Contrast Enhanced Ultrasound Will Be Routinely Used to Assess Myocardial Perfusion in the Future

*A Skeptical Look*
James D. Thomas, M.D., F.A.C.C.
Cardiovascular Imaging Center
Department of Cardiology
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

Conflicts: None

Disclosure

My wife has known Jonathan longer than she’s known me

What Would True Quantitation of Myocardial Perfusion Really Mean???

Myocardial Perfusion [ml/min/100 g]

Bol, et al., *Circulation* 1993; 87: 512
True Quantitation of Myocardial Perfusion

What Does it Mean?

• Absolute flow measurements
  – ml/min/100 g myocardial tissue
• High spatial resolution
  – Distinguish major and branch coronary beds
  – Distinguish endocardial from epicardial flow
• High temporal resolution
  – Response to vasactive infusions
  – Observe intravascular autoregulation
  – Distinguish antegrade from collateral filling
• Noninvasive
  – Observable following venous injections

How Close is Contrast Echo to the Ideal of True Quantitation of Myocardial Perfusion???

Let’s start VERY simple!!

Hypotheses:
1) If 1 bubble returns a signal of X when interrogated by ultrasound, 2 bubbles will return 2X
2) If signal X = concentration C, then 2X = 2C

Numerical Experiment

Three Scatterers Hit by an Ultrasound Pulse of 5 Wavelengths

Spacing: 5λ  Spacing: 0.75λ
Signal: 3  Signal: 1.15
**Numerical Experiment**

*Three Scatterers Hit by an Ultrasound Pulse of 5 Wavelengths*

<table>
<thead>
<tr>
<th>Regular Spacing</th>
<th>Irregular Spacing</th>
</tr>
</thead>
</table>

Critical spacing is half the pulse length. 

No relationship between signal strength and concentration.

---

**In Vitro Experiment**

*Phantom with Linear Line Spacing Across Sector*

\[ r = n \min \left( \frac{\max}{\min} \right)^2 \theta / \pi \]

Equiangular spiral

\( \min \) \( \max \)

---

**In Vitro Experiment**

*Alignment of Phantom with Ultrasound Sector*
In Vitro Experiment
Variability of Signal Across Ultrasound Sector

NOT a monotonic function of line density

Similar results with all vendors

In Vitro and Numerical Experiments
Conclusions

1) In standard and harmonic B-mode imaging, signal strength is not linearly nor even monotonically related to scatterer spacing

2) This is a simple interference effect and is independent of attenuation of the propagating signal
OK, OK, let's assume that we can get around this little problem......what physiological options do we have for quantifying perfusion???

1) Indicator dilution theory

**Principles of Indicator Dilution Theory**

Bolus of contrast injected at $t = 0$.

- Exponential decay curve: $c(t) = k e^{-kt}$
- Transit time ($TT$) \[ \int_{c(t)}^{t} c(t) \, dt = \frac{1}{k} \]
- Flow = \[ \frac{\text{Volume}}{\text{Transit Time}} \]

**Requirements of Indicator Dilution Theory**

- **Inert agent**
  - Must pass through vasculature just like blood
- **Stable agent**
  - Not destroyed or absorbed by the tissue it passes through
- **High quality signal**
  - High signal to noise ratio needed to quantify transit time ($TT$)
- **Known volume ($V$) of distribution**
  - Flow ($Q$) = $V/TT$
- **Linear relation between signal and concentration**
  - Precise curve needed for analysis
**Principles of Indicator Dilution Theory**

Flow into a second chamber broadens and flattens the curve, invalidating simple transit time analysis.

Flow:

- Volume: \( V \)
- Flow: \( Q \)

Transit time (TT) = \( \frac{1}{k} \)

\[ TT = \frac{2}{k} \]

\[ TT = \frac{3}{k} \]

\[ Q = \frac{V}{TT} \]

\[ Q = ? \]

\[ Q = ? \]

**Application of Deconvolution to Contrast Echocardiography**

Fourier analysis of input and output curves.

\[ TT = \int t \ f(t) \ dt \]

\[ \int f(t) \ dt \]

\[ Q = \frac{\text{Volume}}{TT} \]
But Fourier deconvolution is EXTREMELY sensitive to noise………what’s the reality in practice???

Principles of Indicator Dilution Theory

Volume $V_{LV}$
Flow $Q$
Volume $V_{Tissue}$

The myocardial signal is very weak and may barely appear above the noise.

What if the Output Curve is Narrower Than the Input?

Fourier analysis of input and output curves.

$TT = \int_0^T t f(t) \, dt < 0$
$Q = \frac{\text{Volume}}{TT} < 0 (!!)$
Theory, shmeory, what happens in practice???

1) Normal subjects (n=8)
2) Optison bolus injection
3) Power inversion imaging
4) ANOVA to test for variability in contrast effect between walls, depth, and subjects

Pulse Inversion Imaging
Nonlinear Reflections from Bubbles

Contrast Echocardiography
Evidence for Perfusion
Myocardial Contrast Perfusion

Variability by Wall

Pre-contrast

Septal
Lateral
Inferior
Anterior
Post-contrast

Pre vs post contrast: p < 0.0001
Left vs right walls: p = 0.0001
Ap2 vs Ap2: p = NS

-----

Myocardial Contrast Perfusion

Variability by Wall

Pre-contrast

Base
Mid
Apex
Post-contrast

Precontrast: apex lowest, p = 0.04
Postcontrast: apex highest, p < 0.004

-----

Myocardial Contrast Perfusion

Variability by Patient

Pre-contrast

Pre Post

Precontrast: No difference among patients
Postcontrast: Significant intersubject variance (p < 0.001)
Yeah, yeah, yeah.......but what about some of these new methods: power Doppler, bubble destruction and fill-in, dual triggering, etc…??

**Power Doppler**
Quantification of Contrast Perfusion

- Displays amplitude of Doppler signal
- Very sensitive to myocardial contrast
- Triggering enhances signal strength

**Power Angiography**
Dual Pulse Imaging

- Pulse 1 (after 4 beats) shows maximal contrast effect and also destroys the bubbles
- Pulse 2 should show no (less) contrast effect
- (Image 1) – (Image 2) gives net perfusion effect
Problems of Attenuation

63 year old man with recent anterior MI and mid LAD occlusion
(sparing S1)

- Image 1 should show perfusion at base of septum but doesn’t due to attenuation
- Image 2 shouldn’t show perfusion but does since attenuation has protected bubbles
- Distal septum shouldn’t have contrast but does due (?) to heightened sensitivity in near field

Quantification of Myocardial Perfusion

Current Limitations

- **Unstable indicator signal**
  - Reversible effect of pressure
  - Irreversible destruction of bubbles
- **Low signal to noise ratio**
  - Stochastic nature of ultrasound makes signal difficult to detect
- **Unknown and variable blood volume**
  - Myocardium only 5% blood
  - May double under hyperemic conditions

Quantification of Myocardial Perfusion

Current Limitations

- **Shadowing**
  - Contrast in proximal structures may obscure myocardium
- **Nonlinear relationship between contrast concentration**
  - Dominated by noise at low concentrations
  - Saturates and shadows at high concentrations
- **Irreproducible injections**
  - Even under ideal circumstances (open chest, power injection, direct coronary injection) up to 30% interinjection variability
  - Nonideal injections have even more variability
  - Wide 95% confidence intervals of derived parameters
Quantification of Myocardial Perfusion

Conclusions

It may someday be possible to quantify myocardial perfusion with contrast echocardiography, but it will require advances in:
1) bubble technology
2) instrumentation
3) understanding of coronary physiology

James D. Thomas, MD

Contrast Enhanced Ultrasound Will Be Routinely Used to Assess Myocardial Perfusion in the Future

A Skeptical Look (Rebuttal)

James D. Thomas, M.D., F.A.C.C.
Cardiovascular Imaging Center
Department of Cardiology
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

Conflicts: None
Disclosure

Jonathan is my co-chair for Echo Hawaii

Quantification of Myocardial Perfusion
Skepticism Goes Back a Long Way

• The Date: February 9, 1999
• The Setting: Medical Advisory Board, O'Hare Hilton
• The Discussion: the future of contrast perfusion
  – Sanjiv Kaul: “You know, JT, soon even you will be using contrast for perfusion. In fact, I bet you $1000 dollars that within 5 years, there will be more contrast perfusion echo studies done at the Cleveland Clinic than SPECT studies.”
  – Me: “That’s a bet I’ll take, Sanjiv!”

Quantification of Myocardial Perfusion
Skepticism Goes Back a Long Way

• The Year: 2004
• The Score: SPECT 8272, CPE 0
• The Stakes: $1000
• The Discussion
  – Me: “Where’s my money, Sanjiv?”
  – Sanjiv Kaul: “How about double or nothing? Five more years?”
  – Me: “It’s your money…”


**Quantification of Myocardial Perfusion**

*Skepticism Goes Back a Long Way*

- **The Year:** 2009
- **The Score:** SPECT 5663, CPE 0
- **The Stakes:** $2000
- **The discussion**
  - Me: “Where’s my money, Sanjiv?”
  - Sanjiv Kaul: “How about double or nothing? Five more years?”
  - Me: “It’s your money…”

---

**Quantification of Myocardial Perfusion**

*Skepticism Goes Back a Long Way*

- **The Year:** 2012 (two years to go…)
- **The Score:** SPECT 6302, CPE 0
- **The Stakes:** $4000
- **The discussion (projected)**
  - Me: “Where’s my money, Sanjiv?”
  - Sanjiv Kaul: “How about double or nothing? Five more years?”
  - Me: “It’s your money…”

---

**Quantification of Myocardial Perfusion**

*Skepticism Goes Back a Long Way*

- **The Year:** 20??
- **The Score:** SPECT a lot, CPE 0
- **The Stakes:** a lot
- **I finally retire a rich man…**
Discussion

The proper environment for sorting out our differences...

Too Many Mai Tais can be Dangerous

Peace in the contrast kingdom...