Imaging Atheroma

an Application of Molecular Imaging
in Coronary Artery Disease

on the occasion of the 50th anniversary of the
Finnish Society of Nuclear Medicine

H. William Strauss, MD

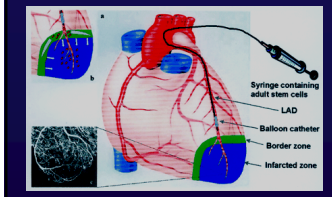
May 15,2009

Fact and Fable

a tribute to Topelius – author of children's books and historical fiction

Two female figures in Helsinki's Esplanade Park
Fact and Fable
one figure holds the flame of truth
the other holds the crown headed bird of fable

Rebuilding the Heart



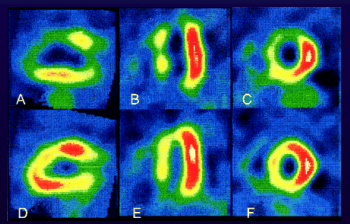
10 patients with AMI had autologous marrow infused at 7-14 days, at the time of PTCA, into infarct artery.

	Pre	3 Mo
LVEF	51%	53%
Hypo/Ak	30%	12%

Stress Thallium Images

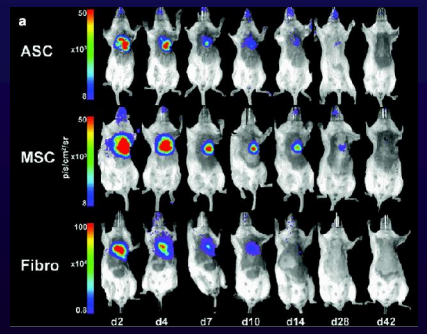
Pre Rx

Post Rx



Strauer et al Circ 2002; 106:1913-8

Mesenchymal Stem Cell Transplant

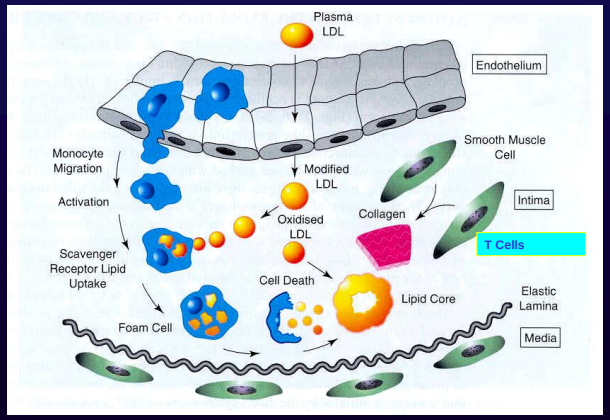


- Permanent occlusion AMI
- Direct injection of cells into infarct region at 10 minutes
- Serial follow-up with optical imaging
- Cells for transplant harvested from mice expressing green fluorescent protein in their tissues

ASC=Adipose Stem Cell
MSC=Mesenchymal Stem Cell
Fibro=Fibroblast

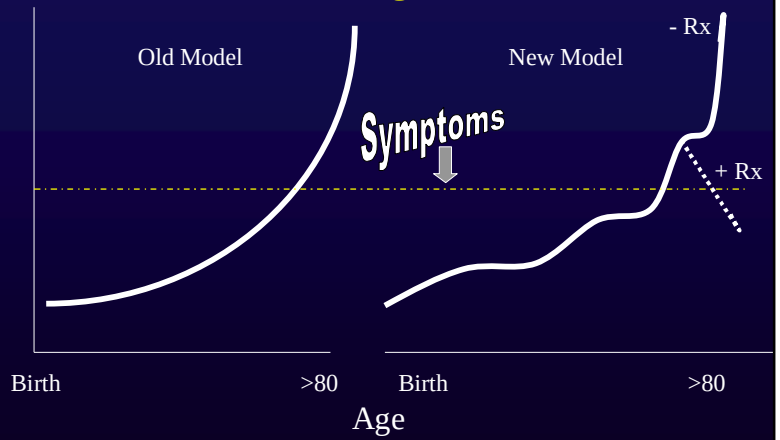
Van der Bogt et al Transplantation 2009;87:642-52

Components of Plaque



Davies MJ – Atlas of Coronary Artery Disease – Lippincott Raven 1999

Lesion Progression

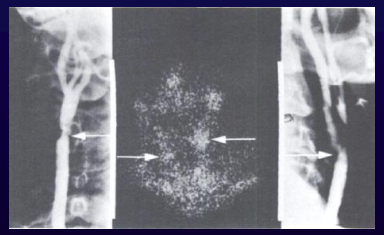


Atheroma BioProfiling

- Lipid turnover - ^{99m}Tc or ^{125}I – low density lipoprotein cholesterol
  - Oxidized LDL
- Macrophage activity
  - Chemotactic receptor expression - ^{99m}Tc-MCP-1
  - Glucose utilization of activated cells - ^{18}FDG
  - Apoptosis (macrophages, smooth muscle cells) - ^{99m}Tc-Annexin
  - MMP expression (^{99m}Tc-RP805)
- Calcification (tombstone)
- Smooth muscle proliferation
  - ^{111}In-Z2D3 – unique epitope on proliferating VSMC
- Vasa Vasorum - Peptide recognizing VCAM or integrin (eg $\alpha_v\beta_3$)

Imaging Atheroma

Carotid uptake of Autologous ^{125}I-LDL 48 hours after injection



LDL Cholesterol pool is large; turnover (equilibration) with serum cholesterol is rapid

Lees RS, Lees AM, Strauss HW. External Imaging of Human Atherosclerosis J Nucl Med 1983; 24:154-6

Oxidized LDL Specific Antibody Imaging

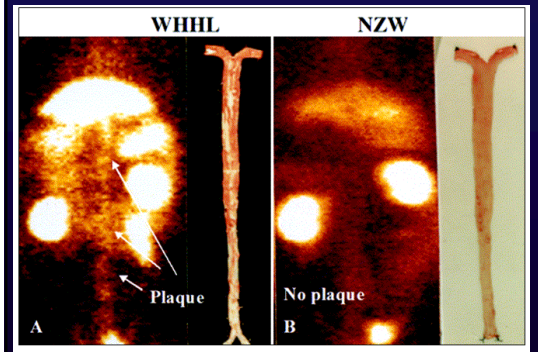
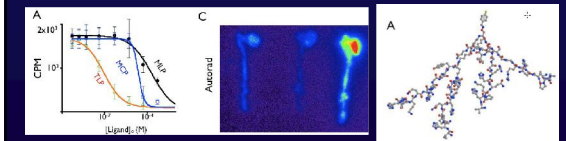


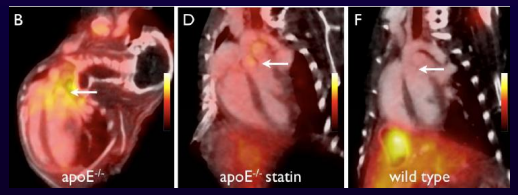
FIGURE 4. In vivo gamma camera images of a Watanabe heritable hyperlipidemic (WHHL) rabbit (*A*) injected with 5 mCi (200 μg) ^{99m}Tc-MDA2 showing selective uptake in the aorta (***arrows***). The control normocholesterolemic, nonatherosclerotic New Zealand White (NZW) rabbit (*B*) shows no aortic uptake. Interestingly, there is significantly more liver, spleen, and gut uptake of ^{99m}Tc-MDA2 in the WHHL rabbit, where increased oxidation-specific epitopes are known to exist.

Tsimkas Am J Cardiol 2002; 90:22L-27L

F-18 labeled Tetrameric Linear Peptide (^{18}F-4V)

Recognizes VCAM-1





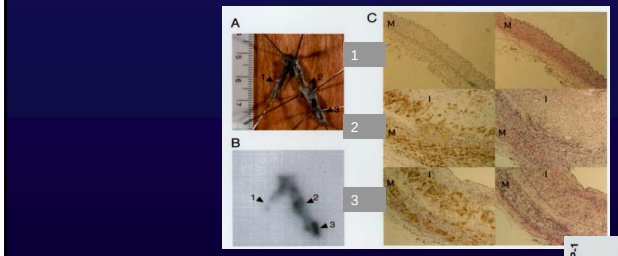
"VCAM-1 mediates inflammatory cell adhesion through interaction with the integrin very late antigen-4 (8). The early induction, confinement of expression to atherosclerotic lesions, and accessible position in proximity to the blood pool render VCAM-1 an attractive imaging biomarker."

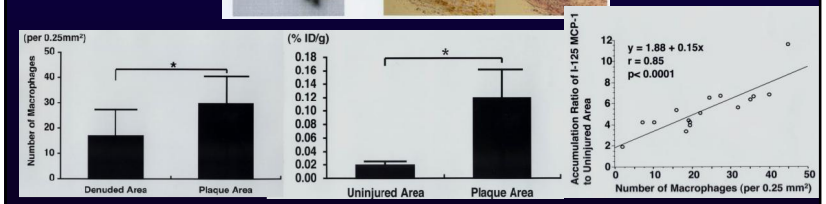
Nahrendorf-M et al JACC-I, 2009; In Press

Imaging Macrophages in Atheroma

- Injured or inflamed endothelium expresses monocyte macrophage chemotactic receptors (CCR2 imaged with ^{125}I-MCP-1)
- Activated macrophages require exogenous glucose; increase their metabolic rate by 30-100x compared to basal metabolism (^{18}FDG)
  - Increased expression of folic acid (folate) receptors (^{111}In-Folic Acid)
- Apoptosis (^{99m}Tc-Annexin)
  - Induced by cytokines from T-cells and mast cells in the plaque
  - Overwhelming extra or intracelluar noxious stimuli in macrophages
    - Especially oxidized low density lipoprotein
- Calcification
  - Dying macrophages express osteopontin and other factors – leading to deposition of calcium in the region of dead macrophages
- MMP production

^{125}I-MCP-1 and Macrophages in Plaque

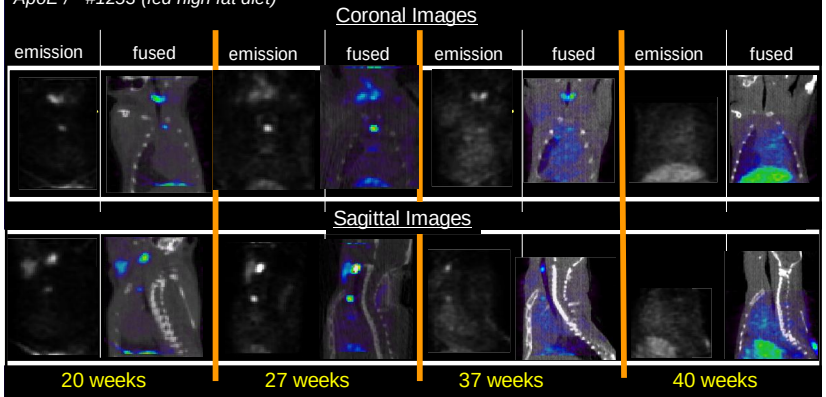




Ohtsuki et al Circ 2001 104(2):203-8

SERIAL IMAGES OF ^{99m}Tc-ANNEXIN-V AT 20, 27, 37 & 40 WEEKS

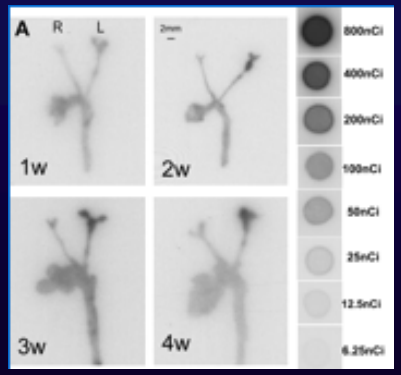
ApoE-/- #1253 (fed high fat diet)



Normalized OS-EM (4 iteration and 3 subsets), Butterworth filter cutoff .3 cycle/pixel

Tsui et al JHH

Image Matrix Metalloproteinase

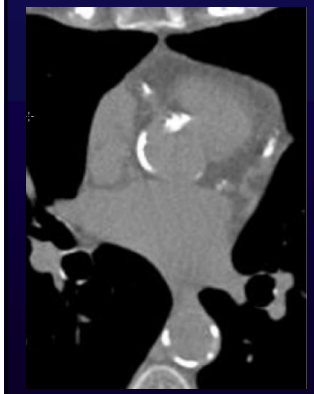


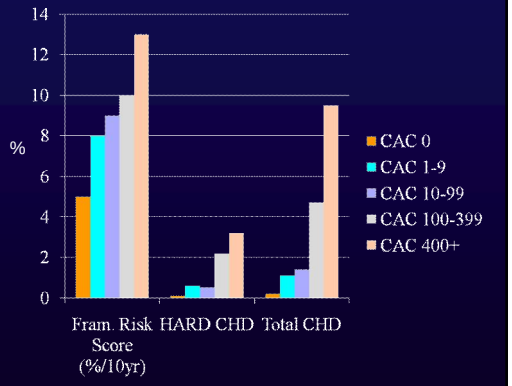
ARG of injured carotid artery following injection of ^{111}In-RP782, an MMP inhibitor

Zhang et al Circ 2008; 118:1953-60

Coronary Calcium vs Events

4.4 yr follow-up

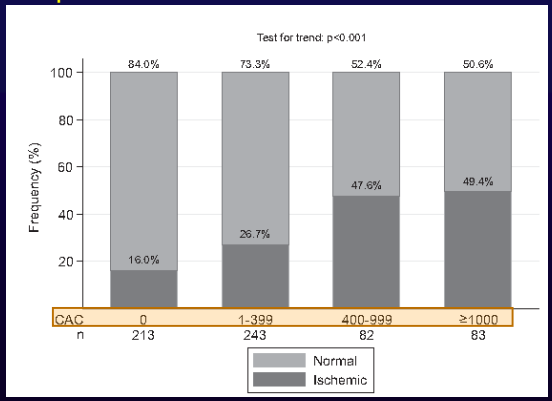




Wong ND et al – JACC-I 2009; 3:319-26

^{82}Rb MPI & Coronary Calcium

in patients with intermediate risk of CAD



Schenker et al Circ 2008; 117:1693-1700

Identifying Patients at Risk

- Genome
- Transcriptome
- Proteome
- Degradome

Scientists lift lid on genetics of coronary artery disease

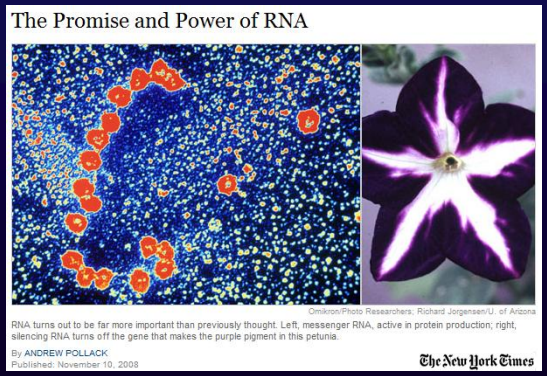
18 July 2007 – Nature News

Scientists … have confirmed six new genetic variants that increase the likelihood of developing coronary artery disease. …The researchers found that changes in DNA on chromosomes 2, 6, 10 and 15 and two on chromosome 1 associated with increased risk of developing coronary artery disease and heart attacks. The study also confirmed the importance of a variant on chromosome 9.

"Professor Nilesh Samani, British Heart Foundation Chair of Cardiology at the University of Leicester and lead author on the paper indicates that "Many of these genetic variants are carried by between one-quarter and three-quarters of white Europeans and (may) explain a significant proportion of the heart attacks that occur."

Genetics Markers are VERY Complex

RNAi



Degradomics:
systems biology of the protease web*

- Do proteinases degrade proteins to biologically inactive components?
  - MMP's can precisely cleave proteins such as CCR-2 (MCP-1) to convert the molecule from a chemoattractant into an anti-inflammatory
  - MMP's degrade collagen and elastin, but also alter cell-cell contact initiating epithelial-mesenchymal transition
- Do factors – such as overexpression of RNAi - change the tissue concentration of proteinase enzymes?

Overall CM and Dean RA Cancer Metastasis Rev 2006; 25:69-75

1: JAMA. 2008 Mar 19;299(11):1345-50.

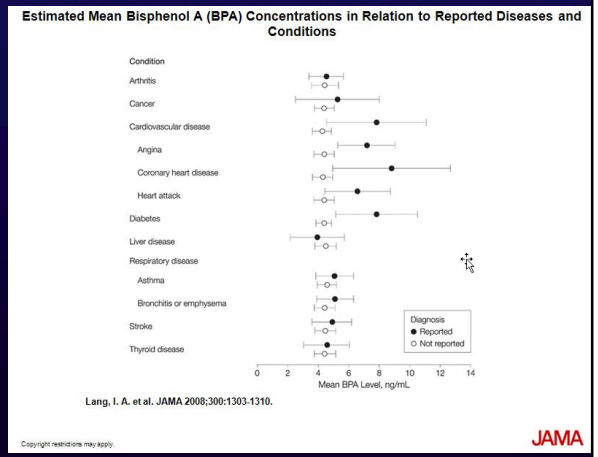
Epigenetics at the epicenter of modern medicine.

Feinberg AP.

Department of Medicine and Center for Epigenetics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. afeinberg@jhu.edu

Epigenetics, the study of non-DNA sequence-related heredity, is at the epicenter of modern medicine because it can help to explain the relationship between an individual's genetic background, the environment, aging, and disease. It can do so because the epigenetic state varies among tissues and during a lifetime, whereas the DNA sequence remains essentially the same. As cells adapt to a changing internal and external environment, epigenetic mechanisms can remember these changes in the normal programming and reprogramming of gene activity. The common disease genetic and epigenetic (CDGE) model provides an epidemiologic framework that can incorporate epigenetic with genetic variation in the context of age-related susceptibility to disease. Under CDGE, the epigenetic program can modify the effects of deleterious genes or may be influenced by an adverse environment. Thus, including epigenetics into epidemiologic studies of human disease may help explain the relationship between the genome and the environment and may provide new clues to modifying these effects in disease prevention and therapy.

Bisphenol-A Urine Concentrations and Coronary Disease



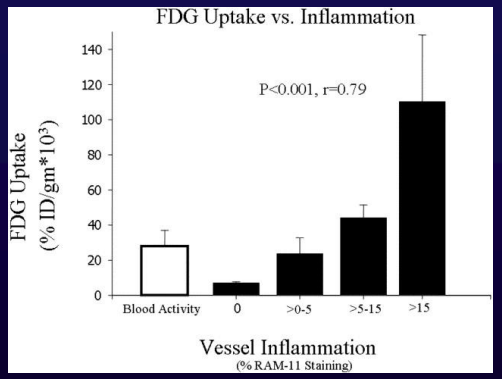
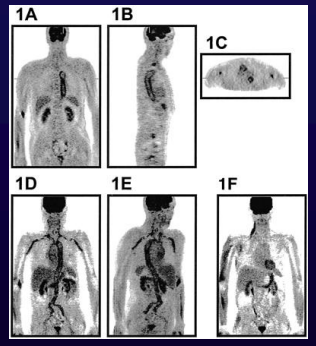


Figure 3. Correlation between FDG uptake and macrophage density in rabbit aortic specimens. There was a significant correlation between FDG activity and macrophage density (r = 0.79, P < .001).

Tawakol et al J Nucl Cardiol 2005; 12: 294-301

FDG in Arteritis



Generalized large vessel arteritis visualized by 18fluorodeoxyglucose-positron emission tomography.

Wenger M, et al Circulation. 2003;107(6):923.

FDG Vascular Graft

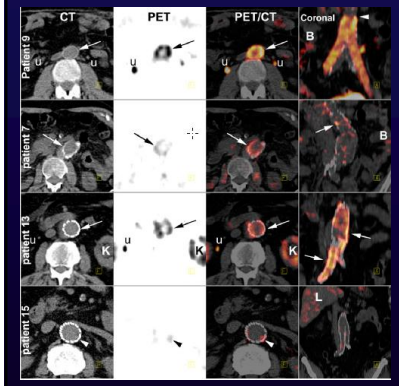
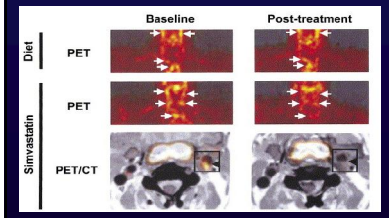


FIGURE 1. CT, PET, and merged PET/CT images in transaxial plane and merged PET/CT images in coronal plane. Top 2 rows illustrate patients who underwent conventional open surgery, and bottom 2 rows illustrate patients operated with EVAR. Normal 18F-FDG accumulation in kidneys (K), ureters (u), liver (L), and bowel segments (B) is indicated in images. Patient 9 illustrates typical appearance of majority of conventional synthetic aortic grafts in material (arrows), with high 18F-FDG accumulation in virtually entire length of graft (SUVmax 4.4. Marked difference between normal vessel wall and graft is seen at site of proximal anastomosis (arrowhead). Patient 7 illustrates that few patients had low levels of 18F-FDG accumulation in their grafts (SUVmax 2.8. Patient 13 illustrates the only case of EVAR graft with high 18F-FDG accumulation (SUVmax 5.4, whereas patient 15 exemplifies low 18F-FDG accumulation seen at the grafts in the other EVAR patients (SUVmax 2.4.

Wasselius et al J Nucl Med 2008; 49:1601–1605

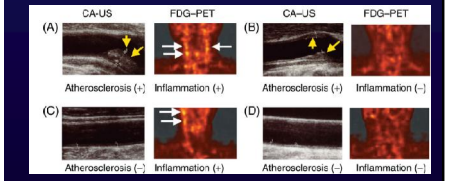
Carotid Inflammation

Control vs 3 mo Simvastatin Rx



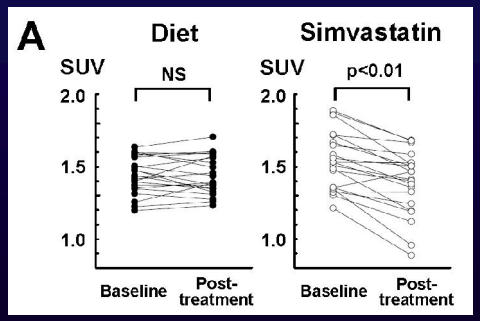
Tahara et al J Am Coll Cardiol 2006; 48:1825-31

100 consecutive patients referred for screening carotid ultrasound, 30% had FDG carotid uptake.



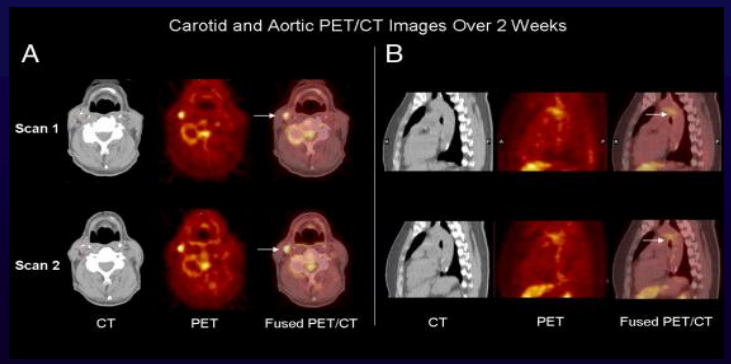
Tahara N et al Eur Heart J 2007; 28:2243-8

Reduction in Carotid FDG SUV with Simvastatin



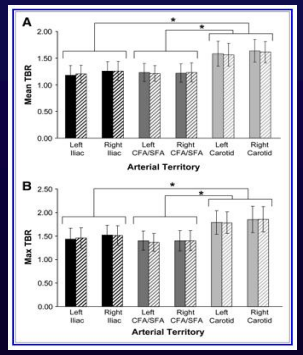
Tahara et al J Am Coll Cardiol 2006; 48:1825-31

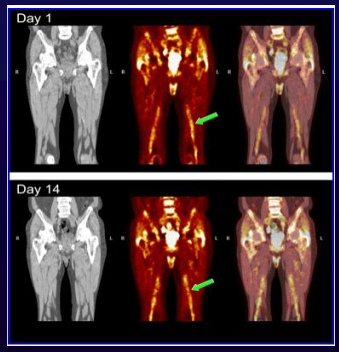
Reproducibility of FDG Uptake in Carotid and Aorta (2 weeks)
Intraobserver correlation r>0.9 (except aorta (r=0.7)



Rudd JH et al J Am Coll Cardiol. 2007 Aug 28;50(9):892-6

Reproducibility of FDG Vascular Uptake in Studies Performed 2 Weeks Apart in Symptomatic Patients

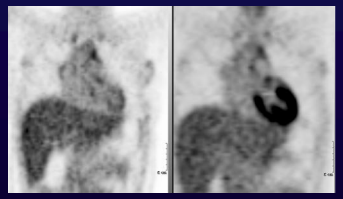




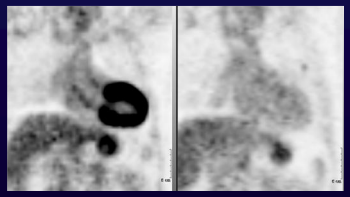
Intraclass correlation r > 0.8

Rudd JH et al Nucl Med. 2008 Jun;49(6):871-8.

Stability of Vascular FDG Uptake



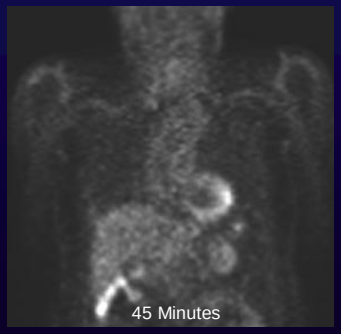
Initial 6 Months

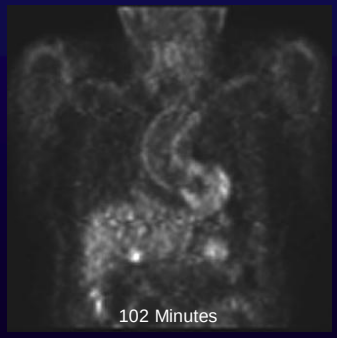


Initial 6 Months

Meirelles et al SNM 2006

Need for Standardization

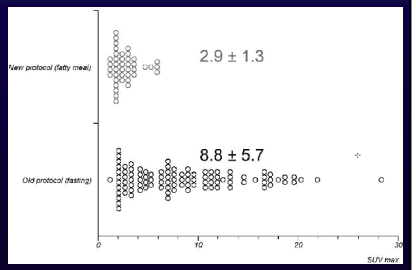




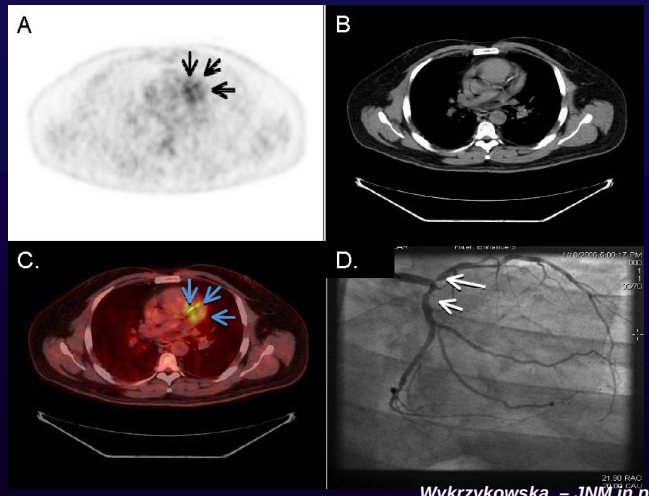
Suppression of Myocardial Uptake

Dietary therapy

"…A high fat / no carbohydrate meal 3 – 6 hours prior to FDG injection suppressed myocardial FDG/glucose uptake. This should facilitate definition of mediastinal pathology by FDG PET, particularly with standalone PET and may permit the detection of biologically active CAD."



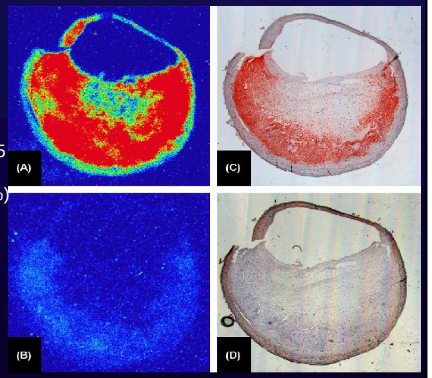
Wykrzykowska – JNM in press



Wykrzykowska – JNM in press

Peripheral Benzodiazepine Receptors in Atheroma

Peripheral benzodiazepine receptors (PBRs) labeled with autoradiography and macrophages labeled with immunohistochemistry in carotid endarterectomy tissue from a single patient. (A) Total binding of [3H]PK 11195 by autoradiography. (B) Residual (or nonspecific) binding of [3H]PK 11195 was determined by co-incubation with excess nonradioactive PK 11195 (20M). Specific binding is defined as total minus nonspecific and represented the majority (90%) of total binding shown in panel A. (C) Immunohistochemical staining of macrophages labeled with an antibody to CD68. (D) Control section was processed without the primary antibody to CD68 and showed negligible staining.



Fujimura et al Atherosclerosis 2008, doi:10.1016/j.atherosclerosis.2008.02.032

PS Group in Turku did not get specific uptake in experimental atheroma with C-11 PK11195
Laitinen et al Eur J Nucl Med 2009; 36:73-80

Tim Russert

Alex Wong / Getty Images file

May 7, 1950 – June 13, 2008.
Asymptomatic; negative exercise stress test; death caused by rupture of LAD plaque