



Agent Preparation, Administration, Contraindications & Lab Policy

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No Disclosures

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Objectives:



1. Describe the preparation of the 3 FDA approved UEA's
2. Discuss the methods of administration and the advantages and disadvantages to each
3. Overview of contraindications to UEA use, the possible reactions and the treatment
4. Discuss administrative policies potential roadblocks for labs

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Ultrasound Enhancing Agents (UEA's)



UEA's are used to enhance ventricular endocardial borders (LVO), thrombus and masses. Lumason has been approved for pediatric echo, liver, and vesicoureteral reflux (VUR).

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Steps in Preparation

Storage requirements (Refrigeration versus Non-refrigeration)

UEA Activation (Mechanical mixing and timeframe for use)

Solution Concentrations (Best practices for Imaging)

Set-up for the Administration of the UEA

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Storage

Refrigerated:

Optison

Definity

(36° to 46°)



Non-Refrigerated:

Lumason (Sonovue)

(Room Temp (77°))



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Activation Methods

All agents need some form of mechanical activation

Definity:



Lumason:



Optison:



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Activation Methods (Definity)



The activation process for Definity is done by a mechanical activator that vigorously agitates the liquid lipid and the gas inside the vial for 45 seconds.

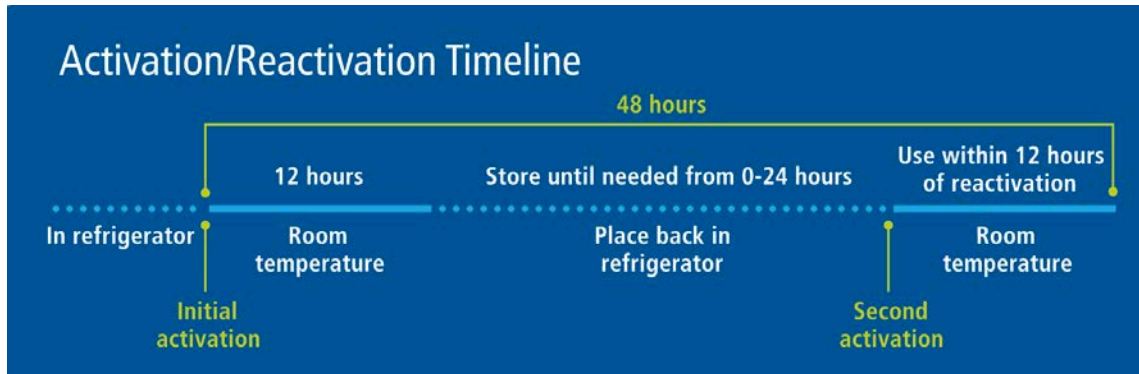
The microbubbles are then formed by this action until a milky-white liquid is seen in the vial.

The vial will have a positive pressure which will need to be released by using a 22 to 20 gauge needle (unless you use a vented spike).



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Activation Methods (Definity)



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Activation Methods (Lumason)



Lumason comes as a Lyophilized powder with a gas head space in the vial.

Lyophilized powder contains lipid which reacts when activated by normal saline to form microbubbles. The lipid layers encase the gas based on hydrophilic/phobic properties.

A vented mini-spike is also provided for easy mixing.

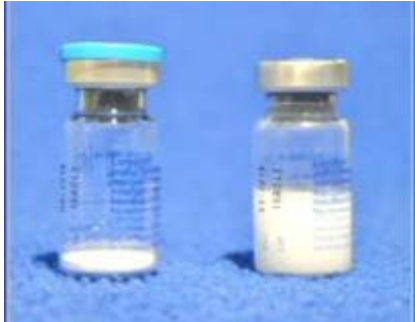
Vigorous hand agitation for 20 seconds until milky white

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Activation Methods (Lumason)



LUMASON is for single use only. LUMASON does not contain an antimicrobial preservative and the suspension should be used within 3 hours after reconstitution. The microspheres should be resuspended by a few seconds of hand agitation before the product is withdrawn into the syringe.



On the left is the pre-activated Lumason vial

On the right is after 20 seconds of vigorous agitation

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Activation Methods (Optison)



Optison comes ready to use. The Albumin shells already contain the gas inside and just a few seconds of rolling between your hands should evenly distribute the microbubbles for a uniform concentration and bring the solution closer to room temperature.

It should appear milky-white. If it does not appear this way, do not use.

The vial has positive pressure and should be vented prior to drawing back.

Because Albumin is a "Blood Product" Do not use in patients that have had reaction to blood products and religious groups that forbid blood transfusions

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Activation Methods (Optison)



Optison should be used within 30 minutes after rubber seal has been penetrated.

Unused and unpenetrated vials can be at room temperature for 24 hours and then must be refrigerated.

Administration of UEA's



GUIDELINES AND STANDARDS

Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update

GUIDELINES AND STANDARDS

(APPENDIX) Various Methods of Administering UEA's:

- Oregon Health & Science University
- Medical University of South Carolina
- Houston Methodist Hospital
- Mayo Clinic, Rochester
- University of Nebraska Medical Center

Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: A Focused Update from the American Society of Echocardiography

Thomas R. Porter, MD, FASE (Chair), Sahar Abdelmoneim, MD, J. Todd Belcik, BS, RCS, RDMS, FASE, Marti L. McCulloch, MBA, RDMS, FASE, Sharon L. Mulvagh, MD, FASE, Joan J. Olson, BS, RDMS, RVT, FASE, Charlene Porcelli, BS, RDMS, FASE, Jeane M. Tsutsui, MD, and Kevin Wei, MD, FASE, *Omaha, Nebraska; Rochester, Minnesota; Portland, Oregon; Houston, Texas; Charleston, South Carolina; São Paulo, Brazil*

(J Am Soc Echocardiogr 2014;27:797-810.)

Administration of UEA's



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Administration of UEA's



The 3-way stopcock method works for any agent however, is the preferred method for Lumason.

It is important to place the UEA filled syringe in the straight line position so the microbubbles do not burst while flowing at a 90° angle.

Chaser with Normal Saline flush

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Administration of UEA's



The pump method is a preferred method for Dobutamine or Perfusion stress test imaging.

Maintains hands-free, continuous concentration delivery of UEA.

All UEA's can be delivered with this method however, the size of the syringe will be determined by the bubble concentration of the UEA.

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Administration of UEA's



UEA diluted in Normal Saline inside a syringe is a fast and effective method for LVO.

Lumason maintains effective microbubble concentration in a dilution of up to 10ml

Optison maintains effective microbubble concentration in a dilution of up to 20ml

Definity maintains effective microbubble concentration in a dilution of up to 35ml

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Administration of UEA's



At OHSU, our department puts together contrast bags that contain:

50cc bag of NSS

35ml Syringe

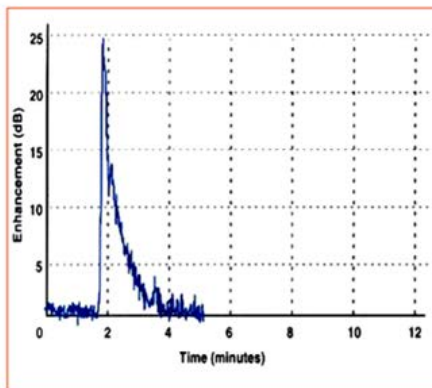
Vented Opti-spike

Micro-bore Tubing

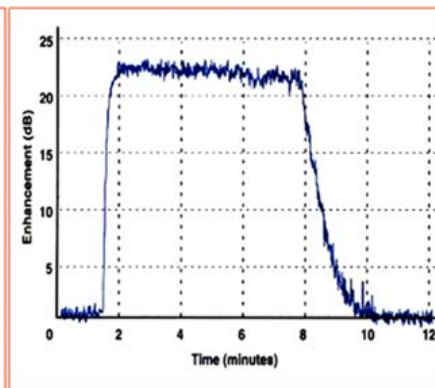
Administration Methods of UEA's



BOLUS CONTRAST INJECTION



CONTINUOUS CONTRAST INFUSION



Administration Methods of UEA's



Advantages to Bolus Infusion:

Less set up = Less time
Less equipment
Quickly Begin Imaging

Advantages to Continuous:

Consistent Concentration
Continuous Scanning
Increase Imaging Duration

Disadvantages:

More Artifacts
Time off the Probe

Equipment Malfunction/Settings
Needs Titration

Regardless of method, It is important to maintain bubble homogeneity

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Contraindications



The **ONLY** contraindications for **ANY** of the FDA approved UEA's are:

Known Hypersensitivity to the UEA agent or the inert gas inside
(Sulfur Hexafluoride, Perflutren)

Known Hypersensitivity to Blood Products (Optison)

NEVER INJECT INTO ARTERY

SULFUR is NOT SULFA and there is NO CONTRAINDICATIONS to patients that have had reactions/allergies to Sulfa drugs

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Contraindications



Not enough data on pregnancy and breast feeding mothers

In 2016, the FDA removed the contraindications for shunts (suspected right-to-left, bidirectional, or transient right-to-left)

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Safety



GUIDELINES AND STANDARDS

Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update

After the infamous FDA Black Box Warning of 2007, the cardiology imaging community mobilized

Large studies totaling 263,518 patients (both inpatient and outpatients) that received UEA showing the extreme safety profile of all UEA's used in the United States

Rare reactions of 1:10,000 individuals and no deaths reported

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Safety

So WHY???

Table 1 New-Onset Adverse Reactions Occurring in $\geq 0.5\%$ of All DEFINITY-Treated Subjects

	DEFINITY (N=1716)	
Preferred term	n	(%)
Total Number of Adverse Reactions	269	
Total Number of Subjects with an Adverse Reaction	144	(8.4%)
Body system		
Application Site Disorders	11	(0.6)
Injection Site Reactions	11	(0.6)
Body as a Whole	41	(2.4)
Back/renal pain	20	(1.2)
Chest pain	13	(0.8)
Central and peripheral nervous system disorder	54	(3.1)
Headache	40	(2.3)
Dizziness	11	(0.6)
Gastrointestinal system	31	(1.8)
Nausea	17	(1.0)
Vascular (extracardiac) disorders	19	(1.1)
Flushing	19	(1.1)

N=Sample size 1716 subjects who received activated DEFINITY
n=Number of subjects reporting at least one Adverse Reaction

**Table 1. Adverse Reactions in Patients*
n = 6856**

Number (%) of Patients with Adverse Reactions	
Headache	65 (1%)
Nausea	37 (0.5%)
Dysgeusia	29 (0.4%)
Injection site pain	23 (0.3%)
Feeling Hot	18 (0.3%)
Chest discomfort	17 (0.2%)
Chest pain	12 (0.2%)
Dizziness	11 (0.2%)
Injection Site Warmth	11 (0.2%)

**Table 1
SELECTED ADVERSE EVENTS REPORTED IN $\geq 0.5\%$ OF THE SUBJECTS WHO RECEIVED
OPTISON™ IN CONTROLLED CLINICAL STUDIES**

No. of Patients Exposed to OPTISON™	279
No. of Patients Reporting on Adverse Event	47 (16.8%)
Body as a Whole	38 (13.6%)
Headache	15 (5.4%)
Warm Sensation/Flushing	10 (3.6%)
Chills/fever	4 (1.4%)
Flu-like Symptoms	3 (1.1%)

Safety

At OHSU

Received: 3 January 2019 | Revised: 12 February 2019 | Accepted: 30 March 2019

DOI: 10.1111/echo.14344

Echocardiography WILEY

Safety profile of ultrasound enhancing agents in echocardiography

Suwen Kumar MD | Chris Purtell MD | April Peterson RDCS | Paul Gibbons RDCS |
Abigail M. Khan MD | Stephen B. Heitner MD

Total of 5521 administrations: 14 AE's (0.25%) reported (none life threatening)

Safety



If a CARPA reaction occurs:

Most of the time, the provider/sonographer can wait until UEA clears

**In significant cases, a H1 inhibitor can be used
(Benadryl, Diphenhydramine)**

**Epinephrine for allergic reactions
(Epi-pen (IM) or IV route)**

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Hospital/Clinic Policy



Ensure system has the proper settings for performing the modalities you need.

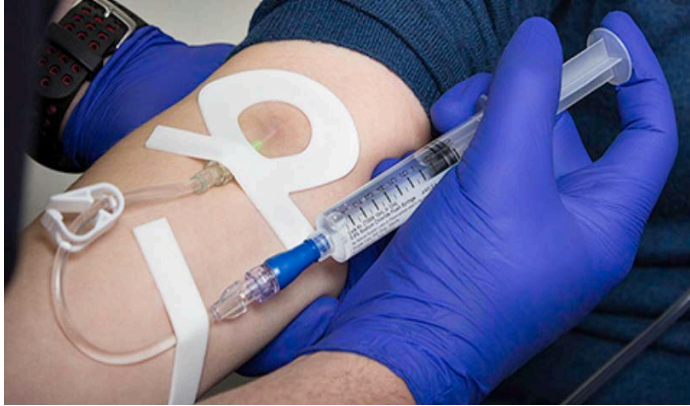
Each manufacture has “Contrast” settings that may or may not come standard on a system.

“Perfusion” setting is an additional add-on

Ensure the probe has contrast abilities.

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Hospital/Clinic Policy



Follow state/hospital/clinic policy on IV access.

It is strongly suggested that a hospital or clinic have sonographers trained in IV access for a streamlined process.

Best to use a 20ga or larger IV catheter however, we have used as small as 24ga on difficult patients without trouble.

DO NOT attempt to push UEA's when resistance is felt (bursts bubbles).

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Hospital/Clinic Policy



Informed Consent is driven by institutional policy. Inpatients usually fall under a "blanket consent" for this type of procedure.

OHSU uses a verbal consent and standing order for administering UEA's in the clinic.

Some clinics in the Portland metro area use written consent.

ANY OFF LABEL or RESEARCH REQUIRES WRITTEN INFORMED CONSENT.

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Hospital/Clinic Policy



Sonographers should be adequately trained in performing studies using UEA's (UEA manufactures have information and training)

Physicians should also be familiar with UEA's and receive supervised training and interpretation by a level-III trained person. Perfusion training requires specific performance and interpretation at a high-volume center with expertise in Myocardial Perfusion.

Nursing staff should support the echo department when needed

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Additional Resources:



ASE website has many informative links

How to Perform a Myocardial Perfusion Study:

Kevin Wei, MD, FASE, from Oregon Health and Sciences Center in Portland, OR discusses how to perform a myocardial perfusion study.

How to Perform a Myocardial Perfusion Study: Part 1 Introduction Dr. Wei demonstrates how to prepare the contrast media for use in a cardiac ultrasound study.

How to Perform a Myocardial Perfusion Study: Part 2 Components Dr. Wei shows how to have materials prepared prior to using contrast media for use in a cardiac ultrasound study.

How to Perform a Myocardial Perfusion Study: Part 3 Diluting Contrast Media Dr. Wei walks us through how to prepare contrast media for injection prior to a cardiac ultrasound study.

How to Perform a Myocardial Perfusion Study: Part 4 Pump Dr. Wei demonstrates how to pump contrast media during a cardiac ultrasound study.

How to Perform a Myocardial Perfusion Study: Part 5 Machine Settings Dr. Wei instructs how to set up an ultrasound machine to maximize the effectiveness of contrast media during a cardiac ultrasound study.

How to Perform a Myocardial Perfusion Study: Part 6 Manual Settings Dr. Wei instructs how to set up an ultrasound machine without automatic presets to maximize the effectiveness of contrast media during a cardiac ultrasound study.

Webinars

Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography
Non-CME webinar recording by Dr. Thomas Porter

Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Update

Non-CME webinar recording by Dr. Thomas Porter

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In 2000, the ASE Cardiac Sonographer Communication Series



CARDIAC SONOGRAPHERS' COMMUNICATION

Incorporating Ultrasound Contrast in the Laboratory: A Series on Contrast Echocardiography, Article 1

Sally Moos, RDCS, Jill Odabashian, RDCS, Susan Jasper, BSN, RN, Jim Bednarz, RDCS, Pam Burgess, RDCS, Dennis Carney, RCVT, Susan Floer, RDCS, Cris Gresser, RDCS, Vickie Moore, RDCS, Eric Sisk, RDCS, Marti Trough, RDCS, Alan Waggoner, RDCS, Sandy Witt, RDCS, and David Adams, RDCS

CARDIAC SONOGRAPHERS' COMMUNICATION

Performing an Echocardiographic Examination with a Contrast Agent: A Series on Contrast Echocardiography, Article 2

Pam Burgess, RDCS, Vickie Moore, RDCS, Jim Bednarz, RDCS, Dennis Carney, RCVT, Susan Floer, RDCS, Cris Gresser, RDCS, Susan Jasper, BSN, RN, Sally Moos, RDCS, Jill Odabashian, RN, Eric Sisk, RDCS, Marti Trough, RDCS, Alan Waggoner, RDCS, Sandy Witt, RDCS, and David Adams, RDCS

CARDIAC SONOGRAPHERS' COMMUNICATION

Ultrasound Contrast Physics: A Series on Contrast Echocardiography, Article 3

Marti McCulloch, RDCS, University of Texas Medical Branch, Galveston, Texas; Cris Gresser, RDCS, Consultant, Heart Vista, Toronto, Ontario, Canada; Sally Moos, RDCS, University of Virginia, Charlottesville, Virginia; Jill Odabashian, RDCS, The Cleveland Clinic Foundation, Cleveland, Ohio; Susan Jasper, BSN, RN, The Cleveland Clinic Foundation, Cleveland, Ohio; Jim Bednarz, RDCS, University of Chicago Hospital, Chicago, Illinois; Pam Burgess, RDCS, Wake Forest University/Baptist Medical Center, Winston-Salem, North Carolina; Dennis Carney, RCVT, Spokane Community College, Spokane, Washington; Vickie Moore, RDCS, Jewish Hospital, Cincinnati, Ohio; Eric Sisk, RDCS, Harborview Medical Center, Spokane, Washington; Alan Waggoner, RDCS, Washington University School of Medicine, St. Louis, Missouri; Sandy Witt, RDCS, Children's Hospital Medical Center, Cincinnati, Ohio; and David Adams, RDCS, Duke University Medical Center, Durham, North Carolina

CARDIAC SONOGRAPHERS' COMMUNICATION

Achieving a Diagnostic Contrast-Enhanced Echocardiogram: A Series on Contrast Echocardiography, Article 4

CARDIAC SONOGRAPHERS' COMMUNICATION

Myocardial Contrast Echocardiography: A Series on Contrast Echocardiography, Article 5

Jim Bednarz, RDCS, Alan Waggoner, RDCS, Sally Moos, RDCS, Sandra A. Witt, RDCS, Marti McCulloch, RDCS, Eric Sisk, RDCS, Cris Gresser, RDCS, Jill Odabashian, RDCS, Susan Jasper, BSN, RN, Pam Burgess, RDCS, Dennis Carney, RCVT, Vickie Moore, RDCS, and David Adams, RDCS, *Durham, North Carolina*



Thank you!!