Cardiovascular Molecular Imaging

Albert J. Sinusas, M.D.
Professor of Medicine & Diagnostic Radiology
Yale University School of Medicine

Molecular Imaging Summit
2008
Molecular Imaging in Cardiovascular Disease:

- Imaging of Cardiac Metabolism
- Imaging of Neuronal Function
- Receptor Imaging
- Targeted Imaging of Biological Processes
  - Atherosclerosis, Vascular Remodeling, Thrombosis, Inflammation
  - Angiogenesis
  - Apoptosis, Necrosis
  - Post Infarct Remodeling
  - Heart Failure
- Imaging of Stem Cell Therapy
Risks of SCD Post-MI

NEJM 352:2581-2588, 2005
Selection Criteria for AICD Implantation

• MADIT-I: Pts with +EP studies for VT or nonsustained VT on Holter may benefit from the preventive insertion of AICDs
• MADIT-II:
  – Trial stopped early because of a 30% reduction in mortality in patients randomized to receive an AICD
  – Pts >1 mon post-MI with LVEF <30% are candidates for AICD implant regardless of whether they undergo Holter monitor or EP studies
• AICD implant costs $30,000-$40,000 and lasts for only 4-5 years
• 400,000 pts will qualify annually to receive AICDs at a prohibitive cost to Medicare and our health care system at large
Peri-Infarct Zone by Contrast-Enhanced Cardiac MR Imaging Predictor of Post-MI Mortality

- 144 pts with CAD and abnormal myocardial delayed enhancement (MDE)
- Mean follow-up 2.4 years, 20% mortality
- Computer-assisted quantification of infarct core and peri-infarct region
  - core: >3 SD above remote
  - peri-infarct: 2-3 SD above remote
  - Peri-infarct expressed % total infarct (%MDE_{periphery})
- %MDE_{periphery} strongest predictor all-cause mortality

Peri-Infarct Zone by Contrast-Enhanced Cardiac MR Imaging Predictor of Post–MI Mortality

Infarct Heterogeneity by MR Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility

- 47 pts post-MI referred for ICD
- LVEF <0.35
- Late (15-30 min) Gd enhanced images (0.2 mmol/kg)
- Subset with first pass perfusion (n = 8) with 0.1 mmol/kg
- Programmed ventricular stimulation
- Quantification of heterogeneity of SI using 2 thresholds
  - dense core (>50% max)
  - heterogeneous periphery (>remote, <50% max)
- Infarct transmurality defined for wedges

Quantification of Infarct Heterogeneity Using 2 SI Thresholds

Infarct Heterogeneity by MR Imaging Identifies Enhanced Cardiac Arrhythmia Susceptibility

- 43% inducible VT
- Infarct size not related to inducibility
- Gray zone extent associated with inducibility
- Wash-in kinetics in gray zone matched remote zone
- Large region of mixed tissue in border may provide substrate for reentrant VT

Imaging of Neuronal Function

- Neuronal function is impaired with myocardial ischemic injury
- Significant denervation post-MI
- Imaging of pre-synaptic uptake-1
  - $^{123}$I-MIBG
  - $^{11}$C-HED
- Prediction of ARhythmic Events with Positron Emission Tomography (PAREPET) – NIH sponsored
  - CAD, LVEF <35%, candidate for AICD, risk for SCD
  - $^{13}$NH$_3$, $^{18}$FDG, $^{11}$C-HED
- Industry sponsored trial of $^{123}$I-MIBG in CHF
## MIBG Sympathetic Nerve Imaging Risk for Death in CHF Patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sex (M/F)</th>
<th>Mean age (years)</th>
<th>Diagnosis (isch/nonisch)</th>
<th>Mean LVEF (%)</th>
<th>Follow-up (months)</th>
<th>Survival rate (%) (low risk/high risk)</th>
<th>P value</th>
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<td>H/M &lt;1.53</td>
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| Total/mean     | 1206/459 | 59 | 566/1099 | 31 | 31 | 87/47 |

H/M - delayed heart to mediastinal uptake ratio of MIBG; WR - washout rate = (early uptake-delayed uptake)/early uptake ×100.

Higuchi T & Schwaiger M. Heart Failure Clinics 2006
\(^{123}\)I-MIBG imaging and HRV analysis: Need for AICD

Approaches for Imaging LV Remodeling

- Assessment of function, geometry
- Assessment of ischemia
  - Perfusion, metabolism, hypoxia
- Assessment of injury
  - Infarction, apoptosis
- Assessment of inflammation
- Assessment of myocardial denervation
- Assessment of angiogenesis
- Assessment of extracellular matrix
LV Remodeling Changes in MMP-9

- Patients s/p acute MI (n=32)
- Control Subjects (n=53)

Targeted MMP Imaging
Hybrid MicroSPECT/CT

201TI
PERFUSION

99mTc-RP805
MMP

IMAGE
FUSION

Su H et al. Circulation 2005
$^{99m}\text{Tc}$-RP805 and $^{201}\text{TI}$ Myocardial Uptake (%ID/g) Control & Post-MI Mice

Role of MT-1 MMP on Post-MI Remodeling

- Wild type mice (WT): n = 14
- Mice with cardiac restricted overexpression of MT-1 (MT1-MMPexp): n = 22
  - 200% increase in MT1-MMP
- MI induced by LAD occlusion
  - WT (n = 8), MT1-MMPexp (n = 14)
- Echocardiography, conductance catheter studies
- Imaging at 2 wks post-MI
  - Injected with $^{99m}$Tc-RP805 (1.3 ± 0.4 mCi)
  - Injected with $^{201}$TI (0.2 ± 0.1 mCi)
- Zymography, immunoblotting
Role of MT-1 MMP on Post-MI Remodeling

• Significant increased post-MI mortality
  - MT1-MMPexp: 56% at 2 wks
  - WT: 12% at 2 wks
  - cause of death:
    • rupture (10%), failure (50%)
• Severe LV dysfunction in MT1-MMPexp
• RP805 uptake increased in MT1-MMPexp mice
• RP805 uptake increased in infarct and remote regions 2 wks post-MI
• MT1-MMPexp mice had increased fibrillar collagen and hydroxyproline in MI and remote regions
• Levels of active form MT-1 increased 5-fold
Role of MT-1 MMP on Post-MI Remodeling

<table>
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<tr>
<th>Whole Heart</th>
<th>FVB (Wild-type)</th>
<th>MT1-MMP OE</th>
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<th>RA</th>
<th>LA</th>
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<th>LA</th>
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| Left Ventricle | | |
|----------------|---|---|---|---|
Role of MT-1 MMP on Post-MI Remodeling

RP805 activity

WT MT1-MMPexp

REM MI REM MI

RP805 Uptake (fraction of ID/g tissue)

0.000 0.002 0.004 0.006 0.008

p<0.05
Role of MT-1 MMP on Post-MI Remodeling

Gelatin Zymography

- **MMP-2 (72kDa)**
- **MMP-2 (64kDa)**
- **MMP-2 Total**
- **MMP-9 (92kDa)**

<table>
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<tr>
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<th>WT</th>
<th>WT-MI</th>
<th>MT1</th>
<th>MT1_MI</th>
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- Total proteins

- MT-1 MMP expression

- MT-1-MMP expression

- WT-MI comparison

- MT1-MMP expression

- MT1-MMP expression-MI
Role of MT-1 MMP on Post-MI Remodeling

- MMP-13 (63kDa)
- MT1-MMP (64/58kDa)
- TIMP-1 (28kDa)
- TIMP-2 (22kDa)

Graph showing the expression levels of MMP-13, MT1-MMP, TIMP-1, and TIMP-2 with asterisks indicating significant differences.

Wawosz Dobrucki
Surgical MI Yorkshire pigs: LCX occlusion
4 groups: 1 wk post-MI (n=6),
2 wk post-MI (n=5),
4 wks post-MI (n=5),
Control (n=5)
Targeted MMP Imaging
In Vivo SPECT

Control

2 Wks s/p MI

4 Wks s/p MI

99mTc-RP805 and 201TI Myocardial Uptake (%ID/g)

* p<0.05 vs. control; # p<0.004 vs 1 wk;  p < 0.03 vs. 4 wk

**99mTc-RP805 / 201TI SPECT**

**Canine MI Model**

- **99mTc-RP805** - 225 min s/p injection
- **201TI** - 15 min s/p injection

**Short Axis**

- **201TI**
- **RP805**

**Vertical LA**

- **201TI**
- **RP805**

**Horizontal LA**
Hotspot Quantification

**Figure:**

- **Tl-201 (A)**
- **Tc-99m MMP (B)**

**Graphs:**

- **APICAL**
  - SPECT (%ID) vs Well Counting (%ID)
  - Equation: $y = 0.933x - 0.0007$
  - $r = 0.84$
  - $n = 12$

- **MID-VENTRICLE**
  - SPECT (%ID) vs Well Counting (%ID)
  - Equation: $y = 0.933x - 0.0007$
  - $r = 0.84$
  - $n = 12$

- **BASAL**
  - SPECT (%ID) vs Well Counting (%ID)
  - Equation: $y = 0.933x - 0.0007$
  - $r = 0.84$
  - $n = 12$

**Note:**

Min_A = 53%  Max_B = 6%

Min_A = 80%  Max_B = 4%

Yi-Hwa Liu
Cardiovascular Molecular Imaging Opportunities

- Application of neuronal imaging post-MI
  - $^{123}$I-MIBG
  - $^{11}$C-HED
- Availability of hybrid imaging systems will facilitate quantification of molecular imaging agents
- Molecular imaging could improve selection of pts post-MI for AICD
- Molecular imaging post-MI could predict post-MI remodeling and CHF, associated with SCD
- Facilitate personalized medicine and significantly reduce medical costs
Cardiovascular Molecular Imaging Challenges

- Majority of cardiac imaging done as outpatient
- Most cardiology practices have invested in and actively employ SPECT imaging
- Limited availability of $^{123}$I, need for $^{99m}$Tc-labeled agents
- Equipment optimized for non-cardiac applications
  - inadequate corrections for cardiac and respiratory motion
  - lack of quantitative software for targeted agents
Cardiovascular Molecular Imaging
Promoting Utilization and Outreach

- Educational efforts with outreach to both basic scientists and clinicians in cardiovascular community
  - AHA, ACC, ASNC
- Encourage NIH support for funding in area of CV molecular imaging
  - 2009 NIH CVMI symposium
- Need for hybrid imaging systems for small and large animal translational research
- Optimization of imaging system to facilitate CV MI
- Standardization of imaging protocols and quantification schemes
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