Contrast Enhanced Ultrasound: Off-label Use Issues and Applications

Ultrasound in the New Millennium: The Cancer Patient

Richard G. Barr MD, PhD
Professor of Radiology, NEOMED
Radiology Consultants Inc. Youngstown, Ohio
What is Off Label Use?

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.
Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.
What are Ultrasound Contrast Agents?

- Ultrasound contrast agents are gas filled lipoproteins.
- They have a non-linear response to the ultrasound beam which allows the subtraction of other tissue (linear response) so that a “vascularity only” image is obtained.
- At high MI bubbles burst, at low MI bubbles have nonlinear fundamental and harmonic signals.
CEUS - Advantages

- Real-time assessment of vascularity.
- True intravascular agents.
- No renal or liver impairment.
- Short half-life (approx. 5 min)
- Can use multiple injections.
- No ionizing radiation.
CEUS - Disadvantages

• IV required
• Need two people (one to scan and one to inject)
• Lots of data - consider PACS issues
• We save 3 minute clip to a USB drive and only send selected images for short clips to the PACS.
When should CEUS be used?

- CEUS for routine use should be considered when it can help a patient.
- Renal impaired patient requiring contrast.
- Patients with CT and/or MRI contrast allergy.
- CT or MRI do not answer clinical question or conflict.
- When it is important to know that no flow is present (e.g. post RFA).
Types of Exams

- Liver (especially good for FNH)
- Kidney (Indeterminate Renal Masses)
- Aortic Stent Graft
- Small bowel (IBS)
- Others

- EFSUMB CEUS guidelines for hepatic and non-hepatic use.
75 yo male with renal failure S/P RFA with CEUS guidance and aortic stent graft placement

CT without contrast

Ablated RCC - confirm no flow
CT without contrast

Type 3 End leak incidentally noted
68 yo BM with multiple renal masses on CT
US without contrast is not always able to confirm a benign cyst or flow in a malignancy
What is Needed to Perform CEUS?

• Contrast Specific Software on your ultrasound system
• Contrast Agent
• IV access
• Two sets of hands (one to scan, one to inject)
How Do I Get Contrast Specific Software?

• All major ultrasound vendors have contrast specific software available for sale outside of the USA.

• The policy varies between vendors if it can be activated in the USA. Contact your sales/application person to start the process. Be patient but persistent.

• May request you obtain IRB approval
What US Contrast Agents Exist?

- Definity - Lantheus Medical
- Optison - GE Medical
- SonoVue - Bracco Diagnostics
- Sonazoid - GE Medical
How Do I Get the US Contrast Agent?

• You must use an ultrasound contrast agent approved for an indicated use in the USA.

• You therefore have two options
  - Definity - Lantheus
  - Optison - GE Medical

• Contact the companies as usual - your cardiology department/pharmacy may already be purchasing these agent for cardiology use.
Contrast Specific US Techniques

- Nonlinear fundamental contrast mode
- Harmonic contrast mode
How to Perform CEUS

- Select Patient (discuss with referring MD)
- Informed Consent
- Start IV
- Activate drug
- Perform a standard exam
- Locate area/lesion of interest
- Activate Contrast specific software
- confirm settings (low MI)
• Activate Dual screen (if desired)
• Inject drug followed by saline flush
• Start timer
• Start clip save (3 minutes)
• Collect data as needed for patient (stay in one position or scan)
• End study - decide if additional injections required
• Remove IV
• Report study
Informed Consent

• If you are not doing research you do not need IRB (ethic board) approval unless required by your institution.

• We do have patient sign a brief informed consent document stating we are using a drug approved for cardiac use in the USA. We are using same dose, same power output, and same method of injection.
Start IV

- Must be at least a 20g needle not to break bubbles
- Consider a 3 way stopcock with contrast in one port and saline flush in the other. Contrast should be “in-line” with needle and saline can be 90 degrees.
- High pressure on injection will “burst” bubbles.
Activate Drug

- Both Definity and Optison need to be activated to form the active bubbles.
- Once activated care should be taken not to induce pressure changes which “burst” the bubbles.
Perform Standard Exam

- Identify lesion or area of interest.
- Find an imaging plane so the lesion remains in the FOV during patient’s breathing.
Activate Contrast Specific Software

Contrast Image  “Reconstructed” B-mode

Dual vs. single display
Inject Drug

- Draw up activated contrast being careful to avoid large pressure changes.

- Drug dose is usually 0.3cc for Definity and Optison. For organs with decreased flow or with higher frequency transducers (e.g. breast) you may want to use a double dose. Use a 1cc syringe.

- Follow contrast injection with 10cc saline flush

- While one person is injecting drug, the sonographer starts timer and begins clip acquisition
Data Collection

- Optimization button (e.g., iscan, TEQ)
Decide if Additional Dose Required

• Have MD present during scanning

• Save select images and send to PACS for review

• Contrast enhancement patterns are similar to CT and MRI.

• Go to the literature for help in interpretation.
Complete Study

- Remove IV
- Report Study
  - Include number of injections, doses, and agent.
Variations

• Perform time-intensity curves
• software is available (e.g., QLABS)
• Burst bubbles and watch refill
• Short burst of high MI followed by low MI imaging - available on most equipment
How To Bill for the Ultrasound Contrast

• No reimbursement for hospital setting at this time.
• For office setting you can bill on Q9957.
• Definity Medicare Part B = 61.79/unit (2 units/vial) in 2011.
• There is no CPT code for CEUS in the abdomen. There is no reimbursement for the additional effort of a CEUS - we bill for the standard non-contrast study.
Where can I go for help?

- Vendors (Drug Companies and Equipment Companies) are not able to help you for off-label use. They can respond to specific questions when asked.

- There are training courses offered in Europe.
What if I want to use CEUS for Research?

- You will need to obtain IRB approval.
- Drug companies may provide you a grant (free drug and/or monetary grant) if they are interested in the study. They can support you if you have an IRB.
- Manufacturers will be more willing to turn on CEUS if you are doing research. They will be able to work with you on the technique.
When Will US Contrast Agents be Approved in the USA

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• They are approved in the rest of the world and have an excellent safety record.
Conclusions

• This is a brief overview of how to perform CEUS in your practice.

• Before you start doing patients.
  • more detailed understanding of physics.
  • more detailed understanding of interpretation.
Conclusions

• CEUS can be performed off-label in the USA.
• You may get reimbursed for the contrast agent, but not for the additional time needed to perform the exam.
• In selected patients, CEUS can make a big impact in diagnosis and/or outcome.