Future Applications of Contrast Echocardiography

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The Evolution of Cardiovascular Imaging

Structure

Function

Metabolism/Perfusion
Molecular Imaging in Cancer Medicine

18F-NOTA-Alfatide

## Roles for Molecular Imaging

<table>
<thead>
<tr>
<th>Basic Research &amp; Discovery</th>
<th>Pre-clinical &amp; Clinical Research</th>
<th>Clinical Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncovering pathophysiology</td>
<td>Rapid evaluation of new therapies</td>
<td>Early diagnosis</td>
</tr>
<tr>
<td>Phenotyping animal models of disease</td>
<td>Optimization of therapies</td>
<td>More definitive diagnosis</td>
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<tr>
<td>Matching molecular process to anatomy or function</td>
<td>Evaluating mechanism of therapy or off target effects</td>
<td>Evaluating response to therapy</td>
</tr>
<tr>
<td>Matching gene expression to molecular or anatomic phenotype</td>
<td>Tracking cell or gene therapy</td>
<td>Customized therapy</td>
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<tr>
<td></td>
<td>Understanding resistance to disease</td>
<td>Monitoring disease progression or prognosis</td>
</tr>
</tbody>
</table>
# Molecular Imaging in Cardiology

**Atherosclerosis – detection and risk**
- Inflammation
- Platelets, VWF
- Vasa vasorum
- Protease activity
- Oxidative stress, oxidized lipids
- TF, fibrin

**Angiogenesis/Regenerative Biology**
- Chemokines and growth factors
- Endothelial markers
- Stem cell recruitment/engraftment

**Ischemia**
- Selectins, hypoxic metabolism, C’ receptors

**Myocarditis/OHT rejection**
- Adhesion molecules, inflammatory cells, chemokines, apoptosis

**Ventricular remodeling**
- Protease activity, inflammatory cells, apoptosis

**Arrhythmogenesis**
- Sympathetic activity
- Cell jxn molecules
MB Targeting by Surface Targeting Ligand

rPSGL-1 or Other targeting ligand

PEG stearate

DSPC

dFB gas core

(CH₂CH₂O-)₄₀

(CH₂CH₂O-)₇₀

(CH₂CH₂O-)₄₀
Potential Clinical Roles of Molecular Imaging in Ischemia

Early detection of infarction and ischemia

Risk stratification based on spatial extent of ischemia

Detection of ischemia/infarction in those with pre-existing perfusion or wall motion abnormalities

Salvaging the disaster stress echo.
**Myocardial Ischemic Memory Imaging**

Anaerobic Metabolism - BMIPP-SPECT

\[
\text{BMIPP} \rightarrow \text{FAT/CD36} \rightarrow \text{BMIPP}
\]

BMIPP

\[
\text{Acyl-CoA synthetase}
\]

\[
\text{BMIPP-CoA}
\]

\[
\text{P-iodophenyl acetic acid}
\]

\[
\text{BMIPP-CoA}
\]

\[
\text{Mitochondria} \rightarrow \text{\boldmath{$\beta$}-oxidation}
\]


\[
\text{125I (CH2)$_{12}$ C(CH3)CH2COOH}
\]
$^{123}$I-BMIPP in 448 Patients with CP

Sensitivity 73% (43% for clinical)
NPV 78% (62% for clinical)

Kontos MC, et al. JACC 2010;56:290
P-Selectin Targeting for Ischemic Memory

mAb SLeX PSGL-1

Lectin EGF CRₙ

PSGL-1

COOH COOH
Selectin-targeted Ischemic Memory Imaging

Risk Area

B-Mode

Selectin-targeted

Wall Motion

[Graph showing signal intensity over time for Ischemic Region and Remote Region]

Davidson BD, et. al. JACC 2012;60:1690
Potential Clinical Roles of Molecular Imaging in Atherosclerosis

Early detection of aggressive disease

Vulnerability to complication (plaque or patient)

Selection/optimization of therapy

Pre-clinical drug development and early clinical proof-of-mechanism studies
Molecular Imaging in Atherosclerosis: Potential Targets

IEL
Monocyte
LDL
Ox-LDL
Th1
SMC
Pro-inflammatory cytokines
apoptosis
Differentiation
GF & Chemok.
Angiogen.
EC
Activation
IFN\(\gamma\)
proteases
Procoagulant effects
OFR
Foam cells
proteases
apoptosis
Angiogen.
Atherosclerotic Disease Progression

- Pre-clinical Disease
- Anatomic disease
- Obstructive Symptoms
- ACS and Ischemic Dysfxn

Disease Severity vs. Age
Vascular Inflammation with $^{18}$FDG-PET
Plaque Development in LDL-R\(^{-/-}\) and Apobec-1\(^{-/-}\) mice

10 wks 20 wks 40 wks

2-D VCAM-1

Signal Enhancement (AU)

Wild Type
DKO

Control P-selectin VCAM-1

Kaufmann BA, et al., ATVB 2010;30:54
Endothelial Phenotype in Insulin Resistance

CIMT (mm)
BL 4 8 12 18 24
Months on HFD
Avg. 260 μm

Signal Intensity
Months
BL 4 8 12 18 24

VCAM-1
P-Selectin
Control

Chadderdon S, et al., Circulation 2014;129:471
Biologic target identification

Screening by bioassay

In vivo testing of candidate agent

Optimization and dose-ranging

Full characterization of effects

Pre-clinical

Defining or refining pathophysiology

In vivo imaging in animal models

IND

Phase 1 clinical trials

Clinical

Phase 2 and 3 clinical trials

Surrogate end-point

NDA
Customizing Atherosclerotic Therapy
Drugs in Development Related to Phenotype

IEL
Monocyte T-cell
LDL
Ox-LDL
Th1
SMC
Pro-inflammatory cytokines
apoptosis
Differentiation
EC
Activation
IFN$\gamma$
proteases
Procoagulant effects
OFR
Foam cells

Anti-OxLDL
Anti-Lp-PLA2
ECAM Inhibitors
TLR/LTB4 Inhibitors
Cytokine/Chemokine Antagonists
5-LO Inhibitors
NADPH-Ox Inhibitors
Protease Inhibitors
Angiogenesis Inhibitors
GPIb and PAR Antagonists

Cytokine/Chemokine Antagonists
5-LO Inhibitors
NADPH-Ox Inhibitors
Protease Inhibitors
Angiogenesis Inhibitors
GPIb and PAR Antagonists
The Power of Bubbles: The Mantis Shrimp

Shiela Patek U.Mass
Therapeutic Contrast Ultrasound: Entraining the Bioeffects

- Thrombolysis
- ↑ Perfusion (↑NO?)
- Gene or protein delivery
- Tumor/tissue ablation
Ultrasound Gene Delivery


Xie Aet al., *JACC CV Imag* (in press)
**Muscle Perfusion (2×10^8 MB, 1.3 MHz)**

**A**

- Equation: $y = 95(1-exp^{1.57X})$
- Equation: $y = 59(1-exp^{0.18X})$
- Graph showing intensity over time with data points for Control and Exposed groups.

**B**

- Control images: $T_0$, $T_{1s}$, $T_{3s}$, $T_{5s}$, $T_{8s}$
- Exposed (MI 1.3, +MB) images: $T_0$, $T_{1s}$, $T_{3s}$, $T_{5s}$, $T_{8s}$

**C**

- Graph showing $\beta$-value (s^-1) with bars for Control and Exposed groups.
- Control: MI 0.6, 1.3; Exposed: MI 0.6, 1.3
- P-values: p<0.001, p<0.01, p<0.05

**D**

- Graph showing MBF (AX\beta) with bars for Control and Exposed groups.
- MI: 0.6, 1.3; Pulsed MB: - + +
- P-values: p<0.01, p<0.05

Coronary Recanalization in MI (porcine)
