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 (TVILVOT) has been demonstrated to correlate with heart failure hospitalization and mortality, but the association of TVILVOT 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 TVILVOT in PAH.

METHODS A total of 225 consecutive patients with a diagnosis of incident PAH were prospectively studied and echocardiology-derived TVILVOT 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 TVILVOT was significantly lower in the nonsurvivors compared with the survivors (P < 0.001). Baseline TVILVOT 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 TVILVOT (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 TVILVOT < 17.1 cm (median value) had a significantly worse survival than those with a baseline TVILVOT ≥ 17.1 cm (P < 0.001).

CONCLUSIONS The findings of this study suggest that noninvasive TVILVOT 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/).
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 Kuwait 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,
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 (SVRHC) 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,

| TABLE 1 Baseline Clinical Characteristics, Hemodynamics and Echocardiographic Features of the Study Cohort |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|----------------------------------|
| **Whole Study Population**                       | **Survivors** (n = 181)                          | **Nonsurvivors** (n = 44)                         |
| Age, y                                           | 34.6 ± 17.0                                      | 35.3 ± 16.7                                      | 31.7 ± 18.4          |
| Sex, female                                      | 170 (75.6)                                       | 138 (76.2)                                       | 32 (72.7)            |
| Height, cm                                       | 160.0 (155.0-166.0)                              | 160.0 (155.0-163.8)                              | 160.0 (152.0-168.0)  |
| Weight, kg                                       | 54.0 (48.0-61.0)                                 | 54.0 (48.0-62.0)                                 | 53.0 (45.0-59.0)     |
| BSA, m²                                          | 1.51 (1.41-1.63)                                 | 1.51 (1.41-1.63)                                 | 1.51(1.38-1.60)      |
| HR_{RHC}, beats/min                             | 80 ± 13                                          | 78 ± 12                                          | 89 ± 13              |
| 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)   |
| 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) |
| **Hemodynamics**                                |                                                   |                                                  | 0.001               |
| Systolic BP, mm Hg                              | 111 ± 16                                         | 113 ± 16                                         | 108 ± 13            |
| Mean PAP, mm Hg                                 | 58 ± 18                                          | 56 ± 17                                          | 67 ± 15             |
| PVR, Wood Units                                 | 14.0 ± 7.9                                       | 12.3 ± 6.5                                       | 20.4 ± 9.7          |
| Cardiac index, L/min/m²                         | 2.87 ± 1.06                                      | 2.98 ± 1.05                                      | 2.44 ± 0.98         |
| **Echocardiogram**                              |                                                   |                                                  | 0.003               |
| TAPSE, cm                                       | 1.60 ± 0.43                                      | 1.67 ± 0.40                                      | 1.29 ± 0.41         |
| STr, cm/s                                       | 10.3 ± 2.6                                       | 10.7 ± 2.4                                       | 9.0 ± 2.9           |
| TVI_{LVOT}, cm                                  | 17.1 (14.0-20.3)                                 | 18.2 (15.3-20.8)                                 | 13.4 (11.0-15.3)    |
| LV ejection fraction, %                         | 72.98 ± 8.13                                     | 72.73 ± 7.82                                     | 73.97 ± 9.29        |
| Pericardial effusion                            | 57 (25.3)                                        | 43 (23.8)                                        | 14 (31.8)           |
| **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). *P 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.
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, SVRHC, TVILVOT, 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 \( (20.4 \pm 9.7 \text{ vs } 12.3 \pm 6.5 \text{ WU}; P < 0.001) \). Concerning the variables obtained by echocardiography, nonsurvivors had a lower TVILVOT (median: 13.4 [IQR: 11.0-15.3] 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
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 TVILVOT 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 TVILVOT and SVRHC 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, SVRHC, TVILVOT, 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 TVILVOT (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 TVILVOT <17.1 cm (median value) had a significantly worse survival than those with a baseline TVILVOT ≥17.1 cm (log-rank test $P < 0.001$) (Central Illustration). According to the quartile of the TVILVOT, patients were divided into 4 subgroups (Q1: TVILVOT <14.0 cm; Q2: 14.0 ≤ TVILVOT <17.1 cm; Q3: 17.1 ≤ TVILVOT <20.3 cm; Q4: TVILVOT ≥20.3 cm). Survival differences across TVILVOT quartiles were assessed by the Kaplan-Meier method and compared using the log-rank test. Patients with a lower TVILVOT 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 TVILVOT <17.1 cm had dramatically reduced survival over a median follow-up period of 33.8 months. Patients with a TVILVOT <14.0 cm had an especially poorest outcome. Our data showed that a lower TVILVOT 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 TVILVOT in PAH, which is the novelty of this study. TVILVOT 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 TVILVOT and by
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 (Q): 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.
cardiac catheterization has been validated.22,23 Ris-tow et al23 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 SVRHC 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 transmural 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

| Variable | Value | Q1 (n = 50) | Q2 (n = 61) | Q3 (n = 57) | Q4 (n = 61) | P Value |
|----------|-------|------------|------------|------------|------------|---------|
| BSA, m²  | 1.49  | 1.40-1.61  | 1.48-1.71  | 1.41-1.63  | 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) | 1,525.5 (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 |
| STi, 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 (Q): 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.
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). ST_{r}, TAPSE, and 6MWD were markers of severity of RV dysfunction and degree of symptoms in patients with PAH. TVI_{LVOT} was correlated to ST_{r} (r = 0.489; 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 pathogeneses 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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