Revascularization of Chronic Total Occlusions

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PCI for Chronic Total Occlusions

“The Last Great Frontier of Interventional Cardiology”
Chronic Total Occlusion - CTO

- 100% narrowing of the artery
- No angiographically detectable antegrade flow (TIMI flow = 0)
- > 1 month old

Baim DS, Ignatius EJ. Am J Cardiol 1998;61:3G-8G
CTOs in Perspective
NHLBI Dynamic Registry and BARI study 1997-1999, n=1,761

- Presence of total occlusion 31%
- Attempted total occlusion 7.5%

Srinivas et al. Circulation 2002
Current Treatment of CTO

30% coronary atherosclerosis
and >50% peripheral atherosclerosis patients present
with total occlusions

Only 12-13% pts currently treated in cath lab
CTO: What’s In the Lumen?

1. Intimal Atherosclerotic Plaque

Necrotic Core, cholesterol, calcium
CTO: What’s in the Lumen?

Proteoglycans common in CTO<1 yr
Increased fibrocalcific plaques with ↑ age

Srivatsa et al, J Am Coll Cardiol 1997;29:955-63
**CTO: What’s in the Lumen?**

**Microvessels**

Intraluminal recanalization channels: 49% of angiographic CTO <99% occluded by histology. No differences according to age of CTO. Microvessels also common in intimal plaque and adventitia.

Srvitsa, JACC 1997:955-63

**Tapered CTO:**

Small luminal recanalization channels.

Katsuragawa, JACC 1993
Microvessels
41% of all CTOs

Proximal “End”

Endoluminal Microchannel
Theoretical rationale for CTO Revascularization

• Increased long-term survival
• Improved left ventricular function
• Electrical stability of myocardium and reduced predisposition to arrhythmic events
• Increased tolerance of future acute coronary syndromes, mainly occlusions
Clinical rationale for CTO intervention

Lamas GA et al, Circulation 1995
Long-term survival associated with successful CTO revascularization
Late open artery theory

<table>
<thead>
<tr>
<th>Trial</th>
<th>Success N</th>
<th>Failure N</th>
<th>Follow-up years</th>
<th>Mortality, % Success</th>
<th>Mortality, % Failure</th>
<th>P</th>
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<tbody>
<tr>
<td>British Columbia Registry</td>
<td>1118</td>
<td>340</td>
<td>1</td>
<td>10.0</td>
<td>19.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Suerro et al.</td>
<td>1491</td>
<td>514</td>
<td>10</td>
<td>26.6</td>
<td>35.0</td>
<td>0.001</td>
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<tr>
<td>TOAST GISE</td>
<td>286</td>
<td>83</td>
<td>6</td>
<td>1.1</td>
<td>3.6</td>
<td>0.13</td>
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</table>
### Long-term outcome after intended revascularization of non-acute CTOs

#### Multivariate mortality model

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Failure</td>
<td>2.27</td>
<td>1.56-3.30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.33</td>
<td>1.12-1.58</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF&lt;50%</td>
<td>2.33</td>
<td>1.58-3.43</td>
<td>&lt;0.0001</td>
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<tr>
<td>Multivessel CAD</td>
<td>1.62</td>
<td>1.09-2.40</td>
<td>0.02</td>
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<tr>
<td>Prior CHF</td>
<td>1.73</td>
<td>1.10-2.76</td>
<td>0.02</td>
</tr>
<tr>
<td>ESRD</td>
<td>2.77</td>
<td>1.36-1.56</td>
<td>0.005</td>
</tr>
<tr>
<td>COPD</td>
<td>1.64</td>
<td>1.01-2.67</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.50</td>
<td>0.99-2.27</td>
<td>0.055</td>
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</table>

Ramanathan and Buller, TCT 2003
Technical Issues

• **Technically challenging**
  – Organized fibrocalcific atherosclerotic plaque
  – Difficult visualization
  – >75% - inability to cross with a guide-wire

• **Time consuming**
  – >60 min procedure
  – >20 min of fluoro time is typical
Guidelines – PCI of CTO

- ESC – class IIa level C

- Class III
  - Small area of viability
  - No ischemia
  - Low likelihood of success
PCI Limitations

- **Success rate:** 20-74% of attempted cases
- **Predictors of success:**
  - Age of occlusion
  - Vessel diameter
  - Location
  - Degree of calcification
  - Bridge collaterals
  - Operator dependent
    - Experience
    - Patience and persistence
- **Time, radiation exposure, and difficulty often discourage CTO revascularization attempts**
Angiographic predictors of poor outcome (traditional)

- Long gap
- Non-tapering stump
- Side-branch at occlusion
- Vessel turtuosity
- Calcification
- Ostial location
- Poor distal vessel visibility
- Bridge collaterals
Other factors to consider

- Access / backup (iliac and aortic turtuosity)

- Renal function

- Risk of CABG

- Operator experience
How to do (CTO) Angioplasty in 3 easy steps!!!

1. Cross CTO with 0.014” Guidewire

2. Inflate balloon that was advanced over the guidewire

3. Deploy stent that is mounted on a second angioplasty balloon catheter
Step #1: Advancing the guidewire through the blockage

- Usually like pushing through concrete
- Conventional guidewires usually unsuccessful

• Mechanical Approaches:
  - Dedicated CTO Guidewires
  - Specialty Guidewires
  - Specialty Devices

• Biological Approaches:
  - Plaque Softening
  - Intraluminal Angiogenesis
Guide-wire selection

- Floppy tip – selection >> penetration
- Intermediate – selection > penetration
- Stiff tip – selection < penetration
- Ultra-stiff tip – selection << penetration
- Tapered tip – selection << penetration
- Coated wire – better torque
Comparison of wires

Tip Push Force
Antegrade wire techniques

- One wire technique
- Parallel wire technique
- Multiple wire technique
Parallel wire technique
Bilateral parallel wire technique
Parallel wire technique
Utility of intravascular ultrasound

- IVUS can differentiate a true lumen from a false lumen by identifying side branches (which arise only from the true lumen) and intima and media (which surround the true lumen, but not the false lumen).

- IVUS can confirm when the guidewire has reentered the true lumen from a false lumen.

- IVUS studies have also revealed that the major reason that it is difficult to penetrate the distal cap into the true lumen is that the guidewire tends to deflect into a false channel, not because of extensive calcification or fibrosis.
1\textsuperscript{st} wire into false lumen
2\textsuperscript{nd} wire in true lumen
C+D: wire is confirmed in true lumen
E+F: IVUS imaging of false lumen
J: septal branch
Ostial occlusion
Initial Success Rate

79.8% (835/1046)
## Guide wire crossing technique

(Jan. ’06 – Dec. ’06, n=170 lesions)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Count</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Antegrade single wire technique</td>
<td>167</td>
<td>98%</td>
</tr>
<tr>
<td>Parallel wire technique</td>
<td>50</td>
<td>29%</td>
</tr>
<tr>
<td>IVUS guide wire crossing</td>
<td>11</td>
<td>6%</td>
</tr>
<tr>
<td>Retrograde approach</td>
<td>50</td>
<td>29%</td>
</tr>
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</table>
Subintimal Tracking and Reentry (STAR)

OTW balloon injection creates tubular dissection

“Umbrella handle” tip wire advanced via OTW balloon

Wire advanced into true lumen
After crossing with wire.....

- Low profile micro-catheters

- Low profile balloon
  - Ryujin 1.25mm
  - Avion 1.25mm

- Tornus
Role of CTA

• Predictors of failure
  – Length > 15 mm
  – Severe calcifications

• Angiographic predictors
  – Blunt entrance into occlusion

• CTA length was routinely longer than angiographic estimation

Mollet et al. Am J Cardiol 2005
Length of the Occlusion
Assessment of distal vessel & sidebranches
Definition of intra-occlusion angle
Dedicated CTO Guidewires

- Asahi
  - Miraclebros – excellent torque (3g-12 g)
  - Confienza, Confienza Pro-pentration (9g-12g)
- Medtronic
  - Persuader
- Cordis
  - Cross-it

Advantages are operator familiarity with conventional guidewires.
However these are stiffer guidewires with risk of perforation.
Specialty Guidewires

- Interesting novel technology
- Require some differences in techniques from conventional guidewires
CTO Technologies

• Specialized guide-wires
  – Shinobi, Miracle Bros., Conquest…

• Lumend Frontrunner Catheter (blunt micro-dissection)

• Safe Cross system - Optical Coherence Reflectometry (OCT)

• US
LuMend Frontrunner Catheter
Controlled Blunt Micro-Dissection Technique

- Separates atherosclerotic plaque in various tissue planes, creating a passage through the CTO

- Uses the elastic properties of adventitia versus inelastic properties of fibrocalcific plaque to create fracture planes
Frontrunner: Controlled Blunt Micro-Dissection
Frontrunner Catheter: Clinical Study

- Prospective, controlled multi-center trial
- 107 patients
- CTOs refractory to 10 min (fluoroscopy time) conventional GW attempt
- Success defined as placement of guide wire beyond CTO in the true vessel lumen
- Mean lesion length: 22 mm (range 2 – 53 mm)
Frontrunner Clinical Results

Success rates

- Access CTO: 89.7%
- Cross CTO: 61.7%
- Wire distal true lumen: 56.1%

Complications

- Death: 0.9%
- Perforation: 1.9%
- MI: 1.9%
- Other: 3.7%

Feb 2002: FDA 510k Clearance
Safe Cross – IntraLuminal Therapeutics

Optical Coherence Reflectometry (near-infrared light) guidance system
Coupled to pulse radiofrequency ablation
January 2004: 510k clearance from the FDA for coronary occlusions
OCR Waveform Displays

No artery wall detected

Artery wall detected

No artery wall detected
GREAT

Guided Radio Frequency Energy Ablation of Total Occlusions
GREAT Study Overview

• Originally begun as a randomized trial at 10 sites
  • Native CTO (> 2.5 mm, < 30 mm length)
  • 1:1 randomization of treatment with the SAFE-CROSS™ RF versus current standard wires
  • 30 day safety and efficacy endpoints
  • Patients who failed the conventional wire can enter GREAT Registry after 30-days -> OCR
• Later converted to 116 patient registry, after a failed 10 minute attempt attempt with a conventional wire (~Lumend study)
• Device Success 55.7%

• Reasons for failure
  • Wire unable to progress 81%
  • Entry of false lumen 25%

• Perforation 12%
  • Wire exit or local stain 6.7%
  • Extravasation 0.7%
GREAT

- Complications: 6.0% (9)
  - Q-MI, CABG, Death: 0%
  - MACE (all NQMI): 4.7% (7)
  - Clinical Perforations: 2.6% (4)
    - Device related: 0.7% (1)
CROSSER System - FlowCardia Inc.

FlowCardia CROSSER System
High frequency mechanical revascularization

High frequency mechanical vibrations at 20 kHz
Vibrational energy provides cavitational effects
CTO: Therapeutic Ultrasound

Device Positioning

US Energy

Wire Passed
# CTO - Results of New Technologies

<table>
<thead>
<tr>
<th>Device</th>
<th>Application</th>
<th>N</th>
<th>tech. success</th>
<th>perforations</th>
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<tbody>
<tr>
<td>LUMEND</td>
<td>Frontrunner</td>
<td>105</td>
<td>56%</td>
<td>1.9%</td>
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<tr>
<td>GREAT</td>
<td>Safe-cross</td>
<td>116</td>
<td>56%</td>
<td>2.6%</td>
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<tr>
<td>GRIP</td>
<td>Safe-cross</td>
<td>72</td>
<td>76%</td>
<td>0</td>
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</table>
Should we develop a non-mechanical, biological modality to facilitate CTO revascularization?

How about enzymatic degradation?
Pathology of Chronic Total Occlusions: Human Coronary Arteries

- Majority (78%) of angiographic CTO are ≈99% occluded by histology
- Collagen: Major structural components of the extracellular matrix
- Proteoglycans are common in CTO < 1 yr
- Intimal plaque micro-vascular channels are common in CTO (>75%)

Courtesy of Dr. Renu Virmani, AFIP, Bethesda
Rabbit Model of Femoral Artery CTO
Rabbit femoral artery

Thrombin injection
Restoration of blood flow after 1 hour
Angiographic confirmation of occlusion at 3-4 months

-thrombus / fibrin is replaced by fibrotic tissue (collagen)
Chronic Total Occlusions: Rabbit Femoral Model

CTO by MRI
Proteinases

Enzymes that catalyze the breakdown of native proteins
Matrix Metalloproteinases

- Zinc and calcium-dependent enzymes
- >20 members
- MMP-1, MMP-2, MMP-9, MMP-3
- degrade all extracellular matrix components
- 3 broad categories: 
  - collagenases (MMP-1), gelatinase, and stromelysins
Gelatinase Activity After Arterial Injury

Strauss et al, Circ Res 1996;79:541

Li et al, JACC 2002;39:1852-8
Type IA Collagenase (Sigma)

- **Source:** Clostridium histolyticum

- **Components**
  - Collagenase
  - Clostripain
  - Neutral Protease
  - Trypsin-like activities
CTO in femoral artery

Advancement of an over-the-wire balloon and local injection of collagenase solution while balloon remains inflated (1 hour)

Balloon removal

Successful guide-wire crossing after 24 hours
Collagenase: Successful Guide Wire Crossing

Rabbit #849
Right side
13 weeks after occlusion

Rabbit 849 Right Femoral Artery
CTO Characteristics

• Occlusion Age: 16 ± 5 weeks
  (range 10-25 weeks)

• Mean occlusion length: 28 ± 9 mm
  (range 14-46 mm)
Guide Wire Crossing Success Rates at 72 Hours Post Infusion

*\( p=0.028 \) vs. placebo
Guide Wire Crossing at 72 hours

- Success
  - Collagenase 450 µg

- Failure
  - Placebo
Treatment Effects At 24 Hours
(No Guide Wire Attempt)

Collagenase 450 µg
Placebo

24 hours: Proteolytic Effects

Gelatin Zymogram

- Lane 1 - Collagenase artery
- Lane 2 - Placebo artery

Collagen Fragments Western Immunoblot
COL 2 3/4 Against Carboxy Terminus

Purified Collagenase:

- 38-fold more potent than Sigma collagenase preparation
- No contaminating proteolytic activity
- Suitable for human studies
Rabbit Femoral CTO Model

Dosing Study:
100-200 µg (n=10) no or mild subcutaneous bruising
250-500 µg (n=7) moderate-severe sc bruising

Guide Wire Crossing at 24 Hours
150 µg (n=10)
100% Successful !!
Subcutaneous Bruising

500 µg collagenase

150 µg collagenase
Rabbit CTO cross sections with successful crossings

Segev A et al. JVIR, Submitted
Gelatinase Activity at 24 Hours: 150 μg

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Collagenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Pro MMP-9
Active MMP-9
Pro MMP-2
Active MMP-2

Segev A et al. Submitted
Intra-coronary Purified Collagenase: Swine Hearts

Site of balloon inflation

Area treated by collagenase

LAD
Control

50μg

75μg

150μg

450μg

1000μg
Arterial Medial Damage
Only at High Dose (450 µg)

Segev A et al. Cardiovasc Pathol, Submitted
1-Month follow-up

- 9 pigs
- Intra-coronary collagenase:
  - 150, 450, 1000µg
- Macroscopically normal
- 2/3 pigs with high dose showed normal myocardium with no fibrosis.
- 1 pig showed mild fibrosis.
Conclusion

• Local delivery of collagenase facilitates guide-wire crossing in chronic total occlusions

• No adverse effects on arterial structure

• Local bruising is a dose related side effect

• Human phase I study is planned
Phase I Clinical Trial

- **Objective**
  - To determine the safety and efficacy of 3 different doses of a human-grade purified collagenase for the treatment of failed coronary chronic total occlusion (up to 1 year old).

- **Inclusion criteria:**
  - Patients with CTO with a clinical indication for revascularization.
  - CTO ≤ 1 year old.
  - Previously failed coronary intervention or if patient recruited as an ad hoc, failure to cross the occlusion with conventional wires after 10 minutes (FDA definition).

- **Exclusion criteria:**
  - Saphenous vein graft occlusion
  - True ostial LAD, LCX or RCA occlusions
  - Major side branch immediately proximal to the occlusion
Phase I Clinical Trial

- **Protocol:**
  - Confirmation of failed conventional PCI attempts and no exclusion criteria.
  - Advancement of a short over-the-wire balloon until against the occlusion and removal of wire.
  - Inflation of the balloon to nominal size.
  - Slow injection of collagenase solution through the balloon lumen.
  - The balloon remains inflated for up to 1 hour depending on patient’s tolerability.
  - ACT > 300 seconds throughout the procedure.
  - Balloon deflation.
  - Patient remains in hospital and will be ECG monitored and serial blood samples for cardiac enzymes taken.
  - The day after, repeat conventional PCI

- Three different doses will be tested: 50µg, 75µg, and 100µg.
- Each group will consist of 6 patients. Total = 18 patients.
- The first dose to be assessed will be 50µg.
Future Research

1) CTO imaging

2) Augmentation of CTO Micro-Vessels by Cell Therapy with Engineered EPCs
MRI
CTO by micro-CT
Fibroblasts delivery into CTO
UNITED STATES PROVISIONAL PATENT APPLICATION

Inventors: Bradley H. Strauss of Toronto, Canada; and Amit Segev of Raanana, Israel.

AUGMENTATION OF INTRALUMINAL MICROVESSEL FORMATION TO FACILITATE GUIDE WIRE CROSSING IN CHRONIC TOTAL OCCLUSIONS
Conclusions

• Remember the pathology
• Clinical indication !!!
• Favorable angiographic appearance
• Consider CTA
• Advanced guide-wires techniques
  – No room for dedicated devices – so far…
• STAR and retrograde techniques – only if your last name rimes with SUZUKI