Valvular Heart Disease
Doppler Dilemmas

Novel Application of Milrinone in the Evaluation of Classical Low-Flow, Low-Gradient Aortic Stenosis

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INTRODUCTION

Severe aortic stenosis (AS) is defined by a peak aortic jet velocity ≥4.0 m/sec, aortic valve area (AVA) ≤1.0 cm², and a transaortic mean pressure gradient (MPG) ≥40 mm Hg.1 Current American College of Cardiology/American Heart Association guidelines recommend transcatheter or surgical aortic valve replacement in patients with severe, symptomatic AS or those with severe, asymptomatic AS with left ventricular (LV) systolic dysfunction given the demonstrated poor prognosis with conservative therapy (class II).1 Low-flow, low-gradient (LFLG) severe AS with reduced LV ejection fraction (LVEF; classical LFLG AS) is defined by an AVA <1.0 cm², transaortic MPG <40 mm Hg, stroke volume index <35 mL/m², and LVEF <50%.2,3 It represents approximately 5%–10% of severe AS cases which is approximately 2 minutes.5

Low-dose dobutamine stress echocardiography (DSE) is recommended to differentiate between true-severe AS and pseudosevere AS in classical LFLG AS.2 Milrinone, an inotropic agent with a different mechanism of action from dobutamine, is typically unsuitable for stress testing given its half-life of about 2 to 4 hours, as opposed to the short half-life of the preferred agent, dobutamine, which is approximately 2 minutes.5

Here, we describe the successful use of milrinone in the evaluation of a patient with LFLG AS.

CASE PRESENTATION

A 53-year-old man presented to our institution reporting progressively increasing abdominal and lower extremity swelling, 9-kg weight gain, and nonproductive cough of 3 months’ duration. His medical history was significant for ischemic cardiomyopathy (prior LVEF 15%) status post automatic implantable cardioverter defibrillator placement in June 2020, coronary artery disease status post coronary artery bypass grafting in 2008, type 2 diabetes mellitus, hypertension, and hyperlipidemia. He had multiple emergency department visits over the 3-month period and received intravenous diuretics, without any alleviation of his symptoms. He was a current smoker and had a history of alcohol, cocaine, and heroin use. In the emergency department, his heart rate was 90 beats/min, blood pressure was 110/70 mm Hg, and oxygen saturation was 95% on room air; complete blood count, basic metabolic panel, troponin, and lactate were within normal limits; N-terminal pro B-type natriuretic peptide level was 3,590 pg/mL; and chest radiography showed cardiomegaly with mild pulmonary edema. Electrocardiography showed sinus rhythm with a left bundle branch block. He received intravenous furosemide in the emergency department for decompensated heart failure and was admitted for further management.

Transthoracic echocardiography revealed a severely reduced LVEF of 23% (calculated using the biplane method of disks with an ultrasound enhancing agent, activated perflutren, for LV opacification), grade III diastolic dysfunction, and severe aortic valve thickening and calcification with severe valvular AS (Videos 1 and 2). AVA calculated using the continuity equation was 0.98 cm², with a transaortic MPG of 24 mm Hg and a stroke volume index of 27 mL/m², meeting criteria for LFLG AS (Figure 3, left).

Right heart catheterization revealed mean right atrial pressure of 31 mm Hg, pulmonary artery pressures of 87, 46, and 61 mm Hg (severe pulmonary hypertension), cardiac output of 3.8 L/min, a cardiac index of 1.6 L/min/m² by the Fick method, and a pulmonary capillary wedge pressure of 39 mm Hg. Pulmonary artery saturation was 41%, and aortic saturation was 94%. The invasively measured peak-to-peak transvalvular gradient was 21 mm Hg, and the calculated AVA was 0.95 cm². Coronary angiography showed occlusive native three-vessel coronary artery disease with patent left internal mammary artery to left anterior descending coronary artery and saphenous vein graft to obtuse marginal, and occluded saphenous vein graft to posterior descending coronary artery with left-to-right collateral vessels. There were no significant obstructive lesions requiring intervention. The patient was initiated on milrinone in the coronary care unit at 0.25 μg/kg/min without dose escalation.

Because of discordant findings for AVA and transaortic MPG in the presence of LV dysfunction, low-dose DSE was considered. However, the patient had been on milrinone for approximately 2 days for inotropic support and had achieved a steady state of the drug. We decided to proceed with a hemodynamic assessment of AS by echocardiography while the patient was still on milrinone. Systolic blood pressure ranged from 116 to 127 mm Hg during the study, while diastolic blood pressure ranged from 52 to 67 mm Hg and heart rate from 82 to 88 beats/min. Compared with the previous echocardiogram on admission, aortic valve leaflet excursion was moderately reduced
VIDEO HIGHLIGHTS

Video 1: Transthoracic echocardiography: parasternal long-axis view showing a severely calcified aortic valve with severely reduced leaflet excursion (baseline, before milrinone).
Video 2: Transthoracic echocardiography: parasternal short-axis view at the level of the aortic valve showing a severely calcified aortic valve with severely reduced leaflet excursion (baseline, before milrinone).
Video 3: Transthoracic echocardiography: parasternal long-axis view showing a severely calcified aortic valve with moderately reduced leaflet excursion (on milrinone).
Video 4: Transthoracic echocardiography: parasternal short-axis view at the level of the aortic valve showing a severely calcified aortic valve with moderately reduced leaflet excursion (on milrinone).
Video 5: Transthoracic echocardiography: apical two-chamber view with ultrasound enhancing agent for LV opacification, showing severely reduced LVEF, mid and basal inferior wall akinesis and anterior wall hypokinesis, and no LV thrombus. LVEF calculated using the biplane method of disks was 23%.
Video 6: Transthoracic echocardiography: apical two-chamber view with ultrasound enhancing agent for LV opacification, showing severely reduced LVEF, mid and basal inferior wall akinesis and anterior wall hypokinesis, and no LV thrombus. LVEF calculated using the biplane method of disks was 30%.

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(Videos 3 and 4); LVEF increased from 23% (Video 5) to 30% (Video 6), the transaortic MPG did not change significantly (from 24 to 25 mm Hg), AVA increased from 0.98 to 1.33 cm², and stroke volume increased from 62 to 91 mL (a 47% increase; Figures 1–3; right). This met the criteria for pseudosevere AS with contractile reserve, and the patient was therefore not considered for aortic valve replacement.

DISCUSSION

In LFLG AS, because of the presence of a low-flow state, peak aortic jet velocity and MPG may underrate the AS severity. In contrast, AVA may overrate the severity of valvular stenosis because of inadequate opening of valve leaflets resulting from a reduced stroke volume.2,6 Valvular heart disease guidelines recommend that true-severe AS and pseudosevere AS be distinguished by performing low-dose DSE in patients with classical LFLG AS.1

Dobutamine is a potent inotrope via its cardiac β₁-stimulatory effects.7 It is administered using a low-dose protocol, starting at 2.5 or 5 μg/kg/min, with escalating increments every 3 to 5 min to a maximum dose of 10 to 20 μg/kg/min, with appropriate hemodynamic monitoring. The infusion is stopped once a positive result is achieved, as determined by a ≥20% increase in stroke volume from baseline, an increase in peak aortic jet velocity to ≥4.0 m/sec, or MPG ≥ 30 to 40 mm Hg, provided AVA does not surpass 1.0 cm² at any flow rate.2 A heart rate increase > 10 to 20 beats/min above baseline or a heart rate > 100 beats/min would also be an indication to stop the infusion.2

Regarding interpretation of results, an increase in MPG to >40 mm Hg with AVA remaining at <1.0 cm² establishes true-severe AS. On the other hand, if MPG remains <40 mm Hg and AVA increases to >1.0 cm² after dobutamine infusion, it denotes pseudosevere AS.

With milrinone, we demonstrated that our patient had pseudosevere AS, as his AVA increased with augmented transvalvular flow, while transaortic MPG remained unchanged (Figure 3). Milrinone is an inotropic agent used in the cardiac unit for the short-term treatment of cardiogenic shock, in low-output states following cardiac surgery, or for patients scheduled to undergo cardiac surgery or transplantation. It is a phosphodiesterase-3 inhibitor that blocks the degradation of intracellular cyclic adenosine monophosphate, leading to increased myocardial contractility and vascular smooth muscle vasodilation. Through its dose-related positive inotropic effects and arteriovenous vasodilator properties, left ventricular–arterial coupling is improved, resulting in increased cardiac output.5,7 Milrinone produces improvements in these hemodynamic indices without a clinically significant effect on heart rate or myocardial oxygen consumption compared with dobutamine. Its vasodilator activity is proposed to be responsible for the compensatory reduction in

Figure 1 Left (baseline, before milrinone): apical two-chamber two-dimensional (2D) transthoracic echocardiographic (TTE) end-systolic image with ultrasound enhancing agent (UEA). Calculated LVEF using the biplane method of disks (MOD) was 23%. Right (on milrinone): apical two-chamber 2D TTE end-systolic image with UEA. Calculated LVEF using the biplane MOD was 30%.
myocardial oxygen consumption despite an increase in cardiac contractility. Milrinone has previously been investigated as an agent for myocardial viability assessment. It was shown to satisfactorily predict recovery of LV function after surgical myocardial revascularization in patients with ischemic cardiomyopathy. Its utility in the evaluation of LFLG AS has not been established.

We carefully considered the choice of milrinone as an inotropic agent in AS with a severely reduced LVEF. We bore in mind the potential risk for hypotension due to its vasodilatory properties, which can worsen transaortic gradient and aggravate outflow obstruction, and the risk for arrhythmias, which are more likely to occur in the setting of myocardial ischemia. Excluding ischemia in our patient was necessary not only to avoid potentiation of arrhythmias with inotrope initiation but also to exclude coronary artery disease progression as a possible trigger for his heart failure exacerbation. His coronary angiogram showed patent grafts to the left anterior descending coronary artery and left circumflex coronary artery territories and collateral vessels from the left supplying the right coronary artery territory. Our patient neither became hypotensive nor developed arrhythmias while on milrinone infusion.

This case demonstrates the utility of milrinone as a safe agent in the evaluation of classical LFLG AS in place of dobutamine in select patients who have already achieved steady state on this medication. Attempting to perform DSE in such a scenario would have been redundant and would have delayed the diagnosis because of deferred testing.

By presenting this case, we introduce a novel concept in which patients with cardiomyopathy who are already on milrinone can undergo evaluation of LFLG AS without the need for DSE, hence

Figure 2 Left (baseline, before milrinone): LV outflow tract (LVOT) pulsed-wave (PW) Doppler profile showing a velocity-time integral (VTI) of 16.3 cm with a calculated stroke volume (SV) of 62 mL. Right (on milrinone): LVOT PW Doppler profile showing a VTI of 29.0 cm with a calculated SV of 91 mL.

Figure 3 Left (baseline, before milrinone): continuous-wave (CW) Doppler profile of transaortic flow showing aortic peak jet velocity of 3.2 m/sec and aortic MPG of 24 mm Hg. Calculated AVA by continuity equation (velocity-time integral [VTI]) was 0.98 cm². Right (on milrinone): CW Doppler profile of transaortic flow showing aortic peak jet velocity of 3.5 m/sec and aortic MPG of 25 mmHg. Calculated AVA by continuity equation (VTI) was 1.33 cm².
CONCLUSION

Because milrinone has a longer half-life, it is not suitable for the evaluation of LFLG AS. However, in a select group of patients with classical LFLG AS already being treated with milrinone, hemodynamic assessment of AS can be performed successfully, negating the need for DSE.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2021.12.003.

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