**Impaired Global Right Ventricular Longitudinal Strain Predicts Long-Term Adverse Outcomes in Patients with Pulmonary Arterial Hypertension**

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**BACKGROUND:** New 2-dimensional strain echocardiography enables quantification of right ventricular (RV) mechanics by assessing global longitudinal strain of RV (GLSRV) in patients with pulmonary arterial hypertension (PAH). However, the prognostic significance of impaired GLSRV is unclear in these patients.

**METHODS:** Comprehensive echocardiography was performed in 51 consecutive PAH patients without atrial fibrillation (40 females, 48 ± 14 years old) with long-term follow-up. GLSRV was measured with off-line with velocity vector imaging (VVI, Siemens Medical System, Mountain View, CA, USA).

**RESULTS:** GLSRV showed significant correlation with RV fractional area change (r = -0.606, p < 0.001), tricuspid annular plane systolic excursion (r = -0.579, p < 0.001), and RV Tei index (r = 0.390, p < 0.001). It showed significant correlations with pulmonary vascular resistance (r = 0.469, p = 0.001) and B-natriuretic peptide concentration (r = 0.351, p = 0.012). During a clinical follow-up time (45 ± 15 months), 20 patients experienced one or more adverse events (12 death, 2 lung transplantation, and 15 heart failure hospitalization). After multivariate analysis, age [hazard ratio (HR) = 2.343, p = 0.040] and GLSRV (HR = 2.122, p = 0.040) were associated with adverse clinical events. Age (HR = 3.200, p = 0.016) and GLSRV (HR = 2.090, p = 0.042) were also significant predictors of death. Impaired GLSRV (≥ -15.5%) was associated with lower event-free survival (HR = 4.906, p = 0.001) and increased mortality (HR = 8.842, p = 0.005).

**CONCLUSION:** GLSRV by VVI showed significant correlations with conventional echocardiographic parameters indicating RV systolic function. Lower GLSRV (≥ -15.5%) was significantly associated with presence of adverse clinical events and deaths in PAH patients.

**KEY WORDS:** Pulmonary arterial hypertension · Right ventricle · Strain echocardiography.

**INTRODUCTION**

Patients with pulmonary arterial hypertension (PAH) have a high mortality rate despite earlier disease recognition and availability of new drug treatments which have improved survival in recent years.1-3 Irrespective of the etiology of PAH, right ventricular (RV) function is the main determinant of symptoms and survival.3-5 Because transthoracic 2-dimensional echocardiography (2DE) gives us important information about...
cardiac structures, RV function and hemodynamic status, it is one of the most commonly used modalities for screening and monitoring of the effect of medical management. However, the complex shape of the RV chamber makes accurate assessment by conventional 2DE imaging difficult. Moreover, conventional velocity and displacement based analyses can be affected by translational motion of the heart and respiratory variation. New 2-dimensional strain echocardiography enables quantification of both regional and global myocardial function in a simple and angle-independent manner. Although 2-dimensional strain echocardiography was introduced to evaluate global left ventricular (LV) function, it has recently been used to assess RV function. Global longitudinal strain of RV (GLSRV) can be measured with 2-dimensional strain analysis and thus can give a more direct assessment of RV mechanics. In patients with PAH, decreased RV strain was associated with poor prognosis in the previous study. Because RV has different anatomy and function compared with LV, the simple application of strain algorithm to RV remains problematic. Also, there are several vendor-specific algorithms in the measurement of strain. Velocity vector imaging software (VVI; Aquis, Siemens Medical Solutions, Mountain View, CA, USA) can measure RV strain without an influence of ventricular wall thickness. So, we measured GLSRV in patients with PAH with VVI and evaluated its prognostic significance.

METHODS

STUDY POPULATION

We studied consecutive adult patients (age more than 18 years old) with PAH evaluated from February 2007 to June 2008 in the PAH clinic of Cleveland Clinic. All patients fulfilled the contemporary diagnostic criteria by the Third World Symposium of PAH and they had regular outpatient follow-ups. Patients with LV systolic dysfunction, significant valvular heart disease, chronic thromboembolic disease and pulmonary parenchymal diseases were excluded in this study. We analyzed total 51 patients with PAH (34 idiopathic, 13 familial, and 4 associated with other diseases (2 with connective tissue disease, 1 with myeloproliferative disease and 1 with systemic to pulmonary shunt)). This study protocol was approved by the Cleveland Clinic Institutional Review Board.

ECHOCARDIOGRAPHY

Conventional 2DE examinations were performed using a Vivid 7 ultrasound system (GE-Vigmed, Horten, Norway) according to the guidelines and standard recommendations of the American Society of Echocardiography. All echocardiographic images were digitally stored and were reviewed by sonographers (J.-H.P. and M.P.) unaware of the clinical, laboratory, and hemodynamic information. Conventional echocardiographic parameters were measured by an investigator (M.P.) and reviewed by an investigator (J.T.). RV fractional area change (RVFAC) was calculated from the apical 4-chamber view using the percentage change in areas of the end-diastolic and endsystolic areas of the RV. The tricuspid annular plane systolic excursion (TAPSE) was recorded with M-mode echocardiography parallel to the lateral RV wall and across the tricuspid annular plane and measured as the distance of systolic movement of the RV annulus in the longitudinal direction. RV myocardial performance (Tei) index was defined as the ratio of isovolumic relaxation time and isovolumic contraction time divided by ejection time of RV. Pulmonary artery systolic pressure was estimated from the maximal continuous-wave Doppler velocity of the tricuspid regurgitation (TR) jet imaged from multiple planes plus estimated central venous pressure calculated by the diameter of inferior vena cava and distensibility. An index of pulmonary vascular resistance was derived by dividing the maximal velocity of the TR jet by the RV outflow tract velocity-time integral. An average of 3 measurements was used for all analyses. RV strain and strain rate were analyzed off-line with VVI by another investigator (J.-H.P.). After manual tracing of the endocardial border of the RV (about 10 to 16 points) over one frame, the endocardial borders were automatically tracked throughout the cardiac cycle. The measurement of RV longitudinal strain by VVI showed relatively good correlation with cardiac magnetic resonance data. Myocardial velocity is derived as the ratio between frame-to-frame displacement of the speckles and the time interval. Systolic longitudinal strain, time-to peak strain, and peak systolic and diastolic strain rate were calculated. Negative strain values indicate tissue shortening and a smaller value (that is, higher absolute value) indicates better RV systolic function. GLSRV was calculated by the average of six segmental values. Longitudinal strain of RV free wall and interventricular septum were measured by the averages of three segmental values (base, mid, and apex) of the lateral wall and interventricular septum. Because strain expresses deformation relative to the initial length, systolic shortening in the longitudinal orientation is expressed in negative numbers. Lower GLSRV value means better RV systolic function.

CLINICAL OUTCOMES

Patients were followed over 45 ± 15 months for a composite of death, cardiac hospitalization due to worsening of heart failure and lung transplantation. The presence of adverse clinical events was determined with reviewing their medical records in patients with regular clinical follow-ups. In patients without clinical follow-up, the presence of death was checked with medical records or the Social Security Death Index.

STATISTICAL ANALYSIS

The data were analyzed using standard software (SPSS version 20.0, IBM Co., Chicago, IL, USA). Summary data were expressed as mean ± standard deviation or percentage of patients.
Linear regression analysis was performed to evaluate the relationship between GLSRV and other variables. The optimal cut-off value of GLSRV for predicting adverse clinical events was determined by the receiver-operating characteristic curve analysis. Reclassification was evaluated with net reclassification improvement (NRI) methods described by Pencina et al.\textsuperscript{16} NRI measures the improvement in response using event-specific reclassification tables. Cox proportional hazard model with bootstrapping was used to assess the association of variables with end points. Hazard ratios (HR) are given with their 95% confidence intervals (CI) and the HR refers to a unit increase in the variables. Variable selection in multivariate analysis was based on statistical significance at univariate analysis. To avoid multicollinearity, redundant echocardiographic variables were dropped from the multivariate regression model in the case of pairwise correlations between continuous variables exceeding 0.50 as Pearson’s correlation coefficient, including the variable with the strongest individual effect size.\textsuperscript{17} The event-free curves were based on Kaplan-Meier analyses stratified by GLSRV value and the comparisons were made by Logrank test.

Intraobserver and interobserver variabilities of the GLSRV were evaluated in 15 random subjects by two investigators (J.-H.P. and M.P.), and measured by calculating the intraclass correlation coefficient (ICC), coefficient of variance (COV) and limits of agreement. A $p$ value less than 0.05 was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

A total 51 patients (40 females mean age $48 \pm 14$ years old) were included in this study. Their mean duration of disease was $46 \pm 35$ months and the majority of patients were World Health Organization functional class II (61%) and III (35%). Twenty two patients were taking a single vasodilator medication (2 on calcium channel blocker (CCB), 5 a phosphodiesterase-5 inhibitor (PDE5I), 3 an oral endothelin receptor antagonists (ERA), and 12 prostaglandins) and 29 patients were taking a combination of vasodilators (2 on CCB and PDE5I, 1 on CCB and ERA, 6 on PDE5I and ERA, 7 on ERA and prostaglandins, 5 on PDE5 and prostaglandins, and 8 on PDE5I, ERA and prostaglandins). Twenty eight patients received oral diuretic therapy to reduce their peripheral edema and 28 were anticoagulated with oral warfarin. The baseline clinical, laboratory, conventional echocardiographic, and right heart catheterization data (Table 1) are typical for a PAH population, with normal LV systolic function, elevated pulmonary arterial pressure, RV enlargement and RV dysfunction.

RV STRAIN FINDINGS

Global and regional two-dimensional strain measurements are listed in Table 2. GLSRV and systolic strain rate of RV were

| Table 1. Baseline characteristics |
|-------------------------------|
| Characteristics               |
| **Clinical**                  |
| Age (years)                   | $48 \pm 14$            |
| Female gender (%)             | $40 (78\%)$            |
| BMI (kg/m$^2$)                | $33.4 \pm 15.2$        |
| **Functional classification** |
| NYHA FC I/II                  | $2 (4\%)/31 (61\%)$    |
| 6 min walking distance (m)    | $411 \pm 101$          |
| **Medications**               |
| Calcium channel blockers      | $9 (18\%)$             |
| Phosphodiesterase-5 inhibitors| $29 (57\%)$            |
| Endothelin receptor antagonists| $26 (51\%)$            |
| Prostacyclines                | $32 (63\%)$            |
| **Laboratory**                |
| Hemoglobin (g/dL)             | $13.5 \pm 1.8$         |
| Creatinine (g/dL)             | $0.9 \pm 0.2$          |
| BNP (pg/mL)                   | $155 \pm 469$ (range: 5–3216) |
| **Echocardiographic data**    |
| RV wall thickness (mm)        | $9.5 \pm 3.0$          |
| RA area (cm$^2$)              | $22.5 \pm 9.4$         |
| RV end-diastolic area (cm$^2$)| $25.6 \pm 9.2$         |
| Pericardial effusion (%)      | $8 (16\%)$             |
| Moderate or severe tricuspid regurgitation (%) | $16 (30\%)$          |
| Septal flattering (systolic/diastolic/systolic + diastolic) | $39 (77\%)/47 (92\%)/48 (94\%)$ |
| LV ejection fraction (%)      | $69.0 \pm 7.7$         |
| RV fractional area change (%) | $32.1 \pm 10.1$        |
| TAPSE (cm)                    | $1.54 \pm 0.49$        |
| RV Tei index                  | $0.51 \pm 0.25$        |
| Notching of RVOT Doppler flow signal | $36 (71\%)$       |
| Estimated RA pressure (mm Hg) | $12.1 \pm 6.3$         |
| TR Vmax (m/sec)               | $3.8 \pm 0.6$          |
| Estimated RV systolic pressure (mm Hg) | $60.2 \pm 19.5$ |
| **Catheterization data (n = 42)** |
| PA pressure (systolic/diastolic, mm Hg) | $86.6 \pm 24.4/36.8 \pm 13.4$ |
| PA pressure, mean (mm Hg)     | $53.5 \pm 18.7$        |
| PCWP (mm Hg)                  | $13.8 \pm 4.1$         |
| RA pressure (mm Hg)           | $10.6 \pm 6.3$         |
| CI (L/min/m$^2$)              | $2.6 \pm 1.0$          |
| PVR (WU)                      | $10.1 \pm 7.9$         |
| Positive vasodilator response (%) | $4 (10\%)$            |

BMI: body mass index, NYHA FC: New York Heart Association Functional Class, BNP: B-type natriuretic peptide, RV: right ventricle, RA: right atrium, LV: left ventricle, TAPSE: tricuspid annular plane systolic excursion, TR: tricuspid regurgitation, CI: confidence interval, PVR: pulmonary vascular resistance, RVOT: right ventricular outflow tract, PCWP: pulmonary capillary wedge pressure, PA: pulmonary artery
significantly decreased than normal RV strain values in the previously reported paper. The average GLSRV was \(-16.1 \pm 5.0\%\) and average systolic strain rate of RV was \(-1.3 \pm 0.4 \text{ s}^{-1}\). GLSRV showed a good negative correlation with RV fractional area change (RVFAC, A), tricuspid annular plane systolic excursion (TAPSE, B), and RV Tei index (C). Also, GLSRV demonstrated a significant correlation with pulmonary vascular resistance calculated by echocardiography (D).

Follow-up

During the follow-up of 45 ± 15 months, 20 patients had experienced one or more adverse events including 12 deaths, 2 lung transplantation and 15 hospital admissions due to worsening heart failure. After univariate analysis, adverse clinical events were associated with age, 6-minute walking distance (6-MWD), B-type natriuretic peptide (BNP) concentration, right atrial
size, TAPSE, RVFAC, and GLSRV. In the prediction of mortality, age, 6MWD, BNP concentration, and GLSRV were statistically significant variables after univariate analysis (Table 3). After multivariate analysis, age and GLSRV remains statistically significant in the prediction of adverse clinical events and mortality (Table 4). The best cutoff value of GLSRV for detec-

| Variable                              | HR    | 95% CI    | p value |
|---------------------------------------|-------|-----------|---------|
|                                      | Lower | Upper     |         |
| Clinical events                       |       |           |         |
| Female gender                         | 1.625 | 0.475     | 5.556   | 0.439   |
| Age (per SD)                          | 2.752 | 1.554     | 4.874   | 0.001   |
| NYHA functional class                 | 1.720 | 0.764     | 3.876   | 0.191   |
| 6MWD (per SD)                         | 0.443 | 0.268     | 0.734   | 0.002   |
| BNP concentration (per SD)            | 1.089 | 1.023     | 1.160   | 0.008   |
| RA size (per SD)                      | 1.449 | 1.023     | 2.052   | 0.037   |
| PASP (per SD)                         | 1.353 | 0.857     | 2.36    | 0.194   |
| TAPSE (per SD)                        | 0.553 | 0.327     | 0.936   | 0.027   |
| RVFAC (per SD)                        | 0.543 | 0.332     | 0.889   | 0.015   |
| GLSRV (per SD)                        | 2.170 | 1.327     | 3.548   | 0.002   |
| All causes of mortality               |       |           |         |
| Female gender                         | 1.341 | 0.292     | 6.152   | 0.705   |
| Age (per SD)                          | 2.903 | 1.395     | 6.040   | 0.004   |
| NYHA functional class                 | 1.433 | 0.503     | 4.083   | 0.032   |
| 6MWD (per SD)                         | 0.481 | 0.246     | 0.940   | 0.032   |
| BNP concentration (per SD)            | 1.109 | 1.034     | 1.190   | 0.004   |
| RA size (per SD)                      | 1.361 | 0.851     | 2.176   | 0.198   |
| PASP (per SD)                         | 1.572 | 0.871     | 2.838   | 0.133   |
| TAPSE (per SD)                        | 0.640 | 0.329     | 1.245   | 0.189   |
| RVFAC (per SD)                        | 0.636 | 0.358     | 1.130   | 0.123   |
| GLSRV (per SD)                        | 2.075 | 1.135     | 3.799   | 0.018   |

Clinical events included hospitalization of heart failure, lung transplantation, and all-cause mortality. HR: hazard ratio, CI: confidence interval, SD: standard deviation, NYHA: New York Heart Association, 6MWD: 6-minute walking distance, BNP: B-type natriuretic peptide, RA: right atrium, PASP: pulmonary artery systolic pressure, TAPSE: tricuspid annular plane systolic excursion, RVFAC: right ventricular fractional area change, GLSRV: global longitudinal strain of right ventricle.

| Variable                              | HR    | 95% CI    | p value |
|---------------------------------------|-------|-----------|---------|
|                                      | Lower | Upper     |         |
| Clinical events                       |       |           |         |
| Age (per SD)                          | 2.343 | 1.127     | 4.872   | 0.040   |
| NYHA functional class (> III)         | 1.169 | 0.411     | 3.329   | 0.766   |
| 6MWD (per SD)                         | 0.532 | 0.251     | 1.127   | 0.166   |
| BNP concentration (per SD)            | 1.077 | 0.999     | 1.162   | 0.205   |
| GLSRV (per SD)                        | 2.122 | 1.257     | 3.582   | 0.040   |
| All causes of mortality               |       |           |         |
| Age (per SD)                          | 3.200 | 1.164     | 8.793   | 0.016   |
| NYHA functional class (> III)         | 1.345 | 0.422     | 5.657   | 0.517   |
| 6MWD (per SD)                         | 0.682 | 0.263     | 1.768   | 0.513   |
| BNP concentration (per SD)            | 1.111 | 1.016     | 1.216   | 0.088   |
| GLSRV (per SD)                        | 2.090 | 1.054     | 4.145   | 0.042   |

Clinical events included hospitalization of heart failure, lung transplantation, and all-cause mortality. HR: hazard ratio, CI: confidence interval, SD: standard deviation, NYHA: New York Heart Association, 6MWD: 6-minute walking distance, BNP: B-type natriuretic peptide, GLSRV: global longitudinal strain of right ventricle.
tion of adverse clinical events was -15.5% (95% CI = -16.9–
-10.9%) with a sensitivity of 70% and specificity 77%. The value (GLSRV ≥ -15.5%) offered an improvement in reclassification of prediction of adverse clinical event or death by TAPSE (< 1.5 cm) or the presence of pericardial effusion (Table 5). PAH patients with impaired GLSRV (≥ -15.5%) showed lower event-free survival (80 ± 7% vs. 42 ± 11% at 4 years, \( p < 0.001 \)) and lower total survival (93 ± 5% vs. 57 ± 11% at 4 years, \( p < 0.001 \)) than preserved GLSRV patients (Fig. 2).

**VARIABILITY**

Intraobserver variability: ICC was 0.950 (95% CI = 0.854–0.983, \( p < 0.001 \)), COV was 9.7% (95% CI = 3.4–14.1%), and 95% limits of agreement was -3.5 to 4.5%.

### Table 5. Incidence, discrimination, and calibration estimates of adverse clinical event and death

| Adverse clinical event | GLSRV | Net correctly reclassified (%) | Reclassified | p-value |
|------------------------|-------|--------------------------------|--------------|---------|
|                        | < -15.5% | ≥ -15.5% | Increased risk* | Decreased risk* |       |
| **Adverse clinical event** | | | | | |
| Individuals with adverse clinical event (n = 20) | | | | | |
| TAPSE ≥ 1.5 cm | 4 | 4 | 10.0 | | |
| TAPSE < 1.5 cm | 2 | 10 | | | |
| Individuals without adverse clinical event (n = 31) | | | | | |
| TAPSE ≥ 1.5 cm | 2 | 6 | 12.9 | | |
| TAPSE < 1.5 cm | 18 | 2 | | | |
| Net reclassification improvement† | | | 22.9 | | |
| p-value | | | 0.067 | | |
| **Death** | | | | | |
| Individuals with death (n = 12) | | | | | |
| TAPSE ≥ 1.5 cm | 3 | 0 | 25.0 | | |
| TAPSE < 1.5 cm | 2 | 3 | | | |
| Individuals without death (n = 39) | | | | | |
| TAPSE ≥ 1.5 cm | 0 | 7 | | | |
| TAPSE < 1.5 cm | 3 | 8 | 12.8 | | |
| Net reclassification improvement† | | | 37.8 | | |
| p-value | | | 0.012 | | |
| **Adverse clinical event** | | | | | |
| Individuals with adverse clinical event (n = 20) | | | | | |
| Pericardial effusion (-) | | | | | |
| Pericardial effusion (+) | | | | | |
| Individuals without adverse clinical event (n = 31) | | | | | |
| Pericardial effusion (-) | | | | | |
| Pericardial effusion (+) | | | | | |
| Net reclassification improvement† | | | 40.3 | | |
| p-value | | | 0.025 | | |
| **Death** | | | | | |
| Individuals with death (n = 12) | | | | | |
| Pericardial effusion (-) | | | | | |
| Pericardial effusion (+) | | | | | |
| Individuals without death (n = 39) | | | | | |
| Pericardial effusion (-) | | | | | |
| Pericardial effusion (+) | | | | | |
| Net reclassification improvement† | | | 50.6 | | |
| p-value | | | 0.003 | | |

*The number of individuals that were reclassified upwards and downwards, respectively. †The proportion correctly reclassified is in those who show adverse clinical event or death, the proportion of individuals reclassified to a higher risk minus the proportion reclassified to a lower risk; in those who do not have adverse clinical event or death, the proportion of individuals reclassified to a lower risk minus the proportion reclassified to a higher risk. ‡The net reclassification improvement is the sum of correctly reclassified individuals with and without adverse clinical event and death. GLSRV: global longitudinal strain of right ventricle, TAPSE: tricuspid annular plane systolic excursion

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Interobserver variability: ICC was 0.918 (95% CI = 0.757–0.973, p < 0.001), COV was 12.9% (95% CI = 5.1–18.8%), and 95% limits of agreement was -5.5 to 5.2%.

**Discussion**

The main findings of this study are that GLSRV is a readily obtained echocardiographic parameter, which correlates well with other conventional indices of RV systolic function on routine transthoracic echocardiographic examination. Furthermore, worse GLSRV (≥ -15.5%) independently predicts adverse clinical events and death in patients with PAH.

Although imaging quality has improved, assessment of the diseased RV by conventional 2DE standards remains a difficult issue. The complex shape and different systolic mechanics of the RV chamber are possible explanations. Delineation of the endocardial border in the measurement of RVEF may limit the reliability in assessing RV function. Tethering and translational motion can affect the use of velocity and displacement based measurements like TAPSE.

Speckle tracking has been introduced for the assessment of the LV function. The use of speckle tracking for the assessment of regional and global LV function has been validated by sonomicrometry, and it enables the measurement of the ventricle non-geometrically. Strain has an advantage over velocity and displacement based measurements as being relatively independent of tethering or translational motion. Myocardial strain can be used to detect early stages of myocardial dysfunction and it has prognostic power in patients with chronic heart failure. Though strain is initially developed to measure LV mechanics, speckle strain has been utilized for the assessment of the RV in some disease categories. Because RV has thinner free wall thickness than LV, simple application of strain algorithm to RV remains problematic. We applied strain to RV including RV free wall and interventricular septum together. In the previous study of the comparison of RV longitudinal strain with RV ejection fraction (RVEF) calculated by cardiac magnetic resonance imaging (CMR), global RV longitudinal strain including RV free wall and interventricular septum showed more better correlation with RVEF by CMR. Our current study showed that the mean GLSRV of the patients with PAH was -16.1%. These absolute values are considerably lower than those of normal subjects (normal mean value of global longitudinal strain of RV by 2-dimensional echocardiography is about -28%). In PAH patients, chronic pressure and volume overload of RV leads to both structural and functional changes. Puwanant et al. reported longitudinal deformation of RV free wall in patients with chronic PAH is significantly decreased compared with control subjects.

Lower GLSRV (≥ -15.5%) was associated with adverse clinical event and death in our study. Moreover, GLSRV ≥ -15.5% offered an improvement in reclassification of prediction of adverse clinical event or death by TAPSE (< 1.5 cm) or the presence of pericardial effusion which are known as bad prognostic factors in PAH patients. This finding correlates with the previous reports by other investigators. In contrast from these aforementioned studies, we used a global longitudinal strain value of the RV which included the interventricular septum. In the strain assessment of the RV, long-axis assessment is per-
formed in the RV free wall only or the RV free wall with interventricular septum together. Because the interventricular septum has both RV and LV mechanical components, its strain assessment can be complicated. However, chronic pressure overload of the RV can affect ventricular geometry and the interventricular septum also plays an important role in the systolic RV mechanics.207 We included the interventricular septum in our overall global RV strain assessment to precisely evaluate RV systolic function by strain analysis. In our study, RV free wall strain showed similar significant correlations with conventional echocardiographic RV parameters. However, using global RV strain including septum [area under the curve (AUC) = 0.734, 95% CI = 0.592–0.848] has larger AUC than that of RV free strain [AUC = 0.677, 95% CI = 0.532–0.801] in the prediction of adverse clinical events and deaths in patients with PAH. If improve

The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest 2000;117:794-804.

Sibson O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780-8.

Condille R, Kiely DG, Coghlan JG, Gibbs JS, Wort SJ, Corris PA, Peacock AJ, Pepke-Zaba J; Adult Pulmonary Hypertension Service of the United Kingdom. Survival in pulmonary hypertension registries: the importance of incident cases. Chest 2011;139:1547-8; author reply 1548-9.

D’Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brandage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Am Intern Med 1991;115:343-9.

Sandoval J, Bauerle O, Palomar A, Gómez A, Martínez-Guerra ML, Beltrán M, Guerrero ML. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation 1994;89:1733-44.

Rusli SG, Lai WW, Aflalo J, Hua L, Handschumacher MD, Chandrasakeran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713; quiz 786-8.

Giunta S, Dambrauskaitė V, Scheuwers C, D’Hooge J, Claus P, Herboos L, Magno M, Redefiners F, Meyn B, Delcour M, Voigt JU. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96:281-8.

Pitot B, McCulloch ME, Zoghbi WA. Evaluation of global and regional right ventricular systolic function in patients with pulmonary hypertension using a novel speckle tracking method. Am J Cardiol 2006;98:699-704.

Jamal F, Bergerot C, Argauld L, Loufourt J, Ovize M. Longitudinal strain quantitates regional right ventricular contractile function. Am J Physiol Heart Circ Physiol 2003;285:H2842-7.

Verhaert D, Mullens B, Borowski A, Popovic ZB, Curtin RJ, Thomas JD, Tang WH. Right ventricular response to intensified medical therapy in advanced decompensated heart failure. Circ Heart Fail 2010;3:340-6.

Fine NM, Chen L, Bastiansen PM, Frantz RP, Pelliccia PA, Oh JK, Kane GC. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging 2013;6:711-21.

Simonneau G, Galli N, Rubin LJ, Langleben D, Seeger W, Domejnhetti G, Gibbs S, Lebec D, Speich R, Beggerti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43(12 Suppl S):S3-12.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pelliccia PA, Peicard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group, American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

Abbas AE, Forruin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol 2003;41:1021-7.

Park JH, Negishi K, Kwon DH, Popovic ZB, Grimm RA, Marwick TH. Validation of global longitudinal strain and strain rate as reliable markers of right ventricular dysfunction: comparison with cardiac magnetic resonance and outcome. J Cardiovasc Ultrasound 2014;22:113-20.

Pencina MJ, D’Agostino RB Sr, D’Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-72; discussion 207-12.

Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.

Amundsen BH, Helle-Valle T, Edwardsen T, Torg H, Crosby J, Lyseggen E, Stusuljen A, Ilhen H, Lima JA, Smitsnet OA, Slordahl SA. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-93.

Toyoda T, Baba H, Akasaka T, Akiyama M, Neshi Y, Tomita J, Suk-
mawan R, Koyama Y, Watanabe N, Tamano S, Shinomura R, Komuro I, Yoshida K. Assessment of regional myocardial strain by a novel automated tracking system from digital image files. *J Am Soc Echocardiogr* 2004;17:1254-8.

20. Thomas JD, Popovic ZB. Assessment of left ventricular function by cardiac ultrasound. *J Am Coll Cardiol* 2006;48:2012-25.

21. Geyer H, Caraccioolo G, Abe H, Wilansky S, Caret S, Gentile F, Neuer HJ, Khandheria B, Narula J, Sengupta PP. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr* 2010;23:351-69; quiz 453-5.

22. Nahum J, Bensaïd A, Dussault C, Macron L, Clémence D, Bouhemad B, Monin JL, Rande JL, Gueret P, Lim P. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients. *Circ Cardiovasc Imaging* 2010;3:249-56.

23. Puwanant S, Park M, Popovic ZB, Tang WH, Farha S, George D, Sharp J, Punlawangagoon J, Loyd JE, Erzurum SC, Thomas JD. Ventricular geometry, strain, and rotational mechanics in pulmonary hypertension. *Circulation* 2010;121:259-66.

24. Park JH, Kusunose K, Motoki H, Kwon DH, Grimm RA, Griffin BP, Marwick TH, Popovic ZB. Assessment of Right Ventricular Longitudinal Strain in Patients with Ischemic Cardiomyopathy: Head-to-Head Comparison between Two-Dimensional Speckle-Based Strain and Velocity Vector Imaging Using Volumetric Assessment by Cardiac Magnetic Resonance as a “Gold Standard”. *Echocardiography* 2014 Sep 18 [Epub]. http://dx.doi.org/10.1111/echo.12740.

25. Brusow MR, Zisman LS, Lowes BD, Abrahim WT, Badesch DB, Groves BM, Voelkel NF, Lynch DM, Quaife RA. The pressure-overloaded right ventricle in pulmonary hypertension. *Chest* 1998;114(1 Suppl):301S-6S.

26. Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Hsiao JF, Maalouf JF, McCully RB, Miller FA, Pellikka PA, Oh JK, Kane GC. Right ventricular strain for prediction of survival in patients with pulmonary arterial hypertension. *Chest* 2011;139:309-316.

27. Bove AA, Santamore WP. Ventricular interdependence. *Prog Cardiovasc Dis* 1981;23:165-88.

28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristics (ROC) curve. *Radiology* 1982;143:29-36.