Performance of Cavopulmonary Palliation at Elevated Altitude
Midterm Outcomes and Risk Factors for Failure

Sunil P. Malhotra, MD; D. Dunbar Ivy, MD; Max B. Mitchell, MD; David N. Campbell, MD; Marshall L. Dines, BA; Shelley Miyamoto, MD; Joseph Kay, MD; David R. Clarke, MD; Francois Lacour-Gayet, MD

Background—Outcomes of patients undergoing cavopulmonary palliation for single ventricle physiology may be impacted by living at altitude, as the passive pulmonary circulation is dependent on the resistance of the pulmonary vascular bed. The objective of this study is to identify risk factors for failure of cavopulmonary palliation at elevated altitude.

Methods and Results—Between January 1995 and March 2007, 122 consecutive patients living at a mean altitude of 1600 m (range 305 to 2570) underwent a bidirectional Glenn (BDG). There was one in-hospital mortality and 7 late deaths. 52 have proceeded to the Fontan procedure. Survival after BDG was 92.4% at 5 years. Freedom from palliation failure, defined as death, transplant, BDG/Fontan takedown, or revision was 81% at 5 years. At a mean follow-up of 39.8 months, 90 patients (75%) were in New York Heart Association class I. Patients with failing cavopulmonary circulation had higher pre-BDG pulmonary artery pressure (PAP) (18.3±6.1 mm Hg versus 14.8±5.1 mm Hg, P=0.016) and higher pre-BDG transpulmonary gradient (TPG) (11.2±6.2 mm Hg versus 7.7±4.3 mm Hg, P=0.014). Post-BDG, patients with palliation failure had increased PAP (15.0±5.7 mm Hg versus 10.8±2.8 mm Hg, P=0.008) and indexed pulmonary vascular resistance (PVRI) (2.43±1.0 Wood U·m² versus 1.52±0.9 Wood U·m², P=0.007).

Conclusions—The majority of patients at moderate altitude have favorable outcomes after BDG or Fontan palliation. Risk factors for palliation failure at elevated altitude include PAP >15 mm Hg, TPG >8 mm Hg, and PVRI >2.5 Wood U·m². (Circulation. 2008;118[suppl 1]:S177–S181.)

Key Words: Fontan procedure ■ single ventricle ■ altitude

The surgical management of cardiac lesions resulting in a functional single ventricle has evolved into a staged pathway that eliminates the need for a subpulmonary ventricle. The bidirectional Glenn (BDG) and Fontan procedures serve to effectively route the systemic venous return into the pulmonary circulation in a passive fashion. The introduction of the Fontan procedure for palliation of tricuspid atresia in 1971 represented a spectacular advance in the management of that lesion, and has been subsequently modified to improve the prognosis for all forms of univentricular physiology.1–4

Selection criteria for optimal outcome after the Fontan operation were initially outlined by Choussat et al.5 Recent data demonstrate that a number of the original criteria have been eliminated as risks in the current era, however elevated mean pulmonary arterial pressure (PAP), elevated pulmonary vascular resistance (PVR), atrioventricular valve insufficiency, and impaired ventricular function remain risk factors for palliation failure.6–8

Fontan circulation is characterized by increased impedance in the pulmonary circulation from the loss of the RV energy source to maintain patency of the distal pulmonary bed. Accordingly, energy efficiency in the Fontan circuit is dependent on low vascular resistance. Altitude may impact outcomes of cavopulmonary palliation by elevating baseline PAP and PVR attributable to pulmonary vasoconstriction and alveolar hypoxia. This study reviews the outcomes of cavopulmonary palliation for single ventricle patients living at elevated altitude to identify risk factors for palliation failure in these patients.

Methods

Patients
All patients who underwent a bidirectional Glenn for treatment of single ventricle physiology at Children’s Hospital, Denver between January 1995 and March 2007 were included in this study. While the modified Fontan procedure results in corrected physiology, the presence of a fenestration incompletely separates the pulmonary and systemic circulations. Accordingly, for the purpose of this study, both the bidirectional Glenn and Fontan procedures are considered palliative operations. A retrospective review of patient records was

From the Department of Cardiothoracic Surgery (S.P.M.), Stanford University, Calif; The Children’s Hospital Heart Institute (D.D.I., M.B.M., D.N.C., S.M., J.K., D.R.C., F.L.-G.), Children’s Hospital, Denver, Colo; and the University of Colorado at Denver Health Sciences Center (M.L.D.).
Correspondence to Sunil P. Malhotra, 300 Pasteur Drive, Falk CVRB, Department of Cardiothoracic Surgery, Stanford University, Stanford, CA 94305.
E-mail spmalhotramd@yahoo.com
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performed in accordance with a research protocol accepted by the Colorado Multi-Institutional Review Board. Because of the retrospective nature of the study, individual patient consent was waived. 122 patients were identified for this study. The median age at BDG was 6.6 months (range 1.4 months to 6.1 years). Prior palliative procedures were performed in 89 patients (73%). These are outlined in Table 1. The remaining 33 patients underwent primary BDG.

Surgical Techniques

Bidirectional Glenn was performed using a median sternotomy and conventional cardiopulmonary bypass techniques. The superior vena cava was transected at the level of the right pulmonary artery (PA) and anastomosed to the superior border of the right pulmonary artery using continuous 7-0 polypropylene suture. As a routine, the main pulmonary artery was ligated at the time of BDG.

The Fontan operation was performed using cardiopulmonary bypass at normothermia. The majority of patients (46/52) underwent an extracardiac Fontan using an 18- or 20-mm ePTFE graft anastomosed to the undersurface of the MPA, offset to the left of the BDG. For patients who underwent a fenestration, a 4- to 5-mm fenestration was created between the Fontan conduit and the common atrial free wall. The remaining 6 patients underwent the lateral tunnel modification of the Fontan operation. A PTFE patch was fashioned in the common atrium to baffle the IVC return to the MPA. Additional patch enlargements of the branch pulmonary arteries were performed when needed.

Diagnosis

Specific cardiac diagnoses are summarized in Figure 1. The functional ventricle was the morphological left ventricle in 90 patients (74%) and the morphological right ventricle in 32 patients (26%).

Altitude

The altitude was recorded at the patient’s place of residence at time of BDG. Mean altitude was 1600±309 m (range, 310 to 2580 m). The altitude distribution is displayed in Figure 2. Surgical procedures were performed at an altitude of 1604 m at Children’s Hospital, Denver.

Outcome End Points

Palliation failure (PF) was defined as death, BDG/Fontan takedown, need for cardiac transplantation, or Fontan revision. The marginal (MG) cohort was characterized as patients who demonstrated failure to thrive because of recurrent pleural effusions, persistent hypoxemia, multiple hospital admissions, or hemodynamic contraindications to proceed to Fontan completion.

Hemodynamic Assessment

Cardiac catheterization was performed to determine patient eligibility for cavopulmonary palliation by measurement of pulmonary arterial pressure (PAP), indexed pulmonary vascular resistance (PVRI), ventricular end-diastolic pressure (VEDP), transpulmonary gradient (TPG), atrioventricular valve function, and adequacy of pulmonary arterial anatomy. Catheterization data reported are those under baseline conditions.

Functional assessment of exercise tolerance was based on guidelines for New York Heart Association (NYHA) classification. Follow-up information was obtained from the most recent patient assessment by the pediatric cardiologist or referring pediatrician at a mean period of 3.4 years (range, 3 months to 10.7 years). Follow-up was complete in 97% of patients, with 4 of 122 patients lost to follow-up.

Data Analysis

Statistical analysis was performed with Prism version 5.0 (Graphpad Inc). Continuous data are described as median with ranges or mean with standard deviation and analyzed by the 2-tailed Student t test. Survival and freedom from reoperation was determined by Kaplan–Meier methodology, and statistical differences were analyzed using the log-rank test. Probability values less than 0.05 were considered statistically significant.

Statement of Responsibility

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Outcomes After BDG

Longitudinal outcomes of all patients are outlined in Figure 3. There was one operative death after BDG for hospital mortality of 0.8%. Survival after BDG at 1 and 5 years was 99.2% and 92.9%, respectively. At follow-up, 90 patients (73%) with successful palliations were in NYHA functional class I. As
shown in Table 2, presence of a functional single right ventricle had no demonstrable effect on outcome \((P=0.70)\).

To date, 52 patients have progressed to Fontan palliation \((43\%)\). The median age at time of Fontan was 3.1 years. There have been no operative deaths after the Fontan operation. The majority of patients underwent an extracardiac Fontan \((46/52, 89\%)\). The remaining 6 patients underwent the lateral tunnel Fontan. A fenestration was performed in 34 of 52 Fontan patients \((65\%)\). 13 patients have since undergone transcatheter fenestration closure. Lack of fenestration was associated with marginal status \((P=0.03; \text{Figure 4})\).

Palliation failure occurred in 16 patients \((13.1\%)\), 12 prior to Fontan operation. Freedom from palliation failure at 1, 5, and 8 years was 95.4\%, 82.0\%, and 70.1\%, respectively \((\text{Figure 5})\).

Cardiac transplantation was required in 11 patients, 8 after BDG and 3 after failed Fontan. Of the 7 late deaths, 5 were attributable to complications associated with chronic rejection after transplantation.

Hospital Outcomes

After BDG, the median length of stay was 6 days and median chest tube drainage was 3 days. After the Fontan operation, median hospital stay was 9 days and the median duration of chest tube drainage was 6 days.

Major complications are summarized in Table 3. The most common complications were need for pleuradesis for recurrent effusions and the development of clinically significant pulmonary arteriovenous malformations (PAVMs), each with an incidence of 7.5\%. No patients developed protein-losing enteropathy.

<table>
<thead>
<tr>
<th>Table 2. Outcomes by Morphological Ventricle</th>
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<tbody>
<tr>
<td>LV</td>
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<tr>
<td>Overall</td>
</tr>
<tr>
<td>NYHA I</td>
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<tr>
<td>Marginal</td>
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<tr>
<td>Palliation failure</td>
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</table>

Six patients moved to sea level because of clinical deterioration. Three moved after BDG because of progressive cyanosis. Of the 3 that moved after Fontan, 1 had a severe form of plastic bronchitis that failed to improve at sea level. One other patient was started on sildenafil and has returned to 2200 m and remains asymptomatic.

Pre-BDG Cardiac Catheterization Data

Cardiac catheterization data before BDG were available in 116 patients \((95\%)\). These data are summarized in Table 4. Pre-BDG mean PAP, PVRI, TPG, and VEDP were elevated in the PF and MG cohorts. The increased baseline PAP and TPG in the PF group was statistically significant. Patients whose pre-BDG mPAP was less than 15 mm Hg \((P=0.02)\) and TPG less than 8 mm Hg \((P=0.014)\) had higher freedom from palliation failure \((\text{Figure 6})\).

Post-BDG Cardiac Catheterization Data

Cardiac catheterization was performed on 76 patients after BDG, either in preparation for the Fontan operation or because of a change in clinical status. These data are summarized in Table 5. Risk factors for palliation failure at pre-Fontan cardiac catheterization were mPAP, PVRI, VEDP. Pre-Fontan mPAP greater than 15 mm Hg \((P=0.003)\)
and VEDP less than 8 mm Hg ($P=0.009$) were predictive of increased risk of palliation failure.

**Effect of Altitude on Outcome**

As displayed in Figure 7, patients who failed cavopulmonary palliation lived at higher mean altitude than those who were asymptomatic at follow-up (1706±270 m versus 1579±313 m, $P=0.05$). The marginal cohort lived at slightly elevated altitude and this was not statistically significant (1598±303 m).

**Discussion**

Intuitively, cavopulmonary palliation of single ventricle physiology should be less effective at elevated altitudes. The Fontan circuit is already compromised by the loss of the energy generated by the right ventricle to maintain patency of the distal pulmonary bed in diastole. The combination of increased PVR and decreased oxygen tension at altitude will only further negatively impact the Fontan circulation.

Scheurer and colleagues recently evaluated outcomes after BDG from a sea level center during the same time period as this study, in which freedom from death or transplantation was 85% at 5 years. As expected, the median prebidirectional Glenn values at that sea level center for mPAP (13.3 mm Hg) and PVRI (1.8 U·m$^{-2}$) were lower than the patients at altitude in this study. Although meaningful comparisons cannot be made without access to raw data, the trends in these two studies would suggest similar results.

Survival in this series was certainly impacted by need for transplantation. Late mortality after transplantation was 45%. The majority of these deaths (80%) were in patients transplanted after failed BDG. Mitchell and colleagues have previously reported a 5-year graft survival of 82% after transplantation in patients with failing Fontan circulations at this institution. The comparatively poor outcome for transplantation after BDG may reflect either enhanced immune surveillance or more severe pulmonary vascular disease leading to poor graft survival in that patient subset.

The patients in the marginal category are constantly testing the limits of single ventricle palliation. While not overt failures of cavopulmonary circulation, they have chronic cardiopulmonary issues, including persistent cyanosis, recurring effusions, and respiratory tract infections. This analysis did not reveal any statistically significant differences in pre-Glenn or pre-Fontan catheterization data between this cohort and well functioning patients. However, fenestration at the time of Fontan operation significantly reduced marginal outcomes after Fontan. Day and colleagues noted a trend toward increased survival at altitude in fenestrated patients with mPAP >15 mm Hg. As a

<table>
<thead>
<tr>
<th>Table 3. Major Complications After Cavopulmonary Palliation</th>
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<tbody>
<tr>
<td>Complication</td>
</tr>
<tr>
<td>Pleuradesis for effusions or chylothorax</td>
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<tr>
<td>PAVM</td>
</tr>
<tr>
<td>Diaphragm plication</td>
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<tr>
<td>Moved to sea level</td>
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<tr>
<td>PPM</td>
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<tr>
<td>Plastic bronchitis</td>
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<td>Stroke</td>
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Table 4. Pre-Glenn Cardiac Catheterization Data

<table>
<thead>
<tr>
<th>Overall</th>
<th>NYHA I</th>
<th>Failed</th>
<th>Marginal</th>
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</thead>
<tbody>
<tr>
<td>PAP</td>
<td>15.4±5.3</td>
<td>14.9±5.1</td>
<td>18.3±6.1</td>
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<td></td>
<td>P=0.016</td>
<td>P=NS</td>
<td>P=0.08</td>
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<tr>
<td>PVRI</td>
<td>2.38±1.8</td>
<td>2.23±1.7</td>
<td>3.04±1.9</td>
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<tr>
<td></td>
<td>P=0.08</td>
<td>P=NS</td>
<td>P=0.08</td>
</tr>
<tr>
<td>TPG</td>
<td>8.1±4.4</td>
<td>7.7±4.3</td>
<td>11.2±6.2</td>
</tr>
<tr>
<td></td>
<td>P=0.015</td>
<td>P=0.07</td>
<td>P=0.015</td>
</tr>
<tr>
<td>VEDP</td>
<td>7.2±3.1</td>
<td>7.1±3.1</td>
<td>8.1±4.1</td>
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<td></td>
<td>P=NS</td>
<td>P=NS</td>
<td>P=NS</td>
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Significant differences are italicized.
Table 5. Pre-Fontan Cardiac Catheterization Data

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>NYHA I</th>
<th>Failed</th>
<th>Marginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP</td>
<td>11.9±4.1</td>
<td>10.8±2.8</td>
<td>15.0±5.6</td>
<td>11.9±5.0</td>
</tr>
<tr>
<td></td>
<td>P=0.008</td>
<td>P=NS</td>
<td>P=0.008</td>
<td>P=NS</td>
</tr>
<tr>
<td>PVRI</td>
<td>1.95±1.42</td>
<td>1.53±0.91</td>
<td>2.43±1.01</td>
<td>2.22±1.35</td>
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<tr>
<td></td>
<td>P=0.007</td>
<td>P=0.10</td>
<td>P=0.007</td>
<td>P=0.10</td>
</tr>
<tr>
<td>TPG</td>
<td>5.2±2.1</td>
<td>5.0±1.9</td>
<td>5.5±2.6</td>
<td>5.7±3.7</td>
</tr>
<tr>
<td></td>
<td>P=NS</td>
<td>P=NS</td>
<td>P=NS</td>
<td>P=NS</td>
</tr>
<tr>
<td>VEDP</td>
<td>8.8±5.3</td>
<td>7.3±2.6</td>
<td>12.1±5.6</td>
<td>7.7±3.1</td>
</tr>
<tr>
<td></td>
<td>P=0.006</td>
<td>P=NS</td>
<td>P=0.006</td>
<td>P=NS</td>
</tr>
</tbody>
</table>

Significant differences are italicized.

rule, all Fontan operations during the last 5 years of this study have been fenestrated.

This study was limited by the retrospective nature of the analysis. Prospectively obtained exercise data would certainly provide more complete functional assessment of this patient population. Moreover, a direct comparison with a matched population of single ventricle patients from a sea level center will be able to better assess the impact of altitude on cavopulmonary palliation.

The results from this study suggest that midterm outcomes of cavopulmonary palliation are comparable to those at sea level. At a mean altitude of 1600 m, the average pre-Fontan pulmonary arterial pressure was 15.4 mm Hg and indexed pulmonary vascular resistance was 2.4 U·m². Despite those elevated values for this patient cohort, a substantial proportion of patients enjoyed favorable outcomes after cavopulmonary palliation, with a 5-year freedom from palliation failure of 82%. Presumably, hemodynamic risk profiles identified in this study can guide future patient selection to further improve outcomes of single ventricle palliation at altitude.

Disclosures

None.

References

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