Ultrasound to Facilitate Drug Delivery and Treat Medial Calcium

Craig M. Walker, MD, FACC, FACP

Clinical Professor of Medicine
Tulane University School of Medicine
New Orleans, LA

Clinical Professor of Medicine
LSU School of Medicine
New Orleans, LA

Founder, President, and Medical Director
Cardiovascular Institute of the South
Houma, LA
### DISCLOSURES

<table>
<thead>
<tr>
<th>Consultant/Medical/Scientific Boards</th>
<th>Stockholders</th>
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<tr>
<td>• Abbott</td>
<td>• CardioProlific</td>
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<td>• Boston Scientific</td>
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<td><strong>PVD Training</strong></td>
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<td>• ACHL/Merck</td>
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<td>• Gore</td>
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<td>• Spectranetics</td>
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CHALLENGES IN PAD THERAPY

• **Calcification**
  - Present in > 75% of all CLI cases
  - Angiographically present in approximately 65% of the people treated
  - Angiograms detect less than 50% of all calcifications

• **CTOs**
  - Present in ~70% of all PAD cases (more in CLI)

• **Acute and Sub-acute thrombus**

• **Long Lesions**
  - Longer than 100mm are present in more than 50% of all PAD cases

• **Outflow**
New Approach to Treat CLI

Ultrasound to cross and remove acute and chronic thrombus and improve compliance + POBA + Ultrasound (to enhance vessel permeability) + Paclitaxel Delivery
• After POBA, Ultrasound Energy is used to change lesion compliance by creating additional cracks and micro channels in the media/intima calcifications to increase drug penetration to the vessel wall

• Contrast agent is used to deliver Paclitaxel (with a distal occlusive balloon to limit outflow) to the vessel wall
Genesis™ System

Hardware
- Generator
- ON/OFF Switch
- Irrigation Pump
- Transducer
- Foot switch cable

P-Catheter
- .8mm tip
- 1.6mm catheter
- RX any 0.014’guidewire
- 200 cm long
- 6F sheath compatible
- Ultrasound active member adjustable between 10-100mm
Crossing Chronic Total Occlusions
CardioProlific System Method of Action (2)

Thrombectomy Without Drugs
CardioProlific System Method of Action (3)

- Catheter Body
- Irrigation Outlet
- Catheter Tip Marker
- Intimal Plaque/Calcium After POBA
- Diseased Area After Balloon Angioplasty
- US Active Member
- Surface/Radial Waves
- Tip
- Vessel

Untreated Calcium Disc

Calcified Disc with US Created Microchannels
CardioProlific System Method of Action (4)

Catheter Body

Intimal Plaque/Calcium After POBA

Surface/Radial Waves

Tip

Vessel

Catheter Tip Marker

Irrigation Outlet

Diseased Area After Balloon Angioplasty

US Active Member

Introducer

Paclitaxel delivery

Intimal Plaque/Calcium Modified

Distal Balloon

\[C_{47}H_{51}NO_{14}\]
Ultrasound Frequencies Used For Medical Applications

- 20-100 kHz
  - Transdermal delivery of insulin, low-molecular weight heparin, vaccines
  - Ocular drug delivery
  - Sono-dynamic therapy

- 20 kHz
  - Audible region
  - Lipoplasty

- 20-50 kHz
  - Angioplasty

- ~200 kHz
  - Drug delivery to brain
  - Thrombolysis

- 25 kHz
  - Faco-emulsification

- 40 kHz
  - Ocular drug delivery

- 600 kHz
  - Gene delivery

- 700 kHz
  - Gene delivery

- 850 kHz
  - Reduced arterial hyperplasia

- 1 MHz
  - Gene delivery
  - Drug delivery to brain
  - Osteoporosis

- 1.5 MHz
  - Gene delivery
  - Drug delivery to brain
  - Osteoporosis

- 1.5 MHz
  - Gene delivery

- Thrombolysis

- Hyperthermia

- Sciatic nerve repair

- 2 MHz

- 2.25 MHz

- 10 MHz
  - Nebulizers (asthma)

- 1 MHz

- Diagnostics
Ultrasound-Mediated Therapies

a - Transdermal drug delivery
b - Targeted drug delivery
c - Clot lysis
d - Healing of bone fractures
e - Ultrasound thrombolysis
Gene expression was enhanced 10-fold.
Animal Study

OBJECTIVE:
Ultrasound Impact on Paclitaxel Vessel Uptake /Permeability

![Graph showing Paclitaxel acute vessel uptake with data points for Vessel #1 Paclitaxel Alone, Vessel #2 Ultrasound 10 sec + Paclitaxel, Vessel #3 Ultrasound 20 sec + Paclitaxel, and Vessel #4 Ultrasound 30 sec + Paclitaxel.](graph1)

![Graph showing Paclitaxel 30 days vessel uptake with data points for Vessel #1 Paclitaxel Alone, Vessel #2 Ultrasound 30 sec + Paclitaxel, Vessel #3 Ultrasound 30 sec + Paclitaxel, and Vessel #4 Ultrasound 30 sec + Paclitaxel.](graph2)
Ultrasound Sonophoresis is commonly used for increasing permeation of drugs to the skin. The application of therapeutic ultrasound significantly increases transdermal drug penetration.

Clinical data shows that endovascular ultrasound energy at 20kHz frequency results in arterial vasodilatation and may help to increase permeation of drugs into the vessel wall:
- W. Steffen MD et al., EHJ 15, 369-376 (1994)
- T. Miyamoto MD et al., JACC Vol 41, No9 (2003)

20kHz frequency ultrasound changes calcific plaque compliance and significantly reduces balloon pressure during angioplasty:
- R. Siegel MD et al., Circulation Vol.189; No. 4 April 1994

Ultrasound energy at 20KHz frequency is capable of inducing cellular change, modify calcific plaque compliance and maybe useful to enhance delivery of drugs to the vessel wall.
Clinical Study

Single Center Clinical Evaluations
Gandini R, MD; Pampana E, MD; Stefanini M, MD; DelGiudice C, MD
Department of Radiology; University Hospital Tor Vergata, Rome, Italy
Approved By Local Ethical Committee

• Primary Objective - SAFETY
  - Freedom from MACE (30 days)
    Death, Amputations, Bypass Surgery, MI (>2x CK upper limit normal elevation)

• Secondary Objective - PROCEDURAL SUCCESS
  - Angiographic Re-Stenosis at 6 month
  - Clinical TLR at 6 and 12 month
Case #1

Pre-procedure  | Post-procedure  | 6m follow-up
Case #2

Pre-procedure

Post-procedure

6m follow-up
**Clinical Results**

**Patient Information**

<table>
<thead>
<tr>
<th>Number of Patients Enrolled</th>
<th>24</th>
<th>CLI/Rutherford Stage 4-6</th>
<th>100% (24/24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74.5 ± 7.7</td>
<td>In-Stent Lesions</td>
<td>17% (4/24)</td>
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<tr>
<td>Males</td>
<td>83% (20/24)</td>
<td>Previous Stroke, TIA</td>
<td>29% (7/24)</td>
</tr>
<tr>
<td>Smokers, P. Smokers</td>
<td>75% (18/24)</td>
<td>Visible Calcifications</td>
<td>75% (18/24)</td>
</tr>
<tr>
<td>SFA Only</td>
<td>71% (17/25)</td>
<td>CTOs</td>
<td>75% (18/24)</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>42% (10/24)</td>
<td>Lesion Length (mm)</td>
<td>162 ±43</td>
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**6 & 12 Month Follow-up Results**

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<tr>
<th>Follow-Up</th>
<th>6 Month</th>
<th>12 Month Clinical</th>
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<tbody>
<tr>
<td>Angiographic FU</td>
<td>74% (17/23)</td>
<td>NA</td>
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<td>Doppler FU</td>
<td>26% (6/23)</td>
<td>NA</td>
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<tr>
<td>Rejected FU*</td>
<td>4.2 % (1/24)</td>
<td>NA</td>
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<td>Restenosis Rate</td>
<td>4.3% (1/23)</td>
<td>N/A</td>
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<tr>
<td>TLR</td>
<td>0% (0/24)</td>
<td>4.5% (1/22)</td>
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<tr>
<td>Amputations of Treated Leg</td>
<td>0% (0/24)</td>
<td>0% (0/22)</td>
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<tr>
<td>Death</td>
<td>0% (0/24)</td>
<td>8.3% (2/24)</td>
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* Bowel Ischemia
Summary

- Ultrasound energy changes compliance of the media-intima plaque/calcium and facilitates Paclitaxel delivery to the vessel wall after POBA.

- US facilitates crossing and removal of Thrombus.

- Non-implant solution with homogenous drug delivery to the vessel wall allowing to treat any lesion length and any vessel diameter with one device.

- Encouraging results in challenging cases demonstrate great potential of this technology for CLI patients, and a whole PAD.

- A larger clinical study is required to validate this promising new approach.
Closing Remarks / Thank You