Vascular Molecular Imaging: Past, Present and Future

Mehran M. Sadeghi, MD
Associate Professor of Medicine
Yale University School of Medicine

Miami, June 10, 2012
Presenter Disclosure Information

Received experimental tracers from GE and Lantheus Medical Imaging
Temporal trends in CV mortality

Death Rates for Coronary Heart Disease in Males, Ages 35–74

http://www.nhlbi.nih.gov/about/factbook/chapter4.htm
Landmark events in CV medicine

- 1958: Coronary arteriography developed (Sones)
- 1962: First beta-blocker developed (Black)
- 1969: First description of CABG (Favaloro)
- 1972: First HMG CoA reductase inhibitor described (Endo)
- 1976: First implantable cardioverter-defibrillator developed (Mirowski)
- 1980: First open-heart procedure developed (Gibbon)
- 1981: Risk factors defined (Julian)
- 1982: NHBPEP
- 1979: Coronary angioplasty developed (Grüntzig)
- 1983: CASS
- 1985: TIMI I
- 1985: NCEP
- 1986: GISSI and ISIS-2
- 1992: SAVE
- 1993: superiority of primary PCI vs. fibrinolysis in acute MI noted
- 2002: Efficacy of drug-eluting vs. bare-metal stents determined
- 2009: Left-ventricular assist device as destination therapy in advanced heart failure shown to be effective
- 2009: Genomewide association in early-onset MI described
- 2009: Deep gene sequencing for responsiveness to cardiovascular drugs performed
Causes of Coronary Thrombogenesis

- Plaque Rupture
- Endothelial Erosion

prevalent in younger patients and women
sometimes on lipid-poor, high SMC, stenotic plaques

Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi

M. J. Davies, N. Woolf, and W. B. Robertson

From the Department of Pathology, St. George's Hospital Medical School and The Bland-Sutton Institute of Pathology, The Middlesex Hospital Medical School

It is hardly credible that there should be continuing debate about what is ostensibly so simple a morphological problem, the relation of coronary thrombosis to acute myocardial infarction. For well over half a century opinion has swung from one extreme to the other and once again it is being suggested, particularly in the United States of America (Roberts, 1974), that the two are not constantly or causally related and even that coronary thrombosis may be a complication of myocardial infarction. The reported proportions of fatal acute myocardial infarcts in which occlusive thrombi are found have varied from less than 50 per cent (Baroldi, 1965; Kagan et al., 1968; Roberts and Buja, 1972) to approaching 100 per cent (Chapman, 1974; Harland and Holburn, 1966). A recent workshop of 10 pathologists (Chandler et al., 1974) in the United States trying to resolve the question succeeded only in once again highlighting the controversy (Burchell, 1974). As
NONINVASIVE REGIONAL MYOCARDIAL PERFUSION WITH RADIOACTIVE POTASSIUM

Study of Patients at Rest, with Exercise and during Angina Pectoris

Major Barry L. Zaret, USAF, MC, Major H. William Strauss, USAF, MC,
Colonel Neil D. Martin, USAF, MC, Master Sergeant Harry P. Wells, Jr., USAF,
and Lieutenant Colonel M. D. Flamm, Jr., USAF, MC

Abstract Myocardial perfusion imaging after intravenously administered radioactive potassium ($^{41}$K) was used to delineate noninvasively areas of myocardial infarction and left ventricular regions that become transiently ischemic during angina pectoris. Forty-three subjects were studied at rest and during maximal treadmill exercise. In 12 normal subjects $^{41}$K distribution was homogeneous both at rest and during exercise. In 13 of 15 patients with previous myocardial infarction studied at rest, regions of decreased radionuclide accumulation corresponded to the anatomic location of the infarct. In 16 of 19 patients with angina pectoris, regions of relatively decreased $^{41}$K accumulation were identified when the tracer was administered during exercise, but were not present at rest. These zones of relative hypoperfusion corresponded to regions supplied by angiographically demonstrable stenotic coronary arteries in all patients so studied.

$^{41}$K myocardial imaging thus provides a safe and simple noninvasive means of assessing regional myocardial perfusion at rest, with exercise and during angina pectoris. (N Engl J Med 288:809-812, 1973)
ISCHEMIA is an international randomized controlled trial comparing the effectiveness of two initial management strategies for stable patients with moderate-to-severe ischemia on nuclear, echo, or cardiac MR stress testing: an invasive strategy with cardiac catheterization and optimal revascularization plus OMT versus a conservative strategy with OMT and cath reserved for patients with a primary endpoint event or refractory symptoms.
Redefining vascular imaging, its role and its value in CV medicine
Visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems.
Potential applications of vascular molecular imaging

- Detection of disease
- Identifying patients at high risk for events
  - Vulnerable plaque
  - AAA prone to rupture
- Tracking therapeutic interventions
  - Cell and gene therapy
  - MMP inhibitors
- Advancing research on pathobiology
Potential clinical applications of vascular molecular imaging

• Early atherosclerosis/atherosclerosis burden
• Plaque vulnerability
• Predicting aneurysm rupture/dissection
• Vascular remodeling
• Transplant vasculopathy
• Restenosis
• Primary pulmonary hypertension
• Angiogenesis and arteriogenesis
• Stem Cell and gene therapy
• ...............
Molecular imaging of atherosclerosis

- Calcification (NaF)
- Endothelial Activation (VACAM-1, P-selectin)
- VSMC proliferation/activation (Z2D3, αvβ3)
- Lipid core (oxidized LDL)
- Inflammation
  - pH/temperature
  - Cell trafficking and recruitment (labeled monocytes, chemokine receptors)
  - Phagocytic activity (nanoparticles)
  - Metabolism (FDG)
  - Integrin expression/activation (αvβ3)
  - Protease activity (MMPs, cathepsins)
- Apoptosis (annexin V)
- Vasa vasorum/angiogenesis (αvβ3, VEGFRs)
Matrix metalloproteinases and Vascular Disease

- Normal arteries express MMP-2 without any detectable in situ enzymatic activity.

- Inflammatory cells are an important source of MMPs and enhance MMP production by vascular cells.

- MMP activity is increased in vascular remodeling, and plays a key role in aneurysm rupture and atherosclerotic plaque vulnerability.

Gelatinase (MMP-2 and -9) expression and activation following murine carotid artery injury

Zhang et al, Circulation 2008:1953-60
MMP-targeted imaging of injury-induced vascular remodeling

(\(^{\text{111}}\)In-RP782)

Zhang et al, Circulation 2008:1953-60
Dietary modification and remodeling in injured arteries

Tavakoli, et al, ATVB, 2011
Serial Imaging of MMP activation following dietary modification in injured arteries

\((^{99}\text{Tc-}}\text{RP805})\)

Tavakoli, et al, ATVB, 2011
MMP-targeted Imaging of Carotid Aneurysm

Razavian, et al, JNM, 2010
MMP-targeted Imaging of Carotid Aneurysm

Razavian, et al, JNM, 2010
RP782 Uptake Specificity

Razavian, et al, JNM, 2010
Predicting aneurysm expansion: Tracer uptake at 2 weeks vs aneurysm size at 4 weeks

Razavian, et al, JNM 2010
MicroSPECT/CT imaging of MMP activation in atherosclerotic mouse aorta

$(^{111}\text{In-RP782})$

Razavian et al, JNM 2011
Effect of dietary modification on plaque development and RP782 uptake

HFD HFW

Relative Plaque Area (%) vs. Background-corrected In-vivo uptake (cpv/MBq)

α-actin

CD31

CD68

EMR1

Razavian et al, JNM 2011
Clinical vascular molecular imaging: Technical challenges

- Sensitivity: small size of the vessel wall
Clinical vascular molecular imaging: Technical challenges

• Sensitivity

• Specificity and selectivity
• Blood activity/TBR/SNR
Clinical vascular molecular imaging: Technical challenges

- Sensitivity
- Specificity and selectivity
- Blood activity/TBR/SNR
- Cardiac motion (compounded by the size of target)
\textsuperscript{18}F-FDG PET/CTA in acute coronary syndrome

18F-FDG PET imaging of carotid atherosclerosis (patients undergoing CEA)

Rudd, et al, Circulation, 2002;105:2708
Assessing global cardiovascular molecular calcification with $^{18}$F-fluoride PET/CT: will this become a clinical reality and a challenge to CT calcification scoring?

Sandip Basu • Poul F. Hoiland-Carlsen • Abass Alavi
Clinical vascular molecular imaging: Non-technical challenges

• Research funding:
  – novelty and "sexiness" vs translation
  – dedicated funding for CVMI
Clinical vascular molecular imaging: Non-technical challenges

• Research funding:
  – novelty and “sexiness” vs translation
  – dedicated funding for CVMI

• Costs of development:
  – $10^8$ Ks
  – process-specific tracers with multiple applications (e.g., inflammation, remodeling)
Clinical vascular molecular imaging: Non-technical challenges

• Research funding:
  – novelty and “sexiness” vs translation
  – dedicated funding for CVMI

• Costs of development:
  – $10^8$ Ks
  – process-specific tracers with multiple applications (e.g., inflammation, remodeling)

• Application:
  – unmet needs (e.g., predicting small AAA rupture)
  – paradigm shift (e.g., imaging plaque vulnerability)
Plaque characteristics on CTA and subsequent ACS

Expansive remodeling and low attenuation plaque


27 ± 10 months follow up

Plaque characteristics on virtual histology and gray-scale IVUS and subsequent MACE

TCFA, minimal lumen area, plaque burden

Clinical vascular molecular imaging is possible and powerful, paradigm-shifting, and potentially effective. but incremental value?
The progress in cardiovascular care and reduction in CV mortality have led to:

- Emphasis on comparative effectiveness
  - Higher threshold for added value
  - ? Effect on outcome

Identify the gaps in CV imaging and the role of molecular imaging in addressing them.
Proposal

Think tank/summit of cardiovascular imagers and non-imager practitioners led by SNM CVC/CMIIT and other professional societies to define the clinical imaging needs of the future and how molecular imaging can address them.
The best way to predict the future is to invent it.

*Alan Kay, Computer scientist*
Cardiovascular Molecular Imaging Laboratory

Masood Ahmed
Abolfazl Asadi
Azariyas Challa
Leila Esmailzadeh
Amir A Gharaei
Xiaojia Guo
Svetlana Krassilnikova
Heloise Mongue-Din
Xuan Li
Gaoxing Luo
Lei Nie
Hooman R Fassaie
Mahmoud Razavian
Teresa Silva
Sina Tavakoli
Jiasheng Zhang

Yale Experimental Nuclear Cardiology Laboratory
Albert J Sinusas
Wawosz Dobrucki

Yale Cardiovascular Immunobiology Laboratory
Jeffrey R Bender

Yale CT Surgery
George Tellides

Lantheus
Scott Edwards
Simon Robinson

Funding
Department of Veterans Affairs
NIH R01 HL085093