PACING OF THE MYOCARDIUM BY HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

Cardiac Arrest

25%

Asystole

Pacing
Electrical/Mechanical

Defibrillator

VF/VT

75%

Integrated Solution is needed

Source: *(New Eng J Med)*

By
Anat Roytberg-Hersch
Dan Adam
• Under emergency conditions of cardiac arrest – fast non-invasive pacing is crucial for saving the patient.

• Electrical stimulation* is a possibility – but inefficient and painful.

• Possible solution: Mechanical stimulation, based on Mechano-Electric Feedback

* FDA approved the use of the ZOLL non-invasive pacing technology - 1982
## Optional Methods

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Stimulation</th>
<th>Adrenalin/Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of operation</td>
<td>Ultrasonic thump</td>
<td>Intravenous Drugs</td>
</tr>
<tr>
<td>Locations of availability</td>
<td>Hospitals, EMS, Public Access, Home</td>
<td>Hospitals, Emergency Medical Services</td>
</tr>
<tr>
<td>Ease of usage</td>
<td>Will be KISS</td>
<td>Requires M.D. or trained and qualified paramedic</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>50% for each thump, multiple thumps per minute (In Vitro / Vivo experiments)</td>
<td>Less than 5% for overall treated by protocol</td>
</tr>
<tr>
<td>Price (est.)</td>
<td>$50K (Hospitals)</td>
<td>$20 per protocol</td>
</tr>
<tr>
<td></td>
<td>$10K (EMS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1.5K (Home)</td>
<td></td>
</tr>
</tbody>
</table>
Mechanical Pacing

- Ultrasonic probe that generates a precordial thump:
  - Non invasive
  - High intensity
  - Focused
  - Does not require contrast agents
  - Fast operated

- Developed at the Faculty of BME, Technion
- Protected by two patents (probe & application)
Two stage operation using the array of transducers (Proprietary IP):

- Production of microbubbles by the cavitation waveform
- Production of stimulation by the positive waveform
The HIFU transducer consists of 3 different frequencies: 350KHz, 700KHz, 1050KHz.

Combination of the above 3 frequencies with a specific phase difference creates the following wave with a cycle time of 2.85us.
IN-VIVO SETUP

The in-vivo experiments setup comprised the following components:

- Degassing system.
- HIFU transducer.
- A specially designed container.
- A rat’s holder.
- The imaging system.
IN-VIVO SETUP

Setup components added after the calibration:

- The Ultrasound Transmission system.
- A system for biological measurements: ECG and Blood Pressure.
- A 5 MHz transducer and Data acquisition system.

![Diagram of in-vivo setup](image-url)

- R-wave detection algorithm
- Biological Measurements: ECG, Blood Pressure
- A/D – ECG Acquisition
- A/D - Blood Pressure Acquisition
- Heater
- Filter 4-6 MHz
- A/D – 5 MHz Acquisition
- Sonication Trigger
- HIFU Transducer
Ultrasonic field of the negative pressure created by the combination of the three frequencies at the lateral direction (X-Y)
DEFINITION OF A SHORT AXIS VIEW OF THE MYOCARDIUM
ULTRASONIC IMAGES OF THE MYOCARDIUM

External Diameter

Left Wall width
PREMATURE CONTRACTIONS (PC)

Small modification of the ECG signal directly after the US pulse.

There is no compensatory period.

The Blood pressure signal is not affected by this type of modification.
PREMATURE VENTRICULAR CONTRACTIONS (PVC)

3 stage reaction: time gap, PVC, compensatory period

No additional blood injection
3 stage reaction: modification, PVC, compensatory period

US Pulse
Small modification
Additional blood injection
Compensatory period
The reaction is detected **directly** after the ultrasonic sonication.

The graph shows the waveform over time, with labels for US Pulse, P-wave, Pressure, ECG, and Trigger. The graph also highlights the compensatory period and additional blood injection.
The prevalence is calculated from the data acquired from the 14 experiments in which premature contractions were documented.
TIME DELAY BETWEEN THE ULTRASONIC PULSE AND THE PREVIOUS R-WAVE

Prevalence of the time delay of the ultrasonic pulses that resulted in PC from the previous R-wave

- US pulse with a delay of 70-80 msec
  - Triggers mainly PVC with blood injection
- US pulse with a delay of 80-90 msec
  - Triggers mainly Local PVC without blood injection
The typical R-R duration in these experiments was 280-340 msec.

Usually the R-wave of the PVC’s appear 140-180 msec after the previous R-wave.
The time delay between the US pulse and the R-wave of the PVC is 70-100 msec.
Prevalence of the length of the compensatory interval after appearance of premature contraction

- 55% of the premature contractions
  - Compensatory pause elongates by 10-20%
- 20% of the premature contractions
  - Compensatory pause elongates by 20-30%
EFFECT OF THE PEAK POSITIVE PRESSURE ON OCCURRENCE OF PC

Occurance of PC with blood injection vs. peak positive acoustic pressure

<table>
<thead>
<tr>
<th>Peak positive acoustic pressure [MPa]</th>
<th>50 ms</th>
<th>5 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>7.7</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>8.4</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

HIFU is more effective when: Pulse length is increased (5 ms → 50 ms)
Future potential applications:

OPTIMAL RESYNCHRONIZATION

- Generate 3D activation maps (non-invasively)
- Determine optimal electrodes locations and pulsing timings
- Guide electrodes placing (using ultrasound)

MARKET ADDRESSED:

- CHF (Congestive heart failure) patients
Future potential applications:

**TREATMENT OF ARRHYTHMIAS**

- Non-invasive detection of ectopic foci and reentrant trajectories (using 3D ultrasonically generated activation maps) and non-invasive ultrasonic activation of suspicious loci (similar to electrophysiological (EP) studies).
- Non-invasive ablation of the desired locations through ultrasonic actuated targeted drug delivery.

**MARKET ADDRESSED:**

- Post-MI patients
- Congenital arrhythmias
- WPW patients
- Other arrhythmias
Future potential applications:

**DIAGNOSIS OF INFARCTED/hibernating myocardium**

- Diagnosis of infracted/hibernating myocardium by analyzing the response to local activation (with/without ultrasonic contrast agent)
- All post-MI patients
68% of the created PC with blood injection resulted from peak negative pressure of 3.89 MPa or combination of 3.89 MPa +6.49 MPa and the optimal time duration 940 µsec or 1034 µsec
MARKET POSITIONING AND EXPANSION

- High Cost
- Low Volumes
- Big Dimensions
- Expert User

- Reduced Cost
- Increased Volumes
- Compact Dimensions
- Any User (Good Samaritan Law)
Shock waves for medical use are acoustic pulse waves similar to ultrasound featuring extremely high pressure (up to 100 MPa), short rise time and low tensile wave components. Shock waves generate transient forces at acoustic interfaces and may cause cavitation which creates strong impulse forces by an asymmetric collapse of cavitation bubbles.

High energy shock waves provide the power to fragmentize kidney stones (extracorporeal shock wave lithotripsy) while soft tissue is passed basically without lesions.

Precise focus
Proprietary shock wave generator technology generates precisely defined focal zones which are adjusted with millimetre-precision utilizing a three-dimensional fine positioning device.

ECG controlled shock wave release
ECG triggering provides shock wave pulses within a few milliseconds after the QRS-complex. Pulses are released only in refractory phase of the cardiac cycle.

Beside fragmentation of body calculi shock waves of lower energy have proven effective in stimulation of nerve cells, metabolism, circulation and permanent pain reduction. Effective shock wave therapies could be established for various indications of chronic pain diseases such as tendinosis calcarea, plantar fasciitis, epicondylitis as well as non-unions and others.

Interactions of shock waves with living tissue are manifold. Mechanical forces at tissue interfaces related to different acoustic impedances, as well as micro-jets of collapsing cavitation bubbles are the primary effects, which, in turn, may generate NO and other free radicals. Subsequent effects are: Activation of ion channels of cell membranes, memory effects of CNS, neo-angiogenesis and release of vascular endothelial growth factors.

Cardiac shock wave therapy (CSWT)

STORZ MEDICAL Solutions
In-line ultrasound imaging
METHOD OF OPERATION