Disclosures

• None
Thank You

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• Dr Michelle Robbin
Objectives

• Describe US contrast agents
  – How they differ from MR/CT agents
• Review safety/administration
• Highlight major applications
• Describe some future applications
Ultrasound Contrast Agents

• Earliest agitated saline (Gramiak, 1968)
• Short half-life, trapped by pulmonary capillaries
• Manufactured microbubbles from 2 – 7 microns
• Smaller than RBC, so can pass through pulmonary circulation

Microbubbles ex vivo

Definity (lipid shells)

Optison (protein shell) against RBCs

Chemical Content

• Microbubbles of gas in an encapsulating shell
  • Air in a polysaccharide (Levovist)
  • perfluorocarbon or sulfur hexachloride stabilized by a thin shell (Definity, Lumason, Imagent-lipid) (Optison-protein)
• Most only intravascular
• Some drugs have hepatic (Levovist, Sonazoid) or splenic (Lumason) phase

Stewart and Sidhu; The British Journal of Radiology, 79 (2006), 188–194
Mode of Administration

- 0.5-2cc IV- bolus (preferred) or infusion
- **Enhances blood signal 500-1000x**
- Lasts 5 min (avg.) with bolus- longer with infusion.
- Bubbles rupture, gas exhaled via lungs, shell metabolized by the body
- Major risk is anaphylaxis- at rate of 1/7000 (U.S.) to 1/10,000 (Europe) less than that of CT, comparable to most antibiotics.

Is it Safe?

- U of R has administered >10,000 doses without a serious adverse event
- Definity does cause mild back pain - self limited - in 1/200 patients.
- October 2007 FDA issued “black box” warning due to a few serious events (possible anaphylaxis) worldwide (4 deaths in the US) in patients having cardiac events - No cause and effect established
- Black Box modified 9 months later
Retrospective Results

- Kusnetsky reviews 18,671 hospitalized patients undergoing echocardiography
- No effect of contrast on mortality
- Patients receiving CEUS exams did better than those who did not get agent

Current FDA recommendations

• Assess all patients for the presence of any condition precluding contrast administration (allergy)

• In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor VS, ECG and O2sat for 30 minutes after Optison or Definity or Lumason

• Have resuscitation equipment available
US Contrast in Radiology

• Approved for Liver in UK, Canada, Europe and Japan since early 2000’s
• 2016- Lumason approved for liver imaging in the US for lesion characterization.

April 4, 2016 -- The long wait is over. The U.S. Food and Drug Administration (FDA) for the first time has approved the use of an ultrasound contrast agent for radiology applications, giving the nod to Lumason from Bracco Diagnostics to be used for focal liver lesions. Lumason was known previously in the U.S. as SonoVue, and it received initial FDA approval in October 2014 for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The agent is still offered by Bracco under the SonoVue brand outside of the U.S.
Current Contraindications

• Known allergy to US contrast
• Patients with right to left or bidirectional cardiac shunts
  – Recent MI
  – Severe Heart Failure
  – Consider Cardiology Consult
• Not for intra-arterial injection
How do they work?

- Unlike blood cells (same size) which we do not see, we see US contrast because
  - Bubbles contain gas which reflects the sound
  - Bubbles oscillate in the 3-5MHz range (same as we use for abdominal US) creating echoes of their own, independent of those transmitted by the machine.
  - These independent echoes are a multiple of the inciting frequency, and are known as harmonics
  - We can selectively receive the harmonic frequency and see only the bubbles signal, suppressing background.
Liver Imaging with Contrast

- Liver image (MIP) 11 sec after injection.
- Note the number and small size of the vessels (down to 5th order branches) seen only with contrast.
- Deficit area is a hemangioma

Liver Mass Characterization

- Benign lesions: Hemangioma, FNH, equivalent to CT or MR - **prolonged delayed enhancement**
- Adenoma has some overlap with HCC - soft washout
- Metastases and HCC equivalent to CT/MR
  - Better for early wash-in and washout due to high frame rate and long observation times (up to 20 minutes)
  - Difficulty with deep lesions, blind spots under diaphragm and behind ribs
Sustained Enhancement, Extended Portal Phase
Equal to or greater than liver?

Yes

No

Benign

Malignant

**Arterial Intensity:**
- Predominant enhancement of lesion less than liver

**Arterial Pattern:**
- Enhancement is peripheral nodular
- Peripheral pools and puddles present

**Time:**
- Centripetal progression

Hemangioma

Focal Nodular Hyperplasia

Hepatocellular Carcinoma

Non-HCC malignancy

**Arterial Intensity:**
- Predominant enhancement of lesion is greater than liver

**Arterial Pattern:**
- Enhancement appears diffuse

**Arterial Intensity:**
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**Arterial Pattern:**
- Enhancement appears diffuse

**Arterial Intensity:**
- Predominant enhancement of lesion less than liver

**Arterial Pattern:**
- Enhancement is sparse or rim
<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>AP</th>
<th>PVP</th>
<th>LP</th>
<th>Variations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN</td>
<td></td>
<td></td>
<td></td>
<td>All phases; Isovascular</td>
<td></td>
</tr>
</tbody>
</table>
| DN                  | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | [Vascular changes transition from RN, DN to well-differentiated HCC](http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732) | AP: Hypovascular  
PVP/LP: Isovascular                                      |
| HCC                 | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) | [Contrast enhancement](http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732) | AP: Hypervascular  
PVP/LP: Late and weak washout                    |
| Cholangiocarcinoma  | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | [Vascular enhancement and rim enhancement](http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732) | AP: Hypervascular or rim enhancement  
PVP/LP: Punched out and/or rapid washout < 60 seconds |
| Hemangioma          | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png) | [Peripheral nodular enhancement and centrifugal progression of enhancement](http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732) | AP: Peripheral nodular enhancement and centrifugal progression of enhancement  
PVP/LP: Complete or partial fill in |

Figure 1: Schematic shows the typical enhancement patterns of common benign and malignant lesions in the cirrhotic liver.  
*RN* = regenerative nodule,  
*DN* = dysplastic nodule,  
*AP* = arterial phase,  
*PVP* = portal venous phase,  
*LP* = late phase.

Radiology,  
http://pubs.rsna.org/doi/abs/10.1148/radiol.2016151732

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Baseline/CDI

C/O Dr Stephanie Wilson
Sustained Enhancement - BENIGN
Rapid Washin and Washout = Metastasis
59/F HBV Surveillance

Nodule with an echogenic rim in liver
Above threshold size of 1 cm - do CEUS

C/O Dr Stephanie Wilson
Peripheral Nodular Enhancement
Centripetal Progression

23 seconds

30 seconds

35 seconds
Sustained Enhancement to 4 M
STOP – no further imaging.
67/M  HCV Surveillance US

D 4.2 cm

C/O Dr Stephanie Wilson
67/M HCV
US 4.2cm Mass

Triphasic CT
Mass 2.5 cm

AP Hypervascular
PVP Washout

C/O Dr Stephanie Wilson
Referral to CEUS to resolve SIZE Discrepancy

“Nodule in Nodule” Appearance
Isovascular at 90 s
Washout HCC
Sustained Enhancement DN

IMPACT: HCC in DN or higher grade focus HCC within lower grade nodule
CEUS in the Kidney

- Solid Mass characterization- equivalent to CT for Clear cell RCC, and superior for Papillary (showed minimal flow better than CT) (1)
- Bosniak II lesions seen with CEUS (31 patients, accuracy 74% by CT, 90% by US, US tended to upstage lesions (thicker septae)- (2)

Number of Septae US > CT

Prospective CEUS vs CT Complex Cysts

- 40 patients with complex cystic masses detected by CT
- 3 readers
- Path outcome or 24 mo F/U
- 21 RCCs, 9 complex cysts, 2MCNs, 8 simple cysts
- CEUS accuracy 80-83%, vs 63-75% CT
- Non-enhanced US accuracy only 30%

Patient with Indeterminate Mass (MR) who cannot get CT or MR contrast
Patient with Indeterminate Mass on MR who cannot get CT or MR contrast
Patient with CRF suspected Mass on CT and unenhanced US.
Patient with CRF suspected Mass on CT and unenhanced US.
Patient with Indeterminate Mass on Contrast CT- 86 yo  female
US Contrast 2\textsuperscript{nd} bolus combined phases
Vascular/Interventional Applications

- Hepatic/Renal transplants- confirm vascular patency
- Endografts- diagnose leaks/monitor therapy
- Monitor ablations
IMPROVED HA VISUALIZATION WITH US CONTRAST

- 8/72 no flow on CDUS
- 6 flow on CEUS (Optison .5ml)
  – confirmed with angio or nl f/u US.
- 2 no flow, angiography confirmed
- US sensitivity rose from .91 to 1.0 (p<.014)

AAA ENDOGRAFT SURVEILLANCE AND THERAPY: ROLE OF US

- CT preferred to assess graft anatomy, and to dx stent migration, leaks
- CEUS equally effective to CT and DSA for endoleaks in small groups of selected patients: 20(a), 30(b) and 24(c) but less effective in overall literature review (d)
- Occasionally better for delayed and/or small leaks
- US potentially useful to guide therapy

84 YO DIABETIC WITH ENDOGRAFT AORTIC REPAIR

endoleak AAA 5cm attempted angiographic rx.

8 mo later persistent endoleak AAA 5.6cm

2 yrs later AAA 6.3cm with renal insufficiency – angio same time shows no endoleak
Gray scale and color Doppler show AAA
Only contrast study shows endoleak
After initial 1000u thrombin injection the leak is no longer seen with repeat contrast bolus (Definity .75cc/bolus)
Other Applications

- Bowel (IBD, Ischemia)
- Cystoscopy (VCUG)
- Trauma
- Ovary, Prostate?

CEUS in Crohn’s Disease Ripolles et al Insights Imaging Dec 2011
Conclusions

- US Contrast a powerful tool to enhance US diagnosis
- Primary use in characterizing focal lesions (liver-Wilson et al)
- Useful in assessing ablation margins (Liver, kidney-European studies)
- Vascular agent for intra-abdominal vessels (transplants, vascular stents)
- Applications in bowel (Wilson), ovary, prostate?
- Great potential use in patients who cannot receive CT or MR contrast due to allergy, renal function or location (interventional, OR, etc)