Advances in Cardiovascular Molecular Imaging: Hybrid SPECT/CT, PET/CT, and PET/MRI

Albert J. Sinusas, MD
Professor of Medicine & Radiology
Director, Advanced Cardiovascular Imaging
Director, Yale Translational Research Imaging Center
Yale University School of Medicine

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Learning Objectives

- Discuss recent advances in the fields of cardiovascular molecular imaging in relation to cardiovascular pathophysiology and personalized medicine.
- Discuss new hybrid radiotracer based imaging technologies; SPECT/CT, PET/CT, PET/MR
- Review new radiotracers and quantitative tools

Angiogenesis associated with the repair following ischemia in the setting of peripheral artery disease and after myocardial infarction can be best imaged by evaluation of changes in which molecular target.

A. Decreased CXCR4 expression
B. Increased AVB3 integrin activation
C. Decreased MMP activation
D. Reduction of reactive oxygen species
Which of the following are sympathetic nerve cardiovascular imaging agents?

- A. ¹⁸F-LMI1195
- B. ¹²³I-mIBG
- C. ¹¹C-HED
- D. All three

Molecular Imaging

- Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems
- Molecular imaging results in personalized patient care by characterizing specific disease processes in different individuals
- Theranostics is the integration of nanomedicine and molecular imaging and represents combined therapy and imaging

CV Molecular Imaging

Ischemic Heart Disease

Molecular Imaging

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Hybrid SPECT/CT

Hawkeye SPECT/CT
4-slice CT

Discovery NM/CT 570c
64-slice CT

- > 5x sensitivity
- ~ 2x spatial resolution
- Better energy resolution
- Dynamic imaging
- Reduction in radiation

Discovery NM/CT 570c Images

19 simultaneous pinhole images

CT Images
SPECT Images
With Contours
CT Images
With SPECT
Contours
Hybrid SPECT/CT
Discovery NM/CT 570c

Courtesy GE Healthcare

Hybrid SPECT / 64-Slice CT
Anomalous RCA

10 y.o. Male
Anomalous RCA
Chest pain and Dyspnea with Exertion
Low dose
Hybrid Imaging
• Anomalous RCA without intramural course
• Normal Perfusion

Atherosclerosis

• Inflammation – VCAM-1, LOX-1
• Macrophages – MCP-1
• Apoptosis (macrophages) – Annexin V
• Matrix Degradation – MMPs
• Angiogenesis – Integrins
• Thrombosis – fibrin binding peptides
• Smooth Muscle Cells – Z203 antibody

Libby P., et al. JNM 2010

Imaging Atherosclerotic Plaque
Inflammation
[18F]-FDG PET


SPECT/CT Imaging in PAD

Normal

PAD

Quantification
Perfusion

SPECT Imaging in Critical Limb Ischemia

Non-healing Heel Ulcer
Pre & Post Revascularization

Perfusion
Necrotic Toe
SPECT Imaging in Critical Limb Ischemia

Approaches for Imaging in Heart Failure
- Assessment of function, geometry
- Assessment of ischemia
  - Perfusion, metabolism, hypoxia
- Assessment of injury
  - Infarction, apoptosis
- Assessment of inflammation
- Assessment of angiogenesis
- Assessment of myocardial denervation
- Assessment of extracellular matrix

68Ga-Pentixafor Indicates Levels of CXCR4 Expression Patients Early Post-MI

Patient 4 Days Post-MI

Patient 7 Days Post-MI

68Ga-Pentixafor Uptake Early Post-MI

Thackeray JT et al. J Am Coll Cardiol Img 2015;8:1417–26

Alpha-v-Beta-3 Integrin
- Transmembrane protein (heterodimer)
  - Cellular attachment
  - Signal transduction
- Activated in angiogenic vessels
- Target for non-invasive imaging of angiogenesis
  - Radiolabeled Peptidomimetics
    - 111In-RP748
  - Arg-Gly-Asp (RGD) peptide conjugated with a radioactive label
    - 99mTc-NC100692 (cyclic RGD)
- 99mTc-RGD

Targeted Imaging of Angiogenesis

99mTc-labeled NC100692
- Peptide conjugate with RGD (Arg-Gly-Asp)
- High affinity and specific binding to αvβ3 integrin

CD31 Endothelial cell marker
RGD Fluorescent NC100692 analog
CD31 + RGD Dual immunofluorescence

Hua et al. Circulation 111:3255-60 2005
**Imaging Angiogenesis**
Chronic Canine Model MI

<table>
<thead>
<tr>
<th>BASELINE</th>
<th>1 WK S/P MI</th>
<th>2 WK S/P MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>99mTc NC100692</td>
<td>99mTc NC100692</td>
<td>99mTc NC100692</td>
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</table>

SPECT Imaging Angiogenesis
Pt 3 Wks s/p MI & PTCA

**Hypertrophic Heart Disease**
MR & Tc99m-NC100692 Imaging
5 Pts (85 segs) 5/9 with LCE had increased uptake

**Evaluation Stem Cell Therapy**
UCL & Barts London - 99mTc-NC100692 Imaging
Imaging before and 4 days post treatment CD34 +/- G-CSF

**PET/CT Imaging**
Angiogenesis
Patient 2 Wks Post Anterior MI

**Labeled MMP Tracers**

- 111In-RP-782
- 111In-RP-788 (control)

- Macrocyclic peptidomimetics
- Based on structure of pharmacological MMP inhibitors

*Images courtesy of Drs Johan Verjans and Leonard Hofstra, University Hospital, Maastricht, the Netherlands.*
Hybrid SPECT/CT - MMP

3 Days Post-MI

4 Weeks Post-MI

Imaging of Reactive Oxygen Species (ROS)


Sympathetic Imaging

- Clinical studies supports value of neuronal imaging for evaluation of patients with heart failure and for prediction of SCD
- Late $^{123}$I-MIBG heart-to-mediastinal ratio improves our ability to predict the risk for SCD
- Potential role for dynamic $^{123}$I-MIBG imaging at rest
- Potential role for PET imaging with $^{11}$C-HED or $^{18}$F-LMI1195

Imaging of Neuronal Function


Structures of Norepinephrine and Radiotracers for Imaging Sympathetic Innervation

J. Med. Chem. 2013, 56, 7312–7323

Quantification of Cardiac $^{123}$I-MIBG Activity - H/M Ratio

Carrío, I. et al. J Am Coll Cardiol Img 2010;3:92-100
**ADMIRE-HF**

- 961 pts, class 2 and 3 heart failure, LVEF <35%
- $^{123}$I-MIBG imaging early and late
- Myocardial perfusion
- Heart:Mediastinal ratio (late) 4 hr planar images
- Followed up for up to 2 years
- 237 subjects (25%) experienced events
- Hazard ratio for H/M 1.60 was 0.40 (p < 0.001)
- Two-year event rate
  - 15% for H/M ≥1.60
  - 37% for H/M <1.60
- $^{123}$I-MIBG imaging provided additional discrimination in analyses of interactions between B-type natriuretic peptide, LVEF, and H/M.


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**Calculation of H/M Ratio**

**Planar vs SPECT**

MIBG 180 min post Injection

**Planar**

**SPECT/CT**

*Courtesy Yi-Hwa Liu, PhD*

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**Dynamic SPECT/CT**

**Tracer Kinetic Modeling**

Dynamic Transaxial mIBG SPECT Images

Kinetic Modeling mIBG SPECT Images

2-tissue (2T) compartmental model provide more accurate fitting than 1-tissue model

For 2T model, K1=0.44, k2=0.09, k3=0.06, k4=0.002

*Courtesy Chi Liu, PhD*

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**Rest SPECT**

$^{99m}$Tc-Tetrofosmin vs $^{123}$I-MIBG

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**3-Hr Dynamic SPECT mIBG Imaging for Normal Human**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>40 - 60 s</th>
<th>60 - 80 s</th>
<th>80 - 100 s</th>
<th>120 - 140 s</th>
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<tbody>
<tr>
<td>LV</td>
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<td>5 - 10 min</td>
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<td>21 - 26 min</td>
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<td>99 - 104 min</td>
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<tr>
<td>132 – 137 min</td>
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<td><img src="image24.png" alt="Image" /></td>
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<tr>
<td>191 – 196 min</td>
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<td><img src="image26.png" alt="Image" /></td>
<td><img src="image27.png" alt="Image" /></td>
<td><img src="image28.png" alt="Image" /></td>
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</table>

*APHA2010*
Kinetic Modeling
Normal Dynamic Human $^{123}$I-mIBG Study
with and without Metabolite Correction

Population-Based
Metabolite Correction Curve

Normal Human $^{123}$I-mIBG Study

PAREPET Study
- Prospective study of CAD patients ($n = 204$) who were candidates for ICD placement for primary prevention of SCA
- Average age 67 ± 11 years
- NYHA CHF functional class - 2.1 ± 0.8
- LVEF - 27 ± 9%
- PET perfusion ($^{13}$N-ammonia)
- PET sympathetic imaging
  - ($^{11}$C-meta-hydroxyephedrine; HED)
- Infarct imaging (insulin-stimulated $^{18}$F-FDG)


PAREPET Study

Median follow-up 4.2 years
Cardiac mortality 34%, half from SCA (16%)


PAREPET Study
- Volume (% LV) of denervated myocardium strong determinant of SCA ($p = 0.001$)
- Multivariate analysis (including EF and BNP),
  - Denervated myocardium remained independent predictor of SCA
  - Viable denervated myocardium independent predictor of SCA
- LVEF, infarct volume and hibernating myocardium were not independent predictors
- Additional predictors by multivariate analysis included:
  - LVED volume index, creatinine, and no ACE/ARB therapy
- Sympathetic imaging could provide a new approach for selecting patients with relatively preserved systolic function who are at risk of arrhythmic death


$^{18}$F-LMI1195
- Novel $^{18}$F labeled benzylguanidine analog
- Ligand for norepinephrine transporter (NET)
- Index of sympathetic function

**18F-LMI1195**

**Phase 1 – Human Study**

- Favorable safety, dosimetry and biodistribution for cardiac imaging
- High initial myocardial uptake in normals
  - 1.6% injected dose (ID)
- Slow washout from normal myocardium
  - 1.5% of ID (decay-corrected) over 4 hours
- Myo/Liver ratio ~1/1 at 1 hr
- Rapid clearance from blood and lung


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- Potential role for PET imaging with 11C-HED or 18F-LMI1195
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- Potential role for dynamic 123I-MIBG imaging at rest and with mental stress

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**Sarcoidosis – PET Imaging**

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**18F-FDG PET/CT**

**Quantitative Analysis**

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**PET/MR Imaging Protocol**

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PET/MR Attenuation Correction

Segmented Dixon Based on Emission

Courtesy Brian Hutton, PhD

Imaging of Post-MI Inflammation
Postmortem PET/MRI Images
14 days after 3 hour LAD occlusion followed by reperfusion
7 days post MI in subject with permanent LAD occlusion
Wisenberg et al. J Cardiovascular Mag Res 2015, 17(Suppl 1):Q19

18F-FDG PET-MRI Detection of Sarcoidosis

Schneider et al. Eur Heart J, 2014

CT + MR Rb + MR FDG + MR
Sagittal Coronal Axial

Courtesy of Mary Germino WT: Rubidium

PET MR Fusion

Sagittal Coronal Axial
Animated GIFs: Fading PET in and out (overlaid on MR)

Courtesy of Mary Germino Subject WT: FDG

PET MR Fusion

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Animated GIFs: Fading PET in and out (overlaid on CT)

Subject WT: FDG

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Molecular Imaging
Comparison with Biomarkers & Alternative Imaging Approaches

- How does proposed targeted imaging compare with existing biomarkers?
- Perform analyses with existing imaging technologies for comparative effectiveness
- Relate targeted images with physiological or anatomic imaging
- Early involvement of clinical colleagues for target identification, implementation, and clinical applications

Role of SPECT / PET / CT
Future Applications

- Validate imaging measurements with postmortem tissue counting
- Apply dual radio-labeled and fluorescent-labeled probes for cellular localization and further validation of images
- Translate small animal imaging to more physiological large animal models and humans
- Develop tools for image fusion with MRI
- Develop quantitative tools for analysis of targeted radiotracers with correction for attenuation and partial volume errors

Cardiovascular Molecular Imaging:

- Clinical translation of molecular imaging technologies will aid in diagnosis and treatment of human cardiovascular disease
- Translation into clinical practice requires
  - Advances in small animal imaging
  - Pre-clinical studies in relevant large animal models
  - Development of novel targeted agents
  - Availability of hybrid imaging systems
  - Development of multidisciplinary teams

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