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Ventricular function and cardiac reserve in contemporary Fontan patients

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ABSTRACT

Background/objective: Total cavopulmonary connection (TCPC) has been the preferred treatment for patients with univentricular hearts. Current TCPC-techniques are the intra-atrial lateral tunnel (ILT) and the extracardiac conduit (ECC). We aimed to determine ventricular function during rest and stress, and to compare results for both techniques and for left (LV) versus right ventricular (RV) dominance.

Methods: 99 patients, aged 12.5 ± 4.0 years underwent echocardiography and magnetic resonance imaging (MRI), and 69 patients underwent stress MRI.

Results: Echocardiography showed impaired systolic and diastolic function. MRI parameters were comparable between ILT and ECC at rest. During dobutamine there was a decrease in end-diastolic volume (EDVi) (91 ± 21 vs. 80 ± 20 ml/m^2 $p < 0.001$). Ejection fraction (EF) and cardiac index (CI) during dobutamine were lower for ILT patients (59 ± 11 (ILT) vs. 64 ± 7% (ECC), $p = 0.027$ and 4.2 ± 1.0 (ILT) vs. 4.9 ± 1.0 L/min/m^2 (ECC), $p = 0.006$), whereas other parameters were comparable. TEI-index was higher in ILT-patients (0.72 ± 0.27 (ILT) vs. 0.56 ± 0.22 (ECC), $p = 0.002$). Diastolic function was frequently impaired in patients with a dominant RV (67% (RV) vs. 39% (LV), $p = 0.011$). Patients with dominant LV's had smaller end-systolic volume (ESVi) (40 ± 13 (LV) vs. 47 ± 16 (RV) ml/m^2, $p = 0.030$) and higher EF (55 ± 8 (LV) vs. 49 ± 9 ml/m^2 (RV), $p = 0.001$) and contractility (2.3 ± 0.8 (LV) vs. 1.9 ± 0.7 mm Hg/ml/m^2 (RV), $p = 0.050$) during rest and higher EF during dobutamine (63 ± 8 (LV) vs. 58 ± 10 ml/m^2 (RV), $p = 0.043$).

Conclusion: Ventricular function is relatively well preserved in modern-day Fontan patients. With dobutamine stress there is a decrease in EDVi. ECC patients have higher CI and EF during stress. Patients with a dominant RV have lower systolic, including impaired contractility, and diastolic function.

1. Introduction

Originally designed for the treatment of tricuspid atresia, the Fontan procedure has evolved into the staged total cavopulmonary connection (TCPC) that has become available for a wide range of univentricular heart defects.

While medium to long term survival has improved drastically over the last decades, it is well known that the exercise capacity and ventricular function of patients who have undergone the Fontan operation are less than those of their healthy peers [1–3]. There is considerable concern over long-term deterioration of clinical state and ventricular performance in older Fontan patients [2,4,5]. Other remaining questions with regard to ventricular function in this population include the role of ventricular anatomy (left vs. right type ventricular dominance), the impact of more recent strategies towards staging and timing of the TCPC and the differences resulting from different surgical techniques available for this operation [6,7]. Few studies have assessed ventricular function in well-defined, homogeneous populations that have been

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treated with recent Fontan strategies, i.e., at least two staged TCPC using the intra-atrial lateral tunnel (ILT) or the extracardiac conduit (ECC) [2,8]. The choice between these surgical procedures is subject of debate [9–11]. It has been advocated that the ECC procedure can reduce aortic cross-clamping times or can be performed without the use of cardiopulmonary bypass. This could impact ventricular function on longer term follow-up. In a recent study we could indeed demonstrate a slightly better exercise capacity for ECC patients [3]. The influence of the type of surgical procedure on ventricular function has not yet been assessed by MRI.

At rest, ventricular function in the modern Fontan population may be relatively well preserved [8]. However, during exercise, Fontan patients are unable to increase their cardiac output to levels that are common among healthy controls. To date, this has only been shown in several relatively small studies, using pharmacological stress or physical exercise [12–14]. The aim of this study was to assess ventricular function during rest and stress in a large and well defined cohort of contemporary Fontan patients. Furthermore we aimed to compare the effect of the two current surgical modifications as well as the effect of left and right ventricular morphology of the single ventricle.

2. Methods

2.1. Patients

We performed a prospective cross-sectional multi-center study of patients after TCPC completion. Inclusion criteria were: having undergone a TCPC through a staged approach with a bidirectional Glenn procedure prior to the completion of the TCPC according to a current technique (ILT or ECC); completion of the TCPC before the age of 7 years and inclusion in the study at an age of at least 8 years or older; and a minimum of 3 years of follow-up since completion of the TCPC. Patients with contra-indications for MRI (including those with pacemakers and ICD's) and patients with mental retardation were excluded from this study.

Patients were recruited from five tertiary referral centers in the Netherlands. The study was approved by the institutional medical ethical review boards of the participating centers. Written informed consent was obtained from all patients and/or their parents. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Medical records were reviewed for anatomical and surgical details. All patients underwent routine physical examination, including weight, height, blood pressure and oxygen saturation and history taking to determine NYHA functional class. Resting heart rate was determined using a standard 12-lead ECG in supine position.

2.2. Echocardiographic imaging

All patients underwent a detailed transthoracic echocardiographic examination following the recommendations of the American Society of Echocardiography [15]. Each echocardiographic study was performed by an experienced echocardiographic technician and supervised by a member of the research team. All images were obtained with an appropriate transducer (based on age and weight of the patients) on locally available machines (GE Vivid7 and Phillips iE33) according to a standardized protocol.

Analysis was performed offline using EchoPAC version 11.0 (GE Healthcare, USA). All measurements were performed in 3 different cardiac cycles and the values were averaged. A single observer (S.B.) performed all measurements at a single workstation.

Measurements were performed according to current guidelines [16–18]. The echocardiographic parameters that were assessed are listed in Table 2. Tissue Doppler measurements were obtained at the basal segment of the lateral wall of the dominant ventricle. Pulsed wave Doppler measurements were obtained at the dominant atrioventricular (AV) valve.

Results of echocardiographic measurements were compared with published reference values [19–22].

2.3. MRI

All patients underwent cardiac magnetic resonance imaging. Ventricular volumes were imaged using a multi-slice, multi-phase, steady-state free precession sequence. The technical details of the sequences were as reported previously [12]. The series were acquired at rest and during simulated exercise, achieved by administering dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) intravenously at a rate of 7.5 μg/kg/min [12]. This dose is known to have a positive inotropic effect and to a lesser extent a positive chronotropic effect [23]. When a new steady-state in heart-rate was achieved after the start of dobutamine administration, measurements were repeated, using the same scanning parameters as in the rest conditions. Dobutamine infusion was reduced to 5 μg/kg/min in case any of the following occurred: an increase in heart rate, systolic, or diastolic blood pressure of more than 50% or a decrease in heart rate, systolic, or diastolic blood pressure of more than 20%. The test was discontinued if the patient experienced significant discomfort.

Volumetric analysis was performed on an Advanced Windows workstation (General Electric Medical Systems) using MASS software (Medis Medical Imaging Systems, Leiden, The Netherlands) as previously reported [24]. Endo- and epicardial contours were manually drawn in end-diastole and end-systole, and papillary muscles and trabeculae were excluded from the lumen. In order to allow comparison between different types of cardiac anatomy, the volumes and mass of left and right ventricles were added together to calculate single ventricular volume and mass [12,24]. All ventricular volumes and stroke volume were indexed for body surface area (BSA). Contractility and afterload were assessed using the following approximations: contractility $\approx$ mean arterial pressure/end systolic volume index (ESVi) and afterload $\approx$ mean arterial pressure/cardiac index [12]. Stress response was expressed as the relative change (%) in end diastolic volume index (EDVi), ejection fraction (EF) and cardiac index (CI).

2.4. Neurohumoral assessment

Blood samples were collected from a peripheral vein without the use of a tourniquet following 30 min of rest after the insertion of the venous cannula. Plasma and serum were separated within 30 min after collection and stored at −80 °C. The following markers were assessed: N-terminal pro-brain natriuretic peptide (NT-proBNP) (Cobas 8000 c702, Roche, Almere, the Netherlands), catecholamines (HPLC with fluorometric detection), plasma aldosterone concentration (radioimmunoassay, Coat-a-Count, Diagnostic Products Corporation, Los Angeles, CA, USA) and plasma renin (radioimmunoassay, Cisbio Bioassays, Codolet, France). C-terminal pro-endothelin-1 (CT-proET-1) was measured in EDTA plasma with the CT-proET-1 assay on a Brahms KRYPTOR system using TRACE (Time Resolved Amplified Cryptate Emission) technology.

2.5. Exercise testing

Exercise tests were performed on a bicycle ergometer according to a previously described protocol [3]. From these exercise tests, maximum oxygen uptake (VO_2 peak) and ventilatory efficiency (VE/VCO_2 slope) were assessed and expressed as percentage of predicted values. To calculate the predicted values, norm values from healthy children were used [25].

2.6. Statistical analysis

Statistical analysis was performed using SPSS 21.0. Data are expressed as frequencies, mean (standard deviation) in case of normal