New Technology/Challenging Cases

Ultrasound-Facilitated Drug Delivery

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Disclosures

Speaker’s Bureau:
- Abbott
- Asahi
- Bard
- Boehringer-Ingelheim
- Bristol-Myers-Squibb/Sanofi
- Cardiva
- Cook Medical
- Cordis
- DSI/Lilly
- Gore
- ACHL/Merck
- Spectranetics

PVD Training:
- Abbott
- Bard
- Boston Scientific
- Spectranetics
- TriReme Medical

Stockholder:
- CardioProlific
- Cardiva
- Spectranetics
- Vasamed

Consultant/Medical/Scientific Boards:
- Abbott
- Boston Scientific
- Cardiva
- Cook Medical
- CR Bard
- Lake Regional Medical
- Medtronic
- Spectranetics
The biggest challenges in treating calcific PAD lesions are difficulty in achieving an adequate initial lumen (Incomplete vessel expansion, elastic recoil, and flow-limiting dissections) and inability of therapeutic drugs to penetrate the media-intimal calcium to reach the adventitial vessel wall to inhibit restenosis.
Ultrasound Frequencies Used For Medical Applications

- Transdermal delivery of insulin, low-molecular weight heparin, vaccines
- Ocular drug delivery
- Lipoplasty
- Angioplasty
- Drug delivery to brain
- Gene delivery
- Reduced arterial hyperplasia
- Bone-fracture healing
- Gener delivery
- Drug delivery to brain
- Osteoporosis
- Gene delivery
- Thrombolysis
- Hyperthermia
- Sciatic nerve repair
- Nebulizers (asthma)
- Diagnostics
- Haemostasis
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Animal Study

OBJECTIVE: Ultrasound Impact on Paclitaxel Vessel Uptake /Permeability

![Graph showing Paclitaxel acute vessel uptake](graph1)

![Graph showing Paclitaxel 30 days vessel uptake](graph2)
20kHz Frequency

• 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, modifying calcific plaque compliance, and may be useful to enhance delivery of drugs to the vessel wall.
CardioProlific System

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

**Catheter**
- .6mm tip
- 1.6mm catheter
- RX any 0.014" guidewire
- 200 cm long
- 6F sheath compatible
- Ultrasound active member adjustable between 10-100mm
Method of Action\(^{(1)}\) *Increased intimal permeability*
Method of Action (2) Microchannel Creation in Calcium

- Low pressure dilation
- Better drug transit from lumen to adventitia
Clinical Study

Single Center Clinical Evaluations
Gandini R, 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
  • Doopler (PSV < 2.5) TLR at 12 month
Case #1

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

Pre-procedure  Post-procedure  6m follow-up
Case #3

Pre-procedure | Post-procedure | 6m follow-up
Case #4

Pre-procedure | Post-procedure | 6m follow-up
Case #5

Pre-procedure  Post-procedure  6m follow-up
Clinical Results

<table>
<thead>
<tr>
<th>Number of Patients Enrolled</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLI/Rutherford Stage 4-6</td>
<td>100% (28/28)</td>
</tr>
<tr>
<td>Age</td>
<td>74.2 ± 7</td>
</tr>
<tr>
<td>In-Stent Lesions</td>
<td>18% (5/28)</td>
</tr>
<tr>
<td>Males</td>
<td>71% (20/28)</td>
</tr>
<tr>
<td>Previous Stroke, TIA</td>
<td>25% (7/28)</td>
</tr>
<tr>
<td>Smokers, P. Smokers</td>
<td>82.1% (23/28)</td>
</tr>
<tr>
<td>Visible Calcifications</td>
<td>75% (21/28)</td>
</tr>
<tr>
<td>SFA Only</td>
<td>68% (19/28)</td>
</tr>
<tr>
<td>CTOs</td>
<td>71% (20/28)</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>43% (12/28)</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>168 ±54</td>
</tr>
</tbody>
</table>

**Follow-Up**

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>6 Month</th>
<th>12 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic FU</td>
<td>100% (28/28)</td>
<td>NA</td>
</tr>
<tr>
<td>Restenosis Rate</td>
<td>3.6% (1/28)</td>
<td>3.8% (1/26)</td>
</tr>
<tr>
<td>TLR</td>
<td>0% (0/28)</td>
<td>3.8% (1/26)</td>
</tr>
<tr>
<td>Amputations of Treated Leg</td>
<td>0% (0/28)</td>
<td>0% (0/26)</td>
</tr>
<tr>
<td>Death (Non-Procedure related)</td>
<td>0% (0/28)</td>
<td>7.1% (2/28)</td>
</tr>
</tbody>
</table>

* Bowel Ischemia
Alternative Approach

**Ultrasound + DEB**

- **Catheter Body**
- **Intimal Plaque/Calcium**
- **Radial Waves**
- **Tip**
- **Vessel**
- **Catheter Tip Marker**
- **Saline Irrigation**
- **Diseased Area After Balloon Angioplasty**
- **US Active Member**
- **Introducer**
- **DEB Paclitaxel delivery**
- **Modified Intimal Plaque/Calcium**

$C_{21}H_{27}NO_{14}$
Summary

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

• 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.
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