

ORIGINAL RESEARCH

Time-Velocity Integral of Left Ventricular Outflow Tract Predicts Worse Long-Term Survival in Pulmonary Arterial Hypertension



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ABSTRACT

BACKGROUND The time-velocity integral of the left ventricular outflow tract (TVI_{LVOT}) has been demonstrated to correlate with heart failure hospitalization and mortality, but the association of TVI_{LVOT} with the severity and prognosis of pulmonary arterial hypertension (PAH) has not been evaluated.

OBJECTIVES The aim of this study was to investigate the predictive value of baseline TVI_{LVOT} in PAH.

METHODS A total of 225 consecutive patients with a diagnosis of incident PAH were prospectively studied and echocardiology-derived TVI_{LVOT} was measured at enrollment followed by right heart catheterization examination within 48 hours. Cox proportional hazards analysis was performed to assess the association between baseline variables and mortality.

RESULTS During a median follow-up period of 33.8 months, 44 patients died of cardiovascular events. Baseline TVI_{LVOT} was significantly lower in the nonsurvivors compared with the survivors ($P < 0.001$). Baseline TVI_{LVOT} was positively correlated with stroke volume obtained by right heart catheterization ($r = 0.709$; $P < 0.001$), and inversely correlated with N-terminal pro-B-type natriuretic peptide ($r = -0.533$; $P < 0.001$), pulmonary vascular resistance ($r = -0.423$; $P < 0.001$). Multivariate analysis showed that baseline TVI_{LVOT} (hazard ratio: 0.856; 95% CI: 0.780-0.941; $P = 0.001$) was an independent predictor of cardiovascular mortality in PAH. Patients with a baseline TVI_{LVOT} < 17.1 cm (median value) had a significantly worse survival than those with a baseline TVI_{LVOT} ≥ 17.1 cm ($P < 0.001$).

CONCLUSIONS The findings of this study suggest that noninvasive TVI_{LVOT} provides a practical method to assess the severity and predict long-term outcome of PAH. (JACC: Asia 2022;2:235-243) © 2022 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/>).

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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****6MWD** = 6-minute walk distance**BSA** = body surface area**CI** = cardiac index**CMR** = cardiac magnetic resonance imaging**CO** = cardiac output**HR** = hazard ratio**LV** = left ventricular**LVOT** = left ventricular outflow tract**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**PAH** = pulmonary arterial hypertension**PVR** = pulmonary vascular resistance**RHC** = right heart catheterization**RV** = right ventricular**STR** = peak systolic tricuspid annular velocity of tissue Doppler**SV_{RHC}** = stroke volume obtained by right heart catheterization**TAPSE** = tricuspid annular plane systolic excursion**TTE** = transthoracic echocardiography**TVI** = time-velocity integral**TVI_{LVOT}** = time-velocity integral of left ventricular outflow tract**WHO-FC** = World Health Organization functional class

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature leading to increased pulmonary vascular resistance (PVR), right ventricular (RV) dysfunction, and ultimately, RV failure and death.^{1,2} Severe PAH frequently causes RV and right atrial dilation, abnormal interventricular septal motion, and compression of the left heart cavities.³⁻⁵ RV dilation and dysfunction also cause abnormal left ventricular (LV) filling and decreased cardiac output (CO).^{6,7} CO can be systematically assessed by transthoracic echocardiography (TTE), using the combination of the left ventricular outflow tract (LVOT) diameter and the time-velocity integral (TVI) of it recorded by pulsed wave Doppler. Lower CO by time-velocity integral of left ventricular outflow tract (TVI_{LVOT}) measurement has been shown to confer worse prognosis among patients with severe aortic stenosis despite preserved LV systolic function.⁸ TVI of LVOT and pulmonary artery have been demonstrated correlating with heart failure hospitalization and mortality in coronary artery disease.⁹ The normal limits of TVI_{LVOT} based on 95th percentiles of healthy adults are 15 to 29 cm.¹⁰ TVI_{LVOT} is a noninvasive echocardiographic parameter, which can be stable obtained for the evaluation of stroke volume and assessment of LV function. Low TVI_{LVOT} is suggestive of reduced LV function that is the long-term sequel of severe PAH. But the impact of TVI_{LVOT} in PAH has not been well established, and it is unclear whether it has correlation with disease severity and prognostic value in long-term survival of PAH patients.

Accordingly, the aim of this study was to investigate whether TVI_{LVOT} on admission is associated with the outcome of PAH patients.

METHODS

Between June 2016 and May 2020, patients with suspected PAH were screened for study enrollment at the time of referral for a clinically indicated TTE examination in our department. An extensive prognostic evaluation including clinical data, biological data, TTE, right heart catheterization (RHC), and 6-minute walk distance (6MWD) test was performed at baseline. Patients underwent clinically indicated D-dimers, pulmonary function test, high-resolution computed tomography, transabdominal ultrasound, or pulmonary ventilation and perfusion scan, if

necessary, to exclude other secondary causes. Female patients underwent urine pregnancy test to exclude pregnancy. Patients underwent RHC within no more than 48 hours after TTE examination to ensure hemodynamic stability. Patients with more than moderate left-sided valvular heart disease were excluded.^{11,12}

A total of 233 consecutive patients with a diagnosis of incident PAH (idiopathic, hereditary, or associated with connective tissue disease) were evaluated at inclusion, with PAH defined as mean pulmonary arterial pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤ 15 mm Hg, measured during RHC. A total of 8 patients were excluded due to a technically inadequate echocardiographic window or with atrial fibrillation or flutter. Thus, 225 patients were monitored in this prospective observational study. None of the patients were on treatment initially before the evaluation.

The investigation complied with the principles outlined in the Declaration of Helsinki. The study was approved by the Fuwai Hospital research ethics committee, and informed consent was obtained from each patient.

Baseline assessments included PAH signs and symptoms, vital signs, World Health Organization functional class (WHO-FC), 6MWD, Borg dyspnea score (immediately after the 6MWD test) and clinical laboratory parameters including: blood chemistry, hematology, arterial blood gas analysis, and measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Patients were followed up until May 31, 2021, and the median follow-up period was 33.8 months. At the end of the study, the status of each patient was confirmed by a review of their medical records, phone contact, and the Social Security Death Index. The endpoint of the study was defined as cardiac death, and 5 patients (2.2%) were lost to follow-up. Patients lost to follow-up were censored as alive on the last day of contact.

Patients underwent a standard TTE examination with electrocardiogram tracings as clinically indicated with a GE Vingmed Vivid E9 Ultrasound (GE, Vingmed Ultrasound) according to the recommendations of the American Society of Echocardiography.¹³

The complete set of standardized views included the parasternal long-axis, parasternal RV inflow, parasternal short-axis, apical 4-chamber, apical 5-chamber, RV-focused apical 4-chamber, and subcostal views.^{13,14}

TVI_{LVOT} (in centimeters) was obtained by placing a 1- to 2-mm pulsed wave Doppler sample volume in the proximal LVOT from an apical 5-chamber view,

TABLE 1 Baseline Clinical Characteristics, Hemodynamics and Echocardiographic Features of the Study Cohort

	Whole Study Population (N = 225)	Survivors (n = 181)	Nonsurvivors (n = 44)	P Value ^a
Age, y	34.6 ± 17.0	35.3 ± 16.7	31.7 ± 18.4	0.503
Sex, female	170 (75.6)	138 (76.2)	32 (72.7)	0.626
Height, cm	160.0 (155.0-166.0)	160.0 (155.0-165.8)	160.0 (152.0-168.0)	0.516
Weight, kg	54.0 (48.0-61.0)	54.0 (48.0-62.0)	53.0 (45.0-59.0)	0.399
BSA, m ²	1.51 (1.41-1.63)	1.51 (1.41-1.63)	1.51(1.38-1.60)	0.380
HR _{RHC} , beats/min	80 ± 13	78 ± 12	89 ± 13	<0.001
Diagnosis				<0.001
IPAH	158	118	40	
CTD-PAH	67	63	4	
WHO-FC				0.007
I-II	80 (35.6)	72 (39.8)	8 (18.2)	
III-IV	145 (64.4)	109 (60.2)	36 (81.8)	
6MWD, m	380.0 (300.0-447.0)	400.0 (342.3-460.0)	267.0 (50.0-358.0)	<0.001
NT-proBNP, pg/mL	963.0 (144.0-2,000.0)	752.5 (137.0-2,000.0)	2,000.0 (253.0-3,742.0)	0.001
Hemodynamics				
Systolic BP, mm Hg	111 ± 16	113 ± 16	108 ± 13	0.053
Mean PAP, mm Hg	58 ± 18	56 ± 17	67 ± 15	<0.001
PVR, Wood Units	14.0 ± 7.9	12.3 ± 6.5	20.4 ± 9.7	<0.001
Cardiac index, L/min/m ²	2.87 ± 1.06	2.98 ± 1.05	2.44 ± 0.98	0.003
Echocardiogram				
TAPSE, cm	1.60 ± 0.43	1.67 ± 0.40	1.29 ± 0.41	<0.001
STr, cm/s	10.3 ± 2.6	10.7 ± 2.4	9.0 ± 2.9	<0.001
TVI _{LVOT} , cm	17.1 (14.0-20.3)	18.2 (15.3-20.8)	13.4 (11.0-15.3)	<0.001
LV ejection fraction, %	72.98 ± 8.13	72.73 ± 7.82	73.97 ± 9.29	0.382
Pericardial effusion	57 (25.3)	43 (23.8)	14 (31.8)	0.136
Therapy				0.682
Only traditional therapy	9	8	1	
Monotherapy	124	101	23	
Combination therapy	92	72	20	

Values are mean ± SD, n (%), or median (IQR). ^aP value is for survivors vs nonsurvivors.

6MWD = 6-min walk distance; BP = blood pressure; BSA = body surface area; CTD-PAH = pulmonary arterial hypertension associated with connective tissue diseases; HR_{RHC} = heart rate obtained by right heart catheterization; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; STr = peak systolic tricuspid annular velocity of tissue Doppler; TAPSE = tricuspid annular plane systolic excursion; TVI_{LVOT} = time-velocity integral of left ventricular outflow tract; WHO-FC = World Health Organization functional class.

with the interrogation beam directed across the LVOT. The filter was optimized to visualize a clear border of the spectral Doppler signal, and the outer boundary of the signal was traced to calculate the TVI. Three consecutive heart beats were recorded, and the average was measured.¹⁵

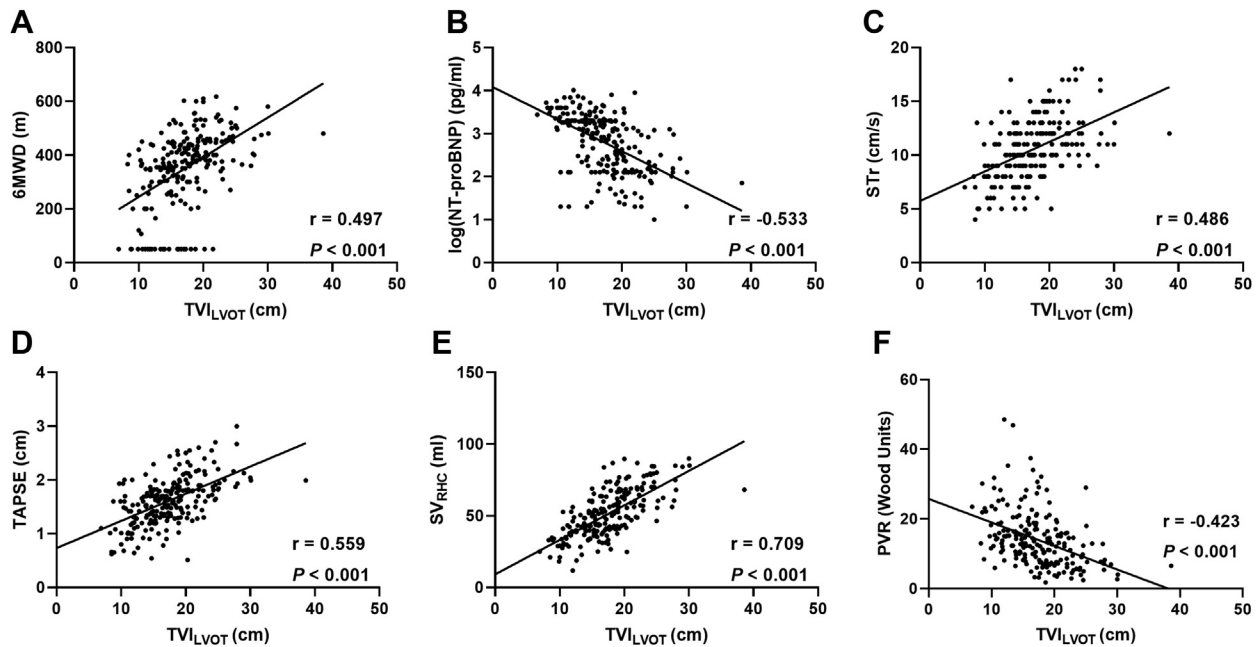
The tricuspid annular plane systolic excursion (TAPSE) and peak systolic tricuspid annular velocity (STr) of tissue Doppler were determined as described previously.¹⁶⁻¹⁸

A single cardiologist (J.Y.), blinded to the clinical and laboratory information, evaluated each comprehensive resting echocardiogram.

Hemodynamic evaluation by RHC was performed at baseline as described previously^{19,20} to obtain measurements of pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure,

CO, PVR, and heart rate. CO was calculated by thermodilution as the mean of 3 consecutive measurements not varying by more than 10%. Cardiac index was calculated by dividing CO by body surface area (BSA). The stroke volume obtained by RHC (SV_{RHC}) was calculated as CO in L/min divided by heart rate in the process of RHC. All patients had a vasodilatory test with inhaled aerosolized iloprost during RHC as described previously.²⁰

The main analysis was performed using SPSS software version 20.0 (Statistic Package for Social Science). Demographic, clinical, and laboratory data were summarized as frequency (%), median (IQR), and mean ± SD, and compared by means of the chi-square test, Student *t*-test, 1-way analysis of variance, or Mann-Whitney *U*-test as appropriate. Correlation between baseline TVI_{LVOT} and clinical,

FIGURE 1 Correlation Between TVI_{LVOT} and Clinical, Echocardiographic, and RHC Parameters

Baseline TVI_{LVOT} was positively and significantly correlated with 6MWD ($r = 0.497$; $P < 0.001$) (A), STr ($r = 0.486$; $P < 0.001$) (C), TAPSE ($r = 0.559$; $P < 0.001$) (D), and inversely and significantly correlated with NT-proBNP ($r = -0.533$; $P < 0.001$) (B), PVR ($r = -0.423$; $P < 0.001$) (F). Baseline TVI_{LVOT} and SV_{RHC} were more closely correlated, with $r = 0.709$; $P < 0.001$ (E). 6MWD = 6-minute walk distance; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SV_{RHC} = stroke volume obtained by right heart catheterization; STr = peak systolic tricuspid annular velocity of tissue Doppler; TAPSE = tricuspid annular plane systolic excursion; TVI_{LVOT} = time-velocity integral of left ventricular outflow tract.

echocardiographic, and invasive hemodynamic variables was assessed using Pearson's correlation or Spearman's correlation.

Cox proportional hazards analysis was performed to assess the association between baseline variables and mortality. The following variables were tested: WHO-FC, 6MWD, NT-proBNP, PVR, SV_{RHC} , TVI_{LVOT} , STr, and TAPSE. Multivariate analysis was then performed using all variables with $P < 0.10$ in the univariate model. Linearity and proportional hazard assumption were tested and satisfied for all covariates. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. A P value of < 0.05 was considered statistically significant.

RESULTS

A total of 225 patients were monitored in this prospective observational study. The female/male sex ratio was 3.2:1 ($n = 170/55$). Overall, 11 of 225 patients (4.9%) showed an acute vasodilator response.

During a median follow-up period of 33.8 months, there were 44 deaths, all of which were cardiovascular. A comparison of the demographic, baseline hemodynamic, and echocardiographic features of the 44 nonsurvivors with the 181 survivors is shown in Table 1. Most nonsurvivors were in WHO-FC III/IV (36/44, 81.8%) at baseline. In comparison with survivors, nonsurvivors were characterized by more severe hemodynamic compromise at diagnosis (Table 1), with a significantly higher PVR (20.4 ± 9.7 vs 12.3 ± 6.5 WU; $P < 0.001$). Concerning the variables obtained by echocardiography, nonsurvivors had a lower TVI_{LVOT} (median: 13.4 [IQR: 11.0-15.3] vs 18.2 [IQR: 15.3-20.8] cm; $P < 0.001$), TAPSE (1.29 ± 0.41 vs 1.67 ± 0.40 cm; $P < 0.001$), and STr (9.0 ± 2.9 vs 10.7 ± 2.4 cm/s; $P < 0.001$).

There were 216 patients (96.0%) receiving PAH-targeted therapies after the baseline evaluation. Over one-half of the patients (61.8%) received a phosphodiesterase-5 inhibitor. A combination of at least 2 types of therapy was commonly used in the study population (42.2%). There was no difference in

TABLE 2 Univariate and Multivariate Analysis Relating Survival to Selected Baseline Variables

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
WHO-FC	2.045	1.166-3.589	0.013	–	–	–
6MWD	0.994	0.992-0.996	<0.001	0.997	0.994–0.999	0.002
NT-proBNP	1.000	1.000-1.000	0.007	–	–	–
PVR	1.082	1.054-1.111	<0.001	1.045	1.011–1.081	0.009
SV _{RHC}	0.939	0.917-0.960	<0.001	–	–	–
TVI _{LVOT}	0.789	0.727-0.855	<0.001	0.855	0.779–0.940	0.001
TAPSE	0.142	0.070-0.288	<0.001	–	–	–
STr	0.779	0.684-0.887	<0.001	–	–	–

SV_{RHC} = stroke volume obtained by right heart catheterization; other abbreviations as in Table 1.

the distribution of only traditional therapy, monotherapy and combination therapy between non-survivors and survivors ($P = 0.682$).

In the total study population, the 1-year, 3-year, and 4-year survival rates were 92%, 80%, and 76%, respectively, estimated by the Kaplan-Meier method.

Baseline TVI_{LVOT} was positively and significantly correlated with 6MWD ($r = 0.497$; $P < 0.001$) (Figure 1A), STr ($r = 0.486$; $P < 0.001$) (Figure 1C), and TAPSE ($r = 0.559$; $P < 0.001$) (Figure 1D), and inversely and significantly correlated with NT-proBNP ($r = -0.533$; $P < 0.001$) (Figure 1B) and PVR ($r = -0.423$; $P < 0.001$) (Figure 1F). Baseline TVI_{LVOT} and SV_{RHC} were more closely correlated ($r = 0.709$; $P < 0.001$) (Figure 1E). These correlations remained significant after correction for the possible confounding effects of age, sex, heart rate, and BSA.

Univariate Cox proportional hazards analysis with reference to the baseline assessment demonstrated that WHO-FC, 6MWD, NT-proBNP, PVR, SV_{RHC}, TVI_{LVOT}, STr, and TAPSE predicted mortality in PAH (Table 2).

Multivariate Cox proportional hazards analysis was performed using baseline variables. Multivariate analysis showed that 6MWD (hazard ratio [HR]: 0.997; 95% CI: 0.994-0.999; $P = 0.002$), PVR (HR: 1.045; 95% CI: 1.011-1.081; $P = 0.009$), and TVI_{LVOT} (HR: 0.855; 95% CI: 0.779-0.940; $P = 0.001$) at baseline were independent predictors of prognosis in PAH (Table 2).

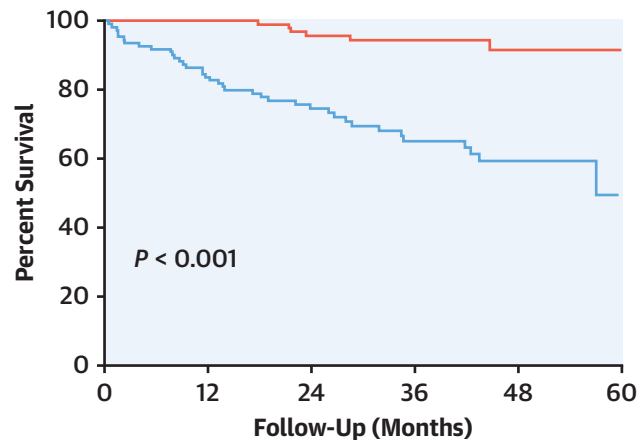
Patients with a baseline TVI_{LVOT} <17.1 cm (median value) had a significantly worse survival than those with a baseline TVI_{LVOT} ≥17.1 cm (log-rank test $P < 0.001$) (Central Illustration). According to the quartile of the TVI_{LVOT}, patients were divided into 4 subgroups (Q1: TVI_{LVOT} <14.0 cm; Q2: 14.0 ≤ TVI_{LVOT} <17.1 cm; Q3: 17.1 ≤ TVI_{LVOT} <20.3 cm; Q4: TVI_{LVOT} ≥20.3 cm). Survival differences across TVI_{LVOT} quartiles were assessed by the Kaplan-Meier

method and compared using the log-rank test. Patients with a lower TVI_{LVOT} were significantly more likely to have a higher mortality (log-rank test $P < 0.001$) (Central Illustration). Pairwise comparison over strata showed the following P values between subgroups: Q1 and Q2 ($P = 0.010$), Q1 and Q3 ($P < 0.001$), Q1 and Q4 ($P < 0.001$), Q2 and Q3 ($P = 0.007$), Q2 and Q4 ($P = 0.005$), and Q3 and Q4 ($P = 0.904$), respectively. Patients in subgroup Q2 had a survival rate of 87%, 83%, and 74% at 1, 2, and 4 years, respectively, which was higher than the corresponding survival rates in patients in subgroup Q1 (78%, 63%, and 47%, respectively). The survival rates at 1, 2, and 4 years in both subgroup Q3 and Q4 were higher.

Among the 4 subgroups, there were statistically significant differences in STr ($P < 0.001$) and TAPSE ($P < 0.001$), the 2 most common echocardiographic parameters of RV function. Clinical and hemodynamic variables for evaluation of disease severity (WHO-FC, 6MWD, NT-proBNP, PVR) were also significantly different (Table 3).

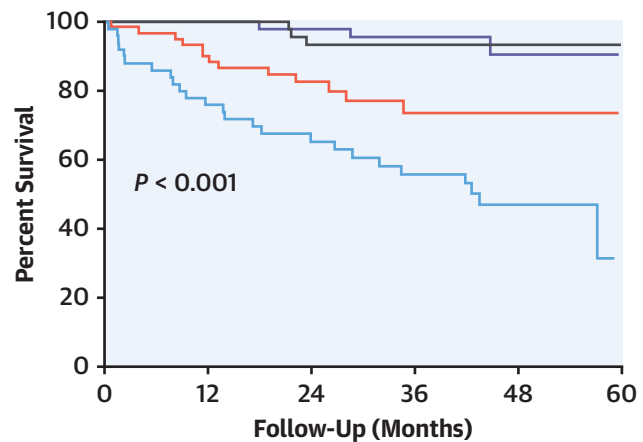
DISCUSSION

In this study of 225 patients with incident PAH, patients with a baseline TVI_{LVOT} <17.1 cm had dramatically reduced survival over a median follow-up period of 33.8 months. Patients with a TVI_{LVOT} <14.0 cm had an especially poorest outcome. Our data showed that a lower TVI_{LVOT} at baseline was associated with more severe RV dysfunction and worse long-term outcome. Our research adopted a noninvasive and practical method to assess prognostic value of an echocardiographic parameter TVI_{LVOT} in PAH, which is the novelty of this study. TVI_{LVOT} is readily measurable by Doppler echocardiography and expresses the average linear distance travelled by red blood cells during systole.²¹ The correlation between CO measured by TVI_{LVOT} and by

CENTRAL ILLUSTRATION Survival Curves According to the Time-Velocity Integral of Left Ventricular Outflow Tract**A**

No. at risk

— TVI _{LVOT} (cm) <17.1 cm	111	92	63	43	19
— TVI _{LVOT} (cm) ≥17.1 cm	114	113	83	61	24

B

No. at risk

— TVI _{LVOT} (cm) <14.0 cm	50	38	28	22	12
— 14.0 ≤ TVI _{LVOT} (cm) <17.1 cm	61	54	35	21	7
— 17.1 ≤ TVI _{LVOT} (cm) <20.3 cm	57	57	40	31	9
— TVI _{LVOT} (cm) ≥20.3 cm	57	56	43	30	15

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Survival curves according to the (A) median and (B) quartiles of TVI_{LVOT}. Patients with a baseline TVI_{LVOT} <17.1 cm (median value) had a significantly worse survival than those with a baseline TVI_{LVOT} ≥17.1 cm ($P < 0.001$) (A). Survival differences across TVI_{LVOT} quartiles (Q1: TVI_{LVOT} <14.0 cm; Q2: 14.0 ≤ TVI_{LVOT} <17.1 cm; Q3: 17.1 ≤ TVI_{LVOT} <20.3 cm; Q4: TVI_{LVOT} ≥20.3 cm) were assessed by the Kaplan-Meier method. Patients with a lower TVI_{LVOT} had a higher mortality ($P < 0.001$) (B). TVI_{LVOT} = time-velocity integral of left ventricular outflow tract.

TABLE 3 Variables for Evaluation of Disease Severity Differ Among Subgroups Q1, Q2, Q3, and Q4

	TVI _{LVOT} Quartiles				P Value
	Q1 (n = 50)	Q2 (n = 61)	Q3 (n = 57)	Q4 (n = 57)	
BSA, m ²	1.49 (1.40-1.61)	1.56 (1.48-1.71)	1.51 (1.41-1.63)	1.50 (1.39-1.60)	0.088
WHO-FC					0.021
I-II	9 (18.0)	20 (32.8)	25 (43.9)	26 (45.6)	
III-IV	41 (82.0)	41 (67.2)	32 (56.1)	31 (54.4)	
6MWD, m	253.5 (50.0-358.8)	355.5 (306.8-428.8)	400.0 (350.0-460.0)	450.0 (380.0-476.3)	<0.001
NT-proBNP, pg/mL	2,336.0 (1,800.0-4,000.0)	1,582.5 (552.3-2,000.0)	661.0 (197.0-1,800.0)	136.0 (125.0-391.8)	<0.001
PVR, Wood Units	18.75 ± 9.05	14.94 ± 6.72	13.05 ± 7.68	9.63 ± 5.46	<0.001
STr, cm/s	8.67 ± 2.50	9.78 ± 2.39	10.98 ± 2.21	11.70 ± 2.39	<0.001
TAPSE, cm	1.29 ± 0.39	1.49 ± 0.33	1.67 ± 0.34	1.90 ± 0.41	<0.001

Values are median (IQR), n (%), or mean ± SD. Quartile of the TVI_{LVOT} (Q1: TVI_{LVOT} <14.0 cm; Q2: 14.0 ≤ TVI_{LVOT} <17.1 cm; Q3: 17.1 ≤ TVI_{LVOT} <20.3 cm; Q4: TVI_{LVOT} ≥20.3 cm). Abbreviations as in Table 1.

cardiac catheterization has been validated.^{22,23} Ristow et al⁹ found that reduced TVI (≤18 cm in the LVOT or ≤17 cm in the pulmonary artery) predicted heart failure hospitalization and mortality independently of clinical and other echocardiographic parameters in ambulatory adults with coronary artery disease. The prognostic value of TVI_{LVOT} has not to our knowledge been independently evaluated among individuals with PAH.

In the present study, a TVI_{LVOT} <17.1 cm identified patients with PAH who had more advanced RV dysfunction and an especially poorer long-term outcome, as compared with subjects with a TVI_{LVOT} of ≥17.1 cm. According to the interquartile of TVI_{LVOT}, patients were divided into 4 subgroups. The worst long-term prognosis was observed in patients in subgroup Q1 (TVI_{LVOT} <14.0 cm). The prognostic significance of TVI_{LVOT} persisted after adjustment for several previously recognized echocardiographic and invasive predictors of outcome. Our results showed that TVI_{LVOT} and SV_{RHC} were closely correlated, with $r = 0.709$; $P < 0.001$. These correlations remained significant after correction for possible confounding effects. Vonk Wolferen et al²⁴ found that a low stroke volume measured by cardiac magnetic resonance imaging (CMR) at baseline is predictive of poor survival in idiopathic PAH. CO in incident PAH has been investigated in several studies and was found to provide prognostic information.^{24,25} Our results have suggested that TVI_{LVOT} is a predictor of survival in PAH patients.

The TVI of transmitral flow has been used in contemporary practice to optimize biventricular pacing settings in cardiac resynchronization therapy.²⁶ The TVI was also used in the calculation of aortic valve area using a continuity equation.²⁷ The TVI in the aortic arch has been shown to predict mortality

after acute myocardial infarction.²⁸ Lower cardiac output by TVI_{LVOT} measurement has been shown to confer a worse prognosis among patients with aortic stenosis and preserved LV systolic function.⁸ Our findings extend the clinical use of the TVI as a useful parameter when measured from the LVOT in predicting long-term prognosis in PAH.

The TVI does not vary with BSA and is a universal expression of stroke volume that is comparable among individuals of different body size. Compared with cardiac output, RV diastolic volume, and LV end-diastolic volume, TVI_{LVOT} has the advantage that it is independent of BSA and sex. Because the TVI can be measured from 1 Doppler waveform, it is usually possible to make the measurement even if technically difficult, and it is relatively simple. TVI_{LVOT} may predict PAH disease severity or mortality among individuals with technically difficult imaging windows, where structural measurements cannot be made accurately.

Geometric alterations and functional decline of the RV results in LV diastolic impairment in patients with PAH. Finally, 1 of the most important consequences of severe PAH is a decrease in CO. Prolonged contraction and shortened filling time of the RV in PAH impair RV output and lead to adverse ventricular-ventricular interactions by limiting LV preload and shortening the filling time of LV. These phenomena have been demonstrated both by CMR and by echocardiography in which septal shift, LV underfilling, and the ratio of RV systolic to diastolic duration are linked to clinical outcome.²⁹⁻³¹ Impaired LV filling was associated with early mortality, highlighting the significance of ventricular interdependence in PAH.⁷ In the hypertensive RV, not only is septal function impaired, but the configuration of the displaced septum into the LV may increase local wall shear stress and regional

injury. An abnormal curvature of the interventricular septum is considered 1 of the echocardiographic hallmarks of pulmonary hypertension. The decrease in transverse diameter and area of LV, TVI_{LVOT} , and isovolumic relaxation time in PAH is a reflection of impaired LV filling. Impaired LV filling in RV pressure overload might be the result of 2 mechanisms: a decrease in stroke volume or compression of the LV due to an increased RV end-diastolic volume.

PVR and NT-proBNP, markers of increased RV afterload and increased ventricular wall stress, were significantly higher in subgroups with a lower TVI_{LVOT} ($P < 0.001$) (Table 3). STr ,¹⁷ TAPSE,³² and 6MWD were markers of severity of RV dysfunction and degree of symptoms in patients with PAH. TVI_{LVOT} was correlated to STr ($r = 0.486$; $P < 0.001$), TAPSE ($r = 0.559$; $P < 0.001$), and 6MWD ($r = 0.497$; $P < 0.001$), suggesting that reduced TVI_{LVOT} is associated with reduced RV function and exercise capacity in PAH.

STUDY LIMITATIONS. First, the cohort was recruited from a single center specializing in pulmonary vascular disease. These data should be reproduced in other centers to validate the prognostic value of the echocardiographic parameters. Second, this study included patients with underlying pathogenesis of PAH, but those with repaired or unrepaired congenital heart disease were excluded. As such, our conclusions cannot be extrapolated to that population. Third, we did not compare TVI_{LVOT} against a volumetric standard of RV function, such as angiographic or CMR-derived RV ejection fraction. However, the relationship of TVI_{LVOT} to SV_{RHC} was well established in the present study. Moreover, the current study was not designed to examine the effects of therapy on TVI_{LVOT} and how such effects relate to outcome, which will be an important future application of TVI_{LVOT} .

CONCLUSIONS

In summary, the novel findings of this study suggested that noninvasive TVI_{LVOT} played an important

role in predicting the outcome of PAH and identifying PAH patients which requires more intensive therapy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Echocardiographic time-velocity integral of left ventricular outflow tract provides prognostic value, not only in severe aortic stenosis, heart failure, and coronary artery disease, but also in pulmonary arterial hypertension, which has been confirmed in this relatively large cohort. Our findings may allow clinicians to identify PAH patients who requires more intensive therapy.

TRANSLATIONAL OUTLOOK: Further studies focusing on the effects of therapy on time-velocity integral of left ventricular outflow tract in different types of pulmonary hypertension are still needed.

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