

Diastolic velocity half time is associated with aortic coarctation gradient at catheterization independent of echocardiographic and clinical blood pressure gradients

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FUNDING INFORMATION

National Institutes of Health, Grant/Award Number: UL1-TR-001857.

Abstract

Objective: The most accurate noninvasive parameter to predict whether a patient with aortic coarctation will meet interventional criteria at catheterization remains elusive. We aim to determine the best independent echocardiographic predictors of a coarctation peak-to-peak pressure gradient ≥ 20 mm Hg at catheterization, the accepted threshold for intervention.

Design: Retrospective query of our catheterization database from 1/2007 to 7/2016 for the diagnostic code of aortic coarctation was performed. Multiple echocardiographic measurements and blood pressure gradients prior to cardiac catheterization were collected. Univariate correlation of variables with the continuous catheterization peak were calculated using Spearman's rho. Univariate association with peak-to-peak gradient at catheterization ≥ 20 mm Hg was tested using Mann-Whitney *U* test and the Pearson chi-square test or Fisher's exact test. Multivariable logistic regression assessed the independent association of the clinically relevant metrics with gradient at catheterization ≥ 20 mm Hg.

Results: Sixty-eight patients met study criteria (median age 9.25 years), of whom 84% underwent intervention at catheterization. Echocardiographic peak and mean coarctation velocity, indexed systolic and diastolic velocity half times (SVHTi, DVHTi), and blood pressure gradient all had moderate correlation (Spearman's rho = 0.529-0.617, $P < .001$) with the continuous catheterization gradient and were significantly associated with the binary outcome of catheterization peak ≥ 20 mm Hg ($P < .001$). Logistic regression found echocardiographic mean systolic gradient (OR 1.213 [95% CI 1.041-1.414]) and DVHTi (OR 1.039 [95% CI 1.004-1.074]) independently associate with catheterization peak ≥ 20 mm Hg after controlling for blood pressure gradient (OR 1.066 [0.987-1.150]).

Conclusions: Most echocardiographic estimates show moderate correlation with arch gradient at catheterization. Noninvasive four extremity blood pressure gradient is significantly associated with peak-to-peak gradient ≥ 20 mm Hg. DVHTi may provide a unique independently associated echocardiographic estimate of coarctation severity. Further study of these variables with larger cohorts may allow for development of predictive models to direct catheterization.

KEYWORDS

aorta, catheterization, coarctation, echocardiogram, gradient, pediatric

1 | INTRODUCTION

Coarctation of the aorta comprises roughly 7% of live births with congenital heart disease and is the fourth most common lesion requiring intervention.¹⁻³ While surgical repair remains the first-line therapy for infants with coarctation, transcatheter balloon angioplasty, and stenting have become standard of care therapeutic options for older children and adults with both native and postoperative coarctation of aorta.^{4,5} Regardless of the initial intervention, there is a significant risk for development of re-coarctation.^{6,7} Balloon angioplasty is the first-line therapy for postoperative coarctation in the young.

Catheter intervention is generally indicated for a peak-to-peak gradient ≥ 20 mm Hg at cardiac catheterization.⁸⁻¹³ Predicting which patients will meet this criterion remains challenging. Many clinical correlates of the peak-to-peak gradient have been used including the four-extremity blood pressure gradient, and a variety of echocardiographic measures of coarctation severity.¹⁴ Peak instantaneous gradient by echocardiogram is used commonly in clinical practice. However, multiple studies have highlighted its poor correlation with peak-to-peak gradient at catheterization.¹⁵⁻¹⁷

The subjective finding of diastolic runoff is a classic finding in severe obstruction, but its qualitative nature limits its predictive value. Diastolic velocity half time (DVHT), a metric similar to the echocardiographic interrogation of pressure decay across a stenotic mitral valve, has been proposed as an alternative. The tighter an area of

coarctation, the longer the time it will take for antegrade diastolic aortic flow to reach half its velocity, or to “run off.” DVHT has previously been shown to correlate with catheter-based intervention criteria including coarctation diameter by angiography and by MRI.¹⁸⁻²⁰ DVHT has not been adopted as a standard metric of coarctation severity. Other noninvasive criteria, such as peak and mean pressure gradients through the coarctation, may lack the predictive ability to direct intervention and prevent unnecessary catheterization.²¹ We hypothesize that alternative echocardiographic parameters or a combination of measures may carry predictive value for significant coarctation gradient at catheterization.

In this study, we sought to identify the noninvasive criteria associated with a peak-to-peak catheterization gradient of ≥ 20 mm Hg and to prove the independent value of utilizing DVHT in assessing coarctation severity.

2 | METHODS

2.1 | Retrospective study population

After Institutional Review Board approval, a query of the Children's Hospital of Pittsburgh cardiac catheterization database was performed to identify all patients with the diagnoses of coarctation, aortic arch obstruction, or aortic arch hypoplasia who underwent catheterization, as

TABLE 1 Echocardiographic measurements

Measurement	View	Description
Abdominal aorta diastolic forward flow	Subxiphoid short-axis	Antegrade flow on PW Doppler following the T wave
Transverse arch diastolic forward flow	Suprasternal long-axis	Antegrade flow on PW Doppler following the T wave
Echo isthmus z-score	Suprasternal long-axis	Maximum systolic dimension immediately beyond the LSA, normalized to BSA
Echo peak systolic velocity (cm/s)	Suprasternal long-axis	Maximum velocity of CW Doppler through the DAO
Echo peak diastolic velocity (cm/s)	Suprasternal long-axis	Maximum velocity at the end of the T wave of a CW Doppler through DAO
Echo systolic mean (mm Hg)	Suprasternal long-axis	Trace of CW Doppler envelope through DAO from start of systole to end of the T wave
Echo systolic + diastolic mean (mm Hg)	Suprasternal long-axis	Trace of CW Doppler envelope through DAO for entire RR interval
SVHT (ms)	Suprasternal long-axis	Time interval between peak systolic velocity and $\frac{1}{2}$ peak systolic velocity
DVHT (ms)	Suprasternal long-axis	Time interval between peak diastolic velocity and $\frac{1}{2}$ peak diastolic velocity

Abbreviations: PW, pulse wave; LSA, left subclavian artery; BSA, body surface area; CW, continuous wave; DAO, descending aorta; SVHT, systolic velocity half time; DVHT, diastolic velocity half time.

well as any patient who underwent balloon angioplasty and/or stenting of the aorta between January 2007 and July 2016. Patients with single ventricle physiology were excluded due to fundamental differences in their physiology relative to patients with biventricular circulation, including inability to accurately measure systemic right ventricular function and the effect of changes in ventriculo-ventricular interactions. Patients with diffuse arch hypoplasia, defined as transverse and/or ascending arch hypoplasia, were excluded given the inability to apply the Bernoulli equation assumptions. Finally, subjects with a patent arterial duct, greater than mild aortic stenosis, or greater than mild aortic insufficiency were excluded. There were no exclusions for age, therefore, the population did include three adult congenital patients.

2.2 | Echocardiography

Echocardiograms were performed a median of 23 days, IQR 4-49, prior to cardiac catheterization using one of two different machines (Philips IE33, Philips, Andover, Massachusetts or GE Vivid 7, General Electric, Waukesha, Wisconsin). A total of five (12.8%) echocardiograms were performed with sedation, three under general anesthesia, two with intranasal midazolam. All of the subsequent catheterizations were performed under general anesthesia with the exception of three adults who received conscious sedation. The following parameters were measured on continuous wave Doppler tracings through the aortic isthmus: peak pressure gradient, mean pressure gradient in systole, mean pressure gradient during both systole and diastole, systolic velocity half time, and diastolic velocity half time (Table 1).

Coarctation isthmus diameter, presence of any diastolic forward flow at the transverse arch, and presence of any diastolic

forward flow in the abdominal aorta were also assessed. Diastolic velocity was defined as the velocity at the end of the T wave, as has previously been reported.²² The diastolic velocity half time (DVHT) was then calculated by measuring the time interval between the end of the T wave and the point at which the velocity measured half of the peak diastolic velocity (Figure 1). Systolic velocity half time (SVHT) was similarly measured from the peak systolic velocity. Both time intervals were indexed to heart rate by dividing by the square root of the electrocardiographic RR interval according to Bazett's method.²³ Heart rate, blood pressure, and sedation use at the time of echocardiogram were recorded from the echocardiogram report. Independent, blinded review of each patient's preprocedure echocardiogram was performed by two authors (AC or DE) who were unaware of the clinical history and catheterization outcome at the time of echocardiogram review. Intraclass correlation coefficient was calculated following independent review of 20% of the studies by both authors on echocardiographic measurements to assess interobserver reliability.

2.3 | Clinical data collection

Preprocedure clinic visit documentation was reviewed to gather baseline heart rate, as well as maximum upper and lower extremity systolic blood pressure gradients acquired through noninvasive four extremity oscillometric blood pressure measurements in the supine position. All invasive hemodynamic data were acquired by retrograde right and left heart catheterization via femoral access. Catheterization data collected included heart rate at catheterization, peak-to-peak pressure gradient measured from ascending to

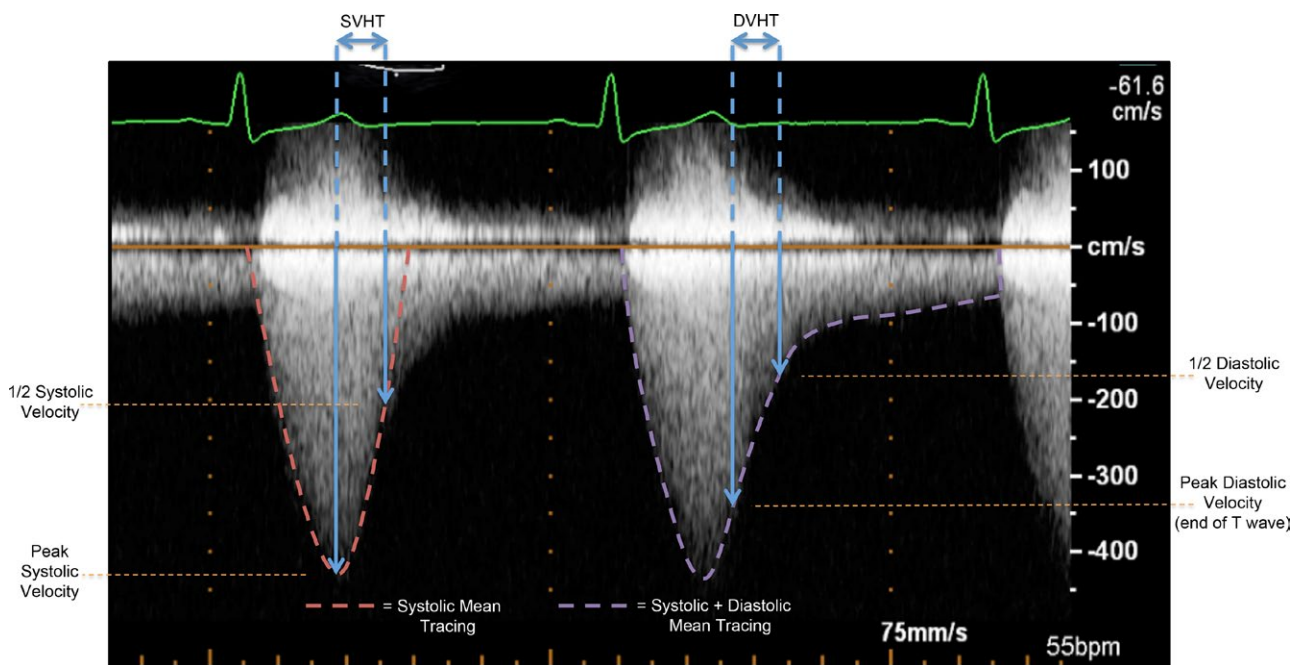


FIGURE 1 Echocardiographic values measured from continuous wave Doppler through the aortic isthmus. Peak diastolic velocity was measured at the end of the T wave. Mean gradients were traced for both a symmetric systolic envelope (red) as well as to include the diastolic tail (purple)

descending aorta, cardiac index estimated by Fick principle, and angiographic isthmus diameter measured at the narrowest part of the lesion in the straight lateral camera position.

2.4 | Statistical analysis

Because there is utility in understanding the association between clinical variables and both the continuous catheterization peak gradient as well as the binary clinical cutoff of 20 mm Hg, we evaluated the data for both outcomes. Descriptive statistics are presented for continuous variables as median with interquartile range (IQR) and for categorical variables as frequency with percentages. Nonparametric Mann-Whitney *U* test (continuous variables) and chi-square or Fisher's exact test (binary variables) were used to assess for significant differences in patient parameters and clinical measures between those who had catheterization peak gradient ≥ 20 mm Hg and those that did not. Nonparametric Spearman's rho was calculated to test for univariate associations between clinical variables and catheterization peak gradient on a continuous scale. Due to sample size limitations, we selected the four variables that showed statistically significant univariate associations and that we felt were most clinically relevant. A multivariable logistic regression with backward selection method was performed between patient weight at catheterization, echocardiographic systolic mean gradient, DVHTi, and clinical blood pressure gradient with catheterization peak gradient ≥ 20 mm Hg. All statistical analysis was performed using IBM SPSS Statistics Version 24 for Windows (IBM Corp., Armonk, New York, *P* value $\leq .05$ was considered statistically significant.

3 | RESULTS

3.1 | Demographics

Of 352 patients who underwent catheterization during the study period with history of the specified diagnoses, 116 were excluded based on review of the catheterization report due to single

ventricle physiology or diffuse arch hypoplasia. Of the remaining 236 subjects, an additional 168 were excluded based on echocardiogram findings of significant aortic stenosis, insufficiency, or multiple levels of arch obstruction, leaving 68 patients that met inclusion criteria. The characteristics of these subjects are presented in Table 2. Thirty-nine of the 68 patients (57%) met the intervention threshold with a peak-to-peak gradient ≥ 20 mm Hg at catheterization. Those patients meeting intervention criteria were significantly younger [median age 14 months (IQR, 4-143 months) vs 188 months (IQR, 126-295 months)], weighed less [median 10 kg (IQR, 6-40 kg) vs 58 kg (IQR, 24-74 kg)], and had higher heart rates at the time of their catheterization [median 115 bpm (IQR, 86-136 bpm) vs 89 bpm (IQR, 75-112 bpm)]. Notably, there was no significant difference in individual heart rates between those measured at the time of echocardiogram and those at cardiac catheterization.

3.2 | Frequency of intervention

Fifty-five of the patients (81%) had undergone previous intervention with either catheterization or surgery. Prior intervention was not associated with whether a subject had a peak-to-peak gradient of ≥ 20 mm Hg. Eighteen (62%) of the patients that did not meet the defined interventional threshold of a peak-to-peak gradient of ≥ 20 mm Hg did receive either ballooning or stenting of their coarctation, which upon further review was justified by alternative criteria including systemic hypertension or significant angiographic narrowing at the isthmus. In total, 11 patients (16%) underwent catheterization, but did not undergo angioplasty or stenting.

3.3 | Univariate correlation with continuous catheterization gradient

Nearly all echocardiographic variables were found to have a moderate correlation ($r = 0.503-0.617$, $P < .001$) with the notable

	Cath peak ≥ 20 mm Hg (<i>n</i> = 39)	Cath peak < 20 mm Hg (<i>n</i> = 29)	<i>P</i>
Age at cath (months)	14 (4, 143)	188 (126, 295)	<.001
Number of patients <3 mo	4 (10.2%)	1 (3.5%)	.384
Weight at cath (kg)	10 (6, 40)	58 (24, 74)	<.001
Heart rate at echo (BPM)	108 (84, 134)	77 (60, 90)	.001
Heart rate at cath (BPM)	115 (86, 136)	89 (75, 112)	.011
Sedation at echo	5 (12.8%)	0 (0%)	.067
Prior intervention	32 (82.1%)	23 (79.3%)	.776
Received intervention at cath	39 (100%)	18 (62.1%)	<.001
Cath peak (mm Hg)	30 (25, 37)	10 (6, 11)	<.001

TABLE 2 Patient characteristics

Abbreviation: BPM, beats per minute.

Data are expressed as median (1st quartile, 3rd quartile) or as number (percentage).

exceptions of the echocardiographic isthmus Z-score as well as the ratio between systolic and diastolic velocity (Table 3). The clinical upper to lower extremity blood pressure gradient also displayed moderate correlation with the continuous catheterization peak gradient ($r = .599, P < .001$).

3.4 | Univariate association with binary catheterization gradient ≥ 20 mm Hg

We found significant associations between catheterization peak gradient ≥ 20 mm Hg and most variables, with the exceptions of the

echo isthmus z-score and the ratio between systolic and diastolic velocity (Table 4). We also demonstrate that patients with high catheterization peak gradient had a higher presence of abdominal aortic diastolic forward flow than patients who had lower peak gradients (77% vs 46%, $P = .015$). Patients with high peak gradient also had a higher presence of diastolic forward flow in the transverse arch than those who did not (76% vs 18%, $P < .001$).

Figure 2 depicts median values and interquartile ranges of two commonly used clinical variables, echocardiogram mean systolic gradient, and upper to lower extremity blood pressure gradient, each significantly associated ($P < .001$) with the catheterization peak

TABLE 3 Univariate correlation of clinical measures with continuous catheterization gradient

	<i>n</i>	Spearman's rho correlation coefficient	<i>P</i>
Echo isthmus z-score	53	-0.023	.869
Echo peak systolic velocity (cm/s)	68	0.529	<.001
Echo peak diastolic velocity (cm/s)	62	0.452	<.001
Echo systolic/diastolic velocity ratio	61	-0.238	.064
Echo systolic mean (mm Hg)	68	0.617	<.001
Echo systolic + diastolic mean (mm Hg)	68	0.503	<.001
SVHTi (ms)	68	0.604	<.001
DVHTi (ms)	61	0.581	<.001
Clinic BP gradient (mm Hg)	51	0.599	<.001

Abbreviations: SVHTi, systolic velocity half time index; DVHTi, diastolic velocity half time index; BP, blood pressure.

TABLE 4 Univariate analysis of clinical measures on catheterization gradient ≥ 20 mm Hg

	Cath peak ≥ 20 mm Hg	Cath peak < 20 mm Hg	<i>P</i>
Abdominal aorta diastolic forward flow*	24 (77.4%)	12 (46.2%)	.015
Transverse arch diastolic forward flow*	29 (76.3%)	5 (17.9%)	<.001
Echo isthmus z-score	-3.6 (-4.0, -3.0)	-3 (-4.4, -1.8)	.448
Echo peak systolic velocity (cm/s)	350 (308, 397)	287 (256, 324)	<.001
Echo peak diastolic velocity (cm/s)	218 (121, 301)	129 (100, 164)	.003
Echo systolic/diastolic velocity ratio	1.6 (1.3, 2.6)	2.1 (1.8, 2.8)	.166
Echo systolic mean (mm Hg)	34 (24, 41)	19 (15, 23)	<.001
Echo systolic + diastolic mean (mm Hg)	20 (15, 26)	12 (7, 18)	<.001
SVHTi (ms)	178 (152, 215)	148 (134, 159)	<.001
DVHTi (ms)	92 (54, 162)	46 (21, 62)	<.001
Clinic BP gradient (mm Hg)	36 (26, 61)	13 (0, 28)	<.001
Clinic BP gradient ≥ 20 mm Hg*	21 (80.8%)	11 (44.0%)	.007

Abbreviations: SVHTi, systolic velocity half time index; DVHTi, diastolic velocity half time index; BP, blood pressure. Data are expressed as median (1st quartile, 3rd quartile) or as number (percentage).

*Not all patients had data available, therefore, proportions were calculated based on the valid *n*.

gradient ≥ 20 mm Hg. A similar significant association ($P < .001$) is shown between DVHTi and the catheterization gradient.

3.5 | Multivariable logistic regression analysis

Patient weight at catheterization, the echocardiographic mean coarctation gradient, the clinic blood pressure gradient, and DVHTi were included in a multivariable logistic regression model to test the independent association with a catheterization peak gradient ≥ 20 mm Hg (Table 5) as they were both significant by univariate analysis and deemed clinically relevant. Inclusion of further variables was limited by the power of the small sample size. Patient weight was not independent or significant and was excluded in the final model. By this fitted model, there is a 3.9% increase in the odds of having a catheterization peak gradient ≥ 20 mm Hg for every 1 ms increase in DVHTi when the echo systolic mean gradient and clinic blood pressure gradient are fixed. When controlling for both the echocardiographic mean gradient and DVHTi, the clinic blood pressure gradient was not independently associated with catheterization peak gradient ≥ 20 mm Hg.

3.6 | Interobserver reliability

The intraclass correlation coefficient was between 0.802 and 0.997 with a mean of 0.934 for the 20% of subjects blindly evaluated by both observers. The specific coefficients for the lesser utilized SVHT and DVHT were 0.851 and 0.902, respectively.

4 | DISCUSSION

There are many variables used to predict catheterization gradients for patients with coarctation, including echocardiographic gradients, presence of diastolic forward flow, and clinical blood pressure gradients. Despite this, the approach to determining whether a patient with coarctation should be put forward for catheter-based intervention remains complex, muddled by limited noninvasive predictors

that at times contradict each other. This study's results reinforce this predicament.

There was not one single metric that proved superior or most-predictive of a significant gradient at catheterization. This study demonstrated only a moderate correlation between echocardiographic and catheterization gradients. This should be kept in mind when referring patients to catheterization due to echocardiographic findings or clinical blood pressure gradients alone. In looking at which parameters predicted a catheterization gradient ≥ 20 mm Hg, the accepted threshold for intervention, we did find several that were independently associated with the outcome. Most echocardiographic parameters were not independently associated with catheterization gradient. However, DVHTi was independent of the other echocardiographic parameters. This is important because it means that DVHTi can stand as yet another tool, in addition to and independent of echocardiographic peak and mean systolic coarctation gradients, to determine whether a patient should undergo catheterization. DVHTi is not a commonly used tool to assess the degree of coarctation. However, given that it is reproducible and has similar but independent correlation to catheterization gradient as other echocardiographic parameters, we recommend that it be considered as part of the protocol for preinterventional assessment in this patient population. Echocardiographic coarctation gradients (eg, mean gradient or peak systolic gradient) and DVHTi, were independent of each

TABLE 5 Multivariate logistic regression analysis with binary catheterization gradient

	Odds ratio	95% CI	P
Echo systolic mean (mm Hg)	1.213	1.041-1.414	.013
Clinic BP gradient (mm Hg)	1.066	0.987-1.150	.102
DVHTi (ms)	1.039	1.004-1.074	.027

Abbreviations: BP, blood pressure; DVHTi, diastolic velocity half time index.

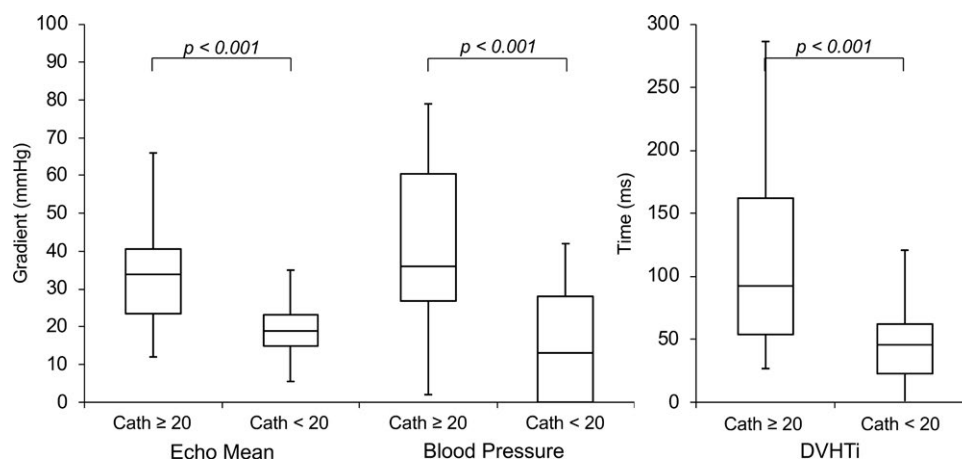


FIGURE 2 Box plot of echo mean gradient, blood pressure gradient, and DVHTi as a function of peak-to-peak gradient at catheterization

other. As such, we suggest that future studies, with a larger patient population, may be able to build a statistical model that incorporates these measures, to better predict which patients will have a significant gradient at catheterization to warrant intervention.

Our data also support the association of low patient weight (and therefore age) with increased likelihood of severe coarctation. Previous studies have shown that younger patients have higher rates of early angioplasty failure and disease progression.²⁴ It is therefore not surprising that not only is our catheterization population skewed toward younger patients, but that the youngest and smallest patients were most likely to meet intervention criteria. This finding supports the need for increased frequency of follow up and a lower threshold for catheterization in patients with lower weight.

We recognize that any echocardiographic measure based on Doppler interrogation is intrinsically different from an invasive metric in that it relies on the maximal instantaneous gradient rather than the peak systolic pressures as measured by catheterization before and after the site of obstruction. However, we propose that by incorporating DVHTi, an indirect metric of coarctation severity into clinical decisions, we may optimize referral for intervention and minimize unnecessary catheterization.

This study is limited by its retrospective nature. The study population was relatively small and included only patients that were referred to the catheterization laboratory, therefore the prediction models may be biased toward the most severe or clinically apparent lesions. Because of missing data for some variables, the multivariable logistic regression model represents 69% of 68 patients in our initial cohort, however, comparisons of patients included and excluded from the model showed no significant differences in patient characteristics. This study is also limited by the definition of the intervention threshold of a peak-to-peak gradient ≥ 20 mm Hg. Though this is the generally accepted threshold for intervention in the literature, other criteria such as baseline systemic hypertension, hypertensive response to exercise in the presence of a true angiographic narrowing, ventricular dysfunction, severe mitral regurgitation, or presence of significant collaterals are also considered possible indications for intervention.^{12,13,25} This explains the high proportion (62.1%) of patients in our study population who underwent intervention despite a peak-to-peak gradient < 20 mm Hg at the time of cardiac catheterization. In addition, the study is further limited by the inability to control for the effect of variable hemodynamic states at the time of echocardiography and cardiac catheterization, though the lack of a significant disparity in heart rates between conditions is reassuring. Less than 10% of all precatheterization echocardiograms were performed with sedation, and though the studies were not performed contemporaneously, these conditions mirror typical clinic practice in our institution, and therefore maintain applicability.

The data from this study of patients with coarctation support the association between many commonly used echocardiographic measures and the peak-to-peak coarctation gradient at catheterization, as well as DVHTi, an underutilized metric of coarctation, which should be considered as an additional tool to guide the decision-making process. Given several significant predictors of coarctation

severity, we postulate that catheterization referral may be optimized by studying larger cohorts and developing a multivariable predictive model.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Assisted in study design, performed literature review, data collection, prepared drafts and final manuscript: Adam Christopher

Performed data analysis, assisted in interpretation: Abraham Apfel.

Performed data analysis, assisted in interpretation: Tao Sun

Assisted in study design, data interpretation, provided critical revision of manuscript: Jacqueline Kreutzer

Conceptualized study, assisted in design, performed data collection, data interpretation, provided critical revision of drafts and final manuscript: David Ezon

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How to cite this article: Christopher AB, Apfel A, Sun T, Kreutzer J, Ezon DS. Diastolic velocity half time is associated with aortic coarctation gradient at catheterization independent of echocardiographic and clinical blood pressure gradients. *Congenital Heart Disease.* 2018;13:713–720. <https://doi.org/10.1111/chd.12637>