BIOABSORBABLE DEVICES IN CONGENITAL HEART DISEASE

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DISCLOSURES

- Abbott Vascular
  - Investigator Sponsored Study grant
HISTORY

- Catheter implantable devices
  - Occlusion devices
  - Stents
  - Valves
- Refinement – device evolution

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DEVICE</th>
<th>SHEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>Ivalon plug</td>
<td>16-22 F</td>
</tr>
<tr>
<td>1979</td>
<td>Rashkind Umbrella</td>
<td>8-11 F</td>
</tr>
<tr>
<td>1993</td>
<td>Botalloccluder</td>
<td>10-16 F</td>
</tr>
<tr>
<td>1996</td>
<td>GGVOD</td>
<td>8 F</td>
</tr>
<tr>
<td>2003</td>
<td>Amplatzer ADO</td>
<td>5+ F</td>
</tr>
<tr>
<td>2013</td>
<td>Amplatzer ADO II</td>
<td>4+ F</td>
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</tbody>
</table>
CHALLENGES

• Why can’t we simply place big devices in small children?
  • Navigation issues
    • Do not tolerate complex catheter passes
      • VSD closure
    • Do not tolerate large caliber delivery sheaths across multiple valves
      • Pulmonary artery stent placement
  • Device size
    • Septal devices too large for surrounding structures
    • Stent length may be too long for the target site
      • Branch pulmonary artery stenosis – stent can “jail” side branches
    • Stents that are sufficiently short do not dilate to “adult size”
CURRENT ALTERNATIVES

- Alternatives to overcome patient / device size challenges
- Cutting or folding back stent cells
- "Hybrid Procedures" - cardiac surgeon creates the path to the target
  - Hybrid Norwood
  - Perventricular VSD closure
  - Intraoperative pulmonary artery stenting
CURRENT CHALLENGES

- Interventional options for small children are inferior to those for their older counterparts

- Interventional Challenges
  - Coarctation of the Aorta
  - Branch Pulmonary Artery Stenosis
COARCTATION

- Comparison of angioplasty and surgery for unoperated coarctation of the aorta
  - “Immediate gradient reduction is similar after balloon coarctation angioplasty and surgical treatment…”
  - The risks of aneurysm formation and possibly restenosis after angioplasty are higher than after surgery”
    Shaddy et al. Circulation 1993

- Long-term randomized comparison of balloon angioplasty and surgery for native coarctation of the aorta in childhood
  - No difference
    - Resting BP, coarctation gradient, exercise performance, reintervention rate
    - Higher incidence of aneurysm formation with angioplasty vs. surgery
    - 35% vs. 0%
    Cowley et al. Circulation 2005
• Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta
  • “Stent patients had significantly lower acute complications compared with surgery patients or angioplasty patients”
  • “At short-term and intermediate follow-up, stent and surgical patients achieved superior hemodynamic and integrated aortic arch imaging outcomes”

2011 JACC – Forbes et al.
## COARCTATION

### How the studies differ...

<table>
<thead>
<tr>
<th></th>
<th>AGE (yrs)</th>
<th>WEIGHT (kg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Angioplasty</td>
<td>Surgery</td>
</tr>
<tr>
<td>Shaddy</td>
<td>6.3 ± 2.0</td>
<td>5.7 ± 2.1</td>
</tr>
<tr>
<td>Forbes</td>
<td>9.0 ± 8.0</td>
<td>10.0 ± 9.7</td>
</tr>
</tbody>
</table>
PULMONARY ARTERY STENOSIS
PULMONARY ARTERY STENOSIS

1 mm
PULMONARY ARTERY STENOSIS
PULMONARY ARTERY STENOSIS

2+ mm
PULMONARY ARTERY STENOSIS
PULMONARY ARTERY STENOSIS

4+ mm
OUTCOMES

• Acute result is excellent

• Future issues
  • Cannot dilate stent further
  • Will require surgical retrieval vs. longitudinal incision and patch angioplasty vs. balloon angioplasty fracture

• Problems
  • Increased risk of surgical intervention
  • Easier for surgeons to perform angioplasty without interference from stents
OUTCOMES

Is this the desired outcome?
WHAT IS NEXT?

• How can we achieve the acute results without the later challenges and risks?

• Sometimes the problem is NOT that you need to get something big into a small patient

• Something small is exactly what is needed ... at the time
BIODEGRADABLE PRODUCTS

ADVANTAGES

• Temporary effects: when only short term result is needed

• Overcomes problem of being “big enough for an adult”
  • No need to re-dilate to accommodate somatic growth
  • Later interventions done without concern of existing hardware
  • Decrease complexity of surgical procedures / device manipulation unnecessary

• Allow restoration of vascular compliance
  • Possible positive remodeling and later growth

• Decrease risk of arrhythmia

• Possible modality for drug or gene therapy delivery
SEPTAL DEFECTS

- Uses in device closure of ASDs / VSDs
- BioSTAR device
- VSD occluder
- 12F delivery
- 13mm disks – polydioxanone (PDO) monofilament framework
- Filled with poly-L-lactic acid (PLLA) non-woven fabric
- Degradation time: PDO = 6 mo; PLLA = 24 mo
- Successful placement in 15/16 dogs
- One developed persistent 3rd degree AV block
- Mild-moderate foreign body giant cell response at 24wks
- Similar to BioSTAR studies
SEPTAL DEFECTS

- Possible benefits
  - Device endothelializes → dissolves → tissue septum
  - A non-rigid septum may improve atrial mechanics and reduce likelihood of erosion
  - Biodegradable devices may reduce the risk of AV block
    - Perimembranous VSDs
BIOABSORBABLE STENTS
CORONARY STENTS – HUMAN STUDIES

- Igaki-Tamai
  - PLLA
  - Kyoto Medical Planning Co., Ltd.

- Abbott ABSORB
  - PLLA
  - Abbott Vascular

- REVA
  - Tyrosine Polycarbonate
  - RevaMedical, Inc.

- BTI
  - PAE - Salicylate
  - Bioabsorbable Therapeutics, Inc.

- Biotronik DREAMS
  - Magnesium alloy
BIOABSORBABLE STENTS
WORK IN PROGRESS

Abbott
- PLLA stent
- PDLLA coating
- Everolimus drug

Medtronic
- Specific target applications to meet unique clinical needs
- Material development focused on less than 6-month degradation
- Ongoing stent design, evaluation and development

Reva
- Tyrosine-based polycarbonate
- Paclitaxel abliminal delivery
- Slide-and-lock design

Cordis
- PLGA/PCL-PGA
- Balloon-expandable
- Longer drug elution than Cypher

Biotronik
- Magnesium alloy (93% Mg)
- Have looked at 7 new alloys and 3 new designs
- Pimecrolimus-eluting stent under development

ART
- PLLA stent made from amorphous polymer
- Balloon-expandable
- Claim of positive remodeling

Biosensors
- PLLA/PLDA stent
- Self-expanding with retractable sheath

Igaki-Tamai
- PLLA material
- Polycaprolactone coating
- DES preclinical studies with ST638, ST494
- Balloon-expandable with covered sheath system

OrbusNeich
- PLGA/PCL-PGA stent
- Abluminal drug coating
- Luminal EPC capture

BTI
- Salicylic acid-based surface eroding stent
- Sirolimus eluting

Endovasc, Inc. (BioFlow, Inc.)
- Biodegradable stent for ureteral applications

TissueGen
- PLLA stent
- Spiral helical design
- Claim of growth factors/enzymes delivery

Tepha
- Combination: polyester based “TephaFLEX” and PLLA for added strength

Sahajanand
- PLLA and heparinized PLLA stent with genistein drug
- Balloon-expandable

Amaranth
- PLLA, self-expanding stent
- Multiple drug delivery
- Peripheral indication
BIOABSORBABLE STENTS

• Compassionate use of a magnesium alloy stent in premature newborn with LPA stenosis
  • B – LPA stenosis
  • D – Immediately post implant
  • E – 1 week post implant
    • White arrows identify stent site
  • F – 1 month post implant

COARCTATION

- Native CoA in a premature infant
- Access: right axillary artery
- Mg stent – 3.5 mm x 10mm

Angiography with 4F Judkins

Pre-Dilation
2mm x 20mm
to avoid stent slipping

AMS-Positioning
3.5 x 10mm

Magnesium Stent
Primary result

– courtesy of Dietmer Schranz
ABBOTT ABSORB STENT

ABSORB: Vasomotor Function Testing

The reappearance of vasomotion in the proximal, distal, as well as treated segments in response to methergine or acetylcholine suggests that vessel vasoreactivity has been restored and that a physiological response to vasoactive stimulus might occur anew.

VASCULAR RESPONSE

- Mass loss data suggests 100% of material mass lost by 2 years
- Although the shape of struts still apparent at 2 years, there has been gradual replacement with provisional matrix
- No inflammation around the pre-existing strut regions

- 3 years – struts fully replaced by tissue
- 4 years – strut sites are indiscernible

Porcine coronary arteries

3 years – courtesy of Abbott Vascular
BIODEGRADABLE STENTS

- Prototype
  - Early profile of a PediaStent biodegradable stent
Poly-L-Lactic acid (PLLA)

Fibers melt extruded
  - PLLA pellets at 180°C
  - Drawn to 100 µm

Novel BDS design
  - Balloon expandable
  - Internally coiled PLLA stent
  - Longitudinal fibers
  - Platinum tip markers for visibility
Finite Element Analysis

- Predicts expansion
- Validated in bench testing
- Permanent set caused by plastic yielding in torsion
- Localized to last converted portion of inner coil (white arrow)

Welch et al. Characterizing the expansive deformation of a bioresorbable polymer fiber stent. Annals of biomedical engineering 2008;36:742-51
**DOUBLE OPPOSED HELIX STENTS**

**Inner loop configuration**

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ø3mm (DH-3)</td>
<td><img src="image1" alt="Crimped" /> <img src="image2" alt="Expanded" /></td>
</tr>
<tr>
<td>Ø4mm (DH-4)</td>
<td><img src="image3" alt="Crimped" /> <img src="image4" alt="Expanded" /></td>
</tr>
<tr>
<td>Ø5mm (DH-5)</td>
<td><img src="image5" alt="Crimped" /> <img src="image6" alt="Expanded" /></td>
</tr>
<tr>
<td>Ø6mm (DH-6)</td>
<td><img src="image7" alt="Crimped" /> <img src="image8" alt="Expanded" /></td>
</tr>
</tbody>
</table>
DOUBLE OPPOSED HELICAL BDS COMPUTER MODEL STENT EXPANSION
DH STENT APPOSITION

Dual Helical
Sections of rabbit iliac artery and lower descending aorta stained with H&E illustrating luminal support at the proximal and distal sections of the stent. The vessels are supported by the stent are wide and patent. Bar = 100 μm.
A contiguous section H&E stain and Hart’s elastin at 1 month and 9 month at 20x magnification (the neointimal response is evident (NI). The internal elastic lamina (IEL) is intact. Bar = 100 μm.
Options:
• more material (triple opposed helix)
• thicker fiber
• blended fiber
• increase MW
8MM STENTS IN DAO: 1 MONTH

16-20kg minipigs.
9Fr sheath
8mm too small for species
9 month follow-up
9 MONTH FOLLOW-UP

Fig. 16. IVUS and H&E staining of 8 mm PLLA stent in DAO at 1 and 9 months. * = stent strut; NI = neointima
Fig. 4 Displaying the different diameter sizes noting the number of coils per design for the crimped and expanded stents.
REMAINING QUESTIONS

• How will the stent behave in the large vessels?
  • Radial strength at larger diameters
  • Effect of aorta pulsatility

• Vessel response as stent loses radial strength?
  • Vessel recoil or restenosis
  • Retain expanded diameter, requiring later reintervention
  • Allow later somatic growth of vessel

• Will fragments embolize after differential dissolution?
  • Where will fragments go?

• What happens when the device dissolves?
  • Will ASDs/VSDs recanalize as device dissolves?
SUMMARY

- Many procedures cannot be offered due to restraints in devices or attributes of patients
- Our smallest patients cannot benefit from some of our more refined techniques
- Biodegradable devices provide an important solution
  - Overcome the limitations of permanent devices
  - Allow small devices to be implanted without concern for somatic growth
- Loss of the device’s rigid scaffold may restore functionality to the target vessel or cardiac region
- These devices will allow us to expand the reach of procedures
  - Avoid unnecessary surgeries
  - Include neonates and small children
Thank you