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Adult Congenital Heart Disease

Right Ventricular End-Diastolic Volume Combined With Peak Systolic Blood Pressure During Exercise Identifies Patients at Risk for Complications in Adults With a Systemic Right Ventricle

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Objectives The aim of this study was to identify which patients with a systemic right ventricle are at risk for clinical events.

Background In patients with congenitally or atrially corrected transposition of the great arteries, worsening of the systemic right ventricle is accompanied by clinical events such as clinical heart failure or the occurrence of arrhythmia.

Methods At baseline, all subjects underwent electrocardiography, echocardiography, cardiopulmonary exercise testing, and cardiovascular magnetic resonance imaging. Clinical events comprised death, vascular events, tricuspid regurgitation requiring surgery, worsening heart failure, and (supra)ventricular arrhythmia. A Cox proportional hazards analysis was used to assess the most valuable determinants of clinical events.

Results A total of 88 patients with a mean age of 33 years were included in the study. Sixty-five percent were men, and 28% had congenitally corrected transposition of the great arteries. During a follow-up period of 4.3 years, 31 patients (35%) experienced 46 clinical events for an annual risk of 12%. Right ventricular end-diastolic volume index measured by means of cardiovascular magnetic resonance imaging or multirow detector computed tomography (hazard ratio: 1.20; $p < 0.01$) and peak exercise systolic blood pressure (hazard ratio: 0.86; $p = 0.02$) were the strongest determinants of clinical events. Patients with a right ventricular end-diastolic volume index above 150 ml/m^2 and peak exercise systolic blood pressure below 180 mm Hg were most likely to experience clinical events with an annual event rate of 19% versus 0.9% in patients without these risk factors.

Conclusions Patients with a right ventricular end-diastolic volume index above 150 ml/m^2 and peak exercise systolic blood pressure below 180 mm Hg had a 20-fold higher annual event rate than patients without these risk factors. Regular cardiovascular magnetic resonance imaging and exercise testing are important in the risk assessment of these patients. (J Am Coll Cardiol 2013;62:926–36) © 2013 by the American College of Cardiology Foundation

In patients with an atrial correction of transposition of the great arteries (TGA) or congenitally corrected transposition of the great arteries (ccTGA), the right ventricle supports the systemic circulation. Although the right ventricle is able to adjust to the high pressures of the systemic circulation remarkably well, progressive right ventricular deterioration and concurrent clinical worsening seem inevitable in the long term (1–7).

In adults with TGA and ccTGA, decline is often heralded by the onset of late sequelae, such as supraventricular

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and ventricular arrhythmia, conduction problems, tricuspid regurgitation, and heart failure (8–11). Consequently, these patients are monitored closely. Clinical follow-up typically involves annual visits to the outpatient clinic with occasional electrocardiography (ECG) and echocardiography, exercise testing, 24-h ambulatory ECG, and cardiovascular magnetic resonance imaging (CMR). The American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend annual follow-up (12,13).

However, there is considerable variation in the incidence and onset of late sequelae. Whereas some patients experience these complications early and often, others are able to live relatively normal event-free lives. To date, it remains unclear how to discriminate between high-risk and low-risk patients and which diagnostic modalities are most informative in this aspect. The aim of this study was to evaluate how to identify patients at high risk for clinical events and to assess which diagnostic modalities are best suited for this purpose.

Methods

Study design and groups. Between July 2006 and July 2009, 88 patients underwent multiple examinations in the setting of the valsartan trial (14). This was a double-blind, randomized, placebo-controlled trial of the efficacy of valsartan in patients with a systemic right ventricle due to ccTGA or atrially corrected TGA. Patients who were already using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were instructed to discontinue these at least 4 weeks before baseline examinations. All patients were followed up from inclusion to August 2012, notwithstanding the end of the trial. Approval by the local ethics committee was obtained, and all patients gave informed consent.

Event definitions. The primary endpoint was a composite endpoint of clinical events. This included death; sustained and nonsustained ventricular tachycardia; vascular events, defined as hemorrhagic or embolic cerebrovascular accidents, transient ischemic attack, or myocardial infarction; tricuspid regurgitation requiring invasive treatment; worsening heart failure, defined as an increase in nonstudy treatment requirements, an increase in New York Heart Association (NYHA) functional class, or hospital admission for worsening symptoms of heart failure (15); and supraventricular bradyarrhythmia or tachyarrhythmia requiring electrical cardioversion, ablation, implantation of a pacemaker, or a permanent change of antiarrhythmic medication. Patients had to be free from supraventricular arrhythmia for at least 1 year since inclusion for an episode to be considered a new event. Baffle leakage or stenosis, failing conduits, or valvular stenosis requiring percutaneous or surgical intervention were additional endpoints but did not contribute to the composite endpoint because they were not indicative of decline of the systemic right ventricle (16).

Determinants of events. All participants underwent extensive history taking, physical examination, regular and 24-h ambulatory ECG, cardiopulmonary exercise testing (CPET), echocardiography, and CMR or, in case of contraindications for CMR, multidetector-row computed tomography (MDCT).

Abbreviations and Acronyms

ccTGA = congenitally corrected transposition of the great arteries
CMR = cardiovascular magnetic resonance imaging
CPET = cardiopulmonary exercise testing
ECG = electrocardiography
HR = hazard ratio
MDCT = multidetector-row computed tomography
NYHA = New York Heart Association
RVEDVi = right ventricular end-diastolic volume index
SBP = systolic blood pressure
TGA = transposition of the great arteries

HISTORY AND PHYSICAL EXAMINATION. Extensive history taking, review of available charts, and physical examination was performed for each patient.

ELECTROCARDIOGRAPHY. Rhythm (sinus or other), RR interval, QRS duration, and corrected QT interval were obtained manually from standard (25 mm/s and 1 mV/cm) 12-lead ECGs.

24-H AMBULATORY ECG. A 24-h ambulatory ECG was acquired with a 3-channel Holter monitor during normal out-of-hospital activities. Underlying rhythm (sinus or other) and the number of premature ventricular contractions, premature atrial contractions, couplets, bigeminal cycles, and runs of nonsustained ventricular tachycardia were recorded. Nonsustained ventricular tachycardia was defined as $\geq$3 consecutive ventricular premature beats at >120 beats/min.

CARDIOPULMONARY EXERCISE TESTING. CPET was performed on a bicycle ergometer. Work load was increased by 5 to 15 W until the patient reached maximum exercise capacity. Continuous measurements of minute ventilation, oxygen consumption (VO_2), carbon dioxide production (VCO_2), heart rate, blood pressure, and ECG were performed. Peak was defined as the value at maximum load.

ECHOCARDIOGRAPHY. Parasternal and apical views were obtained according to the recommendations of the American Society of Echocardiography (17). Tricuspid annular plane systolic excursion was measured by M-mode. Right ventricular volumes and function were assessed using Simpson's method in 4-chamber view. Ventricular volumes were indexed using the Mosteller formula to calculate body surface index (18). The degree of tricuspid regurgitation (mild, moderate, severe) was estimated with color Doppler by the width and length of the regurgitant jet and the Doppler flow pattern in the pulmonary veins (2,19).

CMR/MDCT. Detailed acquisition and analysis protocols are described elsewhere (14). Contour tracing was performed by a single observer using the method recommended by Winter et al. (20). Stroke volume was defined as end-diastolic volume minus end-systolic volume, and ejection fraction was defined as stroke volume divided by end-diastolic volume. Ventricular volumes and mass were indexed to body surface area.

Table 1 Baseline Characteristics

Characteristics	All (N = 88)	Event (n = 31)	No Event (n = 57)	p Value
Age (yrs)	33 ± 10	37 ± 12	31 ± 8	0.008
Male	57 (65)	18 (58)	39 (68)	0.331
Body mass index (kg/m^2)	25 ± 5	25 ± 6	24 ± 4	0.373
Body surface area (m^2)	1.92 ± 0.21	1.92 ± 0.21	1.92 ± 0.22	0.993
ccTGA	25 (28)	7 (23)	18 (32)	0.371
TGA	63 (72)	24 (77)	39 (68)	
Mustard	48 (76)	21 (87)	27 (69)	0.098
Senning	15 (24)	3 (13)	12 (31)	
Medication				
Study medication (valsartan)	44 (50)	16 (52)	28 (49)	0.832
Previous angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist use	18 (21)	11 (36)	7 (12)	0.010
Beta-blockers	14 (16)	6 (19)	8 (14)	0.515
Diuretics	6 (7)	5 (16)	0 (0)	0.004
Antiarrhythmic drugs	10 (11)	7 (22)	3 (5)	0.014
NYHA functional class				
I	60 (68)	15 (48)	45 (79)	0.003
II	20 (23)	9 (29)	11 (19)	0.298
III or IV	8 (9)	7 (23)	1 (2)	0.001
Pacemaker	23 (26)	12 (39)	11 (19)	0.048
ICD	1 (1)	0 (0)	1 (2)	1.000
MDCT	25 (28)	13 (42)	12 (21)	0.038
CMR	63 (72)	18 (58)	45 (79)	

Values are mean ± SD or n (%).

ccTGA = congenitally corrected transposition of the great arteries; CMR = cardiovascular magnetic resonance imaging; ICD = implantable cardioverter-defibrillator; MDCT = multirow detector computed tomography; NYHA = New York Heart Association; TGA = transposition of the great arteries.

Statistical analysis. Analyses were performed using SPSS version 20 (IBM, Armonk, New York) and R version 2.14.1 (The R Foundation for Statistical Computing, Vienna, Austria). Data are summarized as number (%) for categorical variables, mean ± SD for continuous variables with normal distribution, and median (interquartile range) for continuous data with skewed distribution. Chi-square test or Student independent *t* test were used to evaluate differences at baseline between patients with and without clinical events and to compare TGA-affected patients with ccTGA-affected patients. Log-rank test was performed to assess differences in the occurrence of clinical events. Missing data were handled by multiple imputations using SPSS. The relation between determinants and clinical events was assessed using univariate and multivariate Cox proportional hazards analysis. To identify determinants of clinical events, exploratory univariate Cox regression was performed for all relevant variables in the original dataset. Because peak heart rate and systolic blood pressure (SBP) were possibly influenced by β-blockers or antiarrhythmic drugs, the hazard ratio (HR) was adjusted for the use of these agents. We did not aim to evaluate the efficacy of pharmacological regimens, so the use of medication was not entered in univariate or multivariate analysis. When medication possibly influenced the evaluated determinants, we did adjust for its use.

One parameter per diagnostic modality was entered in the multivariate analysis. For each diagnostic modality, the parameter with the lowest Akaike information criterion in univariate analysis was selected. Post-hoc exploratory multivariate analysis was performed to test whether the selected parameters were indeed independent determinants and to evaluate collinearity with other parameters from the same modality.

The selected determinants were then entered in a stepwise multivariate model using 5 imputed datasets. Parameters were entered by decreasing availability and convenience in a clinical setting. ECG and patient history were entered first. Subsequently, determinants obtained by diagnostic modalities requiring increasing expertise (laboratory results, CPET, 24-h ambulatory ECG, echocardiography, and finally CMR or MDCT) were added in turn to assess the additional value of these modalities. Each subsequent model was built with the significant independent predictors from the previous model and the selected parameter from the diagnostic modality that was next in the hierarchy of expertise. Receiver operating curves for censored data (R package survival ROC) were used to visualize the value of the multivariate model at each step. For continuous determinants, relevant cutoffs were obtained using individual receiver-operating characteristic curves. Using the original dataset, Kaplan-Meier curves were plotted for determinants that independently identified patients at risk for clinical events. To evaluate if the most valuable determinants were applicable in both TGA and ccTGA, univariate analysis for each group and interaction

Table 2 Distribution of Events

Events	All	Included in Composite*
Death		
Cardiac	3	1
Noncardiac	1	0
Ventricular tachycardia		
Sustained	0	0
Nonsustained	4	2
Vascular events		
Transient ischemic attack	1	1
Myocardial infarction	1	0
Tricuspid regurgitation		
Repair	1	0
Replacement	1	0
Worsening heart failure		
De novo	11	9
Recurrent	4	3
Supraventricular arrhythmia		
De novo	12	10
Recurrent	7	5
Total	46	31

*In case of multiple events, the first event was included in the composite endpoint.

analysis were performed. For all analyses, a 2-tailed p value of <0.05 was used as the criterion for statistical significance.

Results

A total of 88 patients with a systemic right ventricle were included. The mean age of the patients was 33 ± 10 years, 57 (65%) were male, and 25 (28%) had ccTGA. Twenty-five participants (28%) underwent MDCT because of contraindications for CMR (24 with a pacemaker and 1 with a metal intraocular foreign body). During a cumulative follow-up of 379 years (median of 4.3 years) 31 patients (35%) experienced 46 clinical events for an annual risk of 12%. Patients who experienced events were older, were in a worse NYHA functional class, were more likely to use diuretics and antiarrhythmic drugs, more often had a pacemaker, and more often used renin-angiotensin-aldosterone system inhibitors at baseline screening. There was no difference in the allocation of study medication between patients with and without events (Table 1). One patient with TGA had an implantable cardioverter-defibrillator.

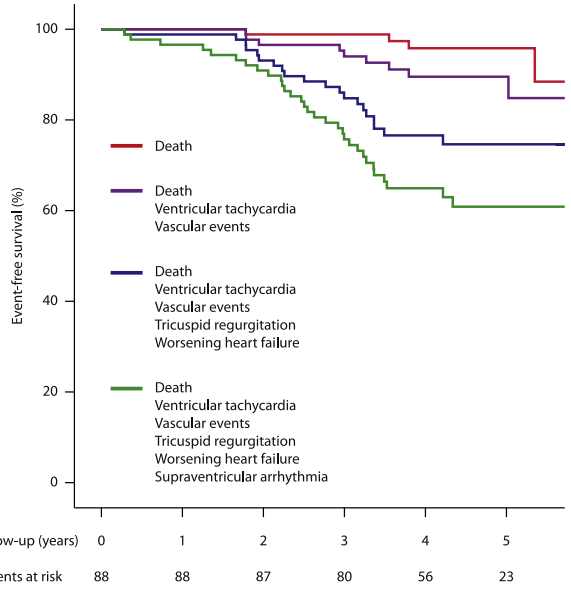

Figure 1 Event-Free Survival

The composite endpoint is represented by the green curve.

Events. Four patients died (3 of end-stage right ventricle failure and 1 of end-stage pulmonary disease). An overview of all clinical events and which comprised the composite endpoint is presented in Table 2. Cumulative event-free survival at 4-year follow-up was 63% (Fig. 1).

Baffle problems occurred in 2 patients during follow-up, for which 1 patient underwent cardiac surgery to relieve symptomatic baffle leakage and 1 patient underwent intrabaffle stenting for symptomatic baffle stenosis. In both patients, turbulent flow was already visible on baseline echocardiography. One patient with ccTGA and pulmonary atresia underwent dilation of a pulmonary homograft stenosis.

Determinants of clinical events. Table 3 lists the results of the univariate analysis. History, ECG, laboratory testing, CPET, 24-h ECG, echocardiography, and CMR/MDCT all yielded prognostic information. The most valuable independent determinants of clinical events for each diagnostic modality were symptoms (NYHA functional class ≥II) (HR: 2.45; $p = 0.01$), the absence of sinus rhythm (HR: 2.16; $p = 0.04$), N-terminal pro-hormone of brain natriuretic peptide (HR: 1.5; $p = 0.06$), peak SBP (HR: 0.78; $p < 0.01$), number of premature ventricular complexes in 24 h (HR: 1.28; $p < 0.01$), right ventricular end-diastolic volume index (RVEDVi) measured by echocardiography (HR: 1.41; $p < 0.01$), and CMR/MDCT (HR: 1.21; $p < 0.01$).

Sex, type of transposition (ccTGA vs. surgically corrected TGA), a history of supraventricular tachycardia, nonsustained ventricular tachycardia on 24-h ECG, tricuspid regurgitation, tricuspid annular plane systolic excursion, and right ventricular ejection fraction measured by echocardiography were not significantly associated with clinical events.

Using only readily available history and ECG, the strongest determinants of clinical events were symptoms (NYHA functional class ≥II) (HR: 2.42; $p = 0.02$) and the absence of sinus rhythm on baseline ECG (HR: 2.16; $p = 0.04$). On receiver-operating characteristic analysis, the area under the curve was 0.66 (Fig. 2). Adding laboratory results (N-terminal pro-hormone of brain natriuretic peptide) did not provide additional prognostic information. Peak exercise SBP was the strongest determinant derived from CPET (HR: 0.82; $p < 0.01$) and improved the model considerably (area under the curve of 0.77). Twenty-four–hour ambulatory ECG did not provide additional information. RVEDVi measured by echocardiography (HR: 1.16; $p = 0.05$)

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Table 3 Univariate Cox Proportional Hazards Analysis

Variables	Total (N = 88)	Event (n = 31)	No Event (n = 57)	Univariate Analysis	
				HR	p Value*
History					
Age (yrs)	33 ± 10	37 ± 12	31 ± 8	1.33†	0.064
Male	57 (65)	18 (58)	30 (68)	0.72	0.375
TGA (vs. ccTGA)	63 (72)	24 (77)	39 (68)	1.75	0.194
Complex (vs. isolated)	30 (34)	9 (29)	21 (37)	0.69	0.347
Symptomatic (NYHA functional class ≥II)	28 (32)	16 (52)	12 (21)	2.45	0.014
Episode(s) of atrial fibrillation	26 (30)	13 (42)	13 (23)	1.66	0.165
Episode(s) of heart failure	7 (8)	5 (16)	2 (4)	2.73	0.042
Complete heart block	7 (8)	4 (13)	3 (5)	2.98	0.095
Sinus dysfunction	21 (24)	8 (26)	13 (23)	0.60	0.505
ECG					
Absence of sinus rhythm	21 (24)	12 (39)	9 (16)	2.16	0.043
QTc (ms)	432 ± 39	445 ± 43	425 ± 36	1.07†	0.068
QRS width (ms)	119 ± 30	128 ± 32	114 ± 28	1.18†	0.083
Laboratory tests					
Hemoglobin (mmol/l)	9.3 ± 0.9	9.1 ± 0.8	9.5 ± 0.9	0.13	0.724
Glomerular filtration rate (ml/min)	124 ± 30	118 ± 26	126 ± 32	0.99	0.382
Aspartate aminotransferase (U/l)	26 ± 9	25 ± 10	27 ± 9	0.98	0.434
Alanaine aminotransferase (U/l)	29 ± 14	26 ± 11	30 ± 15	0.97	0.150
γ-Glutamyltransferase (U/l)	37 (25–78)	31 (24–84)	38 (28–62)	1.00	0.242
NT-proBNP (ng/l)	210 (126–478)	328 (210–791)	159 (101–342)	1.50‡	0.056
Cardiopulmonary exercise testing					
Peak load (W)	169 ± 58	136 ± 54	186 ± 54	0.86†	0.001
Peak heart rate (beats/min)	159 ± 27	148 ± 30	164 ± 23	0.89†§	0.085
Peak systolic blood pressure (mm Hg)	177 ± 28	164 ± 18	184 ± 30	0.78†§	0.002
Peak $V'O_2$ (ml/min/kg)	27 ± 7	24 ± 8	29 ± 7	0.53†	0.016
Holter monitoring					
Absence of sinus rhythm	16 (19)	10 (35)	6 (11)	2.00	0.109
Presence of nonsustained ventricular tachycardia	14 (17)	7 (27)	7 (13)	1.60	0.312
Presence of PVC couplets	27 (34)	8 (32)	19 (35)	0.53	0.171
Presence of bigeminal cycles	24 (29)	13 (48)	11 (20)	2.30	0.036
Number of PVC/24 h	90 (9–378)	248 (71–1,160)	28 (7–218)	1.28‡	0.008
Presence of PAC runs	26 (32)	5 (19)	21 (39)	0.45	0.105
Presence of PAC couplets	30 (37)	8 (31)	22 (40)	0.67	0.347
Echocardiography					
Tricuspid annular plane systolic excursion (cm)	1.4 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	0.57	0.300
Tricuspid regurgitation	37 (45)	15 (50)	22 (42)	2.18	0.164
Left ventricular outflow tract obstruction	20 (23)	6 (19)	14 (25)	1.08	0.890
RVEDVi (ml/m^2)	58 ± 21	70 ± 26	53 ± 17	1.41†	0.001
RVESVi (ml/m^2)	37 ± 16	46 ± 21	32 ± 11	1.50†	0.001
RVEF (%)	36 ± 10	34 ± 9	37 ± 10	0.96	0.196
CMR/MDCT					
RVEF (%)	36 ± 7	33 ± 9	38 ± 7	0.95	0.022
RVEDVi (ml/m^2)	133 ± 35	155 ± 40	120 ± 25	1.21†	0.000
RVESVi (ml/m^2)	86 ± 31	105 ± 37	75 ± 20	1.20†	0.000
Right ventricular mass index (g/m^2)	40 ± 11	46 ± 12	37 ± 9	1.66†	0.001
Left ventricular ejection fraction (%)	53 ± 10	49 ± 11	55 ± 9	0.97	0.041
Left ventricular end-diastolic volume index (ml/m^2)	84 ± 23	95 ± 27	77 ± 17	1.16†	0.005
Left ventricular end-systolic volume index (ml/m^2)	40 ± 18	49 ± 23	34 ± 12	1.19†	0.009
Left ventricular mass index (g/m^2)	35 ± 11	38 ± 12	33 ± 9	1.18†	0.237

Values are mean ± SD, n (%), and median (interquartile range). *p value for HR. †HR per 10 U. ‡HR of log-transformed variable. §Adjusted for use of β-blocker and antiarrhythmic medication.

ECG = electrocardiography; HR = hazard ratio; NT-proBNP = N-terminal pro-hormone of brain natriuretic peptide; PAC = premature atrial complex; PVC = premature ventricular complex; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVi = right ventricular end-systolic volume index; other abbreviations as in Table 1.

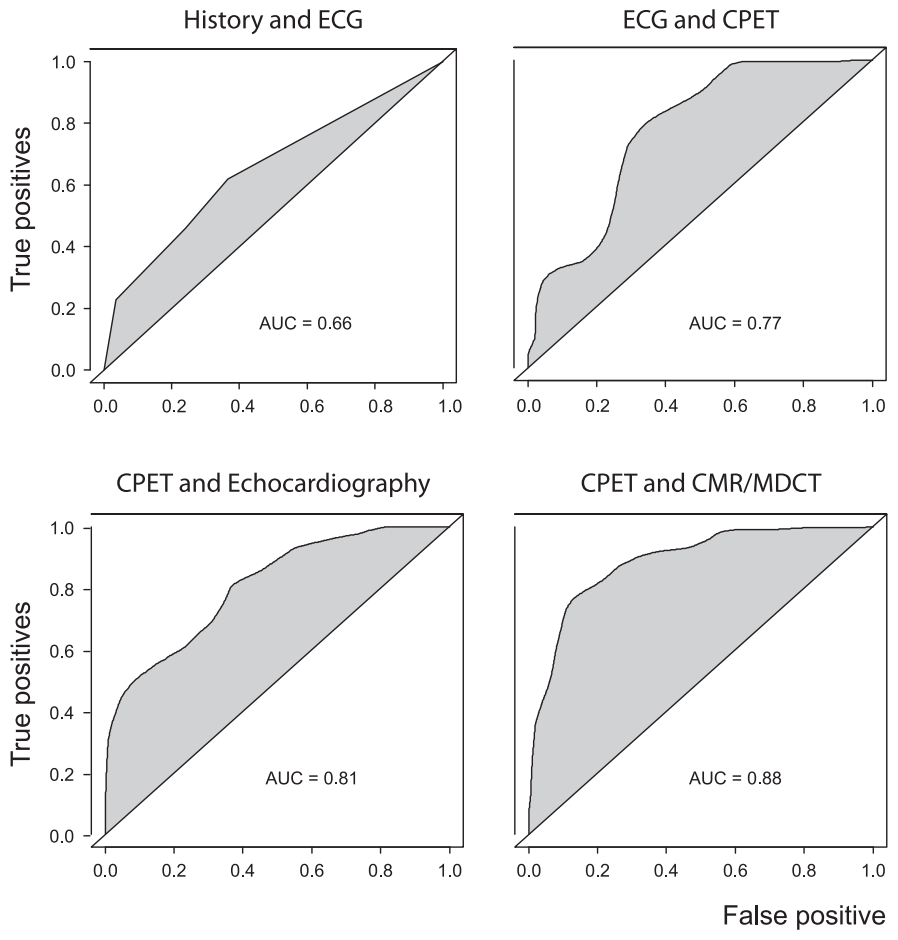

Figure 2 **Receiver-Operating Characteristic Curves at 4 Years**

Time-dependent receiver-operating characteristic curves at 4 years for the best predictors of each diagnostic modality (Table 3). The combination of CMR and CPET is most valuable for predicting events. CMR = cardiovascular magnetic resonance imaging; CPET = cardiopulmonary exercise testing; ECG = electrocardiography; MDCT = multirow detector computed tomography.

improved the model (area under the curve of 0.81). However, measuring RVEDVi with CMR or MDCT (HR: 1.20; $p < 0.01$) was superior (area under the curve of 0.88). The final model included peak exercise SBP, RVEDVi measured by magnetic resonance imaging, and RVEDVi measured by echocardiography (Table 4). The latter was no longer a significant independent predictor.

Kaplan-Meier curves of all determinants that were entered in the multivariate analysis are presented in Figure 3. For peak exercise SBP, RVEDVi measured by echocardiography, and RVEDVi measured by CMR or MDCT, cutoff values of 180 mm Hg, 50 ml/m^2, and 150 ml/m^2, respectively, were chosen by individual receiver-operating characteristic analysis.

Patients (n = 26) with RVEDVi <150 ml/m^2 and peak exercise SBP >180 mm Hg had an annual event rate of 0.9%. The probability of event-free survival was significantly better compared with patients who had RVEDVi >150 ml/m^2, peak exercise SBP <180 mm Hg, or both (Fig. 4). Using the combination of these 2 determinants, a sensitivity of 96% and negative predictive value of 96% was obtained. Conversely, the annual event rate of patients with RVEDVi >150 ml/m^2 and peak exercise SBP <180 mm Hg was 19%. This corresponded to a specificity of 94% and a positive predictive value of 81% (Fig. 5).

TGA versus ccTGA. Table 5 compares patients with TGA and patients with ccTGA regarding some of the baseline characteristics, determinants, and events. Patients with ccTGA were older and experienced fewer episodes of supraventricular arrhythmia. Sinus node dysfunction was more prevalent in the TGA group, whereas complete heart block occurred more in patients with ccTGA.

Both determinants in the final model were equally applicably to patients with TGA and patients with ccTGA. HRs for RVEDVI were 1.3 ($p = 0.009$) in the ccTGA group and 1.2 ($p = 0.001$) in the TGA group and for peak SBP were 0.72 ($p = 0.028$) and 0.80 ($p = 0.031$), respectively. Moreover, there was no significant interaction effect for ccTGA versus TGA (p interaction RVEDVI = 0.902, peak SBP = 0.542).

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Table 4 Multivariate Cox Proportional Hazards Analysis

Variables	HR	p Value	HR	p Value	HR	p Value	HR	p Value	HR	p Value	HR	p Value
History												
Symptomatic NYHA ≥II	2.42	0.02	2.42	0.02		—		—		—		—
ECG												
Absence of sinus rhythm	2.17	0.04	2.17	0.04	2.42	0.02	2.42	0.02		†		—
Laboratory												
NTproBNP (ng/l)*			†			—		—		—		—
Cardiopulmonary exercise testing												
Peak SBP (per 10 mm Hg)					0.82	<0.01	0.82	<0.01	0.81	<0.01	0.86	0.02
Holter								†		—		—
Number of PVC/24 h*												
Echocardiography												
RVEDVi (per 10 ml/m^2)									1.16	0.05		†
CMR/MDCT												
RVEDVi (per 10 ml/m^2)											1.20	<0.01

*Log transformed; †Entered in the model but no longer an independent determinant.
NTproBNP = N-terminal pro-hormone of brain-natriuretic peptide; PVC = premature ventricular complex; RVEDVi = right ventricular end-diastolic volume index; SBP = systolic blood pressure.

Discussion

This study demonstrates a high annual risk of clinical events in patients with a systemic right ventricle. Exercise testing and CMR or MDCT were most useful to identify patients at risk for clinical events. Patients with a peak exercise SBP below 180 mm Hg and an RVEDVi above 150 ml/m^2 had a 20-fold higher annual event rate than patients without these risk factors.

Interpretation. In patients with a systemic right ventricle, further right ventricular deterioration is often accompanied by late sequelae such as arrhythmia or symptomatic heart failure. This study found RVEDVi and peak SBP to be strong determinants of these late clinical events.

Although TGA and ccTGA differ in geometry and fiber orientation, they share many characteristics and both face high systemic pressures, which will eventually lead to decline of the cardiac pump and accompanying events. The TGA and ccTGA groups differed by age and the prevalence of different arrhythmias. However, the most valuable determinants of clinical events were remarkably similar in both groups. This study did not include single systemic right ventricles. Consequently, it remains unclear if similar parameters determine prognosis in these patients.

Ejection fraction does not adequately reflect the condition of the systemic right ventricle, because tricuspid regurgitation, which is common in these patients and an additional burden on the right ventricle, paradoxically increases ejection fraction. The systemic right ventricle compensates for the systemic afterload with right ventricular enlargement and hypertrophy (21). Ventricular enlargement may lead to tricuspid regurgitation, which leads to volume overload and even more dilation (22). Consequently, right ventricular end-diastolic volume might better reflect the status of the systemic right ventricle. This is supported by studies in the setting of pulmonary arterial hypertension, also a pressure-overloaded right ventricle. In these patients, right ventricular end-diastolic volume has been shown to predict outcome better than ejection fraction as well (23).

The right ventricular end-systolic volume index (RVEDVi) was almost as strong a determinant as right ventricular end-diastolic volume. Right ventricular end-diastolic volume not only reflects the dilation of the right ventricle but also the volume that the ventricle can no longer eject. Therefore, it reflects right ventricular function as well. Theoretically, this parameter could be superior to RVEDVi and is equally unbiased by tricuspid regurgitation. However, measuring the right ventricular end-systolic volume is complicated, because it is difficult to discern impacted trabeculae from myocardium. Consequently, the larger measurement error might be responsible for this parameter not making the final model.

Furthermore, there were large discrepancies between ventricular volumes measured by echocardiography and CMR/MDCT. Consequently, different criteria should be applied when identifying patients at risk for late sequelae. Whereas an RVEDVi above 50 ml/m^2 measured by echocardiography

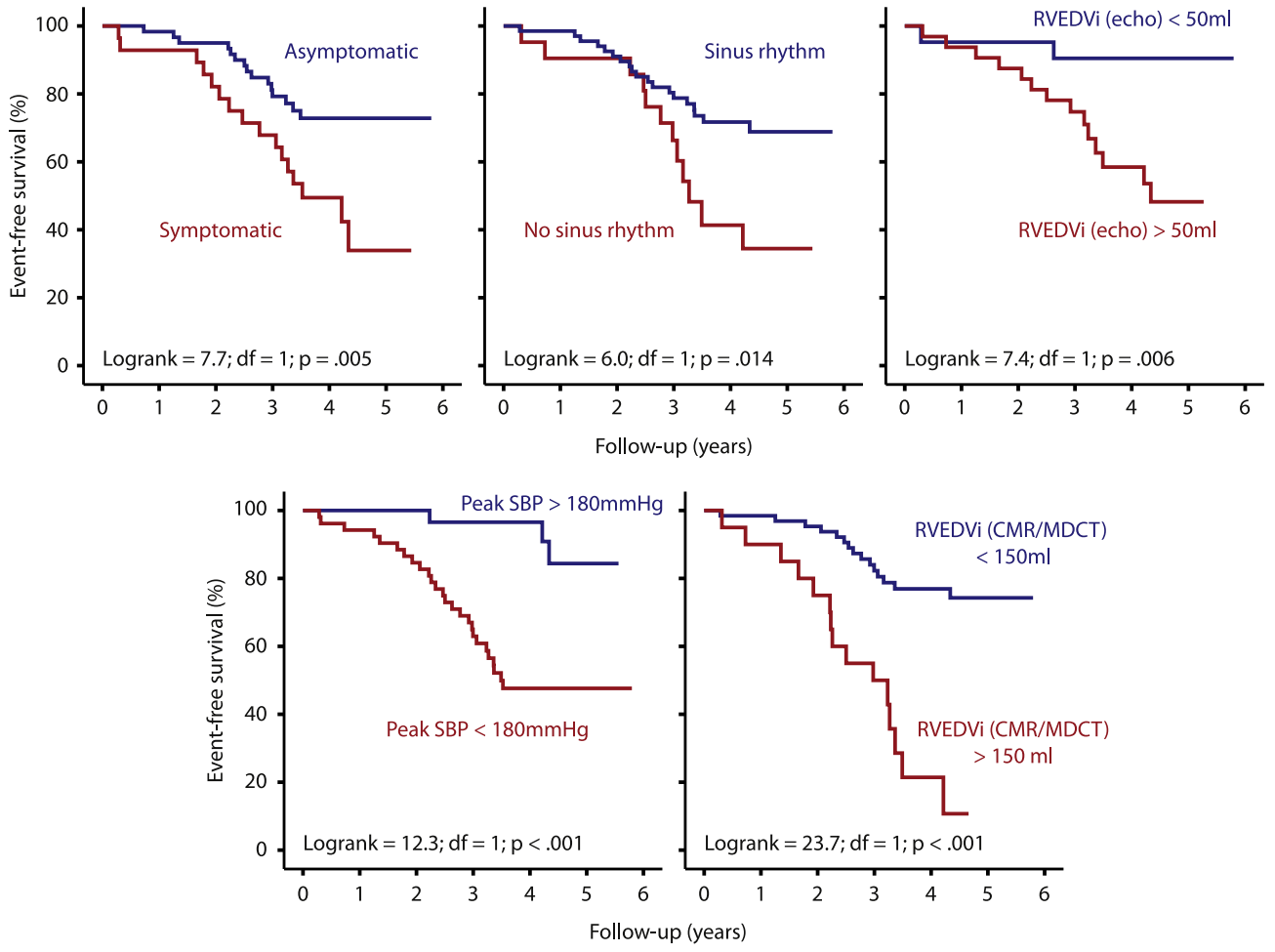

Figure 3 **Kaplan-Meier Analyses**

Kaplan-Meier curves for symptoms, sinus rhythm, RVEDVi (echo), peak exercise SBP, and right ventricular end-diastolic volume index measured by CMR or MDCT). RVEDVi = right ventricular end-diastolic volume index; RVEDVi (echo) = right ventricular end-diastolic volume index measured by echocardiography; SBP = systolic blood pressure; other abbreviations as in Figure 2.

was indicative of an increased risk, the threshold of RVEDVi measured by CMR or MDCT was 150 ml/m^2.

The finding that lower peak SBP provides prognostic information in patients with and without heart failure, either alone or adding to existing predictors, is not a new concept (24–27). Peak SBP has been repeatedly found to be an independent predictor of cardiac events and/or death in patients with heart failure (24,28–31) or post–myocardial infarction (25,26). Moreover, it occasionally outperforms conventional predictors, such as peak VO_2 (24,28,29).

Cardiac response to stress has been shown to be abnormal in patients with a systemic right ventricle (32–36) and prognostic of mortality and clinical events (37,38). Furthermore, during a 4-year follow-up study in patients with systemic right ventricles (atrially corrected TGA), peak SBP was clearly diminished in patients who experienced cardiac-related emergencies compared with patients without events (38). Although it was not the focus of the study, baseline differences in peak SBP were statistically of the same order as peak VO_2 and VE/VO_2 slope, the most valuable predictors according to the multivariate model of the study.

Peak SBP and peak VO_2 both reflect the performance of the cardiac pump, which generates both flow (cardiac output) and pressure. Whereas, according to Fick's principle, peak VO_2 can be seen as a measure of flow, peak SBP is a measure of the pressure-generating capacity (29,39,40). Because the right ventricle is essentially "built" for a high-volume but low-pressure environment, failing to generate adequate pressure (low peak SBP) may be the first sign of imbalance of the compensatory mechanisms of the systemic right ventricle. Accordingly, peak SBP might outperform peak VO_2 as a determinant of events in these patients.

As can be expected, cutoff values for peak SBP differ between groups and endpoints. They ranged from 120 mm Hg

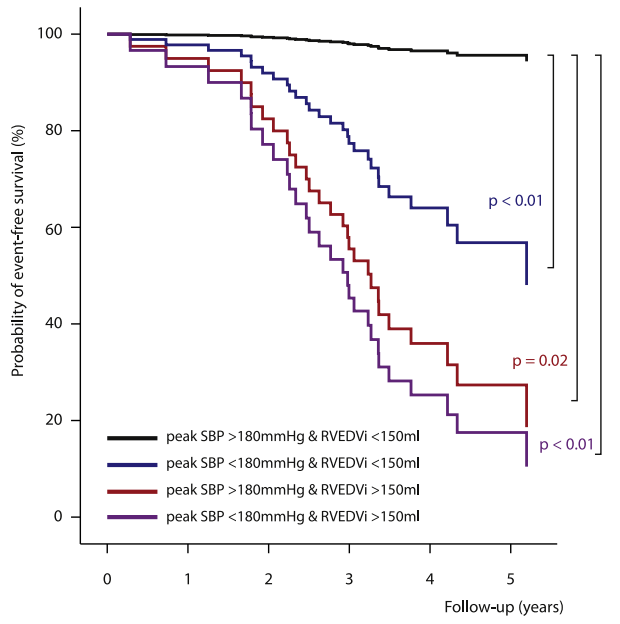

Figure 4 **Prediction Model**

Cox proportional hazards model including RVEDVi and peak exercise SBP. Abbreviations as in Figure 3.

in patients awaiting cardiac transplant to 160 mm Hg in patients with more general heart failure (24,30). In this view, the cutoff value of 180 mm Hg in our cohort was rather high. However, patients with a systemic right ventricle are generally much younger than patients with acquired heart failure and many remain asymptomatic, which may explain why they perform generally well on exercise testing.

There was no difference in valsartan treatment allocation between patients with and without events. Even though valsartan has been shown to reduce mortality and morbidity in patients with acquired heart disease (41), our study was not powered to detect a treatment effect on clinical endpoints (42).

Clinical implications. Patients with a dilated right ventricle and patients with an inadequate blood pressure response to exercise are at increased risk for clinical events. Preventing a decline in exercise capacity and progression of right ventricular dilation might also prevent future events. In patients with a systemic right ventricle, exercise training has been shown to increase VO_{2peak} (43). Moreover, Belardinelli et al. (44,45) showed that, in addition to improved VO_{2peak}, exercise training also reduced clinical events in patients with acquired left ventricular heart failure. Furthermore, in a recent trial by our group, inhibition of the renin-angiotensin-aldosterone system attenuated systemic right ventricular dilation, although the effect was small (42). Finally, patients without these risk factors have a very low risk of complications and might be considered for biannual instead of annual follow-up.

Study limitations. A control cohort to test the consistency of the associations found in this study was not available, which could raise concerns about generalizability. In addition, our primary endpoint was heterogeneous, although composite endpoints combining arrhythmia, heart failure, and other cardiac complications have previously been used in this population (38). However, most late sequelae in these patients stem from underlying right ventricular deterioration. In this light, baffle leakage and stenosis were not considered an event, because these were unlikely to be caused by deterioration of the right ventricle.

Furthermore, the temporal resolution of MDCT is lower than that of CMR. As a result, MDCT tends to

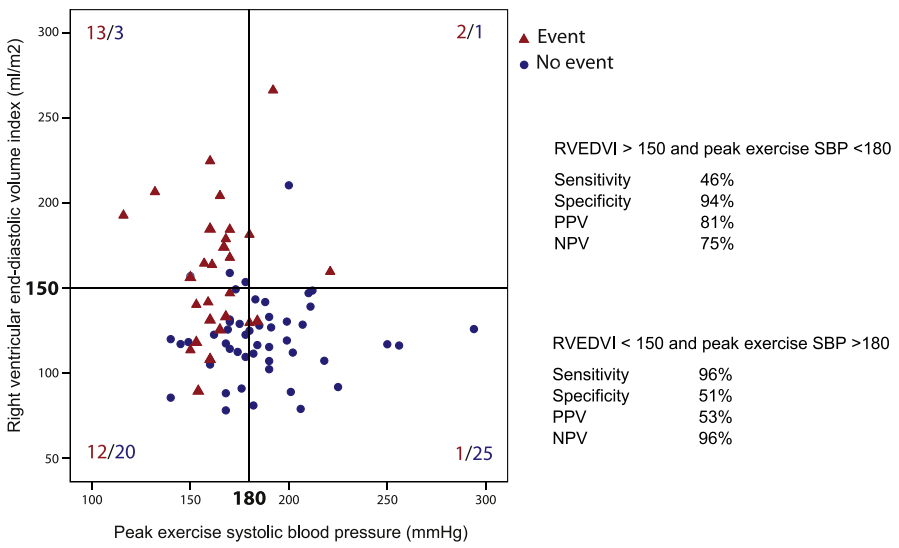

Figure 5 **Scatterplot**

Patients with and without events by RVEDVi and peak exercise SBP. NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Figure 3.

Table 5 Patients With TGA Versus Patients With ccTGA

Characteristics	TGA (n = 63)	ccTGA (n = 25)	p Value
Age (yrs)	30 ± 6	40 ± 13	0.001
Ventricular septal defect	9 (13)	7 (28)	0.133
Atrial septal defect	1 (2)	1 (4)	0.490
Pulmonary stenosis	11 (18)	9 (36)	0.061
Aortic coarctation	2 (3)	0 (0)	1.000
History of supraventricular tachycardia	19 (30)	7 (28)	0.841
Sinus dysfunction	20 (32)	1 (4)	0.006
Complete heart block	2 (3)	5 (21)	0.009
Pacemaker	17 (27)	6 (24)	0.774
ICD	1 (2)	0 (0)	1.000
Predictors			
Symptomatic (NYHA functional class ≥II)	20 (32)	8 (32)	0.982
Absence of sinus rhythm	12 (19)	9 (36)	0.092
NT-proBNP (ng/l)*	209 (131–356)	273 (80–784)	0.182
Peak systolic blood pressure (mm Hg)	177 ± 27	176 ± 30	0.962
Number of PVC/24 h*	52 (7–261)	206 (28–1,239)	0.118
RVEDVi echocardiography (ml/m^2)	61 ± 21	51 ± 21	0.146
RVEDVi CMR/MDCT (ml/m^2)	133 ± 35	134 ± 37	0.865
Events			
Death	2 (3)	2 (8)	0.327
Ventricular tachycardia	2 (3)	2 (8)	0.327
Vascular event	1 (2)	1 (4)	0.490
Tricuspid regurgitation	2 (3)	0 (0)	0.510
Worsening heart failure	10 (16)	5 (20)	0.642
Supraventricular arrhythmia	17 (27)	2 (8)	0.051
Composite	24 (38)	7 (28)	0.371

Values are mean ± SD, n (%), and median (interquartile range). *p value for log-transformed variable.
Abbreviations as in Tables 1 and 3.

underestimate end-diastolic volume (and overestimate end-systolic volume). Because patients who underwent MDCT had more events, this might lead to an underestimation of the predictive value of RVEDVi. Finally, because data on coronary artery anatomy were only sporadically available, we were unable to evaluate the predictive value of this parameter.

Conclusions

Patients with a systemic right ventricle have a high annual risk of clinical events. The combination of exercise testing and CMR was most valuable when determining the risk of clinical events. Patients with a peak exercise SBP below 180 mm Hg during exercise and an RVEDVi above 150 ml/m^2 had a 20-fold higher annual event rate than patients without these risk factors. In addition to echocardiography and ECG, regular CMR and exercise testing are important for risk assessment in these patients.

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Key Words: clinical events ■ prognosis ■ systemic right ventricle.