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Clinical Research

Right Ventricular Diastolic Function and Right Atrial Function and Their Relation With Exercise Capacity in Ebstein Anomaly

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ABSTRACT

Background: Right ventricular (RV) diastolic function and right atrial (RA) function are poorly characterized in patients with Ebstein anomaly (EA) but may influence functional capacity. We aimed to evaluate RV diastolic function and RA function in EA and study their relationship with biventricular systolic function and exercise capacity.

Methods: Seventy-two patients with EA and 69 controls prospectively underwent echocardiography, cardiovascular magnetic resonance imaging, and cardiopulmonary exercise testing to investigate RV systolic and diastolic function, RA function, and exercise capacity.

Results: Altered RV diastolic function was indicated by the reduced tricuspid valve *E/A* ratio, percentage RV filling time, and early and late diastolic strain rate; and by the increased tricuspid valve *E/E′*, isovolumic relaxation time, and RV myocardial performance index. The average of 6-RV-segment early diastolic strain rate correlated modestly

RÉSUMÉ

Contexte : La fonction diastolique du ventricule droit et la fonction de l'oreillette droite sont mal caractérisées chez les patients atteints de l'anomalie d'Ebstein, mais pourraient avoir une incidence sur la capacité fonctionnelle. Notre objectif était d'évaluer la fonction diastolique du ventricule droit et la fonction de l'oreillette droite et d'étudier leur lien avec la fonction systolique biventriculaire et la capacité d'effort.

Méthodologie : Soixante-douze patients atteints de l'anomalie d'Ebstein et 69 sujets témoins se sont soumis de façon prospective à une échocardiographie, à un examen cardiovasculaire par imagerie par résonnance magnétique et à une épreuve d'effort cardiorespiratoire pour évaluer les fonction systolique et diastolique du ventricule droit, la fonction de l'oreillette droite et la capacité d'effort.

Ebstein anomaly (EA) includes abnormalities of the tricuspid valve (TV), right ventricle (RV), and right atrium (RA).[1,2] TV displacement results in atrialized RV (a-RV) and functional RV (f-RV) compartments. The RA is typically enlarged and like the RV has increased fibrosis.[2] Tricuspid regurgitation (TR) is common, imposing volume loading to the abnormal RV.[3] A previous study on EA focused on RV systolic dysfunction,[4] whereas diastolic dysfunction remains poorly studied, but may influence exercise capacity.[5] We aimed to study RV diastolic function and RA function in EA in relation to RV size, systolic function, and exercise capacity.

Methods

Adults (>18 years of age as defined at our institution) and children with EA were prospectively recruited at the Deutsches Herzzentrum in Munich between 2010 and 2016. Patients with associated cardiac anomalies (other than a small atrial communication), cardiac surgery, or pacemaker implantation were excluded. Sixty-nine age- and gender-matched healthy volunteers were recruited as controls. The study was approved by the research ethics board and informed consent obtained.

Echocardiographic measurements (Vivid 7 or E-9; GE Healthcare, Horten, Norway) were obtained in 3 consecutive cardiac cycles and the results averaged. RV diastolic measurements were obtained from the apical 4-chamber view during quiet respiration. We measured tricuspid inflow peak

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with peak VO_2 ($r = 0.38$, $P < 0.01$), RV ejection fraction ($r = 0.41$, $P < 0.01$), and left ventricular ejection fraction ($r = 0.33$, $P < 0.05$). Patients with EA had impaired RA reservoir, conduit, and pump function, which were associated with peak VO_2 ($r = 0.54$, $P < 0.001$ for reservoir function).

Conclusions: Altered RV diastolic function and RA function in patients with EA are associated with impaired biventricular systolic function and exercise capacity. The stronger correlation of RA vs RV function with exercise capacity suggests that it may be important to evaluate RA function in this population.

Résultats : La présence d'une réduction du rapport *E/A* au niveau de la valve tricuspide, du pourcentage du temps de remplissage du ventricule droit et du taux de surcharge diastolique précoce et tardive ainsi que la présence d'une augmentation du rapport *E/E′* au niveau de la valve tricuspide, du temps de relaxation isovolumique et de l'indice de performance myocardique du ventricule droit indiquaient une atteinte de la fonction diastolique du ventricule droit. La corrélation a été modeste entre la moyenne du taux de surcharge diastolique précoce sur 6 segments du ventricule droit et la consommation d'oxygène maximal (volume d'oxygène; VO_2) (coefficient de corrélation [r] = 0,38, $p < 0,01$), la fraction d'éjection du ventricule droit ($r = 0,41$, $p < 0,01$) et la fraction d'éjection du ventricule gauche ($r = 0,33$, $p < 0,05$). Les patients atteints de l'anomalie d'Ebstein présentaient une altération de la fonction de l'oreillette droite en ce qui concerne le réservoir, la conduite et le pompage, altération qui était associée à un VO_2 maximal ($r = 0,54$, $p < 0,001$ pour la fonction de réservoir).

Conclusions : L'altération de la fonction diastolique du ventricule droit et de la fonction de l'oreillette droite chez les patients atteints de l'anomalie d'Ebstein est associée à une atteinte de la fonction systolique biventriculaire et de la capacité d'effort. La corrélation plus étroite entre la capacité d'effort et le fonctionnement de l'oreillette droite plutôt que celle du ventricule droit laisse supposer qu'il pourrait être important d'évaluer la fonction de l'oreillette droite chez cette population.

early (*E*) and late (*A*) velocities and calculated the *E*/*A* ratio. Tricuspid closure-to-opening time was measured as the time from cessation to onset of tricuspid inflow. RV ejection time (ET) was measured from spectral Doppler sampled in the RV outflow tract. From the apical 4-chamber view, pulse-wave tissue Doppler imaging was obtained at the lateral tricuspid annulus. Peak early (*E′*) and late (*A′*) diastolic annular velocities were measured and the *E*/*E′* ratio was calculated. RV isovolumic relaxation time (IVRT) was calculated as the interval between the electrocardiogram (ECG) Q-wave onset and the onset of tricuspid inflow (TV opening time) minus the time from Q-wave onset to the termination of pulmonary blood flow (pulmonary valve closure time) from the outflow view. The RV myocardial performance index (MPI) was calculated as (tricuspid closure-to-opening time − ET)/ET.[6] As RV IVRT and MPI require measurements from 2 different cardiac cycles, we excluded data if the heart rate (HR) varied >10%. RV filling time was calculated as the time from the onset to the termination of tricuspid inflow. To account for HR, the RV filling time was divided by the R-R interval, expressed as a percentage (Fig. 1). When 2-dimensional raw data were acquired on GE systems, speckle-tracking strain was analysed (EchoPAC v.8.0; GE Healthcare) using 2-dimensional apical 4-chamber view images at 60-120 frames/s. In EA, the f-RV endocardial border was traced in the apical 4-chamber view and the region of interest adjusted to the wall thickness. Adequate tracking by the software was visually verified and retraced if necessary until adequate tracking was achieved. Early and late longitudinal diastolic strain rate (SR) was generated for 6 RV segments (basal, mid, and apical segments of the RV free wall and septum). The average of RV early diastolic strain rate (RVEDSR) and RV late diastolic strain rate (RVLDSR) in 3 RV free-wall segments and in all 6 RV segments was calculated (Fig. 2).

The RA was defined as true RA+ a-RV (Fig. 3). We assessed (1) RA total emptying fraction defined as RA filling during ventricular systole, (2) RA passive emptying fraction during early ventricular filling, and (3) RA active emptying fraction during atrial contraction. RA area was measured at 3

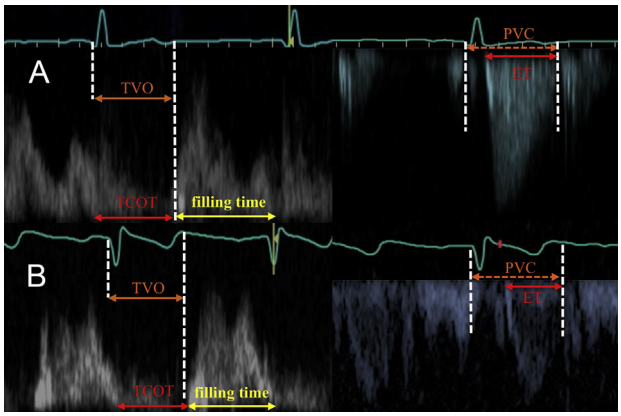

Figure 1. (**A**) Pulsed-wave Doppler RV inflow and outflow in a control subject (43 years of age) with the following values: HR = 67 bpm, ET = 331 milliseconds, TCOT = 358 milliseconds, TVO = 439 milliseconds, PVC = 427 milliseconds, and filling time = 535 milliseconds. IVRT, MPI, and percentage filling time measure 12 milliseconds, 0.08, and 60%, respectively. (**B**) Pulsed-wave Doppler RV inflow and outflow in a patient with EA (38 years of age): HR = 82 bpm, ET = 258 milliseconds, TCOT = 357 milliseconds, TVO = 441 milliseconds, PVC = 365 milliseconds, and filling time = 376 milliseconds. IVRT, MPI, and percentage filling time measures 76 milliseconds, 0.38, and 51%, respectively. EA, Ebstein anomaly; ET, ejection time; HR, heart rate; IVRT, isovolumic relaxation time; MPI, myocardial performance index; PVC, pulmonary valve closure time; RV, right ventricle; TCOT, tricuspid closure-to-opening time; TVO, tricuspid valve opening time.

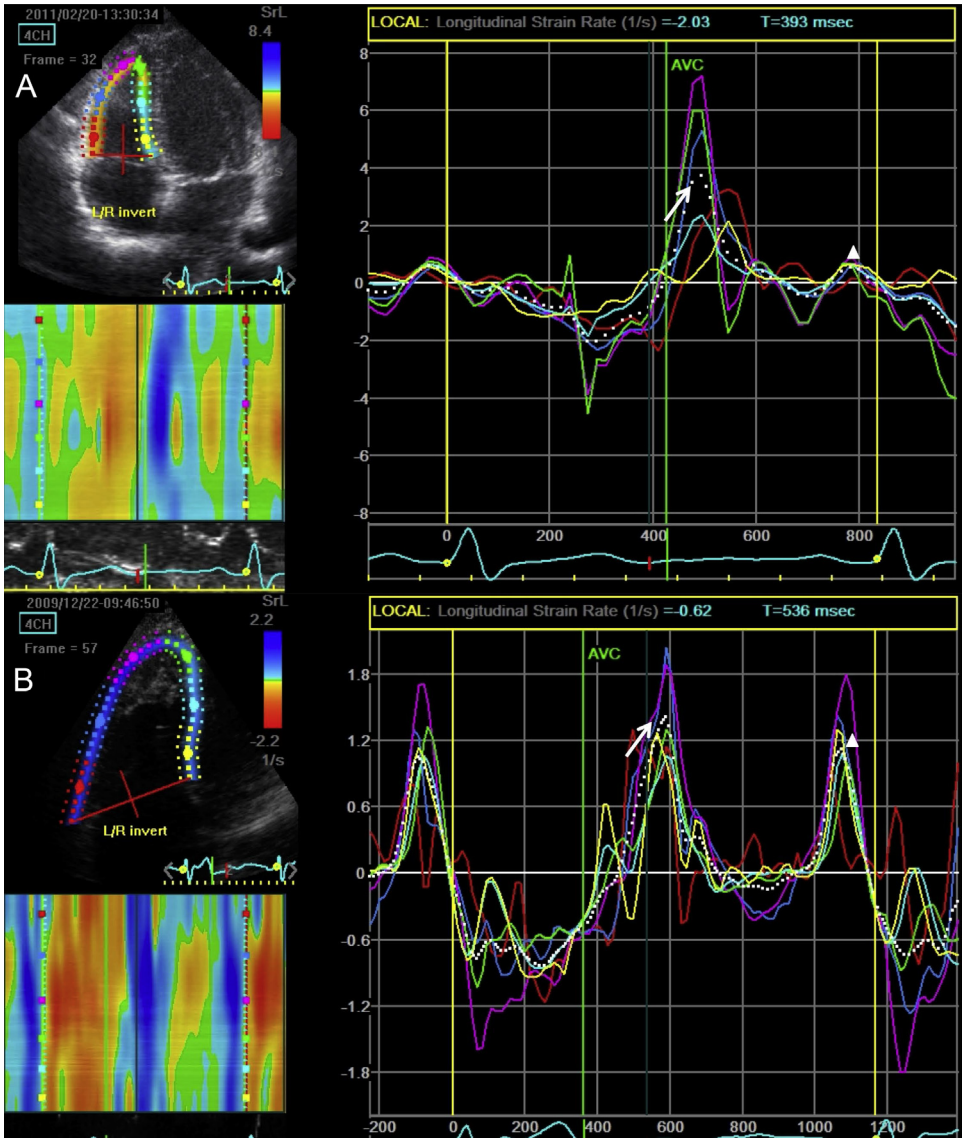

Figure 2. Measurements of RV global early (**arrow**) and late (**arrowhead**) diastolic SR by 2-dimensional speckle tracking in a control (**A**, 25 years of age) and patient with EA (**B**, 39 years of age). EA, Ebstein anomaly; RV, right ventricle; SR, strain rate.

time points: (1) maximal RA area at termination of the ECG T-wave, just before tricuspid opening; (2) minimal RA area at the onset of the ECG QRS complex, at TV closure; and (3) preatrial contraction (pre-A) at ECG P-wave onset. From these, we calculated RA total emptying fraction [(RA max − RA min area)/RA max area] to reflect RA reservoir function, RA passive emptying fraction [(RA max − RA pre-A)/RA max area] to reflect conduit function, and RA active emptying fraction [(RA pre-A − RA min area)/RA pre-A area] to reflect pump function.[7] We also measured total, passive, and active emptying fraction of the true RA, traced to the level of the TV annulus from the 4-chamber view and indexed to body surface area (yellow trace, Fig. 3). RA strain could not be measured because of low feasibility.

Cardiovascular magnetic resonance (CMR) was prospectively obtained on the same day as echocardiography on a 1.5 Tesla scanner (MAGNETOM Avanto; 12-element cardiac-phased array coil with breath-holding in expiration and vectorcardiographic ECG gating). Axial slices were obtained to measure ventricular volumes from the coronal and sagittal localizing images by planning a stack of orthogonal slices to cover the heart from just below the diaphragm to the pulmonary bifurcation.[8] Axial multiphase, steady-state free precession images were retrospectively ECG triggered (4.5, 6, or 8 mm slice thickness depending on body weight, 25 phase/cardiac cycle, with 1 slice per 8- to 12-second breath-hold, and an acquisition matrix of 192 × 192). RV and left ventricular (LV) volumes were calculated from axial data sets using Argus software (Siemens, Erlangen, Germany). End-diastole and end-systole were defined for each ventricle independently, as the phase with the largest and smallest volumes, respectively. We previously reported reproducibility of CMR volume measurements in EA.[9] Flow through the main pulmonary artery was calculated.[10] TR fraction was calculated as follows: (RV stroke-volume − main pulmonary artery antegrade flow)/(RV stroke-volume − main pulmonary

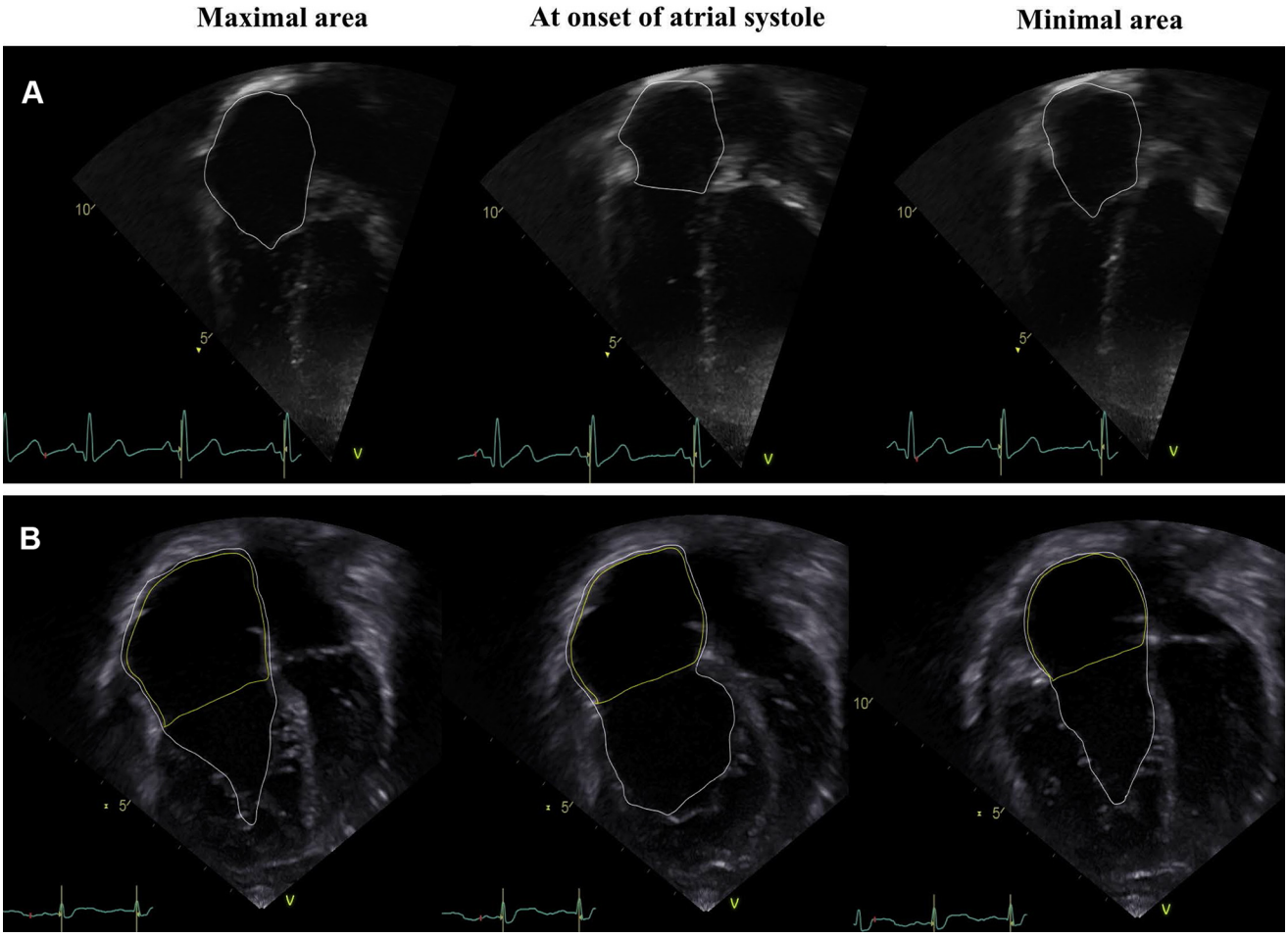

Figure 3. RA area in a control (**A**, 5 years of age) and patient with EA (**B**, 4 years of age) in an apical 4-chamber view at the time of tricuspid valve opening (**left panel**), beginning of the electrocardiogram P-wave (**middle panel**), and tricuspid valve closure (**right panel**). Note that in the patient with EA, the atrialized RV is included in the RA area (**white line**). True RA is traced to the level of the tricuspid valve annulus (**yellow line**). EA, Ebstein anomaly; RA, right atrium; RV, right ventricle.

artery retrograde flow).[9] f-RV stroke volume was measured by subtracting f-RV end-systolic volume from f-RV end-diastolic volume. The severity of TR was classified as follows: < 20% (mild); 20% to 40% (moderate); > 40% (severe).[11]

Patients prospectively underwent a symptom-limited cardiopulmonary exercise test on an upright bicycle.[12] Breath-by-breath gas exchange analysis was performed (Vmax229, SensorMedics; Cardinal Health, Dublin, OH). Peak VO_2 (mL/kg/min) was defined as the highest mean oxygen uptake during any 30-second time interval using age-appropriate reference values.[13]

Results are presented as mean ± standard deviation. Between-group comparisons used an unpaired *t*-test or 1-way analysis of variance with *post hoc* Bonferroni for comparisons between 3 groups. Linear regression analysis was used to test for associations between diastolic parameters and CMR-derived TR fraction, RV size, and systolic function. We did not account further for the multiple correlations performed.

Intra- and interobserver reliability for global early and late diastolic SR from 20 randomly selected participants were determined by intraclass correlation coefficients. Intraobserver variability was assessed by remeasuring parameters after at least 4 weeks. To assess interobserver reproducibility, 2 observers independently measured the variables. Statistical analysis used Microsoft Excel 2011 (Microsoft Corporation, Redmond, WA) and SPSS v.20.0 (IBM, Armonk, NY). *P* values< 0.05 were considered significant.

Results

Patient characteristics are presented in Table 1. In total, 72 patients with EA (mean age: 33.0 ± 17.3 [4.6-69.1] years, 58% female) and 69 healthy controls (mean age: 32.6 ± 16.7 [5.3-68.5] years, 45% female) were studied. Fifty-three subjects with EA were adults, and 19 were children (mean age: 11.7 ± 4.1 [4.6-17.4] years).

Differences in RV diastolic parameters were observed in patients with EA compared with controls including higher TV *E*- and *A*-velocities, lower TV E/A ratio, higher *E*/*E*′ ratio, and prolonged IVRT (Table 2). RV MPI was increased and RVEDSR and RVLDSR were decreased vs controls. RV filling time was shorter in patients with EA vs controls (Table 2).

Patients with EA had lower RA total, passive, and active emptying fraction vs controls. Likewise, total emptying fraction and passive emptying fraction of true RA were decreased in patients with EA vs controls. Indexed true RA maximum

Table 1. Demographics in patients with EA and controls

	EA (n = 72)	Control (n = 69)	*P* value
Age (y)	33.0 ± 17.3	32.6 ± 16.7	0.90
Female, n (%)	42 (58%)	31 (45%)	
Weight, kg	65.6 ± 18.5	66.4 ± 18.0	0.80
Height, cm	164.8 ± 19.3	166.3 ± 15.4	0.53
Body surface area, m^2	1.7 ± 0.33	1.8 ± 0.29	0.048
Heart rate, bpm	77.6 ± 14.8	72.6 ± 12.2	0.048

Data are expressed as mean ± standard deviation.
EA, Ebstein anomaly.

area was larger in EA vs controls (Table 2). RA total emptying fraction was moderately associated with RVEDSR in 6 and 3 segments ($r = 0.41$, $P < 0.01$ and $r = 0.33$, $P < 0.05$, respectively). Passive emptying fraction was weakly associated with RVEDSR in 6 segments ($r = 0.33$, $P < 0.05$). Total emptying fraction and passive emptying fraction correlated weakly with E/E' ($r = -0.47$, $P < 0.01$ and $r = -0.32$, $P < 0.05$, respectively). Indexed true RA maximum area did not correlate with true RA function (Fig. 4).

To assess the possible effects of TR on RV diastolic and RA function, we compared RV and RA function between patients with EA with different degrees of CMR-derived TR fraction in 56 patients with EA. Average TR fraction was 47% ± 21%. Nine patients had mild, 12 moderate, and 35 severe TR. Tricuspid E and E' velocity and indexed true RA maximum area were weakly but significantly related to TR severity. There were no other correlations between the TR fraction and echo parameters of RV diastolic function. Likewise, tricuspid E velocity and indexed true RA maximum area were different between groups based on TR severity, but other parameters were similar (Tables 3 and 4, and Fig. 5).

CMR and exercise measurements are presented in Table 5. Average peak VO_2 was 23 ± 9 mL/kg/min corresponding to 77.6% ± 26.8% of age- and sex-related reference values.

The 6- and 3-segment RVEDSR was weakly associated with peak exercise VO_2 ($r = 0.38$, $P < 0.01$ and $r = 0.28$, $P < 0.05$, respectively; Fig. 6). Other RV diastolic parameters were not significantly associated with peak exercise VO_2. RA total emptying fraction and passive emptying fraction correlated moderately with exercise peak VO_2 ($r = 0.54$, $P < 0.001$ and $r = 0.37$, $P < 0.01$, respectively; Fig. 7). RA active emptying fraction was not associated with peak exercise VO_2. When analysed separately, parameters of true RA function were not associated with peak VO_2.

CMR data were obtained in 67 patients with EA (mean age: 33.0 ± 17.3 [4.6-69.1] years), all on the same day as echocardiography. The 6-segment RVEDSR was moderately associated with CMR RV ejection fraction (EF) ($r = 0.41$, $P < 0.01$; Fig. 8) and weakly with right ventricular end-systolic volume indexed ($r = -0.29$, $P < 0.05$), LVEF ($r = 0.33$, $P < 0.05$; Fig. 8), and left ventricular end-systolic volume indexed ($r = -0.30$, $P < 0.05$). The 3-segment RVEDSR was weakly associated with RVEF ($r = 0.33$, $P < 0.05$). Right ventricular end-diastolic volume indexed and left ventricular end-diastolic volume indexed were not associated with RVEDSR. Among other RV diastolic and RA parameters, only TV annular E' was weakly associated with RVEDVi ($r = 0.27$, $P < 0.05$), whereas other RV diastolic and RA parameters were not significantly related to CMR RV volumes or EF.

Intraobserver intraclass correlation coefficients (95% confidence intervals) were RVEDSR = 0.97 (0.93-0.99) and RVLDSR = 0.99 (0.97-0.99). Interobserver intraclass correlation coefficients (95% confidence interval) were RVEDSR = 0.98 (0.94-0.99) and RVLDSR = 0.98 (0.95-0.99).

Table 2. Echocardiography in patients with EA and controls

	EA (n = 72)	n	Control (n = 69)	n	*P* value
Right ventricular parameters					
Tricuspid E (m/s)	0.67 ± 0.23	54	0.55 ± 0.12	58	< 0.001
Tricuspid A (m/s)	0.55 ± 0.23	54	0.36 ± 0.10	58	< 0.001
Tricuspid E/A ratio	1.4 ± 0.55	54	1.6 ± 0.51	58	< 0.01
Tricuspid E' (m/s)	0.11 ± 0.05	70	0.12 ± 0.02	67	0.058
Tricuspid A' (m/s)	0.09 ± 0.04	70	0.09 ± 0.04	67	0.54
Tricuspid E/E' ratio	7.8 ± 5.2	52	4.8 ± 1.2	57	< 0.001
Isovolumic relaxation time (ms)	60 ± 47	37	23 ± 16	27	< 0.001
RV MPI	0.42 ± 0.23	39	0.16 ± 0.12	48	< 0.001
RV filling time (ms)	375 ± 112	52	488 ± 120	57	< 0.001
Percentage RV filling time	46 ± 7.9	52	57 ± 5.3	57	< 0.001
RVEDSR, 6-segment (s^{-1})	1.6 ± 0.60	57	1.9 ± 0.58	55	< 0.01
RVLDSR, 6-segment (s^{-1})	0.82 ± 0.46	57	1.1 ± 0.32	55	< 0.001
RVEDSR, 3-segment (s^{-1})	2.1 ± 0.74	57	2.7 ± 0.76	55	< 0.001
RVLDSR, 3-segment (s^{-1})	1.1 ± 0.54	57	1.5 ± 0.50	55	< 0.001
Right atrial parameters					
RA total emptying fraction	0.23 ± 0.08	52	0.42 ± 0.10	55	< 0.001
RA passive emptying fraction	0.12 ± 0.08	52	0.29 ± 0.11	55	< 0.001
RA active emptying fraction	0.12 ± 0.08	52	0.18 ± 0.11	55	< 0.01
True RA total emptying fraction	0.35 ± 0.11	52	0.42 ± 0.10	55	< 0.001
True RA passive emptying fraction	0.23 ± 0.10	52	0.29 ± 0.11	55	< 0.01
True RA active emptying fraction	0.15 ± 0.11	52	0.18 ± 0.11	55	0.11
Indexed true RA area (cm^2/m^2)	17.4 ± 6.6	51	8.7 ± 1.7	44	< 0.001

Data are expressed as mean ± standard deviation.
EA, Ebstein anomaly; MPI, myocardial performance index; RA, right atrium; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; RVLDSR, right ventricular late diastolic strain rate.

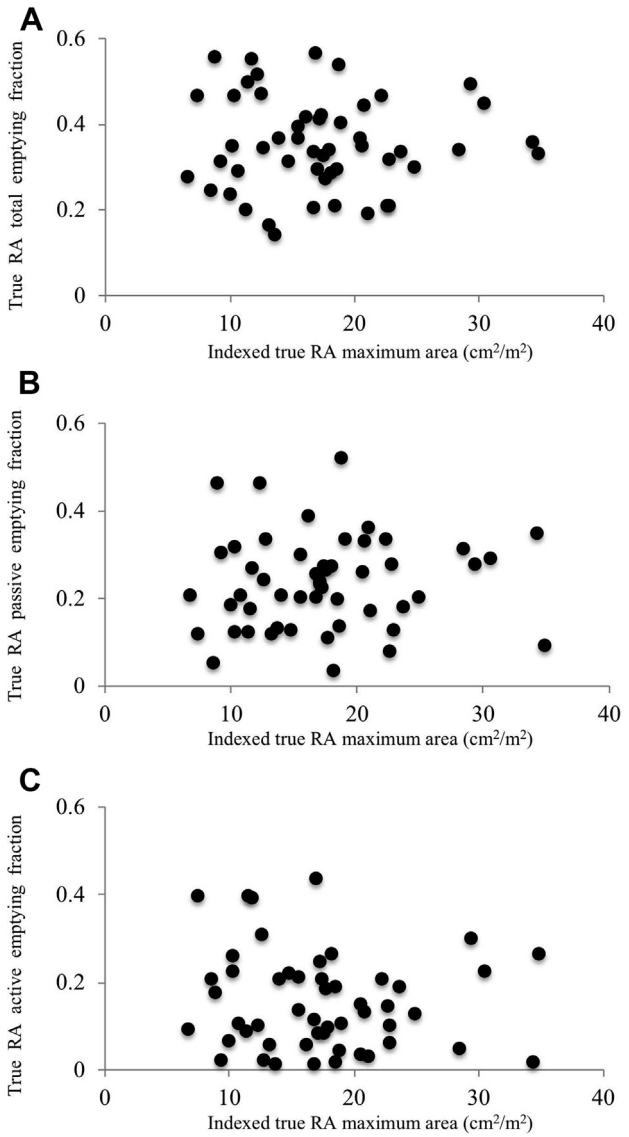

Figure 4. Relationship between the indexed true RA maximum area and the true RA function in EA. (**A**) Relationship between indexed true RA maximum area and true RA total emptying fraction. (**B**) Relationship between indexed true RA maximum area and true RA passive emptying fraction. (**C**) Relationship between indexed true RA maximum area and true RA active emptying fraction. EA, Ebstein anomaly; RA, right atrium.

Table 3. Correlations of TR fraction with RV and RA diastolic parameters

	r	*P* value
Echocardiographic findings of RV function		
Tricuspid *E* (cm/s)	0.36	0.015
Tricuspid *A* (cm/s)	0.27	0.082
Tricuspid *E*/*A* ratio	−0.033	0.83
Tricuspid *E*′ (cm/s)	0.27	0.045
Tricuspid *A*′ (cm/s)	0.039	0.78
Tricuspid *E*/*E*′ ratio	−0.0078	0.96
Isovolumic relaxation time (ms)	0.34	0.060
RV MPI	0.084	0.66
RV filling time (ms)	−0.11	0.47
Percentage RV filling time	−0.070	0.66
RVEDSR, 6-segment (s^{-1})	0.12	0.42
RVLDSR, 6-segment (s^{-1})	−0.025	0.87
RVEDSR, 3-segment (s^{-1})	−0.036	0.81
RVLDSR, 3-segment (s^{-1})	−0.14	0.37
Echocardiographic findings of RA function		
RA total emptying fraction	−0.022	0.89
RA passive emptying fraction	0.018	0.91
RA active emptying fraction	−0.031	0.85
True RA total emptying fraction	−0.027	0.87
True RA passive emptying fraction	0.11	0.51
True RA active emptying fraction	−0.14	0.38
Indexed true RA maximum area (cm^2/m^2)	0.63	< 0.001

MPI, myocardial performance index; RA, right atrium; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; RVLDSR, right ventricular late diastolic strain rate; TR, tricuspid regurgitation.

Discussion

RV systolic function is impaired in patients with EA, but diastolic function is poorly characterized.[4] Our results indicate that: (1) patients with EA have altered RV diastolic filling; (2) lower RV early diastolic SR in patients with EA correlates with lower CMR-derived RVEF, LVEF, and lower exercise capacity; (3) lower RA total and passive emptying fraction are associated with lower exercise capacity.

Ventricular filling is affected by a complex interplay of factors including myocardial relaxation, recoil, compliance, loading conditions, dyssynchrony, and HR. The small f-RV and abnormal RV myocardium contribute to filling abnormalities. Consistent with our previous findings in pediatric cardiomyopathy, our results suggest that diastolic dysfunction in patients with EA is not clearly characterized by either delayed relaxation or restrictive filling, but has features of both.[14] The shorter RV filling time and higher *E*/*E*′ ratio in EA may reflect, at least in part, increased filling pressures, even though IVRT was prolonged. Our results also suggest that the observed RV diastolic alterations in patients with EA may in part be related to RV systolic dysfunction.[15]

Studies of RA function in patients with EA are very limited. Our findings suggest impaired RA total, passive, and active emptying fraction in patients with EA, in association with parameters of RV diastolic function and exercise intolerance. Steinmetz et al.[5] found that impaired reservoir and booster pump function in EA correlated with higher New York Heart Association (NYHA) class and increased brain natriuretic peptide. Atrial function is impacted by ventricular properties, and RA total and passive emptying fraction in patients with EA were weakly related to RV early diastolic SR and *E*/*E*′.

Although both systolic and diastolic function may potentially be impacted by the severity of TR, in this study, we did not find significant associations between the severity of TR and RV diastolic function or RA function except for weak relations with tricuspid *E*, *E*′, and true RA area. Although volume loading is likely to affect diastolic parameters, the lack of differences in diastolic parameters between groups stratified by TR severity may be attributable to adaptation to chronic volume loading. Therefore, we do not interpret these results as that TR has no effect on diastolic function (and additionally our study design cannot deduce cause and effect). There are few studies assessing the association between RV diastolic function and TR, and to our knowledge, none in EA. In a different and diverse population, severe TR negatively impacted RV systolic function, but had a variable effect on the

Table 4. Echocardiographic parameters by TR grade

	Mild	Moderate	Severe	*P* value
RV function				
Tricuspid *E* (m/s)	0.62 ± 0.12	0.53 ± 0.14	0.69 ± 0.18	0.04
Tricuspid *A* (m/s)	0.50 ± 0.11	0.44 ± 0.18	0.54 ± 0.18	0.35
Tricuspid *E*/*A* ratio	1.3 ± 0.18	1.4 ± 0.77	1.4 ± 0.52	0.88
Tricuspid *E*′ (m/s)	0.082 ± 0.025	0.11 ± 0.055	0.12 ± 0.049	0.16
Tricuspid *A*′ (m/s)	0.094 ± 0.046	0.092 ± 0.043	0.092 ± 0.043	0.99
Tricuspid *E*/*E*′ ratio	8.6 ± 2.8	6.9 ± 5.2	7.2 ± 4.9	0.85
Isovolumic relaxation time (ms)	32 ± 38	57 ± 43	64 ± 50	0.56
RV MPI	0.30 ± 0.20	0.50 ± 0.23	0.44 ± 0.22	0.44
RV filling time (ms)	382 ± 118	420 ± 134	354 ± 115	0.34
Percentage RV filling time	47 ± 6.2	47 ± 7.7	45 ± 8.9	0.62
RVEDSR, 6-segment (s^{-1})	1.6 ± 0.51	1.3 ± 0.35	1.7 ± 0.69	0.33
RVLDSR, 6-segment (s^{-1})	0.79 ± 0.33	0.86 ± 0.41	0.79 ± 0.46	0.9
RVEDSR, 3-segment (s^{-1})	2.5 ± 1.1	2.1 ± 0.36	2.1 ± 0.67	0.36
RVLDSR, 3-segment (s^{-1})	1.2 ± 0.44	1.3 ± 0.46	1.1 ± 0.53	0.48
RA function				
RA total emptying fraction	0.26 ± 0.13	0.21 ± 0.074	0.23 ± 0.083	0.58
RA passive emptying fraction	0.13 ± 0.079	0.12 ± 0.082	0.13 ± 0.074	0.98
RA active emptying fraction	0.15 ± 0.13	0.096 ± 0.056	0.12 ± 0.080	0.56
True RA total emptying fraction	0.35 ± 0.11	0.36 ± 0.12	0.35 ± 0.11	0.98
True RA passive emptying fraction	0.20 ± 0.083	0.24 ± 0.13	0.24 ± 0.094	0.62
True RA active emptying fraction	0.19 ± 0.13	0.15 ± 0.13	0.14 ± 0.10	0.65
Indexed true RA maximum area (cm^2/m^2)	14.3 ± 2.8	15.5 ± 5.1	20.8 ± 6.4	< 0.05

Data are expressed as mean ± standard deviation.

MPI, myocardial performance index; RA, right atrium; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; RVLDSR, right ventricular late diastolic strain rate; TR, tricuspid regurgitation.

limited diastolic parameters studied.[16] In addition, in that study, patients with moderate/severe TR had increased pulmonary pressures, which affect RV diastolic parameters.

The impact of TR severity on RA function has not been, to our knowledge, studied in EA. TR negatively impacts RA reservoir function in left heart failure.[17] RA strain, reflecting

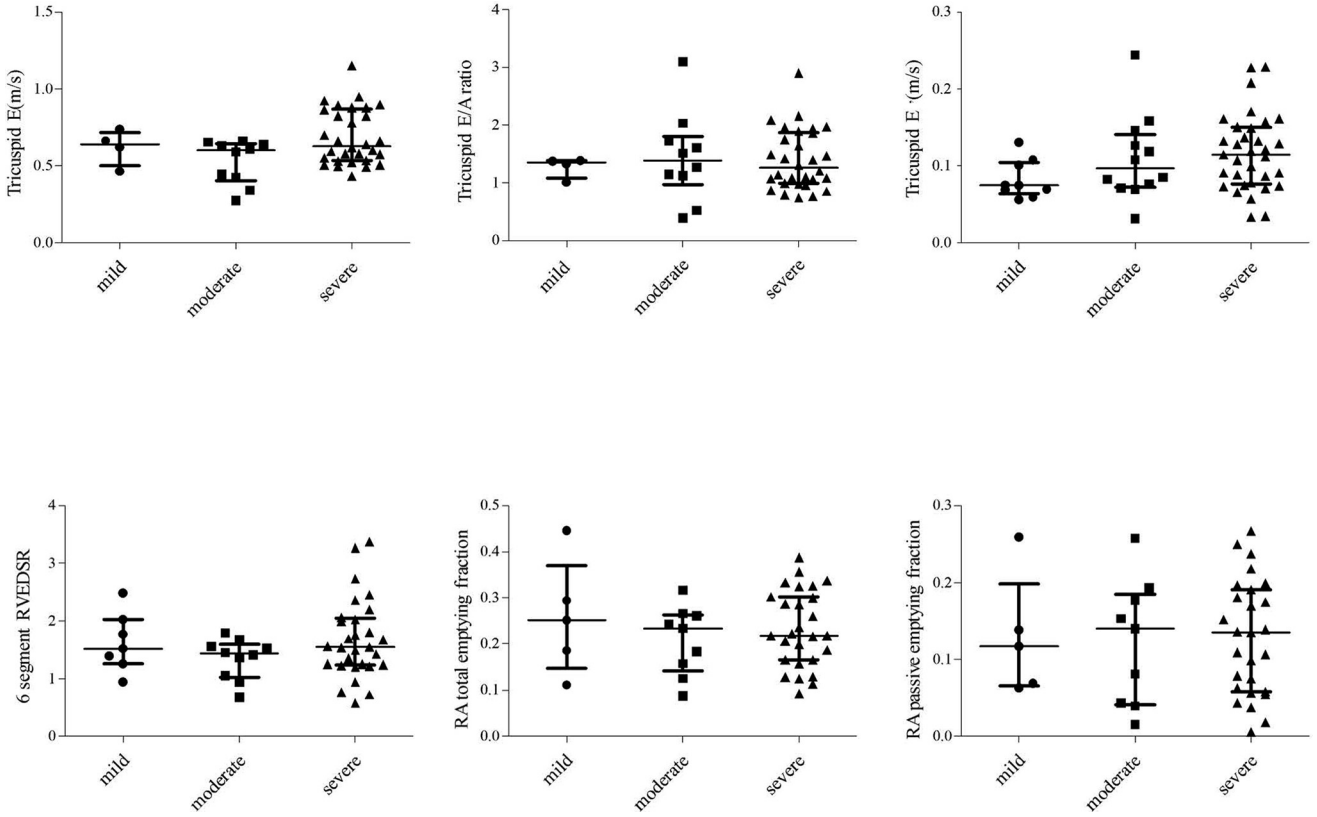

Figure 5. Distribution of RV diastolic measurements in patients with EA with mild, moderate, and severe TR. Central line, median; Whiskers, 25th-75th percentiles. EA, Ebstein anomaly; RA, right atrium; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; TR, tricuspid regurgitation.

Table 5. Cardiac magnetic resonance and exercise testing in patients with EA

	EA	n
MRI		
Indexed RV EDV (mL/m^2)	147 ± 65	67
Indexed RV ESV (mL/m^2)	76 ± 39	67
RV EF (%)	49 ± 11	67
Indexed LV EDV (mL/m^2)	58 ± 11	67
Indexed LV ESV (mL/m^2)	24 ± 8	67
LV EF (%)	59 ± 10	67
TR fraction (%)	47 ± 21	56
Metabolic exercise testing		
Peak VO_2 (mL/kg/min)	23 ± 9	66
Percentage normal reference value of peak VO_2	77.6 ± 26.8	58
Oxygen saturation at rest	96 ± 6	67
Oxygen saturation at peak exercise	91 ± 10	67

Data are expressed as mean ± standard deviation.

EA, Ebstein anomaly; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricle; MRI, magnetic resonance imaging; RV, right ventricle; TR, tricuspid regurgitation.

RA reservoir function, was not associated with TR grade after repair of tetralogy of Fallot, but similar to our results, RA strain correlated with RV strain.[18] Thus, it is possible that impaired RV function may impact RA function more than TR per se.

Decreased exercise capacity in patients with EA reflects disease severity.[19] We found that RV diastolic SR was associated with peak VO_2. Adequate RV filling is dependent, at least partly, on adequate early diastolic myocardial relaxation. With reduced myocardial lengthening in early diastole and decreased RA pump function, RV filling and hence output is likely reduced, affecting exercise capacity. We are not aware of studies investigating the relationship between exercise capacity and RV diastolic function in EA. Our results suggest that RV diastolic function contributes to exercise capacity.

RA reservoir and conduit function also correlated with peak VO_2. RA compliance has a positive impact on cardiac output,[20] and RA (dys)function may be important for RV filling and exercise capacity when RV diastolic function is impaired.

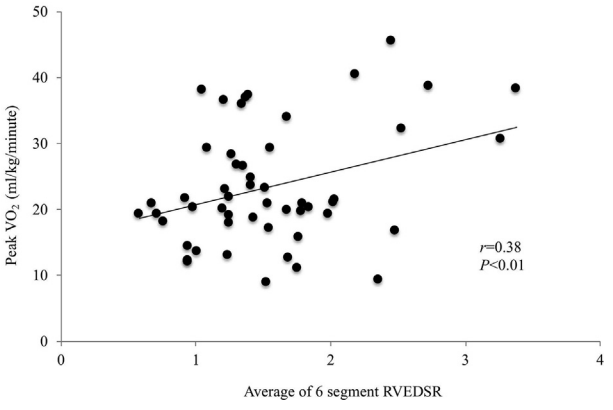

Figure 6. Relationship between the average of 6 RV segments early diastolic SR and peak VO_2 in EA. EA, Ebstein anomaly; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; SR, strain rate.

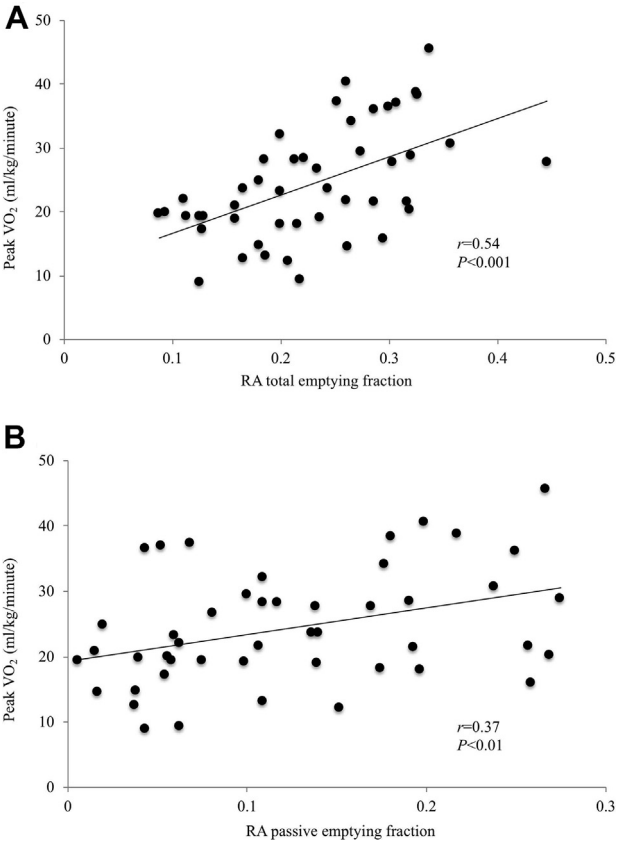

Figure 7. (**A**) Relationship between RA total emptying fraction and peak VO_2 in EA. (**B**) Relationship between RA passive emptying fraction and peak VO_2 in EA. EA, Ebstein anomaly; RA, right atrium.

RV global early diastolic SR was positively associated with biventricular EF. This suggests a relation with systolic function and may reflect systolic-diastolic functional coupling.[15] Early diastolic elastic recoil correlates with LV systolic function and inversely with LV end-systolic volume.[21] Less is known about RV elastic restoring forces, but these may be decreased in the thin EA myocardium.[1] Similar to our results, impaired RV global early diastolic SR correlates with RVEF after tetralogy of Fallot repair.[22] Thus, systolic-diastolic coupling may be important in the volume-loaded RV in EA.[23]

Clinical implications

Although the indications for surgical intervention in EA without clinical symptoms is controversial, exercise capacity of nonoperated EA patients tends to decline over time.[24] In contrast, operated EA patients after tricuspid surgery may demonstrate stable or even increasing exercise performance.[19] Furthermore, reduced exercise capacity in patients with EA has been found to be a strong predictor of adverse outcomes including death, nonelective hospitalization, and surgical repair.[25] As diastolic SR and RA function correlated with exercise capacity in our study, these results may be clinically relevant, especially in the long-term follow-up of EA. Moreover, we believe that our findings that diastolic function correlated with global RV and LV systolic function are important, as these are central parameters that are associated

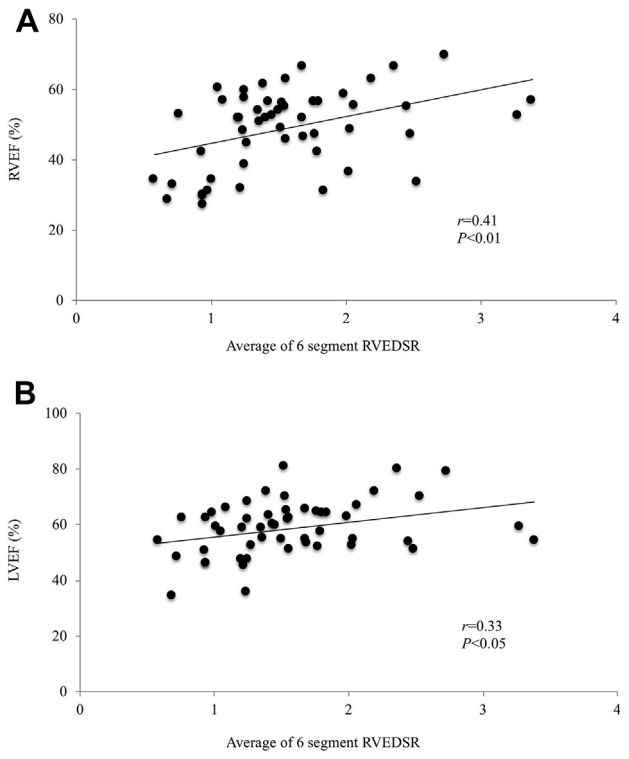

Figure 8. Relationship between the average of 6-RV-segment early diastolic SR and CMR-derived RV and LV function in EA. (**A**) Relationship between the average of 6-RV-segment early diastolic SR and RV EF. (**B**) Relationship between the average of 6-RV-segment early diastolic SR and LV EF. CMR, cardiovascular magnetic resonance; EA, Ebstein anomaly; EF, ejection fraction; LV, left ventricle; RV, right ventricle; RVEDSR, right ventricular early diastolic strain rate; SR, strain rate.

with clinical outcomes in many conditions. Although it is unlikely that any single echo diastolic parameter will dictate patient management, a patient with deteriorating systolic and diastolic function is likely to become symptomatic and may warrant closer follow-up and possibly intervention. Thus, assessment of diastolic dysfunction is another piece of the puzzle of the complex pathophysiology that underlies EA. Nonetheless, the clinical relevance of our results in terms of individual patient management and clinical outcomes such as arrhythmia and death remain to be established.

This study has additional limitations. Measurements were not taken at a standard phase of the respiratory cycle. Not all echocardiographic, CMR, and exercise testing parameters were available in all patients. Our data would have been strengthened by an invasive measure such as end-diastolic pressure. However, patients did not undergo cardiac catheterization. As part of a comprehensive assessment, we used accepted regional parameters to evaluate RV wall motion such as tissue Doppler imaging–derived E', A', and RV longitudinal SR. Although these parameters are often used to reflect RV global diastolic function, they are derived regionally and mainly limited to the RV inflow segments, whereas other RV segments such as the outflow segments were not assessed. This is a limitation in general, and may be particularly important in EA, as the inflow segments are abnormal structurally due to displacement and nondelamination of the tricuspid septal leaflet. In addition, increased RA pressure and local effects of TR may also affect these measurements. Atrial volumes are an important parameter of diastolic assessment.[26] However, in EA, the presence of TR in many patients and the a-RV confound assessment of RA volumes. We did not assess hepatic vein flow for similar reasons. No single echocardiographic parameter adequately characterizes diastolic dysfunction, and therefore, multiple parameters are used. This necessitates multiple statistical tests with possible statistical significance in some instances due to chance alone. The correlations that we found were weak to moderate. Multiple factors affect exercise capacity, of which diastolic function is only one and even then not entirely captured by an individual diastolic parameter. We could not analyse RA strain because of low feasibility. The measurement of diastolic SR by speckle tracking suffers from low frame rates vs the rapid events of early diastole. Thus, we are likely to have underestimated peak diastolic SR values. However, the significant difference from controls is not missed by this limitation. Rhythm disturbances were not systematically investigated, although at the exercise study all patients were in sinus rhythm. Lastly, EA may be part of other congenital abnormalities. We limited our evaluation to a population with "isolated" EA in order to reduce the confounding effects of additional heterogeneous lesions on the already complex topic.

Conclusions

Patients with EA have altered RV diastolic function and reduced filling time. Changes in diastolic parameters were associated with RV and LV systolic function and exercise capacity. Moreover, RA function was associated with exercise capacity suggesting that both RV diastolic function and RA function influence functional capacity in patients with EA.

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Disclosures

The authors have no conflicts of interest to disclose.

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