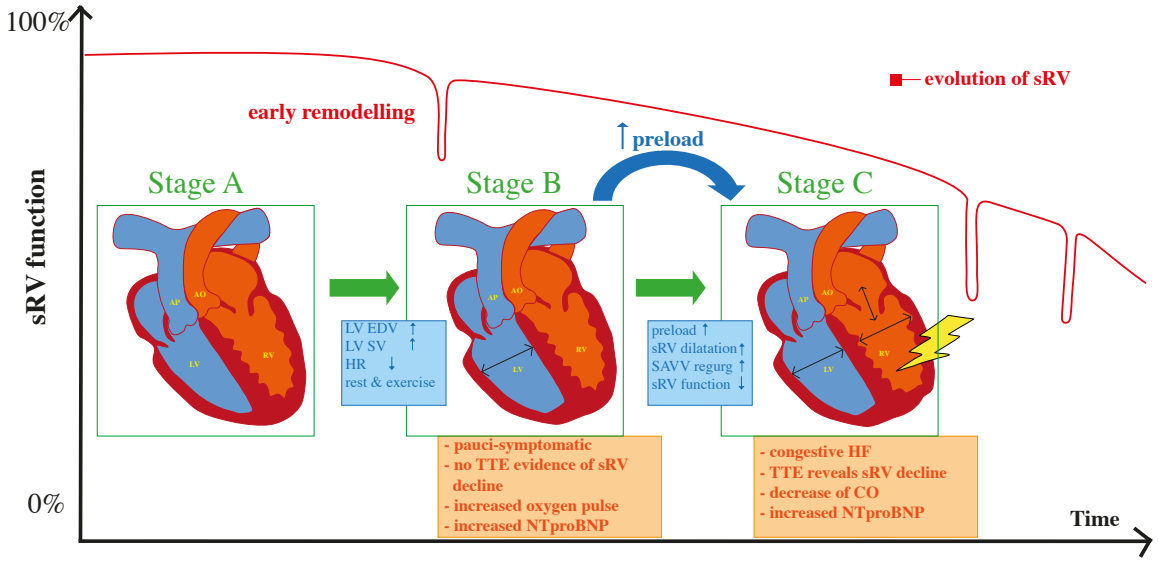
Abstract

Background – Early recognition of adverse remodeling is important since outcome is unfavorable once patients with a systemic right ventricle (sRV) become symptomatic. We aimed assessing prognostic markers linked to short-term clinical evolution in this population.

Methods and results– Thirty-three patients (76% male) with sRV (atrial switch repair for D-transposition of the great arteries and congenitally corrected transposition of the great arteries) underwent detailed phenotyping including exercise CMR and were followed over mean follow-up time of 3 years. Mean age was 40±8 (range 26-57) years at latest follow-up. Adverse outcome was a composite of heart failure and tachyarrhythmia. Descriptive statistics and univariate cox regression analyses were performed. When compared to baseline, (I) most patients remained in NYHA functional class I (76%), (II) the degree of severity of the systemic atrioventricular valve (SAVV) regurgitation rose and (III) more electrical instability was documented at latest follow-up. Six (18%) of a total of nine events were counted as first cardiovascular events (9% heart failure, 9% arrhythmia). NTproBNP, oxygen pulse, left ventricle end-diastolic volume index (LVEDVi) and stroke volume index (SVi) of the subpulmonary left ventricle (LV) both in rest and at peak exercise were significantly associated with the first cardiovascular event.

Conclusion – NTproBNP was by far the best prognostic marker for clinical outcome. Adverse remodeling with increase of LVEDVi and SVi of the subpulmonary LV at rest and during exercise were associated with worse clinical outcome. We theorize that remodeling of the subpulmonary ventricle might be an early sign of a failing sRV circulation.

Central image (figure 1)



Introduction

The morphological right ventricle (RV) supports the systemic high – pressure circulation in patients with complete transposition of the great arteries after atrial switch repair (Mustard or Senning) (D-TGA) and congenitally corrected transposition of the great arteries (ccTGA) resulting in a subaortic or systemic right ventricle (sRV) and a subpulmonary left ventricle (LV) (1, 2). The number of patients with sRV reaching adulthood increased steadily (3, 4) but the major concerns for long-term outcome in those patients are sRV dysfunction, heart failure (HF), arrhythmias and sudden cardiac death (5). Moreover, sRV dysfunction might compromise the subpulmonary LV function as a consequence of a negative ventriculo-ventricular interaction and pulmonary hypertension (6, 7). Although sRV failure is one of the main contributors to mortality and disability in young patients (8), little is known about the early stages of remodeling and its potential impact on short-term outcome. Indeed, hemodynamic deterioration may develop gradually and subclinically for a significant period of time (early remodeling) followed by sudden and sometimes unexpected clinical deterioration (8). Therefore, early recognition of hemodynamic deterioration has significant clinical importance. Standard echocardiography provides valuable information on the sRV, the systemic atrioventricular valve (SAVV) function, and residual lesions or postprocedural sequellae(9). Cardiopulmonary exercise testing (CPET) might help to determine functional capacity and has a predictive value for outcome in sicker patients(10). The same is true for the use of biomarkers(9). However, all this may be not sufficient enough to identify early signs of a sRV failure. Furthermore, assessment of bi-ventricular morphology and function at rest and during exercise has shown benefits in the work-up of congenital heart disease (CHD) patients. For this, cardiac magnetic resonance (CMR) imaging is a modality of choice, because of high feasibility (e.g. acoustic windows). CMR in CHD patients with RV disease should be performed for quantification of RV volumes and RV ejection fraction (RVEF) amongst other things (11). This study aimed to investigate (I) functional, electrical and echocardiographic changes over time and (II) to evaluate whether additional functional and geometric parameters, including chamber size, volumes and function *at rest and during exercise*, could add value in predicting clinical

outcome (death, occurrence of arrhythmia and HF). Newly identified variables might contribute to optimize follow-up, to customize treatment, and improve outcome.

Methods

Patient selection

Thirty-three detailed phenotyped sRV patients from a previously conducted study were included in this trial (12). Baseline data were collected from July 2015 until April 2017 and these patients were thereafter systemically followed-up by the adult congenital heart disease (ACHD) care program of the University Hospitals Leuven, Belgium. The local Ethics Committee of Clinical Research UZ/KU Leuven approved the baseline study and the follow-up protocol (S57925). At inclusion, all participants signed informed consent.

Initial data collection

For the baseline study, demographic and clinical data (anatomy, age, gender, body surface area (BSA), body mass index and New York Heart Association (NYHA) functional class) were retrieved from the electronic patient records. Likewise, standard echocardiographic parameters and NTproBNP levels were collected in all 33 patients at inclusion.

Data from a *CPET* were collected including peak VO2 (mL/min/kg), % of predicted peak VO2, anaerobic threshold (% of peak VO2), peak power output (Watt), maximal heart rate (HR, bpm), VE/VCO2 slope, blood pressure at rest and peak exercise (mmHg) and oxygen pulse (mL/beat). Oxygen pulse was defined as the ratio of oxygen consumption (VO2, ml/min) to heart rate (HR, bpm).

CMR at rest and during exercise was performed in all patients(13). Heart rate reserve (HHR) was calculated by the difference between maximum HR and the resting HR (bpm). Stroke volume (SV, ml) was calculated as the difference between end-diastolic volume (EDV, ml) and end-systolic volume (ESV, ml). Left ventricular ejection fraction (LVEF, %) and right ventricular ejection fraction (RVEF, %) were calculated as ratio of (SV/EDV)*100 (%). Stroke volume index (SVi, mL/BSA) was measured as EDVi - ESVi and cardiac index (CI, L/min*BSA) as the product of SVi and HR (bpm). Total end diastolic volume index (total EDVi, ml/m2) was defined as the sum of EDVi (mL/m2) from both subpulmonary LV and

sRV, similar for total end systolic volume index (total ESVi, mL/m2). Contractile reserve (CR) was obtained by the difference between myocardial contractility at maximal exercise capacity and rest (EF at peak exercise – EF at rest, %). The date when the CMR was performed, was considered as the start of the follow-up.

Follow-up data and endpoints

For the follow-up, all medical records were reviewed from the hospital's electronic database. Data from follow-up visits and hospitalizations were collected, which consisted of clinical data, age, NYHA functional class, BSA (kg/m2), the electrocardiogram and standard echocardiography. Electrical instability was specified as loss of sinus rhythm, lowering heart rate, wider QRS complex and more prevalent fragmented QRS (fQRS)(14).

All cardiovascular endpoints were analyzed: HF, arrhythmia, and sudden death. HF was defined as (1) the need for hospitalization with initiation of diuretic therapy, (2) initiation of standard HF treatment according to the ESC guidelines or (3) the presence of clear ventricular dysfunction on transthoracic echocardiography with clinical signs and symptoms of HF. Supraventricular tachycardia was defined as a new episode of small QRS tachycardia captured on a 12-lead electrocardiogram and the need for (1) direct current cardioversion or (2) adaptation of medical treatment. Non-sustained ventricular tachycardia was defined as a new episode of ventricular tachycardia captured on 12-lead electrocardiography with a HR of at least 120 bpm lasting for at least three beats and persisting less than 30 seconds. Out of hospital cardiac arrest was defined by failing cardiac mechanical activity and no signs of blood circulation. In the end, heart failure and tachyarrhythmias were considered as combined cardiovascular endpoint.

Statistical analysis

Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and presented as mean ± standard deviation (SD) or as median (minimum – maximum range) as appropriate. For categorical variables, frequencies and percentages were used. To compare frequencies, a Chi-square test

or Fisher's exact test was performed. For paired frequencies, a McNemar test was applied. Differences in the same group were calculated using paired t-test, where differences between groups for continuous variables were analyzed with an unpaired t test, Kruskal–Wallis H test or Wilcoxon–Mann–Whitney test where applicable. Spearman's test was applied to assess the correlation between the indices SVi during exercise and the degree of SAVV regurgitation. For outcome analysis, baseline characteristics at the time of CMR were associated with the first event occurring. All statistical tests were 2-sided, and significance was defined as $P<0.05$. For all the comparative variables with P-value <0.1, univariate cox regression analysis was performed. Multivariate cox regression analysis was not performed because of the low number of events and the small sample size. These analyses were performed using IBM SPSS Statistics, version 26 (Armonk, NY: IBM Corp) for Windows.

A more complex multidimensional method that can handle small sample sizes, called a support vector machine (SVM), was also conducted(15). As input served all variables with a $P<0.05$ resulting from the univariate cox regression. A SVM model searches for the hyperplane in a multidimensional space that best segregates the two classes. When unable to separate linearly, the model transforms the data to a higher dimension space in order to find a linear separation. Several kernels exist to achieve this transformation. They each define a different shape of the decision boundary in the original space. In this study the linear, Gaussian and polynomial kernels were tested. To validate the SVM models the leave-one-out cross validation method was applied. Accuracy was used as performance metric to compare the different models. The SVM analysis was implemented in Python 3.6 and documented in Jupyter Notebook.

Results

Patient characteristics

Thirty-three patients with a male preponderance (76%) and mean age of 40±8 (range 26-57) years at latest follow-up were observed. Mean follow-up time since CMR was 3.0±0.6 (range 1-4) years.

Follow – up data

At latest follow-up, average functional class improved (more patients in NYHA I compared to baseline) and no patients were in NYHA functional class IV. During follow-up, body weight increased. At latest follow-up ECG variables were significant different from baseline with a slower HR, loss of sinus rhythm, longer QRS duration and more prevalent fQRS were found. Echocardiography showed that both tricuspid annular plane systolic excursion (TAPSE, mm) and right ventricular fractional area change (RV FAC, %) were significantly higher when compared to baseline. Likewise, more severe regurgitation of the SAVV was found. CPET – analyses of this group at baseline illustrated an overall well-preserved exercise capacity for sRV patients. These data are summarized in **table 1.**

Outcome

The maximal follow-up time was 4 years. The total number of events for the entire cohort was 9 (27%), of which 6 (18%) were counted as a first cardiovascular event. Specifically, 9% suffered from an episode of HF and in 9% had an episode of tachyarrhythmia. The occurrence of HF and/or arrhythmias were considered as combined clinical endpoint. Three patients had recurrent events. Data are summarized in **table 2.** No patients died during follow-up or needed heart transplantation. Mean age at first event was 40±11(range 25-52) years and mean time between first and second event was 1±0.6 (range 0-2) year.

Patient characteristics in the event and non-event group are summarized in **table 3**. Neither TAPSE nor RV FAC differed between groups. Percentage of predicted peak VO2 and the VE/VCO2 slope was similar

in both groups. However, oxygen pulse was significantly higher in the event-group CMR measures at baseline showed that the mean HR was slower in the event group at rest and during peak exercise. Compared to the event-free patients, LV EDVi and SV LVi at rest were significantly larger. At maximum exercise, for those patients who suffered from a cardiovascular event, RVEF and LVEF or CR did not vary, but significantly higher values for LVEDVi, SV LVi and total ESVi were observed.

On univariate Cox analysis NTproBNP (HR 11.02 (95%CI 1.296-93.662), p= 0.028), oxygen pulse (HR 1.202 (95% CI 1.012-1.428), p=0.037), left ventricle end diastolic volume index (LVEDVi) in rest (HR 1.046 (95% CI 1.002-1.092), p=0.041) and during exercise (HR 1.035 (95% CI 1.002-1.069), p=0.038), stroke volume index (SVi) of the subpulmonary left ventricle (LV) in rest (HR 1.154 (95% CI 1.005-1.322), p=0.038) and at peak exercise (HR 1.065 (95% CI 1.007-1.125), p=0.026) were significantly associated with the first cardiovascular event **(figure 2a and b)**. **Table 4a** shows the average accuracies obtained for the different SVM models with the leave-one-out cross-validation method. For a SVM with a Gaussian kernel the highest accuracy, namely 0.91, was found. In **table 4b** the real versus the predicted points of this best model are listed. In conclusion, this model with complex multidimensional method predicted 4 out of 6 six events with SVM model with a Gaussian kernel and high accuracy of 91%.

Discussion

This short follow-up study with 33 detailed phenotyped sRV patients including exercise CMR, observed that clinical outcome is associated with baseline (I) elevated NTproBNP levels, (II) increased oxygen pulse on CPET and (III) adverse remodeling with increased subpulmonary LV EDVi and SVi on CMR. Following findings didn't align to the evolution of the study cohort: (I) the functional capacity improved during follow-up and (II) there was no decline of the sRV function measured by transthoracic echocardiography. In contrast TAPSE and RV FAC even increased. Only the degree of the severity of the SAVV regurgitation rose. Remarkably, the study results put us in a dilemma. Despite no clinical deterioration nor reducing sRV systolic function, events did occur during follow-up. Our data suggest that standard daily practice parameters are insufficient to predict preclinical deterioration. We wondered whether detailed phenotyping of patients with a sRV circulation might have an added value in predicting outcome. Biomarkers in combination with mechanical factors at rest and during exercise could be of added value. Our data implies the importance of the frequently overlooked subpulmonary LV.

This study indicates that during follow-up the proportion of patients with severe SAVV regurgitation increases, which is in line with previous studies (16). Moreover, quite a number of patients experienced electrical instability over the years. It is however of interest that functional status and the sRV function remained unchanged also found in other studies (1). Similarly, parameters reflecting sRV function were stable or even improved during follow-up, despite the occurrence of events.

Over a follow up time of 3 years, *almost 1 in 5 patients experienced a significant clinical event*, either tachyarrhythmia (9%) (one out of hospital arrest in cc-TGA, one patient with nsVT and one with an atrial flutter, both in d-TGA) or heart failure episode (9%) and these findings are comparable with previous studies (17). The occurrence of HF and/or arrhythmias were considered as combined clinical endpoint. Other events such as atrial baffle problems (leakage and/or obstruction) and/or the development of

pulmonary arterial hypertension (5) that may occur in sRV patients were not found, potentially due to the small sample size of the study. So, despite reasonable and stable functional status and sRV function, based on standard follow-up criteria, a significant proportion (18%) encounters a clinical event, underscoring the need for better risk stratification. It was questioned whether parameters from deeper phenotyping would have an added value.

Our data indicated that *NTproBNP, oxygen pulse, LVEDVi and SV LVi at rest and at peak exercise* were significantly associated with worse clinical outcome. Log NTproBNP reflects neurohormonal activation and has shown in prior studies to be strongly related with outcome in patients with a sRV (9, 18, 19). Oxygen pulse is considered as a surrogate marker of the effective SV in patients with normal arterial oxygen content. This was confirmed on CMR where increased SVi at rest and peak exercise related to worse outcome. Moreover, a higher LVEDVi was associated with worse outcome. It is remarkable that in this small group of relatively stable sRV patients with a short follow-up period, factors related to the subpulmonary ventricle predict outcome rather than sRV dysfunction itself. Indeed, authors have shown that subpulmonary LV dysfunction relates to worse outcome in this group of patients (20). Similarly, a 'normal-looking' subpulmonary LV in sRV patients is often indicative of elevated pulmonary artery pressures. Therefore, it is maybe not unexpected that higher LVEDVi was associated with worse outcome in our group of sRV patients reflecting early subpulmonary LV remodeling prior to overt subpulmonary LV dysfunction. The finding that a higher SVi (which is confirmed by a higher peak oxygen pulse on CPET) relates to worse outcome may be counterintuitive. This either reflects the dilating subpulmonary LV and/or chronotropic incompetence, since CI remains unchanged. In contrast to prior studies, there was no relationship between peak oxygen uptake, SAVV regurgitation, CMR LVEF, RVEF, CR and outcome (21), related to sample size, shorter follow up and or better overall clinical status. Despite small sample size, more complex multidimensional method that can handle small sample sizes predicted 4 out of 6 six events with SVM model with a Gaussian kernel and high accuracy of 91%. To our knowledge, there are

no previous studies associating oxygen pulse, LVEDVi and LV SVi as predictors for outcome in sRV patients.

In summary, we know that sRV dysfunction can progress subclinically during a long period of time and then result in a rapid and unexpected development of congestive HF (8). The findings of this study illustrate that even before the rise of symptoms (NYHA and peak oxygen uptake), adverse remodeling of the subpulmonary LV is correlated with worse outcome. In other words, morphological changes in EDVi and SVi of the subpulmonary LV at rest and during exercise could have a prognostic value. Improvement of functional class is remarkable but better lifestyle behavior can be translated in measurable parameters. In a structurally normal heart, the RV was forgotten until recent studies showed evidence that the RV is a barometer for cardiac outcomes across a range of pathologies (22, 23). Similarly, the focus in the evaluation of the sRV has centered on the sRV physiology and function. Until now, the subpulmonary LV is somewhat ignored. Therefore, we conclude that adverse remodeling of the subpulmonary LV might be the first stage of a failing sRV circulation even before developing symptoms and noticeable sRV dysfunction. That is why daily practice parameters have not always a predictive value in early disease progression and that it is crucial to remind that the remodeling of the subpulmonary LV is associated with ventricular dysfunction, arrhythmias and poor prognosis (24). Nevertheless, biomarkers seem to be most accurate tool to detect preclinical deterioration. According to the guidelines regular measurements of the biomarkers is recommended. However, our research data open the perspective that the increase of the biomarkers do not find their origin in the sRV, but in the subpulmonary LV.

Study limitations

This was a single-institution cohort study. Adults with sRV are only a small proportion of all CHD patients, making large studies and subgroup analyses difficult and is the main limitations of the work. We

did not have systematically assessed NT-proBNP, other biomarkers or CPET during follow-up. Invasive hemodynamics are were not systematically conducted in all patients. Fragmented QRS was not significant higher in the event group although previous research showed that appearance of QRS fragmentation late after Mustard/ Senning repair is associated with adverse outcome(14). Presumably this is secondary to the small sample size. Same for TAPSE and RV FAC that not differed between the two groups. Cox regression analysis of log NTproBNP showed a broad confidence interval. Furthermore, we didn't discuss the diastolic function of the ventricles. Although strain analysis and fractional area change of the subpulmonary LV might be much more sensitive to predict early deterioration of the sRV, we did not include these variables (20) since a recent study showed only limited value of strain analysis (25). Exclusive to this study was that we associated in detail CMR measurements at rest and during exercise with outcome but there was no follow-up CMR conducted.

Conclusions

NTproBNP was the best prognostic marker for clinical outcome. Adverse remodeling of the subpulmonary LV with LV dilatation and increase of LVEDV index and SV index at rest and during exercise are associated with worse clinical outcome. We hypothesize that adverse remodeling of the LVEDV and SV could be the first stage of the failing sRV circulation. Daily practice parameters have poor predictive value.

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Disclosures

All authors have no relationships with industry relevant to the content of this paper to disclose.

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Tables

Table 1. Demographic characteristics sRV patients.

Parameter, n (%)	**Baseline**	**Latest follow-up**	**p-value**
D-TGA (M/S) /cc-TGA, n(%)	23 (7/16) (70) / 10 (30)		
Age ± SD, years ± SD (range)	37±8 (24-53)	40±8 (26-57)	**<0.001**
Male, n(%)	25(76)		
NYHA class, I/II/III, n(%)	21(64)/10(30)/ 2(6)	25(76)/ 6(18) / 2(6)	**0.001**
BMI (kg/m2) ± SD	23.5±3.7	24.3±3.5	**<0.001**
ECG			
HR, SR/J/SVT, n(%)	30(91)/ 2(6)/ 1(3)	28(85)/ 3(9) / 2(6)	**<0.001**
HR, bpm ± SD	79±17	68±19	**0.002**
QRS width, ms ± SD	107±18	112±19	**0.040**
fQRS, n(%)	12(36)	26(79)	**<0.001**
Echocardiography at rest			
TAPSE, mm ± SD	12±3	15±5	**0.001**
SAVV regurgitation, mild/moderate/severe, n(%)	10 (30) / 18(55) / 5(15)	13(39) / 13(39) / 7(22)	**<0.001**
RV FAC, %	21±8	23±8	**<0.001**
CPET			
Peak VO2, mL/kg/min ± SD	28±8		
Peak VO2, % of predicted peak VO2 ± SD	77± 5		
Anaerobic threshold, % of peak VO2 ± SD	51±13		
Peak power output, W ± SD	178±47		

Maximal heart rate, bpm ± SD	161±30		
VE/VCO2 slope ± SD	28.5±4.4		
Pulse oxygen (mL/beat) ± SD	12.5±3.7		
CMR measures			
Heart rate reserve, bpm ± SD	84±24		
Rest			
RVEF, %	40±8		
LV EDV index, mL/m2	69±15		
LV ESV index, mL/m2	28±10		
RV EDV index, mL/m2	127±36		
RV ESV index, mL/m2	77±32		
Stroke volume index, mL/m2	40.7±7		
Cardiac index, L/m2	2.7±0.4		
Exercise			
RVEF, %	43±10		
LV EDV index, mL/m2	62±19		
LV ESV index, mL/m2	22±12		
RV EDV index, mL/m2	127±36		
RV ESV index, mL/m2	119±36		
Stroke volume index, mL/m2	40±10		
Cardiac index, L/m2	5.9±1		
Contractile reserve LV, %	6±5		
Contractile reserve RV, %	3±5		

Medical treatment			
Betablocker, n(%)	7(21)	11(33)	0.219
ACE-I/ARB, n(%)	12(36)	14(42)	0.625
Antiarrhythmic therapy, n(%)	4(12)	4(12)	1.000
Loop diuretic, n(%)	1(3)	3(9)	0.500

ACE-I : angiotensin converting enzyme inhibitor; ARB : angiotensin II receptor blockers; bpm : beats per minute; BMI : body mass index; ccTGA : congenitally corrected transposition of the great arteries; CMR : cardiac magnetic resonance inhibitor; D-TGA : dextro transposition of the great arteries; ECG : electrocardiogram; fQRS : fragmented QRS; HR : heart rate; J : junctional rhythm; kg: kilogram; L : liter; LV : left ventricle; LVEDV : left ventricle end-diastolic volume; LVESV : left ventricle end-systolic volume; M : Mustard repair; m2 : square meter; ml : milliliter; ms : milliseconds; NYHA : New York Heart Association; QRS : QRS complex; RV : right ventricle; RV FAC : right ventricle fractional area change; RVEDV : right ventricle end-diastolic volume; RVEF : right ventricle ejection fraction; RVESV : right ventricle end-systolic volume ; S : Senning repair; SAVV : systemic atrioventricular valve ; SD : standard deviation; SR : sinus rhythm; SVT : supraventricular tachycardia; TAPSE : tricuspid annular plane systolic excursion; VE/VCO2 : ventilation/volume of exhaled carbon oxide; VO2 : oxygen consumption; W : Watt.

Table 2. Overview of cardiovascular events during follow-up.

Event	Event 1, n	Event 2, n	Event 3, n
sRV heart failure	3*	1*	0
Arrhythmia			
SVT	1	0	1*
OHCA polymorphic VT	1**	0	0
nsVT	1	1**	0
Death	0	0	0
Total	6	2	1

*refers to the same patient; ** refers to the same patient

nsVT : non-sustained ventricular tachycardia; OHCA : out of hospital cardiac arrest; sRV : systemic right ventricle; SVT : supraventricular tachycardia; VT : ventricular tachycardia

Table 3. Comparison patients' baseline characteristics cardiovascular first event versus no cardiovascular event.

Baseline parameter	**No event**	**First event**	**p-value**
Age, years ±SD	37±8	39±10	0.608
Male, n(%)	20(74)	5(83)	0.621
TGA- Mustard/Senning, n(%)	19(70)	4(67)	0.859
NYHA class, I/II/III	18(67)/ 7(26)/ 2(7)	3(50)/ 3(50)/ 0(0)	0.633
BMI (kg/m2) ±SD	23.2±3.4	24.4±4	0.145
Log NTproBNP (ng/L) ±SD	2.3±0.4	2.7±0.2	**0.012**
ECG			
HR, S/J/SVT	25(93) / 1(4) / 1(4)	4(67)/ 1(17)/ 1(17)	0.290
HR, bpm ±SD	50±17	64±16	0.068
QRS width, ms ±SD	106±18	115±19	0.381
fQRS, n(%)	11(41)	1(17)	0.244
Echocardiography at rest			
TAPSE, mm ±SD	12±4	12±2	0.697
SAVV regurgitation, mild/moderate/severe, n(%)	10(37)/ 14(52)/3(11)	0 (0)/4(67)/2 (33)	0.080
RV FAC, % ±SD	22±7	17±8	0.133

CPET			
Peak VO2, mL/kg/min ±SD	28±7	27±12	0.926
Peak VO2, % of predicted peak VO2 ±SD	77±16	75±15	0.827
Anaerobic threshold, % of peak VO2 ±SD	50±14	55±11	0.433
Peak power output, W±SD	177±46	183±56	0.759
Maximal heart rate, bpm ±SD	166±22	138±50	0.219
VE/VCO2 slope ±SD	29±4	28±5	0.594
Oxygen pulse (mL/beat) ±SD	12±3	15±5	**0.044**
Δ blood pressure systolic, mmHg ±SD	44±22	42±16	0.861
Δ blood pressure diastolic, mmHg ±SD	8±17	-3±17	0.156
Mean blood pressure rest, mmHg ±SD	87±17	88±12	0.863
Mean blood pressure exercise, mmHg ±SD	107±14	100±18	0.327
Δ mean pressure, mmHg ±SD	21±3	12±11	0.232
CMR measures			
Heart rate reserve ±SD	86±20	75±37	0.509
Rest			
Heart rate, bpm ±SD	70±10	63±14	0.162
RVEF, % ±SD	40±8	39±10	0.859
LVEF, % ±SD	60±7	58±7	0.493
LV EDV index, mL/m2 ±SD	66±14	81±11	**0.022**
LV ESV index, mL/m2 ±SD	27±10	34±7	0.105
RV EDV index, mL/m2 ±SD	122±32	148±50	0.128
RV ESV index, mL/m2 ±SD	74±28	94±4	0.180
Total EDV index, mL/m2±SD	189±41	229±57	0.054
Total ESV index, mL/m2±SD	101±33	128±49	0.112

Stroke volume index LV, mL/m2 ±SD	39±7	47±7	**0.020**
Stroke volume index RV, mL/m2 ±SD	48±9	54±8	0.180
Cardiac index LV, L/m2±SD	2.7±0.4	2.9±0.3	0.346
Cardiac index RV, L/m2±SD	3.4±0.6	3.4±0.5	0.988
Exercise			
Heart rate, bpm	156±24	138±42	0.168
RVEF, %	40±10	41±11	0.568
LVEF, %	61±8	63±12	0.304
LV EDV index, mL/m2	59±17	79±21	**0.015**
LV ESV index, mL/m2	20±12	29±12	0.096
RV EDV index, mL/m2	113±29	145±54	0.202
RV ESV index, mL/m2	65±27	89±45	0.095
Stroke volume index LV, mL/m2	38±7	49±16	**0.011**
Stroke volume index RV, mL/m2	47±10	56±19	0.118
Total EDV index, mL/m2	171±39	224±66	0.110
Total ESV index, mL/m2	85±31	118±47	**0.041**
Cardiac index LV, L/m2	5.8±0.9	6.4±1.5	0.469
Cardiac index RV, L/m2	7.3±1.6	7.4±2.1	0.897
Contractile reserve LV, %	7±6	5±6	0.493
Contractile reserve RV, %	4±5	2±6	0.438
Medical treatment			
Betablocker, n (%)	5 (19)	2 (33)	0.441
ACE-I/ARB, n (%)	10 (4)	2 (17)	0.864
Antiarrhythmic therapy, n (%)	2 (7)	2 (33)	0.115

Loop diuretic, n (%)	0 (0)	1 (17)	0.059

ACE-I : angiotensin converting enzyme inhibitor; ARB : angiotensin II receptor blockers; bpm : beats per minute; BMI : body mass index; ccTGA : congenitally corrected transposition of the great arteries; CMR : cardiac magnetic resonance inhibitor; D-TGA : dextro transposition of the great arteries; ECG : electrocardiogram; fQRS : fragmented QRS; HR : heart rate; J : junctional rhythm; kg: kilogram; L : liter; LV : left ventricle; LVEDV : left ventricle end-diastolic volume; LVESV : left ventricle end-systolic volume; m2 : square meter; mL : milliliter; min : minutes; mm : millimeter ; mmHg : millimeter of mercury; ms : milliseconds; ng : nanogram; NYHA : New York Heart Association; QRS : QRS complex; RV : right ventricle; RV FAC : right ventricle fractional area change; RVEDV : right ventricle end-diastolic volume; RVEF : right ventricle ejection fraction; RVESV : right ventricle end-systolic volume ; SAVV : systemic atrioventricular valve ; SD : standard deviation; SR : sinus rhythm; SVT : supraventricular tachycardia; TAPSE : tricuspid annular plane systolic excursion; VE/VCO2 : ventilation/volume of exhaled carbon oxide; VO2 : oxygen consumption; W : Watt.

Table 4A. Average accuracies for different SVM models with leave-one-out cross validation.

Kernel	Linear	Gaussian	Poly – degree 2	Poly – degree 3	Poly – degree 4	Poly – degree 5
Accuracy	0.67	0.91	0.82	0.88	0.88	0.85

SVM: support vector machine

Table 4B. Real versus predicted data points for SVM model with Gaussian kernel (highest accuracy).

		Predicted	
		Negative	Positive
Real	Negative	26	1

	Positive	2	4

SVM: support vector machine

Figure legends

1) Figure 1. Central Image: concept of adverse remodeling of the subpulmonary RV associated with outcome in sRV.

2) Figure 2a Univariate Cox regression analyses: Hazard ratio in deep phenotyping and outcome sRV of all parameters (log scale). Figure 2b Univariate cox regression analyses including variables from deep phenotyping with CMR and CPET.

3) Table 1. Demographic characteristics sRV patients.

4) Table 2. Overview of cardiovascular events during follow-up.

5) Table 3. Comparison patients' baseline characteristics cardiovascular first event versus no cardiovascular event.

6) Table 4a Average accuracies for different SVM models with leave-one-out cross validation. Table 4b. Real versus predicted data points for SVM model with Gaussian kernel (highest accuracy).

Figure 2a and b