

Noninvasive Bedside Vasodilator Testing Using Echocardiography



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INTRODUCTION

Inhaled nitric oxide is a potent vasodilator used routinely for vasodilator testing and treatment in pediatric patients with pulmonary hypertension (PH). Vasodilator testing is an important initial step in the diagnosis and management of PH, and responsiveness to vasodilator testing can predict survival.¹ Traditionally, vasodilator testing is performed during cardiac catheterization, which is invasive and higher risk in pediatric patients with PH because of the need for sedation or anesthesia.² Noninvasive bedside vasodilator testing may be an option to help guide therapy in selected patients. Echocardiographic markers of PH severity, such as the systolic-to-diastolic duration ratio of the tricuspid regurgitation jet or the right ventricular (RV) Tei index have been shown to be associated with hemodynamic measures obtained by cardiac catheterization and may predict long-term outcomes, including survival.^{3,4} We report the use of echocardiography to measure immediate responsiveness to acute vasodilator testing as a noninvasive bedside approach in an infant with postoperative PH. The immediate echocardiographic changes seen with the initiation of vasodilator therapy are novel and previously unreported in the pediatric literature. The use of echocardiography in this patient was instrumental in his diagnosis and management and facilitated his eventual transition to oral targeted therapy without the need for more invasive testing.

CASE PRESENTATION

A 2-week-old boy with d-transposition of the great arteries with restrictive atrial septum underwent balloon atrial septostomy at birth. Routine echocardiography following the septostomy demonstrated left-to-right shunting across a moderately sized atrial communication and left-to-right shunting across a small to moderate patent ductus arteriosus with normal biventricular systolic function and no evidence of elevated RV pressures. He underwent an arterial switch procedure with the Lecompte maneuver and primary closure of the atrial defect at 6 days of life. Postoperative transesophageal echocardiography demonstrated mildly decreased RV systolic function and moderately decreased left ventricular (LV) systolic function with no residual atrial communication and no evidence of elevated RV systolic

pressures. Laminar flow was seen in the bilateral branch pulmonary arteries. With an unremarkable postoperative course, the patient was weaned to room air by the first postoperative day. Vasoactive support with epinephrine and milrinone was weaned off by the third postoperative day. No pulmonary vasodilator medications had been required during the postoperative period. Routine pre-discharge echocardiography demonstrated evidence of severe PH with no evidence of distal pulmonary artery obstruction. Because of these baseline findings, echocardiography with bedside nitric oxide testing was performed.

Baseline echocardiography was performed on room air and demonstrated suprasystemic RV pressures with systolic posterior bowing of the intraventricular septum. There was mild tricuspid regurgitation with a peak tricuspid regurgitant jet of 103 mm Hg, moderate RV dilatation, and qualitatively moderately decreased RV systolic function. LV systolic function was normal by the 5/6 area length method. There was abnormal tricuspid annular plane systolic excursion, tricuspid systolic-to-diastolic duration ratio, RV-to-LV ratio, LV end-diastolic eccentricity index, and RV and LV Tei index (Table 1). Images were repeated 10 min after initiation of 20 ppm nitric oxide via face mask. Images obtained with nitric oxide testing demonstrated qualitative improvement in RV function and improvement in tricuspid annular plane systolic excursion, systolic-to-diastolic duration ratio, eccentricity index, and RV and LV Tei index (Videos 1-4). RV systolic pressures decreased from suprasystemic to near half systemic (Figure 1).

On the basis of the echocardiographic findings, the infant was started on sildenafil and discharged home after 3 days. He has since had normalization of his pulmonary artery pressures and RV function on echocardiography and was weaned off sildenafil 9 months after initiating treatment.

Following this index case, we conducted four more cases of bedside vasodilator testing in pediatric patients. Although complete data were not available for all cases, improvement was demonstrated in echocardiographic markers of PH (Table 2).

DISCUSSION

The risk for mortality and morbidity during cardiac catheterization is known to be higher in children with PH, with risks reported at 1.2% and 5.7%, respectively.^{5,6} Children younger than 2 years and those requiring general anesthesia have a higher risk for catheterization-associated complications.⁵ The risk for cardiac catheterization may be higher in the postoperative period, though there is scant evidence in the pediatric PH population.^{7,8} Therefore, noninvasive diagnosis and treatment of PH without higher risk invasive procedures could affect patient outcomes, especially in the early postoperative period.

Although changes in echocardiographic markers of PH and RV function have been well reported in the pediatric literature, to our knowledge there are no prior pediatric reports demonstrating immediate changes in these markers following the initiation of nitric oxide

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VIDEO HIGHLIGHTS

Video 1: Apical four-chamber view on baseline echocardiography demonstrates diminished RV systolic function with normal LV systolic function.

Video 2: On parasternal short-axis view, baseline echocardiography demonstrates a moderately dilated right ventricle with moderately diminished systolic function. There is systolic septal flattening and end-systolic posterior bowing of the interventricular septum consistent with elevated RV systolic pressure.

Video 3: Apical four-chamber view on echocardiography following initiation of 20 ppm nitric oxide via nasal cannula for 10 min demonstrates improved RV systolic function.

Video 4: Parasternal short-axis view on echocardiography following nitric oxide therapy demonstrates markedly improved RV systolic function and size. Septal wall motion has greatly improved with only mild systolic flattening of the interventricular septum. These findings suggest lower RV systolic pressure with nitric oxide therapy.

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therapy.^{3,9-11} Our patient's systolic-to-diastolic ratio decreased from 2.4 to 1.3, tricuspid annular plane systolic excursion increased from 0.52 to 0.63 cm (Z score \pm 2, 0.68–1.15 cm), RV/LV ratio at end-systole decreased from 1.5 to 1.0, and isovolumic relaxation time decreased from 76 to 42 msec.⁹ These findings suggest improved RV systolic and diastolic function and pulmonary artery pressures, thereby portending better outcomes.^{3,4,9,10} LV Tei index, which can

be increased in pediatric patients with PH because of associated LV diastolic dysfunction, demonstrated improvement from 0.68 to 0.48 following the initiation of nitric oxide, suggesting better RV-LV interaction in our patient.¹²

This single patient report suggests a potential role of vasodilator testing using bedside echocardiography in selected patients. Prior adult literature has suggested that improvements in the RV Tei index and LV end-diastolic eccentricity index portend a good outcome.^{3,13-16} We have demonstrated similar improvement in these indices in our patient, who is now asymptomatic and off vasodilators without signs of PH >15 months later. We noted improvement in the RV isovolumic relaxation time and RV S' velocity (Table 1)¹⁷ and postulate that the corresponding improvement in the RV Tei index may not be immediately appreciable. Our findings suggest that these echocardiographic measures may have utility in the pediatric population that warrant further study.

This initial patient study demonstrates that noninvasive, echocardiography-based vasodilator testing is safe and can be used to guide therapy in selected patients. A decrease in pulmonary artery pressures with nitric oxide during vasodilator testing at cardiac catheterization predicts long-term response to oral calcium channel blockers and a better long-term prognosis.^{1,18} In our patient, echocardiography provided quantitative evidence of vasodilator response. Sildenafil was initiated in lieu of calcium channel blockers because of our patient's age. The use of echocardiography was deemed appropriate and safe in this particular neonate as an initial test, and the echocardiographic findings resulted in initiation of therapy without diagnostic catheterization. We also noted similar results in four additional pediatric patients who underwent bedside nitric oxide testing with echocardiography. Given the potential risks with vasodilator use, especially in the presence of diastolic dysfunction, further studies are needed to identify suitable candidates for bedside vasodilator testing and compare and validate noninvasive testing with diagnostic cardiac catheterization.

Table 1 Comparison of echocardiographic measures before and after vasodilator testing with nitric oxide

Measurement parameter	Prevasodilator testing	Postvasodilator testing
Heart rate, beats/min	140–145	120–125
RV dilatation	Moderate	None
RV dysfunction	Moderate	None
Interventricular septal position	Systolic flattening, end-systolic posterior bowing	Mild systolic flattening, no septal bowing
RV systolic pressure/systolic blood pressure, mm Hg	103/78	48/84
Ratio of RV systolic pressure to systolic blood pressure	1.3	0.58
TR degree	Mild	Trivial
TAPSE, cm	0.52	0.63
Systolic-to-diastolic time ratio from TR velocity	2.5	1.4
RV S' velocity (cm/sec)	4.2	5
Isovolumic relaxation time, msec	76.6	42.5
RV Tei index	0.54	0.5
LV Tei index	0.68	0.48
RV/LV ratio	1.5	1.0
LV end-diastolic eccentricity index	2.1	1.3
RV fractional area change, %	32	36

TAPSE, Tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

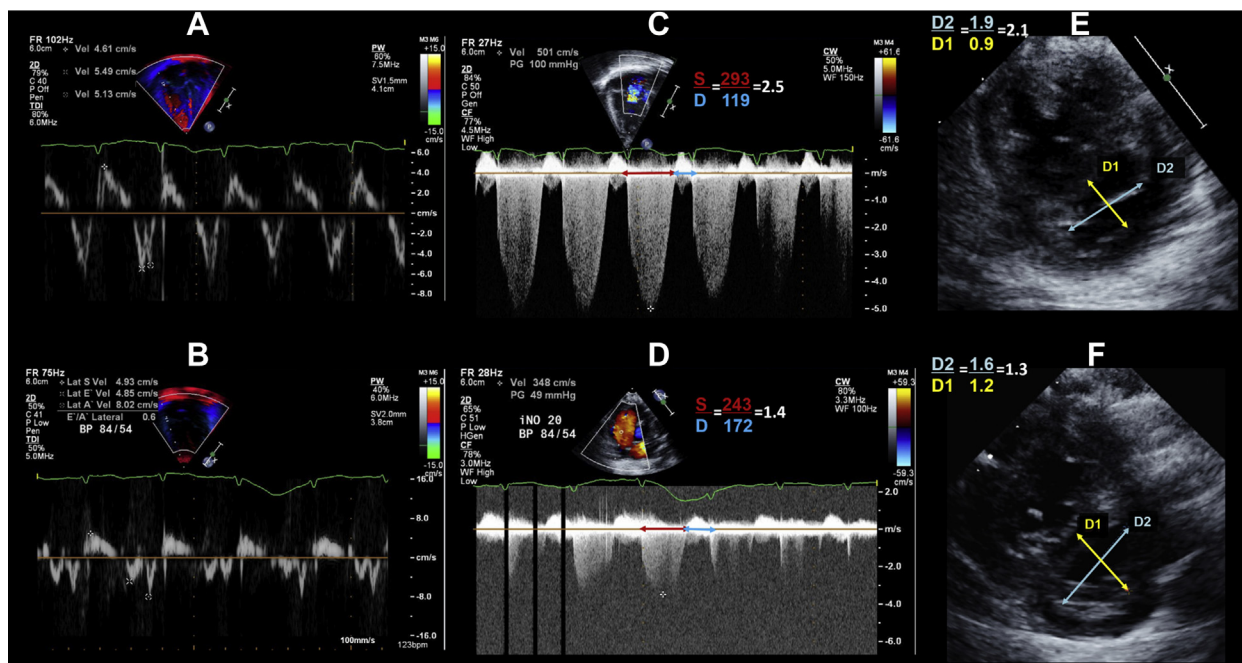


Figure 1 Echocardiographic measurements before and after vasodilator testing. RV Doppler tissue imaging before (A) and after (B) testing, tricuspid regurgitation jet with systolic to diastolic ratio before (C) and after (D) testing, eccentricity index before (E) and after (F) testing. Measurements were obtained before and after testing, with averaging over three consecutive beats.

Table 2 Patient characteristics and echocardiographic findings before and after vasodilator testing for four additional cases performed with nitric oxide

	Case 1		Case 2		Case 3		Case 4	
Patient characteristics								
Diagnosis	Critical aortic stenosis		ASD, VSD, and PDA		TOF and mitral stenosis		ASD, VSD, and mitral stenosis	
Type of intervention	Balloon aortic valvuloplasty		PDA ligation and ASD closure		Mitral and pulmonic valve replacement		None	
Age	1 mo		10 mo		5 y		20 d	
Time from intervention to echocardiography, d	17		3		7		—	
Baseline respiratory support	Continuous positive airway pressure		Room air		Nasal cannula		Room air	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Vasodilator testing								
Heart rate, beats/min	145–155	105–115	—	—	118–130	—	—	—
Shunt direction	Left to right	Left to right	Bidirectional	Left to right	Bidirectional	Left to right	Bidirectional	Left to right
RV dilatation	+++	++	++	+	+++	++	+++	+++
RV dysfunction	+	None	None	None	++	++	+	None
RV systolic pressure/systolic blood pressure, mm Hg	85/82	50/65	58/100	38/109	72/105	50/105	—	—
Ratio of RV systolic pressure to systolic blood pressure	1.03	0.77	0.58	0.35	0.69	0.48	—	—
TR degree	+ to ++	+	+ to ++	+ to ++	++	+	+++	++
TAPSE, cm	1.08	1.3	—	—	0.86	0.78	—	—
Systolic to diastolic time ratio from TR velocity	2.2	1.3	2.0	1.2	2.2	1.0	—	—

ASD, Atrial septal defect; PDA, patent ductus arteriosus; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot; TR, tricuspid regurgitation; VSD, ventricular septal defect; +, mild; + to ++, mild to moderate; ++, moderate; +++, severe; —, parameter was not available for measurement.

CONCLUSION

Noninvasive bedside echocardiographic vasodilator testing may serve as an additional tool in clinical decision making, as it reduces the potential risks inherent in more invasive testing in selected high-risk patients. This report suggests that there are immediate measurable changes in echocardiographic parameters of PH with vasodilator testing. Further prospective studies comparing this modality with the gold-standard, cardiac catheterization, are necessary.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2019.02.001>.

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