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EDITORIAL COMMENT

# Right or Left Heart Failure

## Partners in Crime*

Cho-Kai Wu, MD, PhD,[a] Ning-I Yang, MBChB,[b] Chung-Lieh Hung, MD, MSc, PhD[c,d]

Pulmonary arterial hypertension (PAH) caused by relative blood flow obstruction proximal to the lung capillary bed, namely precapillary PAH, is a progressive disorder. It affects the whole cardiopulmonary unit, with initial adaptation of the right ventricle to the increased afterload and subsequent right ventricular (RV) dysfunction with eventual right heart failure. Beyond the essential role of pulmonary vascular hemodynamics assessment and functional RV evaluation, echocardiography also carries important prognostic information.[1] Due to constraints imposed by the pericardium in PAH, changes in RV heart size are limited, with the featured geometry of interventricular septum bowing toward and compressing the left ventricle (**Figure 1**). In the later stages of PAH, biventricular dysfunction may occur through ventricular interdependency. The impaired filling of the left ventricle caused by the leftward septal bowing and the reduced RV stroke volume causes atrophic left ventricular (LV) remodeling leading to subsequent inefficient contractile function.[2]

Traditional echocardiography assessment in PAH may start from Doppler assessment of the tricuspid regurgitation velocity, which correlates positively with systolic pulmonary artery pressure. In clinical practice, commonly used RV indices in patients with PAH are: RV dimensions and RV fractional area change by two-dimensional echocardiography, tricuspid annular plane systolic excursion, eccentricity index, RV myocardial performance index, tissue Doppler imaging-derived peak systolic tricuspid annular velocity, right atrial end-systolic size, and pericardial effusion.[3] Moreover, advanced RV longitudinal strain-based indices showed promise as useful subclinical markers of RV decline beyond several conventional measures (eg, RV fractional area change, tricuspid annular plane systolic excursion).[4] Risk stratification of patients with PAH allows assessment of patients' prognosis and guidance of therapy; however, pericardial effusion and right atrial size are the only 2 echocardiography parameters mentioned in contemporary guidelines and risk scores.[1,5] Hence, more robust echocardiographic information is required to provide useful clinical risk stratification.

In this issue of *JACC: Asia*, Liu et al[6] investigated the utilization of a Doppler-based LV outflow tract time-velocity integral ($TVI_{LVOT}$) to treatment-naive patients with PAH (**Figure 1**). The appreciable sample size (N = 225) of patients with PAH prospectively enrolled by Liu et al were diagnosed by using invasive right heart catheterization (RHC). The investigators reported a significantly higher RHC-determined pulmonary vascular resistance (PVR) in PAH nonsurvivors than in survivors (20.4 WU vs 12.3 WU; $P < 0.001$). PAH nonsurvivors showed remarkably worsened RV metrics concomitant with a significant reduction in $TVI_{LVOT}$, compared with that among survivors (13.4 cm vs 18.2 cm; all, $P < 0.001$). Notably, LV ejection fraction showed no differences between PAH survivors and nonsurvivors (72.73% vs 73.97%). Because the left ventricle in PAH may be underfilled with inadequate preload rather than being overstretched, the remarkably high N-terminal pro-B-type natriuretic peptide levels in the worst $TVI_{LVOT}$ quartile group (2,336.0 pg/mL vs 136.0 pg/mL in the

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From the [a]Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan; [b]Department of Cardiology, Chang Gung Memorial Hospital, Keelung, Chang Gung University College of Medicine, Taoyuan, Taiwan; [c]Institute of Biomedical Sciences, Mackay Medical College, New Taipei City, Taiwan; and the [d]Division of Cardiology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan.

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**FIGURE 1 Geometric Alteration and Diminished Left Heart Pump Function in PAH**

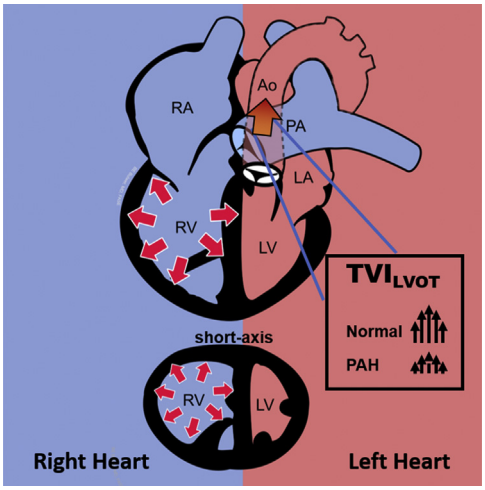


Illustration showing biventricular geometric alterations in pulmonary arterial hypertension (PAH) from leftward shift of the interventricular septum **(red arrows)** compressing the left ventricle (LV), resulting in extracardiac constraint limiting left ventricular filling. Diminished left ventricular outflow tract time-velocity integral ($TVI_{LVOT}$) may occur from restricted left ventricular pump function, reflecting ventricular-interdependence pathophysiology in PAH. Ao = aorta; LA = left atrium; PA = pulmonary artery; RA = right atrium; RV = right ventricle.

highest $TVI_{LVOT}$ quartile) may be attributed to RV dysfunction.[7] This observation is further supported by the remarkably higher PVR in the lowest $TVI_{LVOT}$ quartile group (18.75 WU vs 9.63 WU in the highest $TVI_{LVOT}$ quartile, respectively) and corresponding poor prognosis compared with that of the other quartile groups (Q1 vs Q2, $P = 0.01$; Q1 vs Q3 and Q4, both $P < 0.001$ for log-rank survival, respectively). $TVI_{LVOT}$ reduction closely paralleled stroke volume decline ($r = 0.709$; $P < 0.001$) and was correlated with PVR elevation and RV deteriorations. Multivariate survival analysis revealed that $TVI_{LVOT}$ remained an unchanged predictor of PAH survival (adjusted HR: 0.855; 95% CI: 0.779-0.940; $P = 0.001$) after accounting for several key baseline clinical measures, including functional status (World Health Organization functional class and 6-minute walking distance), N-terminal pro-B-type natriuretic peptide, and RV functional metrics.

Liu et al[6] should be congratulated for their work, as for the first time they proved that noninvasive $TVI_{LVOT}$ can be a practical method in assessing disease severity and long-term prognosis from a large PAH cohort of Asian patients. Although most previously published data focus on the RV function of PAH,[8] Liu et al[6] reported the association of $TVI_{LVOT}$ with RV function, exercise capacity, and prognosis. The investigators also set up a cutpoint ($TVI_{LVOT}$ <17.1 cm) to identify those PAH patients with worst survival. $TVI_{LVOT}$ is independent of body surface area and sex, is less technically dependent, and has proven to be a prognostic marker in the clinical settings of decompensated heart failure and pulmonary embolism.[9,10] The paper by Liu et al[6] pointed out the well-known pathophysiology of ventricular interdependence underlying PAH. The promising findings by using $TVI_{LVOT}$ as a surrogate prognostic marker in PAH also highlighted the drawback of applying LV ejection fraction as the predominant risk stratifier in several clinical scenarios, including PAH.

Nevertheless, several limitations need to be considered when interpreting the results from this study.[6] First, the strong relationship between $TVI_{LVOT}$ and prognosis in patients with PAH, has not been validated in another cohort. The patients were recruited from a single, pulmonary vascular disease center, and functional status (World Health Organization functional class) in the current cohort was mostly III to IV, which limited the generalizability of these results to general patients with PAH. Second, the authors did not include more detailed echocardiographic information reflecting the extent of RV constraint or impaired LV filling (eg, E/e′ by echocardiography or pulmonary capillary wedge pressure by RHC), nor were RV geometric alterations (eg, RV fractional area change, LV transverse diameter, RV/LV diameter ratio) or advanced imaging modalities (eg, strain imaging) incorporated. Some recent data suggested a role for right heart image scores[7,11]; perhaps the authors could compare the difference between $TVI_{LVOT}$ and those scores for predicting prognosis in the same cohort. Third, it is also important to emphasize that the current study focuses on incident treatment-naive patients. Finally, the authors did not compare the change of $TVI_{LVOT}$ after treatment. It is still unknown whether $TVI_{LVOT}$ could be a target for adjustment of treatment strategies.

The current study[6] has provided evidence that measuring $TVI_{LVOT}$ in patients with PAH could possibly identify those who require more intensive therapy. Some future clinical implications from this current study remain to be explored. First, measuring $TVI_{LVOT}$ can be useful for stratifying randomization strategies in phase 2 clinical trials, as matching based only on clinical functional class may not fully capture the complexity of the disease

progress and all variables. Second, $TVI_{LVOT}$ can serve as a clinically convenient "benchmark" against which the incremental value of novel biomarkers can be assessed. Combining this Doppler-based LV indicator along with right heart functional parameters may therefore improve risk stratification for patients with PAH or RV failure. Third, theoretically, patients manifesting lower $TVI_{LVOT}$ could be monitored more closely as they are at higher risk of clinical deterioration.

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**ADDRESS FOR CORRESPONDENCE:** Dr Chung-Lieh Hung, Mackay Medical College, Division of Cardiology, Department of Internal Medicine, No. 92, Sec. 2, Zhongshan N. Road, Taipei City 10449, Taiwan. E-mail: jotaro3791@gmail.com.

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