Potential Role of Ultrasound Technologies in the Development of New Therapies

Hector Lopez, Sc.D.
Program Director, Ultrasound Research Portfolio
Division of Applied Science and Technology, NIBIB
Basics:

-The institute’s mission is to develop new technology that is health-related.

-The Institute is committed to integrating the physical and engineering sciences with the life sciences to profoundly advance basic research and medical care.
NIBIB Usnd Therapy Program

- Opening of BBB (2)
- Therapy through intact skull
- Wound Healing (2)
- Non-invasive drug delivery (2)
- HIFU-enhanced tumor vaccines
- Quantitative US and Image guidance of HIFU treatments (3)
- **Cardiovascular** projects (discuss today):
  - Non-invasive *Coronary thrombosis* treatment
  - Non-invasive *Deep vein thrombosis* treatment
  - Non-invasive *Anti-fibrillation* treatment
  - Non-invasive *cerebral stroke* treatment
What can ultrasound do in cardiovascular therapy?

- **Diagnostic** level ultrasound has **thrombolytic** properties
- Mechanisms not yet understood…
- Combined with microbubbles, therapy levels enhanced
- **HIFU** operates through thermal, mechanical effects, but also has **thrombolytic** properties (different mechanisms?)
1. Coronary and Microvascular Thrombolysis  

Xie, F., Porter, T., et al, U. Nebraska

- Goal: examine effects of impulses from 3D ultrasound on microvascular and epicardial reflow in porcine model of coronary thrombosis.
- Uses diagnostic level Usnd, high MI, non-targeted microbubbles
- Coronaries: porcine atherosclerotic and normal controls
Video: Coronary and Microvascular Thrombolysis

Xie, F., Porter, T., et al, U. Nebraska

Before Usnd

After Usnd
1. Coronary and microvascular thrombolysis

Xie, F., Porter, T., et al, U. Nebraska

Porcine Acute ST-segment elevation myocardial infarction and resolution by use of 3D ultrasound (US), Micro Bubbles (MB) and Tenecteplase (TP)

LAD stenosis (arrow)

Contrast defect (infarct)-arrows

US+MB+TP

LAD recanalization

Reduced contrast defect size (infarct)
2. Deep Vein Thrombolysis by Histotripsy in a Porcine Model

Xu, Z., Maxwell, A, et al, University of Michigan, Ann Arbor

**B-Mode**

*Before*  
Artery  
Clot in Vein

*After*  
No Clot in Vein

**Histotripsy** = short, HIFU pulses to cause soft tissue or clot breakdown by **cavitation**

*Color Doppler*  
No Flow

*After*  
Full Flow

*Therapy Transducer*  
Focus

**Cavitation cloud** guided left to right inside the occluded vein, disintegrates clot sections, allows blood to flow again,
2. Deep-Vein Thrombolysis by Histotripsy in a Porcine Model

Xu, Z., Maxwell, A., et al, University of Michigan, Ann Arbor

Video shows cavitation cloud dissolving clot in vein (left to right)

Conclusion: histotripsy has potential to be an effective non-invasive thrombolysis technique
Clinical significance

- Abnormal electrical activity in the atria
- Most common arrhythmia
- Affect 2.2 million adults in U.S.

Initiation mechanisms

- Automatic focal source
  - Pulmonary Vein (Major)
  - Coronary sinus, SVC, etc.

Treatment Options

- Cox-Maze-surgical--gold std.
  - Complex, long procedure
- Ablation (RF, Cryo, MW, Laser, HIFU)
  - Minimally invasive, some problems
- Pharmacotherapy
  - Global side effect and low efficacy

3. HIFU Ablation for Treatment of Atrial Fibrillation


• High Intensity Focused Ultrasound (HIFU)
  – Goal: develop efficient & safe HIFU ablation for treating AF
  – But—current ablation techniques not optimal:
    • Safety (AE fistula, phrenic nerve injury)
    • Efficacy (1/3 recurrence of AF, especially RF)
    • Technique Problems (HIFU)
      – Overheating
      – Cavitation
      – Incomplete lesions

Critical need for Real-time Monitoring for HIFU based on feedback control

3. HIFU Ablation for Treatment of Atrial Fibrillation

M. Gudur, C. Deng, et al, U. of Michigan

Ultrasound imaging techniques

- Integrated Backscatter (IBS): Echo
- Acoustic Radiation Force Imaging (ARFI): stiffness property
- Spectral analysis: spectral response $\rightarrow$ scatterer size, acoustic concentration
- Shear Wave Elasticity Imaging
- Harmonic motion imaging
- Differential attenuation maps
- Echo de-correlation


Conclusion: Feedback from Imaging, functional, quant. methods will increase safety and efficacy of HIFU ablation
4. HIFU Treatment of Acute Stroke

K. Hynynen, et al, U. Toronto

- Goal: develop new **phased-array** technology for treatment of stroke
- Transcranial sonication using patient-specific **skull** information from CT scans
- Precise localization of Usnd energy
4. HIFU Treatment of Cerebral Stroke

K. Hynynen, et al, U. Toronto

"Helmet "Applicator

High-power phased array with very large number of elements

Use patient-specific skull information from CT scans

Precision of beam eliminates need for thrombolytic agent

Kullervo Hynynen PhD, et al-- R01 EB3268, Sunnybrook Health Center, U. Toronto
4. HIFU Treatment of Acute Stroke

Burgess, Hynynen et al, AIUM 2012

1.5MHz transducer, 1ms pulses, 0.1% duty cycle, 20sec duration

Rabbit model:

- Baseline
- Stroke
- Post-HIFU

<table>
<thead>
<tr>
<th>Power</th>
<th>Baseline</th>
<th>Stroke</th>
<th>Post-HIFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>415 W</td>
<td><img src="image1" alt="Baseline" /></td>
<td><img src="image2" alt="Stroke" /></td>
<td><img src="image3" alt="Post-HIFU" /></td>
</tr>
<tr>
<td>550 W</td>
<td><img src="image4" alt="Baseline" /></td>
<td><img src="image5" alt="Stroke" /></td>
<td><img src="image6" alt="Post-HIFU" /></td>
</tr>
</tbody>
</table>
HIFU Treatment of Acute Stroke

Burgess, Hynynen, et al, AIUM 2012

- Rabbit study:
  - Effective thrombolysis in embolic model of stroke
  - Effectiveness of high frequency phased array capable of focusing and transmitting high power through skull
  - Encouraging results for transfer to the clinical setting
HIFU Treatment of essential tremor

Private Co. and U. Va. study currently conducting FDA clinical trials (not funded by NIH)

Evolution of Surgical Tools in Medicine

Conventional Surgical Instruments and invasive procedures (1000’s years)

Minimally invasive surgical instruments and procedures

Noninvasive ultrasound?