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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 = 0.590, $p < 0.001$). 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.[4)5)] Because transthoracic 2-dimensional echocardiography (2DE) gives us important information about

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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.[6] Moreover, conventional velocity and displacement based analyses can be affected by translational motion of the heart and respiratory variation.[7] New 2-dimensional strain echocardiography enables quantification of both regional and global myocardial function in a simple and angle-independent manner.[8] Although 2-dimensional strain echocardiography was introduced to evaluate global left ventricular (LV) function, it has recently been used to assess RV function.[9][10]

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.[11] Because RV has different anatomy and function compared with LV, the simple application of strain algorithm to RV remains problematic. Also, there are several vender-different algorithms in the measurement of strain. Velocity vector imaging software (VVI; Axius, 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.[12] 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.[13] 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 end-systolic 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.[6] RV myocardial performance (Tei) index was defined as the ratio of isovolumic relaxation time and isovolumic contraction time divided by ejection time of RV.[6]

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.[6] 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.[14] 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.[15] Myocardial velocity is derived as the ratio between frame-to-frame displacement of the speckles and the time interval.[8] 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.[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.[17] The event-free curves were based on Kaplan-Meier analyses stratified by GLSRV value and the comparisons were made by Log-rank 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 ± 14 years old) were included in this study. Their mean duration of disease was 46 ± 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 ± 14
Female gender (%)	40 (78)
BMI (kg/m^2)	33.4 ± 15.2
Functional classification	
NYHA FC I/II	2 (4%)/31 (61%)
6 min walking distance (m)	411 ± 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 ± 1.8
Creatinine (g/dL)	0.9 ± 0.2
BNP (pg/mL)	155 ± 469 (range: 5–3216)
Echocardiographic data	
RV wall thickness (mm)	9.5 ± 3.0
RA area (cm^2)	22.5 ± 9.4
RV end-diastolic area (cm^2)	25.6 ± 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 ± 7.7
RV fractional area change (%)	32.1 ± 10.1
TAPSE (cm)	1.54 ± 0.49
RV Tei index	0.51 ± 0.25
Notching of RVOT Doppler flow signal	36 (71%)
Estimated RA pressure (mm Hg)	12.1 ± 6.3
TR Vmax (m/sec)	3.8 ± 0.6
Estimated RV systolic pressure (mm Hg)	60.2 ± 19.5
Catheterization data (n = 42)	
PA pressure (systolic/diastolic, mm Hg)	86.6 ± 24.4/36.8 ± 13.4
PA pressure, mean (mm Hg)	53.5 ± 18.7
PCWP (mm Hg)	13.8 ± 4.1
RA pressure (mm Hg)	10.6 ± 6.3
CI (L/min/m^2)	2.6 ± 1.0
PVR (WU)	10.1 ± 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

Table 2. Two-dimensional strain analysis of right ventricle

	Peak longitudinal strain (%)	Peak time to strain (msec)	Peak systolic strain rate (s^{-1})
Global RV	-16.1 ± 5.0	387 ± 70	-1.3 ± 0.4
RV free wall, base	-23.5 ± 10.3	406 ± 87	-1.8 ± 0.9
RV free wall, mid	-16.9 ± 6.8	407 ± 80	-1.3 ± 0.4
RV free wall, apex	-13.0 ± 8.0	389 ± 115	-1.1 ± 0.6
RV free wall, total	-17.8 ± 6.0	393 ± 85	-1.4 ± 0.5
VS, base	-16.8 ± 6.0	400 ± 96	-1.3 ± 0.4
VS, mid	-13.5 ± 5.2	381 ± 87	-1.1 ± 0.6
VS, apex	-13.2 ± 6.5	364 ± 93	-1.1 ± 0.6
VS, total	-14.5 ± 4.8	382 ± 66	-1.2 ± 0.4

RV: right ventricle, VS: ventricular septum

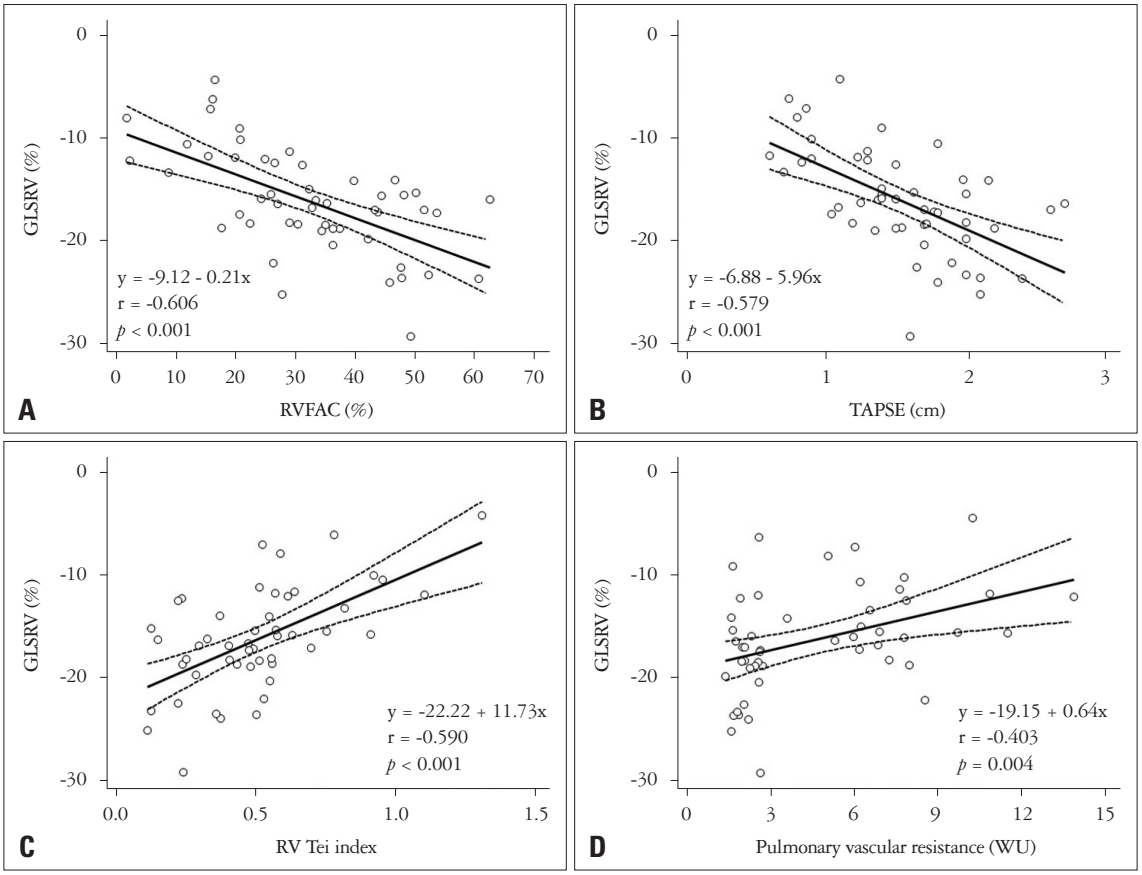

Fig. 1. Correlations between global longitudinal strain of right ventricle (GLSRV) and echocardiographic parameters. GLSRV shows good negative correlation with RV fractional area change (RVFAC, A), tricuspid annular plane systolic excursion (TAPSE, B), and RV Tei index (C). Also, GLSRV demonstrates significant correlation with pulmonary vascular resistance calculated by echocardiography (D).

significantly decreased than normal RV strain values in the previously reported paper.[6] The average GLSRV was -16.1 ± 5.0% and average systolic strain rate of RV was -1.28 ± 0.38 s^{-1}. GLSRV showed a good negative correlation with RVFAC, TAPSE and RV Tei index. GLSRV demonstrated a significant correlation with pulmonary vascular resistance (PVR) calculated by right heart catheterization (Fig. 1). RV free wall strain also revealed significant correlations with RVFAC (r = -0.629, p < 0.001), TAPSE (r = -0.551, p < 0.001), RV Tei index (r = 0.607, p < 0.001) and PVR (r = 0.495, p < 0.001).

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-

Table 3. Univariate analysis with Cox proportional regression analysis for clinical events and all causes of mortality

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	2.136	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	1.133	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

Table 4. Multivariate analysis with Cox proportional regression analysis for clinical events and all causes of mortality

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)	1.545	0.422	5.657	0.517
6MWD (per SD)	0.682	0.263	1.768	0.515
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

	GLSRV		Reclassified		Net correctly reclassified (%)†
	< -15.5%	≥ -15.5%	Increased risk*	Decreased risk*	
Adverse clinical event					
Individuals with adverse clinical event (n = 20)			4	2	10.0
TAPSE ≥ 1.5 cm	4	4			
TAPSE < 1.5 cm	2	10			
Individuals without adverse clinical event (n = 31)			2	6	12.9
TAPSE ≥ 1.5 cm	18	2			
TAPSE < 1.5 cm	6	5			
Net reclassification improvement‡					22.9
p-value					0.067
Death					
Individuals with death (n = 12)			3	0	25.0
TAPSE ≥ 1.5 cm	2	3			
TAPSE < 1.5 cm	0	7			
Individuals without death (n = 39)			3	8	12.8
TAPSE ≥ 1.5 cm	20	3			
TAPSE < 1.5 cm	8	8			
Net reclassification improvement‡					37.8
p-value					0.012
Adverse clinical event					
Individuals with adverse clinical event (n = 20)			12	2	50.0
Pericardial effusion (-)	4	12			
Pericardial effusion (+)	2	2			
Individuals without adverse clinical event (n = 31)			5	2	-9.7
Pericardial effusion (-)	22	5			
Pericardial effusion (+)	2	2			
Net reclassification improvement‡					40.3
p-value					0.025
Death					
Individuals with death (n = 12)			8	0	66.7
Pericardial effusion (-)	2	8			
Pericardial effusion (+)	0	2			
Individuals without death (n = 39)			9	4	-16.1
Pericardial effusion (-)	24	9			
Pericardial effusion (+)	4	2			
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

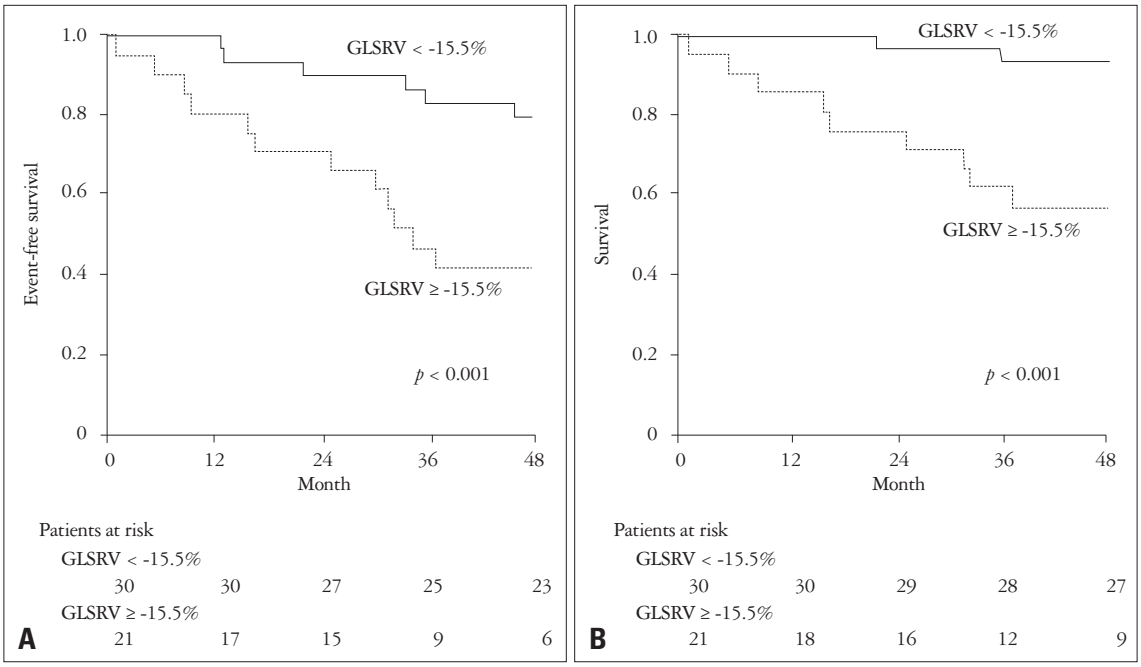

Fig. 2. Event-free survival and total survival curve by Kaplan-Meier analysis. Patients with impaired global longitudinal strain of right ventricle (GLSRV) (≥ -15.5%) showed lower event-free survival (80 ± 7% vs. 42 ± 11% at 4 years, $p < 0.001$) (A) and lower survival (93 ± 5% vs. 57 ± 11% at 4 years, $p < 0.001$) (B) than preserved GLSRV patients. p value refers to Log-rank test.

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.[6] Delineation of the endocardial border in the measurement of RVFAC may limit the reliability in assessing RV function. Tethering and translational motion can affect the use of velocity and displacement based measurements like TAPSE.[10]

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,[18][19] 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.[10] Myocardial strain can be used to detect early stages of myocardial dysfunction and it has prognostic power in patients with chronic heart failure.[20-22] Though strain is initially developed to measure LV mechanics, speckle strain has been utilized for the assessment of the RV in some disease categories.[8][10][23] 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.[24] 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%).[6] In PAH patients, chronic pressure and volume overload of RV leads to both structural and functional changes.[1][25] Puwanant et al.[23] 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.[23][26] 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.[23)27)] 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 (difference = 0.06, p = 0.0448) after comparison of AUC's with the method suggested by Hanley and McNeil.[28)]

This study has several limitations. First, this is a retrospective cohort study with a variety of disease causes and concurrent PAH therapy, which may have affected the pulmonary arterial systolic pressure and subsequent RV loading conditions. Second, there was no reference study like cardiac magnetic resonance imaging in the measurement of RV systolic function objectively. A prospective study with a large number of patients with an objective comparison method will be needed to confirm the correlations and the clinical impact of this measurement.

FUTURE DIRECTIONS

With RV strain validated as an important prognostic variability in PAH patients, it will be critical to test whether it can serve as a surrogate endpoint for novel therapies in PAH. If improvement in GLSRV with vasodilator or other intervention identifies those with better clinical outcomes, then drug development in PAH could be accelerated.

In conclusion, GLSRV showed significant correlations with conventional echocardiographic parameters of the RV systolic function. Lower absolute GLSRV is associated with the presence of adverse clinical events and deaths in patients with PAH.

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