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Determinants and functional impact of restrictive physiology after repair of tetralogy of Fallot: New insights from magnetic resonance imaging

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ABSTRACT

Background: The presence of end-diastolic forward flow (EDFF) in the pulmonary arteries is commonly regarded as a hallmark of restrictive physiology of the right ventricle (RV) which, in turn, has been associated with a better long-term prognosis in patients after TOF repair. However, controversy persists over the beneficial clinical consequences of restrictive physiology. We aimed at determining the clinical relevance of restrictive physiology late after TOF repair.
Methods: Fifty magnetic resonance examinations of 50 patients (age 13.0 ± 2.8 years, 26 males) with repaired TOF were evaluated. The patients were divided into: Group-1 with and Group-2 without EDFF; Group-A with smaller RVs (<170 ml/m2) and Group-B with larger RVs (≥170 ml/m2). Maximum oxygen consumption as percent of predicted (VO_2max-pred) at a recent exercise test was recorded.
Results: Groups-1 and 2 did not differ with regard to their right ventricular end-diastolic volume, pulmonary regurgitant volume, or QRS duration. Patients in Group-1 had a higher VO_2max-pred than patients in Group-2 (70.3% versus 54.7% of predicted, $p<0.01$). In Group-1A versus 2A (RV < 170 ml/m^2, with and without EDFF) this difference persisted, but in Group B there was no difference in VO_2max-pred between patients with and without EDFF. The flow volume of EDFF correlated with VO_2max-pred ($r = 0.444$, $p = 0.007$).
Conclusions: End-diastolic forward flow measured by magnetic resonance is present in patients with small and large RVs. The presence of EDFF is associated with better exercise tolerance, but only in patients with relatively small RVs.

1. Introduction

Restrictive physiology of the right ventricle (RV) is common in patients with pulmonary regurgitation after tetralogy of Fallot (TOF) repair, both during the immediate postoperative period [1–3], but also late after repair.[4,5] The presence of end-diastolic forward flow (EDFF) in the branch pulmonary arteries, if persistent throughout the respiratory cycle, has been regarded a hallmark of "restriction" of the RV, when assessed by Doppler-echocardiography [2–5]. It is generated by flow across the tricuspid valve as a result of atrial contraction that cannot be accommodated by the RV and which is variably transmitted to the pulmonary artery [6]. Restrictive physiology of the RV has been associated with a better functional performance in patients after TOF repair, presumably because the decreased compliance limits progressive dilation of the RV [3,5]. However, controversy persists over the impact of restrictive physiology on long-term outcome, with recent magnetic resonance studies suggesting a negative impact on exercise tolerance and quality of life [7,8].

Cardiovascular magnetic resonance imaging (CMR) has been increasingly used for the postoperative assessment in patients with TOF [9–14]. End-diastolic forward flow can be assessed qualitatively and quantitatively by CMR [4,8]. Using this technique, we aimed to determine whether restrictive physiology after repair of TOF impacts on the patients' clinical status. Further, we sought to unveil potential mechanisms of EDFF. Finally, we hoped to identify reasons for the conflicting previous findings regarding the clinical significance of this phenomenon in patients after TOF repair [5,15].

2. Materials and methods

Following approval of our institutional Research Ethics Board we reviewed 93 consecutive CMR studies that were performed in 76 patients with repaired TOF between August 2007 and January 2009. When there were more than two studies available in a patient during the studied period, only the first examination was used in this

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study. In order to recruit a homogeneous cohort of patients with volume loaded RVs and without confounding flow turbulence from RV outflow tract stenosis we excluded patients with a pulmonary regurgitant fraction < 10% at CMR (n = 8), RV outflow tract obstruction with a pressure gradient > 40 mm Hg at echocardiography (n = 8) or inadequate image quality of CMR due to metallic artifacts or arrhythmias (n = 10). The remaining study population therefore consisted of 50 patients. The patients' mean age at time of CMR was 13.0 ± 2.8 years (range 8 to 18 years). Twenty six patients were male and 24 were female. No patient had a residual intra-cardiac shunt.

2.1. Cardiovascular magnetic resonance

All CMR investigations were performed in a 1.5 T unit ("Avanto", Siemens Medical Solutions, Erlangen, Germany), using a standardized clinical protocol. Cine images were obtained in 2-chamber, 4-chamber, RV outflow tract and short-axis planes with a temporal resolution that was sufficient to accommodate 20 true phases per cardiac cycle. Phase contrast imaging was performed for flow measurements through the right and left atrioventricular valves, ascending aorta at the level of the right pulmonary artery, main and both branch pulmonary arteries with a temporal resolution that was sufficient to accommodate 25 true phases per cardiac cycle. The technical details of these standard acquisitions have been thoroughly described [8,13,14].

2.2. Ventricular volume measurements

Right and left ventricular volumes were measured from a stack of short-axis cine images, using commercially available software (Qmass MR, Version 7.1, Medis Medical Imaging Systems, Leiden, The Netherlands). The end diastolic volume (EDV), end systolic volume (ESV) and ejection fraction were determined. The corrected RV ejection fraction was calculated by dividing the net pulmonary forward stroke volume by the RVEDV.

2.3. Flow measurement and analysis

The phase contrast images were analyzed using dedicated software, (Qflow, Version 5.1, Medis Medical Imaging Systems). Typical time-velocity curves from the ascending aorta, main pulmonary artery (MPA) and atrioventricular valves are shown in Fig. 1. In order to account for differences in RR intervals between the three different time-velocity tracings we used a relative time scale with the RR interval of each curve equaling 100%. If the RR interval varied by more than 10% between any two of the three tracings within the same patient (in 10 studies), we excluded these studies from the comparison of the timing of flow events. The time intervals measured are illustrated in Fig. 1.

2.4. Analysis of the timing of EDFF

Since cine CMR does not allow for beat-to-beat correlations with the electrocardiogram, EDFF was defined as a distinct peak of forward flow immediately prior to, but separate from the upstroke of the systolic forward flow in the MPA (Fig. 2).

The time intervals between the onset and end point of EDFF to the onset, peak and end point of A wave of tricuspid inflow were measured (Fig. 1).

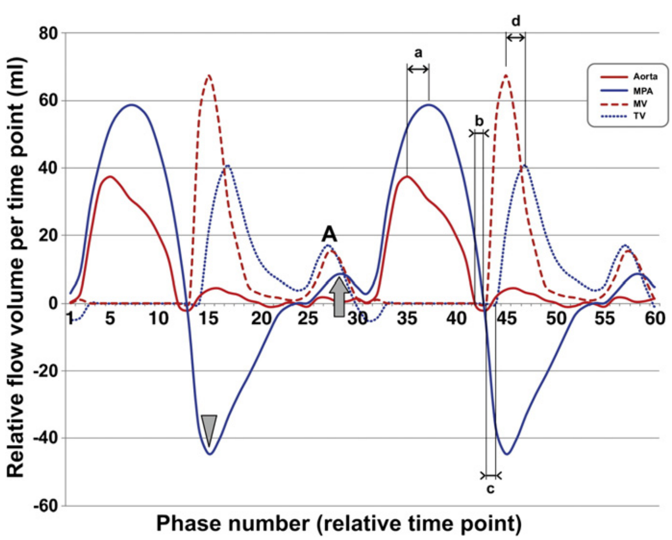

Fig. 1. Example of combined velocity time curve of aorta, main pulmonary artery, mitral valve inflow and tricuspid valve inflow. Magnetic resonance imaging phase encoding flow patterns in the proximal ascending aorta (gray solid line), main pulmonary artery (dotted line), across the mitral valve (dashed line) and tricuspid valve (black solid line) in a patient with repaired TOF. Note the negative deflection of pulmonary arterial flow representing regurgitation (arrowhead) and the positive deflection during end-diastolic forward flow (EDFF, arrow). Peak and onset of EDFF occurs immediately after the tricuspid valve A wave (A).

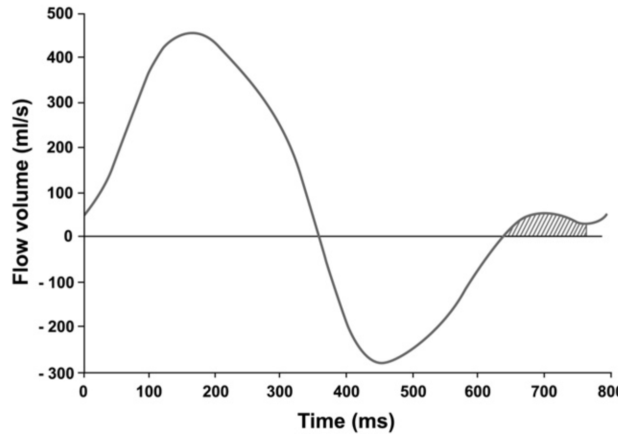

Fig. 2. Flow volume curve of the main pulmonary artery. The area shaded in gray represents volume during end-diastolic forward flow.

2.5. Electrocardiogram, echocardiogram, and exercise test

The results from these tests, occurring at the closest date within 12 months before or following the CMR examination, were recorded, so long as there had been no intervention or clinical deterioration during the intervals between the tests. From the electrocardiogram, the PR interval, QRS duration and presence of right bundle branch block were recorded. The presence or absence of EDFF in the branch pulmonary arteries on a pulsed wave Doppler tracing was also recorded (Fig. 3). A tracing was read as positive for EDFF if it was seen for ≥ 4 continuous beats. The ratio of maximum oxygen consumption to the level of predicted normalized maximum oxygen consumption during clinical exercise testing (VO_2max-pred) was recorded.

2.6. Subgroup analysis by presence of end-diastolic forward flow

The patients were divided into Group 1 and Group 2 according to the presence or absence of EDFF, respectively. Volume of EDFF, if present, was measured (Fig. 2) and its fraction of the net forward flow volume within the MPA was calculated. The clinical, imaging, and electrophysiological findings of each group were compared with those of the two control groups.

2.7. Subgroup analysis by right ventricular end-diastolic volume

The patients were divided into two groups according to the RVEDV, indexed to body surface area (RVEDVi): Group A with an RVEDVi < 170 ml/m^2 and Group B with an RVEDVi ≥ 170 ml/m^2.

2.8. Combined subgroup analysis

In order to differentiate between the effects of RV size and presence of EDFF on the patients' clinical status and functional parameters, we combined the two criteria described above, thus subdividing the patients into the following subgroups:

Group 1A: Patients with EDFF and RVEDVi < 170 ml/m^2
Group 1B: Patients with EDFF and RVEDVi ≥ 170 ml/m^2
Group 2A: Patients with no EDFF and RVEDVi < 170 ml/m^2
Group 2B: Patients with no EDFF and RVEDVi ≥ 170 ml/m^2

2.9. Statistical analysis

All statistical analyses were carried out using standard commercially available software (SPSS, version 17.0, Polar Engineering and Consulting, Chicago, USA). Differences between mean values were evaluated with t-tests. Differences in the prevalence of findings were evaluated with Fisher's exact test. We used the Mann–Whitney U test and Fisher's exact test for subgroup analysis because of the small subject numbers in each group.

Pearson correlation and simple linear regression were used to assess the univariate correlations between CMR measurements as well as other parameters and VO_2max-pred. Multiple linear regression with a stepwise approach was used to assess the isolated influence of one of multiple factors on exercise tolerance. A p value < 0.05 was considered significant for differences or correlations.