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Unraveling the RV Ejection Doppler Envelope

Insight Into Pulmonary Artery Hemodynamics and Disease Severity

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ABSTRACT

OBJECTIVES The purpose of this study was to characterize the profiles of right ventricular outflow tract (RVOT) Doppler flow velocity envelopes in patients with pulmonary arterial hypertension (PAH) and to establish whether changes in the RVOT flow profile related to patient outcome.

BACKGROUND The RVOT systolic flow profile is frequently abnormal, with findings of a mid-systolic flow deceleration and notching, previously proposed as an indicator of elevated pulmonary vascular resistance (PVR).

METHODS We reviewed RVOT systolic flow profiles recorded by pulsed-wave Doppler from 159 consecutive patients with PAH and measured deceleration time (DT) of mid-systolic deceleration slope (mid-systolic DT) and the peak velocity of pre- and post-notching flow. Concurrent right-heart catheterization was available in all (41 of 41) incident patients and in 39 of 118 established patients. Outcomes, defined as time to all-cause mortality or need for lung transplantation, were assessed during 3 years of follow-up.

RESULTS Notched envelopes were identified in 150 of 159 patients. The presence of a notched pattern and a decrease in the mid-systolic DT were associated with higher PA pressures; higher PVR; and, at a threshold of a mid-systolic DT of <120 ms, worse outcome. Those patients with a shorter DT were further subdivided based on the post-notch systolic flow velocity. In these patients, a decline in the post-notch flow velocity to <62% of the pre-notch flow velocity defined a cohort with a marked reduction in systolic function and the worst outcome.

CONCLUSIONS In PAH, the notched profile of RVOT Doppler flow velocity envelope appears to integrate indicators of pulmonary vascular load and RV function and serves as a marker for adverse outcomes. (J Am Coll Cardiol Img 2017;10:1268–77) © 2017 by the American College of Cardiology Foundation.

In patients with pulmonary hypertension (PH), conventional echocardiographic measurements include tricuspid and pulmonary regurgitant flows to evaluate pulmonary artery (PA) hemodynamics and measurements of right ventricular (RV) systolic function. The RV outflow tract (RVOT) systolic Doppler flow velocity envelope is frequently abnormal, with findings of a notched envelope, previously suggested as an indicator of elevated PA pressure or pulmonary vascular resistance (PVR) (1–3). Prior studies have suggested that notching of the RVOT systolic flow profile corresponds to reflected waves from the abnormal pulmonary vascular bed (4,5) and is present in most patients with pulmonary arterial hypertension (PAH) (6). Recent guidelines from the American Society of Echocardiography have suggested "the notch" as a complementary index to suggest an elevation in PVR (7). Others have suggested that the timing in which the notch occurs in the profile may reflect the severity of the pulmonary vascular disease (5,8). However, the factors that underlie the changes seen in the RVOT Doppler profile and whether these changes are linked to prognosis are not well established. Our aim was to

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characterize the RVOT Doppler profiles in a large sequential series of patients with PAH and to establish whether changes in the RVOT systolic flow profile related to patient outcome.

METHODS

STUDY PATIENTS AND RVOT SYSTOLIC FLOW PROFILE ANALYSIS. The study was approved by the Mayo Clinic Institutional Review Board (protocol 08-007824). We enrolled consecutive adult patients (≥18 years of age) at our institution who underwent imaging between January 1, 2008 and March 30, 2013 (n = 175), who fulfilled the contemporary diagnostic criteria for group 1 PH (mean PA pressure: ≥25 mm Hg, occurring in the setting of increases in pre-capillary pulmonary resistance) (9). One patient with congenital heart disease and another who developed PAH after liver transplantation and 7 with atrial fibrillation were excluded. Another 7 patients were excluded due to poor image quality of pulsed-wave Doppler interrogation of the RVOT. The final study cohort consisted of 159 subjects.

SEE PAGE 1278

ECHOCARDIOGRAPHIC PARAMETERS AND HEMODYNAMIC EVALUATION. Transthoracic echocardiography was performed according to standard guidelines (7,10). Pulsed-wave Doppler interrogation of the RVOT was performed from a modified basal short-axis view from the left parasternal or subcostal window. The transducer position was adjusted to open up the RVOT, with the sample volume placed approximately 1 cm proximal to the pulmonic valve. Doppler tracings were recorded at end-expiration. Three contiguous signals were measured and averaged.

Patients who had RVOT systolic flow profiles without notching (Figure 1A) were categorized as no notch (NN). Regarding the RVOT systolic flow profiles with mid-systolic deceleration and notching (Figure 1B), 5 specific measurements were made (Figure 2): the notch position, the deceleration time (DT) of the mid-systolic deceleration slope (mid-systolic DT), the peak velocity of the pre-notching acceleration flow (V_{pre}), the flow velocity at notching (V_{notch}), and the peak velocity of the post-notching acceleration flow (V_{post}). The V_{notch}/V_{pre} and V_{post}/V_{pre} ratios were used in analyses to convert velocity to parameters of flow profiles. The notch position was defined as the time-to-notch ratio, calculated as the time between the onset of the ejection to the notch to the ejection time. Mid-systolic DT was calculated as the time duration of the slope from V_{pre} to baseline. For the RVOT systolic flow profile with an inflection point where flow deceleration rate decreased obviously and no post-notching acceleration flow as shown in Figure 1C, we defined the flow velocity at the inflection point as V_{notch} and V_{post}, and the time to the inflection point as time-to-notch. Representative examples of measurements of ejection flow envelope are shown in Figure 2. Measurements were made offline from digitally stored images, using ImageJ software (U.S. National Institutes of Health, Bethesda, Maryland) from 3 consecutive cardiac cycles, and the results were averaged. Tricuspid annular plane systolic excursion (TAPSE) was measured using the distance of systolic excursion of the RV annular segment along its longitudinal plane from an apical 4-chamber view. Cardiac index was calculated using Doppler-estimated stroke volume measured in the left ventricular outflow tract and heart rate. The severity of tricuspid regurgitation was assessed using color flow imaging and regurgitant jet area. Echocardiographic estimation of PA systolic pressure was obtained as the sum of tricuspid pressure gradient and right atrial pressure estimated in 5-mm Hg increments between 5 and 20 mm Hg on the basis of the size and collapsibility of the inferior vena cava (11). Tricuspid pressure gradient was calculated from the continuous-wave Doppler tricuspid valve regurgitant velocity, using the simplified Bernoulli equation. Right ventricular index of

ABBREVIATIONS AND ACRONYMS

DT = deceleration time

LDT = longer mid-systolic deceleration time (≥120 ms)

NN = RVOT flow profiles with no notching

PAH = pulmonary arterial hypertension

PVR = pulmonary vascular resistance

RVOT = right ventricular outflow tract

SH = shorter mid-systolic deceleration time (<120 ms) and higher V_{post}/V_{pre} (>62%)

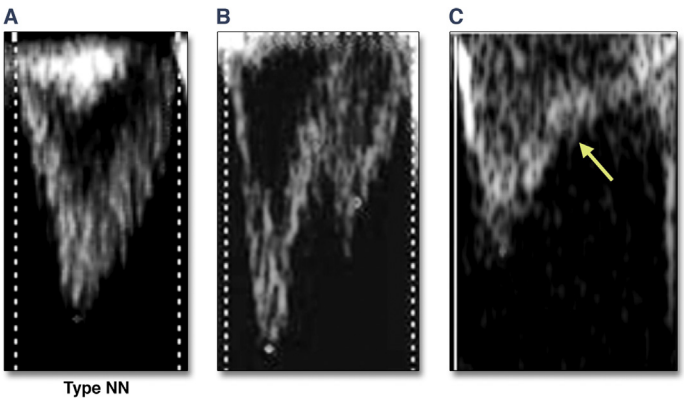
SL = shorter mid-systolic deceleration time (<120 ms) and higher V_{post}/V_{pre} (≥62%)

V_{notch} = velocity of acceleration flow at the time of notching

V_{post} = peak velocity of post-notching acceleration flow

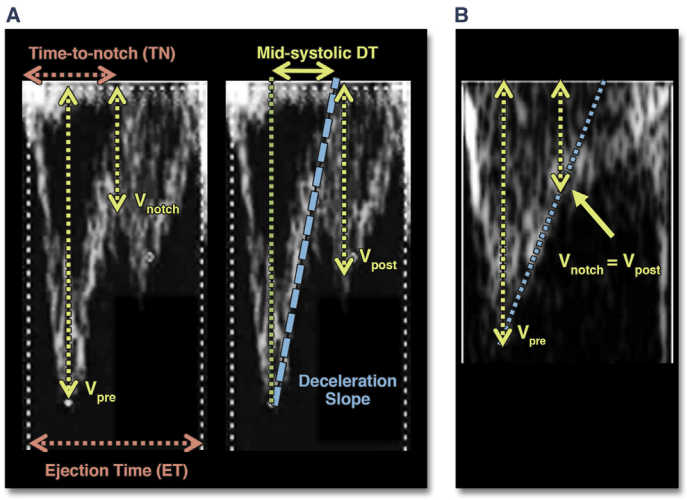
V_{pre} = peak velocity of pre-notching acceleration flow

FIGURE 1 Representative RVOT Flow Systolic Profiles



(A) Pattern without mid-systolic deceleration and notching (no notch [NN] pattern), whereas there is shortening of acceleration time, the flow pattern maintains a parabolic curve. **(B)** The pattern demonstrates mid-systolic deceleration and notching separating 2 distinct acceleration flows. **(C)** The pattern of rectilinear mid-systolic deceleration with an inflection point **(arrow)** and no post-notching acceleration flow. RVOT = right ventricular outflow tract.

FIGURE 2 Examples of Specific Measurements of RVOT Flow Profiles



(A) Measurements in a notched envelope. The **blue dashed line** shows mid-systolic deceleration slope and is prolonged to the baseline to detect mid-systolic DT. **(B)** The measurements in an envelope with an inflection point but no post-notching show acceleration flow. The **arrow** indicates the inflection point where V_{notch} and V_{post} are defined. DT = deceleration time; V_{pre} = the peak velocity of the pre-notching acceleration flow; V_{notch} = the flow velocity at notching; V_{post} = the peak velocity of the post-notching acceleration flow; other abbreviations as in Figure 1.

TABLE 1 Patient Characteristics and Catheterization Data (N = 159)

Age, yrs		56 ± 14
Females		117 (74)
WHO functional class		
I		21 (13)
II		56 (36)
III		67 (42)
IV		15 (9)
Cause		
Idiopathic		71 (45)
Connective tissue disease		51 (32)
Portopulmonary		19 (12)
Other		18 (11)
Clinical status		
New diagnosis		41 (26)
Established		118 (74)
Medication		
Oxygen		24
Calcium channel blocker		30
ET receptor antagonists		56
PDE5 inhibitor		78
Prostacyclin		35
Combination therapy		51
Clinical Testing		
6-min walking distance, m	n = 127	354 ± 144
BNP, pg/ml	n = 44	370 ± 345
NT-proBNP, pg/ml	n = 138	1806 ± 3423

Continued on the next page

myocardial performance, defined as the sum of isovolumic contraction time plus isovolumic relaxation time divided by ejection time, was calculated using the measurements of time from the onset to the cessation of continuous-wave Doppler of the tricuspid regurgitant jet and RVOT systolic flow.

Hemodynamic right-heart catheterization (RHC) was performed as clinically indicated for diagnosis or reassessment of PAH. We restricted invasive hemodynamic analysis of the PA to those procedures performed within 1 month of echocardiographic examination. During RHC, a balloon-tipped fluid-filled catheter was used to obtain right-atrium pressures; PA diastolic, mean, and systolic pressure; and wedge pressure. PVR was calculated by standard formulas, using cardiac output obtained from either Fick procedure or thermodilution technique. Right ventricular stroke work index (RVSWI) was calculated by the following equation (12): [RVSWI = stroke volume index × (mean pulmonary artery pressure - mean right atrial pressure) × 0.0136] where stroke volume index = (cardiac index/heart rate) × 1,000.

CLINICAL OUTCOMES. The primary clinical endpoint for this study was all-cause mortality or lung transplantation. Follow-up was assessed over a period of 3 years.

WAVE SEPARATION ANALYSIS. Measured pressure waves were separated into forward and reflected waves based on the method given by Westerhof et al. (4) and the water hammer equation, as demonstrated previously. The forward and backward waves were calculated from measured pressure and flow waves as: $[P+(t) = {}^1/_2(P_m(t) - Pd + \rho c\, U_m(t)]$ and $[P-(t) = {}^1/_2(P_m(t) - Pd - \rho c\, U_m(t)]$, where $P \pm (t)$ is the forward pressure wave (+) or reflected pressure wave (−) at time t, $P_m(t)$ is the measured pressure at time t, $U_m(t)$ is the measured flow velocity at time t, ρ is the density of blood, and c was the local wave speed. Variable ρc was estimated by a linear regression on the pressure velocity loop in the early systolic phase. We used flow velocity envelopes of the RVOT and pressure tracings obtained from right-heart catheterization. Both the pulmonary artery pressure tracing and the flow velocity envelope of the RVOT were digitized at 4-ms intervals (Graphcel software, T. Kobo, Japan). The digitized RVOT envelope was used as the measured flow wave. Representative examples were chosen based on the following criteria: a heart rate difference of 5 beats/min or less between echocardiography and cardiac catheterization, an interval of within 2 days between echocardiography and catheterization and a heart rate <100 beats/min.

ANALYSIS. Statistical analyses were performed using JMP version 10.0 software (SAS Institute, Inc., Cary, North Carolina). Categorical data are expressed as the number of patients (percentage of population). Continuous variables are expressed as mean ± SD. For comparisons between 2 groups, a 2-sided Student *t* test, a Mann-Whitney *U* test, or the Welch *t* test were uses as appropriate. ANOVA was used to compare across multiple groups, with individual comparisons made where relevant. We used the minimum Bayesian information criterion for multivariate regression modeling. Cox proportional hazards regression models were used to test the association of the measurement or categorization of RVOT flow velocity envelope profiles on the primary clinical endpoints. Long-term follow-up of patients is presented using the Kaplan-Meier product-limit method and compared between groups by log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. Clinical characteristics and echocardiographic and RHC data are described in Table 1. All 159 patients had invasively confirmed Group 1 PH (approximately one-half had idiopathic PAH). Forty-one patients had newly diagnosed PAH, and 118 had established disease (duration 2.3 years; range 1 to 11 years) and ranged across the spectrum of disease severity. Concurrent RHC was available in all (41 of 41) incident patients and in 39 of 118 established patients. Right-heart catheterization and echocardiography were performed within a median of 2 days (interquartile range: 1 to 7 days). Echocardiography was performed prior to RHC in 73 patients.

RVOT SYSTOLIC FLOW PROFILE ANALYSIS. Of 159 patients, 9 patients had NN in their RVOT systolic profile (Figure 1A). One hundred forty-seven patients had mid-systolic deceleration and notching (Figure 1B), and 3 patients had an inflection point as shown in Figure 1C. Each of these 150 patients underwent the specific RVOT systolic flow profile measurements (Figure 2, Table 1).

HEMODYNAMIC CHARACTERIZATION OF NOTCHED RVOT SYSTOLIC FLOW PROFILES. Measurements of the RVOT systolic flow profiles were correlated with echocardiographic and hemodynamic characteristics (Table 2). There was a correlation observed between PVR and components of the early part of the notch such as the mid-systolic DT, V_{pre}, and V_{notch}, especially the mid-systolic DT. The mid-systolic DT was inversely proportional to the noninvasive and invasive measurements of PA pressure (Figures 3A and 3B) and PVR by catheterization (Figure 3C). When patients were stratified by tertiles, those patients with the shortest mid-systolic DT had an average PVR twice that of those with the longer DT (Figure 3C). Of early systolic measurements, the mid-systolic DT was best associated with outcome with longer DT associated with better outcome (Table 3). Those patients with the shortest mid-systolic DT (<120 ms) had significantly worse survival than the remainder (Figure 3D).

In contrast, V_{post} or the V_{post}/V_{pre} ratio components of the later systolic phases of ejection were better correlated with measurements of right ventricular

TABLE 1 Continued

Echocardiographic data, n = 159	
Heart rate, beats/min	76 ± 12
% LV ejection fraction	65 ± 6
> moderate RV dilatation (%)	78 (49)
≥ moderate RV dysfunction (%)	63 (40)
TAPSE, mm	16 ± 5
Doppler-estimated cardiac index, l/min/m^2	3.2 ± 0.8
Tricuspid valve regurgitation	
Trivial to mild (%)	63 (40)
Moderate (%)	64 (40)
Severe (%)	32 (20)
Estimated RV systolic pressure, mm Hg	79 ± 23
Estimated right atrial pressure, mm Hg	11 ± 2
RV index of myocardial performance	0.5 ± 0.2
Concomitant right heart catheterization (n = 80)	
Heart rate, beats/min	78 ± 15
Systolic blood pressure, mm Hg	117 ± 19
Right atrial pressure, mm Hg	10 ± 5
Systolic PA pressure, mm Hg	78 ± 16
Diastolic PA pressure, mm Hg	31 ± 10
Mean PA pressure, mm Hg	50 ± 11
Pulmonary capillary wedge pressure, mm Hg	10 ± 3
Pulmonary vascular resistance, Wood units	10 ± 5
Right ventricular stroke work index, g/m^2/beat	17.5 ± 6
PA capacitance, ml/mm Hg	1.4 ± 0.8
Cardiac index, l/min/m^2	2.5 ± 0.8
RVOT systolic flow profile measures (n = 150)	
Notch position	0.51 ± 0.01
Ejection time, ms	338 ± 31
Mid-systolic DT, ms	143 ± 45
V_{pre}, cm/s	73 ± 18
V_{notch}, cm/s	35 ± 12
V_{post}, cm/s	48 ± 14
V_{pre}/V_{post}	67 ± 12
VTI_{RVOT}, cm	12 ± 4

Values are mean ± SD or n (%). All medications are concomitant.

BNP = brain natriuretic peptide; DT = deceleration time; ET = endothelin; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; PA = pulmonary artery; PDE5 = type 5 phosphodiesterase; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; V_{notch} = flow velocity at the time of the notch; V_{post} = peak flow velocity after the notch; V_{pre} = peak flow velocity prior to the notch; VTI_{RVOT} = right ventricular outflow tract velocity time integral; WHO = World Health Organization.

TABLE 2 Regression Analyses of Hemodynamic Variables for Measurements in RVOT Flow Profiles

	Notch Position					
	Univariate			Stepwise		
	β	p Value	R^2	β	p Value	R^2
PVR	−0.25	0.03	0.06	−0.34	0.004	
RA pressure	−0.15	0.20				
TAPSE	0.15	0.06				0.14
Heart rate	0.19	0.02	0.04	0.34	0.01	
Severe TR	−0.09	0.26				
Mid-systolic deceleration time						
PVR	−0.51	<0.0001	0.26	−0.37	0.002	
RA pressure	−0.34	0.003	0.11			
TAPSE	0.42	<0.0001	0.18	0.27	0.02	0.31
Heart rate	−0.17	0.04	0.03			
Severe TR	−0.20	0.02	0.04			
V_{pre}						
PVR	−0.40	0.0004	0.15	−0.40	0.0004	0.15
RA pressure	−0.11	0.33				
TAPSE	0.38	<0.0001	0.15			
Heart rate	−0.13	0.12				
Severe TR	−0.16	0.05				
V_{notch}						
PVR	−0.33	0.004	0.11	−0.33	0.004	0.11
RA pressure	−0.09	0.45	0.01			
TAPSE	0.40	<0.0001	0.16			
Heart rate	−0.12	0.15	0.01			
Severe TR	−0.14	0.08	0.02			
V_{post}						
PVR	−0.35	0.002	0.12			
RA pressure	−0.11	0.34	0.01			
TAPSE	0.49	<0.0001	0.24	0.49	<0.0001	0.24
Heart rate	−0.18	0.02	0.03			
Severe TR	−0.25	0.002	0.06			
V_{post}/V_{pre}						
PVR	0.05	0.67				
RA pressure	−0.04	0.70				
TAPSE	0.23	0.005	0.05			
Cardiac index	0.27	0.001	0.07	0.27	0.001	0.07
Heart rate	−0.12	0.16				
Severe TR	−0.19	0.02	0.04			

β indicates standardized partial regression coefficient. Stepwise is forward stepwise multivariate regression modeling with the minimum value of Bayesian information criterion.

PVR = pulmonary vascular resistance; RA = right atrial; other abbreviations as in Table 1.

performance, such as TAPSE or cardiac index, than PA hemodynamics (Table 2). The V_{post}/V_{pre} ratio was significantly associated with outcome, with a higher ratio associated with better outcome (Table 3). This relationship of the V_{post}/V_{pre} ratio to outcome was independent of the mid-systolic DT (Table 3).

Based on these results, patients were subdivided based on their RVOT systolic flow profiles into 4 groups (Figure 4), those with: 1) NN); 2) a longer mid-systolic DT (LDT) (≥120 ms) and a shorter mid-systolic DT (<120 ms) who were, in turn, subdivided based on their V_{post}/V_{pre} ratio as group; 3) short DT (SH, higher V_{post}/V_{pre} ratio [≥62%]); and group 4) short DT (SL, lower V_{post}/V_{pre} ratio [<62%]) (Figure 4). Measurements of PA pressure and PVR increased progressively among groups NN and LDT and those with shorter DT. Patients in group SL had worse RV systolic function than SH, although PA pressures were similar (Table 4). This classification of RVOT systolic profiles (Figure 4) characterized groups with progressively worse outcome from NN to LDT to SH to SL (Figure 5). The prediction of risk of the RVOT flow profile types was found to be independent of conventional risk predictors such as pulmonary artery pressure and right ventricular function (hazard ratio [HR]: 1.77; 95% confidence interval [CI]: 1.25 to 2.52; $p < 0.002$ for NN to LDT to SH to SL) with HR of 0.98 per 5 mm Hg (95% CI: 0.91 to 1.06; $p = 0.66$) for estimated RV systolic pressure and HR of 0.84 per 1 mm increase in TAPSE (95% CI: 0.77 to 0.92; $p < 0.001$).

REPRODUCIBILITY. Bland-Altman analysis in 20 randomly selected patients showed no significant intraobserver and interobserver biases for mid-systolic DT (−4.1 ± 6.2 ms and −3.1 ± 4.9 ms) and V_{post} (0.02 ± 0.01 and 0.02 ± 0.02). There was 1 discrepancy in the profiles (SH vs. SL) of 20 samples between the 2 observers (kappa = 0.93).

WAVE SEPARATION ANALYSES. Wave separation analyses were performed in representative cases (Online Figure S1) selected based on suitability for the wave separation analysis: criteria included a heart rate difference of 5 beats/min or less, an interval of within 2 days between echocardiography and catheterization, and stability of the heart rate at <100 beats/min. For type NN (Case 1), RVOT flow was determined almost entirely by the forward wave during RV ejection (Online Figure 1). For type LDT (Cases 2 and 3), a reflected wave that occurred late in systole interrupted forward flow resulting in a diminution of net flow, resulting in late systolic notching. As the PA resistance increased, there was a progressive rise in the presence and earlier peak of the reflected pressure wave, resulting in earlier notching during systole and a shorter mid-systolic DT (e.g., Case 4: SH) and characterized by a prominent steeply peaking reflected wave. Finally (e.g., as in Case 5) an early notch, smallest V_{post}, low right ventricular outflow tract velocity time integral and shortest ejection time characterizes the group SL.

DISCUSSION

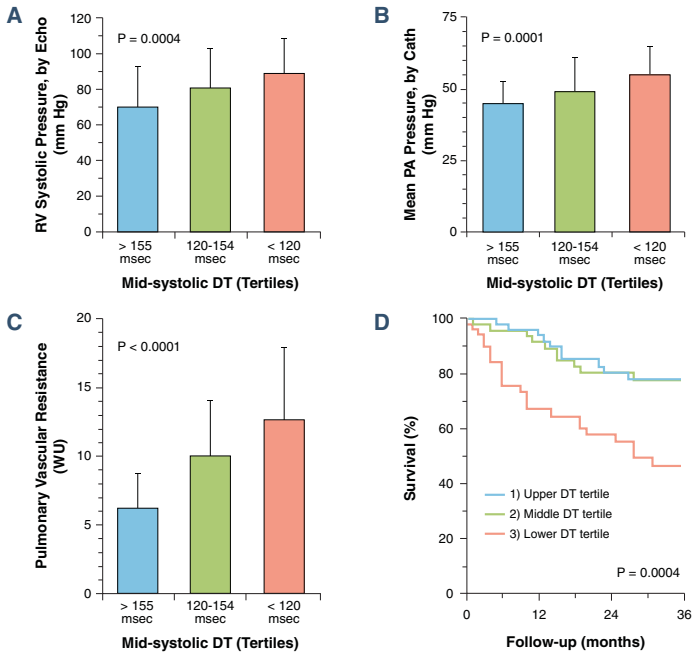
Patients with group 1 PH (PAH) displayed abnormal Doppler profiles through the RVOT with more than 90% having notched patterns. Our results

characterize the underlying PA-RV hemodynamics responsible for the perturbations in Doppler patterns with the mid-systolic DT related to PA vascular hemodynamics and the peak velocity of post-notching flow an indicator of RV performance. Thus, RVOT systolic flow profiles highlight the critical PA-RV relationship in PH underscored by the association of these flow profiles with patient outcomes.

REFLECTED WAVE AND MID-SYSTOLIC NOTCHING. Abnormalities of RVOT flow patterns have long been recognized in patients with PH, initially recognized as mid-systolic partial closure of the pulmonary valve on M mode (the "flying W") and then as mid-systolic notching in pulsed Doppler envelope (3,13,14). Turkevich et al. (15) reported that the decrease in RV-PA pressure gradient and forward flow accompanied by mid-systolic partial closure occurred with earlier and higher prevailing pressure, suggesting forces opposing ejection with higher pressure. However, although present in most patients, not all patients with elevated PA pressure have notching of the systolic Doppler envelope (1), whereas notching can be seen with modest PA pressure elevation in proximal banding or embolism (5,16), thereby implicating an upstream factor in the PA rather than simply the presence of elevated pulmonary pressure; instead, mid-systolic notching occurs due to PA reflected waves. Normal pulmonary vasculature with high compliance produces a reflected wave that propagates slowly, reaching the RVOT after the completion of the systolic phase. In contrast, in the presence of decreased pulmonary vascular compliance, reflected waves propagate more rapidly, with less attenuation, arriving at the RVOT during systole and causing mid-systolic notching. Arkles et al. (6) reported that visual categorization according to presence and location of notch was useful to indicate a pulmonary vascular disease with high PVR and low PA compliance regardless of clinical diagnosis. Herein, detailed evaluation of the notching profiles provides specific insights.

Here we focused on mid-systolic flow deceleration as the primary indicator of reflected wave from the pulmonary vasculature relative to forward ejection flow from the RV and speculated that interruption of RV ejection flow with a shorter mid-systolic DT is a marker of more severe disease. This speculation was based on the wave separation theory. In the method given by Parker and Jones (17), the forward and backward waves were calculated from measured pressure and flow waves as Equation (a): $[dP_{\pm} = {}^{1}/_{2}(dP_m \pm \rho c dU_m)]$, where $dP\pm$ is the changes in forward pressure wave (+) or reflected pressure wave (−), dP_m and dU_m are the changes in measured pressure and flow velocity, respectively, ρ is the density of blood, and c was the local wave speed. Solving equation (a) for dU_m gives $[dU_m = (dP_+ - dP_-)/\rho c]$, equation (b), indicating that mid-systolic flow deceleration (dU_m <0) occurs when the increasing rate of the reflected pressure wave is dominant over that of the forward pressure wave. The relative intensity and the relative initial increasing rate of reflected pressure wave versus the forward pressure wave acceleration are projected on the mid-systolic DT: relatively steeper upstroke induces the shorter mid-systolic DT. In this study, the result of the regression analysis is physiologically supportive of the hypothesis. That is, a shortened mid-systolic DT correlated with increases in PVR, which is likely, a significant determinant of the magnitude of the reflected wave and also related to measurements of RV systolic function, which generates the forward wave. The second flow acceleration (dU_m >0) is also interpreted based on equation (b) as follows: the

FIGURE 3 Association of Mid-Systolic DT With PA Hemodynamics and Outcome



Decreasing mid-systolic DTs were associated with increasing levels of pulmonary artery pressure measurements by echocardiography **(A)** and by catheterization **(B)** along with higher degrees of pulmonary vascular resistance **(C)**. Those patients with the shortest deceleration times (<120 ms) had significantly worse outcome, either death or need for pulmonary transplantation **(D)**. PA = pulmonary artery; other abbreviations as in Figure 2.

TABLE 3 Cox Hazard Regression Analysis for Overall Death and Lung Transplantation up to 3 Years

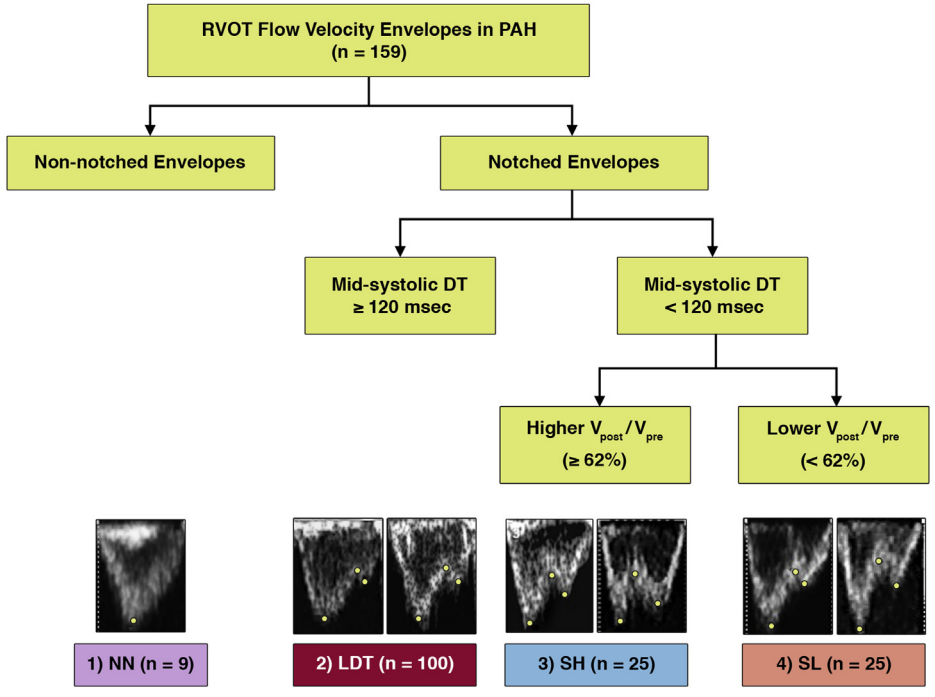
		Univariate Analysis			Multivariate Analysis		
	Increase	HR	95% CI	p Value	HR	95% CI	p Value
Time-to-notch	20 ms	0.93	0.76–1.11	0.41			
Ejection time	20 ms	0.89	0.77–1.03	0.12			
Mid-systolic DT	20 ms	0.82	0.70–0.95	0.007	0.82	0.69–0.96	0.01
V_{pre}	10 cm/s	0.96	0.81–1.13	0.66			
V_n/V_{pre}	10%	0.71	0.53–0.95	0.02			
V_{post}	10 cm/s	0.71	0.54–0.91	<0.01			
V_{post}/V_{pre}	10%	0.56	0.43–0.74	<0.0001	0.55	0.41–0.73	<0.0001
VTI_{RVOT}	1 cm	0.92	0.85–1.00	0.05			

CI = confidence interval; DT = deceleration time; HR = hazard ratio; other abbreviations as in Table 1.

forward pressure wave has again exceeded the reflected pressure wave. This is likely significantly dependent on a sustained if not enhanced level of RV systolic performance. This would support the finding of the association of V_{post} with measurements of RV performance. Pilot analyses of the wave separation for some cases were consistent with these hypotheses and interpretations (Online Figure S1).

Implications of the RVOT flow profile for risk stratification. By grouping patients based on their RVOT profiles, we were able to identify cohorts with differing risk profiles. Pulmonary hypertension patients without notching had the best prognosis, followed by those with longer mid-systolic DTs. However, those patients with progressively shorter DTs, correlating with progressive elevations in PVR,

FIGURE 4 Categorization of RVOT Systolic Flow Profiles



The flow diagram depicts the categorization of patients into 4 groups: 1) those without a systolic notch; 2) those with an LDT; 3) those with a shorter DT and higher V_{post}/V_{pre} ratio (SH); and 4) those with a shorter DT and lower V_{post}/V_{pre} ratio (SL). LDT = longer deceleration time; PAH = pulmonary arterial hypertension; other abbreviations as in Figures 1 and 2.

TABLE 4 Specific Measurements of Disease Severity by Types of RVOT Systolic Flow Profiles

	NN (n = 9)	LDT (n = 100)	SDT (n = 50)	p Value	SH (n = 25)	SL (n = 25)	p Value
WHO functional class							
I	33	18	0		0	0	
II–III	66	76	82	0.002	85	78	0.40
IV	0	6	18		14	22	
6-min walk distance, m	476 ± 68	372 ± 148	296 ± 137	0.002	307 ± 137	288 ± 108	0.60
Doppler-derived RVSP, mm Hg	53 ± 15	76 ± 23	89 ± 20	0.001	86 ± 16	91 ± 22	0.30
Catheter mPAP, mm Hg	45 ± 11	47 ± 11	55 ± 10	0.002	54 ± 10	55 ± 10	0.64
PVR, Wood units	4.8 ± 2.0	8.4 ± 4.0	12.6 ± 5.0	0.0003	10.4 ± 3.0	15 ± 7	0.02
Doppler CI, l/min/m^2	3.8 ± 0.5	3.2 ± 0.1	3.0 ± 0.9	0.03	3.4 ± 0.9	2.5 ± 0.6	<0.0001
TAPSE, mm	20 ± 5	17 ± 5	13 ± 4	<0.0001	14 ± 3	12 ± 4	0.005
RV index myocardial performance	0.48 ± 0.20	0.52 ± 0.20	0.60 ± 0.20	0.04	0.52 ± 0.20	0.68 ± 0.20	0.005
≥Moderate RV dysfunction on echo	11	31	66	<0.0001	48	84	0.006
Severe tricuspid valve regurgitation	0	15	34	0.004	20	44	0.07
RV stroke work index, g/m^2/beat	19.5 ± 7.0	17.7 ± 6.0	16.9 ± 8.0	0.79	20.1 ± 9.0	14.5 ± 6.0	<0.05

Values are % or mean ± SD.

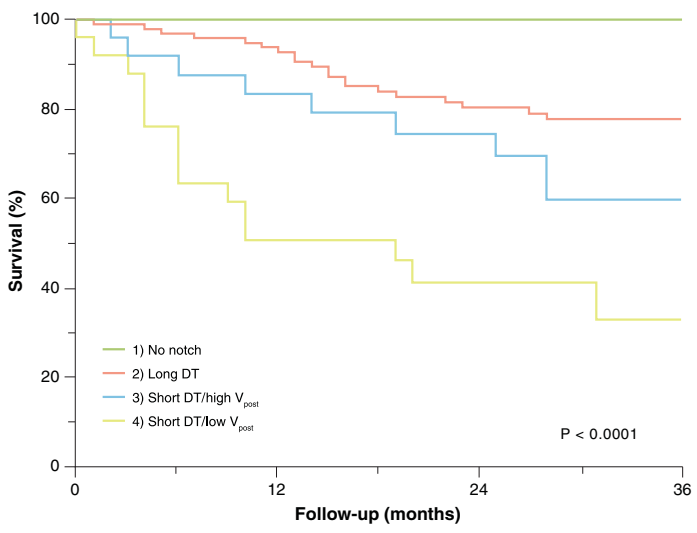
LDT = longer mid-systolic DT; mPAP = mean pulmonary artery pressure; NN = no notching; RVSP = right ventricular systolic pressure; SDT = shorter mid-systolic deceleration time; SH = shorter mid-systolic DT (<120 ms) and higher V_{post}/V_{pre} (> 62%); SL = shorter mid-systolic DT (< 120 ms) and lower V_{post}/V_{pre} (< 62%); other abbreviations as in Tables 1 and 2.

had worse survival. This latter cohort could be further separated based on the late systolic flow. Here those with lower post-notch systolic velocities, likely a consequence of a failing RV, had the worst prognosis. Our interpretation of mid-systolic flow reduction (mid-systolic DT) and the second flow acceleration (V_{post}) found in the RVOT systolic profile is concordant with data for ventriculoarterial coupling and stroke volume (18–20). Here, application of the relative assessment to these measurements, mid-systolic DT, and V_{post}/V_{pre}, allowed characterization of the RVOT flow profile into a single marker of patient outcome in PAH that appears to integrate both PVR and RV functions.

STUDY LIMITATIONS. The principal limitations of this study are the retrospective design and the fact that echocardiography and RHC data were not collected simultaneously. However, the temporal gap may underestimate rather than overestimate the relationship between echocardiography and RHC data. The significant pathophysiological relationship detected in this study had durability beyond the time delay, providing evidence for a strong relationship.

This study focused on notching observed in PAH (group 1 PH) and did not include other forms of PH. It has been reported that most patients with left-sided heart failure (group 2 PH) do not display RVOT flow velocity envelope profiles with notching (6). However, it is not clear whether patients with both passive and reactive PH associated with abnormal tone and/or remodeling of the precapillary pulmonary vascular bed (21) show a notched pattern and, if so, whether capillary wedge pressure has an effect on the notching pattern. Further studies evaluating RVOT profiles in group 2 PH patients may provide insight into the hemodynamics according to interaction between pulmonary vascular load and RV performance in reactive PH and whether or not it links to patient outcomes. In patients with thromboembolic diseases (group 4 PH), proximity to the site that the reflected wave originates from has a strong effect on the early

FIGURE 5 Association Between Type of RVOT Flow Profile and Clinical Outcomes



Kaplan-Meier survival curves indicate freedom from all-cause mortality or lung transplantation. Patients in group 1 with NN had the best outcomes. Of patients with notching, those with LDT had better survival than those with shorter DTs. A significant difference in outcome was seen in those with SDT by separating them into patients with higher V_{post}/V_{pre} (SH) and those with lower V_{post}/V_{pre} (SL). SDT = shorter mid-systolic deceleration time (<120 ms); other abbreviations as in Figures 1 and 2.

return and magnitude of the reflected wave. The relationship between early mid-systolic notching and proximal occlusive lesions rather than PVR has been well described (21,22). Mid-systolic notching is also observed in acute proximal pulmonary embolism or PA banding experimental animal models regardless of pulmonary vascular stiffness and resistance (5,15,21). In these cases, mid-systolic DT or mid-systolic flow reduction might not have correlated with pulmonary vascular load represented by a parameter such as PVR. However, the RVOT profile still results from the mechanical coupling of right ventricular after-load if not pulmonary vascular load and performance; so, we speculate that categorization of the RVOT systolic flow profile could be applied to a wide spectrum of pulmonary vascular diseases and may be linked to patient prognosis. However, this needs to be evaluated further. Due to the retrospective design, limited availability of recorded images restricted multiple measurements in some cases; and whether the profiles vary with time according to disease progression or treatment was not tested in this study. Further studies to investigate a consistent application of our findings across different causes and to observe longitudinal changes are warranted.

CONCLUSIONS

In PAH, Doppler flow velocity envelopes obtained through the RVOT are abnormal, with frequently notched profiles. Here the notched profile was characterized by mid-systolic flow reduction with short deceleration time, reflecting pulmonary vascular load, and the second flow acceleration echoing RV performance. Characterization of 1 Doppler indicator of pulmonary vascular load and RV performance acts as a single marker of patient prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The right ventricular outflow tract systolic flow profile, easily obtainable with standard transthoracic echocardiography, was semiquantitatively assessed in a large population of patients with pulmonary arterial hypertension. Recognition of signal notching, shortening of the mid-systolic deceleration time, and diminution of the late systolic flow velocity characterize features that profile pulmonary vascular hemodynamics and right ventricular function and stratify mortality risk.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the significance of changes in right ventricular outflow tract flow profile in patients with other forms of pulmonary vascular disease such as post-capillary pulmonary hypertension or thromboembolic disease. Additional studies should evaluate whether changes occur in right ventricular outflow tract systolic flow profiles in response to pulmonary vascular therapy.

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KEY WORDS flow, pulmonary hypertension, right ventricular function, survival

APPENDIX For a supplemental figure, please see the online version of this paper.