronary artery bypass grafting was referred to our institution with congestive heart failure. Transthoracic echocardiogram showed severe functional MR and LFLG AS. The results of DSE to determine the severity of AS were inconclusive owing to the absence of flow reserve, usually defined as stroke volume increase of ≥20%. In addition, calcium score by computed tomography scan was also inconclusive. Our heart team decided to reassess the severity of AS after percutaneous edge-to-edge mitral valve repair (PMVR), considering the patient's high surgical risk. Percutaneous edge-to-edge mitral valve repair was uneventful, resulting in marked reduction of MR from severe to trivial. Dobutamine stress echocardiography after PMVR revealed true-severe AS with the presence of flow reserve. Transcatheter aortic valve implantation (TAVI) was performed, and the patient ambulatorily discharged.

Discussion The coexistence of significant AS may lead to overestimation of the severity of MR, and reportedly, concomitant MR improves in the majority of patients after TAVI, especially MR of functional aetiology. However, the coexistence of significant MR often leads to inconclusive DSE results because dobutamine stress may worsen MR and fail to increase the stroke volume. In our case, DSE after PMVR was useful to diagnose the true-severe AS for the patient with LFLG AS and severe functional MR.

Keywords Aortic stenosis • Dobutamine stress echocardiography • Mitral regurgitation • Case report

* Corresponding author. Tel: +81-93-511-2000, Fax: +81-93-511-2029, Email: k.ishizu.04ri@gmail.com
Handling Editor: Pierre Deharo
Peer-reviewers: Hugo Rodríguez-Zanella; Doralisa Morrone; and Luca Moderato
Compliance Editor: Edwina McNaughton
Supplementary Material Editor: Ross Thomson
© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Learning points

- The coexistence of significant mitral regurgitation (MR) often causes low-flow, low-gradient (LFLG) aortic stenosis (AS) by reducing forward stroke volume (SV) and leads to underestimation of the severity of AS.
- Concomitant MR contributes to inconclusive dobutamine stress echocardiography results because dobutamine stress may worsen MR and fail to increase the forward SV.
- Dobutamine stress echocardiography after percutaneous mitral valve edge-to-edge repair may be useful to strictly evaluate the severity of LFLG AS with significant MR.
- The multiparametric evaluation of the AS severity is important particularly for the patients in LFLG state and/or with multivalvular disease.

Introduction

Classical low-flow, low-gradient (LFLG) aortic stenosis (AS), which represents approximately 5–10% of severe AS, is one of the most challenging valvular heart diseases in terms of severity grading and therapeutic management.[1] Some factors, including left or right ventricular dysfunction, atrial fibrillation, and mitral regurgitation (MR), have been reported to be associated with the low flow state.[2] In particular, concomitant MR that is moderate or greater potentially aggravates the low flow state owing to the decrease of forward stroke volume (SV) and makes the confirmation of AS severity more challenging.[3,4] Although recent guidelines recommended dobutamine stress echocardiography (DSE) in classical LFLG AS to differentiate true-severe AS from pseudo-severe AS,[5] DSE for the patients with concomitant significant MR is often inaccurate or inconclusive because of the absence of flow reserve (SV increase of ≥20%). We describe the case of a patient with LFLG AS and functional severe MR, in which the reassessment of DSE after percutaneous edge-to-edge mitral valve repair (PMVR) was useful for AS severity grading.

Case presentation

A 73-year-old Asian man with a history of myocardial infarction treated by coronary artery bypass grafting and congestive heart failure [New York Heart Association (NYHA) Class III], despite the guideline-directed medical therapy including carvedilol of 20 mg, valsartan of 160 mg, spironolactone of 50 mg, furosemide of 40 mg, and aspirin of 100 mg, was referred to our institution for therapeutic intervention in combined valvular heart diseases. Upon arrival, he presented with dyspnoea on mild exertion, while his vital signs were stable (blood pressure, 106/81 mmHg; heart rate, 72 b.p.m.; oxygen saturation, 95% on room air). Physical examination revealed a Levine IV/VI systolic murmur at the upper right sternal border and apex, as well as slight bilateral lower extremity oedema. Laboratory test results were normal except for B-type natriuretic peptide levels of 321.5 pg/mL (<18.4 pg/mL), creatinine levels of 1.17 mg/dL (<1.15 mg/dL), and albumin levels of 31 g/L (41–51 g/L). Transthoracic echocardiography (TTE) revealed severely decreased left ventricular ejection fraction of 30.3% and increased left ventricular end-diastolic volume of 237.3 mL (62–150 mL) with severe functional MR (effective regurgitant orifice area 0.41 cm^2, regurgitant volume 65.8 mL), resulting in quite low forward SV (SV index to body

Timeline

Admission	The patient was referred to our institution for therapeutic intervention in combined valvular heart diseases. Transthoracic echocardiography (TTE) revealed severely decreased left ventricular ejection fraction of 30.3% with severe functional mitral regurgitation (MR) and classical low-flow, low-gradient (LFLG) aortic stenosis (AS).
Day 4	Transoesophageal echocardiography demonstrated a regurgitant jet that originated from the A2-P2 portion of the mitral valve as a result of leaflet tethering and degenerative changes of the aortic valve with a planimetric aortic valve area of 0.80 cm^2.
Day 5	To evaluate the severity of AS, dobutamine stress echocardiography (DSE) was performed. However, the results were inconclusive because the flow reserve was absent (increase of forward stroke volume <20%).
Day 7	Multidetector computed tomography demonstrated the shaggy aorta and the aortic valve calcium score using the Agatston method of 1512.3 arbitrary units, which indicated the unlikelihood of severe AS.
Day 12	Percutaneous edge-to-edge mitral valve repair (PMVR) was successfully performed, and MR was markedly reduced from severe to trivial.
Day 22	DSE after PMVR demonstrated that the patient's LFLG AS was categorized as severe.
Day 31	Transcatheter aortic valve implantation with the 26 mm SAPIEN 3 was performed via a direct transaortic approach.
Day 40	The patient was discharged after an uneventful recovery.
6 months later	The patient had no cardiovascular symptoms. The follow-up TTE showed no AS and trivial MR.

surface area, 22.1 mL/m^2) (*Figure 1A and B*). The aortic valve area (AVA) calculated with the continuity equation was 0.71 cm^2 with a transaortic mean pressure gradient (MPG) of 22.2 mmHg. Doppler velocity index was 0.20. Pulmonary hypertension was suggested by a systolic tricuspid regurgitation pressure gradient of 42.1 mmHg. Transoesophageal echocardiography demonstrated a severe regurgitant jet with vena contracta area of 0.40 cm^2 that originated from the A2-P2 portion of the mitral valve as a result of leaflet tethering (*Figure 2A*, *Videos 1* and *2*) and degenerative changes of the aortic valve with two-dimensional planimetric AVA of 0.80 cm^2 (*Figure 2B*). Three-dimensional planimetric AVA was 0.72 cm^2. Coronary angiography showed that all bypass grafts were patent.

The patient was diagnosed with classical LFLG AS, and DSE was performed to evaluate the severity of his AS. The AVA was slightly increased to 0.75 cm^2 with an MPG of 24.8 mmHg and a mean transvalvular flow rate (Q_{mean}) of 114.5 mL/s after dobutamine stress up to 20 µg/kg/min. However, the results were inconclusive because the flow reserve was absent (increase of forward SV <20%). In addition, the projected AVA at a normal transvalvular flow rate (250 mL/s) calculated by linear regression analysis was 1.06 cm^2, which was unreliable due to no sufficient increase of Q_{mean} (*Figure 3* and *Table 1*). Multidetector computed tomography (MDCT) demonstrated the shaggy aorta (*Figure 4A*) and the aortic valve calcium score using the Agatston method of 1512.3 arbitrary units (*Figure 4B*), which

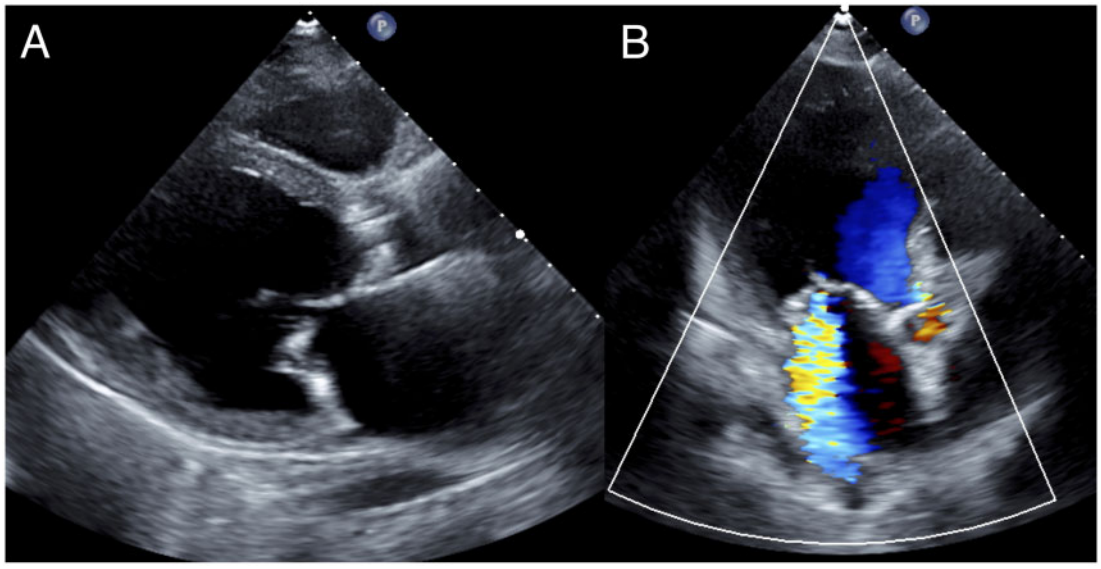
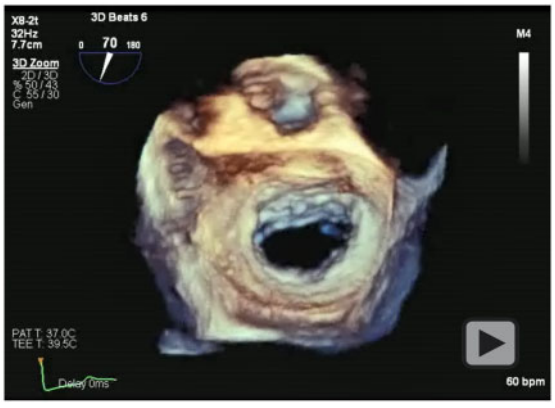
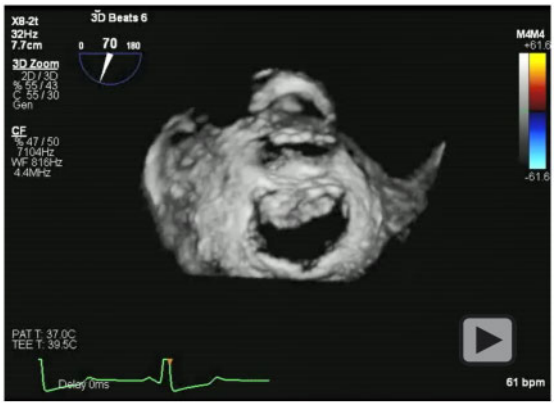


Figure 1 Transthoracic echocardiography on admission. Transthoracic echocardiography images showing severely decreased left ventricular ejection fraction of 30.3% with calcified aortic valve (*A*) and severe functional mitral regurgitation (*B*).



Video 1 Three-dimensional transoesophageal echocardiography before percutaneous edge-to-edge mitral valve repair showing the tethering of mitral valve leaflets.



Video 2 Three-dimensional transoesophageal echocardiography with colour Doppler before percutaneous edge-to-edge mitral valve repair showing a regurgitant jet that originated from the A2-P2 portion of the mitral valve as a result of leaflet tethering.

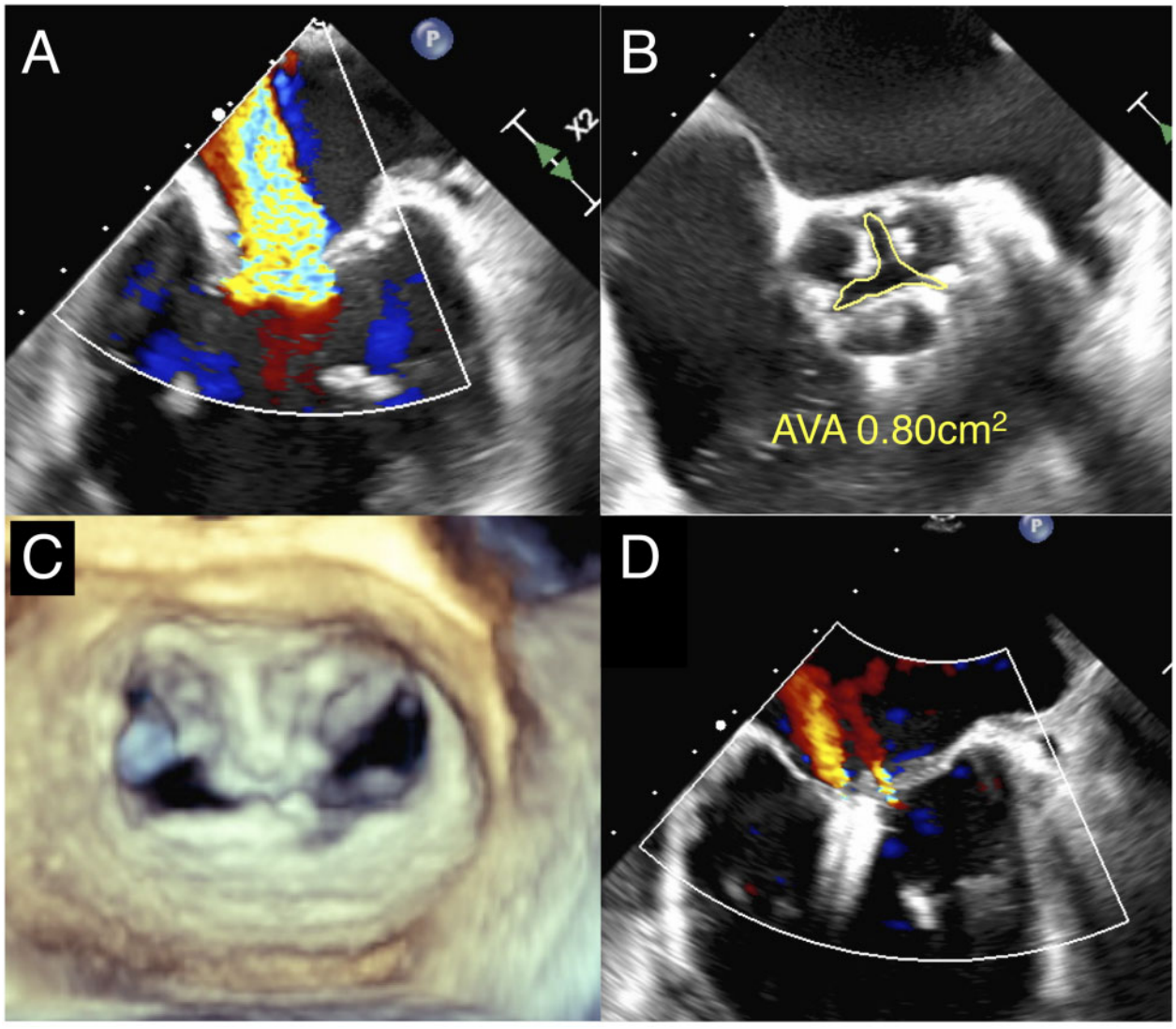


Figure 2 Transoesophageal echocardiography before and after percutaneous edge-to-edge mitral valve repair using the MitraClip. Transoesophageal echocardiography images before percutaneous edge-to-edge mitral valve repair showing a regurgitant jet originated from the A2-P2 portion of mitral valve as a result of leaflet tethering (vena contracta area 0.43 cm^2) (*A*) and degenerative changes of aortic valve with planimetric aortic valve area of 0.80cm^2 (*B*). Transoesophageal echocardiography images after the deployment of two clips demonstrating a tissue bridge between A2 and P2 (*C*) and significant reduction of mitral regurgitation from severe to trivial (vena contracta area 0.05 cm^2) (*D*).

indicated the unlikeliness of severe AS. Although the resolution of AS could have reduced left ventricular end-diastolic pressure and MR, even multiparametric approach did not lead to the confirmation of AS severity. Therefore, our heart team decided to reassess the severity of AS after PMVR using the MitraClip system (Abbott Vascular, Lake Bluff, IL, USA), considering his high surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality, 8.856%). Two clips were successfully implanted at the centre of the A2-P2 portion, and MR was markedly reduced from severe to trivial (*Figure 2C* and *D*). There was no significant post-procedural mitral stenosis with the mean transmitral pressure gradient of 2.4 mmHg and the mitral valve orifice area of 2.60 cm^2.

The patient's symptoms were mitigated but remained (NYHA class II). Dobutamine stress echocardiography performed 10 days after PMVR demonstrated an AVA of 0.77 cm^2 with an MPG of 42.1 mmHg as well as a 20% or more increase of forward SV after dobutamine infusion of 20 μg/kg/min (*Figure 5* and *Table 1*). Thus, his LFLG AS was reassessed and categorized as true-severe AS, and we performed transcatheter aortic valve implantation (TAVI) with the 26 mm SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) via a direct transaortic approach (*Figure 3C*). The patient was discharged after an uneventful recovery. At the 6-month follow-up, he had no cardiovascular symptoms and showed improvements in walking distance on a 6-min walk test. The follow-up TTE showed no AS and trivial MR.

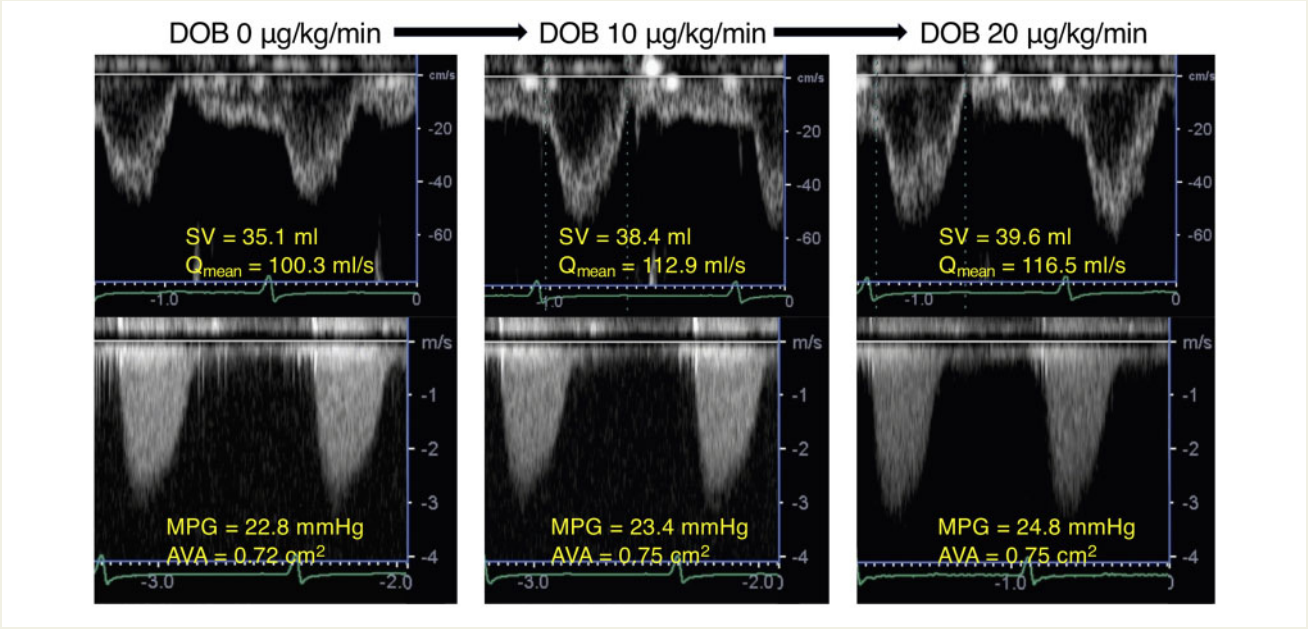


Figure 3 Dobutamine stress echocardiography before percutaneous edge-to-edge mitral valve repair. Transthoracic echocardiography images showing pulsed wave Doppler at the left ventricular outflow tract (the upper panels) and continuous wave Doppler of aortic stenosis jet (the lower panels), during dobutamine stress. Dobutamine stress echocardiography before percutaneous edge-to-edge mitral valve repair demonstrated a slightly increased aortic valve area and transaortic mean pressure gradient to 0.75 cm^2 and 24.8 mmHg with no flow reserve after dobutamine stress up to 20 µg/kg/min. AVA, aortic valve area; DOB, dobutamine; MPG, transaortic mean pressure gradient; Q_{mean}, mean transvalvular flow rate; SV, stroke volume.

Table 1 **Dobutamine stress echocardiography before and after percutaneous edge-to-edge mitral valve repair**

	Pre-PMVR					Post-PMVR				
Dobutamine infusion	**SV (mL)**	**Q_{mean} (mL/s)**	**MPG(mmHg)**	**DVI**	**AVA (cm^2)**	**SV (mL)**	**Q_{mean} (mL/s)**	**MPG (mmHg)**	**DVI**	**AVA (cm^2)**
0 µg/kg/min	35.1	100.3	22.8	0.20	0.72	42.0	124.3	28.8	0.19	0.79
10 µg/kg/min	38.4	113.9	23.4	0.22	0.75	47.1	160.7	33.8	0.20	0.80
20 µg/kg/min	39.6	114.5	24.8	0.21	0.75	52.7	188.2	42.1	0.20	0.77
Projected AVA (cm^2)			1.06					0.76		

The results of DSE pre-PMVR were inconclusive because of the absence of flow reserve, whereas DSE post-PMVR demonstrated the ≥20% increase of forward SV after dobutamine infusion of 20 µg/kg/min with stress MPG ≥40.0 mmHg and stress AVA <1.0 cm^2. In addition, projected AVA pre-PMVR was unreliable due to the insufficient increase of Q_{mean}.
AVA, aortic valve area; DSE, dobutamine stress echocardiography; DVI, Doppler velocity index; MPG, transaortic mean pressure gradient; PMVR, percutaneous edge-to-edge mitral valve repair; Q_{mean}, mean transvalvular flow rate; SV, stroke volume.

Discussion

Mitral regurgitation is commonly observed in patients with severe AS.[6] The coexistence of significant AS may lead to overestimation of the severity of MR, and reportedly, concomitant significant MR improves with resolution of AS in the majority of patients, especially MR of functional aetiology.[7] Hence, the reassessment of MR severity after isolated TAVI is generally recommended for high-surgical-risk patients with severe AS with functional MR.

Conversely, the coexistence of significant MR often causes LFLG AS by reducing the forward SV and leads to underestimation of the severity of AS.[4] In addition, concomitant MR contributes to inconclusive results of DSE to distinguish true-severe AS from pseudo-severe AS because dobutamine stress may worsen MR and fail to increase the forward SV of 20% or greater.[5,8]

In our case, the initial resolution of AS could have led to mitigation of functional MR. However, the results of investigations including DSE and MDCT for determination of the patient's LFLG AS severity were inconclusive, as mentioned above. Although the projected AVA at the normal transvalvular flow rate of 250 mL/s has recently been reported to be useful for assistance in confirming the AS severity in case of the absence of flow reserve, no sufficient increase of flow rate (ΔQ_{mean} > 15%) makes the projected AVA value inaccurate and

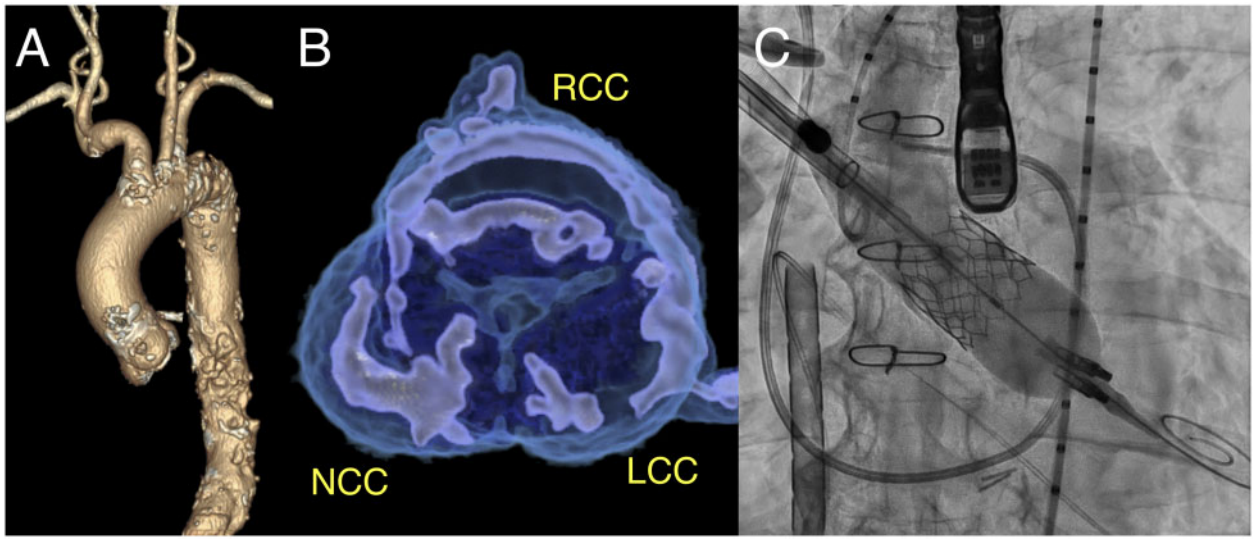


Figure 4 Transcatheter aortic valve implantation via a direct transaortic approach. Three-dimensional reconstruction of multidetector computed tomography showing the shaggy descending aorta (*A*) and the moderately calcified aortic valve (*B*). Fluoroscopic image showing the 26 mm SAPIEN 3 deployed via a direct transaortic approach (*C*). LCC, left coronary cusp; NCC, non-coronary cusp; RCC, right coronary cusp.

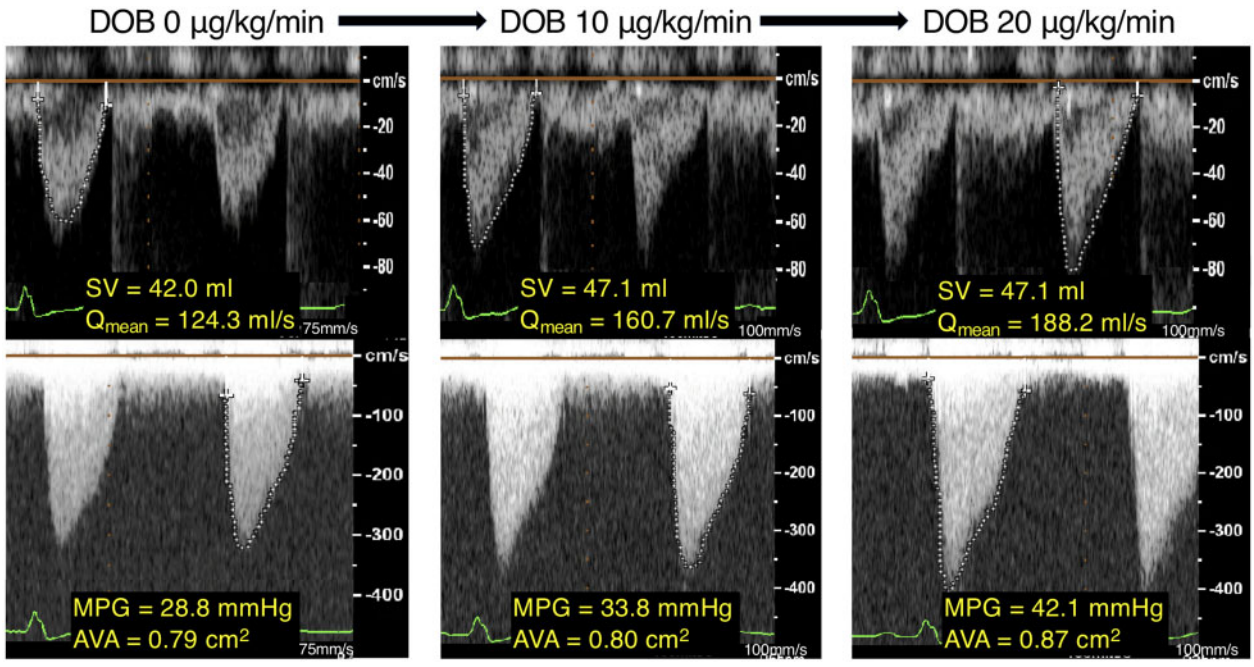


Figure 5 Dobutamine stress echocardiography after percutaneous edge-to-edge mitral valve repair. Transthoracic echocardiography images showing pulsed wave Doppler at the left ventricular outflow tract (the upper panels) and continuous wave Doppler of aortic stenosis jet (the lower panels), during dobutamine stress. Dobutamine stress echocardiography after percutaneous edge-to-edge mitral valve repair demonstrated an aortic valve area of 0.77 cm^2 with a transaortic mean pressure gradient of 42.1 mmHg as well as a 20% or more increase of forward stroke volume after dobutamine infusion of 20 µg/kg/min. AVA, aortic valve area; DOB, dobutamine; MPG, transaortic mean pressure gradient; Q_{mean}, mean transvalvular flow rate; SV, stroke volume.

inconclusive.[9] Thus, after the rigorous discussion in our heart team, we decided to perform isolated PMVR with MitraClip before reassessing the AS severity, although the approach was not specified in the guidelines.[5,10] Dobutamine stress echocardiography after PMVR demonstrated a sufficient increase of the forward SV and was useful to diagnose the true-severe AS in this patient.

Lead author biography

Kenichi Ishizu graduated from Kyoto University and started his career in Kobe City Medical Center General Hospital, Kobe, Japan. He is a general cardiology physician in the Department of Cardiovascular Medicine, Kokura Memorial Hospital, Kitakyushu, Japan, since 2018.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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 including images and associated text was obtained from the patient in line with COPE guidance.

Conflict of interest: S.S., MD, is the proctor of transfemoral-TAVI for Edwards Lifesciences and Medtronic. The other authors have no potential conflicts of interest relevant to this article.

Funding: none declared.

References

1. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. *J Am Coll Cardiol* 2012;**60**:1845–1853.
2. Leong DP, Pizzale S, Haroun MJ, Yazdan-Ashoori P, Ladak K, Sun YY et al. Factors associated with low flow in aortic valve stenosis. *J Am Soc Echocardiogr* 2016;**29**:158–165.
3. Benfari G, Clavel M-A, Nistri S, Maffeis C, Vassanelli C, Enriquez-Sarano M et al. Concomitant mitral regurgitation and aortic stenosis: one step further to low-flow preserved ejection fraction aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2018;**19**:569–573.
4. Katte F, Franz M, Jung C, Figulla HR, Leistner D, Jakob P et al. Impact of concomitant mitral regurgitation on transvalvular gradient and flow in severe aortic stenosis: a systematic ex vivo analysis of a subentity of low-flow low-gradient aortic stenosis. *EuroIntervention* 2018;**13**:1635–1644.
5. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
6. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. *Heart* 2017;**103**:1696–1703.
7. Freitas-Ferraz AB, Lerakis S, Barbosa Ribeiro H, Gilard M, Cavalcante JL, Makkar R et al. Mitral regurgitation in low-flow, low-gradient aortic stenosis patients undergoing TAVR: insights from the TOPAS-TAVI registry. *JACC Cardiovasc Interv* 2020;**13**:567–579.
8. Ong G, Clavel MA, Pibarot P. Concomitant mitral regurgitation: an insidious cause of lowflow, low-gradient severe aortic stenosis. *EuroIntervention* 2018;**13**:1622–1625.
9. Annabi MS, Clavel MA, Pibarot P. Dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis: flow reserve does not matter anymore. *J Am Heart Assoc* 2019;**8**:e012212.
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:e57–e185.