3D Dynamic Contrast Enhanced Ultrasound: Potential Tool for Treatment Response Evaluation

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Stanford Cancer Institute Translational Award
NIH R01 CA195443-02
Philips Healthcare

The vascular system

Circulation

### The vascular system

<table>
<thead>
<tr>
<th></th>
<th>Aorta</th>
<th>Arteries</th>
<th>Arterioles</th>
<th>Capillaries</th>
<th>Venules</th>
<th>Veins</th>
<th>Vena Cava</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal Diameter</strong> (um)</td>
<td>2.5x10^4</td>
<td>3x10^3 – 1x10^4</td>
<td>30</td>
<td>5</td>
<td>70</td>
<td>5x10^3</td>
<td>1.2 x10^4</td>
</tr>
<tr>
<td><strong>Total Area</strong> (cm²)</td>
<td>5</td>
<td>20</td>
<td>40</td>
<td>2500</td>
<td>250</td>
<td>80</td>
<td>250</td>
</tr>
<tr>
<td><strong>Pressure</strong> (mmHg)</td>
<td>100</td>
<td>90</td>
<td>60</td>
<td>17</td>
<td>10</td>
<td>5</td>
<td>&lt; 5</td>
</tr>
<tr>
<td><strong>Mean Flow Velocity</strong> (mm/s)</td>
<td>300</td>
<td>20</td>
<td>20-0.3</td>
<td>0.3</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td><strong>Vessel Class</strong></td>
<td>Feeding</td>
<td>Feeding</td>
<td>Feeding</td>
<td>Exchange</td>
<td>Draining</td>
<td>Draining</td>
<td>Draining</td>
</tr>
</tbody>
</table>


### Microbubbles: Contrast Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Gas</th>
<th>Shell</th>
<th>Mean Size (um)</th>
<th>Concentration (#/ml)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levovist</td>
<td>Bayer Schering/Pharma AG</td>
<td>Air</td>
<td>Galactose, trace palmitin</td>
<td>2-4</td>
<td>1.2-2.0 x 10⁸</td>
<td>1996</td>
</tr>
<tr>
<td>Optison</td>
<td>GE Healthcare AS</td>
<td>C3F8</td>
<td>Human Albumin</td>
<td>2-4.5</td>
<td>5.0-8.0 x10⁸</td>
<td>1997</td>
</tr>
<tr>
<td>Definity</td>
<td>Lantheus Medical Imaging</td>
<td>C3F8</td>
<td>Phospholipid</td>
<td>1.1-3.3</td>
<td>1.2x10⁸</td>
<td>2001</td>
</tr>
<tr>
<td>Sonovue</td>
<td>Bracco</td>
<td>SF6</td>
<td>Phospholipid</td>
<td>2-3</td>
<td>5.0x10⁸</td>
<td>2001</td>
</tr>
<tr>
<td>Sonazoid</td>
<td>Amersham Health</td>
<td>C4F10</td>
<td>Lipids</td>
<td>0.3 x 10⁹</td>
<td></td>
<td>2006</td>
</tr>
</tbody>
</table>

Microbubbles are purely intravascular agents.
Microbubbles

Nonlinear response

Bubble Disruption

Microbubble non-destructive imaging

<table>
<thead>
<tr>
<th>Method</th>
<th>Transmitted Sequence (red have inverted phase)</th>
<th>Algebra to combine</th>
<th>Summed Tissue Echo</th>
<th>Summed Bubble Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode</td>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Inversion</td>
<td></td>
<td>Echo₁ + Echo₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast pulse sequencing (CPS)</td>
<td></td>
<td>Echo₁ + Echo₂ + Echo₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td></td>
<td>Echo₁ - 2*Echo₂</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Injection method 1: Bolus Injection

Bolus injection

Injection method 2: Destruction-replenishment

Constant infusion with destruction-replenishment

\[ A = rBV \] (relative Blood Volume)
\[ \beta \times A = rBF \] (relative Blood Flow)

Biomarker for treatment response

Advantages:
1. Available worldwide at bedside
2. Inexpensive
3. No ionizing radiation/contrast toxicity
4. Versatile and easy transport
5. Good temporal/spatial resolution

Main Limitation:
2D Sampling Errors

Tracked 4D contrast enhanced US imaging

• Potential
  – Elimination of sampling artifacts (3D vs 2D)
  – Comprehensive motion correction
  – 3D fusion with B-mode US or other imaging modality
    • Enabler for follow up studies
  – Parametric (but likely low resolution) maps of heterogeneity of vascular parameters
3D DCE-US (3D Dynamic Contrast Enhanced Ultrasound)

Power Modulation (PM) Contrast Imaging Mode
- MI = 0.09
- Destruction (“Flash”) MI = 0.77
- Elevation resolution: ~3 mm
- Azimuth resolution: 2-4 mm
- Axial resolution 0.5-2 mm
- Acquisition rates (<1 volume/sec, with 4 firings per line)

Parameters evaluated in phantom, 6-12 cm depth

Microbeamforming for Large-Aperture Ultrasound Transducers, Freeman, S., Ultrasound Imaging Symposium, 2011 AAPM/COMP Meeting, 7/31-8/4, Vancouver, CA

Tracked 4D Ultrasound

Automatic 3D ultrasound calibration for image guided therapy using intramodality image registration.
3D DCE-US in mouse colon cancer model


3D DCE-US for monitoring treatment response

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Antiangiogenic Treatment (p = 0.06)</th>
<th>Saline-Only Treatment (p = 0.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>Change</td>
<td>P Value</td>
</tr>
<tr>
<td>F(0) (s)</td>
<td>82 ± 23</td>
<td>.004</td>
</tr>
<tr>
<td>AUC (s)</td>
<td>65 ± 23</td>
<td>.04</td>
</tr>
<tr>
<td>TTP (s)</td>
<td>7 ± 12</td>
<td>.92</td>
</tr>
<tr>
<td>tBF (s)</td>
<td>6 ± 26</td>
<td>.007</td>
</tr>
<tr>
<td>tBF (s)</td>
<td>64 ± 23</td>
<td>.001</td>
</tr>
<tr>
<td>Blood flow velocity (s-1)</td>
<td>−6.5 ± 52</td>
<td>.50</td>
</tr>
</tbody>
</table>

Note: Values are percentage changes from baseline to 24 hours after treatment. P values were calculated between baseline and 24 hours after treatment.

Some parameters change significantly with treatment.
Significant differences between 2D and 3D measured response


3D DCE-US: feasibility and repeatability in patients with liver metastases
3D DCE-US Technical Limitations

Problem Statement

**Limitation:**
- Current commercial 3D DCE-US does not display side-by-side B-mode & contrast-mode.
- Leaves operator with no positioning feedback during acquisition.
- Challenging during long acquisition sessions (i.e. disruption-replenishment) and can affect quantification.

**Solution:**
- Use an optical-tracking and guidance system to assist operators during 3D DCE-US data acquisition.

**Aim:**
- Evaluate the use of optical-tracking to maintain a set position during lengthy acquisition, and to compare performance to Bmode and current 3D DCE-US implementation.
Assessment of Set Up

Can a tracked virtual transducer help sonographers remain in the same position?

1. Place transducer on saved reference position

2. Remain at that location using
   I. Bmode,
   II. Virtual Probe,
   III. Memory

Methods

• 5 experienced operators with > 1 year of experience
• 1 volunteer healthy patient
• Operators were asked to maintain the same position for 4 minutes with:
  • View of Bmode
  • View of live virtual probe
  • Memory
• Optical tracking was used to determine extent of motion of probe relative to original position over the scan time
• Magnitude of displacement of a selected voxel was computed over the whole 4D cine was computed relative to a reference position.
Results on Operator 1

Position Over Time

![Graph showing position over time with three different methods: Bmode, Tracking, and Blind.]

Distribution of Displacements

![Graph showing the distribution of displacements with three different methods: Bmode, Tracking, and Blind.]

---

Results

<table>
<thead>
<tr>
<th>Operator</th>
<th>B mode (mm)</th>
<th>Track (mm)</th>
<th>Memory (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>std</td>
<td>skew</td>
</tr>
<tr>
<td>1</td>
<td>2.11</td>
<td>1.26</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>9.64</td>
<td>12.00</td>
<td>0.48</td>
</tr>
<tr>
<td>3</td>
<td>2.34</td>
<td>0.96</td>
<td>-0.38</td>
</tr>
<tr>
<td>4</td>
<td>2.78</td>
<td>1.62</td>
<td>-0.02</td>
</tr>
<tr>
<td>5</td>
<td>1.91</td>
<td>0.56</td>
<td>-1.03</td>
</tr>
<tr>
<td>Average</td>
<td><strong>3.75</strong></td>
<td><strong>3.28</strong></td>
<td><strong>-0.18</strong></td>
</tr>
</tbody>
</table>
Feasibility and Repeatability in Patients with Liver Metastases: Objective 1

Repeatability

- Injection Method 1: Destruction replenishment
  - Relative blood volume (rBV)
  - Relative blood flow (rBF)

- Injection Method 2: Bolus Injection
  - Peak Enhancement (PE)
  - Area under the curve (AUC)
  - Mean transit the time (MTT)

Analysis of Repeatability

Analysis of Repeatability

For analysis, calculate the interclass correlation coefficient for the 1st and 2nd measurements

\[
\begin{array}{c|c|c|c|c}
 & rBV & rBF & PE & AUC \\
\hline
3D ICC & 0.97 (0.89,0.99) & 0.96 (0.85,0.99) & 0.92 (0.78,0.98) & 0.92 (0.77,0.98) \\
TP & 0.84 (0.58,0.95) \\
MTT & 0.63 (0.27,0.69) \\
\end{array}
\]

ICC >0.90
Good 3D Repeatability

Feasibility and Repetability in Patients with Liver Metastases: Objective 2

Analysis of 2D and 3D measurements of 3D DCE-US

- Heterogeneity measured across 4 2D planes
- Comparison of 2D vs 3D measurements

Heterogeneity of 2D measurements

<table>
<thead>
<tr>
<th>Average COV</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>rBV</td>
<td>0.43</td>
<td>(0.34, 0.42)</td>
</tr>
<tr>
<td>rBF</td>
<td>0.51</td>
<td>(0.40, 0.62)</td>
</tr>
<tr>
<td>PE</td>
<td>0.33</td>
<td>(0.24, 0.42)</td>
</tr>
<tr>
<td>AUC</td>
<td>0.32</td>
<td>(0.25, 0.42)</td>
</tr>
<tr>
<td>TP</td>
<td>0.17</td>
<td>(0.13, 0.21)</td>
</tr>
<tr>
<td>MTT</td>
<td>0.29</td>
<td>(0.21, 0.39)</td>
</tr>
</tbody>
</table>

Large 2D sampling errors

2D Planes show Heterogeneity

Comparing different 2D Planes

Comparison of 2D vs 3D Measurements

Is 2D measurement equivalent to 3D measurement?

3D = 2D

2D measurement is not equivalent to 3D measurements
Significance of vascular damage

REVIEW

Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS)

Heon Joo Park, Robert J. Griffin, Susanta Hui, Seymour H. Levitt, and Chang W. Song

“Little is known about the vascular changes in human tumors treated with high-dose hypo-fractionated radiation such as stereotactic body radiotherapy or stereotactic radiosurgery”

Probe placement map generation

Define target and map attenuation to target from surface
Probe placement map confirmation

Visualize probe in virtual space during actual imaging.

3D DCE-US for RT planning and response evaluation

Real-time DCE-US/CT fusion for acquisition guidance

Patient in SABR simulation position

Optical tracking for DCE-US/CT fusion

Real-time time-intensity curve for timing destruction-replenishment

Continuous Image Acquisition and Visualization
Microwaveable Infusion of 8.3 mL in 50 mL of saline at 6.41 mL/minute
Video: 3D DCE-US for RT planning and response evaluation

3D DCE-US fusion with CT and planned dose distribution
DCE-US: challenges in acquisition and quantification

**Review**

Quantitative contrast-enhanced ultrasound imaging: a review of sources of variability

M.-X. Tung¹,², H. Mulvany³, T. Gauthier³, A. K. F. Lim³, D. O. Coegroev³, R. J. Eckersley³ and E. Stride³

DCE-US is inherently an off-line modality.
- Do we really need real time processing?
- Are we discarding useful data?

**Scanner**
- Output power
- Focal depth
- Dynamic range and gain
- Frequency

**Patient**
- Blood pressure
- Physiological Interactions
- Tissue motion
- Tissue attenuation

**Bubbles**
- Stability
- Injection and handling
- Dosage
- Concentration effects
3D DCE-US: rethink acquisition and quantification

• Lack of concurrent low-MI 3D B-mode data
  – No anatomical guidance for prolonged acquisitions
  – Precludes comprehensive motion correction based on anatomy
  – Precludes 3D fusion with B-mode US or other imaging modality for follow up studies

• Potential Solution
  – Reconstruct only low-MI B-mode guidance mode in real time
  – Save all RF channel data for offline reconstruction of DCE-US and corresponding B-mode
  – Additional benefits: linear signal, attenuation corrections

Data management

• ~23.6 MB/s per channel, sampling at 4 x central frequency (X6-1 transducer)
• ~6 GB/s for a 256 channel system
• ~2 TB (6 min acquisition)
• 6.6 GB/s, 8 lane PCIe 3.0
• ~3 GB/s, sequential write, Intel DC P3608 Solid State Drive, 4 TB

3D DCE-US: rethink acquisition and quantification

• Low volume rates: ~1 volume every 2 sec
  – large respiratory-induced variations from volume-to-volume is a challenge for motion tracking
  – Fast 2D DCE-US allows 7-130 samples with distinct intensity values during a replenishment of a 4 mm thick slice (~10 frames/sec, 0.3 mm/s - 6 mm/s velocities)
  – Slow 3D DCE-US only 1-6 samples for the same conditions

• Potential Solution: ultrafast plane wave imaging
  – For a 10 cm deep lesion, fundamental physics limits number of transmits to 7700/s
  – Line-by-line 3D DCE-US imaging over large FOV: too slow yet low resolution (48x80 lines, 4 transmits per line)
  – Need alternative beamforming and data processing with fewer transmits per image
3D DCE-US: rethink acquisition and quantification

- Ultrafast plane wave imaging

Fast Track Communication

3D ultrafast ultrasound imaging in vivo

Jean Provost, Clément Papadaciotis, Jean Esteban Arango, Mathieu Inbalutt, Mathias Pich, Jean-Luc Genetier, Mickael Tantier and Mathieu Perrot

Combined Perfusion and Doppler Imaging Using Plane-Wave Nonlinear Detection and Microbubble Contrast Agents

Charles Szarmach-Saraiva, Bass William, Louise Mialet, Matthew Dean, Mynko, IEEE, and Peter N. Bowne, Winter, 2022

Contrast enhanced ultrasound by real-time spatiotemporal filtering of ultrafast images

Yann Desoliè, Anne-Marie Tisior, Jean-Michel Corross, and Olivier Coutere

Image 3D DCE-US: rethink acquisition and quantification