The failing Fontan

Y d’Udekem
MD, PhD, FRACS
NHMRC clinician practitioner fellow

Royal Children’s Hospital
Victoria

2014 graduated as medical doctor

2014 best score for Honours

The Fontan procedure
• What is a Fontan
• Outcomes
• Success of the Registry
• Failure
  – Option 1 Fontan conversion
  – Option 2 Hepatic vein separation
  – Option 3 Transplantation
  – Option 4 VAD
Double Outlet right ventricle

Indeterminate single ventricle

Pulmonary atresia intact septum

Multiple VSDs

Straddling AV valve

Atrial isomerism

Tricuspid atresia

Double inlet left ventricle

Unbalanced AVSD

complex heart disease

HLHS

really complex heart disease

Predictors of Survival After Single-Ventricle Palliation

The Impact of Right Ventricular Dominance

Yves d’Udekem, MD, PrfD,* Mary Y. Xu, BMEdSci,* John C. Galati, BSc, PrfD,† Siming Lu, BMEdSci,* Ajay J. Iyengar, MBBS, BMedSci,* Igor E. Konstantinov, MD, PrfD,* Gavin R. Wheaton, MD,‡ James M. Ramsay, MD,¶ Leanne E. Grigg, MBBS,# Johnny Millar, MB, CstB, PrfD,‡ Michael M. Cheung, MD,# Christian P. Brizard, MD*

Melbourne, Adelaide, and Perth, Australia
RCH experience: 499 pts 1990-2008

**Classical Fontan, Atrio-pulmonary connection**

*Fontan and Baudet 1971*
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

Gore-tex conduit

SVC-RA junction closure

RA closure
Fontan for dummies

15 mm Hg

7 mm Hg

8 mm Hg
Why a Registry

- The only way to define real expectations for the entire population after Fontan surgery
- To build up information necessary to provide to the needs of this population.
- To build up the research necessary to improve care of these patients
- **Quality of care!!!**

<table>
<thead>
<tr>
<th>Followup Gap</th>
<th>&lt;2 years</th>
<th>2-4 years</th>
<th>4-6 years</th>
<th>6-8 years</th>
<th>8-10 years</th>
<th>&gt;10 years</th>
<th>No Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>79.6</td>
<td>9.6</td>
<td>14.9</td>
<td>17.6</td>
<td>6.4</td>
<td>7.5</td>
<td>21.3</td>
</tr>
<tr>
<td>Non-Consent</td>
<td>22.9</td>
<td>9.4</td>
<td>4.3</td>
<td>2.1</td>
<td>1.5</td>
<td>1.5</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Percent.
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

- 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%)
Events

- 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

Survival (%)

Years since Fontan completion

# at Risk (# Fail)

<table>
<thead>
<tr>
<th></th>
<th>ECC</th>
<th>Lat. Tunnel</th>
<th>Atriopulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-Cardiac</td>
<td>532</td>
<td>(3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Lateral Tunnel</td>
<td>271</td>
<td>(4)</td>
<td>(2)</td>
</tr>
<tr>
<td>Atriopulmonary</td>
<td>203</td>
<td>(8)</td>
<td>(11)</td>
</tr>
</tbody>
</table>

97%
96%
76%
Survival curve in 2014

Kaplan-Meier survival estimates

Failure: death, heart Tx, reoperation, NYHA > III

<table>
<thead>
<tr>
<th>Years since Fontan completion</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from late failure (%)</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Freedom from failure</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>89 – 93%</td>
</tr>
<tr>
<td>15 years</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>79 – 86%</td>
</tr>
<tr>
<td>20 years</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>63 – 76%</td>
</tr>
<tr>
<td>25 years</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>44 – 66%</td>
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</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>

**SVT: Multivariable analysis**

<table>
<thead>
<tr>
<th># at Risk (# Fail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-Cardiac</td>
</tr>
<tr>
<td>Lateral Tunnel</td>
</tr>
<tr>
<td>Atriopulmonary</td>
</tr>
</tbody>
</table>

# at Risk (Fail)
### Adverse events: Multivariable analysis

- **59%**

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (log scale)</td>
<td>1.7</td>
<td>&lt; 0.001</td>
<td>1.3 – 2.1</td>
</tr>
<tr>
<td>HLHS vs LV</td>
<td>1.9</td>
<td>0.015</td>
<td>1.1 - 3.1</td>
</tr>
<tr>
<td>Arch intervention prior Fontan</td>
<td>1.7</td>
<td>0.005</td>
<td>1.2 - 2.4</td>
</tr>
<tr>
<td>Early pacemaker</td>
<td>2.1</td>
<td>0.046</td>
<td>1 - 4.2</td>
</tr>
<tr>
<td>Pre-Fontan collaterals</td>
<td>1.8</td>
<td>0.001</td>
<td>1.3 – 2.5</td>
</tr>
</tbody>
</table>

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### 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

<table>
<thead>
<tr>
<th>Year</th>
<th>ECC</th>
<th>LT</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>851</td>
<td>264</td>
<td>157</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Years Since Fontan Completion</th>
<th>AP</th>
<th>LT</th>
<th>ECC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>197</td>
<td>269</td>
<td>550</td>
</tr>
<tr>
<td>5</td>
<td>183</td>
<td>261</td>
<td>292</td>
</tr>
<tr>
<td>10</td>
<td>173</td>
<td>232</td>
<td>261</td>
</tr>
<tr>
<td>15</td>
<td>166</td>
<td>158</td>
<td>232</td>
</tr>
<tr>
<td>20</td>
<td>135</td>
<td>17</td>
<td>158</td>
</tr>
<tr>
<td>25</td>
<td>34</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion Surviving

0.00 0.20 0.40 0.60 0.80 1.00

Neurodevelopmental outcomes in preschool survivors of the Fontan procedure

J. William Gaynor, MD,a Richard F. Ittenbach, PhD,b Marsha Gerdes, PhD,c Judy Bernbaum, MD,d Robert R. Clancy, MD,e Donna M. McDonald-McGinn, MS,f Elaine H. Zackai, MD,g Gil Wernovsky, MD,g Susan C. Nicolson, MD,g and Thomas L. Spray, MDa

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

Yves d’Udekerem, MD, PhD, Michael M. H. Cheung, MD, MRCP, Stella Setyapranata, BMedSci, Ajay J. Iyengar, BmedSci, Patricia Kelly, BSc, Naomi Buckland, BSc, B Eng, Leeanne E. Grigg, MBBS, FRACP, Robert G. Wintraub, 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
Lessons from our experience
The ANZ Fontan Registry

Y d’Udekem

The ANZ Fontan registry

• Timeline
  – Project initiated in 2008
  – Seminal paper in Circulation in 2014
• 1450 patients recorded
  – Largest database of Fontan patients
  – The only population-based database.
1,437 participant records in the Registry.

- Consented: 1,043
- Not consented: 191
- **Refused: 10**
- Deceased: 132
- Transplanted: 27
- International patient: 15
- Moved overseas: 4
- Withdrawn consent: 2
- Takedown: 10
- Ineligible (incl. in hospital mortality): 14

- Willing to participate in future research: 916
- Consented to be sent regular information: 942

**Landmarks**

- 2009 NHMRC grant ($124 500 ....!!?!!)
- Mentoring
- Opt out. Phone consent
- 2011 : Gabrielle starts working in Sydney
- 2014 Fontan education day / Facebook page
- 2014 Partnership grant
- 2015 multiplication of primary investigators
Key factors for success

• Driver
• Core group in key locations
• Track record of successful collaboration
• General climate of collaboration
• Mentoring
• Seed funding – Money, money
• Public support / Heartkids
• Limited number of data
• Faith

Some rules

• Be ready to give more than you receive
• The ethics committee are not the problem. The Doctors’ vision of the ethics committee is the problem .... Get someone else to do the job!
• People are busy and stretched. You have to deliver the workforce (money).
• Everybody has to feel that they get benefits
Some of the benefits

• Proof inside Australia that we can work together
• Best clinical results
  – 1% operative mortality (vs 2%)
  – Best ever late survival, lowest rate of SVT,....
• Set Australia and New Zealand as one of the best place in the world for follow-up studies
• Companies are knocking on the door.
• Our research will identify best care
Ongoing projects

- Fontan Liver and Renal study

- Cross-sectional study

- Partnership grant

- Current application: Fontan and exercise.
Cirrhosis

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 vs years since Fontan]

- 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

\[ \frac{1}{3} \text{rd with } \geq \text{mild Kidney disease} \]

Solutions: 1 medications?

Cross-sectional study
A $743,659.50 NHMRC Project grant
Ongoing projects

• Fontan Liver and Renal study

• Cross-sectional study

• Partnership grant

• Current application: Fontan and exercise.

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, David S Winlaw MBBS MD FRACS,
  John C Galati BSc PhD, Gavin R Wheaton MBBS FRACP,
  Thomas L Gentles MBChB FRACP, Leeanne E Grigg MBBS FRACP,
  Robert N Justo MBBS FRACP, Dorothy J Radford MBBS MD FRACP,
  Chantal Attard BSc, Robert G Weintraub MBBS FRACP,
  Andrew Bullock MBBS FRACP, Gary S Sholler MBBS FRACP,
  David S Celermajer MBBS MSc PhD DSc FAHA FRACP FAA,
  Yves d'Udekem MD PhD FRACS, 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.

Annual hospitalization costs of living Fontan recipients 0-18 years of age ($AUS 2014)
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 a, Bryn Jones, MBBS, FRACP b,c,d, Yves d’Udeke, MD PhD FRACS a,b,c,*

aCardiac Surgery Department, Royal Children’s Hospital, Melbourne, Vic, Australia
bMurdoch Childrens Research Institute, Melbourne, Vic, Australia
cDepartment of Paediatrics, Faculty of Medicine, The University of Melbourne, Melbourne, Vic, Australia
dDepartment of Cardiology, The Royal Children’s Hospital, Melbourne, Vic, Australia
Home and hospital-based exercise training program for Fontans

Fontan conversion
Long-term outcomes: 39 Conversion

Freedom from death and/or transplantation

Years since Fontan conversion

# at Risk (# Fail)

Other Centres  20 (6)  6 (1)  4 (0)  4 (0)  3 (1)  1
Early Conversion 19 (1)  12 (0)  12 (1)  10 (0)  7 (0)  5

Other Centres  Early Conversion Centre

p=0.007

86%
51%
Heart transplantation: a solution?

![Heart transplantation image]

- **Fontan:**
  - 1 year: 91±9.6%
  - 5 years: 78±16%
  - 10 years: 71±20%

- **Other univentricular:**
  - 1 year: 85±13%
  - 5 years: 70±18%
  - 10 years: 59±20%

- **Biventricular:**
  - 1 year: 90±7.6%
  - 5 years: 88±8.4%
  - 10 years: 78±12%

[Graph showing survival rates with p-values for comparisons]
NUMBER OF ALL TRANSPLANT TYPES BY YEAR 1984 - 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.
Case report

Successful Left Ventricular Assist Device Bridge to Transplantation After Failure of a Fontan Revision

Andrew E. Newcomb, MBBS\textsuperscript{b}, 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 Kroslowitz, Patricia Friedmann, and Robert Jaquiss, MD

- 26 patients
- Survival: 42%
- 5 Fontans: 3 survivors
- Median length of support: 52 days

When should we intervene?
Fontan Think Tank *Bordeaux June 2016*

- 18 world experts or leaders of major databases (US, Australia, Europe)
- 4 brain-storming sessions over 2 days.
  - End-organ lesions
  - Risk stratification for death
  - Prevention pre-Fontan
  - Conversion, transplantation, VAD
- Outcomes: 4 international collaborative researches/initiatives

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The failing Fontan: the future bionic man

**THE SIX MILLION DOLLAR MAN**