



Does left ventricular size impact on intrinsic right ventricular function in hypoplastic left heart syndrome?

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ARTICLE INFO

Article history:

Received 26 October 2011

Received in revised form 2 March 2012

Accepted 31 March 2012

Available online 23 April 2012

Keywords:

Hypoplastic left heart syndrome

Right ventricular function

Left ventricular size

ABSTRACT

Background: The size of the remnant left ventricle (LV) may influence right ventricular function and thus long-term outcome in palliated hypoplastic left heart syndrome (HLHS). We therefore sought to assess the impact of the size of the hypoplastic LV on intrinsic RV function in HLHS patients after Fontan surgery.

Methods: Fifty-seven HLHS patients were studied 2.5 (range: 0.8–12.6) years after Fontan-type palliation with the pressure-volume conductance system. The patient cohort was divided into two groups according to the median LV area index (group 1: LV area index $\leq 1.33 \text{ cm}^2/\text{m}^2$, $n = 29$; group 2: LV area index $> 1.33 \text{ cm}^2/\text{m}^2$, $n = 28$).

Results: The slopes of the end systolic elastance (Ees) and the preload recruitable stroke work relation (Mw) were not different between group 1 and 2 (Ees: 2.70 ± 1.92 vs. $3.68 \pm 2.68 \text{ mmHg/ml}$; Mw: 52.75 ± 14.98 vs. $51.09 \pm 16.63 \text{ mmHg} \times \text{ml}$; $P = \text{NS}$ for all). Furthermore, the systolic responses to dobutamine were not statistically different between groups. However, the slope of the end diastolic stiffness (Eed) was higher in group 2 and catecholaminergic stimulation resulted in a decrease in Eed in group 2 (group 1: 0.40 ± 0.26 vs. 0.52 ± 0.45 ; group 2: 0.68 ± 0.44 vs. $0.47 \pm 0.38 \text{ mmHg/ml}$, $P < 0.01$). Furthermore Eed was lowest in patients with mitral atresia/aortic atresia, the anatomic subgroup with the smallest LV remnant.

Conclusions: Intrinsic systolic RV function is not affected by the size of the hypoplastic LV in survivors of surgical palliation of HLHS. Diastolic stiffness, however, was higher in patients with a larger LV remnant.

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1. Introduction

Recent refinements of perioperative and surgical treatment strategies have led to a significant decrease in mortality of patients with hypoplastic left heart syndrome (HLHS) [1–3]. Survival rates, however, have been reported to be different in HLHS patients depending on the anatomical subtype. Patients with the mitral stenosis/aortic atresia variant of HLHS appear to have the highest risk for failure of staged palliation [1,4]. Interestingly, these are the patients with the largest left ventricular (LV) remnant and there is some evidence that it is the size of the LV that adversely affects outcome potentially by impairing right ventricular (RV) function [5,6]. However, an association between LV size and RV function has not yet been proven.

In clinical routine, RV function is usually assessed by echocardiography and cardiac magnetic resonance imaging. But these non-invasive techniques cannot separate intrinsic ventricular dysfunction from

complex load-dependent changes. In the present study, therefore, we assessed load-independent indices of RV myocardial function (i.e. contractility) using the pressure-volume conductance system in a contemporary cohort of children who have undergone staged palliation of HLHS. This way we aimed to assess potential differences in intrinsic RV function related to the size of the hypoplastic LV and the anatomical subgroup.

2. Materials and methods

2.1. Patients

A total of 73 patients after three-stage palliation of HLHS were recruited to be studied with the pressure-volume conductance system between January 2005 and March 2011 as part of routine cardiac catheterisation after the fenestrated lateral tunnel Fontan procedure. All except 4 patients had all their palliative surgical procedures performed in our centre by a single surgeon. In all patients, a Norwood operation with modified Blalock-Taussig shunt was performed as stage one followed by a superior cavo-atrio-pulmonary anastomosis (Hemi Fontan) as stage two, and a fenestrated intra-atrial lateral tunnel modification of the Fontan operation as stage three. Only a single patient with an absent truncus brachiocephalicus received a RV to pulmonary artery conduit at the time of the Norwood procedure.

Informed consent was obtained in all patients. The local research ethics committee approved the study protocol.

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2.2. Clinical and echocardiographic data

Pertinent patient data were collected and included age, gender, anatomical data, surgical data including cumulative cardio pulmonary bypass time, number of previous operations, size of the Blalock-Taussig (BT) shunt indexed to body weight at the time of the Norwood operation, and New York Heart Association (NYHA) functional class.

To evaluate the size of the remnant left ventricle the area of the hypoplastic LV was measured from the echocardiogram performed at the time of the catheter study. Measurements were taken from the apical 4-chamber view at end diastole and indexed to body surface area (LV area index). Degree of tricuspid regurgitation was measured (0 = none, 1 = mild, 2 = moderate) at the same time. The diameter of the hypoplastic ascending aorta was measured from echocardiogram prior to the Norwood operation.

2.3. Patient Groups

In order to delineate the relationship between LV size and RV function the patient cohort was divided into two distinct groups according to the median LV area index. *Group 1* consisted of patients with a LV area below or equal to the median of $1.33 \text{ cm}^2/\text{m}^2$ ($n=29$) whereas *group 2* consisted of patients with a LV area index above $1.33 \text{ cm}^2/\text{m}^2$ ($n=28$).

Furthermore, data on LV size and RV function were compared between the four anatomic variants of HLHS. The patients were assigned to the anatomic subgroups (mitral and aortic atresia, MA/AA; mitral atresia and aortic stenosis, MA/AS; mitral stenosis and aortic atresia, MS/AA and mitral and aortic stenosis, MS/AS) based on the echocardiogram that had been performed prior to the Norwood operation.

2.4. Cardiac catheterisation

Cardiac catheterisation was performed under general anaesthesia and included full haemodynamic assessment and biplane (posterior-anterior and lateral) RV angiocardiology. RV volumes were analysed offline from angiocardiograms digitally stored on a UNIX workstation. RV volumes were calculated at end diastole (EDV) and end systole (ESV) using custom made software that allows optimal image pairing and semiautomatic contour detection. The technique has previously been validated, described and used by our group [7–9]. EDV and ESV were corrected with factors appropriate for projection and cardiac phase [10].

2.5. Conductance study

To acquire RV pressure-volume loops a 4 F combined pressure-conductance catheter with 12 electrodes (CD Leycom, Zoetermeer, The Netherlands) was placed in the RV via the aorta. Pressure-volume signals were displayed online and digitised at a sample rate of 250 Hz (CFL 512, CD Leycom, The Netherlands) using a value of blood resistivity determined before data acquisition. The pressure signal was calibrated with a standard calibration pulse from the amplifier (Sentron, Roden, The Netherlands). Conductance derived RV volume was calibrated for parallel conductance and gain factor α using the EDV and ESV obtained from biplane angiocardiology [8]. Finally, a 25-mm Latex balloon catheter (Numed, Hopkinton, NY) was placed in the intra-atrial lateral tunnel and prepared to modify preload. Pressure volume data were recorded for 10–15 seconds with the respirator temporarily interrupted at end expiration during steady state conditions and progressive venous occlusion to generate pressure-volume loops over a wide range of filling pressures. Measurements of pressure and volume relationships were repeated after infusion of $10 \mu\text{g/kg/min}$ of dobutamine for 10 minutes. All data acquisition runs were repeated in triplicate and all runs containing premature ventricular contractions were excluded from analysis.

In 7 of the 73 patients recruited to be studied the conductance catheter could not be advanced into the RV as intended. In an additional 9 patients pressure-volume data could not be analysed due to poor signal quality. In 3 patients signal quality was satisfactory under steady state conditions but inadequate during dobutamine infusion. Therefore, steady state data on RV function could be analysed in 57 patients and full functional data was available on 54 patients. At the time of catheterization 38 patients had an open fenestration and in 19 patients fenestration was closed. We did not observe any complications during cardiac catheterisation.

2.6. Data analysis

Analysis of pressure volume loops (PV loops) was performed with custom made software (Circlab 2010, LUMC, Leiden, the Netherlands). Steady state haemodynamic data were calculated from pressure-volume loop recordings at baseline and during dobutamine infusion as means of all beats during a 10-second period.

Heart rate, cardiac index, stroke volume, EDV and ESV, RV ejection fraction (EF), end systolic and end diastolic pressure (ESP and EDP), maximal and minimal rate of RV pressure change (dP/dt_{max} , dP/dt_{min}) were analysed. The RV volumes were normalised for patients' body surface area with an exponent appropriate for end diastole and end systole since RV volumes increase in an over-proportional manner with respect to body surface area (EDVi, ESVi) [11]. The time constant of relaxation (τ), reflecting the early active relaxation process, was calculated as the time constant of the monoexponential pressure decay during isovolumic relaxation. The isovolumic period was defined as the period between the time point of dP/dt_{min} and the time point at

which dP/dt reached 10% of the dP/dt_{min} value. Stroke work (SW) was calculated as the area enclosed by the pressure-volume loop.

Indices of intrinsic systolic and diastolic ventricular function were derived from pressure-volume loops recorded during the preload reduction manoeuvre. For systolic function, we determined end systolic elastance (E_{es}) as the slope of the end systolic pressure-volume relationship (ESPVR: ESP vs. ESV) and the slope (M_w) of the preload recruitable stroke work relation (PRSW: SW vs. EDV). Diastolic stiffness (E_{ed}) was determined as the slope of the end diastolic pressure-volume relationship (EDPVR: EDP vs. EDV). These slopes are regarded as the optimal load-independent indices of intrinsic systolic and diastolic ventricular function, reflecting contractility and stiffness, respectively [12–14]. All functional data were evaluated by a single investigator blinded to the clinical and anatomical data.

2.7. Cardiac magnetic resonance imaging

Data on right and left ventricular volumes were obtained by cardiac magnetic resonance (CMR) imaging performed during the same hospital admission. Full volumetric CMR data were available in 39 patients.

2.8. Statistical analysis

Data are expressed as mean $\pm$ SD or median (range) as appropriate. Results for each variable were tested for normality using the Kolmogorov-Smirnov method. Comparisons between groups were made with Student *t*-test, Mann-Whitney *U* test, or χ^2 test as appropriate. Comparisons within one group between baseline and dobutamine data were made with Student *t*-test for paired samples. To analyse differences between the four anatomical subgroups the Kruskal-Wallis test was used. If the Kruskal-Wallis test yielded a $P \leq 0.05$ post-hoc pairwise comparison of subgroups was performed [15].

We used a general linear model for repeated measurements to test for within-subjects effects (baseline vs. dobutamine), between-subjects effects (*group 1* vs. *group 2*) and their interaction.

Correlation of parameters was assessed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for not normally distributed data.

Interobserver variability testing of the conductance-derived data was performed on 15 randomly chosen patients by an independent blinded observer and intraclass correlation coefficients were analysed.

For all analyses a $P < 0.05$ was considered statistically significant. Statistical analysis was performed with MedCalc, version 11.1.1.0 (MedCalc Software, Mariakerke, Belgium) and SPSS, version 17.0 (SPSS, Chicago, IL).

3. Results

3.1. Patient demographics

Patient characteristics of the entire study cohort and the two groups are shown in Table 1. Groups were not different in regard to age at study, age at the three surgical stages, follow-up interval, NYHA functional class, degree of tricuspid regurgitation, number of operations, total cardiopulmonary bypass time, and BT shunt index. Patients in *group 1* had a smaller ascending aorta.

3.2. RV size and function at baseline and during dobutamine infusion

Data of haemodynamic parameters and intrinsic RV function at baseline measurement and during dobutamine infusion are given in Table 2. The changes in the mean pressure-volume loop and intrinsic functional data with dobutamine are also illustrated in Fig. 1.

In the entire patient cohort heart rate increased with dobutamine infusion whereas, except for a mild decrease in EDVi, volumes and hence EF remained unchanged. The increase in cardiac index can thus solely be attributed to the increase in heart rate.

Load dependent indices of systolic ventricular function such as SW and dP/dt_{max} increased significantly during dobutamine infusion. The same applied to the load-independent indices E_{es} and M_w . As for diastolic function, the decrease in τ and a trend towards lower E_{ed} indicated a positive lusitropic effect of dobutamine.

3.3. RV function and LV size

Table 2 shows the mean values of haemodynamic parameters at baseline and dobutamine infusion for both groups.

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