Pulmonary vasodilators in Fontan Patients

Maurice Beghetti
Pediatric Cardiology University Children’s Hospital HUG and CHUV
Pulmonary Hypertension Program HUG
Centre Universitaire Romand de Cardiologie et Chirurgie Cardiaque Pédiatrique Congenital Cardiac Center (CURCCCP)
University of Geneva and Lausanne, Switzerland
EUROGUCH Lausanne 2017
Univentricular hearts (UVH)

- 10% of all CHD
- Heterogeneous group
  - Includes defects with hypoplasia of either RV or LV, or impossibility to perform biventricular repair
  - 7-10 Fontan procedures per 100,000 live births (Australia and Denmark)
  - Estimate in Europe (TBC): 3500 to 5000 (75% children)
- UVH: Decreasing incidence due to prenatal diagnosis
  - But number of Fontan procedure increases
- Prognosis
  - Initially poor: Survival 50% at 1 year, 10% at 10 years
  - After palliative surgical treatment by Fontan in 1971:
    - Current mortality down to 10% at 10 years

Fontan circulation: epidemiology

- **Prevalence in Denmark / estimate in Europe**
  - 45 pts per million inhabitant*
  - Extrapolation to EU (with 500 Mio inhabitants) 22,000 patients

- **Prevalence in Australia**
  - 45 living persons with Fontan / million total general population estimate
  - Around 1000 living FONTAN in Australia

- **US prevalence**
  - 50,000 patients in the US

* Idorn et al Int Jl Card 2013
** Iyengar et al Jl Thor Card Vasc Surgery 2007
Normal biventricular circulation

- Output 100 – 500%
- RA pressure low
- PA pulsatility
- Ao sat > 95%
Fontan circulation: new portal system

- Output (50) 70 - 200%
- CV pressure high
- PA pulsatility ↓
- Ao sat (80-)93%

Portal system: dam
- Congestion
- Decreased output

Gewillig TCS 2000
Fontan procedure: Key success factors and complications

- **Key success factors**
  - Main: Low PVR as blood flow is dependent on passive flow through the lungs (PVR > 3 Wood units = CI to surgery)
  - Anatomy of PA, Ventricular function, AV valve status
  - Others: Initial malformation and type of surgical correction (TCPC vs PCPC)

- **Complications (failing Fontan) include (20-30% of Fontan)**
  - Dyspnoea (FC II or III): hypoxaemia with exercise intolerance
  - Right atrium dilation and arrhythmias, acute dyspnoea episodes
  - Portal hypertension, protein losing enteropathy (increased pressure in lymph circulation)
  - Ultimately, all Fontan procedures will fail with time

Complications arising in patients with Fontan circulation

- Ventricular dysfunction
- Atrial dysrhythmia (intra-atrial re-entry tachycardia; atrial flutter)
- Hypoxaemia
- Exercise intolerance
- Elevated pulmonary vascular resistance
- Protein-losing enteropathy
- Plastic bronchitis
- Hepatic complications (fibrosis, cirrhosis; oesophageal varices)
- Thrombosis (pulmonary embolism, stroke)
- Renal complications
Definition of pulmonary hypertensive vascular disease after the Fontan

- Pulmonary Vascular Resistance Index
  - >3 WU/m²
- Transpulmonary gradient (mean pulmonary artery pressure minus left atrial pressure)
  - >6 mmHg
Fontan: evolution of PVR
Cavopulmonary anastomosis

- Role of pulmonary vasculature is essential
- Pulsatile flow is important in regulating the shears stress mediated of endothelial substances and dysregulation of this system induces endothelial dysfunction
- Pulsatile stress is essential for shear stress mediated release of NO and lowering PVR by recruitment of capillaries
Overexpression of endothelin-1 and endothelin receptors in the pulmonary arteries of failed Fontan patients

Morphological analysis of the pulmonary arteries. A: The percent wall thickness of the pulmonary arteries of patients who died after the Fontan procedure and normal controls (NC). Patients who had undergone the Fontan procedure were divided into 3 groups based on the cause of death; failed Fontan group (FF), heart failure group (HF) and sudden or infectious death (non-failed Fontan) group (SD+INF). * P < 0.05. B: Elastica van Gieson stain of the pulmonary arteries of the failed Fontan patients showed severe intimal and medial hypertrophy (a, b and c) as compared to normal controls (d). C: Immunostain of alpha-smooth muscle cell actin showed that proliferation of the vascular smooth muscle cells contributed to intimal and medial hypertrophy of the failed Fontan patients.
TABLE 3. Relationship of PAP and percentage wall thickness related to external diameter of intra-acinar pulmonary arteries

<table>
<thead>
<tr>
<th>PAP (mm Hg)</th>
<th>No.</th>
<th>Diameter 0-50 μm</th>
<th>Diameter 51-100 μm</th>
<th>Diameter ≥101 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤18</td>
<td>35</td>
<td>13.3 ± 6.3*</td>
<td>16.1 ± 7.8</td>
<td>18.3 ± 9.1</td>
</tr>
<tr>
<td>&gt;18</td>
<td>5</td>
<td>22.2 ± 6.9</td>
<td>22.8 ± 7.2</td>
<td>23.5 ± 4.2</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
*P < .01 compared with PAP >18 mm Hg.

TABLE 4. Relationship of histologic evaluation of pulmonary arterial structure and outcome

<table>
<thead>
<tr>
<th>Surgery</th>
<th>No.</th>
<th>Normal or grade 1</th>
<th>Grade 2 or higher</th>
<th>Deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCPC</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>PCPC</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Palliation</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

*All patients who had abnormal biopsy specimens (grade 3).
Sildenafil in Fontan patients

• **Conclusions**
  – Sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise
  – There was a suggestion of improved oxygen consumption at the anaerobic threshold in 2 subgroups

Bosentan in Fontan patients

• Conclusions
  – Six months of bosentan treatment was not beneficial

The TEMPO study

Design:
- Total cavo-pulmonary connection (TCPC) patients
- Age > 12 years
- $n = 75$
- 1:1 randomisation, double-blinded
- Bosentan or placebo for 14 weeks

Primary endpoint:
- Peak $VO_2$ (ml/kg/min)

Secondary endpoints:
- Included CPET duration, NYHA class, SF-36, proBNP

## Baseline characteristics

|                  | Bosentan  
|------------------|------------------|
|                  | \(n = 36\) \n|                  | Placebo  
|                  | \(n = 39\) \n| Age [years], mean (SD) | 20.3 (7.5) | 19.7 (6.6) |
| Male, \(n\) (%)  | 21 (58) | 24 (62) |
| BMI [kg/m\(^2\)], mean (SD) | 21.5 (4.1) | 21.1 (3.7) |
| FC, \(n\) (%)    |                  |                  |
| I                | 22 (61) | 30 (77) |
| II               | 13 (36) | 9 (23) |
| III              | 1 (3) | 0 |
| Peak VO\(_2\) [ml/min/kg], mean (SD) | 28.5 (7.7) | 28.2 (6.1) |

Patients

Fontan patients randomised

*For patients with a body weight < 35 kg, the dose was halved i.e. 31.25 mg b.i.d. for 2 weeks and 62.5 mg b.i.d. for 12 weeks

Primary endpoint: $\Delta$ peak VO$_2$

$\Delta$ peak VO$_2$ (ml/min/kg)

<table>
<thead>
<tr>
<th></th>
<th>Bosentan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>p</td>
<td>$\Delta$ 1.99</td>
<td>0.60</td>
</tr>
<tr>
<td>p-value</td>
<td>= 0.0245</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>0.18, 2.59</td>
<td></td>
</tr>
</tbody>
</table>

VO$_2$: oxygen consumption

Δ CPET duration

CPET: cardio-pulmonary exercise test


Bosentan

Placebo

p = 0.042

Difference 0.39
(95% CI: 0.01, 0.77)
Changes in FC

Odds ratio bosentan vs placebo = 0.069
(95% CI: 0.00, 0.41)
p = 0.0085

EOT: end of treatment

## Summary studies

Some improvements shown with various PAH specific products / N small

<table>
<thead>
<tr>
<th>study</th>
<th>Drug</th>
<th>Type of study</th>
<th>Selection of patients</th>
<th>parameters</th>
<th>results</th>
<th>Patient number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuuring</td>
<td>bosentan</td>
<td>Open label</td>
<td>5 tertiary centers, no specific inclusion criteria</td>
<td>Exercise capacity, CO BNP,NYHA</td>
<td>NS</td>
<td>42</td>
</tr>
<tr>
<td>Ovaert</td>
<td>bosentan</td>
<td>Open label</td>
<td>« failing » Fontan</td>
<td>Sat rest and exercise (6MWT)</td>
<td>NS, large differences between patients</td>
<td>10</td>
</tr>
<tr>
<td>Hirono</td>
<td>bosentan</td>
<td>Open label prefontan</td>
<td>hemodynamic</td>
<td>hemodynamic</td>
<td>Improved PAP and PVR</td>
<td>28</td>
</tr>
<tr>
<td>Giardini</td>
<td>Sildenafil</td>
<td>RCT</td>
<td>Stable for last 3 months</td>
<td>CPET</td>
<td>Improved peakVO2</td>
<td>27</td>
</tr>
<tr>
<td>Goldberg</td>
<td>Sildenafil</td>
<td>Double blind RCT</td>
<td>Able to perform CPET</td>
<td>CPET</td>
<td>Improved ventilatory efficiency</td>
<td>28</td>
</tr>
<tr>
<td>Rhodes</td>
<td>iloprost</td>
<td>Double blind RCT</td>
<td>Willing to perform CPET</td>
<td>CPET</td>
<td>Improve peakVO2</td>
<td>18</td>
</tr>
<tr>
<td>Takahashi</td>
<td>Beraprost</td>
<td>Pre fontan open lable</td>
<td>mPAP&gt;20 and or PVR&gt;3</td>
<td>PVR</td>
<td>Decrease in PVR</td>
<td>20</td>
</tr>
<tr>
<td>Sondegaard</td>
<td>Bosentan</td>
<td>RCT</td>
<td>All Fontan with CPET capacities</td>
<td>Peak VO2 (CPET)</td>
<td>Improved peakVO2</td>
<td>77</td>
</tr>
</tbody>
</table>
Morbidity/Mortality

- So far short term studies
- Morbidity
  - Mainly effect on exercise capacity
  - Few other data
    - Positive if improve plastic bronchitis and PLE
    - No effect on QoL, NtBNP
      - Schuuring EJHF 2013
Planned or ongoing studies

- Study of Remodulin® in Pediatric Pulmonary Hypertension With Single Ventricular Physiology After Fontan Surgery
- The Effects of Ambrisentan on Exercise Capacity in Fontan Patients
- RUBATO: Macitentan in Fontan patients RCT
- Effect of Tadalafil on Exercise Capacity in Pediatric Fontan Patients
- And some small other studies….
Take home message

- Heterogenous population
- Increasing number of patients
- Planned to fail ??
- Frequent and different complications but should be decreased with modern approaches
- Pulmonary vascular bed essential
- Roles of new therapies to be defined and studied
Use of pulmonary vasodilators in Fontan

Conclusion

• In short term studies pulmonary vasodilators show improvement in exercise capacity but.
  – Not always consistent
  – Short term studies with small numbers
  – Effect of pulmonary vasodilators
    • only on PVR?
  – Morbidity
    • Very few data
• Urgent need of a large RCT in this population

Complications of Fontan circulation
Ventricular dysfunction  No Data
Atrial dysrrythmia (intra-atrial re-entry tachycardia; atrial flutter)  No data
Hypoxemia  individual response
Exercise intolerance
Elevated PVR  No hemodynamic data
Protein losing enteropathy  case reports
Plastic bronchitis  case reports
Hepatic complications (fibrosis, cirrhosis; esophageal varices)  No Data
Thrombosis (PE, stroke)  No data
Mortality  No Data