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Chapter 5

Ventricular Response to Stress Predicts Outcome in Adult Patients with a Systemic Right Ventricle

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ABSTRACT

Background

Previous studies demonstrated that ventricular response to stress Cardiovascular Magnetic Resonance (CMR) is frequently abnormal in patients with a systemic right ventricle (RV). However, the clinical implications of these findings remained unknown. We sought to evaluate whether abnormal response to stress CMR predicts adverse outcome in patients with a systemic RV.

Methods

Thirty-nine adult patients (54% male; mean age 26, range 18–65 years) with a systemic RV underwent stress CMR to determine the response of RV volumes and ejection fraction (EF). During follow-up, cardiac events, defined as hospitalization for heart failure, cardiac surgery, aborted cardiac arrest, or death, were recorded. The prognostic value of an abnormal response to stress, defined as lack of a decrease in RV end systolic volume (ESV) or lack of an increase in RV EF, was assessed.

Results

We frequently observed an abnormal response to stress, as RV ESV did not decrease in 17 patients (44%), and RV EF did not increase in 15 patients (38%). After a mean follow-up period of 8.1 years, 8 (21%) patients had reached the composite endpoint. The inability to decrease RV ESV during stress was predictive for cardiac events with a hazard ratio of 2.3 (95%CI 1.19-88.72; p=0.034), as was the inability to increase RV EF with a hazard ratio of 2.3 (95%CI 1.31-81.59; p=0.027).

Conclusions

Stress CMR potentially has important prognostic value in patients with a systemic RV. Patients with a systemic RV who show abnormal cardiac response to stress have a substantially higher risk of adverse outcome.

INTRODUCTION

The number of adult patients with congenital heart disease has grown rapidly over the past few decades.[1] A substantial portion of patients have a morphological right ventricle (RV) that sustains the systemic circulation, i.e. patients with a transposition of the great arteries (TGA) after a Mustard or Senning operation, and patients with a congenitally corrected transposition of the great arteries (ccTGA). Although mid-term survival is acceptable in these patients, complications are common, and frequently relate to dysfunction of the systemic RV.[2] Therefore, careful follow-up of RV function is the cornerstone in the clinical care for patients with either TGA or ccTGA.

Cardiovascular magnetic resonance imaging (CMR) is a widely applied imaging modality that provides a reliable diagnostic tool for the detection of depressed RV function. As such, CMR is frequently used to guide medical therapy and to select patients for surgical interventions.[3;4] The use of stress CMR, either with supine bicycle ergometry or dobutamine infusion, could facilitate early detection of systemic RV dysfunction. Previous studies in which the value of stress CMR was evaluated, demonstrated that ventricular response to stress was frequently abnormal in patients with a systemic RV.[5–8] It was observed that these patients often lack the ability to increase contractility during stress, even when they are asymptomatic.[8;9] These findings suggest that stress CMR provides the possibility to detect subclinical RV dysfunction at an early stage, and could help identify those patients that require medical or surgical intervention. However, the main limitation of these studies was that the relation between the abnormal response to stress CMR and clinical outcome remained unclear, which questioned the clinical applicability of stress CMR.[10] Therefore, the current study aimed to evaluate the relation between cardiac response to stress CMR and cardiac events in patients with a systemic RV.

METHODS

Patient population and study protocol

The study was a two-center investigation, and was set-up to evaluate the ventricular response to stress in patients with TGA or ccTGA and a systemic RV. Patients with a systemic RV (n=39; 54% male; age 26 ± 8 years) were included in 1999 and 2000. Patients were excluded from participation if they were younger than 18 years, had (previous) cardiac arrhythmias, had an intra-cardiac device, or had concomitant cardiac lesions. All patients underwent either dobutamine stress CMR (n=18) in the Academic Medical Centre, Amsterdam, or supine bicycle ergometry CMR (n=21) in the Leiden University Medical Centre.[9;10] After baseline stress CMR evaluation, patients were regularly followed-up at the out-patient clinic for adult congenital heart disease. During follow-up, the occurrence of all cardiac events were recorded. Cardiac events were defined as: hospitalization for heart failure, cardiac surgery, aborted out-of-hospital cardiac arrest or cardiac death. We performed a Cox's regression analysis in which the relation between the cardiac response to stress CMR and the occurrence of cardiac events during follow-up was assessed.

The ethics committees of the participating tertiary referral centers approved the study protocol, and the study protocol complies with the Declaration of Helsinki. All participating patients provided written informed consent. The current study was funded by an unrestricted educational grant from Novartis Pharma, the Netherlands. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Stress CMR acquisition

The supine bicycle ergometry CMR acquisition protocol has previously been published by Roest et al.[11] In short, image acquisition was performed using a Philips Gyroscan ACS/NT 1.5 Tesla MR scanner (Philips Medical Systems, Best, the Netherlands) in the Leiden University Medical Center. Exercise was performed on a MR-compatible bicycle ergometer. Volumetric indexes of the systemic RV were obtained from a short axis stack of 10 images with a slice thickness of 10 mm and a 1 mm slice gap. We used an ultra-fast, turbo field echo planar imaging MR technique with the following parameters: repetition time = 14 ms, echo time = 4.8 ms, flip angle 30 degrees, imaging matrix 128 X 140, field of view 420 X 120 mm. The protocol was repeated at submaximal exercise, which was defined as 60% of peak oxygen consumption, as determined by stationary bike cardiopulmonary exercise testing one day prior to CMR. After reaching a steady heart rate, the individual performed a breath hold of 8 cardiac cycles to obtain 2 short-axis images. This procedure was repeated 5 times to obtain 10 short-axis images.

The dobutamine stress CMR acquisition protocol has previously been published by Tulevski et al.[9] In short, image acquisition was performed using a Siemens 1.5 Tesla MR scanner (Vision, Siemens, Erlangen, Germany) in the Academic Medical Center, Amsterdam. Volumetric indexes of the systemic RV were obtained from a short axis stack of 12–14 images with a slice thickness of 10 mm and a 0 mm slice gap. We used an ultra-fast, turbo field echo planar imaging MR technique with the following parameters: repetition time = R-R interval, echo time = 4.8 ms, flip angle 20 degrees, imaging matrix 256 X 256, field of view 350 mm. Dobutamine was administered through a venous line with an initial dose of 5 ųg/kg/min, which was increased after 3 minutes by 5 ųg/kg/min every 3 minutes up to a maximal dose of 15 ųg/kg/min. The CMR protocol was repeated 3 minutes after reaching the maximal dose.

Previous studies on cardiac response to stress demonstrated that healthy individuals increase cardiac output during exercise through a reduction in end systolic volume and a subsequent increase in ejection fraction.[12] Therefore, we defined an abnormal response to stress as the inability to decrease systemic right ventricular end systolic volume during stress (end systolic volume at rest – end systolic volume at stress ≤0 ml), and/or the inability to increase systemic right ventricular ejection fraction during stress (ejection fraction at rest – ejection fraction stress ≥0%).

CMR image analysis

For image analysis, the MASS Analytical Software System (Medis, Leiden, the Netherlands) was used. Image analysis was performed by a single observer in 2009, who was blinded for patient characteristics and outcome. Cine loops were used to choose end diastole and end systole. End diastole was defined as the phase with the largest RV area and end systole as the phase with the smallest RV area. The slices at the base of the heart were considered to be in the ventricle if the blood was at least half surrounded by ventricular myocardium. Trabeculations and papillary muscles were considered part of the ventricular cavity.[13] Four-chamber view cine loop movies in phase and slice with the short axes views were used in case the distinction between the ventricles, atria and great vessels was unclear. Tracing was performed manually on each end diastolic and end systolic short-axis view. The sums of the traced contours in end diastole and end systole were used to calculate end diastolic volume and end systolic volume using a disc summation technique. End diastolic volume and end systolic volume were used to calculate stroke volume and ejection fraction. Stroke volume was defined as end diastolic volume – end systolic volume, and ejection fraction as [(end diastolic volume – end systolic volume) / end diastolic volume] X 100%. Data on reproducibility of CMR image analysis has been published previously by our group.[14]

Statistical methods

For statistical analyses SPSS 16.0 (SPSS Inc., Chicago, Illinois) for Windows was used. A 2-tailed probability value of <0.05 was used as a criterion for statistical significance. The descriptive data are presented as number (percentage), or as mean with standard deviation, or median with range, as appropriate. Chi-square and unpaired t-tests were performed to assess differences between subgroups in categorical and continuous variables, respectively. A survival analysis was performed to assess the relation between an abnormal response to stress at baseline and the occurrence of adverse events during follow-up. For this purpose, the patient population was divided into two groups. The first group consisted of patients who had a normal ventricular response to stress; the second group of patients had an abnormal response to stress, as defined above. Kaplan-Meier survival charts were generated to depict the difference in incidence of adverse events between the two groups and Log-rank tests were used to assess whether the survival curves differed significantly. In addition, the prognostic value of an abnormal response to stress was assessed using Cox's proportional hazard regression analysis. For each stress CMR-derived variable, which was categorized as either normal or abnormal, a univariate hazard ratio (HR) with corresponding 95% confidence intervals (CI) was calculated. Furthermore, the univariate HRs were adjusted for age, and sex to obtain the multivariate HRs.

RESULTS

Thirty-nine adult patients (54% male; mean age 26.4, range 18.4 – 65.2 years) underwent stress CMR at baseline. The characteristics of these patients are summarized in table 1. At baseline, 26 patients (67%) were in NYHA functional class I, 13 (33%) patients were in NYHA functional class II and none were in NYHA class III or IV. Six patients were diagnosed with ccTGA, and 33 patients were diagnosed with complete TGA (19 had undergone a Mustard, and 14 had undergone a Senning operation). Patients with ccTGA were older at the time of baseline stress CMR investigation, as compared to patients with an atrially switched TGA (34.3 ± 16.3 years vs. 24.9 ± 4.6 years, $p<0.01$). Patients who had undergone a Mustard operation were significantly older compared to patients who had undergone a Senning operation (26.6 ± 4.3 years vs. 22.7 ± 4.2 years; $p<0.05$). There were no differences in gender distribution or in NYHA class between the TGA and ccTGA patients, nor between patients with a previous Mustard and Senning operation.

Table 1. Baseline Characteristics.

Characteristics		All patients* (*n*=39)	Cardiac event* (*n*=8)	Death* (*n*=3)
TGA / ccTGA		33 / 6	6 / 2	2 / 1
Age (years)		26.4 ± 8.0	33.0 ± 13.3	42.5 ± 19.6
Male		21 (54%)	4 (50%)	2 (67%)
NYHA class	I	26 (67%)	6 (75%)	1 (33%)
	II	13 (33%)	2 (25%)	2 (67%)

* Data are number of patients (percentage), or mean ± standard deviation. ccTGA: congenitally corrected transposition of the great arteries; NYHA: New York Heart Association; TGA: transposition of the great arteries.

Ventricular Response to Stress Cardiovascular Magnetic Imaging

CMR parameters are summarized in table 2. Stress CMR was well tolerated by most patients, as only 1 dobutamine-stress examination was discontinued due to a supraventricular tachycardia with a heart rate around 260 beats/min that was managed by carotid sinus massage.[6] At baseline we found no differences in resting end diastolic volume, end systolic volume, stroke volume and ejection fraction between patients with an atrially switched TGA and patients with a ccTGA. Resting end diastolic volume was significantly larger at baseline in patients with a Mustard operation, compared to those with a Senning operation (158.1 ± 48.7 ml vs. 127.8 ± 22.2 ml; p<0.05), however, no differences in end systolic volume, stroke volume and ejection fraction were observed between these two groups.

Table 2. Systemic RV volumes and function at rest and response to stress.

Characteristics	All patients (*n*=39)	Cardiac event (*n*=8)	Death (*n*=3)
Rest			
end diastolic volume (ml)	148 ± 44	156 ± 69	178 ± 112
end systolic volume (ml)	68 ± 30	77 ± 50	92 ± 83
stroke volume (ml)	79 ± 23	79 ± 24	86 ± 35
ejection fraction (%)	55 ± 10	53 ± 9	52 ± 14
Δ Stress - Rest			
end diastolic volume (ml)	-12 ± 28	-2 ± 18	-9 ± 29
end systolic volume (ml)	-8 ± 18	3 ± 15*	-2 ± 22
stroke volume (ml)	-4 ± 16	-4 ± 5	-7 ± 7
ejection fraction (%)	3 ± 8	-1 ± 7	4 ± 10

Data are mean ± standard deviation. * p<0.05 in comparison with all patients.

Overall, systemic RV end diastolic volume decreased during stress (147.6 ± 44 ml vs. 135.6 ± 51.9 ml; p=0.01), as did end systolic volume (68.0 ± 29.9 ml vs. 60.01 ± 33.9 ml; p=0.01). Subsequently, systemic RV stroke volume remained unchanged (79.4 ± 22.8 ml vs. 75.5 ± 23.3 ml; p=N.S.). Systemic RV ejection fraction increased significantly during stress (54.7 ± 9.5% at rest vs. 57.3 ± 8.1% during stress; p<0.05). Furthermore, heart rate increased from 68.5 ± 12.1 beats per minute to 141.6 ± 33.6 beats per minute (p<0.001). There were no statistically significant differences in cardiac response to stress between patients with an atrially switched TGA, and patients with a ccTGA, nor between patients with a Mustard operation, and patients with a Senning operation.

An abnormal systemic RV response to stress was frequently observed. In 17 patients (44%), end systolic volume remained equal or even increased during exercise. In addition, 15 patients (38%), showed no increase, or a decrease in RV ejection fraction during stress, 2 of whom showed normal response in end systolic volume.

Abnormal Response to Stress and Future Cardiac Events

After a mean follow-up period of 8.1 years; range 0.5 to 9.8 years, 8 (21%) patients had reached the composite endpoint of hospitalization for heart failure (n=2), intra-cardiac surgery (n=2, both tricuspid valve replacement), aborted out-of-hospital cardiac arrest (n=1), or cardiac death (n=3), with an annual event rate of 2.5%. Figure 1.

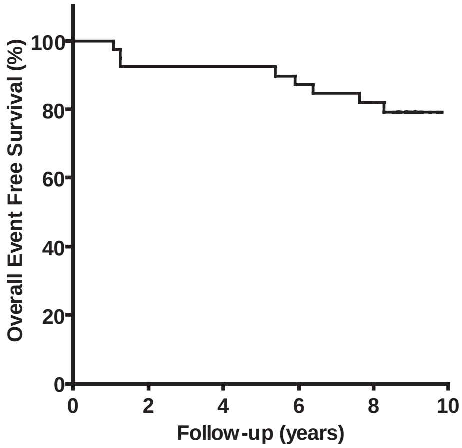

Figure 1. Kaplan-Meier survival curve for freedom from cardiac events plotted for follow-up duration after stress CMR in all patients (*n*=39).

Univariate analysis showed that older age at baseline was significantly associated with worse outcome (HR 1.1; 95% CI 1.0-1.1; p=0.02). The other baseline patient characteristics; sex, NYHA class at baseline, type of condition (ccTGA vs. TGA), type of operation (Mustard vs. Senning), and higher age (≥2 years) at Mustard/Senning operation, were not associated with the risk of cardiac events during follow-up. In addition, end diastolic volume, end systolic volume, stroke volume, and ejection fraction measured at rest were not predictive for future cardiac events, nor for cardiac death. An abnormal cardiac response to stress, on the other hand, was related to the occurrence of cardiac events during follow-up. As can be readily seen in figure 2, both the absence of a decrease in systemic RV end systolic volume during stress, as well as the absence of an increase in systemic RV ejection fraction during stress were predictive of future cardiac events. The absence of a reduction in end systolic volume was a risk factor for cardiac events in the univariate analysis (HR=1.58; 95% CI 0.98-24.1; p=0.054), and remained a risk factor for cardiac events after adjusting for age and sex (HR=2.33; 95% CI 1.19-88.72; p=0.034). The inability to increase ejection fraction was a risk factor for cardiac events in the univariate analysis (HR=1.81; 95% CI 1.23 – 30.37; p=0.027), and remained a risk factor in the multivariate analysis (HR=2.34; 95% CI 1.31-81.59; p=0.027). An abnormal response

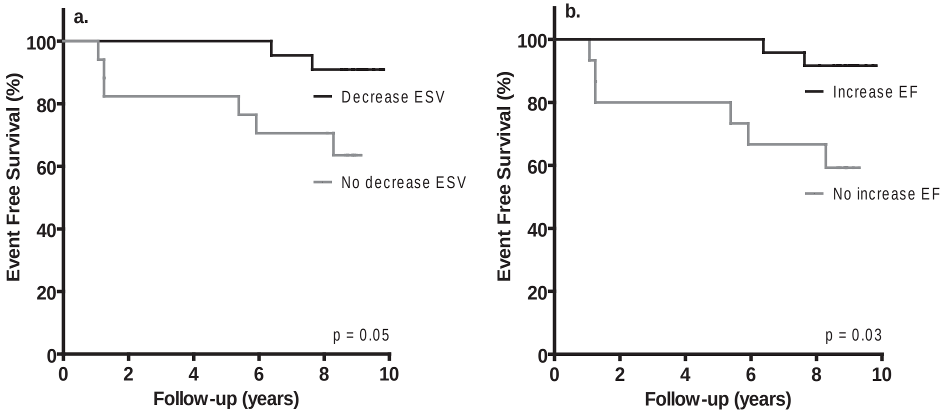

Figure 2. Kaplan-Meier survival curve for freedom from cardiac events plotted for follow-up duration after stress CMR. **A.** patients with (*n*=22) versus patients without (*n*=17) the ability to decrease systemic right ventricular end systolic volume (ESV) during stress. **B**. patients with (*n*=24) versus patients without (*n*=15) the ability to increase systemic right ventricular ejection fraction (EF) during stress.

to stress was not predictive for cardiac death. The stress related changes in end diastolic volume, increase stroke volume, and heart rate during stress, were not predictive for future cardiac events, nor for cardiac death.

DISCUSSION

The present study, for the first time, demonstrates that stress CMR is a valuable prognostic tool in patients with a systemic RV. Patients with a systemic right ventricle, who show no decrease in RV end systolic volume or no increase in RV ejection fraction during stress, have a significantly higher risk of future cardiac events.

The diagnostic and prognostic value of stress CMR in patients with acquired heart disease has already been established. Dobutamine stress CMR has been proven useful to detect myocardial ischemia in patients with chest pain,[15–18] and to predict future myocardial infarction and cardiac death in patients with coronary artery disease.[19;20] Moreover, in patients with mildly to moderately reduced LV ejection fraction stress CMR is prognostic for future myocardial infarction and cardiac death.[21] On the other hand, patients without inducible ischemia during stress CMR, and with a resting ejection fraction >40% are known to have excellent cardiac prognosis.[20] Notwithstanding the knowledge on the prognostic role of stress CMR in patients with acquired heart disease, the predictive value of stress CMR in patients with congenital heart disease was unknown.[22]

Previous studies on stress CMR in patients with a systemic RV have demonstrated that these patients often show an abnormal cardiac response to stress.[6;7;9] In healthy individuals, end systolic volume decreases, whereas end diastolic volume remains unchanged during stress, causing an increase in both stroke volume and ejection fraction.[12;23] Frequently, the systemic RV of patients with an atrially switched TGA lack the ability to increase myocardial contractibility during stress, as they often show no decrease in end systolic volume, and no subsequent increase in stroke volume and ejection fraction during stress.[5;8;24] Moreover, it is known that patients with a systemic RV have a reduced ability to increase heart rate during exercise, due to chronotropic incompetence, which further diminishes the increase in cardiac output during stress.[8;25] Overall, we found an adequate chronotropic response to stress, with a substantial increase in heart rate during stress in all patients. However, our study demonstrates that almost half of the patients could not decrease end systolic volume and almost one third of patients could not increase ejection fraction during stress. This is the first study in which an abnormal cardiac response to stress is demonstrated to be prognostic for future cardiac events in patients with a systemic RV. These findings suggest that impaired myocardial contractility during stress identifies a more deteriorated state of the systemic RV, and thus relates to worse patient outcome as observed in the current study.

At the time of stress CMR most patients were in NYHA functional class I, and none were NYHA class III or IV. Moreover, RV ejection fraction was not impaired in most patients, as compared to RV ejection fraction of subjects with normal cardiac anatomy.[26] Survival analysis revealed that neither functional status nor resting RV function was predictive for the occurrence of adverse events. Stress CMR, however, facilitates the detection of cardiac dysfunction that is not apparent at rest.[9] Subsequently, stress related cardiac dysfunction demonstrated to be predictive of adverse events during long-term follow-up, in the current study. Hence, stress CMR provides timely detection of systemic RV dysfunction and could thus guide early therapeutic intervention to prevent or decelerate further ventricular deterioration and the occurrence of cardiac events.[27] However, sufficiently powered, prospective trials are needed to establish the role of early therapeutic intervention in asymptomatic or minimally symptomatic patients with a systemic RV and an abnormal response to stress.

Although CMR is considered an accurate and noninvasive tool to assess systemic RV volumes and function, there are some limitations for the use of stress CMR.[13;28;29] For example, 20% of patients with a systemic RV is pacemaker dependent, and an increasing number of patients with a failing systemic RV benefits from cardiac resynchronization therapy.[30] As most intra-cardiac devices are considered to be CMR incompatible, these patients are unsuitable to undergo CMR. Moreover, studies in patients with coronary artery disease have proven dobutamine infusion to be safe, although ventricular ectopy and atrial arrhythmias were seen when administrating high doses of dobutamine (40 ųg/kg/min).[21] As no trials had been performed addressing safety issues when performing stress CMR in patients with a systemic RV, we chose to administer dobutamine at a maximum dosage of 15 ųg/kg/min dobutamine, which is known to be sufficient to assess contractile reserve.[31–33] In the present study, one examination was discontinued due to supra-ventricular tachycardia (260 beats per minute), which was managed with carotid sinus massage. Although our study was not set-up to evaluate safety issues, this was the only complication that we experienced.

Limitations

As with most studies on CMR in patients with congenital heart disease, the number of patients included in the study was relatively small. Larger-scaled studies should be pursued to definitely establish the value of our findings. However, despite the relatively small sample size and possible bias in favor of healthier patients, we were still able to show that patients with a systemic RV, who show no decrease in RV end systolic volume or increase in RV ejection fraction during stress, have a significantly higher risk of future cardiac events. Our study was importantly limited by the inability to perform adequate flow measurements at the time of baseline data acquisition. Therefore, our data could not be corrected for potential tricuspid valve regurgitation, or baffle stenosis/leakage. As it is known that tricuspid valve regurgitation predicts for reverse outcome in patients with a systemic RV, some of the complications reported in our study could have been due to tricuspid valve regurgitation, rather than to abnormal stress response. Another limitation is the fact that we used two different CMR image acquisition protocols (in the Leiden University Medical Center, and in the Academic Medical Center in Amsterdam), as well as two different stress protocols (dobutamine stress and physical exercise CMR).[34] Nonetheless, the current study was set-up to evaluate the prognostic value of an abnormal cardiac response to stress for each individual patient, irrespective of the diagnostic modality used, and not to compare patients from different medical centers, or to compare two different diagnostic modalities. We excluded patients with irregular rhythms to avoid the risk of life-threatening arrhythmias during stress, and patients with intra-cardiac devices because of CMR incompatibility. This could have lead to a biased sample, favoring healthier patients with lower risk of cardiac events.

CONCLUSION

Stress CMR potentially has important prognostic value in patients with a systemic RV. Patients with a systemic RV who are unable to decrease end systolic volume, or to increase ejection fraction during stress have a substantially higher risk of future cardiac events.

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