The Contrast Basics: Contrast Agents and the Ultrasound Approaches to Detect Them

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Disclosures: Investigator-initiated grants from Lantheus and GE LIfesciences

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Ultrasound Contrast Agents

- Encapsulated microbubbles with albumin or lipid shell
- 2-5 microns in diameter
- Stability enhanced by high-molecular weight gas
- Signal produced by their “ringing” in an ultrasound field (volumetric oscillation)
- Special “bubble-specific” imaging presets available

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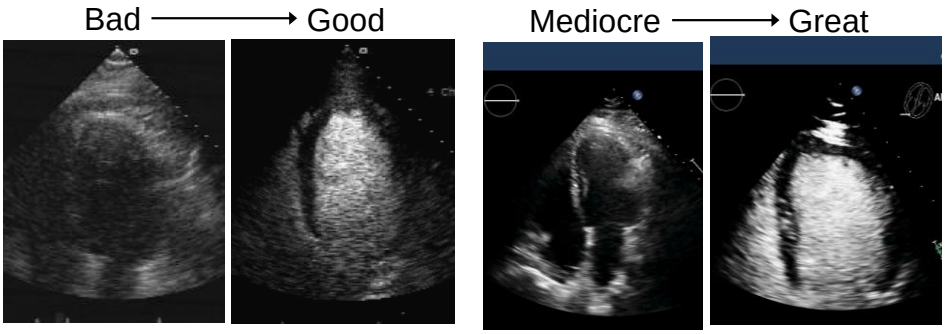
Impact on Assessment of LV Size and Function



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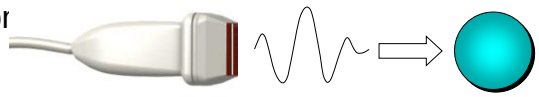
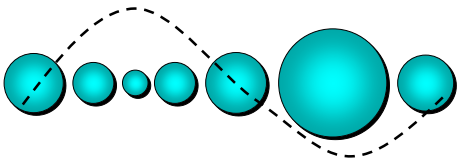
Acoustic Signal Generation During MCE

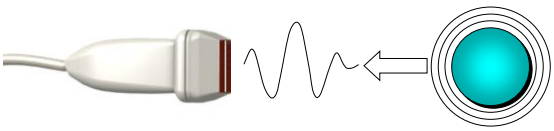
1. Ultrasound stimulation of microbubbles



2. Oscillation of microbubble diameter (volume) according to acoustic pressure



3. Ultrasound signal produced by oscillation



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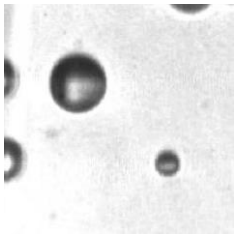

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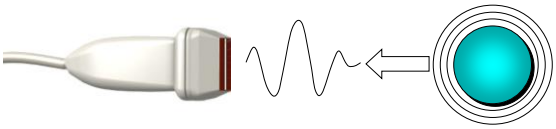

Video courtesy of Dr. Flordeliza Villaneuva

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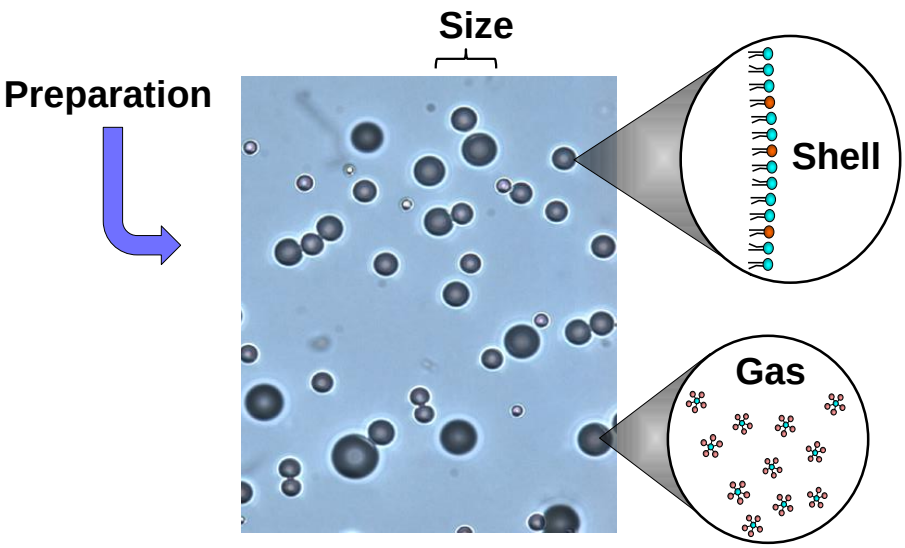
Microbubble Characteristics



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Examples of Commercially-Produced Microbubble Contrast Agents

Name	Shell	Gas	Size (μm)
Optison	Albumin	Octafluoropropane	2-4.5
Definity	Lipid/surfactant	Octafluoropropane	1.1-3.3
Sonovue/Lumason	Lipid	Sulfur hexafluoride	1.5-2.5
Imagent	Lipid	Perfluorohexane	6.0
Sonazoid	Lipid	Decafluorobutane	2-3
Levovist	Lipid-galactose	Air	
Cardiosphere	PLGA/albumin	N_2/Air	2-3
Acusphere	PLGA polymer	Perfluorocarbon	

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UEAs Approved by the United States FDA

Agent	Manufacturer/vial contents	Mean diameter	Shell	Gas
Lumason (sulfur hexafluoride lipid-type A microspheres)	**Bracco Diagnostics, 5 mL (reconstituted)**	**1.5–2.5 μm (maximum 20 μm, 99% ≤10 μm)**	**Phospholipid**	**Sulfur Hexafluoride**
Definity (perflutren lipid microsphere)	**Lantheus Medical Imaging, 1.5 mL**	**1.1–3.3 μm (maximum 20 μm, 98% ≤10 μm)**	**Phospholipid**	**Perflutren**
Optison (perflutren protein type-A microspheres)	**GE Healthcare, 3.0 mL**	**3.0–4.5 μm (maximum 32 μm, 95% ≤10 μm**	**Human albumin**	**Perflutren**

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Composition-related Issues

- Stability – “shelf life” and in vivo
- Practicality – steps to preparation
- Safety
- Microvascular behavior
- Non-linear signal generation (SNR)
- Acoustic robustness (SNR)

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Definity (Perflutren Lipid Microspheres)

- Requires refrigeration
- Requires activation in vialmix
- Bolus or infusion indication; latter good for perfusion

Lumason (Sulfur Hexafluoride Lipid)

- No refrigeration needed
- Kit that requires reconstitution with saline
- Bolus only indications

Optison (Perflutren Albumin)

- Requires refrigeration
- No assembly required

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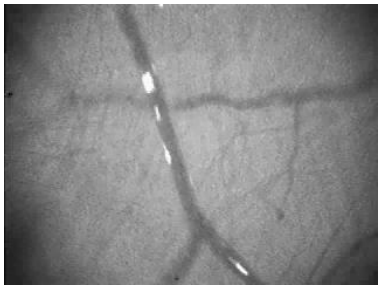
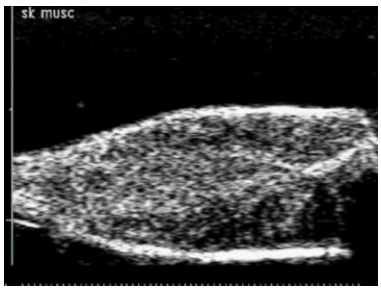
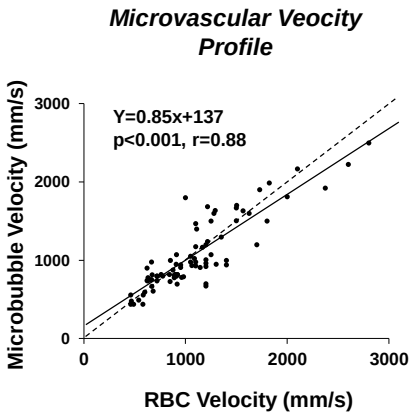
Microvascular Behavior of MBs







Lindner JR, et al. J Am Soc Echocardiogr 2002;15:396

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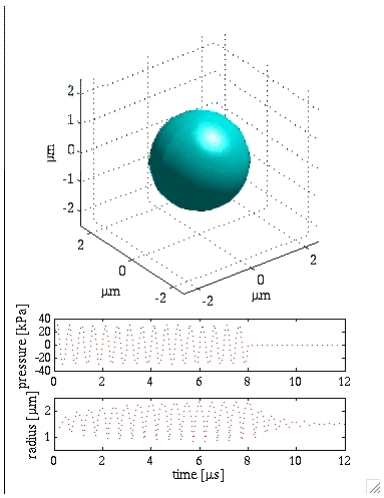
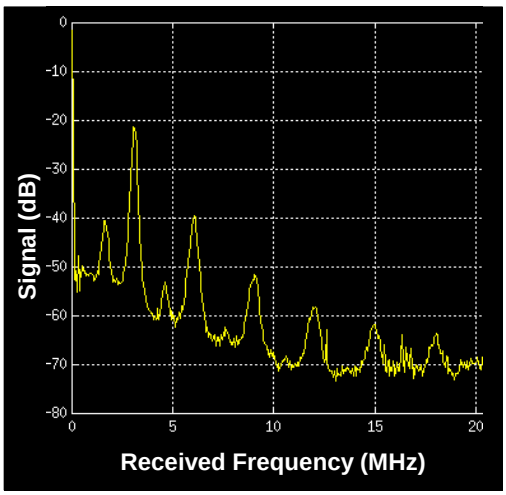
Acoustic Signal Generation





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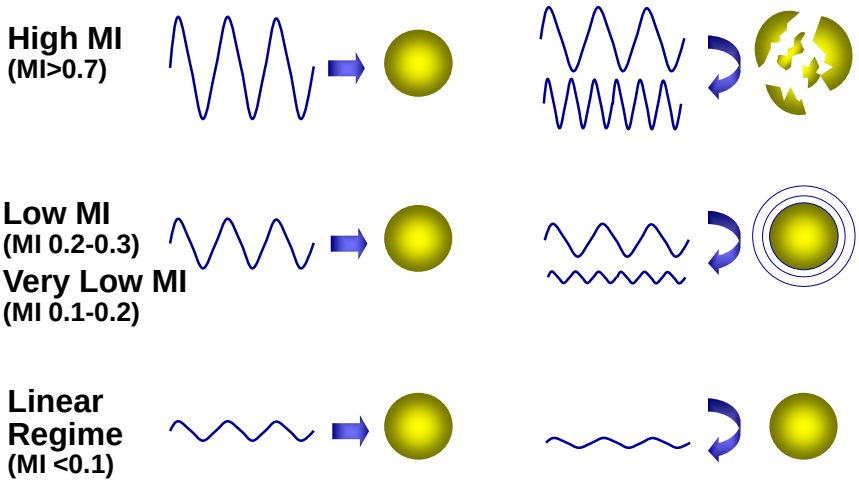
Mechanical Index and Microbubble Responses



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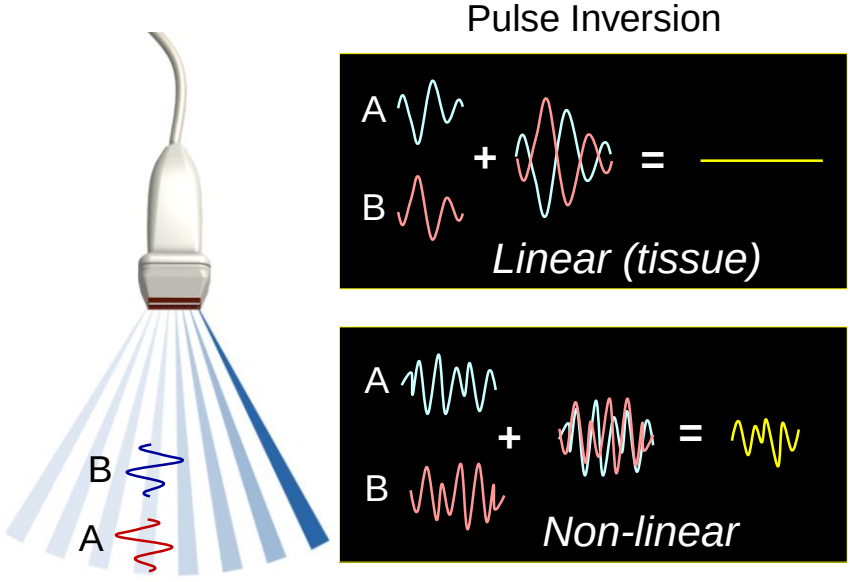
Tissue Suppression with Phase Inversion



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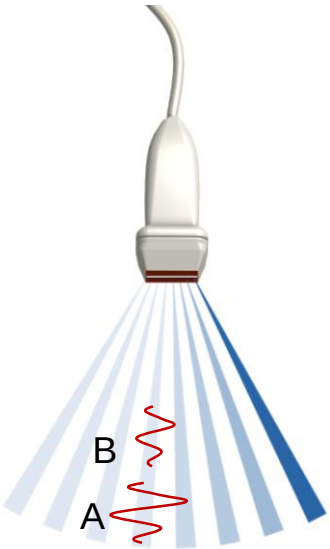
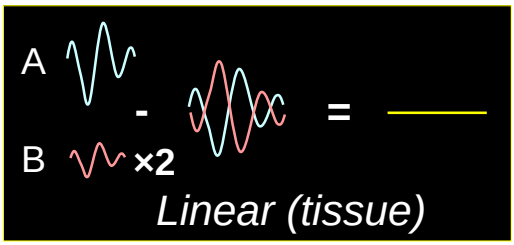
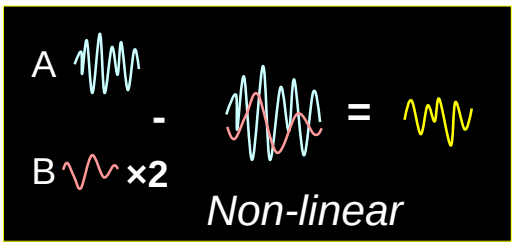
Tissue Suppression with Power Modulation



Power Modulation





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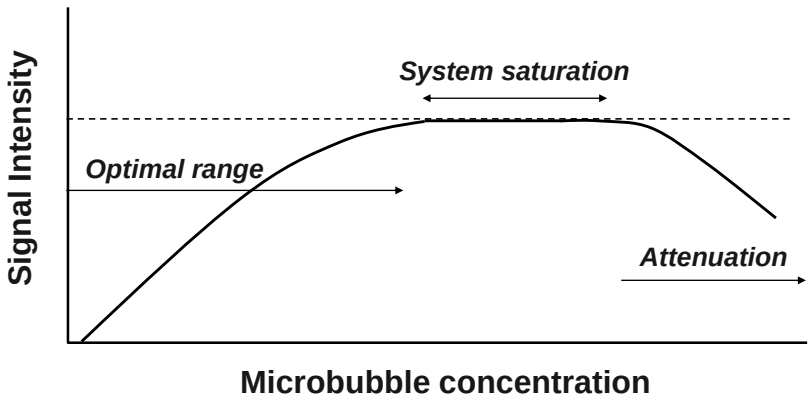
Microbubble Concentration vs Signal



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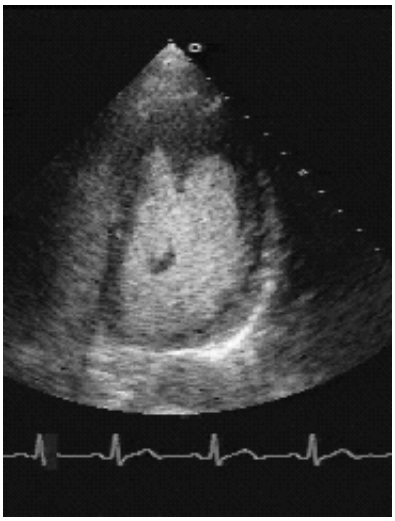
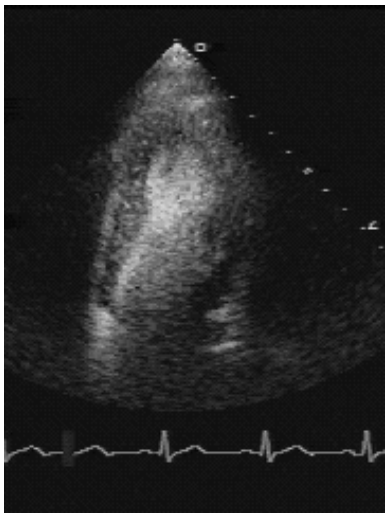
Concentration Issues

Too Low ***Too High***





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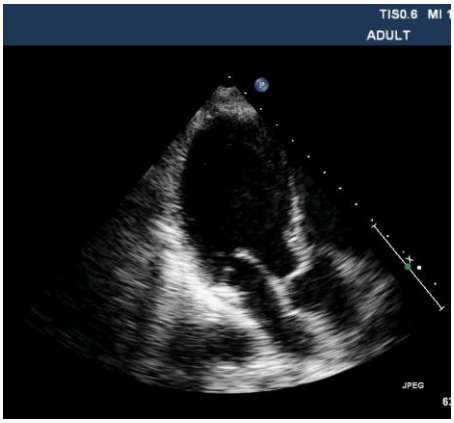
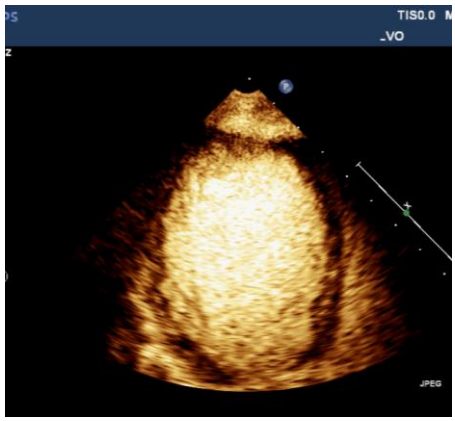
Optimal Concentration





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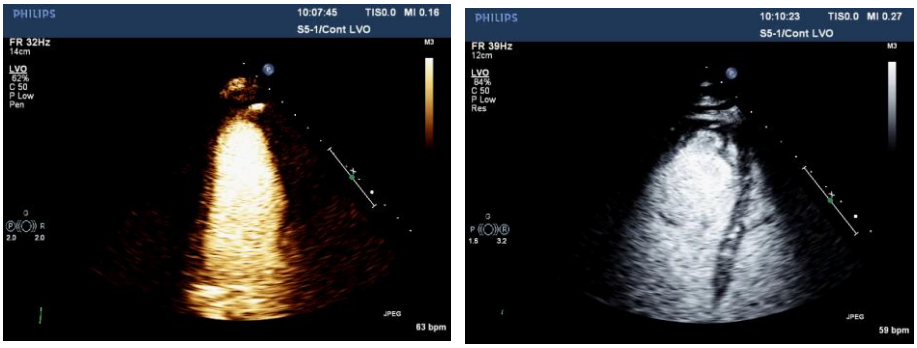
Rib Attenuation



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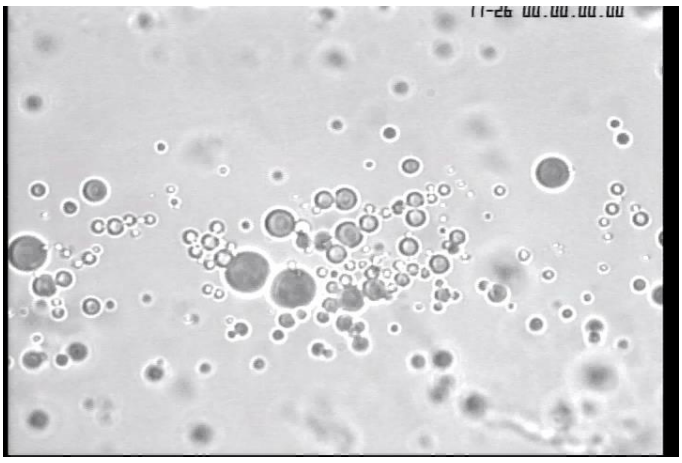
Microbubble Destruction



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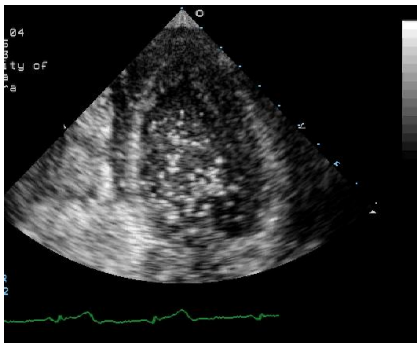
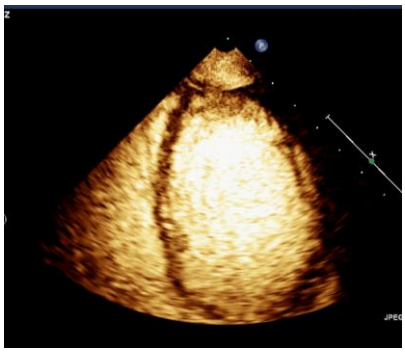
Acoustic Power and LV Opacification



High Power (MI 1.3)



Low Power (MI 0.2)

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Safety of Lipid-shelled Contrast (Definity)

- 66,164 doses of Definity, and 12,219 doses of Optison administered
- Severe reactions in 8 patients (<1:10,000)
- Anaphylactoid reactions in 6 patients
- No deaths
- No events in patients with possible ACS or CHF

Wei K, et al. J Am Soc Echocardiogr 2008;21:1202

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Safety Issues

- Only contraindication for ALL agents is known allergy to the agent or its components
- R to L shunts have been removed
- Patients with allergy to blood products (Optison only)
- Do not administer as an arterial injection
- Religious reasons may preclude use of Optison
- Pregnancy categories are B or C
- Package insert mentions PVCs when used with intermittent high-MI bursts
- Safety has been established in small studies of with pulmonary hypertension, although not all studies evaluated those with severe PH
- Main concern is pseudoanaphylaxis (CARPA)

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Pseudoanaphylaxis: Treatment in Adults

Epinephrine	0.3-0.5 mL of 1:1,000 by SQ or IM route 0.5-1.0 mL of 1:10,000 by IV route	Maintain airway and BP
Diphenhydramine	25-50 mg IV or IM	Anti-histamine
Albuterol or other beta-2 agonist	0.5 mL of 0.5% soln nebulized in 2.5 mL	Maintain airway
Cimetidine	200 mg IM or PO	Anti-histamine
Methylprednisone or other IV steroid	125 mg IV q 6 hr	Late phase reactions

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