Contrast enhanced ultrasound of the liver

Mary K. Henne, MS, CNMT, RDMS, RVT
Education Leader
Contrast enhanced ultrasound for the liver

objectives

At the end of the presentation the attendees will be able to:

• Recall the approximate size, composition, physics, and the pathway of a microbubble.

• Review how ultrasound waves interact with different media and the unique response generated from the liver and contrast microbubbles.

• Discover the ultrasound system’s acquisition technologies that help improve visualization of the vascular patterns of the liver and focal liver lesions.

• Reference the International Guidelines for Contrast Enhanced Ultrasound to characterize benign and malignant lesions of the liver based on enhancement patterns.

• Discuss the indications for use, safety, and applications of ultrasound contrast agents for the liver.
Microbubble

✓ Recall the approximate size, composition, physics, and the pathway of a microbubble
Microbubble

What is a microbubble?

• They are less than 8 microns in size
  – Smaller than red blood cells
  • Mean microbubble diameter: 1.5–2.5 μm
  • Their size allows them to pass through the capillaries and lungs
• Comprised of a gas surrounded by an elastic shell
Ultrasound defined

A mechanical, longitudinal, and compressional wave

• We will see how the compressional nature of sound makes ultrasound an appropriate modality for microbubble imaging

• The speed that sound travels is based on density and stiffness of the medium
  
  - The average speed is 1.54mm/µs or 1540 m/s in soft tissue
    • Air- .33mm/µs
    • Fat- 1.44mm/µs
    • Bone- 4.0mm/µs
  
  - While air is not a friend of a sonographer on the outside of the body, it is an exceptional medium and contrast agent on the inside of the body!
Impedance defined

Resistance the tissue offers to sound travel based on speed of sound and tissue density

- The speed that sound travels is based on density and stiffness of the medium
- Density is the mass of a material divided by its volume
- Impedance is the product of propagation speed times density
  - This makes sound diagnostic because it produces unique reflections for every boundary between different tissue types

\[
\text{Impedance} = \text{density} \times \text{propagation speed}
\]

\[
z (\text{Rayls}) = p (\text{kg/m}^3) \times c (\text{m/s})
\]
Impedance

<table>
<thead>
<tr>
<th>Tissue or Medium</th>
<th>Impedance (Rayls)</th>
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</thead>
<tbody>
<tr>
<td>Air</td>
<td>$0.0004 \times 10^4$</td>
</tr>
<tr>
<td>Lung</td>
<td>$0.18 \times 10^6$</td>
</tr>
<tr>
<td>Fat</td>
<td>$1.34 \times 10^6$</td>
</tr>
<tr>
<td>Water</td>
<td>$1.48 \times 10^6$</td>
</tr>
<tr>
<td>Kidney</td>
<td>$1.63 \times 10^6$</td>
</tr>
<tr>
<td>Liver</td>
<td>$1.65 \times 10^6$</td>
</tr>
<tr>
<td>Blood</td>
<td>$1.65 \times 10^6$</td>
</tr>
<tr>
<td>Muscle</td>
<td>$1.71 \times 10^6$</td>
</tr>
<tr>
<td>Bone</td>
<td>$7.8 \times 10^6$</td>
</tr>
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This formula determines how much sound is reflected at these boundaries.

$$\%Reflection = \left( \frac{Z_2 - Z_1}{Z_2 + Z_1} \right) \times 100 \quad ^2$$
Reflection

When sound strikes a boundary between two tissues the amount of sound that returns is based on the impedance difference between the tissues.
Reflection and transmission

Soft tissue/soft tissue boundary
1% of the sound is reflected
and
99% of the sound is transmitted

Soft tissue/bone boundary
50% of the sound is reflected
and
50% of the sound is transmitted

Air/Anything
99% of the sound is reflected
and
1% of the sound is transmitted
Microbbules

The boundary between gas in the microbubble and the microvasularity of the focal liver lesion provide a large impedance mismatch that produces a strong reflection.

The compressional properties of a sound waves cause the microbubbles to vibrate as they contract with the waves compression and expand with the waves rarefaction.
Bioeffects of ultrasound

What are they?

• Absorption-monitored by the ultrasound system using the Thermal Index
• Cavitation-monitored by the ultrasound system using the Mechanical Index

\[ MI = \frac{PNP}{\sqrt{Fc}} \]

• The peak negative pressure of the ultrasound divided by the center frequency of the wave.
• FDA stipulates diagnostic ultrasound cannot exceed an MI of 1.9.

What is the link between MI and CEUS?

• The ultrasound system uses an appropriate MI for peak response to the microbubble
Microbubble pathway

Optical recording of a microbubble at 4 million frames per second

• Pure blood pool agent
• Remains in the vascular system after IV injection
• Cleared by the lungs in minutes
  – 40-50% of the gas is exhaled after 1 minute
Microbubble

✓ Recall the approximate size, composition, physics, and the pathway of a microbubble
Liver and microbubble response to ultrasound

- Review how ultrasound waves interact with different media and the unique response generated from the liver and contrast microbubbles.
Response of Tissue and Bubbles

Tissue: Linear Response to positive and negative Pressure Changes

Bubbles: Non-Linear Response to Pressure Changes

Gas in Bubbles hard to compress – minor Compression on positive Pressure
Gas expands significantly more than Tissue on negative Pressure
Acoustic bubble properties

System is optimized for enhancement

- Bubble vibration causes resonant frequency harmonics that return to the system

Liver and microbubble response to ultrasound

✓ Review how ultrasound waves interact with different media and the unique response generated from the liver and contrast microbubbles.
Amplitude modulation and phase inversion

✓ Discover the ultrasound system’s acquisition technologies that help improve visualization of the vascular patterns of the liver and focal liver lesions.
Amplitude Modulation

AM under Gen, Res, and Pen varies the amplitudes of the transmitted pulses

- Great penetration
- High image uniformity
- Superb contrast sensitivity
- Excellent tissue suppression
Phase Inversion

PI under HRes uses inverted pulses and the harmonics of tissue and bubbles

- Great Spatial Resolution
- Outstanding contrast
- Higher Temporal Resolution
Amplitude modulation and phase inversion

✓ Discover the ultrasound system’s acquisition technologies that help improve visualization of the vascular patterns of the liver and focal liver lesions.
Characterization and enhancement patterns

Reference the International Guidelines for Contrast Enhanced Ultrasound to characterize benign and malignant lesions of the liver based on enhancement patterns.
Terminology for the degree and characteristics of enhancement

**Degree of enhancement**

Refers to the intensity of the contrast signal compared to the liver parenchyma.

- **Hyperenhancing** - contrast bubbles are greater in intensity than the liver tissue
- **Hypoenhancing** - contrast bubbles are less intense than the liver tissue
- **Isoenhancing** - bubbles and liver are equal

**Sustained enhancement**

Refers to a situation where the intensity of the signal from the contrast continues to enhance in the lesion over time.

**Complete absence of enhancement**

Refers to a situation where a region of interest is free of the contrast bubbles so it is not enhancing or demonstrates an enhancement defect.

**Characteristics of enhancement**

- **Wash in** refers to the period of progressive enhancement within a region from arrival to peak enhancement.
- **Wash out** refers to the period of reduction following peak enhancement.
Vascular phases in CEUS of the liver—visualization postinjection time

<table>
<thead>
<tr>
<th>Phase</th>
<th>Start (s)</th>
<th>End (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>10-20</td>
<td>30-45</td>
</tr>
<tr>
<td>Portal Venous (PV)</td>
<td>30-45</td>
<td>120</td>
</tr>
<tr>
<td>Late</td>
<td>&gt;120</td>
<td>Bubble disappearance ~4-6 minutes</td>
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The portal and late phases start at the end of the preceding one. Individual hemodynamics and other factors may influence their time of onset.
Characteristics of lesions based on vascular phase

Hemangioma

In the arterial phase, most hemangiomas have initial peripheral globular/nodular enhancement that progresses toward the center of the lesion. This centripetal filling lasts from seconds to minutes and is more rapid in smaller lesions.

Enhancement is sustained through the late and postvascular phases.

In the late phase, the majority of solid benign lesions are iso- or hyperenhancing.

Wilson and Burns 2006; Claudon et al. 2008; Strobel et al. 2008; Trillaud et al. 2009; Bernatik et al. 2010; Seitz et al. 2010; Seitz et al. 2011
### Characteristics of lesions based on vascular phase

**Focal nodular hyperplasia**

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<th>Arterial Phase</th>
<th>Portal Venous/Late Phases</th>
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<td>Enhancement of the whole lesion is typical of focal nodular hyperplasia</td>
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<td>Hyperenhancement is obvious and usually marked in the arterial phase, with a rapid fill-in from the center outwards with an eccentric vascular supply</td>
<td>During the portal venous/late phases, FNH may show a hypoenhancing scar in the late phase</td>
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Wilson and Burns 2006; Claudon et al. 2008; Strobel et al. 2008; Trillaud et al. 2009; Bernatik et al. 2010; Seitz et al. 2010; Seitz et al. 2011
Characteristics of lesions based on vascular phase

Malignancies

In the arterial phase, it is typical to see hyperenhancement with a chaotic vascular pattern.

In the Portal venous phase, most malignancies show isoenhancement, hypoenhancement, or nonenhancing regions.

Hypoenhancement of most solid lesions in the late phase, corresponds to the wash out phenomenon that characterize malignancies.

In the late phase most malignant lesions are hypoenhancing.

Wilson and Burns 2006; Claudon et al. 2008; Strobel et al. 2008; Trillaud et al. 2009; Bernatik et al. 2010; Seitz et al. 2010; Seitz et al. 2011
Characteristics of lesions based on vascular phase

**Metastases**

In the arterial phase, it is typical to see hyperenhancement with typical rim or halo enhancement.

Mets appear as punched-out “black foci” against the background of the liver.

In the portal venous phase, wash out starts early and is typically obvious.

In the late phase, most liver metastases are characterized as hypoenhancing lesions.

Wilson and Burns 2006; Claudon et al. 2008; Strobel et al. 2008; Trillaud et al. 2009; Bernatik et al. 2010; Seitz et al. 2010; Seitz et al. 2011.
Characterization and enhancement patterns

Reference the International Guidelines for Contrast Enhanced Ultrasound to characterize benign and malignant lesions of the liver based on enhancement patterns.
Indications for use, safety, and applications

Discuss the indications for use, safety, and applications of ultrasound contrast agents for the liver.
Indications for use

- To characterize incidental findings on routine ultrasound
- Lesion(s) or suspected lesion(s) detected with US in patients with a known history of a malignancy, as an alternative to CT or MRI
- When CT and MRI contrast are contraindicated
- Inconclusive MRI/CT especially in nodules not suitable for biopsy
Indications for use

• To contribute to the selection of nodule(s) for biopsy when they are multiple or have different contrast patterns

• To monitor changes in size and enhancement patterns over time when a nodule is not diagnostic for HCC and is being followed

• Inconclusive cytology/histology results

Indications for use

- Assessment of tumor progression when follow-up CECT or CEMRI are contraindicated or not conclusive.
- In addition to CECT and/or CEMRI, CEUS may be used in follow-up protocols.

Indications for use

• As a complement to CECT and/or CEMRI for pretreatment staging and assessment of target lesion vascularity

• Assistance of needle positioning in cases of incomplete or poor lesion delineation on unenhanced US

• Evaluation of the treatment effect post ablation and guidance for re-treatment of residual unablated tumor.

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Limitation

- the smallest detectable lesions range between 3 and 5 mm in diameter, so very small focal liver lesions may be overlooked
- Sub diaphragmatic lesions, especially those in segment VIII, may not be accessible to conventional ultrasound
- deep-seated lesions may not be accessible
- the falciform ligament and surrounding fat can cause an enhancement defect that may be confused with a focal liver lesion

Safety

- Use of microbubbles is safe with a very low incidence of side effects
- There are no liver or nephrotoxic effects
- Anaphylactoid reactions in abdominal applications have been reported with a rate of 0.001%

Check package labeling

- Caution should be exercised when using contrast agents in patients with severe coronary artery disease
- Resuscitation facilities must be available
- The use of contrast agents should be avoided 24 hours prior to extracorporeal shock wave therapy

Study procedure

- Perform B-mode and Doppler exam
- Once the target lesion is identified, the transducer is held still while the operator enters the Contrast Package
- A dual screen format showing a low MI B-mode image alongside the contrast-only display aids anatomic guidance and may be image overlaid with different color scales
  - the gray scale display is noisy so that smaller and low contrast lesions may be difficult to image
- The contrast agent is administered following package insert as a bolus injection followed by a flush of normal saline 0.9%
- Ideally, the diameter of the venous line should not be higher than 20 G to avoid destruction of microbubbles during injection. Central line and port systems can be used as long as there is no filter requiring a high injection pressure but contrast arrival time will be shorter.
Study procedure

• Imaging should be started at the time of injection

• To capture the dynamic nature of real-time CEUS clips are recorded for each vascular phase

• Assessment of the arterial and portal venous phases should be carried out without interruption. For the late phase, intermittent scanning may be used until the disappearance of the microbubbles from the liver’s microvasculature. Under some circumstances, especially for HCC, the examination may need to be continued for up to 5 min because wash out may be delayed (Mork et al. 2007)

• Injection can be repeated when a lesion has been detected in the portal venous phase or in the late/postvascular phase to study the arterial phase and in the case of multiple FLL. Reinjection should be postponed until most microbubbles have vanished and the CEUS screen is almost black again
Characteristics of lesions based on vascular phase

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In the arterial phase, most hemangiomas have initial peripheral globular/nodular enhancement that progresses toward the center of the lesion. This centripetal filling lasts from seconds to minutes and is more rapid in smaller lesions.

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Hemangioma
Hemangioma
Hemangioma at 15 seconds
Hemangioma at 52 seconds
Hemangioma
Hemangioma
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Focal Nodular Hyperplasia
Focal Nodular Hyperplasia
Arterial phase
Focal Nodular Hyperplasia
Portal phase
Focal Nodular Hyperplasia
Late phase
Focal Nodular Hyperplasia

Arterial Phase

Portal Phase

Late Phase
Focal Nodular Hyperplasia
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Hepatocellular Carcinoma
Arterial phase
Hepatocellular Carcinoma
Late phase

2.4 ML

T1: 2:57
Characteristics of lesions based on vascular phase
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Liver Metastases
B mode
Liver Metastases
Contrast arterial phase
Liver Metastases
Contrast late phase
Liver Metastases
Contrast late phase
**Characteristics of lesions based on vascular phase Metastases**

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Indications for use, safety, and applications

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Intraoperative CEUS

Late Phase
HCC post ablation

Arterial Phase