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Clinical Research

Myocardial Deformation in the Systemic Right Ventricle: Strain Imaging Improves Prediction of the Failing Heart

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See editorial by Chen-Tournoux et al., pages 1341—1343 of this issue.

ABSTRACT

Background: Predicting heart failure events in patients with a systemic right ventricle (sRV) due to transposition of the great arteries (TGA) is important for timely intensification of follow-up. This study assessed the value of strain compared with currently used parameters as predictor for heart failure—free survival in patients with sRV.

Methods: In participants of a multicentre trial, speckle-tracking echocardiography (STE) was performed to assess global longitudinal strain (GLS), mechanical dispersion (MD), and postsystolic shortening (PSS). Cox regression was used to determine the association of STE parameters with the combined end point of progression of heart failure and death, compared with cardiovascular magnetic resonance (CMR) and computed tomography (CT) derived parameters.

Results: Echocardiograms of 60 patients were analyzed (mean age 34 $\pm$ 11 years, 65% male, 35% congenitally corrected TGA). Mean GLS was -13.5 ± 2.9%, median MD was 49 (interquartile range [IQR]

RÉSUMÉ

Contexte : La prévision des manifestations d'insuffisance cardiaque chez les patients présentant un ventricule droit systémique (VDs) en raison d'une transposition des gros vaisseaux (TGV) s'avère importante pour l'intensification du suivi en temps opportun. Cette étude a permis d'évaluer la valeur de la déformation myocardique comme facteur prévisionnel de survie sans insuffisance cardiaque par rapport aux paramètres actuellement utilisés chez les patients présentant un VDs.

Méthodologie : Chez les participants d'un essai multicentrique, une échocardiographie de suivi des marqueurs acoustiques (ESMA) a été réalisée afin d'évaluer la déformation longitudinale globale (DLG), la dispersion mécanique (DM) et le raccourcissement postsystolique (RPS). Le modèle de régression de Cox a servi à déterminer l'association des paramètres d'ESMA et du paramètre d'évaluation regroupant la progression de l'insuffisance cardiaque et le décès,

In patients with transposition of the great arteries (TGA), either congenitally corrected (ccTGA) or corrected by means of a Mustard or Senning atrial switch procedure (TGA-M/S), the morphologic right ventricle (RV) supports the systemic circulation. Gradual systemic right ventricle (sRV) failure is a major source of morbidity and mortality in these patients.[1,2] Predicting clinical heart failure in patients with sRV remains difficult and risk stratification based on conventional clinical findings and patient history alone still falls short.

Increasing data suggest that global measures of myocardial deformation by speckle-tracking echocardiography (STE) are associated with ventricular function and worse clinical outcome in patients with sRV.[3,4] In the systemic left ventricle (LV), global longitudinal strain (GLS) has been shown to

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30-76) ms, and 14 patients (23%) had PSS. During a median 8 (IQR 7-9) years, 15 patients (25%) met the end point. GLS, MD, and PSS were all associated with heart failure—free survival in univariable analysis. After correction for age, only GLS (optimal cutoff $> -10.5\%$) and CMR/CT-derived sRV ejection fraction (optimal cutoff $< 30\%$) remained associated with heart failure—free survival: hazard ratio (HR) 8.27, 95% confidence interval (CI) 2.50-27.41 ($P < 0.001$), and HR 4.34, 95% CI 1.48-12.74 ($P = 0.007$), respectively). Combining GLS and ejection fraction improved prediction, with patients with both GLS $> -10.5\%$ and sRV ejection fraction $< 30\%$ at highest risk (HR 19.69, 95% CI 4.90-79.13; $P < 0.001$).

Conclusions: **The predictive value of GLS was similar to that of CMR/CT-derived ejection fraction. The combination of GLS and ejection fraction identified patients at highest risk of heart failure and death. Easily available STE parameters can be used to guide follow-up intensity and can be integrated into future risk prediction scores.**

comparativement à des paramètres d'imagerie par résonance magnétique cardiovasculaire (IRMC) et de tomodensitométrie (TDM).

Résultats : **Les échocardiogrammes de 60 patients (âge moyen de 34 ± 11 ans, 65 % de sexe masculin, 35 % présentant une transposition congénitalement corrigée des gros vaisseaux) ont été analysés. La DLG moyenne était de -13,5 ± 2,9 % et la DM médiane, de 49 ms (intervalle interquartile de 30-76 ms), et un RPS a été noté chez 14 patients (23 %). Sur une période médiane de 8 ans (7-9 ans), le paramètre d'évaluation a été atteint chez 15 patients (25 %). La DLG, la DM et le RPS étaient tous associés à la survie sans insuffisance cardiaque dans une analyse unidimensionnelle. Après correction pour tenir compte de l'âge, seules la DLG (valeur seuil optimale > -10,5 %) et la fraction d'éjection du VDs en IRMC/TDM (valeur seuil optimale < 30 %) sont demeurées associées à la survie sans insuffisance cardiaque : rapport des risques instantanés (RRI) de 8,27 et de 4,34, intervalle de confiance (IC) à 95 % de 2,50-27,41 et de 1,48-12,74, $p < 0,001$ et $p = 0,007$, respectivement. La combinaison de la DLG et de la fraction d'éjection a amélioré la valeur prévisionnelle; les patients les plus à risque présentaient une DLG > -10,5 % et une fraction d'éjection du VDs < 30 % (RRI de 19,69, IC à 95 % de 4,90-79,13; $p < 0,001$).**

Conclusions : **La valeur prévisionnelle de la DLG a été similaire à celle de la fraction d'éjection en IRMC/TDM. La combinaison de la DLG et de la fraction d'éjection a permis de cibler les patients présentant le risque le plus élevé d'insuffisance cardiaque et de décès. Des paramètres d'ESMA faciles à mesurer peuvent servir à déterminer le degré de suivi nécessaire. Leur intégration aux scores de prévision du risque est envisageable à l'avenir.**

be a better predictor of outcome than traditional echocardiography-derived LV ejection fraction (EF).[5-7] STE enables detection of more subtle changes in cardiac contractile function, including mechanical dispersion (MD), a marker of electromechanical heterogeneity of the myocardium, and postsystolic shortening (PSS), late systolic shortening appearing after aortic valve closure that may stem from pathologic prolonged contraction or delayed relaxation.[8] In hypertrophic cardiomyopathy, MD has been shown to correlate with myocardial fibrosis,[9] which in turn is associated with clinical outcome in patients with sRV.[10] In addition, PSS has prognostic value for cardiovascular events and death in the general population.[11]

The prognostic value of STE measures for heart failure in patients with sRV remains elusive. Guidelines recommend cardiovascular magnetic resonance (CMR) for serial evaluation of sRV function,[12] even though echocardiography is the first-line diagnostic tool and STE measures may be sensitive prognostic markers. Therefore, the present study aimed to determine the value of STE measures as predictors for heart failure—free survival in patients with an sRV, and to compare this to the value of conventional measures of sRV function.

Methods

Study population

Speckle-tracking analysis was performed on echocardiograms of participants in the VAL-SERVE (Valsartan in Systemic Right Ventricle) trial.[13] A detailed description of the design, conduct, and long-term follow-up of this trial has been published previously.[13-15] In short, the VAL-SERVE trial was a multicentre double-blinded placebo-controlled trial that enrolled 88 adults with TGA-M/S or ccTGA from 2006 to 2009 and randomly assigned them to valsartan or placebo (1:1) for 3 consecutive years. The primary outcome, change in RV EF, was evaluated by means of CMR or, in patients with contraindications for CMR (n = 25; 28%), multidetector-row cardiac computed tomography (CT) with the use of standardized protocols.[14] Volume and function analysis was performed by a single blinded observer (T.v.d.B.) at baseline and end of follow-up.[13] The study was approved by the Ethics Committees of all participating centres and complies with the declaration of Helsinki.

Speckle-tracking echocardiography

Echocardiographic examinations were performed at baseline and 1-year intervals throughout the study period, as previously described.[14] In the present study, cine loops for assessment of longitudinal 2-dimensional strain of the sRV were retrieved and offline analysis performed with the use of Echopac software version 13.1.1 (GE Medical Systems, Horten, Norway). Echocardiograms obtained with the use of Philips echocardiography machines were excluded because of reservations about intervendor variability of the STE measures, especially of regional measurements.[16,17] STE analysis was performed on the first available 4-chamber images with adequate image quality and a frame rate of ≥ 40 Hz (median frame rate 56 [interquartile range (IQR) 47-65] Hz). One patient had atrial fibrillation during echocardiography, but because there was no tachycardia and low heart rate variability, this patient was included in the analysis. The interventricular septum was included in the analysis of the sRV. Patients were included if all 6 segments of the sRV from the 4-chamber view could be adequately traced, and they were followed from date of STE measurements forward. STE analysis was performed by a single observer blinded for clinical outcome (O.I.W.) by marking the endocardium, defining the width of the region of interest, and triggering the automatic computation. The consistency of the movement of the myocardium and the automatically defined tracking contour was assessed visually, and manually readjusted if necessary. Peak global longitudinal strain (GLS) was defined as the peak negative value on the strain curve during the entire cardiac cycle across the entire sRV wall. Mechanical dispersion (MD) was calculated as the standard deviation of contraction durations of the 6 sRV segments. The postsystolic index (PSI) was calculated per segment as 100 × ([GLS − systolic peak longitudinal strain]/GLS). PSI was averaged over the segments to provide a mean value. Based on previous evidence evaluating PSS, PSS was defined as being present in an sRV wall segment if PSI was ≥ 20% (Fig. 1).[8,11,18]

Outcome

Our primary outcome was defined as heart failure–free survival, a composite of progression of heart failure (defined as increase of New York Heart Association [NYHA] functional class, start or increase of diuretics dose related to clinical heart failure, hospital admission for heart failure, or need for heart transplantation)[15] and all-cause mortality.

Statistical analysis

Data are expressed as n (%), mean ± standard deviation (SD), or median (interquartile range [IQR]), as appropriate. Statistical analyses were performed with the use of Rstudio version 1.1.453 (RStudio Team, Boston, MA) and SPSS version 25 (IBM, Armonk, NY). P values of < 0.05 were considered to be statistically significant. Intraobserver variability for GLS was assessed by means of intraclass correlation coefficient (ICC) and Bland-Altman plot on a random subset of patients. Clinical differences between included and excluded patients, as well as differences in STE measures between patients with TGA-M/S and ccTGA, and between patients with and without ventricular pacing, were evaluated with the use of Student independent t tests and χ^2 tests, as appropriate.

Heart failure–free survival was expressed with the use of Kaplan-Meier survival curves. Univariable and multivariable Cox proportional hazards regression was performed to identify associations between clinical features, CMR/CT-derived measures of ventricular function, STE measures, and heart failure–free survival. Continuous parameters with a nonlinear relation with the outcome were dichotomized based on individual receiver operating characteristic curves. Bivariable nested models with age and the imaging parameters of significance in univariable analysis were performed to assess which parameters remained predictive independently from age. Model performance over baseline was compared by means of likelihood ratio χ^2 statistics. Patients with ccTGA, ventricular pacing, and CT instead of CMR were excluded in sensitivity analyses. In addition, sensitivity analysis for a composite end point combining only heart failure admissions and all-cause mortality was performed, excluding patients with start or increase of diuretics or increase in NYHA functional class.

Finally, Cox regression was performed with the use of other commonly used parameters previously associated with clinical outcome in patients with sRV, including N-terminal pro–B-type natriuretic peptide (NT-proBNP), tricuspid regurgitation, electrocardiography-derived parameters, and parameters derived from cardiopulmonary exercise testing.[19-21] Exploratory multivariable Cox regression with Firth penalized likelihood[22] including STE variables, patient characteristics significantly associated with heart failure–free survival in univariable analysis, and the parameters with the highest C-statistic per diagnostic modality was performed to form a hypothesis on the additional value of STE measures in the complete clinical analysis of patients with sRV, creating a final model by means of backward-stepwise selection.

Results

Of the 88 trial participants, 13 did not have echocardiograms obtained with a GE Vivid scanner. Of the remaining 75 participants, 60 patients with STE measures of the entire sRV wall could be included (65% male, 35% ccTGA, mean age 34 ± 11 years, 13% with ventricular pacing). Intraobserver agreement of GLS was excellent (ICC 0.94, 95% confidence interval [CI] 0.87-0.97; Bland-Altman plot in Supplemental Fig. S1). In 75% of patients (n = 45), STE was adequately measured at inclusion of the VAL-SERVE trial, and the remaining 25% were included at follow-up echocardiography during the trial period (1.2 [IQR 0.5-4.1] years after inclusion in the original trial). Baseline characteristics are presented in Table 1. One ccTGA patient had a prior tricuspid valve replacement. Excluded patients more often had TGA-M/S (84% vs 65%; P = 0.045), were more often symptomatic (NYHA functional class ≥ II in 50% vs 23%; P = 0.012), and had slightly lower RV EF (34 ± 7% vs 39 ± 9%; P = 0.005).

Speckle-tracking echocardiography

Mean GLS of the sRV was −13.5 ± 2.9% with a median mechanical dispersion of 49 (IQR 30-76) ms and presence of postsystolic shortening in 14 patients (23%). There were no significant differences in GLS and MD between TGA-M/S and ccTGA patients: −13.2 ± 2.4 vs −14.1 ± 3.8 (P = 0.28) and 41 (25-73) vs 69 (49-80) (P = 0.23), respectively (Table 2). Fewer TGA-M/S patients than ccTGA patients had PSS (15% vs 38%; P = 0.047), especially in the free wall (5% vs 38%; P = 0.001).

Patients with ventricular pacing (n = 8) had a lower GLS (−10.5 ± 2.1 vs −13.9 ± 2.8; P = 0.001) and more MD (87 [61-103] vs 46 [28-71]; P = 0.015) than patients without ventricular pacing, but no significant difference in PSS was seen (3/8 patients vs 11/51 patients; P = 0.31).

Adverse events

During a median of 8.2 (IQR 7.0-8.8) years, 15 patients reached the composite end point. Fourteen patients had worsening heart failure (1 increased from NYHA functional class I to class III, 5 were started on diuretics (4 in NYHA I, 1 in NYHA II), 1 patient (already NYHA III at baseline) was increased in dose of diuretics, 7 were admitted for heart failure, and none needed heart

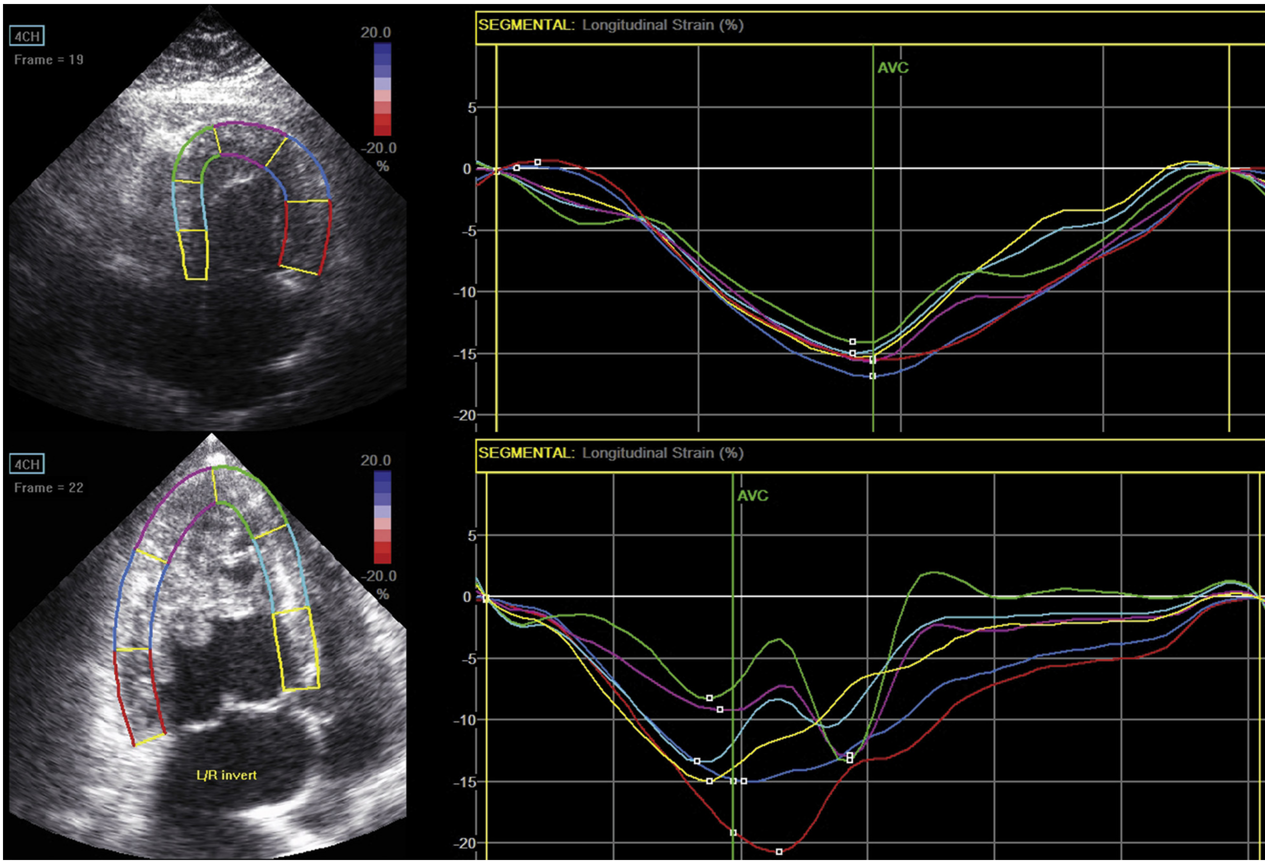

Figure 1. Longitudinal strain analysis of the systemic right ventricle. (**Top**) Strain analysis of a patient with congenitally corrected transposition of the great arteries, with a normal strain profile with little mechanical dispersion and no signs of postsystolic shortening. (**Bottom)** Strain analysis of a patient with transposition of the great arteries corrected by means of a Mustard or Senning atrial switch procedure, with mechanical dispersion and postsytolic shortening of the apical segments.

transplantation). In total, 4 patients died (2 of end-stage heart failure, 1 of sepsis, and 1 suddenly while sleeping). Only 1 death was included in the composite end point, because the other patients had prior heart failure events. Cumulative heart failure—free survival at 9-year follow-up was 60% (Supplemental Fig. S2).

Optimal imaging parameters for event prediction

Patients who experienced events were older, more often had ccTGA, and more often had symptoms at baseline. Of the clinical characteristics, age was the most valuable determinant for heart failure—free survival (HR = 2.19/10years [95% CI 1.53-3.14]; $P < 0.001$) with the largest C-statistic (0.77). GLS, MD, and PSS were all associated with heart failure—free survival in univariable analysis (HR = 1.25/% [95% CI 1.01-1.54], $P = 0.037$, HR = 1.13/10ms [95% CI 1.00-1.27], $P = 0.048$, and HR = 4.00 [95% CI 1.44-11.10]), $P = 0.008$, respectively) (Table 1). GLS and CMR/CT derived RV EF did not show a linear relation with the outcome (Supplemental Figs. S3 and S4) and were therefore dichotomized, with optimal cutoff values of −10.5% (sensitivity 40%, specificity 92%) and 30% (sensitivity 46%, specificity 96%), respectively. Both GLS > −10.5% and RV EF < 30% were significantly associated with heart failure—free survival in univariable analysis (HR 6.01, 95% CI 1.99-18.13 [$P < 0.001$] and HR 6.18, 95% CI 2.13-17.90 [$P < 0.001$], respectively; Fig. 2), with similar predictive value (C-statistics 0.69 and 0.68, respectively).

After correction for age, only GLS > −10.5% and CMR/CT-derived RV EF < 30% remained independently associated with heart failure—free survival: HR 8.27, 95% CI 2.50-27.41 ($P < 0.001$) and HR 4.34, 1.48-12.74 ($P = 0.007$), respectively. A model combining GLS and RV EF significantly improved the predictive value over models with only one of them (C-statistic 0.74; $P = 0.019$). Of the 15 patients with decreased GLS (> −10.5%) or RV EF (< 30%), 6 had decreased GLS without decreased RV EF, 5 had decreased RV EF without decreased GLS, and 4 had decreased GLS and RV EF both. Patients with either GLS > −10.5% or RV EF < 30% had a 4-fold higher risk of events compared with patients with preserved GLS and RV EF (HR 4.21, 95% CI 1.19-14.77; $P = 0.026$), whereas the risk was 19-fold higher in patients with both GLS > −10.5% and RV EF < 30% (HR 19.69, 95% CI 4.90-79.13; $P < 0.001$; Fig. 3).

Sensitivity analyses

Univariable sensitivity analyses are presented in Supplemental Table S1. When excluding ccTGA patients or

Table 1. Baseline characteristics and univariable analysis for heart failure–free survival

	All patients (n = 60)	No events (n = 45)	Events (n = 15)	Univariable regression	
				HR (95% CI)	*P* value
Patient characteristics					
Age at inclusion, y*	34 ± 11	31 ± 8	44 ± 13	2.19 (1.53-3.14)	< 0.001
Male	48 (65)	39 (67)	9 (60)	0.56 (0.20-1.61)	0.28
ccTGA	21 (35)	13 (29)	8 (53)	3.21 (1.15-8.94)	0.026
Complex TGA†	20 (33)	14 (31)	6 (40)	1.31 (0.46-3.74)	0.62
NYHA ≥ II	14 (23)	7 (16)	7 (47)	3.52 (1.27-9.76)	0.016
History of SVT	18 (30)	13 (29)	5 (33)	1.24 (0.42-3.62)	0.70
Pacemaker	14 (23)	10 (22)	4 (27)	1.60 (0.51-5.09)	0.42
Medication					
Study medication (valsartan)	27 (45)	19 (42)	8 (53)	1.42 (0.51-3.91)	0.50
β-Blocker	9 (15)	5 (11)	4 (27)	2.23 (0.71-7.03)	0.17
Diuretics	5 (8)	1 (0)	4 (27)	6.02 (0.89-19.17)	0.002
CMR/CT					
CT	16 (27)	11 (24)	5 (33)		
RV EDV, mL*	267 ± 71	245 ± 69	292 ± 69	1.06 (1.00-1.12)	0.047
RV ESV, mL*	158 ± 58	146 ± 51	196 ± 64	1.09 (1.02-1.16)	0.017
LV EDV, mL*	163 ± 43	162 ± 36	166 ± 61	1.07 (0.93-1.24)	0.32
LV ESV, mL*	73 ± 30	70 ± 22	83 ± 48	1.19 (1.01-1.39)	0.044
RV EF, %	39 ± 9	41 ± 7	34 ± 13	0.92 (0.87-0.98)	0.013
LV EF, %	56 ± 10	57 ± 8	52 ± 12	0.96 (0.91-1.01)	0.12
RV EF < 30%	9 (15)	2 (4)	7 (46)	6.18 (2.13-17.90)	< 0.001
Speckle-tracking echocardiography					
RV GLS, %	−13.5 ± 2.9	−13.9 ± 2.5	−12.2 ± 3.7	1.25 (1.01-1.54)	0.037
RV MD, ms*	49 (30-76)	44 (27-74)	68 (46-82)	1.13 (1.00-1.27)	0.048
RV PSS	14 (23)	6 (13)	8 (53)	4.00 (1.44-11.10)	0.008
RV GLS > −10.5%	10 (17)	4 (9)	6 (40)	6.01 (1.99-18.13)	< 0.001
Other diagnostic modalities					
Ventricular paced rhythm	8 (13)	5 (11)	3 (20)	2.50 (0.69-9.10)	0.17
QRS duration*	111 [100-126]	110 [97-124]	114 [100-158]	1.29 (1.05-1.58)	0.014
Absence of sinus rhythm	13 (22)	8 (18)	5 (33)	3.34 (1.09-10.27)	0.036
Severe tricuspid regurgitation	8 (15)	2 (5)	6 (43)	10.32 (3.14-33.98)	< 0.001
NT-proBNP, ng/L (n = 53)‡	270 (136-573)	190 (102-324)	534 (338-2142)	3.61 (2.02-6.48)	< 0.001
Peak heart rate, beats/min (n = 57)*§	155 ± 7	160 ± 31	138 ± 31	0.80 (0.67-0.95)	0.010
Peak systolic blood pressure, mm Hg (n = 55)*§	174 ± 26	175 ± 26	169 ± 27	0.91 (0.69-1.20)	0.51
Peak $V'O_2$, mL/min/kg (n = 55)	28 ± 7	29 ± 7	24 ± 7	0.90 (0.83-0.97)	0.005

Values are presented as n (%), mean ± SD, or median (interquartile range).

ccTGA, congenitally corrected transposition of the great arteries; CI, confidence interval; CMR, cardiovascular magnetic resonance; CT, computed tomography; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricle; MD, mechanical dispersion; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PSS, postsystolic shortening; RV, right ventricle; SVT, supraventricular tachycardia; TGA, transposition of the great arteries; $V'O_2$, oxygen consumption.

* HR per 10-unit increase.

† TGA with ventricular septal defect or pulmonary stenosis.

‡ HR for log-transformed variable.

§ HR corrected for β-blocker and antiarrhythmic medication use.

patients with ventricular pacing, the HR of MD remained similar to that of the full cohort, although no longer significant. In TGA-M/S patients, the HR of GLS increased (HR 6.85, 95% CI 1.35-24.85), whereas that of RV EF decreased (HR 5.51, 95% CI 1.09-27.79). When excluding patients with ventricular pacing, GLS, PSS, and RV EF remained associated with events: HR 6.01 (95% CI 1.69-21.34), HR 3.17 (1.02-9.89), and HR 5.52 (1.60-19.06), respectively. The predictive value of RV EF but not GLS seemed to increase when excluding patients with CT-derived RV EF: HR 6.56 (95% CI 1.73-24.82) and HR 3.05 (0.61-15.18), respectively.

Sensitivity analysis did not change the direction of the association (HR = 3.22 [95% CI 0.64-16.17]) of GLS > −10.5% for the end point combining heart failure admissions and death only.

Other parameters for event prediction

The most valuable determinants of heart failure–free survival from other diagnostic modalities were QRS duration (HR 1.29/10 ms, 95% CI 1.05-1.58), presence of severe tricuspid regurgitation (HR 10.32, 95% CI 3.14-33.98), NT-proBNP level (HR 3.61, 95% CI 2.02-6.48), and peak heart rate (HR 0.80/10 beats/min, 95% CI 0.67-0.95; Table 1). In exploratory multivariable analysis including these determinants and basic patient characteristics (age, ccTGA, symptoms), addition of GLS > −10.5% improved the model (C-statistics of 0.90 and 0.95, respectively; $P < 0.001$), whereas the addition of RV EF < 30% did not improve the predictive model (C-statistic 0.91; $P = 0.14$). GLS > −10.5% remained a promising predictor included in the final model after backward stepwise selection (Table 3).

Table 2. Right ventricular myocardial deformation parameters in TGA-M/S and ccTGA patients

Parameter	TGA-M/S (n = 39)	ccTGA (n = 21)	*P* value
GLS, %	−13.2 ± 2.4	−14.1 ± 3.8	0.28
Postsystolic index, %	1.6 (0.4-2.7)	4.9 (1.6-9.0)	0.059
PSS	6 (15)	8 (38)	0.047
PSS in sRV free wall	2 (5)	8 (38)	0.001
PSS in sRV septal wall	6 (15)	1 (5)	0.22
MD (ms)	41 (25-73)	69 (49-80)	0.23

Values are presented as n (%), mean ± SD, or median (interquartile range).

ccTGA, congenitally corrected transposition of the great arteries; GLS, global longitudinal strain; MD, mechanical dispersion; PSS, postsystolic shortening; sRV, systemic right ventricle; TGA-M/S, transposition of the great arteries corrected by means of a Mustard or Senning atrial switch procedure.

Discussion

This study showed that GLS, MD, and PSS of the sRV are associated with heart failure–free survival in patients with sRV. Furthermore, GLS had similar value as, and added value to, commonly used parameters in the prediction of heart failure-free survival.

STE measures in the sRV

To our knowledge, this study is the first to investigate MD and PSS in patients with sRV. Many patients had MD above the published upper range of normal for systemic LVs (56 ms),[23] which might relate to the high prevalence of myocardial fibrosis in the sRV.[24] In contrast, prevalence of PSS seemed to be lower in our cohort than in previously described low-risk cohorts (31%-35%).[8,11] PSS is thought to occur because of passive elastic recoil caused by heterogeneity between dyskinetic myocardial segments and healthy tissue, and its prevalence increases with age.[11,25] Patients with sRV are young, and heterogeneity may also be limited because the sRV is often diffusely affected. This study included both patients with TGA-M/S and patients with ccTGA. Despite the shared burden of systemic pressures, the RVs in these patients have functional and morphologic differences,[26] making comparisons between the two groups important. We did not detect significant differences in GLS and MD between TGA-M/S and ccTGA patients. This study also included patients with ventricular pacing, which is known to negatively affect GLS, regional strain, and dyssynchrony of the subaortic left ventricle.[27] In accordance, we saw decreased GLS and increased MD in sRV patients with ventricular pacing.

Optimal event prediction

Previous studies evaluating STE measures in patients with sRV showed associations of GLS with markers for heart failure and clinical outcomes during short-term follow-up.[3,4,28-30] GLS was found to correlate more than RV EF with exercise capacity and was previously suggested to be noninferior in prediction of adverse outcome to CMR-derived RV EF.[3,28] In contrast, regional sRV strain was not associated with heart failure in a recent study, possibly because regional strain values have higher variability than GLS.[16,30,31] The different analysis methods, including intervendor differences, might have contributed to the different results.

In our study, GLS was nonlinearly related to a composite of heart failure and death, with poor outcome in patients with GLS > −10.5%. Two previous studies investigating GLS described linear associations between GLS and clinical end points combining heart failure and arrhythmias.[3,4] One of those studies provided a cutoff point of > −10%.[4] Our more strict outcome definition and longer follow-up may have affected the linearity of the association.

The clear association between GLS and clinical heart failure is in line with previous research. Adding knowledge of GLS adds valuable information to event prediction, because patients with either decreased GLS or decreased RV EF already had higher risk of events than patients with both preserved GLS and RV EF. Exploratory multivariable analysis suggests that GLS could be a more potent predictor of heart failure–free survival than RV EF, because GLS and not RV EF added information to a multivariable model including other clinically relevant parameters, although this must be replicated in a larger cohort.

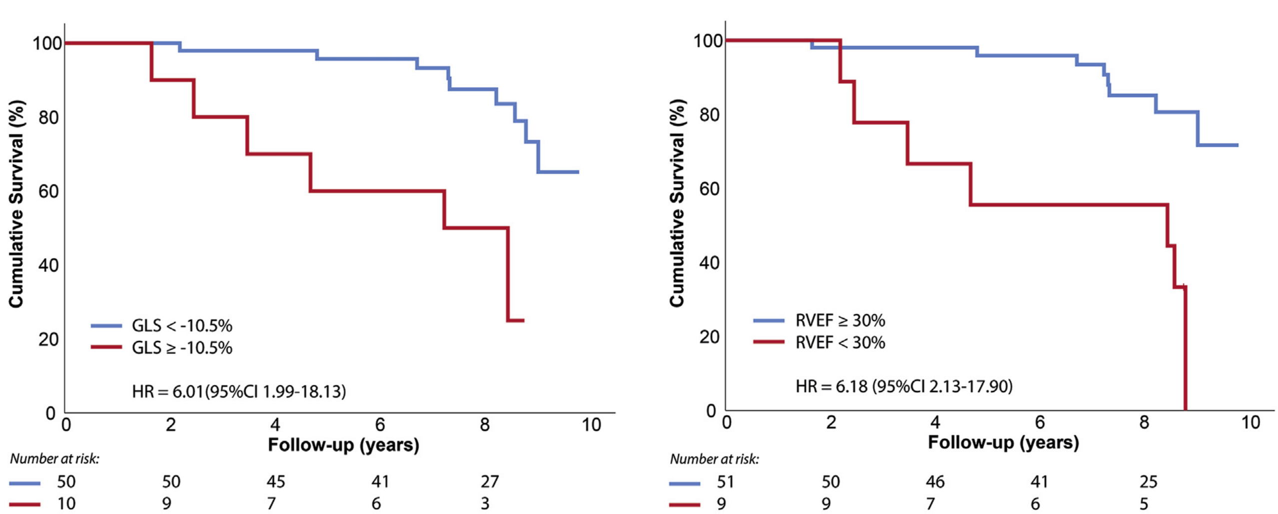

Figure 2. Kaplan-Meier analyses. Heart failure–free survival curves for systemic right ventricle global longitudinal strain (GLS) and right ventricle ejection fraction (RVEF). CI, confidence interval; HR, hazard ratio.

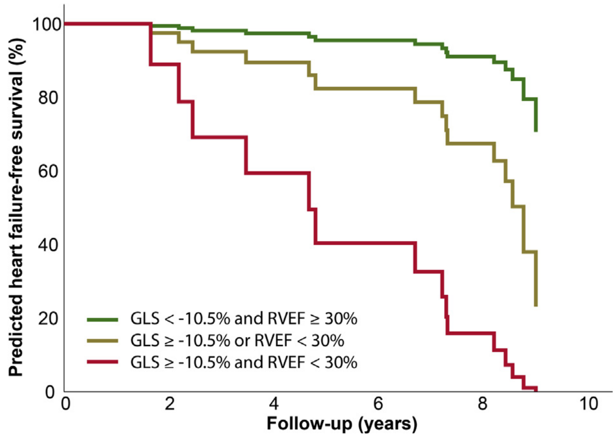

Figure 3. Prediction model. Cox proportional hazards model including systemic right ventricle global longitudinal strain (GLS) and right ventricle ejection fraction (RVEF).

Numerous studies have evaluated event-free survival in patients with sRV and aimed to identify risk predictors. Previously studied parameters associated with clinical outcome include NT-proBNP levels, severe tricuspid regurgitation, loss of sinus rhythm, and peak systolic blood pressure,[19-21,32,33] although the importance of these predictors differs among studies. Furthermore, previous investigations used combined clinical end points. The pathophysiology underlying the distinct components of these combined end points may vary, therefore studies regarding more uniform outcomes are valuable. The long follow-up in our cohort made it possible to study heart failure in patients with sRV. To place the value of STE measures in the complete clinical context, we assessed multiple parameters in our cohort, showing that a comprehensive examination has value in prognostication of heart failure in these patients. The exploratory analysis showed that including STE measures in the comprehensive analysis of these patients may be of great value, as it remained associated with the outcome.

Clinical implications

Gradual deterioration of sRV function leading to clinical heart failure is one of the main reasons for regular follow-up of patients with sRV. CMR is considered to be the gold standard for serial assessment of systolic sRV function.[12] However, its association with functional decline and exercise capacity remains limited.[28,34] Furthermore, access to CMR may be restricted by scanner availability, costs, and noncompatible implantable devices or other metallic objects. Adding STE measures to routine echocardiography in patients with sRV is a simple and low-cost way to quantitatively assess the sRV, which can also be done in patients unsuitable for CMR. Furthermore, STE measures contain information about myocardial deformation beyond systolic function. These easily available parameters can be used during follow-up and can be of value in future risk-prediction scores. Large studies including parameters of multiple diagnostic modalities including STE will help to create risk models to determine follow-up intensity of these patients. As in other populations, STE markers of myocardial dyssynchrony may also be of value in predicting ventricular arrhythmias in patients with sRV and may help in the decision making regarding primary prevention implantable cardioverter-defibrillator placement.[9,35]

Table 3. Multivariable regression model

	Full model		Final model	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Basic characteristics				
Age at inclusion, y*	2.23 (0.75-8.28)	0.16	1.76 (0.91-4.05)	0.093
ccTGA	0.87 (0.16-6.74)	0.88	–	
NYHA ≥ II	0.33 (0.01-3.60)	0.35	–	
ECG				
QRS duration, ms*	0.46 (0.18-0.98)	0.045	0.58 (0.30-1.00)	0.051
Standard echocardiography				
Severe tricuspid regurgitation	6.86 (1.05-54.8)	0.044	8.14 (1.08-84.9)	0.041
Cardiopulmonary exercise testing				
Peak heart rate*	0.70 (0.46-1.07)	0.10	0.85 (0.67-1.06)	0.15
Blood biomarkers				
NT-proBNP†	8.24 (1.92-97.6)	0.003	6.35 (2.22-24.5)	< 0.001
CMR/CT				
RV EF < 30%	1.89 (0.33-11.8)	0.46	–	
Speckle-tracking echocardiography				
RV GLS > −10.5%	60.5 (4.42-2501)	< 0.001	36.92 (4.70-444)	< 0.001
RV MD (ms)*	0.93 (0.76-1.14)	0.49	–	
RV PSS	0.47 (0.04-3.88)	0.49	–	

Variables included in multivariable Cox regression with backward stepwise selection, variables with HRs provided were included in the final model.

ccTGA, congenitally corrected transposition of the great arteries; CI, confidence interval; CMR, cardiovascular magnetic resonance; CT, computed tomography; ECG, electrocardiography; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricle; MD, mechanical dispersion; NYHA, New York Heart Association functional class; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PSS, postsystolic shortening; RV, right ventricle; SVT, supraventricular tachycardia.

* HR per 10-unit increase.

† HR for log-transformed variable.

Limitations

For this study, we retrospectively measured strain in a multicenter cohort that started including patients in 2006. Some patients were excluded because of vendor differences between the centers. Twenty percent of the remaining patients were excluded owing to poor image quality with low frame rates or suboptimal echocardiography windows for speckle-tracking analysis. Newer studies, with a truly prospective study design and including more recent echocardiograms with higher image quality, will most likely have lower exclusion rates. Patient numbers remain small, although we used data of the largest existing trial in patients with sRV. With only 15 events, multivariable analyses were overfitted and only hypothesis generating. The study cohort consisted of TGA-M/S and ccTGA patients, patients with and without ventricular pacing, and some patients with CT instead of CMR as the gold standard imaging modality, which slightly overestimates RV volumes.[36] The heterogeneity in the cohort may have disturbed significant associations. However, sensitivity analysis showed no decreasing HRs for STE measures in more homogeneous subsets. Like previous investigators, we only examined longitudinal strain on the 4-chamber view, because the anteriorly placed sRV proves difficult to visualize in other directions. Although circumferential strain may also be of interest, because there is a shift from longitudinal to circumferential strain in the sRV,[37] longitudinal strain remains the most reproducible and sensitive marker on echocardiography.[38]

Conclusion

Global longitudinal strain of the sRV is associated with heart failure–free survival. The predictive value GLS $> -10.5\%$ is similar to CMR/CT-derived sRV EF $< 30\%$ and patients with both reduced GLS and reduced RV EF are at high risk of heart failure and death. Measuring GLS should be incorporated in routine echocardiographic follow-up of patients with sRV, and STE measures could be useful in future risk prediction scores.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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