Contrast echo and evaluation of cardiac function: basic principles

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Contrast in echocardiography: Why?

- **To delineate the endocardium by cavity opacification.**
  - for assessment of global and regional systolic function, LV volumes and ejection fraction.
  - LV opacification (LVO) for improved visualisation of structural abnormalities
  - enhanced visualisation of wall thickening during stress echocardiography

- To enhance Doppler flow signals from the cavities and great vessels.

- **To determine myocardial ischaemia and viability using myocardial perfusion contrast echocardiography (MCE)**

- Quantification of the coronary flow reserve, which has prognostic value in various disease conditions
TISSUE: Incident frequency results in equal and opposite vibration (i.e. LINEAR RESPONSE)

MICROBUBBLES: Can only become so small but can expand to a greater degree, resulting in unequal oscillation (i.e. NON-LINEAR RESPONSE)

This results in asymmetrical vibrations which produce harmonic frequencies

http://www.escardio.org/communities/EAE/contrast-echo-box/
TISSUE HARMONIC IMAGING
Blood appears black on conventional two-dimensional echocardiography, not because blood produces no echo, but because the ultrasound scattered by red blood cells at conventional imaging frequencies is very weak—several thousand times weaker than myocardium—and so lies below the displayed dynamic range.

• It is a remarkable coincidence that gas bubbles of a size required to cross the pulmonary capillary vascular bed (1–5 mm) resonate in a frequency range of 1.5–7 MHz, precisely that used in diagnostic ultrasound.

### The properties of the ideal UCA

- **High Echogenicity**: strong ultrasound reflectors
- **Linear relationship between concentration and signal intensity**
- **Ability to cross the pulmonary capillary bed**
- **Stability over the duration of the procedure**
- **Minimal imaging artefacts**
- **Ability for rapid disruption at higher power outputs**
- **Safety**: Non toxicity
- **Additional special properties** (e.g. site-specific therapeutic drug delivery)
The ultrasonic characteristics depends on:

a) size of the bubbles
b) composition of the shell
c) the gas in the shell

• In general, the stiffer the shell, the more easily it will crack or break with ultrasonic energy. Conversely, the more elastic the shell, the greater its ability to be compressed or resonated and to produce a nonlinear backscatter signature.
Types of agents

• **Blood pool agents**
  – Free gas bubbles – Gramiak and Shah first injected saline with air bubbles in the aorta in 1968; agitated fluids: indocyanine green, renografin, etc.
  – Encapsulated air bubbles (first generation agents) – nitrogen in gelatin (Carrol, 1980); human serum albumin (Feinstein, 1984) - Albunex; microcrystalline galactose microparticles with palmitic acid – Levovist
  – Low solubility gas bubbles – 2\textsuperscript{nd} generation - perflurocarbons – Optison, Echogen, SonoVue, Definity

• **Selective uptake agents** – 3\textsuperscript{rd} generation agents in the cell metabolism – colloidal suspensions of liquids as perfluorocarbons or durable shell
2nd generation contrast agents

| Table 1 Characteristic of currently available contrast agents in UK and Europe |
|---------------------------------|---------------------------------|---------------------------------|
|                                 | SonoVue\(^6\)                      | Optison\(^7\)                  | Luminity\(^8\)                  |
| Gas                             | Sulphur hexafluoride              | Perfluoropropene                | Perfluoropropene                |
| Bubble size                     | 2–8 μm                           | 3.0–4.5 μm                      | 1.1–2.5 μm                      |
| Surface coating                 | Surfactant/powder                 | Human albumin                   | Naturally occurring lipids      |
| Contraindications and precautions|                                  |                                 |                                 |
| Patients experiencing side effects in clinical trials (%) | 11                               | 17                              | 8                               |
| Most frequent side effects in clinical trials | Headache (2.1%), nausea (1.3%), chest pain (1.3%), taste perversion (0.9%), hyperglycaemia (0.6%), injection site reaction 0.6%, paresthesia (0.6%), vasodilation (0.6%), injection site pain (0.5%). | Headache (5.4%), nausea and/or vomiting (4.3%), warm sensation or flushing (3.6%), dizziness (2.5%). | Headache (2.0%), flushing (1.0%), back pain (0.9%). rash/urticaria, wheezing/allergic/anaphylaxis |
| Manufacturer                    | Bracco Diagnostics                | GE Healthcare                   | Lanthescus Medical Imaging      |
|                                 | (formerly Bristol-Myers Squibb)   |                                 |                                 |

• At low power output (PO) settings, there is mostly a linear response (fundamental enhancement) with some generation of harmonic frequencies.

• As the PO is increased, the bubbles generate more nonlinear resonance and thus generate greater harmonic frequencies.

• At a high power setting, fracture and destruction of the microbubble occur, allowing the air or gas inside to be released.

(<100 kPa)

(100 kPa–1 Mpa)
• Power output is usually measured with the mechanical index (MI)

\[ MI = \frac{P_{\text{neg}}}{\sqrt{f}} \]

where \( P_{\text{neg}} \) – peak negative pressure of ultrasound ; \( f \) – ultrasound frequency

• Different behavior in various MI
CE modalities

IMAGING MODALITY

HIGH MI: Intermittent / triggered

ULTRAHARMONIC
POWER DOPPLER
POWER PULSE INVERSION

LOW MI: Real time

PULSE INVERSION
POWER MODULATION
COHERENT IMAGING

http://www.escardio.org/communities/EAE/contrast-echo-box/
Patients most likely to benefit from contrast echocardiography

• With obesity
• With chronic obstructive pulmonary disease
• In intensive care settings
• Mechanically ventilated
• With chest deformities
• With oncology diseases on chemotherapy
LEFT VENTRICULAR OPACIFICATION

- Assessment of left ventricular (LV) systolic function.

- Accurate assessment and quantification is dependent on visualising the entire endocardium.

- Contrast opacification enhances endocardial border definition.

- PV Doppler signal is also enhanced for diastolic LV function.
## Machine settings for LVO

<table>
<thead>
<tr>
<th>Setting</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanhead frequency</td>
<td>2.5-3.5 MHz</td>
</tr>
<tr>
<td>Transmit power</td>
<td>Mechanical index (MI) &lt; 0.6</td>
</tr>
<tr>
<td>Dynamic range</td>
<td>Low-medium</td>
</tr>
<tr>
<td>Line density</td>
<td>Medium or high</td>
</tr>
<tr>
<td>Compression</td>
<td>Medium-high</td>
</tr>
<tr>
<td>Persistence</td>
<td>Disabled</td>
</tr>
<tr>
<td>Focus</td>
<td>Bellow mitral valve (apical views), bellow posterior wall (parasternal view)</td>
</tr>
<tr>
<td>Receive gain</td>
<td>Slightly reduced to decrease the grey levels in the myocardium before contrast injection</td>
</tr>
</tbody>
</table>
Figure 2  Left ventricular opacification. Apical four chamber view, end diastolic (A) and end systolic (B) frames, in a patient with recent myocardial infarction referred for assessment of left ventricular systolic function. Images acquired utilizing tissue harmonic imaging at frequency of 3.8/1.9 MHz and a mechanical index of 1.0. Lateral wall endocardium was not clearly defined making accurate measurement of left ventricular volumes difficult. Apical four chamber view, end diastolic (C) and end systolic (D) frames, imaged after intravenous bolus injection of 0.5 ml of Sonovue. The mechanical index has been reduced to 0.5 but all other parameters are unchanged. The entire endocardial border is now clearly defined and systolic thickening of entire lateral wall appreciated.
Efficacy of CE in assessment of LV EF volumes and wall motion abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Cont-</th>
<th>Contr+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean correlation coefficient [95% CI]</td>
<td>0.85 (EF)[0.82-0.88]</td>
<td>0.94 (EF)[0.91-0.97]</td>
</tr>
<tr>
<td></td>
<td>0.81 (EDV)[0.6-1.02]</td>
<td>0.94 (EDV)[0.92-0.96]</td>
</tr>
<tr>
<td></td>
<td>0.92 (ESV)[0.87-0.97]</td>
<td>0.97 (ESV)</td>
</tr>
<tr>
<td>Mean % agreement with gold standard</td>
<td>77% (EF)</td>
<td>94% (EF)</td>
</tr>
<tr>
<td></td>
<td>61% (RWMA)</td>
<td>83% (RWMA)</td>
</tr>
</tbody>
</table>
Apical Thrombus in AMI

Becher H, Burns PN. 2000
Figure. Systolic and diastolic scans of the 4 imaging modalities using different views. There was agreement among contrast-enhanced echocardiography (CE), MRI, and cineventriculography (CINE) in the detection of an inferior/posterior wall motion abnormality, which was not detected on unenhanced echocardiography (UE). LAO indicates left anterior oblique; RAO, right anterior oblique. (Reprinted with permission from Hoffman R, von Bardeleben S, Kasprzak J, et al. Analysis of regional left ventricular function by CINE, cardiac MRI, and UE and CE. J Am Coll Cardiol. 2006;47[1]:121-128.)
Apical HCM

The EAE Textbook of Echocardiography.

BMJ Case Reports. 2009;doi:10.1136/bcr.04.2009.17
Contrast-enhanced echo: apical HCM
Tako-Tsubo cardiomyopathy

Arch Cardiovasc Dis 2010; 103: 447-453
Non-compaction LV
Indications for LV contrast imaging

Indications for resting left ventricular opacification contrast echo

In patients with suboptimal images:

(1) To enable improved endocardial visualization and assessment of LV structure and function when two or more contiguous segments are NOT seen on non-contrast images.
(2) To have accurate and repeatable measurements of LV volumes, and ejection fraction by 2D Echo.
(3) To increase confidence of the interpreting physician in the LV function, structure and volume assessments.
(4) To confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when non-enhanced images are suboptimal for definitive diagnosis:

- apical hypertrophic cardiomyopathy
- ventricular non-compaction
- apical thrombus
- ventricular pseudoaneurysm
CE in stress testing

Improvement in quality assessment with CE: OPTIMIZE

*P < 0.001 vs. No Contrast
Contrast application in stress echocardiography

Indications for use of contrast in stress echocardiography

When two or more endocardial border contiguous segments of LV are not well visualized in order to:

- To obtain diagnostic assessment of segmental wall motion and thickening at rest and stress
- To increase the proportion of diagnostic studies
- To increase reader confidence in interpretation

Improvement in quality of image after CE in 632 difficult cases

Improvement in number of segments visualized after CE

* p < 0.0001; † p=0.0016

LV assessment before and after CE


LV thrombus

Before
3 definite
35 suspected

After
8 definite
1 suspected

Before Contrast
65.20%

After Contrast
73.90%
Total Impact of Contrast on Patient Management

Contrast in echocardiography:

Figure 1 Interaction of cost quality with new advances in echocardiography. ECG, electrocardiography; LV, left ventricular.

Clinical and economic outcomes assessment with myocardial contrast echocardiography

Leslie J Shaw, Mark J Monaghan and Petros Nihoyannopolous

Heart 1999;82;16-21
SAFETY:

• A multicenter registry of 4,300,966 hospitalized patients with and without CE echo – 24-h death rate 1.08% vs. 1.06%; HR for contrast agent vs. no contrast 0.76, 95%CI 0.70-0.82

• Study of 14,500 critically ill patients – contrast vs no contrast OR for same-day mortality 1.18, 95%CI 0.82-1.71 (p=0.37)

• Retrospection of 18,671 consecutive echo studies – 24-h death rate was 0.42% in the contrast group vs. 0.37% in the non-contrast group (p=0.6)
  J Am Coll Cardiol 2008;51(17):1704-6.

• A meta-analysis of 8 studies in more than 5.2 mil pts – all-cause mortality 0.34% in contrast group vs. 0.9% in the non-contrast one, pooled OR =0.57, 95%CI 0.32-1.01 (p=0.05) and MI incidence 0.15% vs. 0.2%, OR=0.85, 0.35-2.05 (p=0.72)
  Am J Cardiol 2010;106(5):742-7

• A retrospective analysis of 78,383 administered contrast doses between 2001 and 2007 – severe reaction probably related to contrast agent Definity in 0.01% of outpatient pts, anaphylactoid reactions in 0.006%, no deaths, no reactions in in-hospital pts.
SAFETY:

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Echo</td>
<td>1:145 000 (SonoVue), 1:500 000 (Definity)</td>
</tr>
<tr>
<td>Myocardial Scintigraphy</td>
<td>1:10 000</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>1:2500 (or AMI)</td>
</tr>
<tr>
<td>Coronary arteriography</td>
<td>1:1000</td>
</tr>
</tbody>
</table>

*Modified from Main et al.*

WHEN CONTRAST SHOULD NOT BE USED

• Unstable angina or acute coronary syndrome in past 7 days
  for SonoVue only

• Unstable (NYHA Class IV) heart failure

• Right-to-left intra-cardiac shunt

• Significant pulmonary hypertension
CONCLUSIONS:

• CE is an effective way to improve the opacification of LV for function assessment in difficult cases

• It may help in the diagnosis of additional findings, such as thrombi, apical HCMP, pseudoaneutysms, etc.

• CE enhances the segment delineation in stress testing

• The cost-effect ratio seems beneficial at a relatively low cost increment

• CE is relatively safe with no more additional adverse reactions than other contrast procedures or other diagnostic procedures in cardiology

• It may be used for assessment of myocardial perfusion and future target for treatment procedures