Chapter 1

The effect of additional pulmonary blood flow on timing of the total cavopulmonary connection

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Abstract

Background The staged Fontan procedure is used to palliate functionally univentricular hearts. The effect of additional pulmonary blood flow combined with a bidirectional cavopulmonary shunt in these patients remains a controversial subject.

Methods This retrospective study included all 82 patients with a unilateral or bilateral bidirectional cavopulmonary shunt at our institution between April 1990 and July 2010. Patients with hypoplastic left heart syndrome were excluded. Two groups, based on the presence (n = 57) or absence (n = 25) of additional pulmonary blood flow after the bidirectional cavopulmonary shunt, were compared.

Results Patients with a bidirectional cavopulmonary shunt combined with additional pulmonary blood flow had higher arterial oxygen saturations postoperatively (86% [interquartile range, 85% to 90%] vs 82% [80% to 85%]; p = 0.001) and had a longer median interval before the total cavopulmonary connection (3.42 [2.43 to 4.89] years vs 2.90 [2.08 to 3.32] years; p = 0.06). At the total cavopulmonary connection, they were older (4.59 [3.88 to 6.49] years vs 3.94 [3.10 to 4.57] years; p = 0.03) and had a larger median body surface area (0.73 [0.65 to 0.87] m² vs 0.68 [0.59 to 0.73] m²; p = 0.04).

Conclusions Patients with a bidirectional cavopulmonary shunt and additional pulmonary blood flow have a longer interval before the total cavopulmonary connection without evident untoward effects. This may theoretically be advantageous for the pulmonary artery growth needed for a successful Fontan circulation. Furthermore, postponement of the final Fontan may ensure the insertion of a larger extracardiac conduit to avoid prosthesis-patient mismatch.
Introduction

The staged Fontan procedure has been proven to reduce death and provide early volume unloading in patients with functionally univentricular hearts [1-3]. The bidirectional cavopulmonary shunt (BCPS) combined with additional pulmonary blood flow (APBF) on track to the total cavopulmonary connection (TCPC) remains a controversial subject. Theoretical advantages of APBF may include higher oxygen saturations, increased pulmonary artery growth, and implantation of a larger extracardiac conduit at completion of the TCPC. Disadvantages may include elevated central venous pressure in the upper body, increased ventricular volume load, a negative effect on final Fontan candidacy, and increased interval morbidity [4-7]. In this study we analyzed some of the effects of APBF on the timing of the TCPC in patients with functionally univentricular hearts.

Patients and Methods

This study is a retrospective, single-center cohort study of patients with single ventricle physiology. We included all 82 patients who received a unilateral or bilateral BCPS at our institution between April 1990 and July 2010. Patients with hypoplastic left heart syndrome were excluded because they follow a set palliative protocol and are at higher risk of left pulmonary artery narrowing [8]. For each included patient, baseline, perioperative, and follow-up data were collected. Two groups of patients were created according to the presence or absence of APBF.

Initial Palliation

Initial palliation consisted of pulmonary artery banding or a modified Blalock-Taussig shunt to calibrate pulmonary flow to the desired amount and to attain an equivalent balance between the flows [9]. Other operations, such as enlargement of an atrial septal defect, were documented but not included in the analysis.

Bidirectional Cavopulmonary Shunt (BCPS)

Timing of the BCPS was not at a set age in our institution but was prompted by a combination of increasing cyanosis, the wish to decrease ventricular volume overload,
and as an inevitable step in the conviction that, ultimately, the TCPC is probably the superior method of palliation. Intraoperatively, a cardiopulmonary bypass procedure or a passive shunt was used to maintain systemic circulation while pulmonary circulation was maintained by means of the pulmonary stenosis or the Blalock-Taussig shunt in addition to natural collateral aortopulmonary flow. The BCPS consisted of an end-to-side anastomosis between the superior caval vein(s) and one or both pulmonary artery branches. The azygos vein was ligated in all cases to prevent untoward shunting from the superior to the inferior caval vein. Arterial oxygen saturations from before the BCPS and within 6 months after the BCPS were collected.

**Additional Pulmonary Blood Flow (APBF)**

The decision of preserving APBF, consisting of a naturally stenotic or banded pulmonary trunk or a modified Blalock-Taussig shunt, was made by the surgeon during the BCPS operation. Making this decision intraoperatively is necessary because arterial oxygen saturation needs to be assessed while APBF is calibrated surgically. At our institution, APBF was calibrated to improve arterial oxygen saturation without raising the superior caval vein pressure above 16 mm Hg. In general, APBF was used to increase arterial oxygen saturation from below 75% to a saturation of approximately 85%. In selected cases, the pulmonary trunk was rebanded to create a balance between arterial oxygen saturations and central venous pressures that the surgeon believed was tolerable.

**Total Cavopulmonary Connection (TCPC)**

The TCPC consisted of an end-to-side connection of the inferior caval vein to the right pulmonary artery. Lateral tunnels and extracardiac conduits have both been used, depending on the cardiac anatomy, the space available, and anticipated somatic growth. If possible, the preferred technique for TCPC completion was an extracardiac conduit because of its expected protective effect on sinus nodal rhythm. All known sources of APBF were ligated at the TCPC, leaving an unknown quantity of residual collateral aortopulmonary flow. Arterial oxygen saturations from before the TCPC and within 6 months after the TCPC were collected.
Follow-Up

Completion of a TCPC was the primary end point for follow-up. Death, contraindications for the TCPC, and maintained by means of the pulmonary stenosis or the Blalock-Taussig shunt in addition to natural collateral aortopulmonary flow. The BCPS consisted of an end-to-side anastomosis between the superior caval vein(s) and the last check-up date in case of TCPC candidacy were secondary end points (censored values). Death within 30 days of an operation was considered an early death.

Statistics

For statistical analysis, SPSS 16.0 and 18.0 software (SPSS Inc, Chicago, IL) were used. The data were shown to be nonparametric and are reported as median with interquartile range (IQR) and were analyzed using the Mann-Whitney U test. A p-value less than 0.05 was considered statistically significant. A Kaplan-Meier analysis was used to study the primary and secondary end points. Results are presented as “(APBF+ vs APBF-; p = x),” representing patients with (APBF+) and without (APBF-) APBF. Data for 3 patients (4%) were excluded from statistical analyses for the length of the BCPS-TCPC interval, and age and body size at TCPC, due to delayed parental permission for TCPC (n = 1) or TCPC contraindication (n = 2), as described in the results.

Results

Tricuspid atresia was present in 37% of patients in this study, followed by double-inlet left ventricle in 27%, and unbalanced atrioventricular septal defect in 8% (table 1). No patients were lost to follow-up.

Initial Palliation

The initial palliation consisted of a Blalock-Taussig shunt in 33 patients (40%) and pulmonary banding in 32 (39%). The remaining 17 patients (21%) had no initial palliation (figure 1). Of the patients that received a Blalock-Taussig shunt, 18 (55%) had an atretic pulmonary trunk, and the remaining 15 (45%) had an open, but congenitally stenotic, pulmonary trunk.
Figure 1 - The initial palliation preceding the bidirectional cavopulmonary shunt is shown. The total population was divided in two groups based on atresia or nonatresia of the pulmonary arterial trunk.

APC: common pulmonary artery.

Figure 2 - Various end points of the study population are shown by groups according to the absence (-) or presence (+) of additional pulmonary blood flow (APBF).

BCPS: bidirectional cavopulmonary shunt; TCPC: total cavopulmonary connection.
### BCPS and TCPC

The additional source of pulmonary flow in patients with BCPS and APBF consisted of a stenotic or banded pulmonary trunk in 51 or a Blalock-Taussig shunt in 6. Figure 2 represents the total study population divided into patients with a solitary BCPS (30%) and those with a BCPS and APBF (70%) and their subsequent end points. Of the patients with a solitary BCPS, 15 (60%) reached the primary end point (TCPC) by July 2010, whilst 40 (70%) with APBF reached the primary end point.

The median systemic oxygen saturation that played a role in the timing of the TCPC was 82% (IQR, 80% to 85%). The percentage of children who received an extra-cardiac conduit instead of a lateral tunnel at TCPC was significantly higher in patients with APBF (68% vs. 33%; p = 0.02). The size of the extracardiac conduit primarily correlated positively with body length (r = 0.54; p = 0.001). In this study, 80% of patients taller than 1.13 m and eligible for an extracardiac conduit at TCPC received a conduit of 20 mm. In the group with APBF, 2 patients (3%) were not eligible for a TCPC because 1 patient had discontinuous pulmonary arteries and the other had severe, atrioventricular septal defect valve regurgitation. Patient characteristics at BCPS and TCPC are summarized in table 2. Median follow-up after completion of the TCPC was 5.14 years (IQR, 2.78 to 9.06 years).

<table>
<thead>
<tr>
<th>Etiology of single-ventricle physiology</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid atresia</td>
<td>30 (37)</td>
</tr>
<tr>
<td>Double-inlet left ventricle</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Pulmonary valve atresia with intact ventricular septum</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Unbalanced atrioventricular septal defect</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Hypoplastic tricuspid valve</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Mitral valve atresia</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Hypoplastic mitral valve</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Ebstein-like tricuspid valve</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Double-inlet right ventricle</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>82 (100)</td>
</tr>
</tbody>
</table>

Table 1 - Preoperative patient characteristics

29
<table>
<thead>
<tr>
<th>Stage</th>
<th>Variables</th>
<th>APBF</th>
<th>No APBF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCPS</td>
<td>Age (years)</td>
<td>1.35 (0.99-2.25)</td>
<td>1.16 (1.02-1.48)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>BSA (m$^2$)</td>
<td>0.44 (0.40-0.52)</td>
<td>0.44 (0.39-0.47)</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>SaO$_2$ pre-BCPS (%)</td>
<td>80 (75-83)</td>
<td>78 (73-85)</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>SaO$_2$ post-BCPS (%)</td>
<td>86 (85-90)</td>
<td>82 (80-85)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Hospital stay$^a$ (days)</td>
<td>8 (7-11)</td>
<td>8 (7-14)</td>
<td>0.60</td>
</tr>
<tr>
<td>TCPC</td>
<td>Age (years)</td>
<td>4.59 (3.88-6.49)</td>
<td>3.94 (3.10-4.57)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>BSA (m$^2$)</td>
<td>0.73 (0.65-0.87)</td>
<td>0.68 (0.59-0.73)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>SaO$_2$ pre TCPC (%)</td>
<td>82 (80-85)</td>
<td>82 (79-86)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>SaO$_2$ post TCPC (%)</td>
<td>96 (94-98)</td>
<td>95 (91-96)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Table 2** - Characteristics of study cohort at various stages. Values are presented as median (IQR).

$^a$: Includes intensive care unit stay. APBF: additional pulmonary blood flow; BCPS: bidirectional cavopulmonary shunt; BSA: body surface area; SaO$_2$: arterial oxygen saturation; TCPC: total cavopulmonary connection.

<table>
<thead>
<tr>
<th>Surgical stage</th>
<th>Post-op</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCPS</td>
<td>&lt; 1 day</td>
<td>Intra-op MI in a PA-IVS RV-dependent coronary circulation</td>
</tr>
<tr>
<td>BCPS</td>
<td>16 days</td>
<td>Complicated pneumonia</td>
</tr>
<tr>
<td>BCPS</td>
<td>7 months</td>
<td>Complicated pneumonia</td>
</tr>
<tr>
<td>BCPS + APBF</td>
<td>2 days</td>
<td>Thrombotic Blalock-Taussig shunt</td>
</tr>
<tr>
<td>BCPS + APBF</td>
<td>4 months</td>
<td>Complicated pneumonia</td>
</tr>
<tr>
<td>BCPS + APBF</td>
<td>7 months</td>
<td>Out of hospital sudden death</td>
</tr>
<tr>
<td>BCPS + APBF</td>
<td>2 years</td>
<td>Complicated pneumonia in the setting of functional asplenia</td>
</tr>
<tr>
<td>BCPS + APBF</td>
<td>2 years</td>
<td>Increasing pulmonary resistance</td>
</tr>
<tr>
<td>TCPC$^a$</td>
<td>14 days</td>
<td>Extracardiac conduit obstruction / multiple pulmonary thrombi</td>
</tr>
<tr>
<td>TCPC$^a$</td>
<td>2 months</td>
<td>Out of hospital sudden death</td>
</tr>
</tbody>
</table>

**Table 3** - Details of mortality in the study cohort.

APBF: additional pulmonary blood flow; BCPS: bidirectional cavopulmonary shunt; MI: myocardial infarction; PA-IVS: pulmonary atresia with intact ventricular septum; RV: right ventricular; TCPC: total cavopulmonary connection.

$^a$: Following BCPS + APBF
Pre-TCPC Interval

The median (IQR) interval before the TCPC was longer in patients with APBF than in patients without APBF (3.42 [2.44 to 4.89] years vs 2.90 [2.08 to 3.32] years, p = 0.06). Figure 3 illustrates the distribution of the interval lengths in patients with and without APBF in an inverted Kaplan-Meier survival curve (p = 0.002). No pulmonary arterio-venous fistulas were evident during this interval.

Figure 3 - Inverted Kaplan-Meier survival curve illustrating the interval from the bidirectional cavopulmonary shunt (BCPS) to the total cavopulmonary connection (TCPC) and the effect of additional pulmonary blood flow; p = 0.002.

Mortality

In this study, APBF had no effect on death after BCPS (9% vs 12%, p = 0.65).

Of the 55 patients who received a TCPC, 2 (4%) died. Both patients had APBF before the conversion to a TCPC and died within 2 months of the TCPC. One patient died of sudden death outside the hospital, and the other died of TCPC conduit obstruction or pulmonary embolisms. No parental permission was given to perform autopsy in either patient. The causes of death in this study are summarized in table 3.
Comment

The major finding in this retrospective study is that APBF is associated with a longer interval before the TCPC was indicated and performed. Postponement of the TCPC may allow the child to grow and the pulmonary arteries to develop before conversion to the final Fontan. As described in the literature, theoretic advantages of APBF may include higher oxygen saturations. In concurrence, we found that our patients with APBF had initial higher arterial oxygen saturations after a BCPS than patients with a lone BCPS. This may have contributed to the longer interval as the TCPC is prompted by clinical symptoms and arterial oxygen saturations. The arterial oxygen saturations just before the TCPC, one of the factors on which the decision to operate was made, were similar in the two groups.

We predominantly use an extracardiac conduit for the TCPC because of the expected protective effect on sinus nodal rhythm. However, as seen in all patients with congenital heart disease needing cardiovascular prosthetic materials at a young age, these patients face an increased risk of prosthesis-patient mismatch when they grow into adulthood. By allowing patients to grow in anticipation of the final Fontan, we believe a larger extracardiac conduit may be inserted at the TCPC. Ideally, one should be able to predict the exact size of the extracardiac conduit that will sustain future (adult) full-grown Fontan hemodynamics. However, data on cardiovascular dimensions in congenital heart disease are very scarce, particularly on caval veins.

In 1962 Ettinger and Steinberg [10] published that patients with congenital heart disease had a larger caliber inferior vena cava at the age of 15 years compared with healthy individuals. Alexi-Meskishvili and colleagues [11] suggest, unsubstantiated, that implantation of extracardiac conduits that oversize the diameter of the inferior caval vein by less than 20% is preferred. They also found that the actual diameter of the inferior vena cava in patients undergoing a TCPC varied widely and correlated only weakly with age, weight, height, and body surface area. Sluysmans and Colan [12] more recently investigated cardiovascular allometric relationships in children but, unfortunately, did not investigate caval vein diameters. Steinberg and colleagues [13] did find a relationship between inferior caval diameter and body size in healthy children. Of note, adult body size can vary greatly among different ethnicities. For example, Dutch men and women reach an average height of 184 and 170 cm, respectively, whereas Indonesian men and women have an average height of 158 and 147 cm,
respectively. Using the average Dutch measurements, this would mean inferior vena cava diameters of 29 and 27 mm, respectively, extrapolating the Steinberg formula [12], whereas in Indonesia, this would result in 25 and 23 mm, respectively. We hypothesize that because patients with a Fontan circulation cannot increase their cardiac output as much as normal heart can, the inferior caval vein in univentricular hearts may suffice with a smaller maximum diameter compared with healthy individuals. Furthermore, just as in normal caval veins, the polytetrafluoroethylene graft can be flattened by the balance between intravascular and extravascular pressures varying (amongst other factors) with the respiratory cycle and the position of the body. The actual cross-sectional area of the conduit may therefore be smaller than the maximal cross-sectional area calculated using the diameter of the conduit.

How the cross-sectional area of a (large) conduit changes during growth has not been reported. Many surgeons maintain that 16 mm is adequate, we tend to use 20 mm at minimum, if possible, while a 24-mm polytetrafluoroethylene vascular prosthesis is the largest available. In our cohort, 80% of patients taller than 1.13 m received a 20-mm conduit, which may last into adulthood. Ocello and colleagues [14] found that a body weight of at least 15 kg allowed the insertion of a 20- to 22-mm conduit, which is the same size often used in adults.

A disadvantage of inserting a large, adult-sized conduit into a very young patient is that the larger diameter graft has to be plied to be anastomosed onto the smaller diameter pulmonary artery and inferior vena cava by nonabsorbable suture material. This anastomosis will not grow with the patient and may become a flow-restricting factor in the Fontan circulation in adult life. Because our follow-up is relatively short, we do not know which proportion of patients may be spared from untimely Fontan failure and subsequent reoperation due to gradual prosthesis-patient mismatch of the conduit. In the future, one could use magnetic resonance imaging to measure the cross-sectional areas of the caval veins, the anastomoses, or the conduit, as well as blood flow over these vessels, to quantify the flow volumes within a Fontan circulation [15].

The use of body surface area to predict cardiovascular dimensions may need to be revised. The various formulas for body surface area were never primarily designed to be a reference value for cardiovascular sizes but were for various physiologic processes; thus, one could question their validity for this purpose. Many surgeons use
body weight as an indicator for body size; however, with the current obesity epidemic, this is questionable, particularly because cardiovascular structures are not reported to grow with increasing body mass index. Body height may be a better predictor for adult cardiovascular dimensions, omitting the influence of excessive weight gain, but more research is needed.

Another theoretic advantage of APBF described in the literature is increased pulmonary artery growth. Yoshida and colleagues [16] demonstrated that APBF has a positive effect on pulmonary artery growth. They found a decrease in the Nakata index in patients without APBF, whereas this index remained normal with APBF. The same was reported by Gray and colleagues [6] in 2007. Pulmonary artery growth diminishes after the Fontan completion [17]. Because smaller pulmonary artery diameters correlate to more energy loss within the TCPC [18], one should aspire to the promotion of pulmonary artery growth before the TCPC. In this retrospective study, measurements on pulmonary artery dimensions throughout the stages of the Fontan procedure were not available systematically.

Proponents of the “ticking clock theory” maintain that the Fontan palliation has a limited life span in itself. One could therefore argue that (even further) postponement of the TCPC allows for postponement of the failing Fontan. This situation is complicated by the problem that attrition of these patients is slow, so that meaningful comparisons can only be made with a follow-up of 2 to 3 decades.

Described disadvantages of APBF include elevated central venous pressure in the upper body and increased ventricular volume load. At our institution, the APBF was calibrated to a maximum mean pressure of 14 to 16 mmHg in the superior caval vein. Undeniably, APBF combined with a BCPS will increase the ventricular preload. However, we believe that by limiting APBF, the increase in preload is less significant than some suggest. Before the BCPS, some form of antegrade pulmonary blood flow is promoted by a (banded) pulmonary trunk or a systemic-to-pulmonary artery shunt also to support superior caval vein(s) and pulmonary artery growth [19]. This, however, causes volume overloading of the systemic ventricle and may cause dilation and hypertrophy. By creating the BCPS, the superior caval venous flow bypasses the functional ventricle, and the overall volume load on the overloaded ventricle will be reduced to “normal.” If a calibrated amount of APBF is preserved at BCPS, that flow will represent the additional volume load on the systemic ventricle, not taking any
addtional aortopulmonary collateral flow into account.

Because these single functional ventricles are larger at birth than the systemic ventricle in a normal heart, a “normal” volume load after BCPS may well be too small to produce a normal stroke volume according to the Frank-Starling mechanism. The ideal volume load, acceptable for the ventricle in this setting and enabling somatic growth such that an adequately sized extracardiac conduit can be inserted, still needs to be determined [12]. Owing to the retrospective nature of this study, no measurements were available on central venous pressures after the operations or on the actual preload of the functional ventricle during the stages of the Fontan circulation.

Other reported theoretic disadvantages of APBF are the negative effect on final Fontan candidacy and increased interval morbidity. In our cohort, we found no significant direct effect of APBF on mortality after the BCPS. This is in contrast to Mainwaring and colleagues [20], who found that APBF had a negative effect on survival in a rather heterogeneous group of patients. A clear survival advantage has not been reported. APBF had no effect on TCPC candidacy in our cohort. In retrospect, APBF allowed for a later timing of the TCPC, which resulted in the patients being older at this stage. We found no correlation between the age at volume unloading at TCPC and death, which concurs with Pace Napoleone and colleagues [21]. The mortality rate after the TCPC in our cohort is yet to be determined because more follow-up time is needed.

An essential element in our protocol is that the timing of the TCPC depends on the patient’s oxygen saturation or exercise capacity, or both. This strategy contrasts with other studies that use a set age to complete the various stages of the Fontan circulation [3, 4, 9]. This study was limited by its relatively small cohort of 82 patients, retrospective nature, and thus, limited data, and by the heterogeneity of the patients with congenital disease. The follow-up time after completion of the TCPC was limited. Despite the less than perfect method used in calibrating APBF in all but the last patients in this study, no lasting untoward effects could be attributed to APBF. To improve the intraoperative calibration of APBF, a theoretic background has been devised following this study that quantifies the multiple sources of pulmonary blood flow in the setting of BCPS [22].

In conclusion, although results of Fontan completion have improved in recent decades, conflicting evidence still complicates the palliative protocol for these patients [23]. We found that a bidirectional cavopulmonary shunt, combined with a limited amount of additional pulmonary blood flow, contributes to a longer interval between the bidirectional cavopulmonary shunt and the total cavopulmonary connection, with
no evident untoward effects. The increase in interval length may, in theory, facilitate the pulmonary artery growth needed for successful Fontan circulation. In addition, the longer interval may ensure the implantation of a larger (adult) extracardiac conduit. This may prevent prosthesis-patient mismatch in the growing child. We therefore suggest that the preservation of a calibrated amount of additional pulmonary blood flow combined with a bidirectional cavopulmonary shunt can be beneficial. However, further research is needed to confirm these possible advantages.
References


