Impact of Diastolic Interventricular Septal Flattening on Clinical Outcome in Patients With Severe Tricuspid Regurgitation

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BACKGROUND: Little is known about the impact of diastolic interventricular septal flattening on the clinical outcome in patients with severe tricuspid regurgitation. This study sought to evaluate the association of diastolic interventricular septal flattening with clinical outcome in patients with severe tricuspid regurgitation.

METHODS AND RESULTS: We retrospectively studied 407 patients who underwent 2-dimensional transthoracic echocardiography and were diagnosed with severe tricuspid regurgitation between January 2014 and December 2015. Cardiovascular events were defined as cardiovascular death or admission for heart failure. The magnitude of interventricular septal flattening was calculated by the eccentricity index (EI) of the left ventricle, and hemodynamic parameters were obtained from transthoracic echocardiography. During follow-up (median, 200 days; interquartile range, 35–1059), 117 of the patients experienced cardiovascular events. By multivariate analysis including potential covariates, EI at end-diastole and left ventricular ejection fraction were independent predictors of cardiovascular events (hazard ratio, 5.33 [1.63–17.41]; hazard ratio, 0.98 [0.97–0.99], respectively). An EI of 1.2 at end-diastole was the optimal cutoff value for identifying poor hemodynamic status defined as cardiac index ≤2.2 L/min per m² and right atrial pressure 15 mm Hg, both on transthoracic echocardiography. Patients with D-shaped left ventricle defined as EI ≥1.2 at end-diastole showed worse outcomes than those without (adjusted hazard ratio, 1.80 [1.18–2.74]).

CONCLUSIONS: Increasing EI at end-diastole was strongly associated with worse outcomes in patients with severe tricuspid regurgitation. Furthermore, the presence of D-shaped left ventricle defined as EI ≥1.2 at end-diastole provides prognostic value for cardiovascular events.

Key Words: eccentricity index ■ prognosis ■ tricuspid regurgitation

Severe tricuspid regurgitation (TR) is associated with an increased risk for mortality and morbidity,1–4 and new transcatheter treatment options for TR have emerged. However, TR treatment indications are not well defined and remain controversial.5 Despite the differences of the anatomy and hemodynamics, most of the knowledge with regard to management of TR has been derived from patients with mitral regurgitation.6–8 The only class I indication in the current clinical guidelines for tricuspid valve surgery is during open heart surgery for another indication such as mitral valve surgery.5,9 Furthermore, the current guidelines of TR management are mostly derived from level C evidence.9 Thus, the recommended current TR management is limited because of the lack of strong supporting data. Accordingly, establishing evidenced-based TR management is a major unmet clinical need, and we believe that risk stratification is essential to establishing optimal guidelines for patients with TR.
Interventricular septal flattening is an important echocardiographic finding and could be caused by increased right ventricular (RV) wall tension because of RV volume and/or pressure overload. Diastolic interventricular septal flattening, which reflects RV volume overload, is one of the characteristic features in patients with severe TR. Previous reports showed the relationship between the abnormal motion of the interventricular septum and poor hemodynamics in patients with severe TR. Louie et al demonstrated that the left ventricle (LV) compressed by the volume-overloaded right ventricle an impairment of the left LV filling in patients with severe TR who underwent tricuspid valvulectomy. However, despite the poor hemodynamics, little is known about the impact of the diastolic interventricular septal flattening on clinical outcome in patients with severe TR.

The LV eccentricity index (EI) at end-systole had been used to predict outcomes in patients with RV chronic pressure overload because of pulmonary hypertension (PH). Thus, we hypothesized that LV EI at end-diastole would also be useful for risk stratification in patients with RV chronic volume overload because of severe TR.

Therefore, in this study, we sought to investigate the impact of diastolic interventricular septal flattening quantified using LV EI at end-diastole on clinical outcome in patients with severe TR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

We retrospectively reviewed 972 consecutive 2-dimensional transthoracic echocardiography (TTE) that included diagnosis of severe TR at our heart institute between January 2014 and December 2015. We excluded repeat examinations of the same patient. Also, we excluded patients on mechanical circulatory or respiratory support during TTE. Patients with LV segmental wall motion abnormalities, ventricular pacing, or left bundle branch block were excluded, because these conditions can influence the interventricular septal motion or LV EI. As a result, 407 patients with severe TR remained for final analysis.

The Cedars-Sinai Institutional Review Board approved this retrospective study with a waiver of informed consent.

Clinical Data

All data were collected from the medical charts and our echocardiographic database. Baseline patient characteristics were collected for the same date as TTE or when not possible within 3 days before or after TTE. Renal function was estimated as glomerular filtration rate by using the simplified Modification of Diet in Renal Disease equation. The heart rhythm and the presence or absence of left bundle branch block were diagnosed by electrocardiography.

Echocardiography

Two-dimensional and Doppler echocardiography was performed according to American Society of Echocardiography guidelines by experienced sonographers using an ultrasound system (iE33; Philips, Andover, MA) with SS-1 phased array transducer. Analysis of TTE images was performed by experienced cardiologists. In patients with atrial fibrillation, parameters were calculated as the mean of 3 to 5 measurements.
LV end-systolic and end-diastolic volume and LV ejection fraction (LVEF) were measured by using the biplane Simpson method.\textsuperscript{19} LV wall thickness and left atrial volume were measured by using the biplane disk summation method, and right atrial volume by using the single disk summation method was measured according to the current recommendation.\textsuperscript{19} Left atrial volume index was calculated dividing left atrial volume by body surface area. The right ventricle was also imaged from multiple views, including the RV-focus and RV-modified apical 4-chamber views. RV basal diameter at end-diastole, 2-dimensional RV end-systolic and diastolic area, and RV fractional area change (FAC) were obtained according to the current recommendation.\textsuperscript{19,20} Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain the peak early velocity (E wave) and late diastolic velocity (A wave) of the mitral inflow. Early diastolic mitral annular velocity ($e'$) was obtained from the lateral aspect of the mitral annulus, and E/e' was calculated by using E wave and lateral $e'$.\textsuperscript{21} Stroke volume was calculated using LV outflow tract diameter and the velocity time integral at LV outflow tract using pulse-wave Doppler.\textsuperscript{22} Cardiac output was calculated using SV and heart rate, and cardiac index (CI) was obtained by cardiac output indexed to body surface area. Primary TR was diagnosed by careful tricuspid valve examination for any structural leaflet abnormality.\textsuperscript{23} Tricuspid leaflet tethering height was defined as vertical distance from the coaptation of the leaflets to the tricuspid annulus line at mid-systole. Tricuspid annular dimension was measured from the apical 4-chamber view at end-diastole.\textsuperscript{25} The severity of TR and other valvular heart diseases was defined by using semiquantitative and quantitative parameters according to the American Society of Echocardiography current guidelines.\textsuperscript{23,24} Integrative assessment of TR severity was performed using a multiparametric approach including vena contracta width, shape and density of continuous wave Doppler jet, and hepatic vein reversal as recommended in current guidelines.\textsuperscript{23} Vena contracta width of TR jet was measured as the narrowest portion of the jet in mid-systole from the RV-modified apical 4-chamber and RV inflow parasternal views. The systolic pressure gradient between the right ventricle and atrium was calculated by applying the modified Bernoulli equation. Right atrial pressure (RAP) was estimated by the diameter of the inferior vena cava (IVC) and its response to a sniff and was classified using three grades: 3, 8, and 15 mm Hg according to the current guideline.\textsuperscript{20} Systolic pulmonary artery pressure (SPAP) was calculated from RAP and the systolic pressure gradient between right ventricle and atrium.\textsuperscript{20} SPAP on electrocardiogram over 60 mm Hg was defined as PH.

Eccentricity Index

To quantify the degree of interventricular septal flattening, septal wall configuration was measured with TTE according to previous reports.\textsuperscript{12,25} In the parasternal short-axis view at the level of the mitral valve–chordae tendineae transition, one LV diameter bisecting and perpendicular to the interventricular septum ($D_1$) was measured. A second LV diameter ($D_2$) was the longest one that was perpendicular to $D_1$. An EI was defined as the ratio $D_2/D_1$ and was calculated to 2 decimal places at both end-systole and end-diastole (Figure 1). End-systole was defined as the frame in which the smallest short-axis area was contained. End-diastole was defined as the peak of the R wave by electrocardiography.\textsuperscript{12} Extrasystolic and first postextrasystolic beats were not analyzed.

Follow-Up Data

Follow-up data were obtained from the medical charts. Clinical outcomes were defined as cardiovascular death or admission for heart failure (HF) and were ascertained through careful review of patients’ medical charts written by the cardiologists. Patients’ follow-up was censored at the time of cardiac transplantation or any tricuspid valve intervention.

Statistical Analysis

Normality of distribution was tested by the Shapiro-Wilk test. Continuous variables with normal distributions were presented as means±SD, and those without were presented as median (interquartile range). Categorical data were presented as number (percentage). Covariates with a univariate statistically significant association with cardiovascular events ($P<0.10$) and age were included in the multivariate analysis by Cox proportional hazard model to determine the independent prognostic predictors of cardiovascular events after confirming the absence of strong collinearities. The Kaplan-Meier curve and log-rank test were used to describe the occurrence of cardiovascular events during the follow-up period. The relationship between CI and EI at end-diastole was assessed by the Spearman rank correlation test. Receiver operating characteristic curves were generated to determine the optimal cutoff value of EI at end-diastole for predicting poor hemodynamic condition defined as CI ≤2.2 L/min per m$^2$ and RAP 15 mm Hg, both from TTE. When we performed receiver operating characteristic analysis, we used EI at end-diastole, which was rounded off to one decimal place to make it more suitable for clinical use. The best cutoff value of EI at end-diastole was calculated by using the Youden index. The risk of a given variable was expressed by a hazard ratio (HR) with corresponding 95% confidence interval. All 2-sided $P$ values were used, taking $P<0.05$
Figure 1. Assessment of the interventricular septal flattening.
LA indicates left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; and TR, tricuspid regurgitation.

Figure 2. Flowchart of the study population.
2D indicates 2-dimensional; TR, tricuspid regurgitation; and TTE, transthoracic echocardiogram.
to be statistically significant. All data were statistically analyzed using the SPSS software package version 26.0 (IBM, Armonk, NY).

RESULTS
Study Population
In 972 TTE examinations that included diagnosis of severe TR, we excluded 239 repeated examinations of the same patients. In 733 patients who were diagnosed with severe TR, we excluded 54 patients on mechanical support during TTE, 58 who had LV segmental wall motion abnormalities, 146 with ventricular pacing, and 37 with left bundle branch block. Also, we excluded 31 examinations that showed poor quality images to calculate EI. The remaining 407 patients with severe TR were included in the final analysis (Figure 2).

Baseline Clinical Characteristics and Echocardiographic Findings
Median age was 73 years (60–85), and 249 (61%) patients were women (Table 1). TTE findings are shown in Table 2. Median LVEF was 58% (41–65), EI at end-systole and end-diastole were 1.03 (0.98–1.14) and 1.13 (1.02–1.27), respectively. RV FAC, which is one of the parameters for assessment of RV systolic function, was 41±13%. One hundred ninety-seven (48%) patients had left heart valvular disease defined as moderate or severe grade, and 41 (10%) were classified as primary TR.

Table 1. Patients’ Characteristics

| All patients with severe TR, n=407 |
|-----------------|-----------------|
| Age, y          | 73 (60–85)      |
| Women, n (%)    | 249 (61)        |
| Height, cm      | 165 (158–173)   |
| Weight, kg      | 67 (59–78)      |
| Body mass index, kg/m² | 24 (21–28)    |
| Hypertension, n (%) | 244 (60)      |
| Dyslipidemia, n (%) | 204 (50)     |
| Diabetes mellitus, n (%) | 104 (26)      |
| Implantable device lead, n (%) | 71 (17)       |
| Chronic atrial fibrillation, n (%) | 186 (46)      |
| Coronary artery disease, n (%) | 81 (20)       |
| eGFR, mL/min per 1.73 m² | 50 (32–73)    |
| Total bilirubin, mg/dL | 0.8 (0.5–1.5) |
| Albumin, g/dL   | 3.6±0.6         |

Data are mean±SD, median (interquartile range), or number (percentage). eGFR indicates estimated glomerular filtration rate; and TR, tricuspid regurgitation.

Clinical Outcomes
Outcome data were available in 398 (98%) patients. During follow-up (median 200 days [35–1059]), 117 (29%) of the patients experienced cardiovascular events (13 cardiovascular death and 104 admissions for heart failure). Table 3 shows the results of univariate analysis. Multivariate analysis by Cox proportional hazard regression model including age, sex, LVEF, EI at end-systole and end-diastole, RV basal diameter, RV end-systolic area, RV FAC, tricuspid leaflet tethering height, vena contracta width of TR, SPAP, and IVC diameter showed that EI at end-diastole and LVEF were independently associated with cardiovascular events (Table 4).

Hemodynamics
Two hundred sixty-nine (66%) patients permit assessment of CI with TTE. The remaining 138 (34%) patients who did not permit CI assessment showed no significant differences in baseline clinical characteristics and echocardiographic findings except for IVC diameter compared with the whole cohort. However, both groups showed larger IVC diameter than the cutoff value proposed for identifying IVC dilatation in current guidelines (patients without CI assessment [2.3±0.6 cm] versus whole cohort [2.4±0.6 cm]). In patients who permit CI assessment, there was a significant negative correlation between CI and EI at end-diastole (R=−0.14, P=0.018) (Figure 3A). Figure 3B shows the distribution of RAP with TTE across EI at end-diastole quartiles. For each one-unit increase of EI at end-diastole, the proportion of RAP 15 mm Hg increased as opposed to the proportion of RAP 3 or 8 mm Hg. There was no significant correlation between CI and RAP in patients who had the 2 parameters (Figure S1).

Ninety-nine patients had both CI ≤2.2 L/min per m² and RAP 15 mm Hg. We subsequently drew a receiver operating characteristic curve to determine the optimal cutoff value of EI at end-diastole for the presence of poor hemodynamic status defined as both CI ≤2.2 L/min per m² and RAP 15 mm Hg. We subsequently drew a receiver operating characteristic curve to determine the optimal cutoff value of EI at end-diastole for the presence of poor hemodynamic status defined as both CI ≤2.2 L/min per m² and RAP 15 mm Hg. The optimal cutoff value of EI at end-diastole was 1.2 with a sensitivity of 60%, specificity of 61%, and with area under the curve 0.63 (95% confidence interval, 0.56–0.70; P=0.001; Figure 4).

Kaplan-Meier Curves According to the Presence or Absence of D-Shaped Left Ventricle at End-Diastole
We defined the D-shaped left ventricle (D-LV) at end-diastole as EI ≥1.2 at end-diastole from the standpoint of hemodynamics. Kaplan-Meier curves demonstrated that patients with D-LV at end-diastole were at higher risk for cardiovascular events than those without (HR, 1.86; 95% confidence interval, 1.29–2.68; P=0.001; Figure 5). Furthermore, when D-LV at end-diastole was added...
to the multivariate analysis model instead of EI at end-diastole as a continuous variable, D-LV at end-diastole was independently associated with poor prognosis (adjusted HR, 1.80; 95% confidence interval, 1.18–2.74; P=0.006).

### The Implication of D-LV at End-Diastole in Patients With or Without Pulmonary Hypertension

In 398 patients who allowed prognostic analysis, SPAP estimated with TTE was available in 387 patients, and 165 (43%) patients were classified as PH. In both patients with PH and those without, the presence of D-LV defined as EI ≥1.2 was significantly associated with worse outcomes (HR, 1.85; 95% confidence interval, 1.12–3.07; HR, 1.79; 95% confidence interval, 1.04–3.08, respectively) (Figure S2).

### DISCUSSION

In this study, we demonstrated that increasing diastolic interventricular septal flattening was independently associated with worse clinical outcomes in patients with...
severe TR. Furthermore, D-LV defined as EI ≥1.2 at end-diastole was significantly associated with cardiovascular outcomes in patients with severe TR.

Outcomes
The diastolic interventricular septal flattening is one of the hallmarks of RV volume overload.26 Previous reports suggested that RV volume overload is the most common pathway that ultimately leads to cardiovascular events in patients after tetralogy of Fallot repair,27,28 Also, the primary indication for ASD closure is right heart volume overload, as evidenced by right atrial or RV enlargement.29 These findings led us to hypothesize that the diastolic interventricular septal flattening would be a relevant prognostic marker of clinical outcomes in patients with severe TR. Our study results demonstrated that increased diastolic interventricular septal flattening was independently associated with worse clinical outcome in patients with severe TR. As far as we know, this is the first report elucidating the association of the diastolic interventricular septal flattening with clinical outcomes in patients with severe TR.

LVEF, which was also independently associated with cardiovascular events in our study, is a relevant predictor because it is the most important and widely accepted prognosticator in clinical practice.30 RV systolic function is also a major determinant for morbidity and mortality in many diseases such as valvular heart diseases or PH.31 However, severe TR can induce misleading overestimation of RV systolic function.32 On the other hand, EI increases with increasing RV volume overload. This may be a reason why the diastolic interventricular septal flattening is a stronger and more suitable prognosticator than covariates related to RV dysfunction.

**Association Between Hemodynamics and Diastolic Interventricular Septal Flattening**
Belenkie et al reported that acute saline loading decreased LV stroke work because the left ventricle at end-diastole was compressed by the distended right ventricle in a canine model.32 Also, Andersen et al demonstrated that impairment of cardiac output reserve on exercise in patients with significant TR is coupled with a decrease of LV filling pressure caused by the distended right ventricle.14 These reports support our study results that the increasing diastolic interventricular septal flattening was significantly associated with worse hemodynamics. LV geometry change because of RV volume overload contributes to decreased LV distending pressure that drives LV filling. Decreasing LV filling causes limitation to the Frank-Starling mechanism use, leading to reduced SV and CI (ie, diastolic ventricular interaction).31,33,34 Increasing diastolic interventricular septal flattening, therefore, may cause worse hemodynamics through the diastolic ventricular interaction in patients with severe TR. Furthermore, the poor hemodynamics explain the relevance of the association between increased diastolic interventricular septal flattening with worse outcomes in our study.

**EI for Clinical Use**
Although we estimated the degree of LV compression by using EI as a continuous variable, decision of cutoff value is expected to be more useful for clinical use. We determined, therefore, the optimal cutoff value as EI 1.2 at end-diastole from the standpoint of hemodynamics and defined D-LV as EI ≥1.2. Importantly, the presence or absence of D-LV at end-diastole provided significant prognostic value of risk stratification in patients with severe TR. EI measurement for quantification of LV geometry is a simple method12 and has visual
appeal, suggesting that it appears to be a useful and feasible method to predict clinical outcomes in patients with severe TR.

### Subgroup Analysis According to the Presence or Absence of PH

In patients with RV pressure overload, LV deformity persists throughout the cardiac cycle including diastole,\(^\textsuperscript{12}\) meaning that RV pressure overload can affect the diastolic interventricular septal flattening. Thus, we evaluated the impact of D-LV at end-diastole on prognosis in both patients with PH and those without. As a result, the presence of D-LV defined as EI ≥1.2 was significantly associated with worse outcomes in both groups (Figure S2), suggesting the relevance of clinical impact of D-LV at end-diastole regardless of the presence or absence of PH in patients with severe TR. Further studies are needed to identify the optimal cutoff value of EI at end-diastole according to the presence or absence of PH.

### Limitations

First, this is a single-center retrospective study and thus affected by selection bias. Second, SPAP assessed by TTE in patients with severe TR may be underestimated because of an early equalization of...
right ventricular and atrial pressure.\textsuperscript{20} Third, RV systolic function was assessed with FAC alone, because adequate images were not available. However, other echocardiographic parameters for assessment of RV systolic function, such as peak systolic tricuspid annular velocity or tricuspid annular plane systolic excursion, had poorer correlation to RV systolic function compared with RV FAC in patients with severe TR,\textsuperscript{35} justifying the use of RV FAC to assess RV function in our study cohort. RV strain parameters may be better to estimate RV systolic function in patients with severe TR, because the parameters are angle independent and less load dependent compared with RV FAC.\textsuperscript{36} Fourth, in our study, hemodynamic parameters were obtained with TTE. The correlation between CI and EI at end-diastole was weak despite being significant, and the specificity and sensitivity of EI at end-diastole to identify poor hemodynamic status was only fair. Thus, further studies using invasive hemodynamic parameters are needed to establish the optimal cutoff value of EI at end-diastole for identifying poor hemodynamic status.

**CONCLUSIONS**

This study demonstrated that increasing EI at end-diastole was independently associated with worse prognosis in patients with severe TR. Furthermore, this study identified worse outcomes of severe TR patients with D-LV defined as EI $\geq 1.2$ at end-diastole compared with those without. Adding EI measurement to the clinical assessment may provide additional value for the management and treatment decisions of patients with severe TR.

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SUPPLEMENTAL MATERIAL
Figure S1. Relationship between CI and RAP.

There is no significant correlation between the two parameters (correlation coefficient = 0.02).

CI, cardiac index; RAP, right atrial pressure
Figure S2. Kaplan-Meier curves according to the presence or absence of D-LV at end-diastole in the PH and non-PH group.

In both (A) the PH and (B) non-PH groups, patients with D-LV at end-diastole showed worse outcomes than those without.

D-LV, D-shaped left ventricle; PH, pulmonary hypertension