Long-Term Mortality After the Fontan Operation: Twenty Years of Experience at a Single Center

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Disclosures

• Funding Sources: None

• Conflicts: None

• Off-label Use: None
Background

• Since the advent of the Fontan operation in 1971, peri-operative mortality has decreased from 35-40%, to 2-3%  (Khairy, Circulation 2008)

• Existing studies of long-term outcomes have limitations
  • Predominance of atrio-pulmonary Fontans  (Khairy, Circulation 2008)
  • Few patients with HLHS  (d’Udekem, Circulation 2014)
  • Limited follow-up time  (Hirsch, Ann Surg 2008)
Objectives

1. Describe long-term survival in a modern cohort of Fontan patients

2. Identify risk factors associated with early and late post-Fontan mortality
Study Design & Methods

• Single center retrospective review of all patients undergoing 1st Fontan at CHOP between 1992 and 2009

• Baseline demographic, clinical, and surgical variables were abstracted

• **Primary outcome:** Mortality on/before 12/31/12
  • For patients lost to follow-up, vital status was ascertained using the National Death Index

• Transplant status not included in this analysis
## Baseline Covariates

<table>
<thead>
<tr>
<th>Demographics &amp; Anatomy</th>
<th>Pre-Operative &amp; Surgical</th>
<th>Post-Operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Pre-op AV valve regurgitation</td>
<td>Ventilator time</td>
</tr>
<tr>
<td>Age/weight at Fontan</td>
<td>Pre-op hemodynamics:</td>
<td>Length of ICU stay</td>
</tr>
<tr>
<td>Age at Stage 2</td>
<td>PA pressure</td>
<td>Length of admission</td>
</tr>
<tr>
<td>Type of Stage 2</td>
<td>End diastolic pressure</td>
<td>Pleural drainage time</td>
</tr>
<tr>
<td>Ventricular morphology</td>
<td>Fontan type</td>
<td></td>
</tr>
<tr>
<td>Common AV valve</td>
<td>Fenestration</td>
<td></td>
</tr>
<tr>
<td>Heterotaxy</td>
<td>Bypass parameters:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPB time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cross-clamp time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DHCA time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Modified ultrafiltration</td>
<td></td>
</tr>
</tbody>
</table>

- **Pre-op AV valve regurgitation**
- **Pre-op hemodynamics:**
  - PA pressure
  - End diastolic pressure
- **Fontan type**
- **Fenestration**
- **Bypass parameters:**
  - CPB time
  - Cross-clamp time
  - DHCA time
  - Modified ultrafiltration
Statistical Analysis

• Kaplan-Meier curves to describe overall survival

• Multivariate regression to identify risk factors for mortality
  • Candidate covariates: univariate p value < 0.2 and data in > 90% of subjects
  • Only 80% of subjects had a pre-Fontan catheterization, subset analyses were used to incorporate hemodynamic data

• Early (1-year) and late mortality analyzed separately
  • Logistic regression model for 1-year mortality
  • Cox regression model for late mortality – conditional on survival to 1 year.
Cohort Characteristics

- n = 773 total patients
- Median age at Fontan 2.3 yrs
- Median weight at Fontan 12 kg
- 97% had staged palliation
- HLHS in 49%
- Common AV valve in 12%

Ventricular Morphology

- Right 69%
- Left 30%
- Both 1%
Surgical Characteristics

90% Fenestrated

1992-1996
1997-2002
2003-2009

LT
EC

53%
47%

216
117
76
79
275
Results

- Vital status as of 12/31/2012 is known for 99.2% of patients
- 7781 patient-years of follow up
- Median follow-up of 9.2 years
- 25% of patients with f/u > 15 years
- 79 deaths during study period
- 37 deaths within 1 year after Fontan
Overall Survival

Years Post-Fontan

0 1 5 10 15 20

773 581 364 197 34 0 5 10 15 20

95% 92% 88% 79%
Overall Survival – By Era

*P < 0.001
Late Survival
(conditional on survival to 1 year)

P = NS
Risk Factors for 1-Year Mortality

Multivariate logistic regression:

<table>
<thead>
<tr>
<th>Variable (n=746)</th>
<th>Odds Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural drainage &gt; 14 days</td>
<td>7.1 (3.4 – 14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fontan before 1997</td>
<td>4.5 (2.1 – 9.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cross-clamp time (per 10 min)</td>
<td>1.3 (1.02 – 1.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Not significant: Age/weight at Fontan, ventricular morphology/HLHS, AV valve morphology, Fontan type
## Risk Factors for 1-Year Mortality

Multivariate logistic regression, subset analysis:

<table>
<thead>
<tr>
<th>Variable (n=603)</th>
<th>Odds Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Fontan PA pressure &gt; 15 mm Hg</td>
<td>6.8 (2.9 – 16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural drainage &gt; 14 days</td>
<td>6.1 (2.6 – 14.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fontan before 1997</td>
<td>4.1 (1.7 – 9.8)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Risk Factors for Late Mortality

Multivariate Cox regression, conditional on survival to 1 year:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay &gt; 1 week</td>
<td>4.8 (2.5 – 9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Common AV Valve</td>
<td>2.6 (1.1 – 6.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>AVVR pre-Fontan</td>
<td>1.9 (1.0 – 3.7)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Not significant: Fontan era, age/weight at Fontan, ventricular morphology, HLHS, Fontan type, bypass parameters, pleural drainage time
## Risk Factors for Late Mortality

Multivariate Cox regression, subset analysis, conditional on survival to 1 year:

<table>
<thead>
<tr>
<th>Variable (n=572)</th>
<th>Hazard Ratio</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay &gt; 1 week</td>
<td>4.7 (2.4 – 9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Common AV Valve</td>
<td>2.9 (1.2 – 7.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-Fontan PA Pressure &gt; 15 mm Hg</td>
<td>2.5 (1.1 –5.8)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Late Survival by Fontan Type
(conditional on survival to 1 year)

![Graph showing late survival by Fontan type](image)

- Lateral Tunnel
- Extracardiac

$p = \text{NS}$

Numbers at each time point:

<table>
<thead>
<tr>
<th>Years Post-Fontan</th>
<th>Lateral Tunnel</th>
<th>Extracardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>373</td>
<td>355</td>
</tr>
<tr>
<td>5</td>
<td>334</td>
<td>247</td>
</tr>
<tr>
<td>10</td>
<td>286</td>
<td>78</td>
</tr>
<tr>
<td>15</td>
<td>189</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>34</td>
<td>0</td>
</tr>
</tbody>
</table>
Late Survival by Ventricular Morphology

(conditional on survival to 1 year)

Years Post-Fontan

- Left
- Right

p = NS

Survival rates over time for left and right ventricular morphologies, with labels indicating the number of patients at each year post-Fontan.
Limitations

• Mortality analysis only – transplant status not included currently

• Retrospective study design
  • Small percentage of missing covariate information
  • Potential for unmeasured covariates
  • Inability to separate collinear covariates

• Unable to assess the impact of Fontan fenestration or staging
Conclusions

• In a large cohort of modern Fontan patients, 20-year survival is estimated at 79%

• Risk factors for early and late mortality differ
  • Early: Era, pleural drainage, cross-clamp time
  • Late: CAVV, pre-op AV valve regurgitation, ICU time

• Elevated pulmonary artery pressure associated with early and late mortality

• No difference in mortality based on Fontan type or ventricular morphology
Implications

• Some anatomic risk factors are not modifiable

• Potentially modifiable
  • Pulmonary artery pressure
  • Duration of chest tube drainage

• Active areas of investigation
  • Impact of PDE-5 inhibition on pre and post-Fontan physiology
  • Importance of systemic to pulmonary collaterals and impact of pre-Fontan embolization
Fontan Follow-Up Team

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