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CASE REPORT

CLINICAL CASE

Cardiac Myosin Inhibition for Treatment of LVOT Obstruction in a Patient With Severe AS

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ABSTRACT

Aortic stenosis and obstructive hypertrophic cardiomyopathy are common conditions. When both are present in the same patient, the management can be challenging. We report what we believe to be the first time a cardiac myosin inhibitor has been used before transcutaneous aortic valve replacement. (J Am Coll Cardiol Case Rep 2024;29:102381) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An 81-year-old woman with a history of hypertension presented with progressive dyspnea upon exertion and fatigue for several years. She walked very slowly on level ground and found it very arduous to ascend any incline. She was treated with metoprolol succinate 12.5 mg and verapamil 180 mg daily. Her height was 65 cm; she weighed 65.9 kg. She appeared frail, but in no distress. Blood pressure was 128/79 mm Hg, heart rate 78 beats/min and regular, and respirations were 12 breaths/min. There was no jugular venous distension, and the lungs were clear. A loud systolic murmur was present throughout the precordium. There was no edema. 12-lead electrocardiogram demonstrated normal sinus rhythm with a PR interval of 204 ms. There was left ventricular hypertrophy with nonspecific repolarization abnormalities.

Echocardiography demonstrated a hyperdynamic left ventricle with an estimated ejection fraction of 75%. The basal septal thickness was 2.7 cm, the unprovoked left ventricular outflow tract (LVOT) gradient caused by systolic anterior motion of the mitral valve was 95 mm Hg, and the peak velocity across the aortic valve was 5.3 m/s (**Figures 1 and 2**, Videos 1 and 2). Mild aortic regurgitation was present. The magnitude of the peak systolic left ventricular pressure, which can be inferred from the continuous wave Doppler signal of the mitral regurgitation, was >300 mm Hg (**Figure 3**).

LEARNING OBJECTIVES

- To recognize that AS and obstructive HCM can coexist in the same patient, and that this combination can be challenging to manage.
- To consider a novel way to address this problem using new a new class of pharmacologic agent to treat obstructive HCM.

DIFFERENTIAL DIAGNOSIS

The patient's syndrome was assumed to be caused by the combination of hypertrophic cardiomyopathy (HCM) with severe dynamic LVOT obstruction and severe aortic stenosis (AS).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

ASA = alcohol septal ablation

HCM = hypertrophic cardiomyopathy

TAVR = transcutaneous aortic valve replacement

MANAGEMENT

The traditional approach to the treatment of combined dynamic LVOT obstruction and severe AS has been a basal septal myectomy combined with aortic valve replacement. However, the patient was not considered a good candidate for open heart surgery.

Transcutaneous aortic valve replacement (TAVR) is a common procedure used to treat AS. Because relief of AS can worsen the degree of subvalvular obstruction caused by systolic anterior motion of the mitral valve, the patient was offered treatment with mavacamten, a cardiac myosin inhibitor, before TAVR. However, she decided to undergo alcohol septal ablation (ASA) at another institution. Despite isolation of an angiographically suitable septal perforator, the ASA procedure did not diminish the LVOT gradient over the ensuing 3 months (Video 3, **Figures 4 and 5**). She required permanent pacing after ASA.

With continued symptoms of dyspnea provoked with minimal exertion and recognizing that she was not an appropriate surgical candidate, the patient decided to try treatment with mavacamten with close echocardiographic monitoring. Treatment with verapamil was discontinued. Four weeks after initiation of therapy (5 mg daily), there was no further evidence of LVOT obstruction with a marked decrease in the LVOT gradient (Video 4, **Figure 6**). Severe calcific AS remained unchanged (**Figure 7**). The left ventricle remained hyperdynamic, with an estimated

FIGURE 1 Continuous-Wave Doppler Through the Left Ventricular Outflow Tract

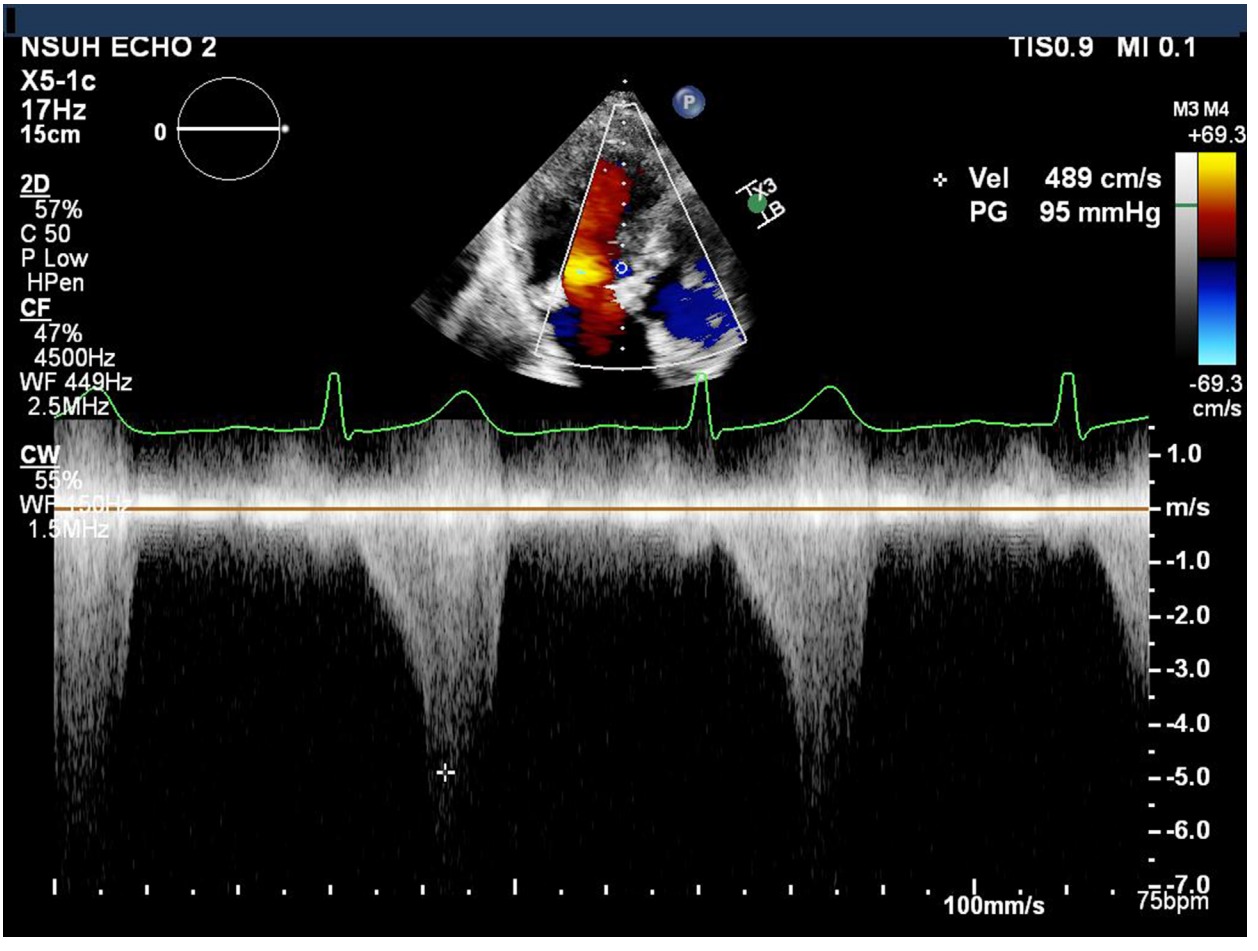
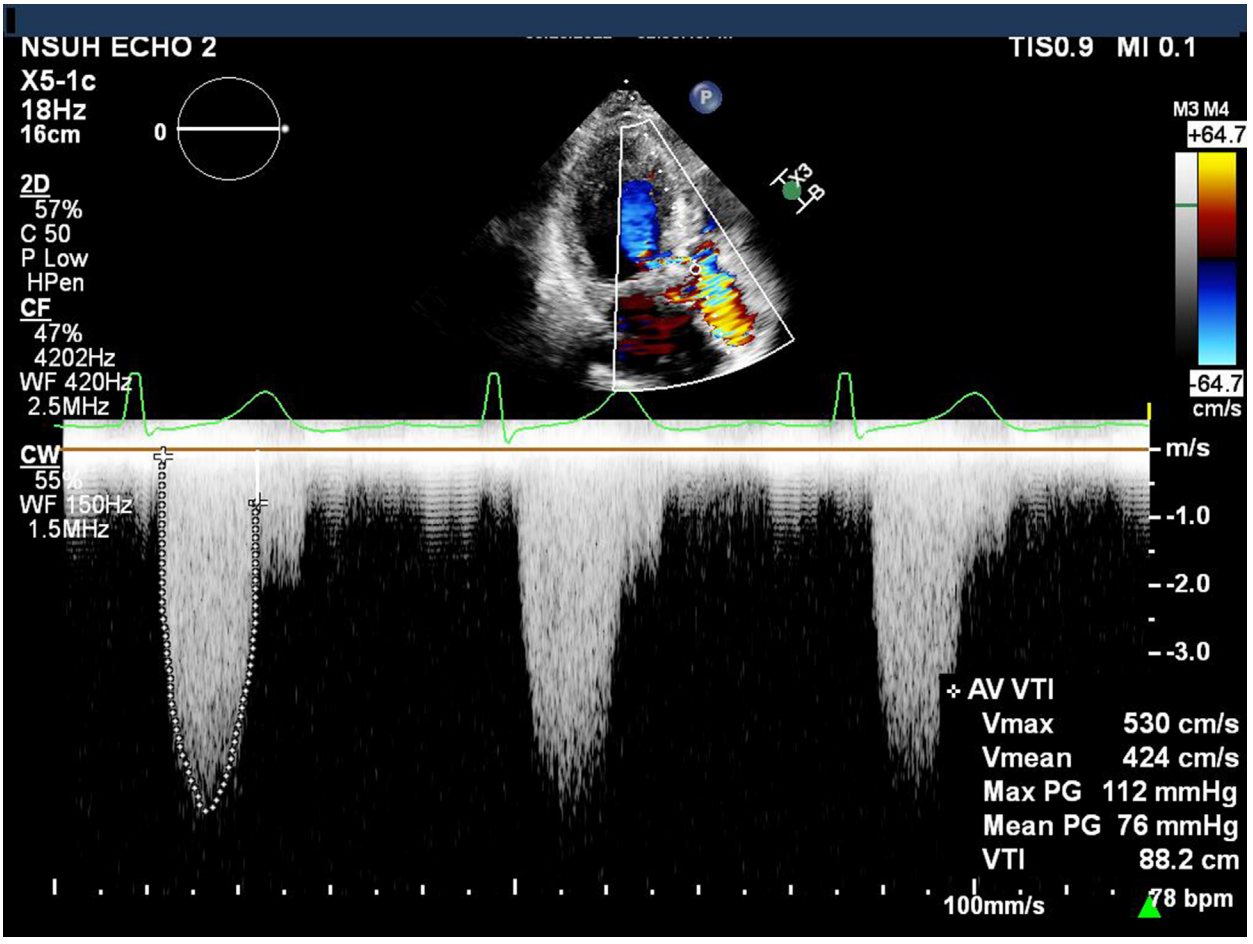


FIGURE 2 Continuous-Wave Doppler Through the Aortic Valve



ejection fraction of 75%. A few weeks later, a 29-mm Evolut FX TAVR was implanted without complication (Videos 5 and 6, **Figures 8 and 9**).

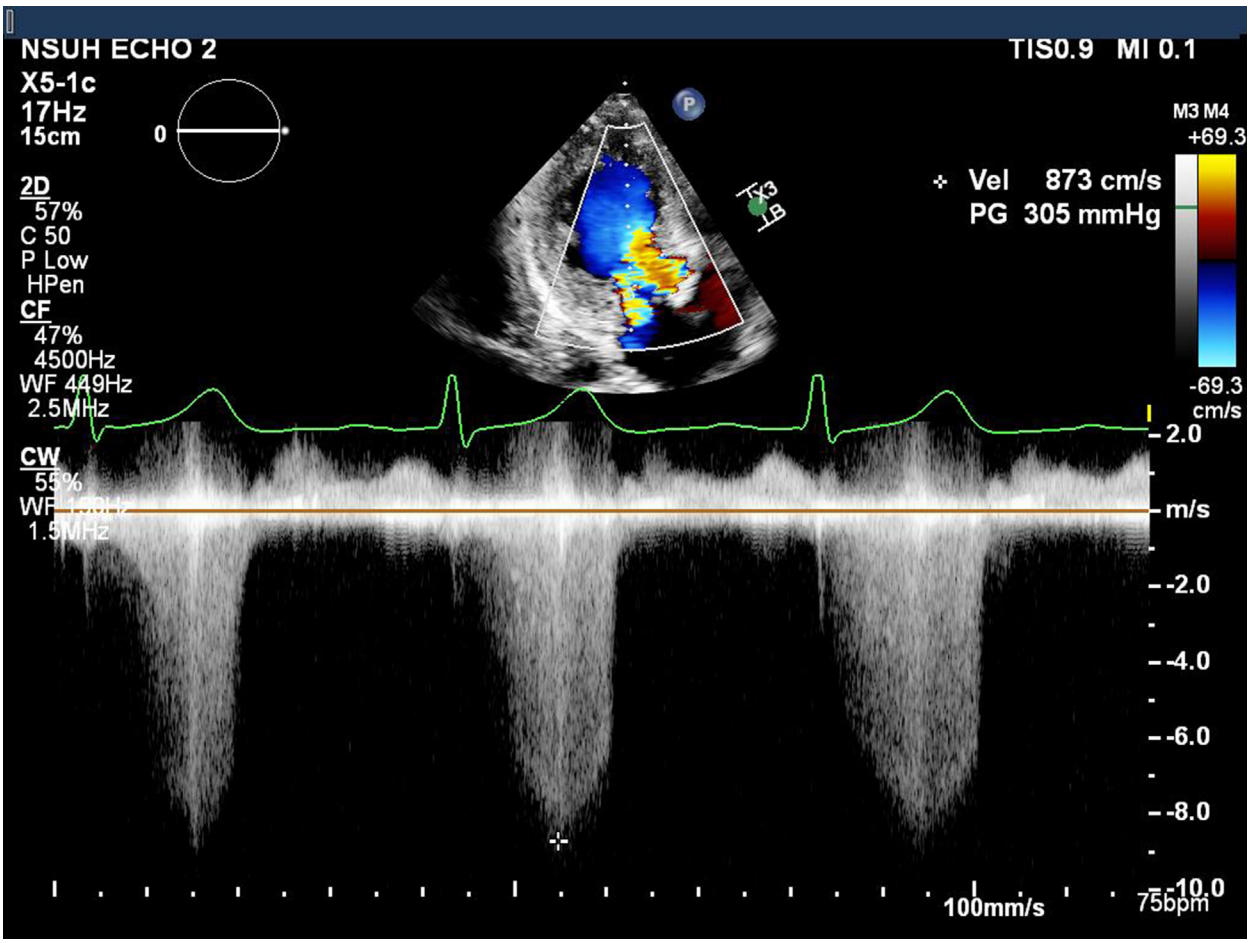
DISCUSSION

By the age of 65 years, significant AS is estimated to be present in approximately 5% of the population, with a prevalence that increases with age.[1] The treatment of AS has been revolutionized since the advent of TAVR which was first approved in the United States in 2011.

It is estimated that the prevalence of HCM is between 0.2% and 0.5% of the population.[2] Most of these patients have the obstructive form, characterized by dynamic LVOT obstruction caused by systolic anterior motion of the mitral valve.

Given that AS and HCM are relatively common, and the population is aging, the combination of serial outflow obstructive lesions is now seen more frequently. Although open surgery, including myectomy and valve replacement, remains an option, TAVR is rapidly becoming standard of care, especially for older, more complicated patients. The use of TAVR to treat AS/HCM patients, however, may be complicated because the immediate relief of the pressure afterload, without addressing LVOT obstruction, may exacerbate the degree of subvalvular obstruction. Although transcatheter ASA can be performed to reduce the degree of dynamic LVOT obstruction, ASA results are less predictable compared with myectomy surgery, with a 7% to 20% risk of requiring a repeat procedure because of inadequate reduction of the LVOT obstruction[3] and an

FIGURE 3 Continuous-Wave Doppler, Mitral Regurgitation, Apical Long Axis



approximate 10% risk of needing permanent pacing and repeat procedures to reduce obstruction.[4]

Mavacamten, a selective inhibitor of cardiac myosin ATPase, was approved by the U.S. Food and Drug Administration for the treatment of patients with obstructive HCM in April 2022. However, patients with concomitant AS were excluded in the pivotal trials,[5,6] and there have been no published reports using this medication in the presence of serial LVOT obstructions.

In 2000, Sherrid et al[7] described the mechanism of LVOT obstruction in HCM, demonstrating that the mitral valve is "pushed" into the LVOT because of changes in the flow patterns in the left ventricle that occur in this condition. This is likely why the left ventricular ejection fraction did not significantly change in any of the cardiac myosin inhibition trials. Although the force of left ventricular contraction is reduced with these novel agents, the mitral valve is no longer pushed into the LVOT; therefore, the afterload is also reduced. This case highlights this precise mechanism of action and mavacamten allowed for safe placement of a TAVR valve in a patient with severe LVOT obstruction from HCM.

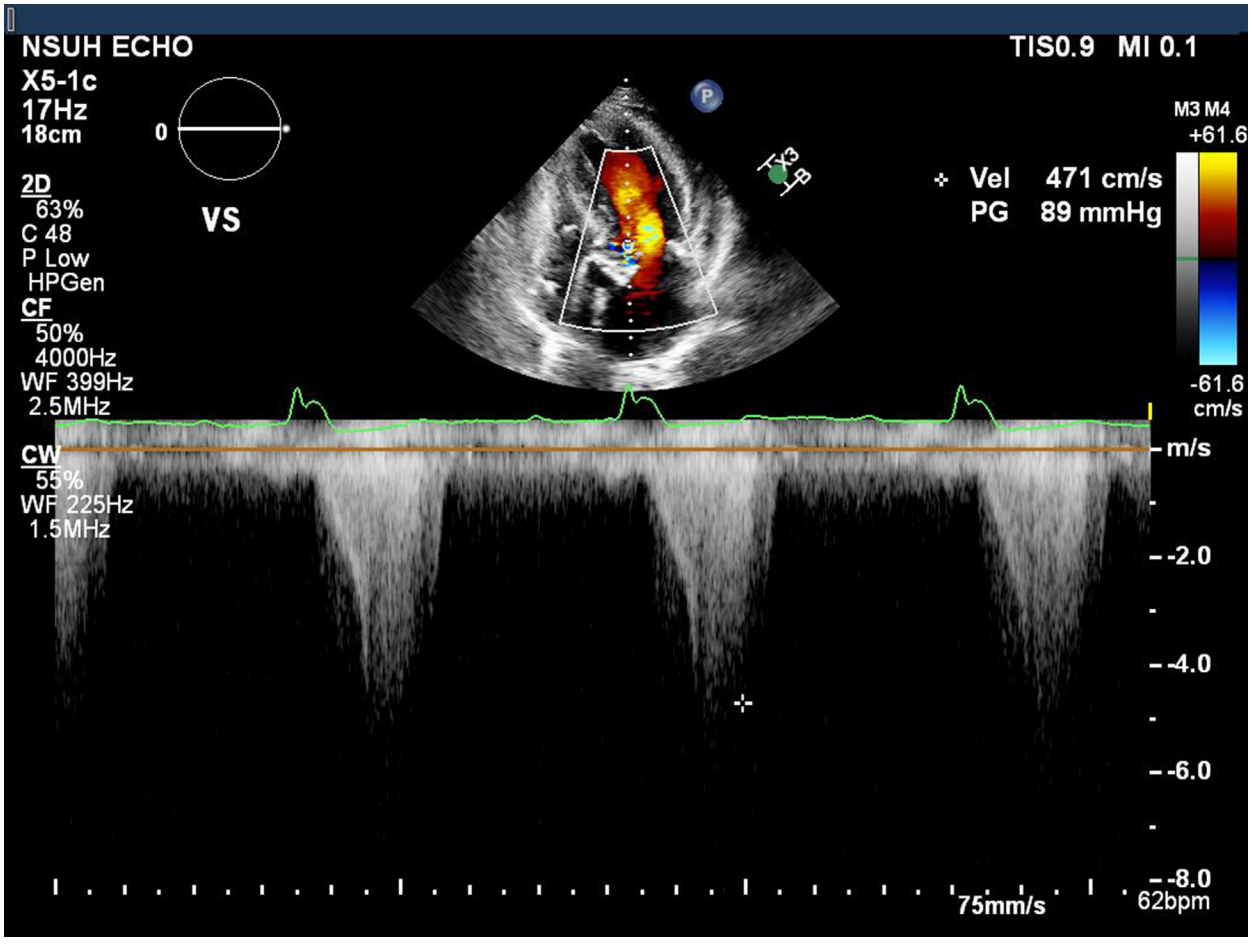
FOLLOW-UP

No longer encumbered by serial obstruction of the left ventricle, the patient no longer experiences dyspnea, and has been able to lead a more active lifestyle.

CONCLUSIONS

We believe this is the first reported case of the use of a cardiac myosin inhibitor in the setting of severe dynamic LVOT obstruction with concomitant AS, with excellent outcomes. This provides further exciting potential for expanding indications for cardiac myosin inhibition.

FIGURE 4 Continuous-Wave Doppler Through the Left Ventricular Outflow Tract Status Post Alcohol Septal Ablation



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Dr Wharton serves on an Advisory Board for Bristol Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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FIGURE 5 **Continuous-Wave Doppler Through the Aortic Valve Status Post Alcohol Septal Ablation**

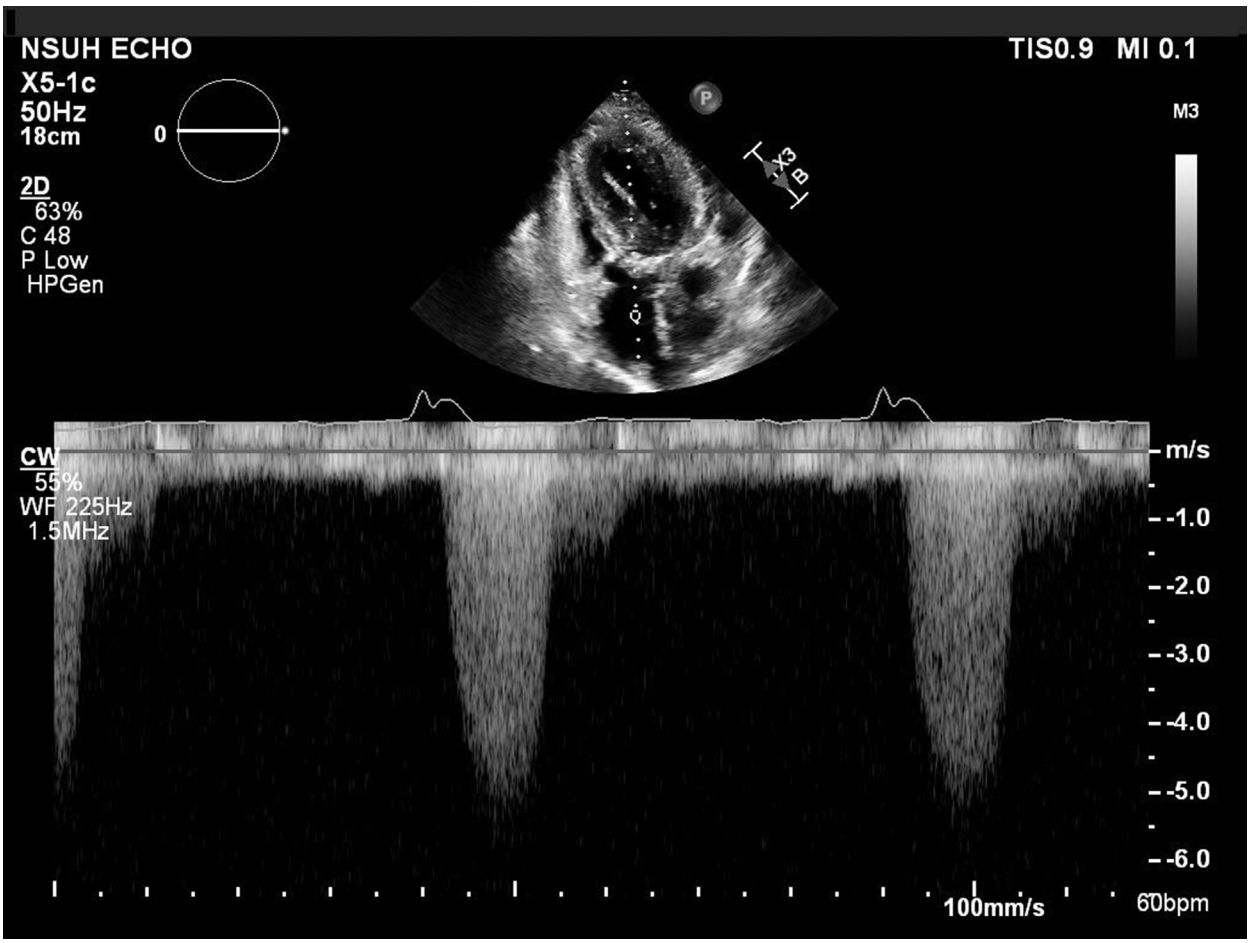


FIGURE 6 Pulsed Wave Doppler in the Left Ventricular Outflow Tract After Initiation of Mavacamten

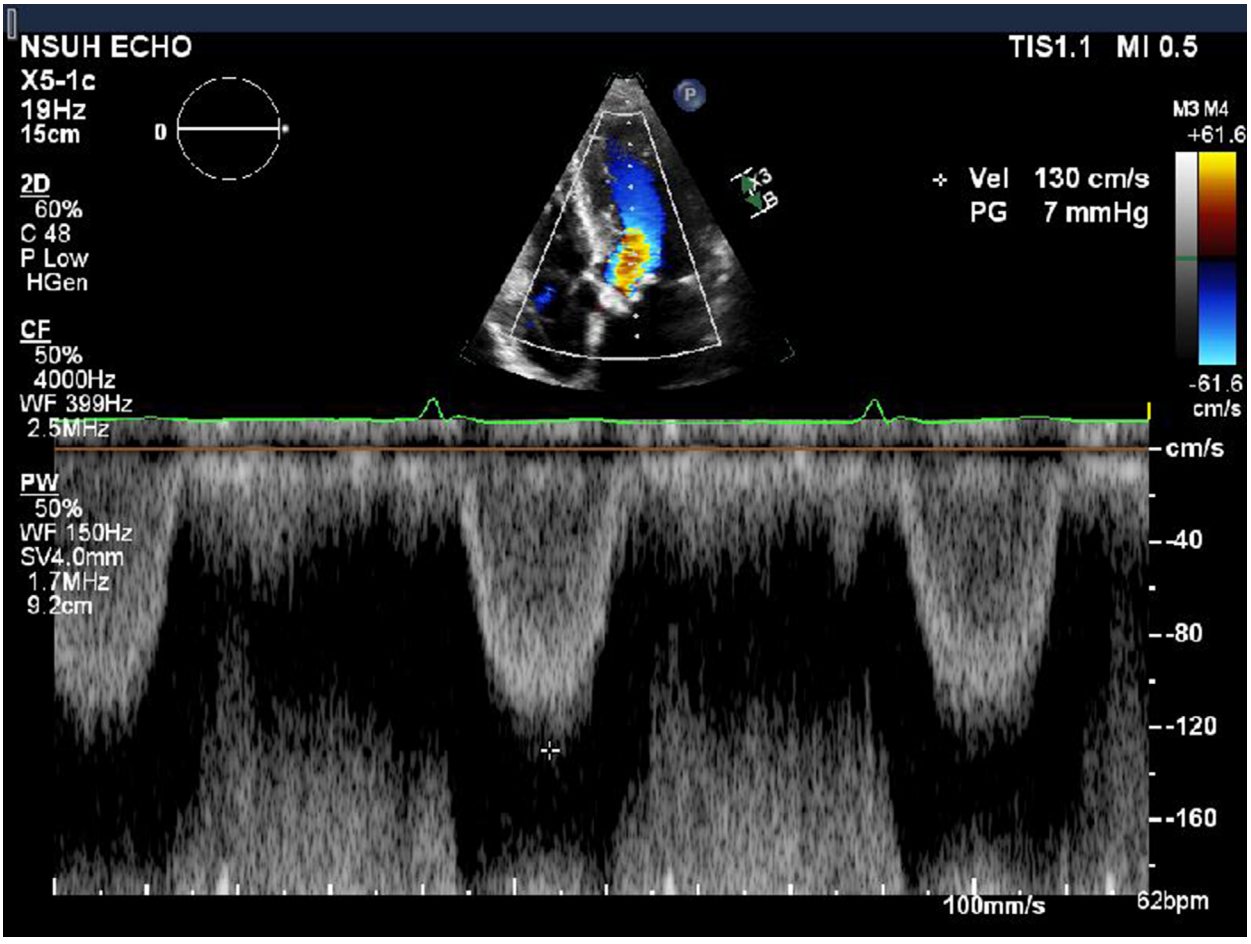


FIGURE 7 **Continuous-Wave Doppler Through the Aortic Valve After Initiation of Mavacamten**

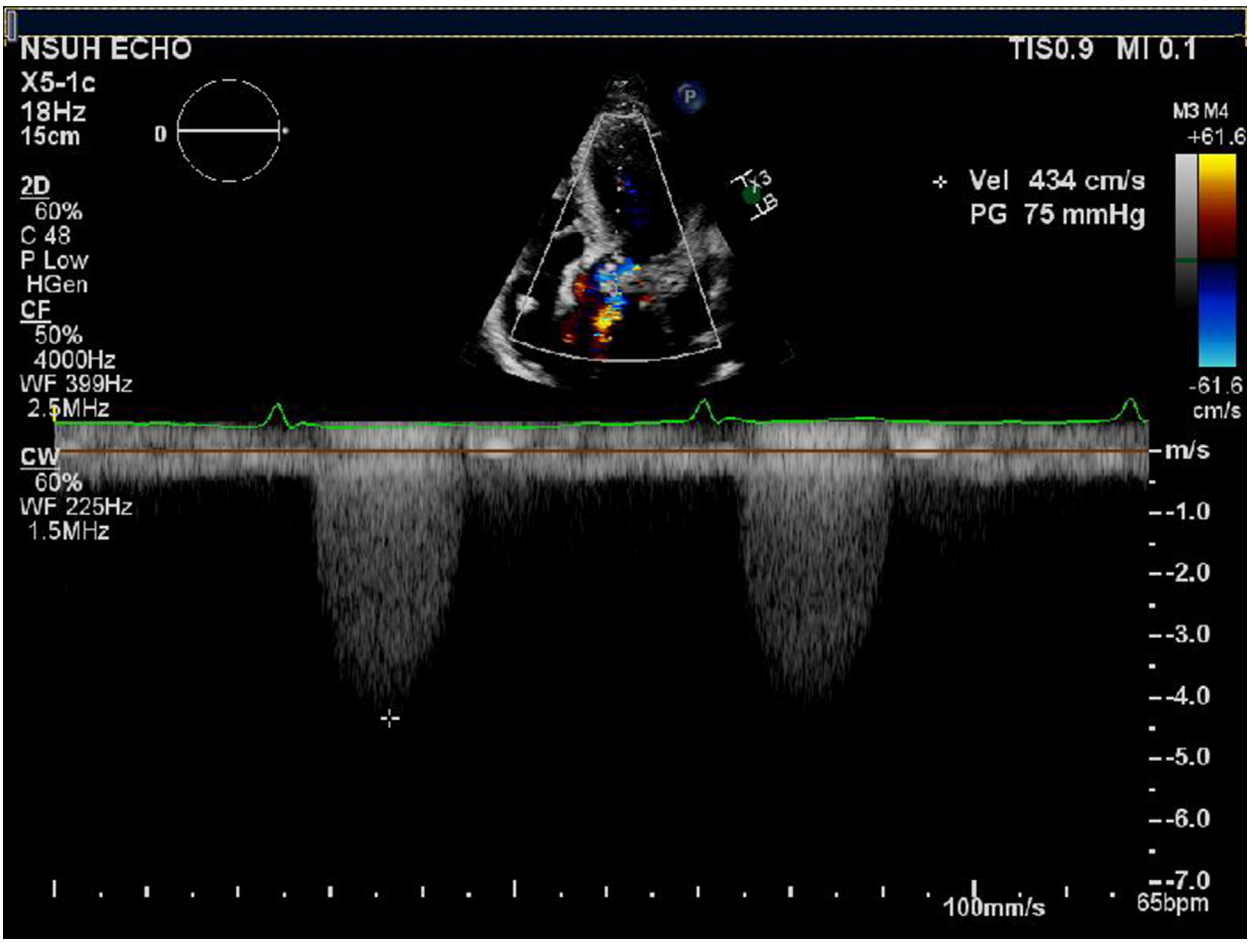


FIGURE 8 Pulsed-Wave Doppler in the Left Ventricular Outflow Tract Status Post Transcutaneous Aortic Valve Replacement

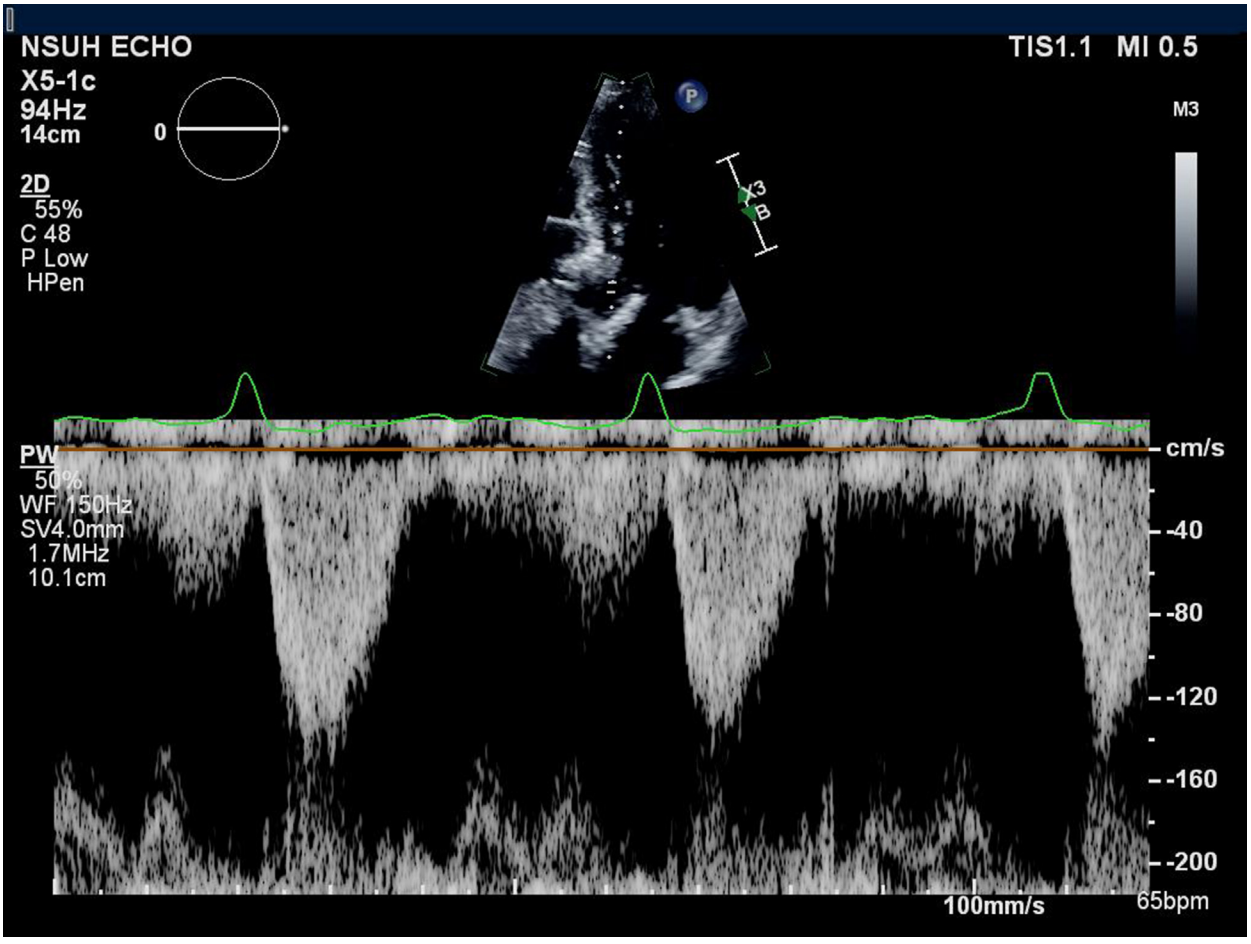
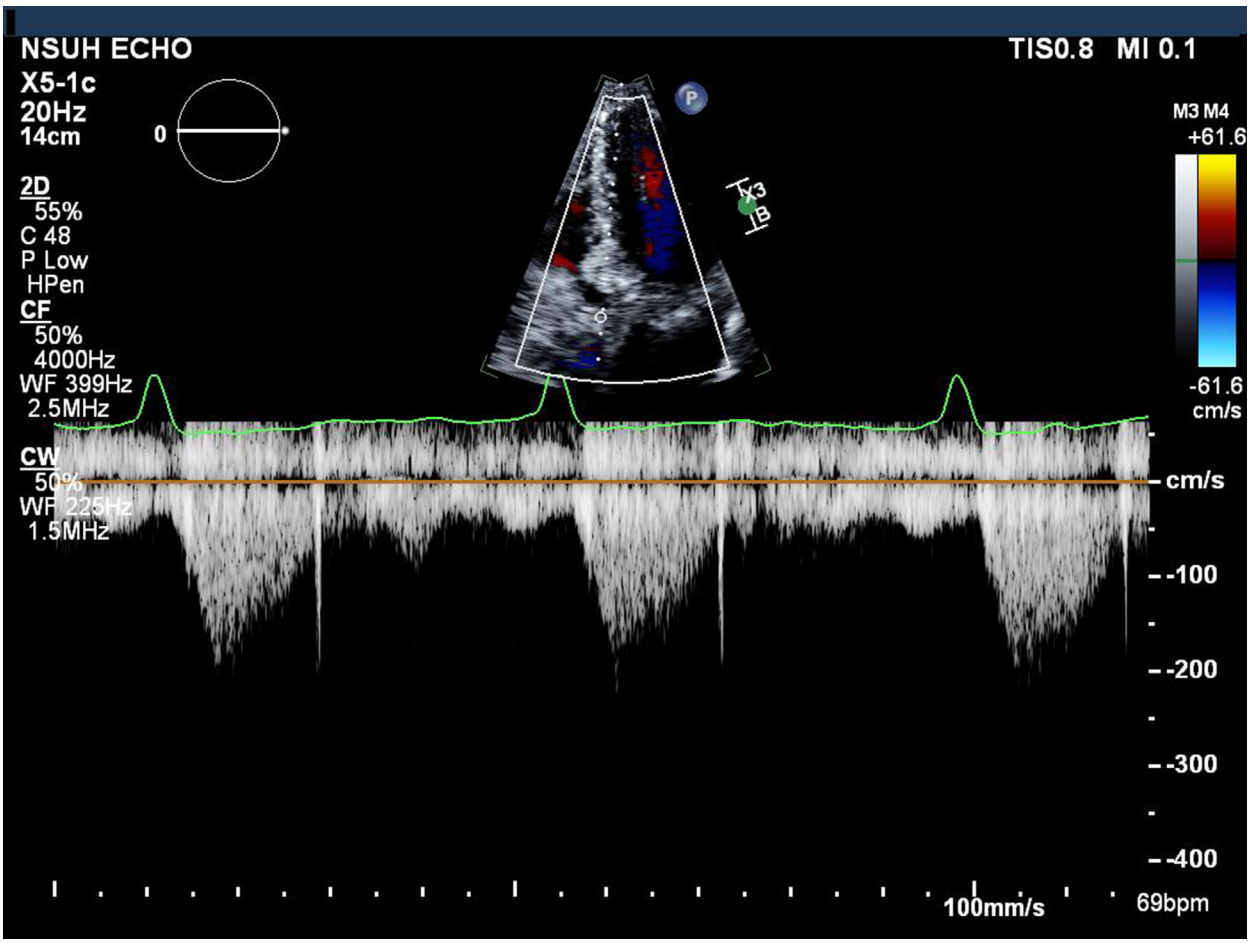


FIGURE 9 **Continuous-Wave Doppler Through The Aortic Valve Status Post Transcutaneous Aortic Valve Replacement**



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KEY WORDS **aortic valve, cardiomyopathy, mitral valve**

APPENDIX **For supplemental videos, please see the online version of this paper.**