Results of staged total cavopulmonary connection for functionally univentricular hearts; comparison of intra-atrial lateral tunnel and extracardiac conduit

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Abstract

Objectives: This study aims to compare the outcome of the two co-existing modifications of staged total cavopulmonary connection (TCPC) — the intra-atrial lateral tunnel (ILT) and the extracardiac conduit (ECC). Methods: We included 209 patients after staged TCPC (102 ILT and 107 ECC), operated on between 1988 and 2008. Medical and surgical records were reviewed for (1) patient demographics and cardiac anatomy; (2) pre-Fontan procedures; (3) pre-Fontan haemodynamics and cardiac functional status; (4) operative details; (5) postoperative hospital course; (6) follow-up information on arrhythmias and thrombo-embolic events; (7) post-Fontan interventions; and (8) clinical status at last follow-up until June 2008. Results: Median follow-up duration was 4.3 years (interquartile range 1.5–7.4 years). At 6-year follow-up, freedom from Fontan failure (i.e., mortality or re-operations for Fontan failure) was 83% for the ILT and 79% for the ECC groups (p = 0.6); freedom from late re-operations (other than re-operations for Fontan failure) was 79% for the ILT and the ECC groups and freedom from arrhythmias was 83% for the ILT, and 92% for the ECC groups (p = 0.022). Multivariable Cox regression analysis identified intensive care unit stay and cardiopulmonary bypass time as risk factors for Fontan failure, but they were not strong predictors. Right ventricular morphology was identified as a risk factor for arrhythmias. The occurrence of thrombo-embolic events was low with no difference between the ILT and the ECC groups, and irrespective of the postoperative use of anticoagulant or anti-platelet aggregation therapy. At most recent follow-up, sinus rhythm was present in 70% of patients; in 23% of the patients, ventricular function was found to be moderately or severely impaired at echocardiography. Conclusions: Outcome after staged ILT- and ECC-type Fontan operations is good, with comparable freedom from late re-operations and freedom from Fontan failure at 6-year follow-up. The incidence of arrhythmias was significantly lower in the ECC group. Right ventricular morphology was identified as a risk factor for arrhythmias.

Keywords: Total cavopulmonary connection; Intra-atrial lateral tunnel; Extracardiac conduit; Survival; Arrhythmias; Re-operations

1. Introduction

The Fontan operation is a palliative procedure for patients in whom biventricular repair of their complex congenital heart defect — resulting in a functionally univentricular heart — cannot be performed. In 1988, De Leval et al. described the total cavopulmonary connection (TCPC) as a modified approach to Fontan reconstruction [1], a modification with superior hydrodynamic characteristics than the previously used atrio pulmonary connection. In this reconstruction, systemic venous return is directed to the pulmonary arterial circulation by means of a bidirectional Glenn anastomosis (BDG), connecting the superior caval vein to the pulmonary artery, and a connection from the inferior caval vein to the pulmonary artery. The latter can be done by either an intra-atrial lateral tunnel (ILT), according to the report by De Leval et al. [1], or by an extracardiac conduit (ECC) [2]. TCPC results in separation of the systemic and pulmonary venous return and in volume unloading of the systemic ventricle. Nowadays, this is performed as a staged procedure since volume unloading with a BDG prior to TCPC improves outcome and ventricular energetics after TCPC [3–5]. The BDG is usually performed in the first year of life and
completion with an ILT or ECC usually takes place in the third or fourth year of life [6,7].

Since the introduction and implementation of the TCPC in the late 1980s, morbidity and mortality have decreased significantly as compared with outcome after atrio-pulmonary connection [7,8]. Recent survival cohorts of Fontan patients have shown improved survival, but most of these studies also included patients with older Fontan types (right atrium to right ventricle conduit and atrio-pulmonary connection) [5,8,9]. It is of importance to study the outcome of Fontan patients operated on according to the current treatment strategies, and to compare the outcome of patients with an ILT and ECC. The current survival reports that include patients with a TCPC have limited patient numbers (especially for comparison of ILT and ECC), or include patients with and without staging or have a limited follow-up duration [9—12]. The objective of our study was to compare the outcome of staged ILT and staged ECC.

2. Materials and methods

2.1. Patients

We searched for patients after TCPC, operated on between January 1988 and January 2008, in the surgical databases of three tertiary referral centres for paediatric cardiac surgery and cardiology. The following patients were excluded: (1) patients who had undergone conversion of a right atrium to right ventricle conduit or atrio-pulmonary connection into a TCPC; (2) patients who did not have a preceding BDG anastomosis; and (3) patients who had undergone a Kawashima operation for functionally univentricular hearts with azygos continuation of the inferior caval vein.

2.2. Data inclusion

Medical and surgical records of all patients were reviewed for the following data: (1) patient demographics and cardiac anatomy; (2) pre-Fontan procedures; (3) pre-Fontan haemodynamics and cardiac functional status from cardiac catheterisation, echocardiography and electrocardiography reports; (4) operative details; (5) postoperative hospital course; (6) follow-up information on occurrence and treatment of arrhythmias and thromboembolic events; (7) post-Fontan interventions; and (8) clinical status at last follow-up from medical history, physical examination, echocardiography and electrocardiography reports. These data were included until June 2008.

2.3. Definitions

Early sequelae were defined as complications within 30 days after Fontan completion. All other complications were considered late. The primary endpoint was Fontan failure, defined as death, or re-operation for revision of the Fontan circulation. Fontan take-down or heart transplantation has not been performed in this cohort. Secondary endpoints were arrhythmias and late re-operations other than re-operations for Fontan failure. Arrhythmias were defined as documented bradyarrhythmias or tachyarrhythmias that required intervention.

2.4. Statistical analysis

Continuous data were tested for normality using the Kolmogorov—Smirnoff test. Data with a normal distribution are expressed as mean value ± one standard deviation (SD), whereas the median (interquartile range, 25th and 75th percentile) is shown for data with a non-normal distribution. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square tests or Fischer’s exact tests, as appropriate. A p-value < 0.05 (two-sided test) was considered to indicate statistical significance.

The incidence of the primary and secondary endpoints over time was evaluated according to the Kaplan—Meier method. Follow-up time was defined as the time from Fontan surgery to the endpoint event or the last follow-up visit. Differences in the incidence of the endpoints between the two Fontan types were evaluated by the log-rank test.

Predictors of Fontan failure or arrhythmias were explored in univariable Cox regression models. Variables with a p-value < 0.15 were entered in a stepwise multivariable Cox regression model, which was corrected for the participating centres and for the year of operation. Variables with a skewed distribution (e.g., intensive care stay and cardio-pulmonary bypass time) were entered in the model as a single term and as a quadratic term to test for possible non-linear contributions. The quadratic terms for these two variables were not significant in a multivariable model, implying a linear relationship between the risk factor and outcome. A p-value < 0.05 was required for a variable to be retained in the equation.

3. Results

3.1. Demographics and anatomy

From 1988 to 2008, 277 patients had undergone a TCPC in the three institutions. The following patients were excluded: (1) 15 patients for a previous atrio-pulmonary connection (n = 13) or right atrium to right ventricle conduit; (2) 41 patients who did not have a preceding BDG anastomosis; and (3) 12 patients for a Kawashima-type operation. In this study, 209 patients (118 men) were included. Characteristics of the study population are listed in Table 1.

Six patients were lost to follow-up. Three patients returned to their home country immediately after hospital discharge. Another three patients moved after 1.7—2.7 years of follow-up and were excluded at that time. These six patients and 26 patients who died after Fontan completion were excluded from the assessment of current clinical status. Median follow-up duration of the remaining patients was 4.3 years (1.5—7.4 years). Median age at most recent follow-up visit and follow-up duration were significantly longer in patients with an ILT (Table 2).
3.2. Surgical procedures

Before Fontan completion, 502 procedures were performed in 209 patients. Subtypes of pre-Fontan procedures are displayed in Table 3. Of note, five patients received a pacemaker before the TCPC. Two of these patients had a congenital complete atrioventricular block. The other three patients developed complete atrioventricular block or symptomatic bradycardia during the pre-Fontan period.

Median age at BDG anastomosis and the median interval between BDG and TCPC were comparable in patients with an ILT or ECC. The BDG was bilateral for persisting left superior vena cava in 19 patients. There was no difference in pre-Fontan haemodynamics and variables of cardiac function for the two subgroups (Table 3, cardiac catheterisation reports available in 97%, echocardiography reports available in 93% of patients). Between 10% and 15% of patients had moderately or severely impaired ventricular function or moderate-to-severe atrioventricular valve insufficiency on pre-Fontan echocardiography.

The first staged TCPC (ILT) in this study was performed in 1990. Before this year, staged volume unloading with a BDG was not performed. The first staged ECC in this study was performed in 1996. An ILT or an ECC was performed according to the surgeon’s preference. Age and weight at the time of Fontan completion were comparable in the two groups (Table 4). In both groups, circulatory arrest was performed in only one patient. In the ECC group, the majority of operations (76%) was performed with continuous coronary perfusion. Seventeen patients received a 16-mm Vascutek conduit, one patient had a 16-mm Goretex conduit, 33 had an 18-mm Goretex conduit and in 56 patients the Goretx conduit diameter was at least 20 mm. Fenestrations were performed on haemodynamic indications (Table 4).

In 35 patients (19 ILT and 16 ECC), 54 late procedures were performed after Fontan completion other than re-operations for Fontan failure (Table 2). The Kaplan–Meier estimates of freedom from re-operation were (Fig. 1a): (1) ILT: 1 year, 98% (SE 2%); 3 years, 92% (SE 3%); and 6 years 79% (SE 5%); (2) ECC: 1 year, 94% (SE 3%); 3 years, 82% (SE 4%); and 6 years, 79% (SE 5%) (log-rank test \( p = 0.6 \)).

3.3. Fontan failure

Thirty-day mortality was 4% (four ILT and five ECC). Late mortality occurred in 10% (13 ILT and five ECC). Twelve patients required a re-operation of the Fontan circulation (two ILT and 10 ECC). These included seven early interventions, one of whom died shortly after re-operation: creation or enlargement of a fenestration (\( n = 3 \)), shortening of the ECC for distortion (\( n = 1 \)), stenting of the superior caval vein for obstruction (\( n = 1 \)), ECC replacement and fenestration for thrombosis of the conduit (\( n = 1 \)) and extracorporeal membrane oxygenation for severe pulmonary hypertension (\( n = 1 \)). Two patients with thrombosis in the Fontan circulation and pulmonary hypertension were treated with sildenafil postoperatively. In five patients, the ECC had to be revised or

Table 1
Characteristics of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ILT (males)</th>
<th>ECC (males)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>102 (62)</td>
<td>107 (56)</td>
</tr>
<tr>
<td>Ventricular morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle (n)</td>
<td>48</td>
<td>44</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome (n)</td>
<td>15</td>
<td>29^</td>
</tr>
<tr>
<td>Left ventricle (n)</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Tricuspid atresia (n)</td>
<td>16</td>
<td>38^</td>
</tr>
<tr>
<td>Indeterminate (n)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ECC: extracardiac conduit; ILT: intra-atrial lateral tunnel. ^ Statistical significantly different from ILT.

Table 2
Follow-up details.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ILT (n = 83)</th>
<th>ECC (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at most recent follow-up visit (years)</td>
<td>10.7 (7.0–14.3)</td>
<td>7.5 (5.0–9.5)^*</td>
</tr>
<tr>
<td>Follow-up time since Fontan completion (years)</td>
<td>7.4 (4.3–10.0)</td>
<td>3.8 (1.6–5.6)^*</td>
</tr>
<tr>
<td>Medication: none (n)</td>
<td>1</td>
<td>13^</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors (n)</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Anti-arrhythmics (n)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Platelet inhibition (n)</td>
<td>11</td>
<td>64</td>
</tr>
<tr>
<td>Anticoagulants (n)</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>Rhythm status: sinus rhythm (n)</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Atrial rhythm (n)</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Moderately/severely impaired ventricular function (n)</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Moderate/severe atrioventricular valve insufficiency (n)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Moderate/severe (neo-) aortic insufficiency (n)</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: ECC: extracardiac conduit; ILT: intra-atrial lateral tunnel. ^ Statistical significantly different from ILT.
replaced during follow-up 0.3—9.5 years after Fontan completion. Four of these were 16-mm conduits, which are currently not in use. The Kaplan—Meier estimates for freedom from Fontan failure were (Fig. 1b): (1) ILT: 1 year, 86% (SE 4%); 3 years, 85% (SE 4%); and 6 years, 83% (SE 4%); and (2) ECC: 1 year, 88% (SE 3%); 3 years, 88% (SE 3%); and 6 years, 79% (SE 6%) (log-rank test $p = 0.93$). Table 5 shows the variables identified as risk factors for Fontan failure by univariable Cox regression analysis. In a multivariable model, intensive care unit stay and total cardiopulmonary bypass time were statistically significant predictors of Fontan failure; however, both hazard ratios were only minimally over 1.0.

3.4. Arrhythmias

Early postoperative arrhythmias occurred in 15 patients (12 ILT and three ECC). Six patients received a (temporary) pacemaker for bradyarrhythmias while nine patients experienced tachyarrhythmias. Late arrhythmias occurred in 16 patients (13 ILT, three ECC). New atrial tachyarrhythmias were documented in six patients, two of whom were on anti-arrhythmic medication at last follow-up. Two patients received a pacemaker. One patient had ventricular fibrillation and died. Bradaryrhythmias were diagnosed in nine patients, six of whom received a pacemaker. The Kaplan—Meier estimates of freedom from arrhythmias were (Fig. 1c): (1) ILT: 1 year, 87% (SE 4%); 3 years, 87% (SE 4%); and 6 years, 83% (SE 4%); (2) ECC, 1 year, 96% (SE 2%); 3 years, 96% (SE 2%); and 6 years, 92% (SE 4%) (log-rank test $p = 0.022$). In a multivariable model, right ventricular morphology was a predictor for arrhythmias (Table 6).

3.5. Thrombo-embolic events

Early thrombo-embolic complications occurred in 13 patients (five ILT and nine ECC), five of whom were on routine anticoagulation after TCPC. These included throm-
basis of the ECC (n = 3), or ILT (n = 1), branch pulmonary arteries (n = 2), inferior caval vein/hepatic veins (n = 2), pulmonary embolisms (n = 2) and cerebrovascular accidents (n = 3). Late thrombo-embolic events occurred in three patients (two ILT and one ECC), 0.2—10.1 years after Fontan completion: complete thrombosis of the 16-mm Vascutek ECC 4 months after Fontan operation, multiple pulmonary embolisms and veno-occlusive disease and a transient ischaemic attack. The first patient was on platelet aggregation inhibition, the latter two patients were on anticoagulation therapy. Evaluation of haemostasis did not reveal any abnormalities.

3.6. Clinical status at last follow-up

Median room air oxygen saturation was 95% (92—97%). Echocardiographic or angiographic evidence of persistent right-to-left connections was present in 29 patients: in 25 patients (21 ILT (eight after fenestrated Fontan), four ECC; p < 0.001) there was a connection through the intra-atrial baffle, and in four patients (one ILT, three ECC) there were veno-venous collaterals.

Rhythm status is displayed in Table 2 and was available in 171 patients (97%). A sinus rhythm was present in 70%; 13 (8%) patients had a pacemaker. The atrial rhythm was present in 22%, and only two patients had a junctional rhythm (1%). A summary of the medication used is displayed in Table 2. The difference in anti-platelet and anticoagulant therapies between the ILT and ECC groups is explained by the fact that two institutions are performing ECC Fontan operations nowadays and prefer platelet inhibition, at least during childhood. The third institution performs ILT Fontan operations and prefers anticoagulants as anti-thrombotic prophylaxis. One patient was on sildenafil therapy for pulmonary hypertension.

Echocardiography at the most recent follow-up was available in 158 patients (89%) (Table 2). Global ventricular function was moderately or severely reduced in 23% of patients, the majority having had an ILT. Moderate or severe
atrioventricular valve insufficiency was present in 12% of patients and moderate or severe (neo-)aortic insufficiency in 6% of patients.

4. Discussion

In this article, we describe a cohort of Fontan patients who were all operated on according to the current techniques; that is, TCPC preceded by BDG. Shortly after De Leval et al.'s publication on ILT [1], Marcelletti et al. reported on the use of ECC for completion of TCPC [2]. The latter technique was proposed for patients with complex anomalies of the atrioventricular valve and the pulmonary or systemic venous return. Advantages of the ECC are the possibility to perform the Fontan completion without aortic cross-clamping, and possible reduction of the incidence of arrhythmias compared with ILT. However, there are concerns on the incidence of thrombo-embolic complications and late re-operations. In this study, we compared the outcome between 102 patients with an ILT and 107 patients with an ECC.

4.1. Fontan failure

Thirty-day mortality was 4% in this cohort and late mortality was 10%. At 6 years of follow-up, there was no significant difference in Fontan failure between the ILT and the ECC groups (Fig. 1b). We identified two risk factors for Fontan failure with multivariable Cox regression analysis: intensive care stay and total cardiopulmonary bypass time. The hazard ratios of intensive care stay and total cardiopulmonary bypass time were only marginally over 1.0. Both variables were not strong predictors of Fontan failure in this study. Others have identified right ventricular morphology as a risk factor for early mortality [13] and Anderson et al. recently demonstrated that right ventricular morphology is associated with poorer mid-term ventricular and valvular function [14]. However, we recently reported preserved contractile reserve with low-dose dobutamine stress testing in patients with a dominant right ventricle at a median follow-up time of 8.1 years after TCPC [15].

Re-operations for Fontan failure were more frequent in the ECC group. Most of the late re-operations included replacement of conduits with a diameter of 16 mm, which are currently not in use. Excluding these patients from the analysis resulted in a non-significant comparison of re-operations between the ILT group and ECC group. Recently, Lee et al. [16] showed that even at only 3 years of follow-up, extracardiac conduit diameter decreased by about 14%, irrespective of the original conduit diameter. The ideal conduit diameter still has to be assessed at long-term follow-up.

4.2. Arrhythmias

Early and late arrhythmias occurred in 7% and 9% of patients, respectively. Freedom from arrhythmias was significantly higher in patients with an ECC, analysed up to 6 years after Fontan completion. In our study, right ventricular morphology was identified as a risk factor for arrhythmias in a multivariable model.

The incidence of late arrhythmias in our study is slightly lower than in a large cohort from the Pediatric Heart Network [17], but the North American cohort also included some patients with an atriopulmonary connection. In comparison with the atriopulmonary connection, the incidence of atrial arrhythmias is lower in patients with an ILT [5,18], but can still run up to 20% during follow-up [7,19]. In patients with an ECC, the incidence of arrhythmias has been reported up to 15%, at a follow-up duration of 15 years [20,21]. There are only a few studies comparing the incidence of arrhythmias in ILT and ECC groups [10—12]. Fiore et al. did not find any difference in arrhythmias between their ILT and ECC groups. In the study by Kumar et al., sinus node dysfunction occurred more frequently in patients with an ECC [12]. They concluded that staging with a BDG, as opposed to performing a hemi-Fontan, was a risk factor for developing sinus node dysfunction. Azakie et al. identified the ILT as a risk factor for mid-term arrhythmias (up to 6 years of follow-up) and found a higher incidence of atrial rhythm in the ILT group [11]. In our cohort, after staging with a BDG, there was a clear difference in the incidence of arrhythmias, with a low incidence of 3% in the ECC group up to 6 years after TCPC. However, in a multivariable model corrected for year of Fontan operation, the ILT was not identified as a risk factor for arrhythmias. Possibly, in our study, the evolution of operation techniques was an important factor in the incidence of arrhythmias throughout follow-up.

At the most recent follow-up, the majority of our patients was in sinus rhythm, with comparable proportions in the ILT and ECC groups, and a comparable percentage to other reports [14]. Surprisingly, more patients in the ECC group had an atrial rhythm. This difference could not be explained by differences in atrioseptectomies or staging procedures between the two groups. The above-mentioned studies do not show a superiority of one Fontan modification over the other in the incidence of arrhythmias. However, different studies use different definitions of arrhythmias and all studies have been retrospective. This emphasises the need for longer follow-up times to study the incidence of arrhythmia and preservation of sinus rhythm using uniform definitions.

4.3. Thrombo-embolic events

In theory, the ECC can be a risk factor for the development of thrombo-embolisms. In our study, as in other reports [20,21], there was no difference in the incidence of thrombo-embolic events between the ILT and ECC groups. The incidence of early events was 6%; late incidence was only 2%. This is considerably lower than earlier studies that reported incidences of up to 20% [22–24].

There is still much debate on the appropriate anti-thrombotic therapy after Fontan operation. In our study, two institutions preferred anti-platelet therapy at least during childhood, with anticoagulants in selected cases. The third institution preferred anticoagulant therapy as the standard. Until now, neither of these two options has proven to be superior to the other in the prevention of late thrombo-embolic events [23,24]. Seipelt et al. recommended the use of anticoagulants in the early follow-up, since they saw a peak incidence of thrombo-embolisms in the first post-operative year [23]. Although there were more early
thrombo-embolic complications in our study than late complications, the preventive effect of anticoagulants was not evident.

4.4. Cardiac functional status at last follow-up

A considerable proportion of patients (23%) had moderately or severely reduced ventricular function as assessed with conventional echocardiography. The majority of these patients had an ILT and a longer follow-up time than the patients with an ECC. In a recent large cohort from the Pediatric Heart Network [14], average ejection fraction was preserved even in patients over 15 years of age and 10 years after Fontan completion. However, from these data one can also calculate that 25% of patients had an ejection fraction <50% and diastolic dysfunction was present in >70% of patients. Deterioration of systolic and diastolic ventricular function is an important complication that is inherent to both the underlying cardiac anatomy and to Fontan physiology. In addition, we recently reported reduced survival at rest and during stress [15], which is an important limiting factor in this process and should be the target of therapeutic interventions for preservation of adequate ventricular function on the long term.

4.5. Study limitations

This study is limited by its retrospective nature. Operations took place from 1990 to 2008, leading to differences in peri- and postoperative care throughout this time. We corrected for this time-related bias by including year of Fontan completion in the multivariable analyses. Exclusion of patients with a Kawashima-type operation for abnormal systemic venous return in patients with heterotaxy might have influenced our outcome, since heterotaxy has been identified as a risk factor by others [9,25]. Currently, magnetic resonance imaging (MRI) is the technique of choice for prospective evaluation of the single ventricular circulation. For logistic reasons this technique was not available to all patients in this study, as has been the case in other recent cohort studies [14].

5. Conclusions

Outcome after staged ILT- and ECC-type Fontan operations is good, with comparable freedom from late re-operations and freedom from Fontan failure at 6-year follow-up. The incidence of arrhythmias was significantly lower in the ECC group. Right ventricular morphology was identified as a risk factor for arrhythmias.

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References


