Natural and modified history of single-ventricle physiology in adult patients†

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Abstract

OBJECTIVE: To define the evolution of the single-ventricle (SV) heart in adult patients in terms of morbidity, mortality and quality of life.

METHODS: Sixty-two patients with SV physiology and aged older than 16 years were retrospectively reviewed. Three patients (5%) were in natural history, one had received a Blalock-Taussig shunt, one a Waterstone anastomosis, one a pulmonary artery banding, three a bidirectional cavopulmonary anastomosis, eight a classic Fontan procedure and 46 a total cavopulmonary connection (TCPC). The morphology of the SV was left in 48 patients (77%), right in nine (14%) and indeterminable in five (8%). Thirty-three patients underwent magnetic resonance imaging (MRI) to assess ventricular mass (VM), ventricular systolic function, pulmonary artery branch diameter and potential thrombosis of the conduit. Cardiopulmonary exercise testing (CPTE) was carried out to evaluate exercise tolerance. The quality of life was monitored with two different specific tests, the Short Form-36 (SF-36) and the congenital heart disease-TNO/AZL adult quality of life (CHD-TAAQOL). The mean follow-up time was 8.0 ± 9.1 years.

RESULTS: Two of the three patients in natural history underwent primary TCPC. Re-interventions were necessary in seven patients (11%). Three patients (5%) died during follow-up. Five patients (8%) underwent cardiac transplantation. Protein losing enteropathy appeared in six (10%), while the arrhythmic disorder was detected in 13 patients. On the MRI, the mean end-diastolic ventricular volume was 106 ± 448 ml/m2, the mean ejection fraction (EF) was 52.3 ± 10% and VM was 56 ± 22.1 g/m2. On CPTE, the peak of oxygen uptake (peak VO2) was moderately impaired in 92% of patients, while 4% presented a severely impaired and 4% a normal peak of VO2. No correlations were found among the peak of VO2 and the quality-of-life evaluation.

CONCLUSIONS: Adult patients with SV are at high risk of reoperations and need of transplant and complications. Nevertheless, in the presence of a moderately reduced peak of VO2 and a moderate reduction in the EF detected at the MRI, the results of the evaluation of daily quality of life are incredibly high.

Keywords: Single-ventricle physiology • Fontan operation • Quality of life • Cardiopulmonary exercise test

INTRODUCTION

Patients with single-ventricle (SV) physiology reaching adult age must be considered an incoming reality in our population. Owing to the improved results of surgery, of paediatric cardiology and medical therapy, the outcome and the quality of life of these patients are continuously improving [1, 2]. The management of SV physiology includes the classic Fontan operation, and all the modifications of this surgical technique up to the total cavo-pulmonary connection in order to achieve an ideal separation between the pulmonary and systemic circulations and a more adequate arterial blood saturation [3]. Nevertheless, complications such as thromboembolic events, development of protein-losing enteropathy (PLE), arrhythmias, ventricular dysfunction and diminished quality of life need to be managed during growth [4, 5].

Increasing life expectancy and the long-term treatment of this complex cardiac anomaly influence daily life status, and adult patients are often presumed to have a diminished quality of life [5].

We describe a single-centre experience of adult patients with SV physiology with respect to the clinical outcome, cardiovascular function and quality-of-life status.

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MATERIALS AND METHODS

Patient population

The clinical and surgical histories beyond 16 years of age of patients with SV physiology was studied by a retrospective analysis of all the clinical sheets in our institution. The mean age at follow-up was 24 ± 9 years. The underlying anatomy of the univentricular connection is described in Table 1. The dominant ventricle was anatomically left in 48 patients (77%), right in nine (14%) and indeterminate in five patients (8%). Three patients (5%) were in natural history, one had received a Blalock-Taussig (BT) shunt (1.6%), one a Waterstone anastomosis (1.6%), one a pulmonary artery banding (PAB) (1.6%), two a bidirectional cavo-pulmonary anastomosis (BCPA) (3.2%), eight a classic Fontan procedure (13%) and 46 were already treated by total cavopulmonary connection (TCPC) (74%). There were 30 females and 32 males. All patients underwent clinical assessments, including physical examination, functional status, New York Heart Association functional class (NYHA) and the presence of arrhythmias. The cardiopulmonary exercise test with peak oxygen uptake was obtained to evaluate their exercise tolerance. Magnetic resonance was used to calculate the ventricular mass (VM), volume systolic function, pulmonary artery branch diameter and thrombosis of the conduit.

Problems and concerns regarding the quality of life of young adults were investigated with two different specific tests: a subjective health status questionnaire (SF-36) and a cardiac-specific questionnaire created on the experience of paediatric cardiologists and psychologists (CHD-TAAQOL). These studies assess the evaluation of quality of life as well as self-perceived health status [5–9].

Cardiopulmonary exercise testing

Cardiopulmonary exercise tests were performed to assess the maximal exercise capacity and the maximal heart rate, according to the guidelines of the American Thoracic Society [10].

Patients were placed on a cycle ergometer and continuous measurements consisted of minute ventilation (VE), oxygen consumption (VO₂), carbon dioxide output (VCO₂), heart rate, blood pressure and electrocardiography (Ergoline, Germany). Patients performed an exercise test using an incremental bicycle protocol, and the work load was increased by 10 W every 1 min in a stepwise manner, depending on the individually predicted maximum exercise capacity and in such a way that the calculated maximal effort was attained in ~10–15 min. All patients exercised to their maximum capability.

VO₂peak was determined as the largest value in the terminal phase of the test, a respiratory exchange ratio ≥ 1.09 being the criteria for terminating the test.

A 12-lead electrocardiogram and oxygen blood saturation (SaO₂) were also continuously monitored throughout the study and the cuff blood pressure was determined manually every 2 min.

The heart rate reserve was calculated as the difference between the peak and resting heart rates.

Measured cardiopulmonary exercise test parameters were compared with predicted normal values.

Calibration of the system occurred prior to every test according to the manufacturer specifications.

Cardiovascular magnetic resonance

Magnetic resonance imaging (MRI) was performed to assess the VM, volume systolic function, pulmonary artery branch diameter and the presence of thrombosis [11].

All MRI studies were performed using a commercially available 1.5 Tesla scanner (GE Medical System, Milwaukee, WI, USA) following a standard protocol for cardiac imaging, comprising of an ECG-gated black-blood fast-spin-echo sequence on an axial plane covering the whole thorax, a time resolved magnetic resonance angiography (TR-MRA) and a non-enhanced 3D TR-MRA steady-state free precession (SSFP) sequence with respiratory gating (navigator echo). Ventricular function was assessed using an ECG-gated SSFP cine MR sequence, acquired on a short-axis view as contiguous stack of cine images from the atrioventricular junction to the cardiac apex. MRI data for ventricular function were analysed using commercially available software (Advantage 4.4, GE Medical System, Milwaukee, WI, USA).

<table>
<thead>
<tr>
<th>Underlying anatomy of the univentricular connection</th>
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<tbody>
<tr>
<td>TA</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>38%</td>
</tr>
</tbody>
</table>

TA: tricuspid atresia; MA: mitral atresia; DILV: double-inlet left ventricle; DORV: double-outlet right ventricle; PA-IVS: pulmonary atresia, intact ventricular septum; Unbal AVC: unbalanced atrio-ventricular canal; HRHS: hypoplastic right heart syndrome; HLHS: hypoplastic left heart syndrome; USV: undetermined single ventricle; DOLV: double outlet left ventricle; DIRV: double inlet right ventricle.
Computed tomography angiography (CTA)

Patients excluded from the MRI study, because of claustrophobic syndrome or cardiac pacemaker implantation, were studied by CTA, using a 16-row MDCT (Somatom Sensation 16 Cardiac, Siemens, Forcheim, Germany).

Congenital heart disease-TNO/AZL adult quality of life (CHD-TAAQOL)

The CHD-TAAQOL has been developed on the basis of a cardiac-specific questionnaire (the QOL-CHD) [12] and the TAAQOL format was used. Recent studies [5, 7] confirmed that this instrument can achieve ‘potential determinants of quality of life rather than quality of life itself’ [5]. This test can be applied in patients over 16 years of age. Three hypothesized scales were considered important and relevant: ‘Symptoms’ (9 questions); ‘Impact Cardiac Surveillance’ (7 questions) and ‘Worries’ (10 questions). Scores for each scale range from 0 to 100, with higher scores indicating a better quality of life. Patients could respond by telephone interview, by auto evaluation or face to face with the interviewer.

Short form-36 (SF-36)

The SF-36 is a subjective health status questionnaire based on short-time answering (the patient requires an average of 10 min to compile it) and on precision (the test is feasible and reproducible). This is a generic instrument designed in the 1980s for use across a wide range of clinical conditions, based on 36 items representing 8 multi-item scales [5–9]. These questions are essentially referred to as follows: Physical function (PF, 10 questions), Role limitations due to physical health problems (RP, 4 questions); Bodily pain (BP, 2 questions); General health perceptions (GH, 5 questions); Vitality (VT, 4 questions); Social function (SF, 2 questions); Role limitations due to emotional health problems (RE, 3 questions) and Mental health (MH, 5 questions). One single additional question includes changing of the health status. Scores range from 0 to 100. All questions except one are referred to 4 weeks recall time. The SF-36 scores have psychometrically-based physical and mental health summary measures and a preference-based health utility index.

RESULTS

Late survival and functional status

The majority of our population (87%) had already undergone some kind of Fontan operation before the age of 16 (atrio-pulmonary connection 13%, TCPC 74%), while 8% had received other palliative operations, and 5% were in natural history. The mean follow-up since their 16th year of age was 8.0 ± 9.1 years. Three patients (5%) died during follow-up, at the ages of 36, 23 and 26 years, respectively. All of them had anatomical left ventricle. Two of them had been operated on before the age of 16, one had a classic Fontan operation (later converted in an extra-cardiac TCPC) and the other an intracardiac TCPC. Both patients were in NYHA class IV. One of them had an atrial fibrillation (AF) rhythm and required pacemaker implantation after conversion to an extracardiac TCPC. He developed a huge sepsis with thrombosis of the conduit requiring urgent conduit replacement. Both patients developed a severe PLE. The third patient underwent BPCA at the age of 31 after a Waterstone shunt. Previously, the patient had refused all surgical procedures. The patient was in NYHA class IV, with severe exercise intolerance and great reduction of arterial oxygen saturation. Clinical conditions moderately improved after surgery, however, the patient died at the age of 36 years (Fig. 1).

Five patients underwent cardiac transplantation (8%). All of them were in NYHA class IV before transplant.

Three patients (5%) were lost to follow-up 2, 3 and 1 years after enrolment in the study.

At the last follow-up, the NYHA class was described as I in 36% of patients, II in 39%, III in 21% and IV in 4%. The NYHA class and the ventricular morphology are described in Table 2.
The Kaplan–Meier estimated survival was 100, 95.8, 90.5 and 72.4%, respectively, at 5, 10, 15 and 20 years.

**Surgical procedures.** Two of the three patients in natural history (66%) underwent a first extracardiac TCPC at the age of 39 years and an intracardiac TCPC at the age of 45, respectively.

Two patients who had been already submitted to a BT shunt and Waterstone anastomosis in another institution were staged to BCPA at the age of 42 and 31. One patient with BCPA underwent the extracardiac TCPC at the age of 19 years.

Seven patients (11%) underwent unexpected reoperations. A conversion of the atrio-pulmonary Fontan to the extra cardiac TCPC was accomplished in six patients and to the intracardiac TCPC in one. The mean age at reoperation was 22 ± 4 years. The concomitant A Cox maze procedure was performed in 2/7 patients. One of them developed, 2 years after the conversion to the extra cardiac TCPC, a septic thrombosis of the conduit, which was immediately replaced. Indications for the conversion to the TCPC were advanced NYHA class in six patients, debilitating atrial arrhythmias in two patients and thrombosis of the conduit in one. Five patients (8%) underwent cardiac transplantation. The mean age at transplantation was 25 ± 7 years. Two of them had a previous TCPC and one a previous classic Fontan; they were transplanted, respectively, at the ages of 28, 28 and 29 years. One adult patient referred to our unit with PAB was transplanted at 27 years of age. One patient with previous BCPA received a cardiac transplantation at the age of 17 years.

No patient died at transplantation. Pre-transplant data including NYHA class, cardiac rhythm, EF, PLE, pulmonary vascular resistance (PVR) and VO2 are expressed in Table 3.

The Kaplan–Meier estimated freedom from cardiac transplant for all patients was 95.6, 95.6, 82.1 and 73.9%, respectively, at 5, 10, 15 and 20 years (Fig. 2a and b).

**Cardiopulmonary exercise testing.** Fifty-four patients (87%) with a univentricular physiology were enrolled in this retrospective cohort study and underwent cardiopulmonary exercise testing (CPTE). Two patients could not undergo the CPTE due to their severe intolerance to exercise. No difference was evident between patients with the TCPC and the conversion of the classic Fontan.

The VO2 peak was moderately reduced in patients with single ventricular physiology. Peak oxygen consumption averaged 25.05 ± 5.31 ml/kg/min with the predicted being 55.61 ± 13.09% (Fig. 3a). Only two patients (3.7%) had a normal peak VO2 (i.e. 80–90% predicted). The anaerobic threshold averaged 1.09 ± 0.43 ml/kg/min.

The averaged VE/VCO2 was quite high at 35.5 ± 7.7 in comparison with the control subjects and with other congenital heart diseases. The averaged VE was 53.1 ± 15.5 l/kg/min (Fig. 3b).

Table 3: Pre- and post-transplant data

<table>
<thead>
<tr>
<th>Before transplant</th>
<th>NYHA class</th>
<th>RHYTM</th>
<th>EF%</th>
<th>A-V regurgitation</th>
<th>PLE</th>
<th>PVR/m²</th>
<th>VO2 (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.G. Classic Fontan</td>
<td>IV</td>
<td>AF</td>
<td>35</td>
<td>Severe</td>
<td>Yes</td>
<td>0.7</td>
<td>15.4</td>
</tr>
<tr>
<td>A.A. Extracardiac TCPC</td>
<td>IV</td>
<td>AF</td>
<td>25</td>
<td>Severe</td>
<td>Yes</td>
<td>2.7</td>
<td>10</td>
</tr>
<tr>
<td>N.G. Pulmonary artery banding</td>
<td>IV</td>
<td>SR</td>
<td>20</td>
<td>Severe</td>
<td>No</td>
<td>6.1</td>
<td>13.8</td>
</tr>
<tr>
<td>M.M. BCPA</td>
<td>IV</td>
<td>SR</td>
<td>18</td>
<td>Moderate</td>
<td>No</td>
<td>2.1</td>
<td>12.5</td>
</tr>
<tr>
<td>A.E. Extra cardiac TCPC</td>
<td>IV</td>
<td>SR</td>
<td>20</td>
<td>Moderate</td>
<td>No</td>
<td>1.68</td>
<td>14.2</td>
</tr>
</tbody>
</table>
increase of peak $\text{O}_2$ pulse ($P = 0.01$, median increase + 16%) [13] (Fig. 4b). The arterial $\text{O}_2$ saturation before and after conversion was similar. Pre- and postoperative data of conversion are expressed in Table 4.

### Magnetic resonance imaging and computed tomography.
A ventricular dilation was evident in all patients (the mean end-diastolic value of $106 \pm 44 \text{ ml/m}^2$ with a VM of $56 \pm 22.1 \text{ g/m}^2$).

The mean ventricular EF was $52 \pm 10\%$ (range 20–70%).

No correlation was found between the peak oxygen uptake on CPTE and the EF estimated on MRI ($P = 0.2$).

### Other problems.
Protein-losing enteropathy was present in six patients (10%), two with the classic Fontan, two with an intra-cardiac tunnel and two with an extracardiac tunnel. Two patients (33%) died, and one is currently awaiting heart transplantation. In two cases, a complete resolution of PLE was achieved after the conversion of a classic atrio-pulmonary Fontan to a fenestrated extracardiac TCPC.

Arrhythmias were found in 13 patients: three were in AF (5.5%) and 10 showed the presence of ventricular ectopic beats (18.5%). All patients in this group failed to achieve the maximum rate on CPTE.
Four patients needed a pacemaker implantation, after a Fontan to TCPC conversion and Cox maze surgery in two cases, for a complete AV block in one patient and the presence of severe bradycardia in another.

One patient developed thrombosis of the extracardiac conduit, probably due to a chronic sepsis secondary to infection of the pacemaker implant site. He underwent replacement of the conduit but died of untreated sepsis.

**CONGENITAL**

**Congenital heart disease-TNO/AZL adult quality of life, Short Form-36.** All 51 patients enrolled underwent telephone interviews.

As far as SF36 is concerned, the PF, SF, RP, RE and BP scales show high results, meaning, respectively, that patients do not feel to be inhibited in their physical and social activities, do not perceive limitations in their role due to their physical and emotional state and do not feel pain.

The GH, VT and MH scales show good but a little lower results, meaning that patients perceive their health status, their vitality and mental health in a satisfactory way, but they do not feel as good as in the other domains.

The results, as a whole, could indicate that these patients do not perceive themselves to be very limited by their illness in living their lives and are carrying on as if it did not exist. However, when they are asked more specifically about their physical and mental health and vitality, they seem to express more clearly the impact of the disease on their living activities.

The CHD-TAAQOL results seem to confirm that when showing high results in the ‘symptoms’ and ‘problems’ scales, they lean more to subjective answers, while when showing lower results in the ‘Impact Cardiac Surveillance’ scale they lean more to objective answers.

Furthermore, both from the administration of questionnaire and from further conversations with patients and parents, we stated that telephone interviews may not be the best way of getting information about the disease from these patients, especially from the younger ones.

We found a correlation between the SF36 and TAAQOL scales, but the absence of correlation between the SF36 and ‘Impact Cardiac Surveillance’ scales was an unexpected finding, confirming that these patients are used to difficulties connected with their disease and perceive the frequent follow-ups as part of the activities of their daily lives. This also may confirm our hypothesis of a lean to cope with denial, that may also be encouraged by the presence of only a moderate reduction of cardiopulmonary function.

No correlations were found between the peak of VO2 and quality-of-life scales. Nevertheless, on CPTE, the VE/VCO2 slope > 41.25 appeared as a strong independent factor of a lower perception of the quality of life. One more predictive factor of a reduced perception of quality of life is chronotropic incompetence.

Among the population with a self-perception of a low quality of life (TAAQOL < 80), in 60% of them, it was associated with a cardiac rhythm disturbance, including AF, atrial flutter and bradycardia, consequently considered as a strong clinical predictor for a worse quality of life.

**DISCUSSION**

Patients with SV physiology are inevitably affected in the long-term by a high mortality and morbidity.

The surgical course for patients with underlying SV physiology is essentially represented by staged surgery, up to the Fontan operation. Patients remaining in natural history directly underwent the Fontan operation, in the presence of severe reduction in arterial blood saturation and dilatation of the SV.

The classic atrio pulmonary connection presents a high tendency towards failure in the long-term and represents the major cause of re-interventions in our population. The conversion of the atrio pulmonary connection to the extracardiac TCPC is associated with an improvement of the peak VO2 and the peak O2 pulse, as a consequence of an increased stroke volume during exercise, as previously reported [13]. Cardiac transplantation is the endpoint treatment of SV [14] physiology. We did not experience the need for replacement of the extracardiac TCPC conduit due to the somatic overgrowth of the patient, probably due to our policy of deferring the TCPC operation to later in life in order to use larger extracardiac conduits suitable for adults [3]. In only one case was conduit replacement necessary, after a septic thrombosis.

Exercise intolerance, arrhythmias, risk of thromboembolic events or severe PLE can lead to re-interventions or even to cardiac transplantation [15].

The reduction in exercise capacity is not only to be considered expression of Fontan failure, but also can be influenced by other problems such as a ventilation-perfusion mismatch, the presence of residual shunts, reduced vital capacity or deterioration of the normal heart rhythm [16-19]. We can finally speculate that all these factors can have a relevant impact on the perception of the quality of life.

MRI measurements yield precise information on the VM as well as the volume and function of the SV, especially after the Fontan operation [11, 20]. Moreover, the patency of the cavo-pulmonary conduit can be easily assessed. In our population, MRI showed the ventricular systolic function to be mostly within normal limits, despite a few cases with depressed myocardial contractility.

Signs of increasing heart failure are often silent and do not correlate with subjective perception of the health status and the quality of life. Most of the patients get used to enduring the symptoms and difficulties due to the disease, thus getting habituated to them and not considering them as problems. Moreover, since birth, they have been dependent on their parents, particularly on their mothers, for everything concerning the congenital heart disease and therefore may present difficulties in being consciously aware of it.

The perception of these patients of their quality of life is not so highly affected by the disease because denial plays an important role in coping with it. This defence mechanism might be fostered by the development of dependence relationships that allow patients to delegate their problems related to the disease, especially if they are accompanied only by a moderate reduction in their physiological activities.

Obviously, although denial is an immature defence mechanism [8, 9], it may help patients in particular phases of their lives, but its permanence over many years may require psychological therapy in order to enable them to better face problems both connected with developmental tasks and with possible disease evolution.

The evaluation of these patients calls for a complete clinical assessment, supported by specific diagnostic methods as magnetic resonance and cardiopulmonary exercise testing.
CONCLUSIONS

Adult patients with SV physiology have a high risk of mortality and morbidity, with reoperations, reduced exercise tolerance, PLE and arrhythmias as the major causes. In our experience, failure of the classic Fontan operation represented the main cause of re-interventions. Cardiac transplantation can offer patients their last chance of survival, but the number of patients requiring this endpoint is fortunately limited in our series.

Moderately reduced exercise tolerance did not prevent patients from perceiving their health as good even in cases in whom this may seem in contradiction to the data achieved from the CTPE and MR.

Bearing in mind the high severity of this pathology, we can consider the global results, in terms of mortality, morbidity and quality of life, surprisingly acceptable in adult patients.

Conflict of interest: none declared.

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