Twin-to-twin transfusion syndrome: The Heart

Josep M Martínez, Fàtima Crispi, Olga Gómez, Eduard Gratacós

1st Fetal Cardic Function Symposium
TTTs and the heart

1. What we already know
2. Congenital heart disease
3. Prenatal cardiac function
4. Postnatal cardiac function
5. The future
TTTs and the heart

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Epidemiology twins

- Resulting from:
  - Fertilization > 1 oocyte (polyzygotic)
  - Splitting from 1 embryonic mass (monozygotic)
  - 1/250 newborns

- Prevalence: ± 3% newborns (ICGON: 4%)

- Responsible 10-14% perinatal mortality
  - morbimortality MC x10
• 70%: DZ twins
  - DC BA 100%
• 30%: MZ twins (‘identical’)
  - DC BA (< 4 days) 25%
    - MC BA (4-8 days) 70%
    - MC MA (> 8 days) 2-5%
    - Siameses (> 12 days) 1%
• 1%: higher range multiples (1%)
± 100% diagnosis accuracy by US < 14 sg

Single placenta + thin membrane + delta vs ‘T’ + sex
## Perinatal risk twins

### Chorionicity matters, not zygosity

<table>
<thead>
<tr>
<th></th>
<th>DC</th>
<th>MC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major malformation</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Intrauterine death</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Growth restriction</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Preterm delivery (&lt;32 wks)</td>
<td>9%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Severe brain damage</strong></td>
<td><strong>0.3%</strong></td>
<td><strong>3%</strong></td>
</tr>
</tbody>
</table>
Monochorionic twins: the problem is the single placenta
Vascular anastomosis
Artery to artery / vein to vein anastomosis ('superficial')
Artery to vein anastomosis ('deep')
Complications in MC twins (30-40%)

1. TTTS (15%)
2. sIUGR (10%)
3. Monoamniotics (1-2%)
4. TRAP (< 1%)
5. Discordant anomaly (5%)
Complications in MC twins (30-40%)

1. TTTS (15%)
2. sIUGR (10%)
3. Monoamniotics (1-2%)
4. TRAP (< 1%)
5. Discordant anomaly (5%)
Epidemiology TTTS

- 1/250 deliveries is MC
  - 500,000 deliveries in Spain
  - 2000 MC/year

- TTTS: 10-15% MC
  - > 200-300 cases/year

- Both fetuses affected + structurally normal + great morbimortality
Unbalanced transfusion: 15%
### Fetal consequences TTTS

#### DONOR TWIN
1. Hypovolemia, hypotension
2. Olygoanury: renal failure
3. Placental IUGR
4. Death

#### RECIPIENT TWIN
1. Hypervolemia
2. Polyury
3. Cardiac overload, hydrops
4. Death

**OLYGOHYDRAMNIOS** (*< 2 cm*)

**POLYHYDRAMNIOS** (*> 10 cm*)
Donor vs recipient
TTTs diagnosis:
olygoH + polyH sequence

- **Recipient**
  - Polyhydramnios: > 8 cm (> 10 cm)
  - Prominent urinary bladder
- **Donor**
  - Olygohydramnios: < 2 cm
  - Minimal or no visible urinary bladder
Maternal consequences

- Twin pregnancy + polihydramnios
  1. Miscarriage
  2. Extreme preterm delivery
Fetal/neonatal consequences

1. Death

2. Severe sequelae
   a. Brain
   b. Bowel
   c. Limbs
   d. Heart
Mortality > 95%
Severe sequelae > 50%
Brain damage
Bowel damage
Limbs damage
Heart damage
Fetoscopic laser
Hospital Clínic results
fetoscopic laser for TTTS (n> 500)

- **Survival**
  - At least 1 alive: 92%
  - 2 alive: 72%
  - 0 alive: 8%

- **Preterm < 32 wks:** 10-15%

- **CNS damage:** 6-10%
Hospital Clínic results
fetoscopic laser for TTTS (n> 500)

- **Survival**
  - At least 1 alive: 92%
  - 2 alive: 72%
  - 0 alive: 8%

- **Preterm < 32 wks:** 10-15%

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And the heart?
TTTs and the heart

1. What we already know
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3. Prenatal cardiac function
4. Postnatal cardiac function
5. The future
Structural heart defects

- Overall incidence: 5-10%
- ↑ donor + ↑↑↑ recipients
  - ± 15% recipient: RVOT obstruction
    - 2/3: pulmonary stenosis
    - 1/3 pulmonary atresia
Pulmonary stenosis

1. thickened or narrow PV
2. PSV > 120 cm/s
Pulmonary atresia

1. Reverse flow DA
2. Cardiomegaly, tricuspid regurgitation, poor contractility
Pulmonary atresia + Ebstein
Structural heart defects

• Overall prevalence: ± 5-10%
  – 25% concordant

• ↑ donor + ↑↑↑ recipients

• ± 10-15% recipient: RVOT obstruction
  – 2/3: pulmonary stenosis
  – 1/3 pulmonary atresia

Structural vs functional?
RVOT obstruction (n > 50) after laser (n > 300)

1. 40-50%: intrauterine resolution
2. ± 20%: perinatal death
   - 1/2 IUFD
   - 1/2 prematurity
3. 30-40%: postnatal cardiac surgery
   - 3/4: percutaneous valvuloplasty
   - 1/4: other valvular surgeries, Fontan
TTTs and the heart

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Fetal Cardiac Function: Technical Considerations and Potential Research and Clinical Applications

Fatima Crispi  Eduard Gratacós

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Table 1. Most commonly used systolic and diastolic parameters to assess fetal cardiac function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction volume estimation</td>
<td>Fraction of blood ejected from the ventricle with each heart beat</td>
<td>2D, M-mode, 2D speckle tracking</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Volume of blood being pumped by the ventricle per minute</td>
<td>2D, conventional Doppler, STIC</td>
</tr>
<tr>
<td>Cardiac output</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial motion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annular displacement</td>
<td>Distance of the movement of the atrioventricular valve annulus</td>
<td>M-mode or 2D speckle tracking</td>
</tr>
<tr>
<td>Systolic annular peak velocity</td>
<td>Speed of movement of the atrioventricular valve annulus in systole (S')</td>
<td>Spectral or color TDI</td>
</tr>
<tr>
<td><strong>Myocardial deformation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td>Amount of deformation (change in length of a myocardial segment from its original length)</td>
<td>Color TDI or 2D speckle tracking imaging</td>
</tr>
<tr>
<td>Strain rate</td>
<td>Speed of deformation (change of strain over time)</td>
<td>Color TDI or 2D speckle tracking imaging</td>
</tr>
<tr>
<td><strong>Diastolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precordial vein blood flow patterns (DV and others)</td>
<td>Pattern of blood in precordial veins during atrial contraction that indirectly reflects cardiac compliance</td>
<td>Conventional Doppler</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>Ratio between early (E) and late (A) ventricular filling velocity</td>
<td>Conventional Doppler</td>
</tr>
<tr>
<td>Diastolic annular peak velocities</td>
<td>Speed of movement of the atrioventricular valve annulus in early (E') and late (A') diastole</td>
<td>Spectral or color TDI</td>
</tr>
<tr>
<td>E/E' ratio</td>
<td>Transmirtal-to-mitril annular diastolic velocity ratio</td>
<td>Conventional Doppler and spectral TDI</td>
</tr>
<tr>
<td>IRT</td>
<td>Time between closure of the aortic valve and opening of the mitral valve</td>
<td>Conventional Doppler or spectral/color TDI</td>
</tr>
<tr>
<td><strong>Global cardiac function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPI</td>
<td>Ratio between isovolumetric times (contraction plus relaxation) and ejection time</td>
<td>Conventional Doppler or spectral/color TDI</td>
</tr>
</tbody>
</table>

STIC = Spatiotemporal Image correlation; TDI = tissue Doppler imaging; IRT = isovolumetric relaxation time; MPI = myocardial performance index.
Donors

• **At diagnosis**: normal cardiac function
  – Decreased preload: hypovolemia and hypotension
  – Increased afterload:
    • activation renin-angiotensin system
    • high placental vascular resistance

• **After laser**: transient signs relative hypervolemia and cardiac overload
Donors

• **At diagnosis**: normal cardiac function

• **After laser**: transient signs relative hypervolemia and cardiac overload
  – Abnormal DV
  – Increased umbilical vein flow
  – Tricuspid regurgitation
  – Edema / hydrops
Recipients

• **At diagnosis**: volume overload (hypervolemia) + pressure overload (donor’s vasoactive factors)
  – Cardiomegaly (> 75%)
    • Tricuspid ± mitral insufficiency
  – Hypertrophy (50%)
    • Early impaired diastole: E/A, tissue
    • Normal systole until end-stages: ejection and shortening fraction, PVS… but
      – Reduced V strain
      – RVOT obstruction

• **After laser**: improved cardiac output + improvement
Volume overload: normal function

1. Increased umbilical blood flow
2. Increased ductus venosus pulsatility
3. Cardiomegaly
4. Tricuspid and mitral insufficiency
Pressure overload: diastolic failure

1. Cardiac hypertrophy (> 50%)
2. Increase in ejection fraction
3. Impaired relaxation and increased ventricular filling pressures
4. reduced E/A ratios or a monophasic Doppler inflow profile
5. increased E/E’ ratios
6. increased MPI

www.medicinafetalbarcelona.org/
Systolic failure

1. decrease in ventricular shortening fraction
2. worsening of atrioventricular valve regurgitation
3. low cardiac output, hydrops, and fetal death

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Recipients

- **At diagnosis**: volume overload (hypervolemia) + pressure overload (donor’s vasoactive factors)
- **After laser**: improved cardiac output + improvement in all parameters
  - DV, UV
  - E/A
  - MPI
  - hydrops resolution
After laser ...
After laser ...
Severity scores

1. Quintero stages
   1. Major changes related to stages III-IV
   2. Subclinical changes in stages I-II

2. CHOP cardiovascular score

3. Cincinnati cardiovascular score
Quintero’s stages

1. Visible bladder in donor
2. Absent bladder in donor
3. Critically abnormal Doppler
   - AREDV umbilical artery \((\text{donor})\)
   - AR atrial contraction ductus venosus \((\text{recipient})\)
   - Pulsations umbilical vein \((\text{recipient})\)
4. Hydrops \((\text{recipient})\)
5. Death either twin
Quintero’s stages

1. Visible bladder in donor
2. Absent bladder in donor
3. Critically abnormal Doppler
   - AREDV umbilical artery (donor)
   - AR atrial contraction ductus venosus (recipient)
   - pulsations umbilical vein (recipient)
4. Hydrops (recipient)
5. Death either twin

Fetoscopy < 24 hours
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Numerical score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical artery</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Decreased diastolic flow</td>
<td>1</td>
</tr>
<tr>
<td>Recipient</td>
<td>Absent/reversed diastolic</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular hypertrophy</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac dilatation</td>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;Mild</td>
<td>2</td>
</tr>
<tr>
<td>Tricuspid valve regurgitation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;Mild</td>
<td>2</td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;Mild</td>
<td>2</td>
</tr>
<tr>
<td>Tricuspid valve inflow</td>
<td>Double-peak</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Single-peak</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve inflow</td>
<td>Double-peak</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Single-peak</td>
<td>1</td>
</tr>
<tr>
<td>Ductus venosus</td>
<td>All antegrade</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Absent diastolic flow</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Reverse diastolic flow</td>
<td>2</td>
</tr>
<tr>
<td>Umbilical vein</td>
<td>No pulsations</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pulsations</td>
<td>1</td>
</tr>
<tr>
<td>Right-sided outflow tract</td>
<td>PA &gt; Ao</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PA = Ao</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>PA &lt; Ao</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>RV outflow obstruction</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary regurgitation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

**Maximum total cardiovascular score**: 20 points

PA, pulmonary artery; Ao, aorta; RV, right ventricle.
# Cincinnati score

<table>
<thead>
<tr>
<th>Stage</th>
<th>Donor</th>
<th>Recipient</th>
<th>Recipient cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oligohydramnios*</td>
<td>Polyhydramnios†</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Bladder absent</td>
<td>Bladder seen</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>Abnormal Doppler</td>
<td>Abnormal Doppler</td>
<td>None</td>
</tr>
<tr>
<td>IIIA</td>
<td>± Abnormal Doppler</td>
<td>± Abnormal Doppler</td>
<td>Mild</td>
</tr>
<tr>
<td>IIIB</td>
<td>± Abnormal Doppler</td>
<td>± Abnormal Doppler</td>
<td>Moderate</td>
</tr>
<tr>
<td>IIIC</td>
<td>± Abnormal Doppler</td>
<td>± Abnormal Doppler</td>
<td>Severe</td>
</tr>
<tr>
<td>IV</td>
<td>Hydrops</td>
<td>Hydrops</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Death</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Grading of severity of recipient-twin cardiomyopathy in twin–twin transfusion syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild (Stage IIIA)</th>
<th>Moderate (Stage IIIB)</th>
<th>Severe (Stage IIIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV regurgitation</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>RV/LV thickness</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>MPI*</td>
<td>&gt; +2 Z-score</td>
<td>≥ +3 Z-score</td>
<td>≥ +4 Z-score</td>
</tr>
<tr>
<td>LV-MPI</td>
<td>&gt; 0.43 &lt; 0.48</td>
<td>≥ 0.48 &lt; 0.53</td>
<td>≥ 0.53</td>
</tr>
<tr>
<td>RV-MPI</td>
<td>&gt; 0.48 &lt; 0.56</td>
<td>≥ 0.56 &lt; 0.64</td>
<td>≥ 0.64</td>
</tr>
</tbody>
</table>

*Mean MPI in normal fetuses in our institution: RV-MPI, 0.32 ± 0.08; LV-MPI, 0.33 ± 0.05. AV, atrioventricular valve; LV, left ventricle; MPI, myocardial performance index; RV, right ventricle. The most severely affected parameter determines the stage.
Cardiovascular scores

1. Quintero stages
   – Major changes related to stages III-IV
   – Subclinical changes in stages I-II

2. CHOP score

3. Cincinnati score

No useful as diagnostic or pronostic markers, more studies are needed
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3. Prenatal cardiac function
4. Postnatal cardiac function
5. The future
Scanty information

• ‘Normal’ (no obvious clinical symptoms) if treated by fetoscopy
• Need treatment for RVOT
• Small series:
  – Tolosa 1993, Mercanti 2011, neonates
    • Ex-recipients: increased blood pressure
  – Gardiner 2002, childhood
    • Ex-donors: lower arterial distensibility
  – Halvorsen 2009, at school age
    • Ex-recipients: reduced diastolic function
    • Ex-donors: abnormal cardiac dimensions
  – Takahashi 2011
    • Ex-recipients: persistent pulmonary hypertension

Need of further studies in survivors
TTTs and the heart

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Future (current) research

1. More subtle and fine methods to assess cardiac function
   – At diagnosis
   – After laser

2. Prenatal medical intervention??

3. Postnatally: early identification and intervention at childhood
Early changes in longitudinal assessment!!!
Table 1. Comparison between twins and normal controls

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 25)</th>
<th>Donors (n = 25)</th>
<th>p value, (donor vs. control)</th>
<th>Recipients (n = 25)</th>
<th>p value (recipient vs. control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial deformation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-S, %</td>
<td>-24.85 ± 4.81</td>
<td>-20.71 ± 3.65</td>
<td>0.06</td>
<td>-11.66 ± 4.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV-SRs, s⁻¹</td>
<td>-2.43 ± 0.51</td>
<td>-2.18 ± 0.43</td>
<td>0.11</td>
<td>-1.26 ± 0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV-SRd, s⁻¹</td>
<td>2.48 ± 0.61</td>
<td>1.78 ± 0.36</td>
<td>&lt;0.001</td>
<td>1.15 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV-S, %</td>
<td>-17.68 ± 3.16</td>
<td>-18.82 ± 3.72</td>
<td>0.25</td>
<td>-10.62 ± 2.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV-SRs, s⁻¹</td>
<td>-1.69 ± 0.36</td>
<td>-2.27 ± 0.50</td>
<td>&lt;0.001</td>
<td>-1.09 ± 0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV-SRd, s⁻¹</td>
<td>1.66 ± 0.36</td>
<td>1.69 ± 0.42</td>
<td>0.97</td>
<td>0.99 ± 0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV/LV-S, %</td>
<td>1.42 ± 0.27</td>
<td>1.15 ± 0.36</td>
<td>&lt;0.01</td>
<td>1.16 ± 0.51</td>
<td>0.03</td>
</tr>
<tr>
<td>RV/LV-SRs, s⁻¹</td>
<td>1.45 ± 0.27</td>
<td>0.98 ± 0.44</td>
<td>&lt;0.001</td>
<td>1.21 ± 0.41</td>
<td>0.02</td>
</tr>
<tr>
<td>RV/LV-SRd, s⁻¹</td>
<td>1.51 ± 0.30</td>
<td>1.17 ± 0.49</td>
<td>&lt;0.01</td>
<td>1.31 ± 0.75</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Vascular impedance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA-PI</td>
<td>1.41 ± 0.25</td>
<td>1.92 ± 0.45</td>
<td>&lt;0.001</td>
<td>1.59 ± 0.34</td>
<td>NS</td>
</tr>
<tr>
<td>MCA-PI</td>
<td>1.87 ± 0.21</td>
<td>1.46 ± 0.28</td>
<td>&lt;0.001</td>
<td>1.75 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Echocardiographic features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DV A/S ratio</td>
<td>0.44 ± 0.09</td>
<td>0.40 ± 0.18</td>
<td>NS</td>
<td>0.12 ± 0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PE, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>4 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C/T ratio (%)</td>
<td>0.30 ± 0.02</td>
<td>0.29 ± 0.19</td>
<td>NS</td>
<td>0.42 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TR, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>16 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MR, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>9 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tricuspid fusion, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>13 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral fusion, n (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>7 (28%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>