Ultrasound Contrast Media

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Bubbles

Gas

+ Intravenous
+ Big difference in acoustic impedance
+ Hyperechoic
- Hyperattenuating
- Reverberation artifacts

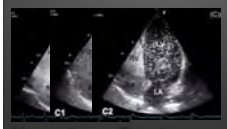
Material	Density (kg/m3)	Speed of sound (m/s)	Acoustic Impedance (kg/m²s)
Air	1,2	330	400
Water	1000	1480	1 488 000
Soft tissue	1100	1540	1 630 000
Bone	1900	4080	7 800 000

Albrecht T, Hohmann J. Contrast Agents in Sonography. Toshiba Visions. 2004

Bubbles

Agitated Saline

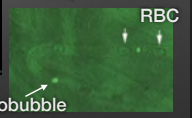
- Larger than capillaries
- Doesn't cross lungs
- Used to identify R to L shunts



Normal R to L

Contrast Media

- 1-7 µm
- Crosses to left-sided circulation
- Can identify and assess vessels and tissue perfusion throughout the body



Gazzaniga P, Buscarini E, et al. Contrast Echocardiography for Pulmonary Arteriovenous Malformations: Does Any Bubble Matter? Eur J Echocardiogr 2009;10:513-518.
Albrecht T, Hohmann J. Contrast Agents in Sonography. Toshiba Visions. 2004

Contrast Media

Composition

- Air or high molecular gas
- Albumin or lipid microsphere

Elimination

- Small doses
- Short 1/2 life
- Exhaled
- Metabolized

Quaia E. Microbubble Ultrasound Contrat Agents: An Update. Eur Radiol 2007;17:1995-2008.

Contrast Media

Table 1 Microbubble contrast agents classified according to the filling gas

Air (Nitrogen)	Perfluorocarbon	Sulfur hexafluoride
-Albunex (Mallinckrodt)[7]	-BR14 (Sonco)	-SonoVue (Bracco)[7]
-Echovist (Sharing)[7]	-Definity (Bristol-Myers Squibb Medical Imaging)	
-Levovist (Sharing)[7]	-Echogen (Sonus Pharmaceuticals)[7]	
-Myomap (Quadrant)[7]	-Imagent-Imavist (Alliance)	
-Quantison (Quadrant)[7]	-Optison (GE Healthcare)[7]	
-Sonovist (Sharing)[7]	-Sonazoid (GE Healthcare)	

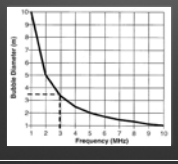
Drugs reported in the literature for veterinary use

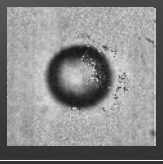
Commercial agent (Manufacturer)	Dosage for veterinary use	Reference
Levovist (Schering AG)	Dogs, cats: 80 mg/kg	Schlief et al. (2005) Rademaker et al. (2005)
Definity (Bristol-Myers Squibb)	Dogs: <20 kg: 0.1 mL, >20 kg: 0.2 mL Cats: 0.1 mL	O'Brien et al. (2006) R. O'Brien (unpublished data)
Optison (Amersham Health Inc.)	Dogs: 0.5 mL/dog	Yamaya et al. (2002)
Sonovist (Bracco)	Dogs: 0.04–0.06 mL/kg (0.2–0.3 mg/kg) Dogs: <20 kg: 0.5 mL (2.5 mg), >20 kg: 1.0 mL (5 mg) Dogs: 0.03 mL/kg (0.15 mg/kg)	Nyman et al. (2005) O'Brien et al. (2006) Ohlerth et al. (2005)

Quaia E. Microbubble Ultrasound Contrat Agents: An Update. Eur Radiol 2007;17:1995-2008.
Ohlerth S, O'Brien RT. Contrast Ultrasound: General Principles and Veterinary Clinical Applications. Vet J 2007;174:501-512.

Imaging

- Ultrasound sine waves have + and - deflections
- Resonant frequency - in sync with microbubble oscillations
- Mechanical Index - force of compression and rarefaction





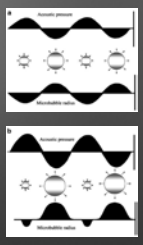
Citations

Mechanical Index

Low MI (<0.1)
- Linear Oscillation

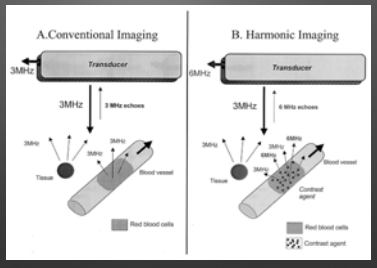
Intermediate MI (0.1-0.5)
- Nonlinear Oscillation
- Expands > shrinks
- Harmonic frequencies

High MI (>0.5)
- Transient nonlinear echo
- Destructive
- "Stimulated Acoustic Emission"



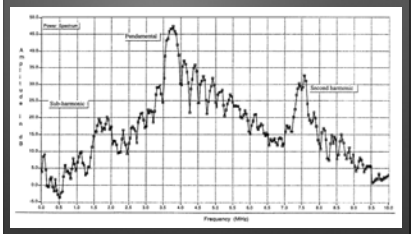
Quaia E. Microbubble Ultrasound Contrat Agents: An Update. Eur Radiol 2007;17:1995-2008.

Harmonic Frequencies



Burns PN. Instrumentation for Contrast Echocardiography. Echocardiography 2002;19:241-258

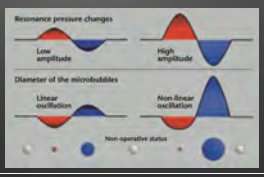
Harmonic Frequencies



Burns PN. Instrumentation for Contrast Echocardiography. Echocardiography 2002:19:241-258

Contrast Specific Imaging

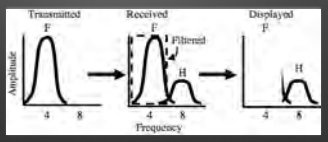
- Second harmonic imaging
- Pulse-inversion harmonic imaging
- Cadence-contrast pulse sequencing



Albrecht T, Hohmann J. Contrast Agents in Sonography. Toshiba Visions. 2004

Second Harmonic Imaging

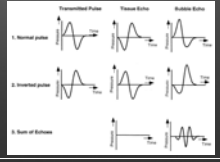
- Fundamental frequency is transmitted
- Only second harmonics are received



Citations

Pulse-Inversion Harmonic Imaging

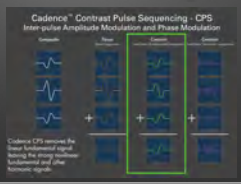
- 2 pulses of sound are transmitted with sine waves in opposite directions
- Return echo of linear oscillators cancel out
- Return echo of nonlinear oscillations of contrast media have a return signal



Burns PN. Instrumentation for Contrast Echocardiography. Echocardiography 2002:19:241-258

Cadence Contrast Pulse Sequencing

- 3 pulses of varied phase and amplitude
- Return echo of linear oscillators cancel out
- Nonlinear oscillators have return fundamental and harmonic signals



Citations

LV Opacification

Improved Imaging of:

- Delineation of the wall-lumen interface
- LV volume
- Ventricular wall motion
- Mural perfusion

Citations

LV Opacification

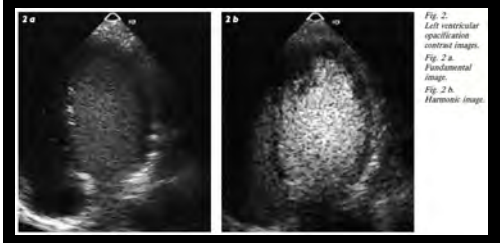


Fig. 2. Left ventricular opacification contrast images.
Fig. 2 a. Fundamental image.
Fig. 2 b. Harmonic image.

Powers J, Porter TR, et al. Ultrasound Contrast Imaging Research. MedicaMundi 2000;44:28-36.

Normal Myocardium

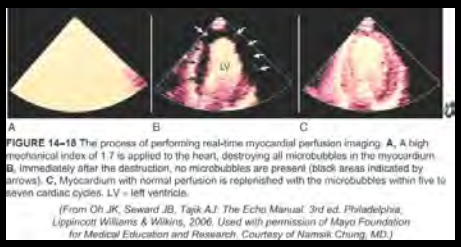


FIGURE 14–18 The process of performing real-time myocardial perfusion imaging. **A,** A high mechanical index of 1.7 is applied to the heart, destroying all microbubbles in the myocardium. **B,** Immediately after the destruction, no microbubbles are present (black areas indicated by arrows). **C,** Myocardium with normal perfusion is replenished with the microbubbles within five to seven cardiac cycles. LV = left ventricle.

(From Oh JK, Seward JB, Tajik AJ: The Echo Manual. 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2006. Used with permission of Mayo Foundation for Medical Education and Research. Courtesy of Namsik Chung, MD.)

Citations

Normal Myocardium

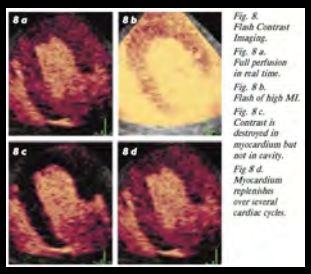


Fig. 8. Flash Contrast Imaging. Fig. 8 a. Full perfusion in real time. Fig. 8 b. Flash of high MI. Fig. 8 c. Contrast is destroyed in myocardium but not in cavity. Fig 8 d. Myocardium replenishes over several cardiac cycles.

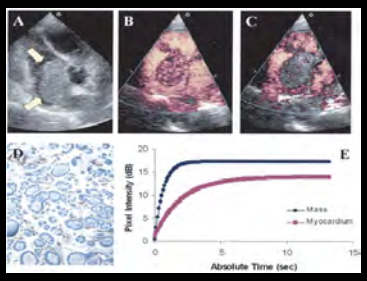
Powers J, Porter TR, et al. Ultrasound Contrast Imaging Research. MedicaMundi 2000;44:28-36.

Intracardiac Mass

- Contrast detects whether is mass is perfused or not
- 16 patients
- Optison or Definity
- High MI flashed to destroy microbubbles and observe replenishment

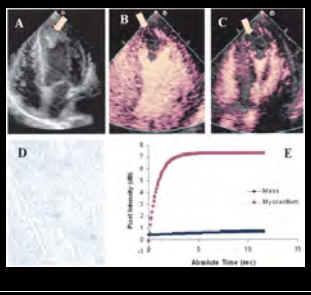
Kirkpatrick JN, Wong T, Bednarz JE, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol 2004; 43: 1412-1419.

Intracardiac Mass



Kirkpatrick JN, Wong T, Bednarz JE, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol 2004; 43: 1412-1419.

Thrombus



Kirkpatrick JN, Wong T, Bednarz JE, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol 2004; 43: 1412-1419.

Cardiovascular Events

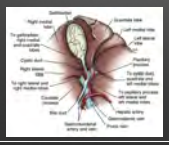
- Destroy microbubbles with a flash of high MI
- Normal myocardium replenishes
- Mild or no contrast in poorly perfused areas

Non-human primate studies:

- Contamin H, et al. A Minimally-Invasive Closed Chest Myocardial Occlusion-Reperfusion Model in Rhesus Monkeys (*Macaca mulatta*): Monitoring by Contrast-Enhanced Ultrasound Imaging. Int J Cardiovasc Imaging. 2012;28:531-542.
- Grauer SE, Xu J, et al. MRX 115, an Echocardiographic Contrast Agent, Produces Myocardial Opacification after Intravenous Injection in Primates: Studies Before and After Occlusion of Left Anterior Descending Coronary Artery. Acad Radiol 1996;Suppl 2:S405-6.

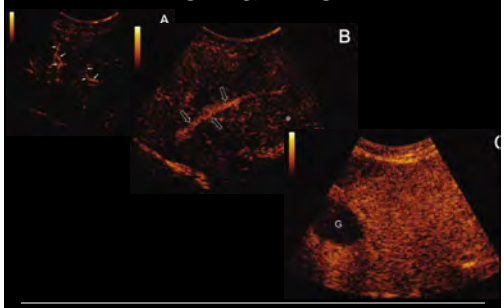
Liver

- 20% hepatic artery, 80% portal vein
- 3 phases of contrast enhancement
  - Arterial: 10-25 s
  - Portal: 30-120 s
  - Delayed: 30 s - several minutes



Citations

Normal Liver



Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Malignant Liver Tumors

- Have increased arterial blood supply
- Early wash-in, early wash-out
- Hypoechoic in portal and delayed phase
  - Sensitivity: 100%
  - Specificity: 94%
  - PPV: 94%
  - NPV: 100%
  - Accuracy: 97%

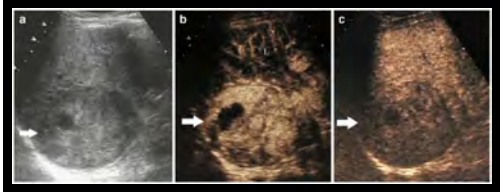
O'Brien RT, Iani M, Matheson J, et al. Contrast Harmonic Ultrasound of Spontaneous Liver Nodules in 32 Dogs. Vet Radiol Ultrasond 2004;45:547-553.

Malignant Liver Tumors

B-Mode Arteries and Arterial Phase Delayed

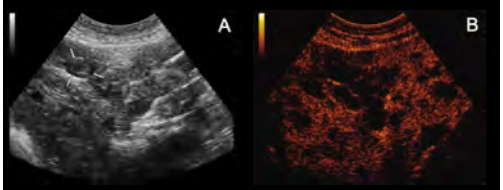
Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Malignant Liver Tumors



Quaia E. Microbubble Ultrasound Contrat Agents: An Update. Eur Radiol 2007;17:1995-2008.

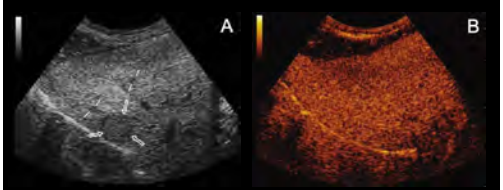
Malignant Liver Tumors



B-Mode Delayed Phase

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Benign Liver Tumors



B-Mode Delayed Phase

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Introduction
Agents
Imaging
Harmonics
Heart
Liver
Spleen
Pancreas
Kidneys
Lymph Nodes
Intestine
OB/GYN
Conclusion

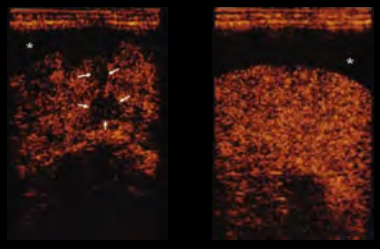
Spleen

2 phases of contrast enhancement

- Arterial phase
  - Non-homogeneous enhancement
  - Variable flow rates through sinuses
  - Unreliable interpretation
- Delayed phase
  - 1-7 minutes

Citations

Normal Spleen



Arterial Phase

Delayed Phase

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

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Conclusion

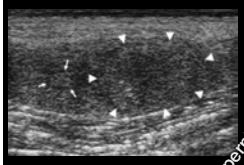
Splenic Lesions

- Not very accurate for discriminating between benign and malignant lesions
  - HSA and LSA - distinct perfusion patterns
  - Malignant lesions and hematomas - Hypo
- Improved detection of:
  - Hemangiosarcoma
  - Lymphoma
  - Microabscesses
  - Traumatic lesions
  - Infarctions

Catalano O, Sandomenico F, et al. Contrast-Enhanced Sonography of the Spleen. Am J Roentgenol 2005;184:1150-1156.

Splenic Tumors

B-Mode



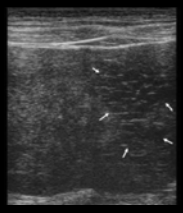
Delayed Phase

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Lymphoma Nodules

Quaia E. Microbubble Ultrasound Contrat Agents: An Update. Eur Radiol 2007;17:1995-2008.

Splenic Hematoma



B-Mode

Delayed Phase

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Pancreas

- Pancreatic carcinomas - Hypo in all phases
- Insulinomas - Hyper
- Pancreatitis - Heterogeneous with variably areas of hyperperfusion and edema

D'Onofrio M, Zamboni G, et al. Mass-Forming Pancreatitis: Value of Contrast-Enhanced Ultrasonography. World J Gastroenterol 2006;12:4181-4184.
D'Onofrio M, Martone E, et al. Contrast-Enhanced Ultrasonography of the Pancreas. JOP 2007;8:71-76.

Pancreatic Cystadenoma

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Kidneys

Contrast Enhancement

- Renal arteries - 10 s
- Cortex - 15 s
- Medulla - 30 s

Characterization of various lesions:

- Renal carcinoma
- Hemangiosarcoma metastases
- Renal cysts
- Hematomas

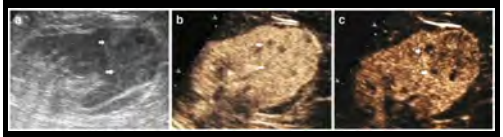
Waller KR, O'Brien RT, et al. Quantitiative Contrast Ultrasound Analysis of Renal Perfusion in Normal Dogs. Vet Radiol Ultrasound 2007;48:373-377.

Normal Kidneys

Arteries Cortex Medulla

Haers H, Saunders J. Review of Clinical Characteristics and Applications of Contrast-Enhanced Utrasonography in Dogs. JAVMA 2009;234:460-470.

Renal Carcinoma



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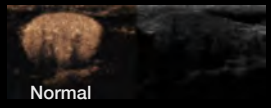
Acute Renal Infarction



Normal

Infarct →

Citations

Renal Nodule

Normal

Citations

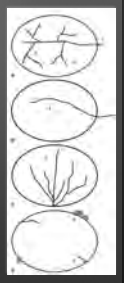
Lymph Nodes

Characteristics to differentiate benign vs malignants

- Size
- Vascular architecture
- Pulsatility Index

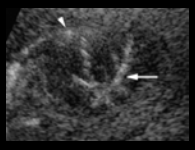
Contrast Ultrasonography

- Over 2x vessel detection compared to power Doppler



Nyman HT, Kristensen AT, et al. Characterization of Normal and Abnormal Canine Superficial Lymph Nodes using Gray-Scale B-Mode, Color Flow Mapping, Power, and Spectral Doppler Ultrasonography: A multivariate Study. Vet Radiol Ultrasound 2005;46:404-410

Early Detection of LSA



Citations

Small Intestine

Normal values:

- Wash-in & wash-out perfusion pattern
- Dose: Definity 0.03 mL/kg IV bolus

May provide baseline information for studying:

- Infarction
- Necrosis from obstruction
- Infiltrative inflammatory or neoplastic disese

Jimenez DA, O'Brien RT, et al. Intraoperative Contrast-Enhanced Ultrasonography of the Normal Canine Jejunum. Vet Radiol Ultrasound 2011;52:196-200.

Small Intestine

Jimenez DA, O'Brien RT, et al. Intraoperative Contrast-Enhanced Ultrasonography of the Normal Canine Jejunum. Vet Radiol Ultrasound 2011;52:196-200.

Time-Intensity Curve

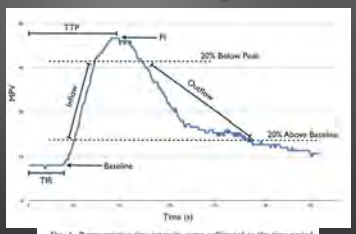


FIG. 1. Representative time-intensity curve collimated to the time period of visible contrast enhancement. The baseline mean pixel value (MPV) is unchanged throughout the time to initial rise (TIR). Contrast enhancement increases during inflow until reaching peak intensity (PI). Time to peak (TTP) is the time from injection to the PI. Outflow of contrast medium is more gradual than inflow.

Jimenez DA, O'Brien RT, et al. Intraoperative Contrast-Enhanced Ultrasonography of the Normal Canine Jejunum. Vet Radiol Ultrasound 2011;52:196-200.

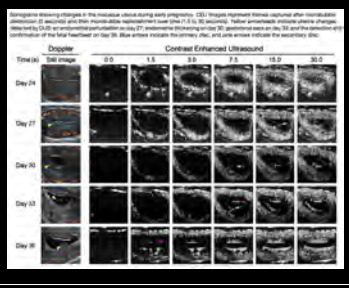
Genitourinary

- Assess uterine perfusion during embryo implantation
- Identify corpus luteum from adjacent ovarian tissue
- Evaluate uterine intervillous flow in early pregnancy

Non-human primate studies:

- Hastings JM, Morris KD, et al. Contrast Imaging Ultrasound Detects Abnormalities in the Marmoset Ovary. Am J Primatol 2012;74:1088-1096.
- Keator CS, Lindner JR, et al. Contrast-Enhanced Ultrasound Reveals Real-Time Spatial Changes in Vascular Perfusion During Early Implantation in the Macaque Uterus. Fert Steril 2011;95:1316-1321.
- Schmiedl UP, Komarniski K, et al. Assessment of Fetal and Placental Blood Flow in Primates Using Contrast Enhanced Ultrasonography. J Ultrasound Med 1998;17:75-80.
- Simpson NA, Nimrod C, et al. Sonographic Evaluation of Intervillous Flow in Early Pregnancy: Use of Echo-Enhancement Agents. Ultrasound Obstet Gynecol 1998;11:204-208.

Gravid Uterus



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Conclusion

- Ultrasound contrast agents enhance evaluation of cardiac, abdominal, and superficial soft tissue structures
- Increase sensitivity for perfusion deficits
- Can increase accuracy diagnosing certain specific diseases
- Large potential for expanding research