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ORIGINAL ARTICLE

Cardiac MRI predictors of adverse outcomes in adults with a systemic right ventricle

Matthew J. Lewis[1]*, Alexandra Van Dissel[2], Jonathan Kochav[1], Michael P. DiLorenzo[3], Jonathan Ginns[4], Noa Zemer-Wassercug[1], Maarten Groenink[2], Barbara Mulder[2] and Marlon Rosenbaum[1]

[1]*Division of Cardiology, Department of Medicine, Schneeweiss Adult Congenital Heart Center, Columbia University Medical Center, New York, NY, USA;* [2]*Division of Cardiology, Amsterdam University Medical Center, Amsterdam, The Netherlands;* [3]*Division of Pediatric Cardiology, Department of Pediatrics, NewYork-Presbyterian/Morgan Stanley Children's Hospital, Columbia University Irving Medical Center, New York, NY, USA; and* [4]*Austin Heart, Austin, TX, USA*

Abstract

Aims Predicting risk in individuals with a systemic right ventricle (SRV) remains difficult. We assessed the value of cardiac MRI (CMR) for predicting death, heart transplantation (HT), or need for a ventricular assist device (VAD) in adults with D-transposition of the great arteries (DTGA) post Mustard/Senning and in adults with congenitally corrected transposition of the great arteries (ccTGA) at two large academic centres.

Methods and results Between December 1999 and November 2020, 158 adult patients with an SRV underwent CMR. Indexed right ventricular end-diastolic volume (RVEDVI), indexed right ventricular end-systolic volume (RVESVI), right ventricular ejection fraction (RVEF), and right ventricular mass (RV mass) were determined by a core laboratory. Receiver operating curves, area under the curve (AUC), and cut-points maximizing sensitivity and specificity for the endpoint for each CMR parameter were calculated. Over a median of 8.5 years, 21 patients (13%) met a combined endpoint of HT referral, VAD, or death. Each CMR parameter was significantly associated with the endpoint in both cohorts. The AUCs for RVEDVI, RVESVI, RVEF, and RV mass to predict the endpoint were 0.93, 0.90, 0.73, and 0.84 for DTGA and 0.76, 0.74, 0.71, and 0.74 for ccTGA, respectively. Optimized cut-points for RVEDVI were calculated for DTGA and ccTGA and were 132 and 126 mL/m^2, respectively. RVEDVI cut-points were simplified to 130 mL/m^2 for survival analysis, which was significantly associated with survival in both cohorts.

Conclusions Cardiac MRI parameters are associated with an increased risk of death, HT, or VAD in patients with an SRV and should be considered to facilitate risk stratification.

Keywords Adult congenital heart disease; Systemic right ventricle; Transposition of the great arteries; Cardiac MRI; Heart failure; Heart transplant

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**Correspondence to: Matthew Lewis, MD, Division of Cardiology, Department of Medicine, Schneeweiss Adult Congenital Heart Center, Columbia University Medical Center, Herbert Irving Pavilion, 161 Fort Washington Ave Suite 627, New York, NY 10032, USA. Tel: 212-305-6936; Fax: 212-305-0490. Email: ml3329@columbia.edu*

Introduction

The population of patients with a systemic right ventricle (SRV) includes those who have undergone a Mustard or Senning procedure for D-transposition of the great arteries (DTGA) and those with congenitally corrected transposition of the great arteries (ccTGA).[1] In each case, the morphologic right ventricle supports the systemic circulation. While patients with an SRV tend to have a relatively good prognosis, a subset will develop progressive cardiac dysfunction resulting in end-stage heart failure and death.[2–9] Unfortunately, our ability to prognosticate which patients are at highest risk for death or end-stage heart failure is limited.[10]

The relation between systemic left ventricular dysfunction and clinical outcomes is well supported by published studies.[11–14] In contrast, the relation between SRV function and clinical outcomes is less clear. Because right ventricular (RV) hypertrophy and dilation are adaptive responses to exposure to systemic pressure, some degree of remodelling appears to be the norm.[15,16] However, excessive remodelling may play a role in eventual RV failure.[16,17] Determining when remodelling becomes maladaptive is complicated by the

anatomy of the SRV and the limitations of two-dimensional imaging in the evaluation of SRV size and function.[18–20] As a result, prior studies utilizing SRV parameters have provided inconsistent results with respect to prognosis.[5,21–23]

Cardiac MRI (CMR) offers distinct advantages over transthoracic echocardiography (TTE) for assessment of ventricular volume and function in the SRV and is the gold standard for quantification of RV volume and mass.[24–26] No study has assessed the prognostic value of CMR-derived indices of SRV function and size as independent risk factors for death or end-stage heart failure. Given the increasing clinical use of CMR for SRV evaluation, and the lack of simple, reproducible tools for risk stratification in this population, it is essential to determine the predictive value of CMR for important clinical outcomes. Therefore, we sought to assess if CMR imaging parameters independently predict which patients with an SRV are at risk for end-stage congestive heart failure or death at two large congenital heart disease centres with all CMRs over-read at a core laboratory.

Methods

Patients and study design

We performed a retrospective, case–control study of all adult patients (age $>$ 18 years) with a diagnosis of ccTGA or DTGA following a Mustard/Senning procedure seen at the Schneeweiss Adult Congenital Heart Center at Columbia University Irving Medical Center or Amsterdam University Medical Center between December 1999 and November 2020. Since 1999, all patients with an SRV who did not have a non-CMR compatible device were referred for a baseline CMR as part of their routine evaluation. Only patients with complete CMR data were included. This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of Columbia University Irving Medical Center and Amsterdam University Medical Center prior to data acquisition.

Outcomes of interest

The primary outcome was pre-specified as a composite of death, heart transplantation (HT) referral, or destination therapy with a ventricular assist device (VAD). HT referral and destination therapy with a VAD were determined by review of the medical records and patient contact. Date and mode of death was determined from review of the medical records and adjudicated by an internal Columbia University resource that queries the National Death Index and a national database at Amsterdam University Medical Center. Time to event was defined as time from each patient's CMR to the time of first event or last known date of patient status.

In order to determine if event rates were reflective of the SRV population as a whole, we assessed the rate of the primary outcome in all patients with an SRV and a non-CMR compatible device at one centre. In addition to the primary outcome, we also defined the number of cardiac hospitalizations between the CMR and non-CMR groups.

Baseline clinical evaluation

A set of clinical variables and imaging characteristics based on prior studies[1,8,27] were pre-specified prior to data acquisition and determined via review of written and electronic medical records. Medications were determined via chart review. Degree of systemic tricuspid valve regurgitation was graded as severe, moderate to severe, moderate, or mild by adult congenital cardiologists using TTE. Only TTE reports from the study performed closest to the time of CMR were reviewed.

Cardiac MRI image acquisition

Cardiac MRI studies were performed with breath holding and electrocardiogram gating using either a Signa 1.5 Tesla MRI scanner (General Electric, Milwaukee, WI) or a Siemens Avanto 1.5 Tesla MRI scanner (Siemens, Erlangen, Germany) with an eight-channel phased array. Short-axis cine images were acquired using a steady-state free precession pulse sequence with the following typical parameters: TR 3.6 ms, TE 11.5 ms, flip angle of 45°, 24 views per segment, field of view 35 cm, acquisition matrix 192 × 160, slice thickness 8 mm with no gap, and receiver bandwidth 125 kHz.

Cardiac MRI image analysis

Two blinded readers performed CMR image analysis using Circle for all studies. Inter-reader reproducibility between the designated readers for CMR volumetric measurements was tested in a random cohort of 10 patients. Readers were blinded to clinical history and to initial measurements by the other reader.

Cine loops were used to select images at end-diastole and end-systole. End-diastole and end-systole were defined independently for both the right and left ventricles as the phases with the largest and smallest volumes, respectively. Endocardial segmentation was performed by manual tracing of each end-diastolic and end-systolic short-axis view and used to calculate right and left ventricular volumes. Measurements were indexed to body surface area to yield indexed right ventricular end-diastolic volume (RVEDVI) and indexed right ventricular end-systolic volume (RVESVI). Right ventricular ejection fraction (RVEF) was calculated from end-diastolic and end-systolic volumes ((RVEDV − RVESV)/RVEDV). Epicardial segmentation was performed by manual tracing of each

end-diastolic short-axis frame of the right ventricle and used to calculate right ventricular mass (RV mass) using a myocardial specific gravity of 1.05 g/cm^3. By convention, trabeculations and papillary muscles were considered part of the ventricular blood pool in both systole and diastole. In accord with prior studies, all of the septum was considered part of RV mass.[15]

Statistical analysis

Data were expressed as number (%), mean (standard deviation), or median (interquartile range) when appropriate. Inter-rater reliability amongst the two raters was estimated using the single measures intra-class correlation coefficient. Logistic regression was used to assess the impact of each systemic RV parameter on the outcome of interest. Age at CMR and moderate or greater tricuspid regurgitation were pre-specified covariables for inclusion in an adjusted model. Receiver operating curves and the corresponding area under the curve (AUC) were calculated for RVEDVI, RVESVI, RVEF, and RV mass, and AUCs were compared using standard methods.[28] Cut-point values of CMR variables of interest for the primary outcome were identified using receiver operating curve analysis. An optimum cut-point that optimizes sensitivity and specificity was determined for each CMR variable of interest using the Youden methodology for cut-point selection.[29] Following, Cox-proportional hazard models was utilized for each cut-point with the greatest AUC to assess the impact of each predictor on survival. All statistical analyses were performed using STATA statistical software (Version 16.1, Stata Corp, College Station, TX, USA).

Results

Between December 1999 and November 2020, 158 patients with an SRV, including 101 with DTGA status post Mustard/Senning and 57 with ccTGA, had a baseline CMR at either centre. Patient characteristics, including mean RVEDVI, RVESVI, RVEF, and RV mass, are displayed in *Table 1* for both groups. Notably, patients with ccTGA had a significantly higher mean RVEDVI and mean RVEF when compared with patients with DTGA post Mustard/Senning, and a significant higher proportion of individuals with moderate or greater TR. The remainder of CMR parameters were similar between groups. Inter-class correlation coefficients between readers for CMR parameters were high: RVEDV: 0.95 (confidence interval 0.82–0.99), RVESV: 0.99 (0.95–0.997), and RV mass: 0.86 (0.57–0.96).

Additional procedures performed in our cohort prior to CMR included pulmonary stenosis repair in 21 patients, ventricular septal defect repair in 20 patients, baffle revisions in 8 patients, atrial septal defect closure in 6 patients, superior vena cava/inferior vena cava baffle limb stents in 4 patients, patent ductus arteriosus ligation in 4 patients, end-to-end anastomosis for aortic coarctation in 3 patients, mitral valve repair and tricuspid valve replacement (TVR) in 2 patients, and 2 with prior pulmonary artery banding. There

Table 1 Patient characteristics

	DTGA (n = 101)	ccTGA (n = 57)	P-value
Gender (male)	58 (57%)	31 (54%)	NS
Age at CMR, mean (SD), years	30 (7)	37 (13)	<0.001
Follow-up time from CMR, mean (SD), years	8.5 (5.5)	8.7 (5.5)	NS
≥Moderate tricuspid regurgitation	35 (35%)	39 (70%)	<0.001
Medications (at last clinical encounter)			
Beta-blockers	24 (28%)	19 (45%)	NS
ACE-inhibitors/ARBs	36 (42%)	25 (60%)	NS
Diuretics	15 (17%)	11 (26%)	NS
Cardiac hospitalization	15 (15%)	15 (27%)	NS
SVT requiring ablation	8 (8%)	4 (7%)	NS
ICD placement	6 (6%)	8 (14%)	NS
BMI, mean (SD)	25.6 (2)	25.1(3)	NS
Right ventricular EDVI, mean (SD), mL/m^2	122 (34)	135 (31)	0.016
Right ventricular ESVI, mean (SD), mL/m^2	74 (30)	78 (26)	NS
Right ventricular ejection fraction, mean (SD), %	41 (8)	43 (9)	0.042
Right ventricular mass, mean (SD), g	105 (4)	107 (4)	NS
RV stroke volume, mean (SD), mL	90 (22)	129 (176)	0.029
Left ventricular EDVI, mean (SD), mL/m^2	78 (28)	85 (22)	NS
Left ventricular ESVI, mean (SD), mL/m^2	33 (17)	36 (14)	NS
Left ventricular ejection fraction, mean (SD), %	58 (8)	59 (11)	NS
Left ventricular mass, mean (SD), g	41(16)	47 (15)	0.04
Death/VAD/transplant referral	9 (9%)	12 (21%)	0.029

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; ccTGA, congenitally corrected transposition of the great arteries; CMR, cardiac MRI; DTGA, D-transposition of the great arteries; EDVI, indexed end-diastolic volume; ESVI, indexed end-systolic volume; ICD, implantable cardioverter defibrillator; NS, not significant; RV, right ventricular; SD, standard deviation; SVT, supraventricular tachycardia; VAD, ventricular assist device.
Data are represented as number (%), mean, or median.

were no significant differences between the number or types of additional procedures performed in patients with ccTGA when compared with those with DTGA post Mustard/Senning.

Primary and secondary outcomes

In our cohort, 21 patients (13%) met the primary endpoint over a cumulative follow-up of 1320 patient-years. Patients with ccTGA were more likely to meet the primary endpoint (9% vs. 21%, $P = 0.029$). Of all patients, 15 died (71%), 4 were referred for heart transplant (20%), and 2 (10%) underwent destination VAD placement. Cause of death included nine from progressive heart failure, three from sudden cardiac death, and three with an unknown cause. Univariable and multivariable predictors of the primary outcomes are shown in *Table 2*. RVEDVI, RVESVI, RV mass, and RVEF were each independently significantly associated with the primary outcome for both ccTGA patients and those post Mustard/Senning. After controlling for age and ≥moderate tricuspid regurgitation, all CMR SRV parameters remained associated with the primary endpoint for both groups.

Seventeen patients had a TVR after their CMR, including 15 ccTGA patients and 2 Mustard/Senning patients ($P < 0.001$). There was no significant association between TVR and the primary endpoint. All CMR SRV parameters for both patient cohorts remained significantly associated with the endpoint after need for TVR was included in a multivariable model (*Table 2*).

Thirty-nine patients with an SRV, including 25 with ccTGA (64%), who did not have a CMR secondary to non-compatible device were also identified during this time period. Within this cohort, eight patients (21%) met the primary endpoint. Importantly, there was no significant difference in the proportion of patients meeting the primary endpoint or in total hospitalizations between patients who had a CMR and those who did not.

Receiver operating curve analysis and volumetric cut-points

For DTGA patients post Mustard/Senning, the AUCs for RVEDVI, RVESVI, RVEF, and RV mass were 0.93, 0.90, 0.73, and 0.84, respectively. For ccTGA patients, the AUCs for RVEDVI, RVESVI, RVEF, and RV mass were 0.76, 0.74, 0.71, and 0.74, respectively. The AUCs for RVEDVI and RVESVI were significantly greater than the AUC for RVEF ($P = 0.005$ and $P = 0.002$, respectively) for DTGA patients only. Otherwise, there were no significant differences between the AUCs for any of the remaining CMR parameters for either group. The cut-points of CMR-derived indices that maximized both sensitivity and specificity for the primary outcome are shown in *Table 3*.

We performed a subgroup analysis analysing the impact of ≥moderate TR on the optimal RVEDVI cut-points for each

Table 2 Predictors of the primary outcome

Univariable analysis				
	DTGA		ccTGA	
Variable/increment of odds ratio	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Right ventricular EDVI (mL/m^2)	1.07 (1.03–1.10)	<0.001	1.03 (1.01–1.06)	0.011
Right ventricular ESVI (mL/m^2)	1.07 (1.03–1.11)	0.001	1.04 (1.01–1.07)	0.008
Right ventricular ejection fraction (per % decrease)	1.14 (1.02–1.26)	0.006	1.09 (1.01–1.18)	0.038
Right ventricular mass (g)	1.04 (1.01–1.06)	0.003	1.03 (1.00–1.05)	0.024
Multivariable analysis				
	DTGA		ccTGA	
Variable/increment of odds ratio	Adjusted OR[a] (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
Right ventricular EDVI (mL/m^2)	1.06 (1.02–1.10)	0.001	1.03 (1.00–1.05)	0.018
Right ventricular ESVI (mL/m^2)	1.07 (1.03–1.11)	0.001	1.04 (1.01–1.07)	0.013
Right ventricular ejection fraction (per % decrease)	1.13 (1.03–1.26)	0.010	1.09 (1.01–1.19)	0.034
Right ventricular mass (g)	1.04 (1.01–1.07)	0.004	1.01 (1.00–1.05)	0.028
	Adjusted OR[b] (95% CI)	*P*-value	Adjusted OR[b] (95% CI)	*P*-value
Right ventricular EDVI (mL/m^2)	1.07 (1.03–1.10)	<0.001	1.03 (1.01–1.06)	0.010
Right ventricular ESVI (mL/m^2)	1.07 (1.03–1.11)	0.001	1.04 (1.01–1.07)	0.007
Right ventricular ejection fraction (per % decrease)	1.14 (1.04–1.26)	0.005	1.10 (1.01–1.19)	0.038
Right ventricular mass (g)	1.04 (1.01–1.06)	0.003	1.03 (1.00–1.05)	0.024

ccTGA, congenitally corrected transposition of the great arteries; CI, confidence interval; DTGA, D-transposition of the great arteries; EDVI, indexed end-diastolic volume; ESVI, indexed end-systolic volume; OR, odds ratio.
[a]Model includes ≥moderate tricuspid regurgitation and age at cardiac MRI.
[b]Model includes tricuspid valve replacement after cardiac MRI.

Table 3 Cut-points for each cardiac MRI parameter and associated sensitivity and specificity for predicting the primary endpoint

DTGA after Mustard or Senning				
	Cut-point	Sensitivity (%)	Specificity (%)	NPV/PPV (%)
RVEDVI (mL/m^2)	≥132	100	76	100/29
RVESVI (mL/m^2)	≥81	89	74	99/25
RV mass (g)	≥115	89	69	98/22
RVEF (%)	<38	67	67	95/17
ccTGA				
	Cut-point	Sensitivity (%)	Specificity (%)	NPV/PPV (%)
RVEDVI (mL/m^2)	≥126	100	53	100/36
RVESVI (mL/m^2)	≥84	75	66	91/38
RV mass (g)	≥112	75	73	92/43
RVEF (%)	<39	75	75	92/45

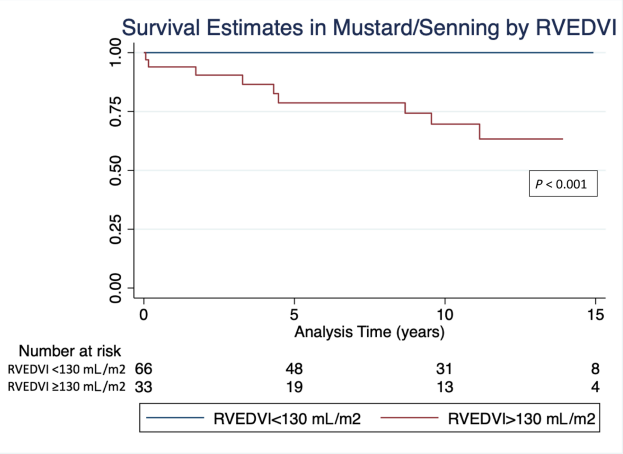
ccTGA, congenitally corrected transposition of the great arteries; DTGA, D-transposition of the great arteries; NPV, negative predictive value; PPV, positive predictive value; RV mass, right ventricular mass; RVEDVI, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVI, indexed right ventricular end-systolic volume.

group. For both DTGA and ccTGA patients with ≥moderate TR, the optimal cut-point of RVEDVI was higher when compared with patients with <moderate TR (DTGA: 141 vs. 130 mL/m^2; ccTGA: 131 vs. 124 mL/m^2).

Survival analysis

As the systemic RV parameter with the highest AUC, we utilized RVEDVI cut-points in survival analysis for each group. For simplicity, we utilized an RVEDVI value of 130 mL/m^2 for both groups based on the derived optimal cut-points. Graphs of the cumulative survivor function for an RVEDVI ≥ 130 mL/m^2 for DTGA patients post Mustard/Senning and for patients with ccTGA are provided in *Figures 1* and *2*. For DTGA patients post Mustard/Senning, the median (interquartile range) time from CMR to the primary outcome was 9.4 years (9.3 years), and 8.9 years (8.7 years) for those with ccTGA.

Figure 1 Kaplan–Meier survival estimates for individuals with D-transposition of the great arteries post Mustard/Senning by indexed right ventricular end-diastolic volume (RVEDVI).

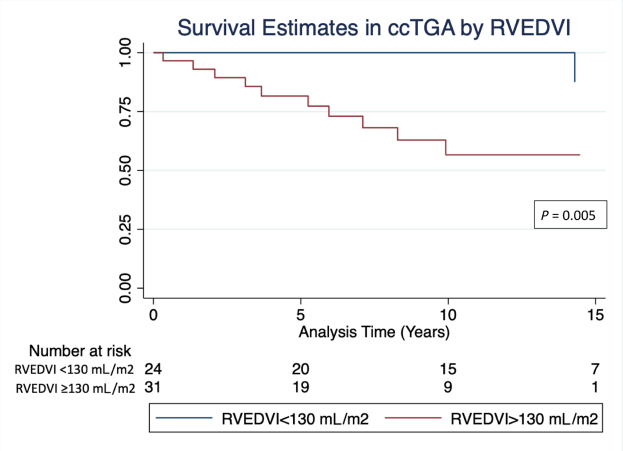


Discussion

Systemic right ventricle enlargement and dysfunction is common in adult patients with ccTGA and DTGA post Mustard or Senning procedure.[30] In a compensatory response to systemic pressure, the right ventricle undergoes remodelling resulting in dilation and hypertrophy.[31] While prior studies have suggested a relationship between progressive RV dilation and clinical events, data showing a direct correlation between RV indices and prognosis are lacking.[27] Our study is the first to identify CMR-derived parameters of RV function and size as risk factors for death, HT, or need for destination VAD.

Prior studies attempting to define the relation between SRV function and mortality or end-stage heart failure have shown variable results. In a study of 188 patients with an SRV or single ventricle, Piran *et al*. demonstrated that RVEF as measured by echocardiography or radionuclide scan was a predictor of overall mortality.[5] Similarly, Rutledge *et al*. found that moderate to severe SRV dysfunction, as assessed by two-dimensional echocardiography, was predictive of mortality in a population of 121 patients with ccTGA.[22] However, other studies utilizing echocardiography have failed to demonstrate this relationship.[21] In a study by Dos *et al*., for example, there was no correlation between SRV dysfunction and mortality in patients with a Mustard or Senning repair.[23] While the value of three-dimensional echocardiographic assessment of SRV function has yet to be determined in this population, the visual grading of systemic RV function by TTE is complicated by discordant subjective and qualitative

Figure 2 Kaplan–Meier survival estimates for individuals with congenitally corrected transposition of the great arteries (ccTGA) by indexed right ventricular end-diastolic volume (RVEDVI).



assessment between apical and short-axis views from trabecular hypertrophy, the location of the SRV in the chest, and geometric variation between patients.[32] Consequently, the value of two-dimensional TTE for quantification of SRV function is limited[20] and can lead to significant variability.

Cardiac MRI allows for accurate and reproducible evaluation of the SRV and has replaced echocardiography as the gold standard for SRV assessment.[15] Given the relatively recent adoption of CMR for evaluation of the SRV, longitudinal studies delineating the relationship of CMR parameters to prognosis are scant. In a prospective study performed in 88 patients with an SRV over a median time of 4.3 years, van der Bom *et al*. found that an RVEDVI above 150 mL/m^2, when assessed in conjunction with a peak exercise systolic blood pressure, was associated with a higher rate of a heterogeneous composite endpoint that included worsening heart failure, tricuspid valve surgery, arrhythmias, and death.[27] Similarly, several studies have shown a correlation between CMR parameters of SRV function and brain natriuretic peptide levels.[33,34] While these studies have suggested a relationship between CMR-derived SRV parameters and heart failure, our study is the first to show a definitive relationship with patient prognosis.

We found that CMR measurements of RV volume were strong predictors of death and end-stage heart failure in both univariate and multivariable analyses and, for patients with a history of Mustard or Senning repair, were superior to systemic ventricular ejection fraction for predicting adverse events. Because ejection fraction may not decline until after significant remodelling of the systemic ventricle has occurred, quantification of the degree of ventricular enlargement may be the best method for screening patients with an SRV. Increased systemic RV volume is associated with increased systemic AV valve regurgitation, creating a feedback loop that may with time yield more ventricular dilation.[10,21,35] Progressive RV enlargement may also alter ventricular function by impairing contractility, a phenomenon that is only partially mitigated by RV hypertrophy from exposures to chronic systemic pressure.[36] While no prior study has directly linked measurements of RV volume by CMR with mortality or transplant in patients with an SRV, several have demonstrated its value as a marker to assess the relative health of the right ventricle in general. In particular, measurements of RVEDVI have been shown to be useful in patients with pulmonary hypertension.[37] Furthermore, measurements of ventricular volume have been shown to correlate with sudden cardiac death in patients with a non-ischaemic dilated cardiomyopathy.[38] It is possible that assessment of ventricular volume in patients with an SRV may capture both patients at risk for decompensated heart failure and those with an increased risk of malignant ventricular arrhythmias.

In our cohort, all CMR parameters remained associated with the endpoint after inclusion of need for TVR or moderate or more TR underscoring the probability that multiple mechanisms of progressive remodelling are present in individuals with SRV. Notably, we derived a higher optimal cut-point for patients with moderate or greater TR, implying that some degree of RV remodelling may be remediable in patients with significant tricuspid valve disease. In aggregate, our study would suggest that there is a point beyond which further RV dilation and hypertrophy increases an individual's risk for a cardiac event regardless of the degree of systemic AV regurgitation.

Our results suggest that CMR at an experienced centre should be considered as part of the standard evaluation for patients with an SRV. While echocardiography remains important in the assessment of patients with an SRV and is the gold standard for evaluation of systemic tricuspid valve pathology, periodic CMR provides additional data to facilitate patient care. Specifically, our findings demonstrate that systemic RV measurements by CMR can provide quantitative data regarding patient prognosis. By providing a reproducible method for risk stratification, CMR allows for the identification of patients at highest risk for poor outcomes, which may have important clinical implications. Patients with enlarged RV volumes may require more frequent follow-up and may stand to benefit from closer monitoring. While studies focusing on traditional heart failure therapies have yet to provide definitive evidence of improved outcomes in this population,[39] no study has focused on patients at increased risk as defined by CMR parameters. Such patients may yield greater benefit from advanced heart failure therapeutics, a question that should be addressed in future studies. Finally, monitoring RV volumes may be beneficial in helping to make decisions regarding more invasive therapeutic strategies such as tricuspid valve surgery, defibrillator use, and eventual HT and mechanical support.

Study limitations

This multicentre study comprised a large cross-section of patients, contributing to the applicability of real-world patient management of those in adult congenital heart disease care. However, because all CMRs were read by a core lab with expertise evaluating patients with adult congenital heart disease, our findings may not be generalizable to all centres. Finally, as a retrospective study, we may have missed important, masked confounders during data collection and analysis.

Conclusions

Cardiac MRI parameters predict an increased risk of death, HT, or VAD in patients with an SRV. CMR risk stratification should be considered in adult patients with an SRV.

Conflict of interest

None declared.

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