RESEARCH HIGHLIGHTS IN THE NEWS

Dr. Steven Bradley was interviewed for Twin Cities Public Television’s (TPT) Coronavirus – An Almanac Special on April 17. Follow MHIF on social media or visit tpt.org/Almanac/ to see the full episode.

Dr. Santiago Garcia was interviewed by Health News Daily and quoted in a story published in U.S. News & World Report. Is COVID-19 Causing More People to Suffer Heart Attacks at Home?

Interested in MHIF Updates During COVID-19? Visit mplsheart.org/coronavirus/

MHIF FEATURE:

HemoLung Emergency Use of ECCO2R
Dr. Saavedra-Romero

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MHIF Research Tiger Team ready to support HemoLung with 24/7 onsite research coverage!

Carina Benson, Jake Jensen, Andrew Nauertz, Alyssa Taffe, Lisa Tindell, Kari Williams
Vascular brachytherapy, the rise of the Phoenix

Michael Megaly, MD, MS
April 20th, 2020

Still no disclosures!!
Objectives

1- What is recurrent (resistant) in-stent restenosis?

2- Vascular brachytherapy; mechanism, outcomes, and current use

3- Future directives

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In-stent restenosis (ISR)

Not only important for interventional cardiologists

Major limitation

Understand options of treatment
Restenosis

- Lumen diameter reduction after PCI
- Angiographic diagnosis

Target lesion revascularization (TLR)
(revascularization of the same lesion)

- 1-Angiography driven (ISR >70%) or Ischemia driven (symptoms or stress test)
- 2-TVV (target vessel revascularization) is revascularization of the same vessel.
Pre-stent era
(32%-55%)

BMS
17-44 % (2-5 years)
DES

ISR up to 20%
TLR 2-6% at 1 year (and increasing)

10% of PCI in NCDR are for ISR

Is it bad?

Recurrence of angina symptoms

Acute coronary syndrome (10%)

Independently associated with 4-year mortality (Cassesse 2015, EHJ) 10,004 patients
Patterns

**ISR Pattern I: Focal**

- **Type IA:** Articulation or Gap
- **Type IB:** Margin
- **Type IC:** Focal Body
- **Type ID:** Multifocal

**ISR Patterns II, III, IV: Diffuse**

- **ISR Pattern II:** Intra-stent
- **ISR Pattern III:** Proliferative
- **ISR Pattern IV:** Total Occlusion
1-Elastic recoil
Elastin fibers
few seconds up to minutes after balloon deflation

2-Vascular remodeling
Vessel injury
Vascular smooth muscle cell proliferation or migration and activation, mitogens and cytokines
3-Inflammation by stent struts

Injury, Inflammation, hypersensitivity, discontinuity of endothelium trapping blood elements

Inflammation around stent struts; Minimal remodeling because of the stent
Fibro-intimal hyperplasia
VSMCs migration, proliferation, and ECM production (neo-intimal hyperplasia)

Post-stent implantation
Stent struts
Activation of platelets, leukocytes, coagulation cascade, and VSMCs
Endothelial denudation, rupture of BM, medial dissection, and apoptosis
Atherosclerosis/stenosis
Endothelium and BM
Sub-endothelial space with lipids
Internal elastic membrane
Medial VSMC layer
In-stent Restenosis
116 stented lesions (at least 90 days) → postmortem detailed histological analysis
Greater accumulation of inflammatory cells (2.4-fold increase) in restenosis lesions

What else?
4-Neoatherosclerosis

What??

Atherosclerotic lesions affecting the neointima

Can be calcific

Can occur at anytime (earlier in DES)

Correlated with late stent thrombosis

(Nakamura 2016 Circ Intv.)
More frequent in DES and occurs earlier

Autopsies of 406 stented vessels
DES mean 1.5 years; BMS median 6 years
Longitudinal extension is less in the DES and higher fibrous cap thickening

OCT of 98 lesions (1st gen DES neoatherosclerosis 68%, second gen DES 30%)

Nakamura 2019 Circulation J
Patients

Diabetes (IGF-1 induced neointimal hyperplasia)

Hemodialysis

Certain polymorphisms

Lesions

Inhomogeneous distribution of the drug calcification, tortuosity

Underlying unstable lesion

Stent deployment problems (malapposition, underexpansion, edge dissection)

Long stents (>32 mm) Small stents (< 3 mm)

Stent fracture
Stent under expansion
Minimum lumen area <90% of the average reference lumen area

Mal-apposition

Detected by IVUS/OCT only
Gaps > 200 microns
Mal-apposition has more concern with DES than BMS.
Non-contact zones lack drug delivery resulting in inhomogenous neo-vascularisation.

How many struts?
200 Microns?*
One strut thickness?*
Late stent malapposition

1- Positive remodeling of the vessel

2- Dissolution of the thrombus or partial regression of atherosclerotic plaque
   SCAD

3- Chronic stent recoil.

Edge dissection
Stent fracture (1-8%)

Type 1

Type 2

Type 3

(a)

(b)

Residual stenosis or major neointimal dissection $\rightarrow$ diffuse ISR $\rightarrow$ TLR

(Tanaka 2016, JACC)

Target lesion revascularization

<table>
<thead>
<tr>
<th>No at risk</th>
<th>Inadequate</th>
<th>Adequate</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

A

B

$P = 0.04$

$P = 0.04$

$P = 0.57$
Prevention

1- Good lesion preparation

2- Post-dilation

3- Using intravascular Imaging

Drug-eluting stents

1- platform (e.g., thin-strut cobalt chromium vs. thick-strut stainless steel)

2- polymer (thinner and/or biodegradable and/or its absence)

3- drug (biolimus and zotarolimus).

TLF in newer generation stent is about 5% first year, 12% over 5 years
What about treatment?

FFR cut-off 0.80 is validated to guide treatment

Guidelines for Treatment of ISR

Balloon angioplasty, BMS, DES

DES, DCB
Guidelines recommendations mostly apply to the treatment for first episode of ISR.

Treatment of DES ISR is not clear like BMS ISR (Drug failed one already).

ISAR-DESIRE 2
DES for SES-ISR

450 patients
Clinical follow-up at one year

![Graph showing outcomes for ISAR-DESIRE 2 study]
Garg et al. 2007 CCI

116 patients

<table>
<thead>
<tr>
<th>Table IV. Twelve-Month Major Cardiac Adverse Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different DES</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>TVR</td>
</tr>
<tr>
<td>TLR</td>
</tr>
<tr>
<td>MACE-TVNR</td>
</tr>
<tr>
<td>MACE-TLR</td>
</tr>
<tr>
<td>Stent thrombosis</td>
</tr>
</tbody>
</table>

TVR, target vessel revascularization; TLR, target lesion revascularization; MACE, major adverse cardiac events.

Siontis 2015, Lancet
Largest network meta-analysis to date

First line
DES (EES)
DCB

BA, VBT, ROTA, and BMS are inferior

The study did not include resistant ISR
Resistant (recurrent) intrastent restenosis

Recurrent (resistant) ISR

1. More than one episode of ISR.
2. Last layer of stenting is DES.
Theodoropoulos et al. 2016, CCI

19,982 patients (PCI with DES)

- 10.8% ISR
- 1.4% resistant ISR
Theodoropoulos 2016, CCI

Kawamoto et al. 2015, JACC INT (171 lesions with resistant ISR)
Kubo et al. 2013 EuroIntervention

142 patients with resistant ISR (2 layers) - 4 years
Compared BA vs. DES

Yabushita et al. 2018, Circ Int. (304 patients)

TLR

at 1 year
14.5%, 14.9%, and 41.2%
Log rank $P < 0.01$
Conclusion of these numbers?

1-highly complex lesions

2- high incidence TLR
   27% in 2 years (the least complex subset)

41% in one year (the most complex subset with 3 layers of stents).

Why does it happen?

1- More metal layers→ more difficult to expand

2- Inflammatory responses to drugs/polymers/struts

3-Drug resistance
Intracoronary vascular brachytherapy (VBT)

1-Reduces neointimal growth  
   a-reduces vascular smooth muscle proliferation  
   b-reduces adventitial fibrosis and vessel remodeling  
   c-Interrupting the cell cycle and causing apoptosis

2-Reduces inflammation  
   a-reduces leukocyte chemotaxis and cytokine induction  
   b-reduces matrix secretion by macrophages  
   c-reduces proinflammatory cells

Ionizing radiation

Waksman 1997 Circulation  
Kuchulakanti 2005 CRM
Intravascular radiation

**Gamma** (Iridium Ir 192)

**Beta** (stronium-90/yttrium-90 isotope)

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**Safety**
- Single arm studies
  - Silber 2000. Z Kardiolo

**RCTs (BMS ISR)**
- Waksman 2000 Circulation (15 Gy)
- Leon 2001 NEJM

Approval for BMS ISR

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**Human studies**

![Graph showing freedom from TLR (%)](image)

- **Iridium**
- **Placebo**

**p = 0.0001**
Drug-eluting stents were superior in BMS ISR
Holmes 2006 JAMA
Stone 2006 JAMA

Death of the phoenix
VBT in DES ISR

• Torguson 2006, AJC (VBT vs. DES)
  TLR was similar between both at 8 months
  (10% vs 18%, p was nonsignificant)

• Bonello 2008, J Int Card
  TLR 11% at one year

Maluenda et al. 2012, Circ Interventions (VBT vs. DES)
10.3% re-DES, 14.1% (VBT), 14.6% (balloon)
Resistant DES-ISR

Re-DES is challenging and unlikely to be successful

VBT
- No additional layers of metal or polymers
- No encroachment on an already narrowed lumen
- Less inflammation
- Avoid drug resistance
**Negi et al. 2016 JACC**

Medstar, Washington
186 patients (283 lesions) (2004-2012)

![Table](image)

**Mangione et al. 2017 AJC**

Brigham and Women’s hospital, Boston
101 patients (101 lesions) (2009-2015)

![Table](image)
Mangione et al. 2017 AJC

Table 4
Adjusted model for target vessel revascularization

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.37</td>
<td>1.02 - 5.52</td>
<td>0.04</td>
</tr>
<tr>
<td>Previous stroke/transient ischemic attack</td>
<td>2.40</td>
<td>0.55 - 10.48</td>
<td>0.24</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0.49</td>
<td>0.20 - 1.20</td>
<td>0.17</td>
</tr>
<tr>
<td>Left internal mammary artery treated</td>
<td>3.95</td>
<td>0.88 - 17.90</td>
<td>0.07</td>
</tr>
<tr>
<td>Diffuse in-sit resting</td>
<td>2.95</td>
<td>1.21 - 7.17</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.14</td>
<td>0.02 - 1.35</td>
<td>0.09</td>
</tr>
</tbody>
</table>

p < 0.05 are indicated in bold.

Meraj et al. 2020 CCI

Northwell Hospital, NY
290 patients (290 lesions) (2011-2016)

Number of previous ISR procedures

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160(61.33%)</td>
<td>70(26.8%)</td>
<td>24(9.2%)</td>
<td>3(1.1%)</td>
<td>3(1.1%)</td>
<td>1(0.4%)</td>
</tr>
</tbody>
</table>

Events on follow up

<table>
<thead>
<tr>
<th></th>
<th>1-year (n = 290)</th>
<th>2-year (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instant re-stenosis</td>
<td>36 (12.4%)</td>
<td>42 (14.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5 (1.7%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (3.4%)</td>
<td>11 (3.9%)</td>
</tr>
</tbody>
</table>
Only study to have a control arm
Resistant ISR with at least 2 layers of stents (2011-2015)

197 patients/lesions in VBT group/131 in control group

Propensity matched analysis (91 patients/lesions in each group)
Our results

Outcomes of intravascular brachytherapy for recurrent drug-eluting in-stent restenosis

Michael Megaly MD, MS1,2 | Matthew Glogoza MD1 | Iosif Xenogiannis MD1 | Evangelia Vemmou MD1 | Ilias Nikolakopoulos MD1 | Laura Willson MD3 | David J. Monyak MD3 | Patsa Sullivan MD3 | Larissa Stanberry PhD1 | Paul Sorajja MD1 | Ivan Chavez MD1 | Michael Mooney MD1 | Jay Traverse MD1 | Yale Wang MD1 | Santiago Garcia MD1 | Anil Poulou MD1 | Martin Nicholas Burke MD1 | Emmanouil S. Brilakis MD, PhD1

2014-2018

116 patients (143 lesions) with recurrent drug-eluting stent restenosis (95.5% after second-generation DES)

Vascular brachytherapy

Mean radiation activity: 22.6 Gray
Median radiation time: 4.55 minutes
Reference vessel diameter: 3.5 ± 0.8 mm
History of CABG (53.8%) Target vessel is a vein graft (11.9%)
### Clinical presentation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable angina</td>
<td>67</td>
<td>46.9%</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3</td>
<td>2.1%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>47</td>
<td>32.9%</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>25</td>
<td>17.5%</td>
</tr>
<tr>
<td>STEMI</td>
<td>1</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

### Restenosis pattern on the initial angiogram

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Count</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>55</td>
<td>60.4%</td>
</tr>
<tr>
<td>Diffuse</td>
<td>21</td>
<td>29.9%</td>
</tr>
<tr>
<td>Proliferative</td>
<td>5</td>
<td>1.5%</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>12</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

### Last DES type

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation</td>
<td>137</td>
<td>95.8%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

### Previous stent layers

<table>
<thead>
<tr>
<th>Layers</th>
<th>Count</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>16.8%</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>46.2%</td>
</tr>
<tr>
<td>3 or more</td>
<td>53</td>
<td>37%</td>
</tr>
</tbody>
</table>

### Total ISR episodes

<table>
<thead>
<tr>
<th>Episodes</th>
<th>Count</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16</td>
<td>11.2%</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>42%</td>
</tr>
<tr>
<td>4 or more</td>
<td>57</td>
<td>40%</td>
</tr>
</tbody>
</table>
A little reminder

1- highly complex lesions

2- high incidence TLR
   27% in 2 years (the least complex subset)
   41% in one year (the most complex subset with 3 layers of stents).

Using IVUS was associated with lower risk of target lesion revascularization
14.3% vs. 39.6% (log-rank p = 0.038)

Log rank p=0.038
Independent predictors of Target lesion failure

Initial presentation with acute coronary syndrome (HR 2.04 (95% CI 1.16-3.59), p=0.019)

The procedure
Novoste Beta-Cath 3.5F System

**Beta radiation**
stronium-90/yttrium-90 isotope  
(less penetration- safer)

Energies up to 2.27 Mev  
Radioactive half-life of 28.8 years.

Source lengths of **40 and 60 mm**

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**Amount of radiation delivered**
18.4 or 23 Gy at a depth of 2 mm from the center of the source

**Dwell (treatment time)**
Up to 5 minutes  
determined by both the source length and vessel diameter.
Connect to the catheter
Active seeds are pushed in and then back through a train by hydraulic pressure.
Seed retraction
Survey at the end
VBT concerns and are they addressed currently

1- Edge restenosis (geographic mismatch)
Radiating proximal and distal to the lesion

2- Late stent thrombosis especially with concurrent stent placement.
No stenting, Newer antiplatelet agents

3- Late catch up phenomenon between 6 and 60 months
**Proposed approach to drug-eluting stent in-stent restenosis**

### First restenosis event

**Intravascular imaging (OCT or IVUS)**

- **Mechanical factors**
  - Stent underexpansion
  - Stent malapposition
    1. Full expansion and apposition of the stent
    2. Second-generation DES, DCB, or consideration of CABG (according to patient preference)

- **Stent fracture**
  - Second-generation DES or consideration of CABG according to patient preference

- **No mechanical factors**
  1. Confirm compliance with medications and control other comorbidities (e.g., DM)
  2. Second-generation DES, DCB, or consideration of CABG according to patient preference

### Recurrent restenosis

**Intravascular imaging (OCT or IVUS)**

- **Mechanical factors**
  - Stent underexpansion
  - Stent malapposition
    1. Full expansion and apposition of the stent
    2. Second-generation DES
    3. DCB (only for second restenosis event)
    4. Consider VBT
    5. Consider CABG

- **Stent fracture**
  - 1-second-generation DES
  - 2-Consider VBT
  - 3-Consider CABG

- **No mechanical factors**
  1. Confirm compliance with medications and control other comorbidities (e.g., DM)
  2. DCB (only for second restenosis event)
  3. Consider VBT with or without stenting with a second-generation DES

(Megaly 2020 CCI)
Take home


2. First step in evaluation of ISR is intravascular imaging.

3. Vascular brachytherapy for resistant DES ISR. TLR in complex subset of lesions is 30% at 3 years.

Thank you

@MichaelMegalyMD
Michaelmegaly3@gmail.com
http://www.youtube.com/c/CathEdLearningInterventionalCardiology