Right atrial dysfunction is associated with atrial arrhythmias in adults with repaired tetralogy of fallot

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Background Adults with repaired tetralogy of Fallot (TOF) have right atrial (RA) remodeling and dysfunction, and RA function can be measured using speckle tracking echocardiography. There are limited data about the role of RA strain imaging for risk stratification in this population. We hypothesized that RA reservoir strain can identify TOF patients at risk of developing atrial arrhythmia. To test this hypothesis, we assessed the relationship between RA reservoir strain and atrial arrhythmias in adults with repaired TOF.

Method Retrospective cohort study of adults with repaired TOF, and no prior history of atrial arrhythmias. Atrial arrhythmia was defined as atrial fibrillation, atrial flutter/atrial tachycardia, and categorized as new-onset versus recurrent atrial arrhythmias.

Results We identified 426 patients (age 33 ± 12 years; males 208 (49%)) that met the inclusion criteria. The mean RA reservoir strain, conduit strain, and booster strain were 34 ± 11%, 20 ± 9%, and 15 ± 12%, respectively. Of 426 patients, 73 (17%) developed new-onset atrial arrhythmias (atrial flutter/tachycardia n = 42; atrial fibrillation n = 31); annual incidence 1.9%. RA reservoir strain was associated with new-onset atrial arrhythmias (adjusted HR 0.95, 95% CI 0.93-0.97) after multivariable adjustment. Of 73 patients with new-onset atrial arrhythmia, 41 (56%) had recurrent atrial arrhythmia (atrial flutter/tachycardia n = 18; atrial fibrillation n = 23); annual incidence 11.2%. Similarly, RA reservoir strain was associated with recurrent atrial arrhythmias (adjusted HR 0.92, 95% CI 0.88-0.96) after multivariable adjustment.

Conclusions RA strain indices can identify patients at risk for atrial arrhythmias, and this can in turn, be used to guide the type/intensity of therapy in such patients. (Am Heart J 2023;263:141–150.)

Atrial arrhythmias are common in adults with repaired teratology of Fallot (TOF) and are associated with heart failure hospitalization and all-cause mortality.[1-4] The high prevalence of atrial arrhythmia in this population is attributed to the presence of arrhythmia substrates such as surgical scars, as well as ongoing right atrial (RA) remodeling from the hemodynamic stress resulting from residual/recurrent lesions.[1-4] RA remodeling manifests as RA enlargement and RA dysfunction, and these changes can be assessed by 2-dimensional and speckle tracking echocardiography, respectively.[5,6] RA strain imaging has been shown to have superior prognostic performance in identifying patients at risk for adverse outcomes as compared to RA volume, in studies conducted in patients with acquired heart disease.[7-10] Similar findings, endorsing the prognostic role of RA strain imaging, have been observed in some congenital heart lesions such as coarctation of aorta, Ebstein anomaly, and congenital corrected transposition of great arteries.[11-14] However, similar data are sparse in adults with repaired TOF.[15] Considering the high risk of atrial arrhythmias in adults with repaired TOF, and the higher prevalence on this lesion in the adult congenital heart disease population, data regarding the prognostic role (or lack thereof) of RA strain for atrial arrhythmia risk stratification would be beneficial. We hypothesized that RA reservoir strain at baseline echocardiogram can identify patients with repaired TOF at risk for developing atrial arrhythmia. To test this hypothesis, we assessed the relationship between RA reservoir strain and atrial arrhythmias (new-onset and recurrent atrial arrhythmias) in adults with repaired TOF.

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Methods

Study population

The Mayo Clinic Institutional Review Board approved the study. This is a retrospective cohort study of adults (age ≥18 years) with repaired TOF that underwent comprehensive echocardiogram and had at least 12 months of clinical follow-up from the time of echocardiogram at Mayo Clinic from January 1, 2003 to December 31, 2021. From this cohort, we excluded patients with following conditions: (1) Prior history of atrial arrhythmia defined atrial fibrillation, atrial flutter, or atrial tachycardia. (2) ≥Moderate tricuspid regurgitation at the time of echocardiogram or prior history of tricuspid valve replacement. (3) Inadequate echocardiographic images for offline assessment of RA strain. The first clinic visit to the adult congenital heart disease clinic within the study period was considered as the baseline encounter, and the clinical and imaging indices obtained within 3 months from the baseline encounter were used to define the baseline characteristics of the cohort.

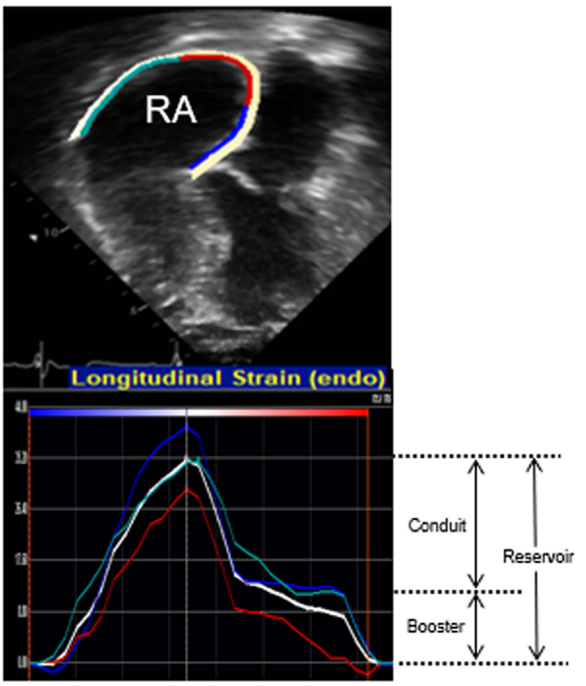
Echocardiography

Assessment RA function

RA function was assessed using RA strain imaging which had 3 different components: (1) RA reservoir strain which is dependent on RA compliance and is modulated by right ventricular (RV) systolic function through descent of the base of the RV in systole. (2) RA conduit strain which is dependent on RV relaxation and chamber stiffness. (3) RA booster strain which is dependent on intrinsic RA contractility and RV end-diastolic compliance.[5] We chose RA reservoir strain as the primary metric of RA function based on previous data demonstrating superior prognostic performance of RA reservoir strain as compared to other indies of RA remodeling.[7-14] The reproducibility of RA strain was assessed in 20 randomly selected patients. Intra- and interobserver agreement was evaluated after the same sonographer and another sonographer repeated the analysis using intraclass correlation coefficient and mean absolute difference.

The procedural details for speckle tracking strain imaging in our laboratory have been described.[13,14] The echocardiograms were performed according to contemporary guidelines, and offline analyses of all echocardiographic indices were performed by two research sonographers. Atrial and ventricular function were assessed using speckle tracking strain imaging, obtained using Vivid E9 and E95 (General Electric Co, Fairfield, Connecticut) with M5S and M5Sc-D transducers (1.5 to 4.6 MHz) at frame rate of 40 to 80 Hz, and these images were exported (DICOM) and then analyzed offline using TomTec (TomTec Imaging Systems, Unterschleissheim, Germany). The offline assessment of RA reservoir strain involved manual endocardial tracing of a single frame at end-systole by a point-click approach, starting from the lateral tricuspid annulus to the septal tricuspid annulus using images from an RV focused view (Fig. 1). The periodic displacement of the tracing was automatically tracked in subsequent frames. Adequate tracking by the software was visually verified and retraced if necessary until adequate tracking was achieved. RA reservoir strain, RA conduit strain, and RA booster strain were assessed using the QRS as the fiduciary point. Left atrial (LA) reservoir strain was assessed using a similar technique. Other indices of right and left heart structure, function, and hemodynamics were assessed as per guidelines.[5,6]

Fig. 1

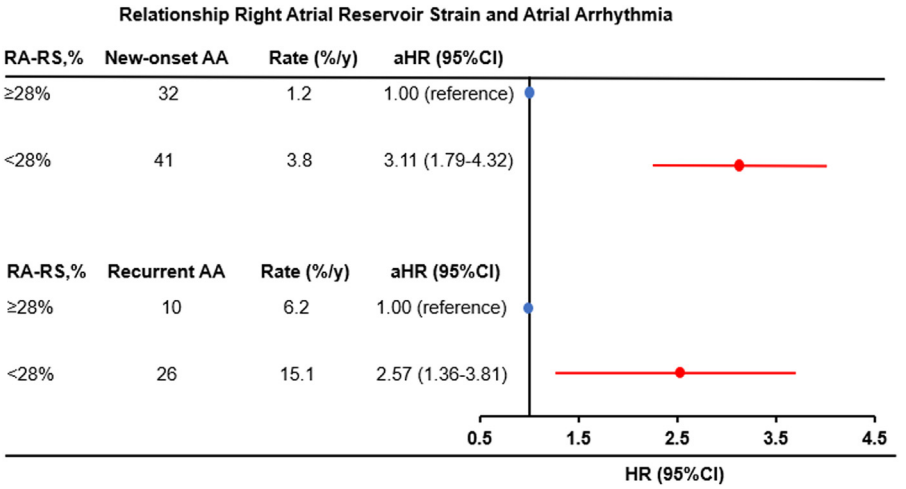


2D and graphical tracing of right atrial (RA) strain which is an average of strain indices from right wall, left wall and roof of the RA. Reservoir strain is measured at end of ventricular systole, booster strain is measured at the end of atrial systole, and conduit strain is calculated as the difference between reservoir strain and booster strain.

Atrial arrhythmias

The primary outcome was new-onset atrial arrhythmias, defined as atrial arrhythmias occurring from the time of baseline echocardiogram to the last clinical encounter. The secondary outcome was recurrent atrial arrhythmias, and this outcome was assessed only in the subset of patients that developed new-onset atrial arrhythmia during follow-up. Recurrent atrial arrhythmia was defined as atrial arrhythmia occurring from the time of first episode of arrhythmia to the last clinical

Fig. 2



Forest plot showing the relationship between right atrial reservoir strain (RA-RS) and atrial arrhythmias. The incidence of new-onset and recurrent atrial arrhythmias were calculated as a quotient of the number of events and the total duration of follow-up (patient-years) and expressed percent per year (%/y). The adjusted hazard ratios (aHR) were derived from multivariable Cox regression models (Tables 2 and 3), and RA-RS was modeled as a binary variable with RA-RS ≥28% as the reference.

encounter. The occurrence of new-onset or recurrent atrial arrhythmias was ascertained between the time of baseline echocardiogram and last clinical encounter. The patients without the outcome of interest (atrial arrhythmias), patients that died, and patients that were lost to follow-up were censored at the time of last clinical encounter.

Atrial arrhythmia was defined as atrial fibrillation, atrial flutter, or atrial tachycardia documented on electrocardiogram, Holter monitor, rhythm strip or device interrogation reports. Atrial fibrillation was defined by a lack of a constant atrial activity/*P*-wave and at electrophysiological study by irregular atrial activation with cycle lengths below 200 milliseconds. Atrial flutter was defined as a macroreentrant atrial arrhythmia that is typically characterized by sudden onset and termination clinically, and at electrophysiological study, had a constant cycle length with a stable activation sequence, but entrainable.[16] Atrial tachycardia was defined by origination from a focal source and not entrainable. Atrial flutter and atrial tachycardia were grouped together because of difficulty to reliably differentiate between a focal atrial tachycardia and reentrant atrial tachycardia/atrial flutter on surface electrocardiogram. Paroxysmal atrial arrhythmia was defined as atrial arrhythmia <7 days duration while persistent atrial arrhythmia was defined as atrial arrhythmia >7 days duration.[16]

The antiarrhythmic therapies initiated at the time of arrhythmia diagnosis were categorized into 3 groups: (1) Rate control antiarrhythmia drug therapy defined as class II/IV antiarrhythmia drugs (beta blockers and calcium channel blockers) based on the Vaughan-Williams classification; (2) Rhythm control antiarrhythmia drug therapy defined as class I/III antiarrhythmia drug based on the Vaughan-Williams classification; (3) Rhythm control therapy using catheter ablation Fig. 2.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range), and count (%). Between-group comparisons were performed using unpaired t-test, and chi-square test. Pearson correlation was used to assess the relationship between continuous variables. Receiver operating characteristics (ROC) curve was used to determine the optimal cut-off point for RA reservoir strain to detect atrial arrhythmias based on Youden index. The cummulative incidece of atrial arrhythmias was assessed using the Kaplan Meier method, and log-rank tests was used for between-group comparisons of the incidence of atrial arrhythmia.

Cox regression was used to assess the relationship between RA function (strain) and outcomes (new-onset and recurrent atrial arrhythmias). The Cox models were adjusted for demographic indices (age, sex), surgical history (age at time of TOF repair, transannular patch repair, prior systemic to pulmonary shunt, and pulmonary valve replacement prior to baseline), right heart indices (RA volume, RV global longitudinal strain, moderate pulmonary regurgitation, RV systolic pressure), left heart indices (LA volume, LA reservoir strain, left ventricular [LV] global longitudinal strain), and comorbidities (hypertension, diabetes, coronary artery disease). Age and

sex were forced into all the models. For all analyses, RV and LV global longitudinal strain were modeled as absolute values (i.e., without the negative sign). The time of echocardiogram was considered as the baseline (beginning of at-risk period) for the assessment of new-onset atrial arrhythmia, and the patients without new-onset atrial arrhythmias were censored at the time of last clinic visit. The selection of covariates for the multivariable model was based on known association with outcomes, and only the covariates with $P < .1$ on univariable analysis were entered into the multivariable model. The final multivariable Cox model was determined by stepwise backwards selection of covariates with a $P < .05$ required for a covariate to remain in the model. For the Cox regression analysis for the correlates of recurrent atrial arrhythmias, we restricted the analysis to the patients with new-onset atrial arrhythmia during follow-up, and the time of diagnosis of new-onset atrial arrhythmia was used as beginning of at-risk. In addition to the covariates described above, the risk model for recurrent atrial arrhythmia was adjusted for type of antiarrhythmia therapy.

To assess the incremental prognostic power of RA reservior strain to predict new-onset and recurrent atrial arrhythmias, we first created a base model (a multivariable Cox regression model using the same covariates and methods described above). We then added the RA reservior strain to the base model and compared the Harrell's *c*-statistics between 2 models.

Exploratory analysis was performed to compare the prognostic performance (i.e., ability to predict atrial arrhythmias) of the different RA strain indices (RA reservoir strain, conduit strain, and booster strain), based on Harrell's *c*-statistic comparison. All statistical analyses were performed with BlueSky Statistics software (version. 7.10; BlueSky Statistics LLC, Chicago, IL), and P value $< .05$ was considered to be statistically significant for all analyses.

Results

Baseline characteristics

We identified 426 patients that met the study inclusion criteria. The mean age at the time of baseline echocardiogram was 33 ± 12 years, and 208 (49%) were males. The mean RA reservoir strain, conduit strain, and booster strain were 34 ± 11%, 20 ± 9%, and 15 ± 12%, respectively. Table 1 shows the baseline clinical and imaging data of the cohort. There was excellent intraobserver and interobserver reproducibility for RA reservor strain (intraclass correlation coefficient [ICC] 0.94, 95% confidence interval [CI] 0.91-0.97, and ICC 0.92, 95% CI 0.88-0.96, respectively). Similarly, we also observed excellent intraobserver and interobserver reproducibility for RA conduit strain (ICC 0.93, 95% CI 0.90-0.96, and ICC 0.91, 95% CI 0.88-0.95, respectively), and for RA booster strain (ICC 0.93, 95% CI 0.89-0.97, and ICC 0.92, 95% CI 0.88-0.96, respectively).

Table 1. Imaging data (n = 426).

Clinical indices	
Age, years	33 ± 12
Male sex	208 (49%)
Body mass index, kg/m^2	28 ± 6
Anatomic/surgical history	
Prior systemic-pulmonary shunt	98 (23%)
Age at time of TOF repair, years	4 (0.8-7)
PVR prior to baseline	224 (53%)
CIED prior to baseline	31 (7%)
Comorbidities	
Hypertension	70 (36%)
Diabetes	8 (4%)
Coronary artery disease	11 (6%)
Laboratory data	
GFR, ml/min/1.73m^2	90 ± 21
NT-proBNP, ng/l	241 (183-905)
Echocardiographic indices	
Right heart indices	
RA reservoir strain, %	34 ± 11
RA conduit strain, %	20 ± 9
RA booster strain, %	15 ± 7
RA volume index, mL/m^2	37 ± 15
Estimated RA pressure, mmHg	7 ± 3
Estimated RV systolic pressure, mmHg	41 (32-54)
RV end-diastolic area, cm^2	33 ± 9
RV end-systolic area, cm^2	24 ± 7
RV fractional area change, %	38 ± 9
RV global longitudinal strain, %	-19 ± 4
≥Moderate pulmonary regurgitation	246 (58%)
Pulmonary valve mean gradient, mm Hg	16 ± 9
Left heart indices	
LA reservoir strain, %	41 ± 12
LA conduit strain, %	15 ± 9
LA booster strain, %	13 ± 10
LA volume index, mL/m^2	27 ± 8
LV end-diastolic volume index, mL/m^2	56 ± 10
LV end-systolic volume index, mL/m^2	25 ± 7
LV ejection fraction, %	56 ± 8
LV global longitudinal strain, %	-20 ± 5
CMRI (n = 291)	
RV end-diastolic volume index, mL/m^2	141 ± 43
RV end-systolic volume index, mL/m^2	78 ± 31
RV stroke volume index, mL/m^2	62 ± 19
RV ejection fraction, %	45 ± 9
LV stroke volume index, mL/m^2	41 ± 11
LV ejection fraction, mL/m^2	59 ± 9

Abbreviations: CIED: cardiac implantable electronic devices, CMRI: cardiac magnetic resonance imaging, GFR: glomerular filtration rate, LA: left atrium, LV: left ventricle, NT-proBNP: N-terminal pro-brain natriuretic peptide, PVR: pulmonary valve replacement, RA: right atrium, RV: right ventricle, TOF: Tetralogy of Fallot.

There was a modest correlation between RA reservoir strain and LA reservoir strain (r = 0.62, $P < .001$), and between RA reservoir strain and RV global longitudinal strain (r = 0.59, $P < .001$). However, there was only a weak correlation between RA reservoir strain and RA volume index (r = -0.42, $P = .008$), RA pressure (r = -0.49, $P < .001$), RV systolic pressure (r = -0.42, $P = .009$), RV

Table 2. Cox model showing clinical and hemodynamic correlates of new-onset atrial arrhythmia.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
RA reservoir strain, per 1% increase	0.94 (0.92-0.96)	<.001	0.95 (0.93-0.97)	.008
Demographics				
Age, years	1.05 (1.04-1.07)	<.001	1.02 (1.01-1.04)	.006
Male sex	1.22 (0.91-1.64)	.2	1.18 (0.94-1.76)	.4
Surgical history				
Age at TOF repair, years	2.11 (1.06-3.36)	<.001		
Transannular patch repair	1.87 (0.93-2.14)	.3		
Prior systemic to pulmonary shunt	1.52 (0.86-2.75)	.4		
PVR replacement prior to baseline	1.18 (0.81-1.72)	.4		
Comorbidities				
Hypertension	1.43 (1.05-195)	.02		
Diabetes	1.29 (0.88-1.86)	.3		
Coronary artery disease	1.31 (0.89-1.91)	.2		
Right heart indices				
RA volume index, mL/m^2	1.03 (1.02-1.04)	<.001	1.02 (1.01-1.03)	.03
RV global longitudinal strain*, %	0.95 (0.89-1.02)	.2		
RV systolic pressure, mm Hg	1.02 (1.02-1.03)	<.001	1.04 (1.01-1.07)	.04
≥Moderate pulmonary regurgitation	1.69 (1.23-2.34)	.003		
Left heart indices				
LA volume index, mL/m^2	1.03 (1.01-1.04)	<.001		
LA reservoir strain, %	0.96 (0.94-0.98)	.008	0.97 (0.95-0.99)	.01
LV global longitudinal strain*, %	0.97 (0.95-0.99)	.03		

Abbreviations: CI: confidence interval; HR: hazard ratio; LA: left atrium; LV: left ventricle; MRI: magnetic resonance imaging; PVR: pulmonary valve replacement; RA: right atrium; RV: right ventricle; TOF: tetralogy of Fallot.

* LV and RV global longitudinal strain were modeled as absolute values (i.e., without the negative sign). Note that only the covariates with statistically significant association with outcome are displayed in the multivariable model.

fractional area change (r = 0.38, $P = .01$), and LV global longitudinal strain (r = 0.41, $P = .006$).

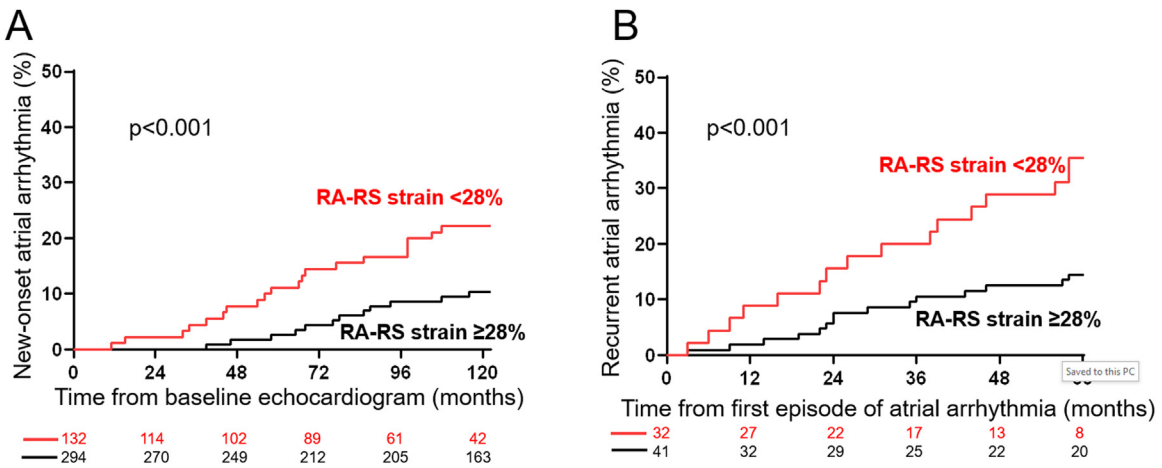
Of the 426 patients, 291 (63%) underwent cardiac magnetic resonance imaging (CMRI), and the average duration between echocardiogram and CMRI was 2 (1 to 5) days. There was a weak correlation between RA reservoir strain and CMRI-derived RV ejection fraction (r = 0.37, $P = .02$), but no correlation between RA reservoir strain and CMRI-derived RV end-diastolic volume index or RV end systolic volume index.

New-onset atrial arrhythmias

Of the 426 patients, 73 (17%) developed new-onset atrial arrhythmias during a median follow-up of 9.2 (4.7-11.6) years, yielding a 10-year cummulative incidence of 19% (95% CI 16-22). At the time of new-onset atrial arrhythmia, 42 of 73 (58%) presented with atrial flutter/tachycardia while 31 of 73 (42%) presented with atrial fibrillation. The diagnosis of atrial arrhythmia was based on electrocardiogram in 53 patients, Holter/event monitor in 28 patients, and/or device interrogation report in 7 patients. At the time of new-onset arrhythmia diagnosis, 62 (85%) patients have been in atrial arrhythmia for ≤7 days (paroxysmal atrial arrhythmia), 3 (4%) have been in atrial arrhythmia for >7 days (persistent atrial arrhythmia), while the duration of arrhythmia was undetermined in 8 (11%) patients.

RA reservoir strain was associated with new-onset atrial arrhythmia (unadjusted hazard ratio [HR] 0.94, 95% CI 0.92-0.96, Harrell's *c*-statistic 0.722, 95% CI 0.674-0.782), as well as with the individual types of atrial arrhythmia (atrial flutter/tachycardia: unadjusted HR 0.93, 95% CI 0.90-0.96, Harrell's *c*-statistic 0.704, 95% CI 0.683-0.739, and atrial fibrillation: unadjusted HR 0.96, 95% CI 0.93-0.99, Harrell's *c*-statistic 0.692, 95% CI 0.658-0.724). The association between RA reservoir strain and atrial arrhythmia remained significant after adjustment for demographic indices (age, sex), surgical history (age at time of TOF repair, transannular patch repair, prior systemic to pulmonary shunt, and pulmonary valve replacement prior to baseline), right heart indices (RA volume, RV global longitudinal strain, pulmonary regurgitation severity, and RV systolic pressure), left heart indices (LA volume, LA reservoir strain, and LV global longitudinal strain), and comorbidities (hypertension, diabetes, and coronary artery disease) (adjusted HR 0.95, 95% CI 0.93-0.97, Harrell's *c*-statistic 0.842, 95% CI 0.794-0.893), Table 2. Based on ROC analysis, RA reservoir strain ≥28% provided the optimal cut-off point to detect atrial arrhythmias (area under the curve 0.788, 95% CI 0.753-0.823, Youden index 0.76, Supplementary Fig. S1). Patients with RA reservior strain <28% had a higher 10-year cummulative incidnce of new-onset arrhythmia as compared to patients with RA reservior strain ≥28% (24% vs

Fig. 3



Kaplan Meier curves comparing the cummulative incidence of new-onset atrial arrhythmias (A) and recurrent atrial arrhythmias (B) between patients with right atrial reservoir strain (RA-RS) < 28% (red) and RA-RS ≥ 28% (black).

11%, $P < .001$), Fig. 3. RA reservoir strain <28% was associated with more than a 3-fold increase in the risk of new-onset atrial arrhythmias (adjusted HR 3.11, 95% CI 1.79-4.32, $P < .001$).

Recurrent atrial arrhythmias

Of the 73 patients with new-onset atrial arrhythmias, 34 (47%) received class II/IV antiarrhythmia drug therapy (rate control therapy), 28 (38%) received class I/III antiarrhythmic drug therapy (rhythm control therapy), and 11 (15%) underwent catheter ablation in addition to antiarrhythmia drug therapy. Of the 34 patients that received rate control antiarrhythmic drug therapy, 7 (21%) had severe pulmonary regurgitation and severe RV dilation at the time of atrial arrhythmia diagnosis, and these patients subsequently underwent surgical pulmonary valve replacement (n = 6), and transcatheter pulmonary valve replacement (n = 1).

The 73 patients with new-onset atrial arrhythmias were followed for additional 4.7 (3.3-6.1) years from the time of initial arrhythmia diagnosis, and during this period, 41 (56%) had recurrent atrial arrhythmias (atrial flutter/tachycardia n = 18, and atrial fibrillation n = 23), yielding a 5-year cummulative incidence of 33% (95% CI 27-39). RA reservoir strain at baseline echocardiogram was associated with recurrent atrial arrhythmias (unadjusted HR 0.90, 95% CI 0.87-0.93, Harrell's *c*-statistic 0.712, 95% CI 0.674-0.745), as well as with the individual types of atrial arrhythmia (atrial flutter/tachycardia: unadjusted HR 0.89, 95% CI 0.85-0.94, Harrell's *c*-statistic 0.729, 95% CI 0.693-0.756, and atrial fibrillation: unadjusted HR 0.92, 95% CI 0.87-0.98, Harrell's *c*-statistic 0.671, 95% CI 0.626-0.722). The association between RA reservoir strain and recurrent atrial arrhythmia remained significant after adjustment for demographic indices (age, sex), surgical history (age at time of TOF repair, transannular patch repair, prior systemic to pulmonary shunt, and pulmonary valve replacement prior to baseline), right heart indices (RA volume, RV global longitudinal strain, pulmonary regurgitation severity, and RV systolic pressure), left heart indices (LA volume, LA reservoir strain, and LV global longitudinal strain), and comorbidities (hypertension, diabetes, and coronary artery disease) (adjusted HR 0.92, 95% CI 0.88-0.96, Harrell's *c*-statistic 0.793, 95% CI 0.718-0.868), Table 3. Patients with RA reservior strain <28% had a higher 5-year cummulative incidnce of recurrent arrhythmia as compared to patients with RA reservior strain ≥28% (38% vs 16%, $P < .001$), Fig. 3. RA reservoir strain <28% was associated with more than a 2-fold increase in the risk of recurrent atrial arrhythmias (adjusted HR 2.57, 95% CI 1.36-3.81, $P < .001$).

Incremental prognostic value of RA reservior strain

A multivariable Cox regression model (base model) was created to determine the clinical and echocardiographic correlates of new-onset atrial arrhythmias. The complete model is shown in Supplementary Table S1. The correlates of new-onset atrial arrhythmias were older age, RA volume index, RV global longitudinal strain, RV systolic pressure, and LA reservoir strain (Supplementary Table S1). The addition of RA reservoir strain to the base model resulted in an increase in prognostic power of the base model from a Harrell's *c*-statistic 0.791 (95% CI 0.763-0.822) to Harrell's *c*-statistic 0.842 (95% CI 0.794-0.893), Harrell's *c*-statistics difference 0.053, $P < .001$).

Table 3. Cox model showing clinical and hemodynamic correlates of recurrent atrial arrhythmia.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
RA reservoir strain, per 1% increase	0.90 (0.87-0.93)	<.001	0.92 (0.88-0.96)	.001
Demographics				
Age, years	1.03 (1.02-1.04)	.007	1.02 (1.01-1.03)	.02
Male sex	1.41 (0.84-1.97)	.4	1.13 (0.91-1.42)	.5
Surgical history				
Age at TOF repair, years	1.86 (1.22-2.71)	.006		
Transannular patch repair	1.48 (0.84-2.02)	.2		
Prior systemic to pulmonary shunt	2.04 (0.81-4.11)	.5		
PVR replacement prior to baseline	1.34 (0.75-1.98)	.3		
Antiarrhythmia therapy				
Class II/IV antiarrhythmia drug	1.05 (0.92-1.18)	.4		
Class I/III antiarrhythmia drug	0.93 (0.90-0.96)	<.001		
Catheter ablation	0.98 (0.73-1.28)	.6		
Comorbidities				
Hypertension	1.28 (1.09-1.84)	.007		
Diabetes	1.21 (0.82-1.75)	.4		
Coronary artery disease	1.08 (0.82-1.75)	.3		
Right heart indices				
RA volume index, mL/m^2	1.04 (1.02-1.06)	<.001	1.03 (1.02-1.04)	.02
RV global longitudinal strain, %	0.91 (0.83-1.08)	.3		
RV systolic pressure, mm Hg	1.05 (1.03-1.07)	.005	1.03 (0.96-1.10)	.1
≥Moderate pulmonary regurgitation	1.28 (0.93-1.74)	.3		
Left heart indices				
LA volume index, mL/m^2	1.05 (1.03-1.07)	<.001		
LA reservoir strain, %	0.94 (0.92-0.96)	<.001	0.96 (0.94-0.98)	.008
LV global longitudinal strain, %	0.95 (0.93-0.97)	.009	0.96 (0.93-0.99)	.03

Abbreviations: CI: confidence interval; HR: hazard ratio; LA: left atrium; LV: left ventricle; MRI: magnetic resonance imaging; PVR: pulmonary valve replacement; RA: right atrium; RV: right ventricle; TOF: tetralogy of Fallot.
Antiarrhythmia therapies were modeled as time-dependent covariate.
*LV and RV global longitudinal strain were modeled as absolute values (i.e., without the negative sign). Note that only the covariates with statistically significant association with outcome are displayed in the multivariable model.

Supplementary Table S2 shows the base model for the clinical and echocardiographic correlates recurrent atrial arrhythmias, and these correlates were older age, RA volume index, RV global longitudinal strain, RV systolic pressure, LA reservoir strain, and LV global longitudinal strain (Supplementary Table S2). The addition of RA reservoir strain to the base model resulted in an increase in prognostic power of the base model from a Harrell's *c*-statistic 0.764 (95% CI 0.727-0.799) to Harrell's *c*-statistic 0.793 (95% CI 0.768-0.828), Harrell's *c*-statistics difference 0.031, $P = .008$).

Exploratory analysis

Exploratory analysis was performed comparing the prognostic power (ability to predict atrial arrhythmias) of the different components of RA function. Using RA reservoir strain as the reference, the Harrell's *c*-statistic for RA reservoir strain (i.e., ability to predict new-onset atrial arrhythmia) was 0.722 (95% CI 0.674-0.782), and was comparable to that of RA booster strain (Harrell's *c*-statistic 0.722, 95% CI 0.674-0.782 vs 0.731, 95% CI 0.688-0.781, $P = .2$), and RA conduit strain (Harrell's *c*-statistic 0.722, 95% CI 0.674-0.782 vs 0.704, 95% CI 0.680-0.731, $P = .09$). When considering recurrent atrial arrhythmia, the Harrell's *c*-statistic for RA reservoir strain (i.e., ability to predict recurrent atrial arrhythmia) was 0.712 (95% CI 0.674-0.745) and was comparable to that of RA booster strain (Harrell's *c*-statistic 0.712, 95% CI 0.674-0.745 vs 0.716, 95% CI 0.678-0.760, $P = .5$), and RA conduit strain (Harrell's *c*-statistic 0.712, 95% CI 0.674-0.745 vs 0.694, 95% CI 0.653-0.729, $P = .1$).

Discussion

In this study, we tested the hypothesis that RA reservoir strain at baseline echocardiogram can identify patients with repaired TOF at risk for developing atrial arrhythmia during follow-up. The main findings were: (1) RA reservoir strain at baseline echocardiogram was associated with new-onset and recurrent atrial arrhythmias after multivariable adjustments. (2) The prognostic power of RA reservoir strain was comparable to that of RA conduit strain and booster strain. (3). There was a poor correlation between RA reservoir strain and CMRI-derived RV ejection fraction, and no correla-

tion between RA reservoir strain and CMRI-derived RV volumes.

Atrial arrhythmias are common in adults with repaired TOF, with a prevalence of 20%, and with atrial fibrillation now becoming the predominant type of atrial arrhythmia in the older TOF population.[1,17] The presence of atrial arrhythmia, especially atrial fibrillation, was an independent risk factor for heart failure hospitalization and mortality.[3,4,17] In a multicenter study involving 556 adults with repaired TOF, Khairy et al identified the risk factors associated with diagnosis of atrial arrhythmias, and these risk factors were RA and LA enlargement, systemic hypertension, older age, number of cardiac surgeries, and LV systolic dysfunction.[1] However, the underlying mechanism(s) by which these risk factors lead to atrial arrhythmia remain poorly understood, but has been postulated to be due to RA remodeling (RA enlargement and RA dysfunction), which in turn, provided the substrate for atrial arrhythmias.[1,2] In the current study, we observed that RA function, as measured by RA reservoir strain, was associated with atrial arrhythmias, independent of other indices of right heart remodeling. To the best of our knowledge, the only other study that assessed the relationship between RA strain and atrial arrhythmias in adults with repaired TOF was a study based on a cross-sectional analysis of 100 patients, among whom 26 had prior history of atrial arrhythmias.[15] In that study, Timoteo et al observed that RA and RV strain were associated with atrial arrhythmia only in the subset of patients without prior history of pulmonary valve replacement.[15] A limitation of the Timoteo et al study was that it relied on cross-sectional analysis, and hence it is unclear whether RA dysfunction preceded the diagnosis of atrial arrhythmia or vice versa. The current study overcame this limitation by using a cohort study design, thereby demonstrating a temporal relationship between RA function (or dysfunction) and onset of atrial arrhythmias. Furthermore, by excluding patients with prior history of atrial arrhythmias at baseline, the results of the study address the important clinical question of identifying patients at risk for developing atrial arrhythmias during follow-up.

The relationship between RA strain and atrial arrhythmias was consistent across the different components of RA function (reservoir strain, conduit strain, and booster strain), suggesting that RA strain is a robust prognostic indicator. We postulated that is likely related to the fact atrial strain is related to the presence of atrial fibrosis, which is a critical link in the mechanistic pathway for the initiation and propagation of atrial arrhythmias.[18-23]

An important negative finding from the current study was the absence of correlation between RA reservoir strain and CMRI-derived RV volumes, and only a weak correlation between RA reservoir strain and CMRI-derived RV ejection fraction. This is consistent with a previous study by Kutty et al that showed an absence of correlation between CMRI-derived RA strain indices and RV volumetric indices.[24] This may be because CMRI-derived RV volumetric indices measure systolic function, while RA strain provides a composite assessment of both RV systolic function, RV diastolic function, and RA compliance.[5,25,26] These may account for the robust prognostic performance of RA strain indices in this population.

Clinical implications and future directions

The results of the current study show that RA reservoir strain <28% was associated with a 3-fold increase in the risk of new-onset atrial arrhythmias and a 2-fold increase in the risk of recurrent atrial arrhythmias, suggest that RA reservoir strain can be used to identify patients at risk for atrial arrhythmias, and to guide therapy. For instance, patients with RA reservoir strain <28% may be considered for, therapies targeted at reducing right heart pressure and volume overload (such as pulmonary valve replacement or optimization of volume status with diuretics) at an earlier stage as compared to other patients. Such interventions may lead to a reduction in right heart pressures (RV systolic pressure and RA pressure) which are inversely related to RA function. Another potential application of the results of the current study is with regards to deciding on the type/intensity of antiarrhythmia therapy after the initial episode of atrial arrhythmias. Perhaps, patients with RA reservoir strain <28% should have more intensive antiarrhythmia therapy such as catheter ablation since they are at a higher risk of recurrent atrial arrhythmia, because catheter ablation has been shown to improve atrial reverse remodeling based on data from the acquired heart disease population.[27] Of note, the current study did not provide data to support the efficacy (or lack thereof) of the interventions proposed above, and hence the need for further research.

Limitations

This is a retrospective single center study, and it is therefore prone to selection and ascertainment bias. The timing/intensity of antiarrhythmia therapies received by the patients with new-onset arrhythmia was not standardized, and hence it is unclear how these differences in therapy would influence the observed relationship between RA strain and recurrent atrial arrhythmias. As already stated above, the study design did not allow for the assessment of the effect of medical or surgical interventions on RA function, and how such changes would modify the risk for future atrial arrhythmias. Finally, we relied on a single echocardiogram for the assessment of RA function, and hence we were unable to account for the effect of temporal changes in RA function on the risk of subsequent atrial arrhythmia.

Conclusions

RA function, as measured by RA strain, was associated with new-onset and recurrent atrial arrhythmias, after

multivariable adjustments. RA reservoir strain <28% was associated with a 3-fold increase in the risk of new-onset atrial arrhythmias, and a 2-fold increase in the risk of recurrent atrial arrhythmias. These results suggest that RA strain can be used for arrhythmia risk stratification in this population. Additionally, the absence of correlation between RA strain indices and CMRI-derived RV volumetric indices suggests that both sets of indices measure different aspects of right heart function and adaptation, and their prognostic benefits may be complementary when used together for risk stratification.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.05.018.

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