Long-term outcomes after Fontan surgery

Y d’Udekem

Royal Children’s Hospital
Melbourne Australia
Disclosures

• Consultancy fees from MSD, Actelion
Fontan: Maybe the most significant innovation in paediatric surgery!!!
Double Outlet right ventricle

Pulmonary atresia intact septum

Multiple VSDs

Straddling AV valve

Atrial isomerism

Indeterminate single ventricle

Tricuspid atresia

Double inlet left ventricle

Unbalanced AVSD

complex heart disease

HLHS

really complex heart disease

Ebstein
Victoria: medical doctor

Cam: double degree commerce/politics

Megan: risk taker
DOOM  GLOOM
Test

Who believe …

that more than 60% of patients will be alive 40 years after Fontan
Classical Fontan, Atrio-pulmonary connection

Fontan and Baudet 1971

Right Auricle

ASD closed
Tricuspid valve closed
Classical Fontan, Atrio-pulmonary connection

Fontan and Baudet 1971
Lateral tunnel technique

de Leval 1988
Lateral tunnel technique

de Leval  1988

Fenestration

Staging with BCPS
Extra-cardiac conduit

Marceletti 1990
Why a Registry

• The only way to define real expectations for the entire population after Fontan surgery

• To build up the research necessary to improve care of these patients

• To build up information necessary to provide to the needs of this population.

• Quality of care!!!
The Australia and New Zealand Fontan Registry

• **Inclusion**: All patients after Fontan surgery in Australia and New Zealand

• **Exclusion**: Bjork procedures

• Prospective central collection of health data

• **Design**:
  – Opt out consent for prospectively enrolled patients
  – Written and phone consent for retrospectively recruited patients
  – Waiver of consent for deaths and not traceable patients
The Australia and New Zealand Fontan Registry

- **Steering committee:**
  - Representatives of all paediatric and adult centers of congenital heart disease
  - Parents and patients representatives

- **Complete collection of a limited dataset**

- **More in-depth research**
  - By targeted retrospective analysis
  - Cross-sectional study: exercise study, brain MRI, CPX study, cardiac exercise MRI, liver US and fibroscan, nuclear med GFR, Qol and neurologic assessment
The Australia and New Zealand Fontan Registry

• Today close to 1500 Fontan entries

• Only 10 pts refusal to participate

• Data cross-checked with National Death Registries
Redefining Expectations of Long-Term Survival After the Fontan Procedure
Twenty-Five Years of Follow-Up From the Entire Population of Australia and New Zealand

Yves d’Udekem, MD, PhD*; Ajay J. Iyengar, MBBS(Hons), BMedSci, GCALL*;
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Andrew Bullock, MBBS, FRACP; Robert N. Justo, MBBS, FRACP;
Leeanne E. Grigg, MBBS, FRACP; Gary F. Sholler, MBBS, FRACP;
Sarah Hope, BSc, BMedSci(Hons), MBChB, FRACP, PhD;
Dorothy J. Radford, MBBS, MD, FRACP; Thomas L. Gentles, MBChB, FRACP;
David S. Celemajer, MBBS, PhD, DSc, FRACP; David S. Winlaw, MBBS(Hons), MD, FRACS
The Australia and New Zealand Fontan Registry

• A total of **1089 Fontan procedures** performed between 1975 and 2010
  – 27 international patients
  – 36 hospital mortalities
  – 20 Fontan take-downs before Hospital discharge

• **1006 Hospital survivors**
  • No follow-up information at all after hospital discharge in 46 patients (4.6%)

→ **960 survivors of a Fontan procedure**
Events : 960 survivors

• Late deaths: 55 pts
• Reoperations on the Fontan circuit: 38 pts
  – 7 late take-downs
  – 31 Fontan conversions
• PLE and plastic bronchitis: 15 pts
• Sustained SVT: 102 pts
• Thrombo-embolic events: 56 pts

• Heart transplantations: 16 pts
Survival

Years since Fontan completion

# at Risk (# Fail)
Extra-Cardiac 532 (3) 365 (3) 129 (0) 0 (0) 0 (0) 0 (0) 0
Lateral Tunnel 271 (4) 220 (2) 187 (3) 120 (3) 25 (0) 0 (0) 0
Atriopulmonary 203 (8) 175 (11) 158 (7) 125 (3) 72 (5) 28

ECC Lat. Tunnel Atriopulm.
Survival: Multivariable analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Fontan</td>
<td>6.2</td>
<td>&lt; 0.001</td>
<td>2.4 - 16</td>
</tr>
<tr>
<td>Age at Fontan &gt; 7y</td>
<td>2.6</td>
<td>0.0012</td>
<td>1.2 – 5.7</td>
</tr>
<tr>
<td>Extended pleural effusions (&gt; 30 d)</td>
<td>2.9</td>
<td>0.028</td>
<td>1.1 – 7.4</td>
</tr>
<tr>
<td>Female</td>
<td>0.4</td>
<td>0.004</td>
<td>0.2 – 0.7</td>
</tr>
</tbody>
</table>
Failure: death, heart Tx, reoperation, NYHA > III

### Freedom from failure

<table>
<thead>
<tr>
<th>Years since Fontan completion</th>
<th>Freedom from failure (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>91%</td>
<td>89 – 93%</td>
</tr>
<tr>
<td>15 years</td>
<td>83%</td>
<td>79 – 86%</td>
</tr>
<tr>
<td>20 years</td>
<td>70%</td>
<td>63 - 76%</td>
</tr>
<tr>
<td>25 years</td>
<td>56%</td>
<td>44 – 66%</td>
</tr>
</tbody>
</table>
Failure: Multivariable analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (log scale)</td>
<td>2.2</td>
<td>&lt; 0.001</td>
<td>1.6 – 2.8</td>
</tr>
<tr>
<td>HLHS vs LV</td>
<td>3.8</td>
<td>&lt; 0.001</td>
<td>2 – 7.1</td>
</tr>
<tr>
<td>Age at Fontan &gt; 7y</td>
<td>2</td>
<td>0.005</td>
<td>1.2 – 3.2</td>
</tr>
</tbody>
</table>
Failure: HLHS vs RV (non-HLHS) vs LV

Years since Fontan completion

Years since Fontan completion

# at Risk (# Fail)

<table>
<thead>
<tr>
<th></th>
<th>LV</th>
<th>RV (non-HLHS)</th>
<th>HLHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>610</td>
<td>230</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>459</td>
<td>165</td>
<td>41</td>
</tr>
<tr>
<td>10</td>
<td>275</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>134</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>46</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Freedom from late Failure (%)

86 41(11) 10(1) 0(1) 0(0) 0(0)

92% LV

79% RV (non-HLHS)

HLHS
Failure: death, Heart Tx, reoperation, NYHA > III

# at Risk (# Fail)

<table>
<thead>
<tr>
<th>LOS</th>
<th>294 (3)</th>
<th>234 (4)</th>
<th>143 (3)</th>
<th>74 (2)</th>
<th>28 (1)</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS &lt; 12 days</td>
<td>305 (6)</td>
<td>234 (3)</td>
<td>167 (9)</td>
<td>104 (8)</td>
<td>50 (5)</td>
<td>20</td>
</tr>
<tr>
<td>LOS 12-18 days</td>
<td>279 (19)</td>
<td>214 (16)</td>
<td>140 (10)</td>
<td>81 (5)</td>
<td>43 (6)</td>
<td>19</td>
</tr>
</tbody>
</table>

< 12 days | 12-18 days | > 18 days

Years since Fontan completion

Freedom from late Failure (%)

279 214 (19) 140 (16) 81 (10) 43 (5) 19 (6)
SVT: Multivariable analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Fontan (vs ECC)</td>
<td>11.9</td>
<td>&lt; 0.001</td>
<td>5 – 28.5</td>
</tr>
<tr>
<td>Lateral tunnel Vs ECC</td>
<td>4.1</td>
<td>0.003</td>
<td>1.6 – 10.4</td>
</tr>
<tr>
<td>Heterotaxia</td>
<td>2.3</td>
<td>0.023</td>
<td>1.1 – 4.6</td>
</tr>
</tbody>
</table>
SVT: Multivariable analysis

Years since Fontan completion

Freedom from SVT

# at Risk (# Fail)

<table>
<thead>
<tr>
<th>Procedure</th>
<th># at Risk</th>
<th># Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-Cardiac</td>
<td>532 (4)</td>
<td>341 (2)</td>
</tr>
<tr>
<td>Lateral Tunnel</td>
<td>271 (10)</td>
<td>203 (6)</td>
</tr>
<tr>
<td>Atriopulmonary</td>
<td>203 (12)</td>
<td>161 (12)</td>
</tr>
</tbody>
</table>

Legend:
- ECC
- Lat. Tunnel
- Atriopulmonary
Adverse events: Multivariable analysis

**Factors** | **HR** | **P-value** | **95% CI HR**
--- | --- | --- | ---
Length of stay (log scale) | 1.7 | < 0.001 | 1.3 – 2.1
HLHS vs LV | 1.9 | 0.015 | 1.1 – 3.1
Arch intervention prior Fontan | 1.7 | 0.005 | 1.2 – 2.4
Early pacemaker | 2.1 | 0.046 | 1 – 4.2
Pre-Fontan collaterals | 1.8 | 0.001 | 1.3 – 2.5
Speculations: why so good?

- Bjork procedures excluded
- Fontan experience started late
- Patient selection
- Aggressive policy of conversion
The Australia and New Zealand Fontan Registry

www.fontanregistry.com
ANZ Fontan Registry

- 1,425 participant records

Number of Patients Alive with a Fontan Circulation

Year
Number Living

1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014

ECC = 851
LT = 264
AP = 157
Survival curve in 2014

Kaplan-Meier survival estimates

Number at risk
fontan_type = AP 208
fontan_type = LT 283
fontan_type = ECC 869

Years Since Fontan Completion

0 5 10 15 20 25 30 35

0.00 0.20 0.40 0.60 0.80 1.00

Proportion Surviving

fontan_type = ECC

fontan_type = LT

fontan_type = AP
How Good Is a Good Fontan? Quality of Life and Exercise Capacity of Fontans Without Arrhythmias

Yves d’Udekem, MD, PhD, Michael M. H. Cheung, MD, MRCP, Stella Setyapranata, BMedSci, Ajay J. Iyengar, BMedSci, Patricia Kelly, BScI, Naomi Buckland, BScI, B Eng, Leeanne E. Grigg, MBBS, FRACP, Robert G. Weintraub, MBBS, FRACP, Alasdair Vance, MD, PhD, Christian P. Brizard, MD, and Dan J. Penny, MD, PhD

Departments of Cardiac Surgery, Cardiology, and Academic Child Psychiatry Unit, Royal Children’s Hospital, Department of Pediatrics of the University of Melbourne, Murdoch Children’s Research Institute, and the ANZCHRC, Department of Cardiology, Royal Melbourne Hospital, Parkville, Victoria, Australia
## Results – Exercise Capacity

<table>
<thead>
<tr>
<th></th>
<th>AP</th>
<th>LT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VO2max (ml/kg/min)</strong></td>
<td>20.2 ± 4.5</td>
<td>23.4 ± 5.1</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>AT (ml/kg/min)</strong></td>
<td>16.4 ± 5.1</td>
<td>19.9 ± 4.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% Predicted VO2max</td>
<td>54 ± 7 %</td>
<td>62 ± 8 %</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>% Predicted AT</td>
<td>72 ± 14 %</td>
<td><strong>88 ± 14 %</strong></td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

No correlation with age, interval since Fontan, preop variables.
Sympathetic and vascular dysfunction in adult patients with Fontan circulation

Elisabeth Lambert a,e,*, 1, Yves d’Udekkem f,g,1, Michael Cheung g,h, Carolina Ika Sari a, Julia Inman a, Anna Ahimastos c, Nina Eikelis a, Atul Pathak j, Ingrid King f,g, Leanne Grigg i, Markus Schlaich b,d, Gavin Lambert a,d

Clinical microneurography
Parent- Versus Child-Reported Functional Health Status After the Fontan Procedure

Linda M. Lambert, L. LuAnn Minich, Jane W. Newburger, Minmin Lu, Victoria L. Pemberton, Ellen A. McGrath, Andrew M. Atz, Mingfen Xu, Elizabeth Radojewski, Darlene Servedio and Brian W. McCrindle

*Pediatrics* 2009;124;e942; originally published online October 19, 2009;
At 4 years of age, ND evaluation was performed in 365 children, 112 after the Fontan [HLHS (n=91), other SV (n=21)] and 253 after BV repair.

In this cohort, unadjusted ND outcomes for preschool aged survivors of the Fontan procedure are similar to those for children with CHD undergoing BV repair for most domains. Among the Fontan patients, HLHS was not associated with worse outcomes compared to other forms of SV.
Recruitment

• Victoria:
  – 147 contacted
  – 57 refused
  – 35 non-contactable
  – 3 did not attend
  – 52 participated

• NSW:
  – 160 contacted
  – 9 refused
  – 45 participated
  – 5 more scheduled

• NZ:
  – 23 participated
  – 24 recruited
FibroScan

![Graph showing stiffness (kPa) vs. years since Fontan surgery, with a shaded area representing 2/3rds of the data points.](image)
Ultrasound

• **No** patient in the study had liver cancer

• “Fibrosis” in 39/95 (41%, 95% CI 31-51%)
Kidney Function

\[ \beta = -0.8, \ p = 0.003 \]

Lower kidney function with time since Fontan

$1/3^{rd}$ with ≥ mild Kidney disease
40-Year Follow-Up After the Fontan Operation

Long-Term Outcomes of 1,052 Patients

Overall survival by surgical era

- Surgical era:
  - ≤ 1990
  - 1991–2000
  - 2001+

Follow-Up Time (Year)

- ≤ 1990: 775, 576, 490
- 2001+: 86, 48, 19
Conclusion: Contemporary Outcomes

- 30 years expectations of survival: **85%**

- Majority in good condition (QOL)
- Majority without SVT
- 40% will have a major complication before adulthood (Reop, SVT, pacemaker, bleeding/embolism/stroke,...)
Solutions?
Solution: Sort out the medications

$A 2,677,680.76  NHMRC partnership grant with National Heart Foundation, Heartkids
MCRI leading institution and main partner funder
No benefit of warfarin over aspirin after the extracardiac Fontan in a propensity score analysis of 478 patients.

- Ajay J Iyengar MBBS BMedSci 1,2,3, David S Winlaw MBBS MD FRACS 4,5, John C Galati BSc PhD 2,6, Gavin R Wheaton MBBS FRACP 7, Thomas L Gentles MBChB FRACP 8, Leeanne E Grigg MBBS FRACP 9, Robert N Justo MBBS FRACP 10, Dorothy J Radford MBBS MD FRACP 11, Chantal Attard BSc 12, Robert G Weintraub MBBS FRACP 2,3,13, Andrew Bullock MBBS FRACP 14, Gary S Sholler MBBS FRACP 4,5, David S Celermajer MBBS MSc PhD DSc FAHA FRACP FAA 5,15, Yves d'Udekem MD PhD FRACS 1,2,3, The Australia and New Zealand Fontan Registry
Use of ACE Inhibitors in Fontan: Rational or Irrational?

- 462/1268 (36%) of the Fontans of the Registry on ACE inhib
- Relatively strong indication in a third
  (> mild ventr. Dysfunction. > mild AV valve Regurg, semi-lunar valve Regurg, HTA)
- 27% of the treatment initiated in hospital and pursued thereafter.
Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology

Rachael L. Cordina a,b, Shamus O'Meagher a,b, Alia Karmali a, Caroline L. Rae c,d, Carsten Liess e, Graham J. Kemp f, Raj Puranik a,b, Nalin Singh g,h, David S. Celermajer a,b,*
Should We Recommend Exercise after the Fontan Procedure?

Nigel Sutherland, BPhysio\textsuperscript{a}, Bryn Jones, MBBS, FRACP\textsuperscript{b,c,d}, Yves d’Udekem, MD PhD FRACS\textsuperscript{a,b,c}\textsuperscript{a}

\textsuperscript{a}Cardiac Surgery Department, Royal Children’s Hospital, Melbourne, Vic, Australia
\textsuperscript{b}Murdoch Childrens Research Institute, Melbourne, Vic, Australia
\textsuperscript{c}Department of Paediatrics, Faculty of Medicine, The University of Melbourne, Melbourne, Vic, Australia
\textsuperscript{d}Department of Cardiology, The Royal Children’s Hospital, Melbourne, Vic, Australia
Home and hospital-based exercise training program for Fontans
Fontan conversion


Ten-year outcomes of Fontan conversion in Australia and New Zealand demonstrate the superiority of a strategy of early conversion

In one centre, indications for Fontan conversion seemed different ......

“Any atrio-pulmonary Fontan with significantly dilated atrium”

“First episode of atrial arrhythmia”

“Arrhythmia only responsive to amiodarone”
Long-term outcomes: 39 Conversion

Freedom from death and/or transplantation

Other Centres

Early Conversion Centre

<table>
<thead>
<tr>
<th>Years since Fontan conversion</th>
<th>Other Centres</th>
<th>Early Conversion Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20 (6)</td>
<td>19 (1)</td>
</tr>
<tr>
<td>2</td>
<td>6 (1)</td>
<td>12 (0)</td>
</tr>
<tr>
<td>4</td>
<td>4 (0)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>6</td>
<td>4 (0)</td>
<td>10 (0)</td>
</tr>
<tr>
<td>8</td>
<td>3 (1)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Freedom from death and/or transplantation (%)

- Other Centres: 86%
- Early Conversion Centre: 51%

p=0.007
Heart transplantation: a solution?
NUMBER OF ALL TRANSPLANT TYPES BY YEAR 1984 - 2013

ANZCOR 2013
The ultimate solution: VAD??
“... heart transplantation (HTx) is still regarded as the gold standard in the surgical treatment of terminal heart failure. Whether this is still justified in the year 2012 in Europe, and especially in Germany, needs to be seriously questioned.”

- 22 % mortality at 1 year for heart transplantation due to more liberal use of donor
- 20 -30 % mortality on the waiting list.
HVAD® System Demonstrates Long-Term Survival

HeartWare is first to present multicenter long-term data (>2 years) in a peer-reviewed forum.

Kaplan Meier Continued Survival in Patients Supported on HVAD >2 years

- Survival at: 3 years = 89%
- 4 years = 77%

The HVAD System successfully supported 74 of 382 patients in the BTT & CAP study for more than two years.

Patients on support for >2 years demonstrate excellent quality of life outcomes and stable adverse event profiles.

The world's longest-supported HVAD patient has been on support for over 7 years and counting.

---

1. Aaronson K et al Patients Awaiting Heart Transplantation on HeartWare Ventricular Assist Device Support for Greater than Two Years. AHA Poster, 2014.
3. Data on file with manufacturer, HeartWare, Inc, Framingham, MA.
Successful Left Ventricular Assist Device Bridge to Transplantation After Failure of a Fontan Revision

Andrew E. Newcomb, MBBS\textsuperscript{a}, Justin C. Negri\textsuperscript{b} (FRACS), Christian P. Brizard, MD\textsuperscript{a}, Yves d’Udekem, MD\textsuperscript{a}
KH, supported for 6 months
The use of the Berlin Heart EXCOR in patients with functional single ventricle

Samuel Weinstein, MD, MBA, Ricardo Bello, MD, PhD, Christian Pizarro, MD, Francis Fynn-Thompson, MD, James Kirklin, MD, Kristine Guleserian, MD, Ronald Woods, MD, Christine Tjossem, BS, Robert Kroselowitz, Patricia Friedmann, and Robert Jaquiss, MD

- 26 patients
- Survival: 42%
- 5 Fontans: 3 survivors
- Median length of support: 52 days
When should we intervene?
Solution

• One aspirin a day and
• ….. 3 times a week: 40 minutes exercise

• Let us work on assist devices!!