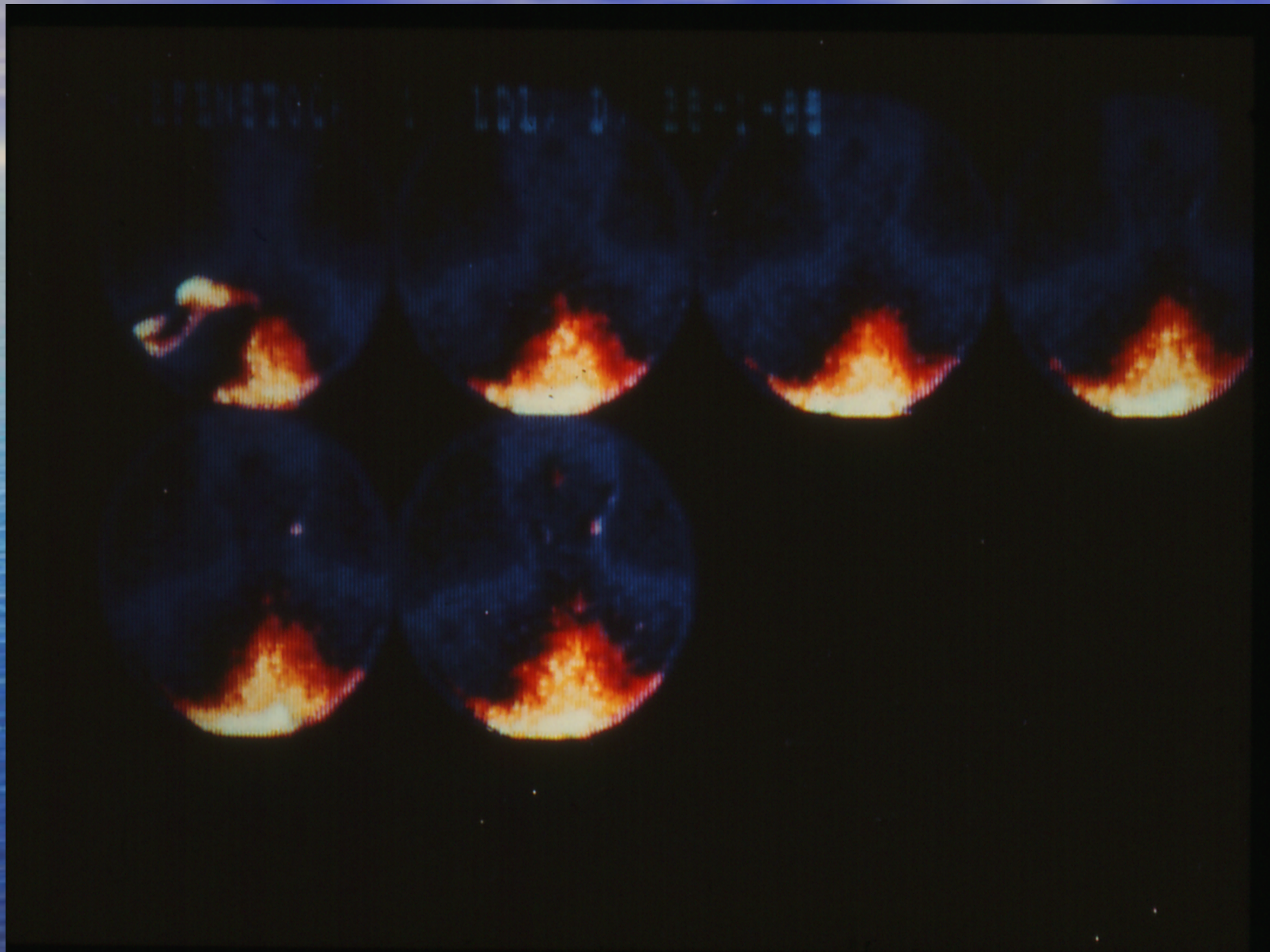
DOES RADIONUCLIDE IMAGING OF ATHEROSCLEROSIS HAVE A CHANCE AND WHICH TECHNIQUE MIGHT SUCCEED?

Helmut SINZINGER

Department of Nuclear Medicine, Medical University of Vienna, Austria

16th ISORBE, Pretoria, 21-23 March 2013

EARLY CAROTID UPTAKE OF ^{123}I-LDL



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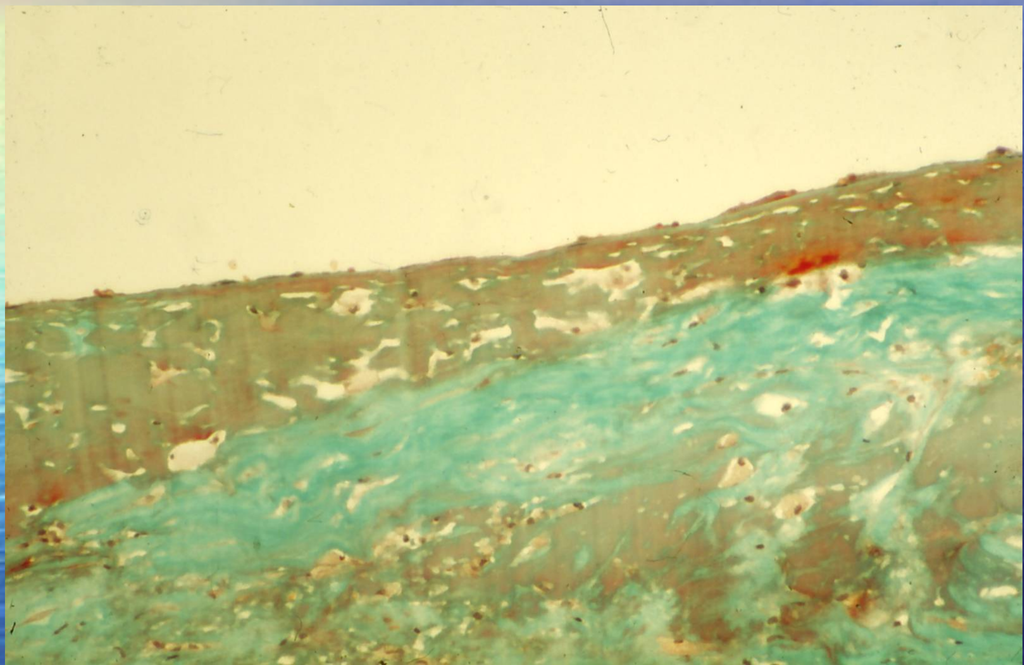
HOW TO IMAGE ATHEROSCLEROSIS?

MECHANISM

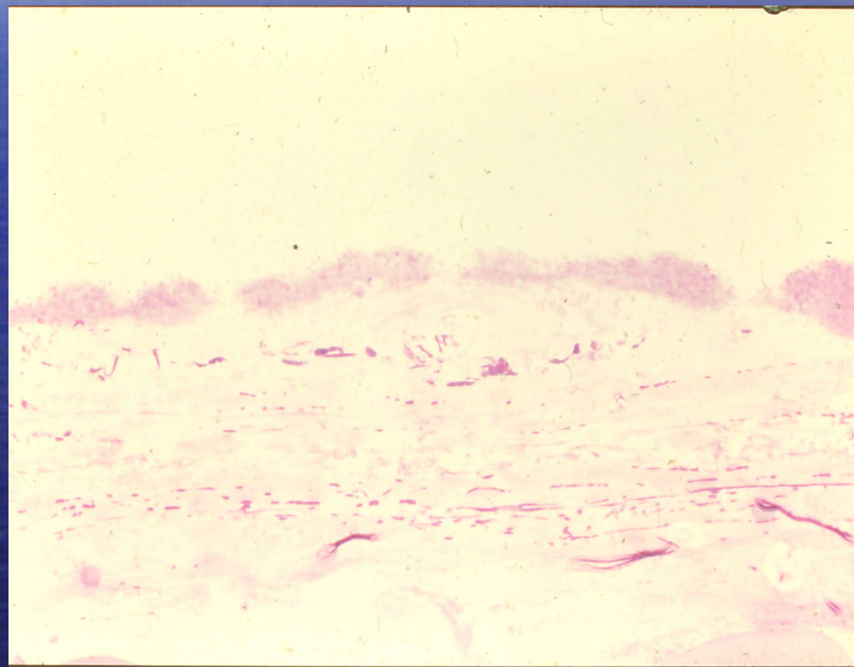
- PROLIFERATION
- LIPIDS
- THROMBOSIS
- INFLAMMATION

VULNERABLE LESION

PARIETAL THROMBOSIS (FIBRIN)



PARIETAL THROMBOSIS (PLATELETS)



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THE NEW CONCEPT

UNSTABLE ATHEROSCLEROTIC PLAQUE

EXTRACELLULAR MATRIX ↓

THIN LESION CAP (< 65 μ)

LIPID RICH CORE

DYING (APOPTOTIC) CELLS

INFLAMMATION

OXIDATION

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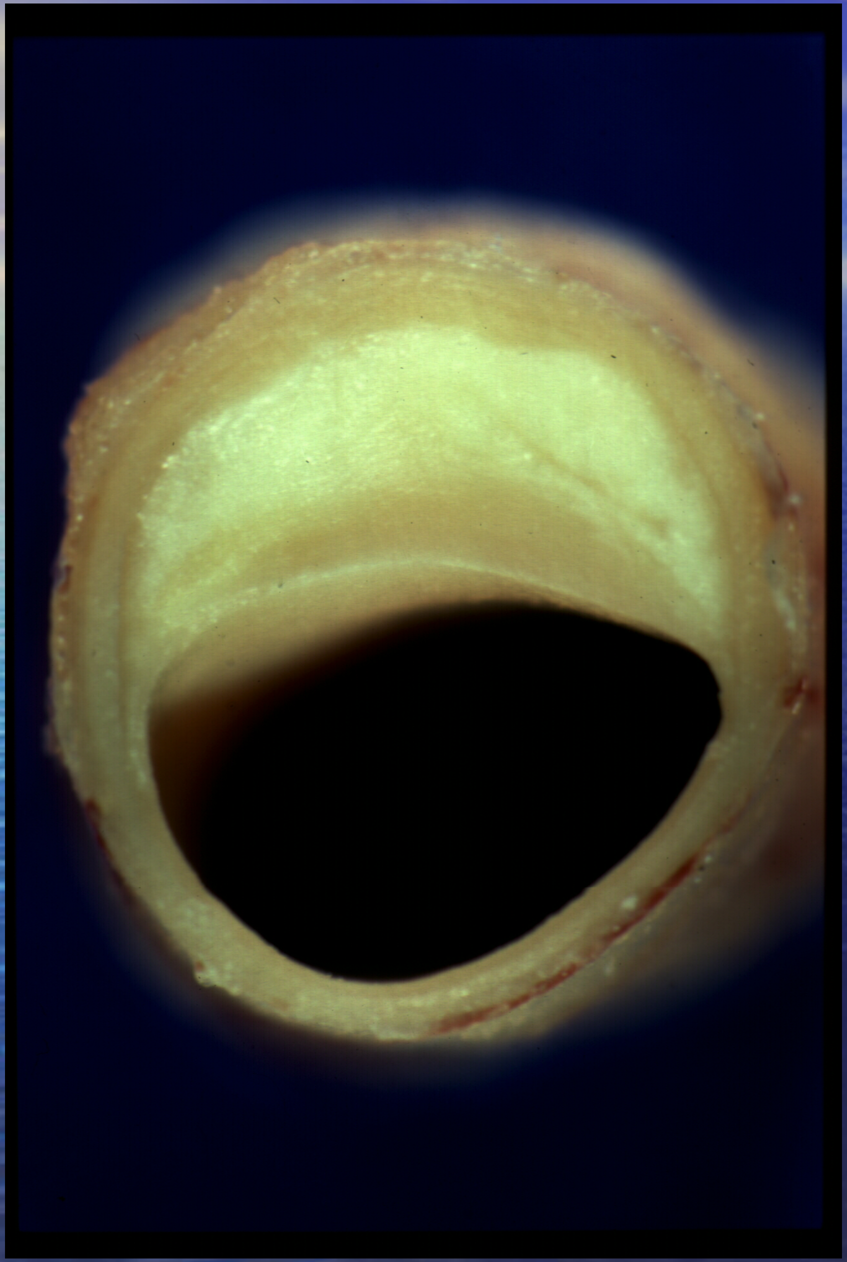
HIGH-RISK LESION (LCA)



24 a, male,
homicide victim

from H.C. Stary

THE NEW CONCEPT

UNSTABLE ATHEROSCLEROTIC PLAQUE

EXTRACELLULAR MATRIX ↓
THIN LESION CAP (< 65 μ)
LIPID RICH CORE
INTRAPLAQUE HEMORRHAGE
DYING (APOPTOTIC) CELLS
INFLAMMATION
OXIDATION
NECROSIS

(< 70% OF ACUTE EVENTS)

Vulnerable plaque imaging

- apoptosis
- thrombogenicity
- lipoprotein accumulation
- inflammation
- proteolysis
- angiogenesis
- extracellular matrix

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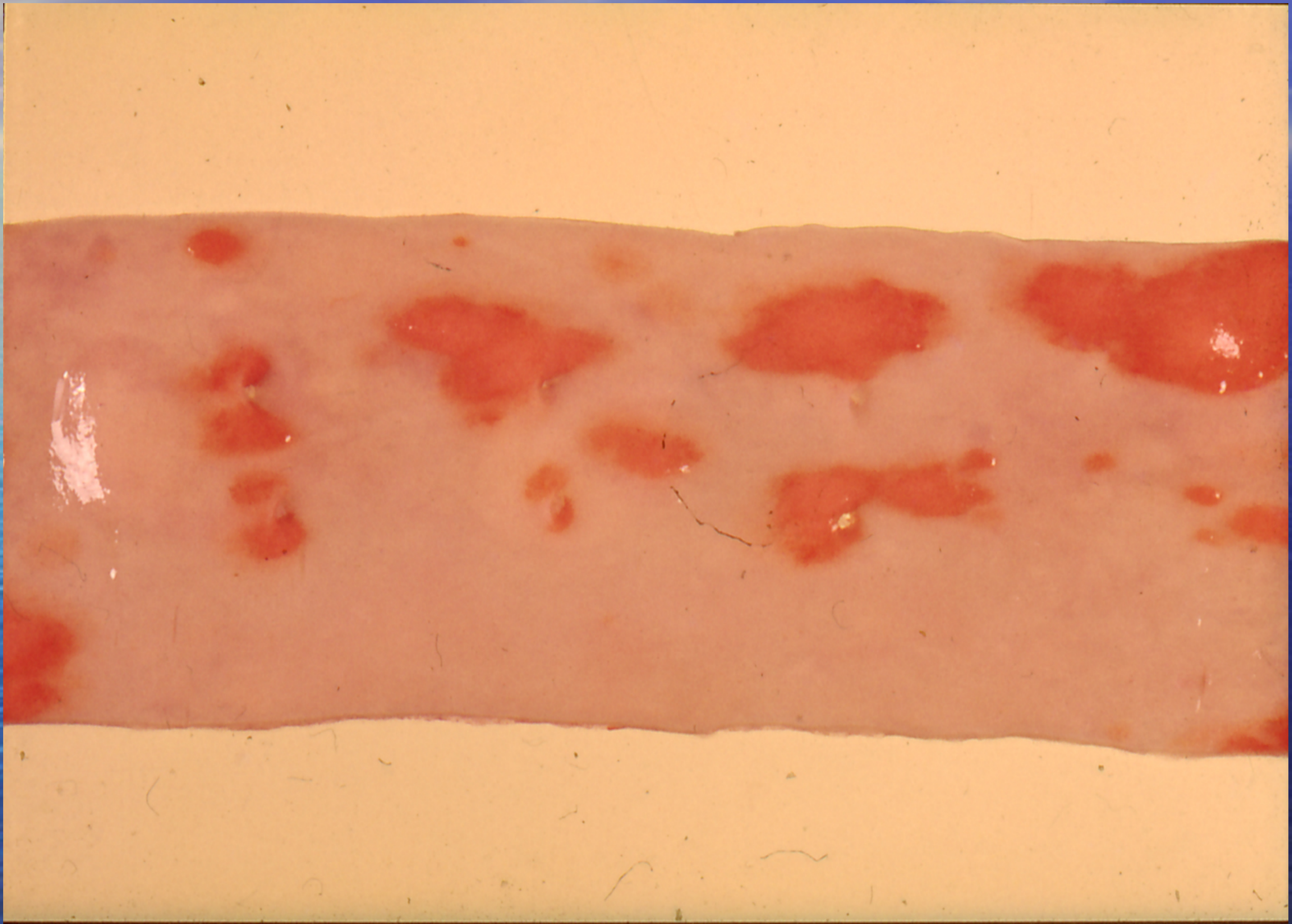
SUDANOPHILIC LESION



ox Lp(a) > oxLDL > LDL > HIG > FDG

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UPTAKE (EXPERIMENTAL)

	FDG	LDL	Lp(a)	HIG
MONONUC.	0.8612	0.8380	0.8544	0.9133
SUDAN III	0.7217	0.8623	0.8914	0.8512
OIL RED D	0.7016	0.8433	0.8563	0.8617

$p < 0.01$ (all); $n = 8$ each (rabbits)

CORRELATION

EXPERIMENTAL+)	
oxLp(a)/SUDAN III	0.9204
oxLDL/SUDAN III	0.8843
LDL/SUDAN III	0.8623
HIG/SUDAN III	0.8245
FDG/SUDAN III	0.7217
FDG/CD 68	0.8510
LDL/CHOL.	0.8931
HIG/CHOL.	0.8377
HUMAN+)	
FDG/OIL RED D	0.5600; < 0.05

x)p < 0.01 if not otherwise; +)n = 8 each; °)Richter et al. 2010

CORRELATION

LIPID DEPOSITION

oxLp(a) > oxLDL > Lp(a) > LDL > HIG > FDG

FOAM CELL CONTENT

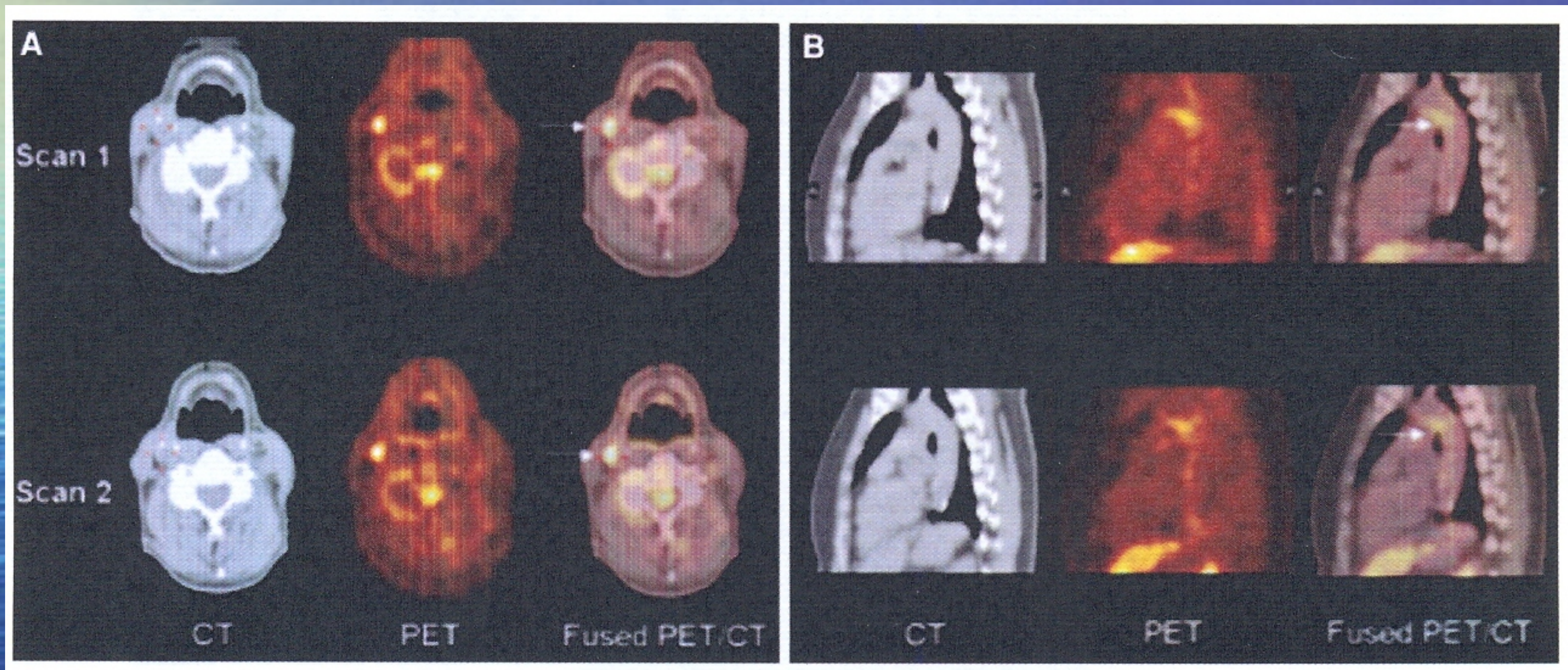
HIG > oxLp(a) > FDG > LDL

EXPERIMENTAL

	LDL	FDG	HIG	PLAT
EXP	Y	Y	Y	Y
EXP-RE	Y	Y	Y	Y
HU-RE	Y	Y	Y	Y
RISK CALC	Y	Y	Y	Y

REPRODUCIBILITY OF 18F-FDG (2 WEEKS APART)

CAROTID AORTIC



REPRODUCIBILITY OF FDG-UPTAKE

2 WEEKS: IDENTICAL (RUDD 2007, 2008)

7 MONTHS: ONLY 50% IDENTICAL (WASSELIUS 2009)

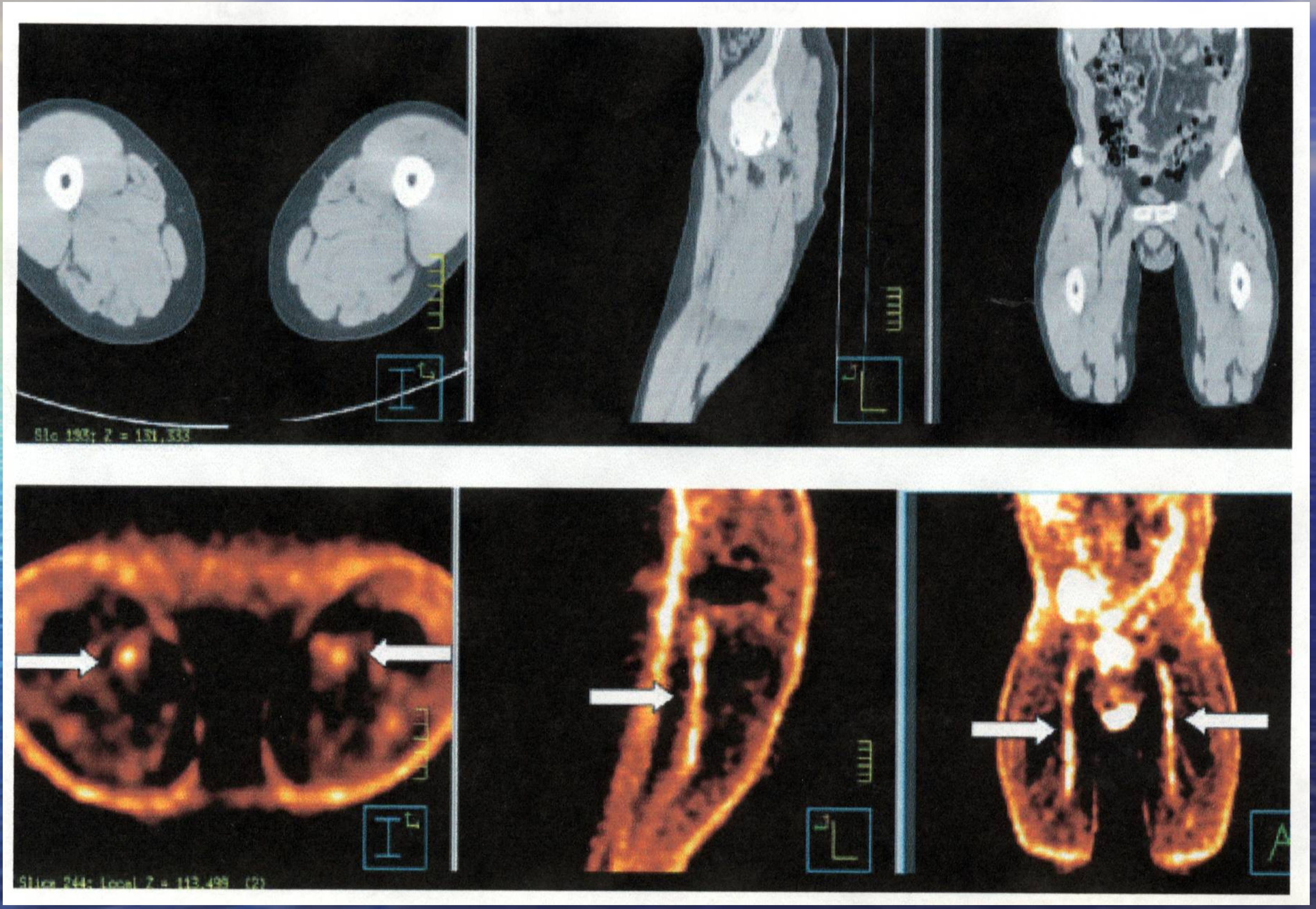
SIGNIFICANT LONG-TERM FLUCTUATIONS (BEN-HAIM 2006)

OPTIMAL (PLATEAU) IMAGING TIME?

WHAT LESION COMPONENTS ARE PROMISING FOR PET-TARGETING

- ALMOST ALL STUDIES RETROSPECTIVE IN CANCER PATIENTS (INFLUENCE OF THERAPY?)
- CONTROLLED, RANDOMIZED, PROSPECTIVE STUDIES SHOWING DIAGNOSTIC VALUE FOR INDIVIDUAL EVENTS AND MORTALITY RATHER THAN MORPHOLOGICAL, RISK AND BIOCHEMICAL ASSOCIATIONS
- NO PROSPECTIVE (VASCULAR) EVENT STUDIES
- NO STANDARDIZED PROTOCOL

FEMORAL ARTERIAL UPTAKE OF ^{18}FDG



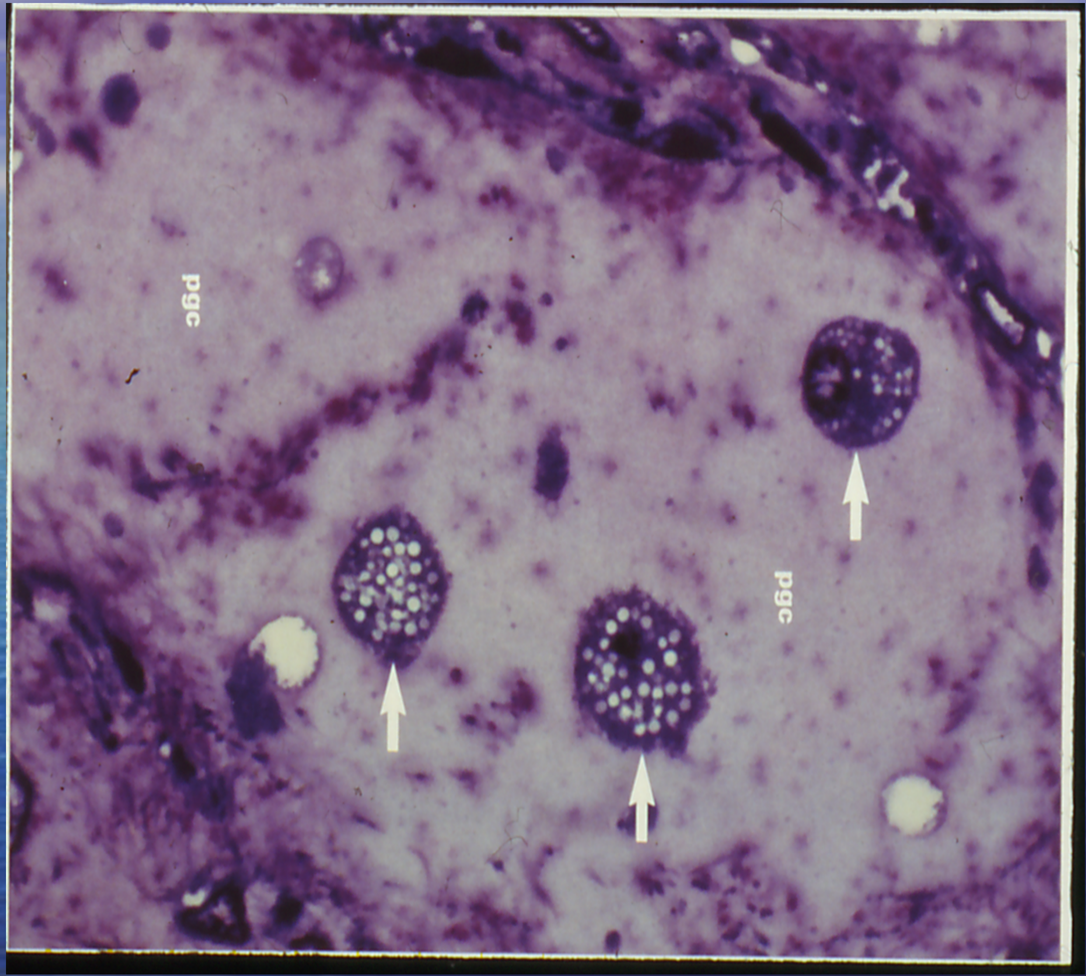
Paulmier et al, 2008

FDG-UPTAKE ↑

29% P (vs 10% Co) CAROTID SONOGRAPHY (TAHARA 2007)

11 (OUT OF 13) WITH 50% ANGIOGRAPH. ICA STENOSIS (ARAUZ 2007)

MONONUCLEAR FOAM CELLS



A ROLE FOR FDG
OR MONOCYTES
OR HIG ?

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ROLE OF MACROPHAGES

^{68}Ga UPTAKE (MICE) HIGHER IN LESIONS, CORRELATES TO MACROPHAGES (n)

SLOW CLEARANCE WILL LIMIT USABILITY

SILVOLA et al., EJNM 14 (2011)

^{18}F-FDG (MICE) CORRELATES TO MAGROPHAGE DENSITY

SILVOLA et al., JACC 1294 (2011)

DIRECT EVIDENCE OF ^{18}F-FDG UPTAKE STILL LACKING

COCKER (2012)

^{18}F-FDG UPTAKE

DAVIS 2005 (ONLY) 25% OF NON-STENOTIC LESIONS IMAGED BY FDG
↑ BY FOAM CELL FORMATION, BUT
⊥ AT DIFFERENTIATION TO FOAM CELLS

OGAWA et al., JNM 53 (2012) 55 ff

KIM 2010: FDG-UPTAKE CORRELATES WITH FRAMINGHAM SCORE
RUDD 2002: SYMPTOMATIC LESIONS > FDG vs. ASYMPT. ^{11}C-ACETATE
COLOCALIZED WITH ARTERIAL CALCIFICATION;
ONLY 13.3% OF CALCIUM → INCREASED UPTAKE

DEVLIN et al., JNM 52 (2011) 1848 ff

MONO vs SMC-OXYGEN CONSUMPTION (3:1)
HOW TO DIFFERENTIATE

BJÖRNHEDEN, ART 7 (1987) 238 ff

VASCULAR CORRELATION OF FDG-UPTAKE

YES

- MACROPHAGES (n) (OGAWA 2004)
- MAGROPHAGE DENSITY (VALLABHAJOSULA 1996)
- I/M-RATIO (LEDERMAN 2001)
- NEOVASCULARIZATION IN PLASMA (CALCAGNO 2008)
- CALCIFICATIONS (LAITINEN 2006)
- PATIENT'S AGE (YUN 2002)
- HYPERCHOLESTEROLEMIA (YUN 2002)
- TNF

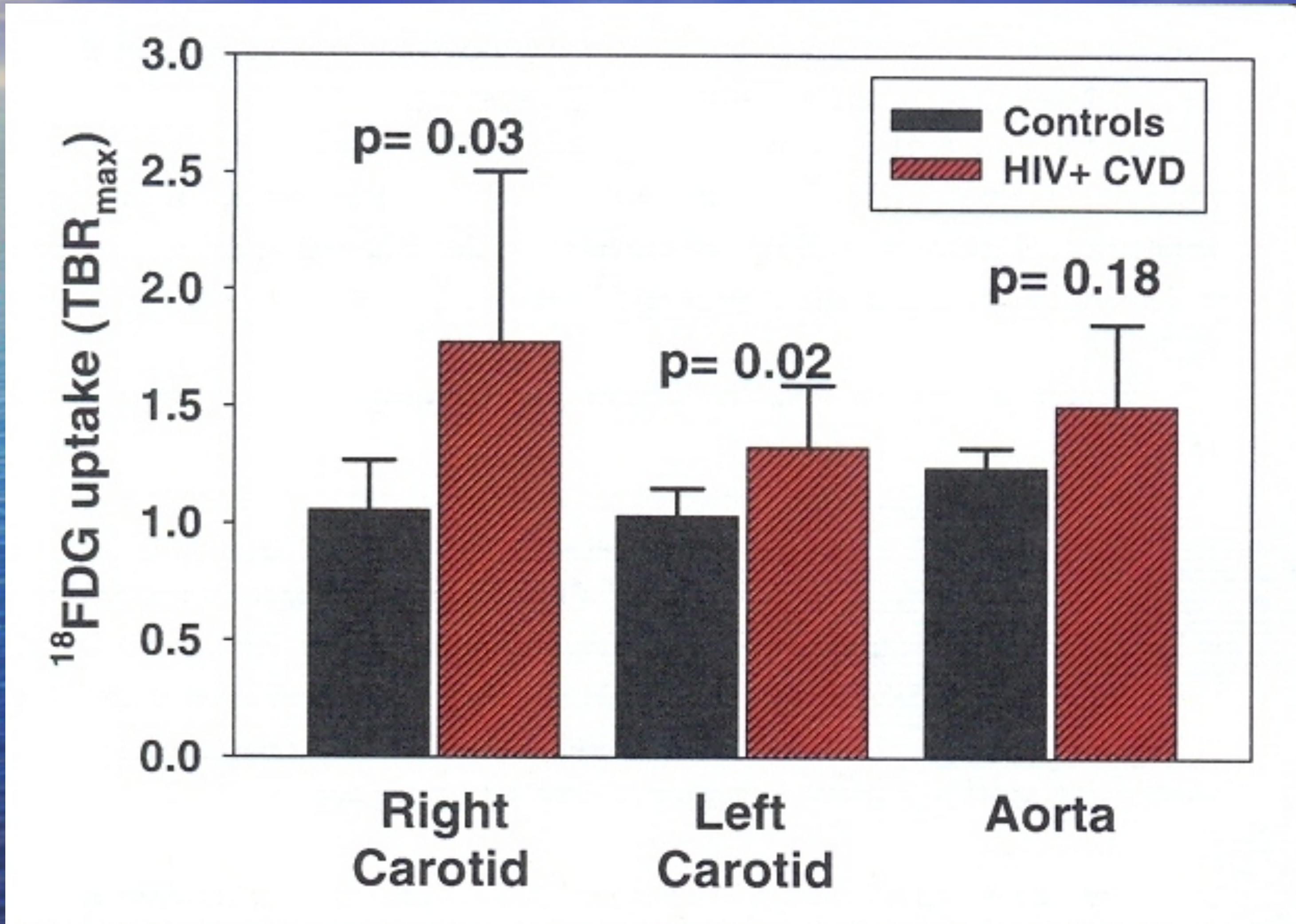
NO

- SMC (TAWAKOL 2005)
- AORTIC WALL THICKNESS (TAWAKOL 2005)
- PLAQUE AREA (TAWAKOL 2006)
- I/M-RATIO (OGAWA 2004)
- PLAQUE THICKNESS (TAWAKOL 2006)
- AMOUNT OF COLLAGEN (TAWAKOL 2006)
- CALCIFICATIONS (TATSUMI 2003)

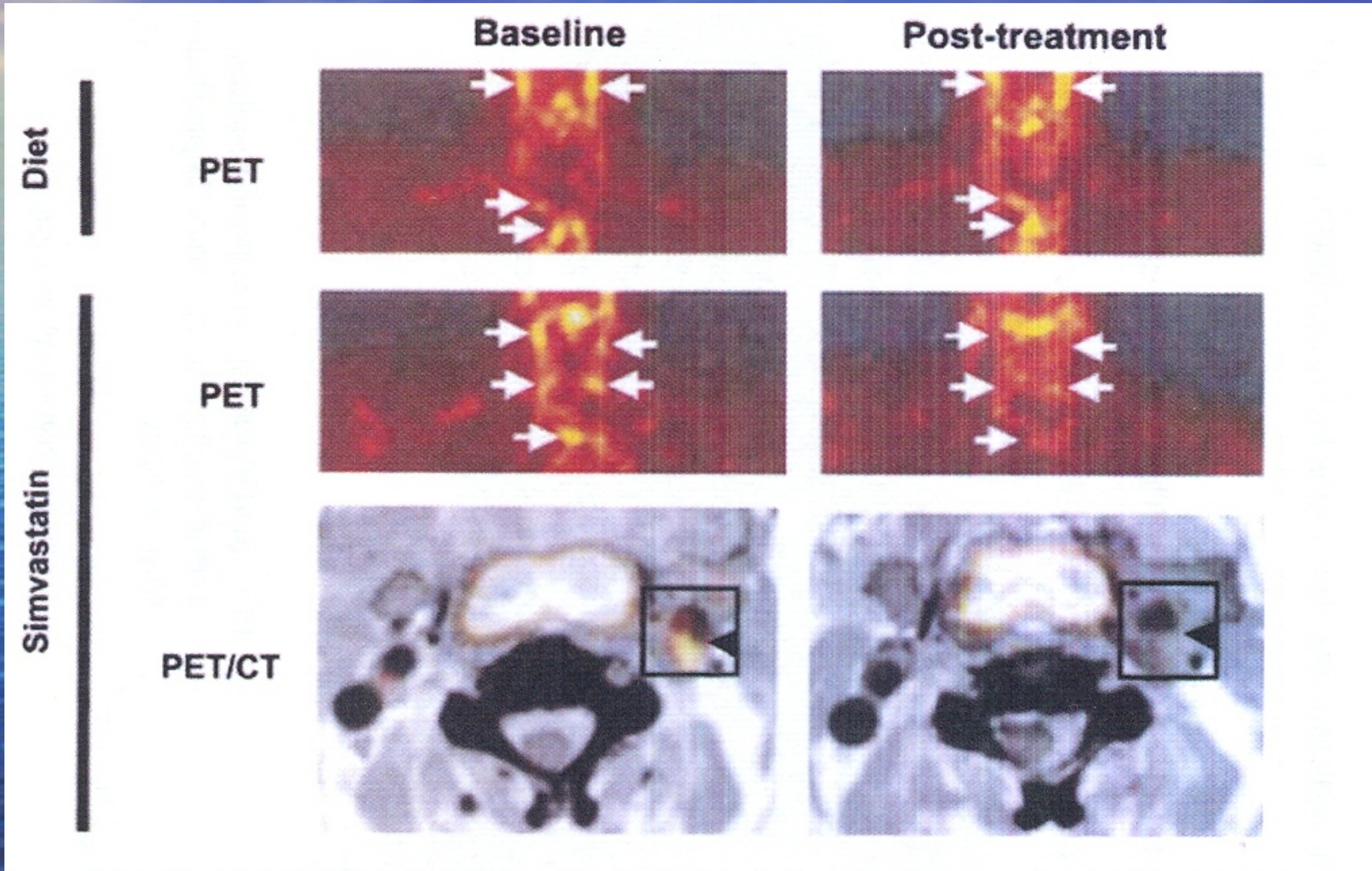
FDG-UPTAKE – CLINICAL CORRELATIONS

- COMPONENTS OF METABOLIC SYNDROME (WASSELIUS 2009)
- BMI, WC, I/M-CAROTID, CRP, HYPERTENSION (TAHARA 2007)
- VASCULAR CALCIFICATION (DUNPHY 2005)
- MMP-1 (WU 2007)
- HISTORY OF CVD (WILLIAMS 2009)
- PATIENTS WITH EVENTS (ROMINGER 2009)
- HDL (TAHARA 2006)
- FRAMINGHAM RISK SCORE (KIM 2010)
- SUV INCREASES WITH AGE

18F-FDG CAROTID UPTAKE (HIV VS. Co)



THERAPEUTIC INTERVENTION



FDG-UPTAKE AND THERAPEUTIC INTERVENTION

↓ PROBUCOL (OGAWA 2006)

↓ STATINS (S-TAHARA 2006, S-WASSELIUS 2009, A-ISHII 2010, A-WU 2012) > 12 wk

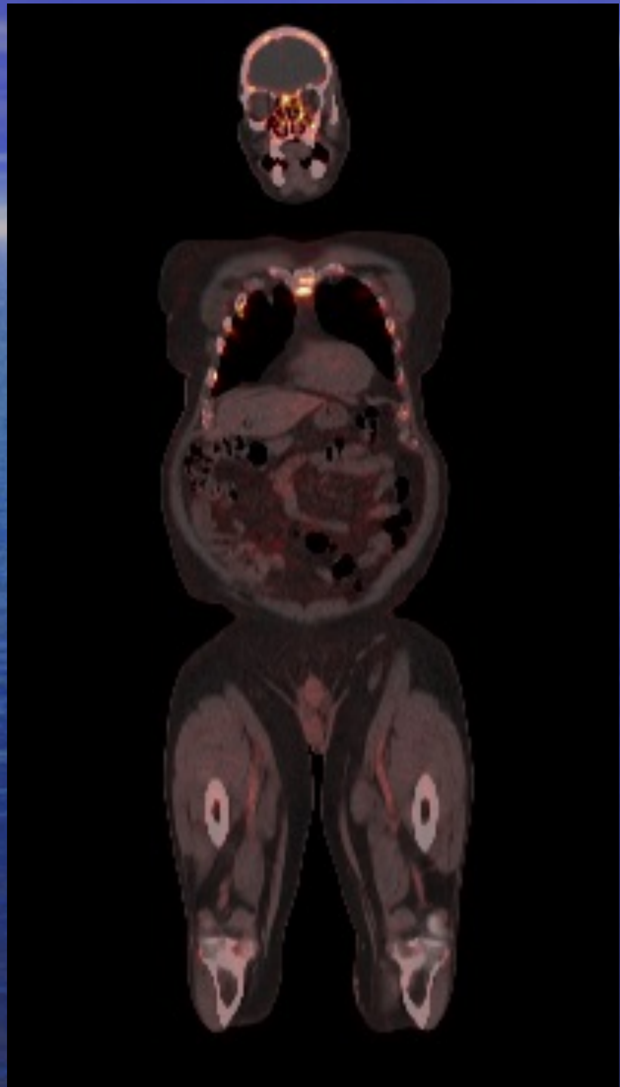
- HCy (POTTER 2009)

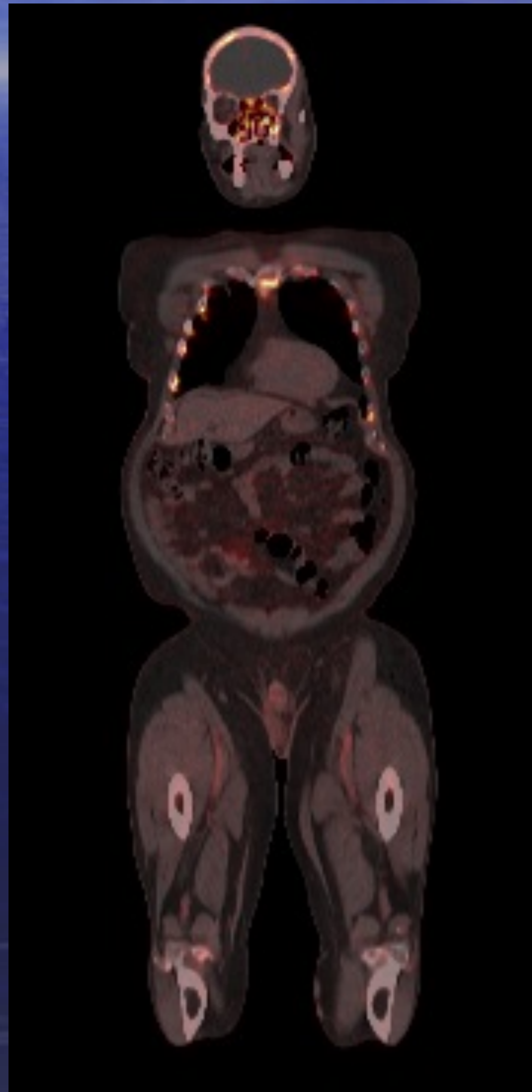
↓ LIFESTYLE (LEE 2008) – 16 mo

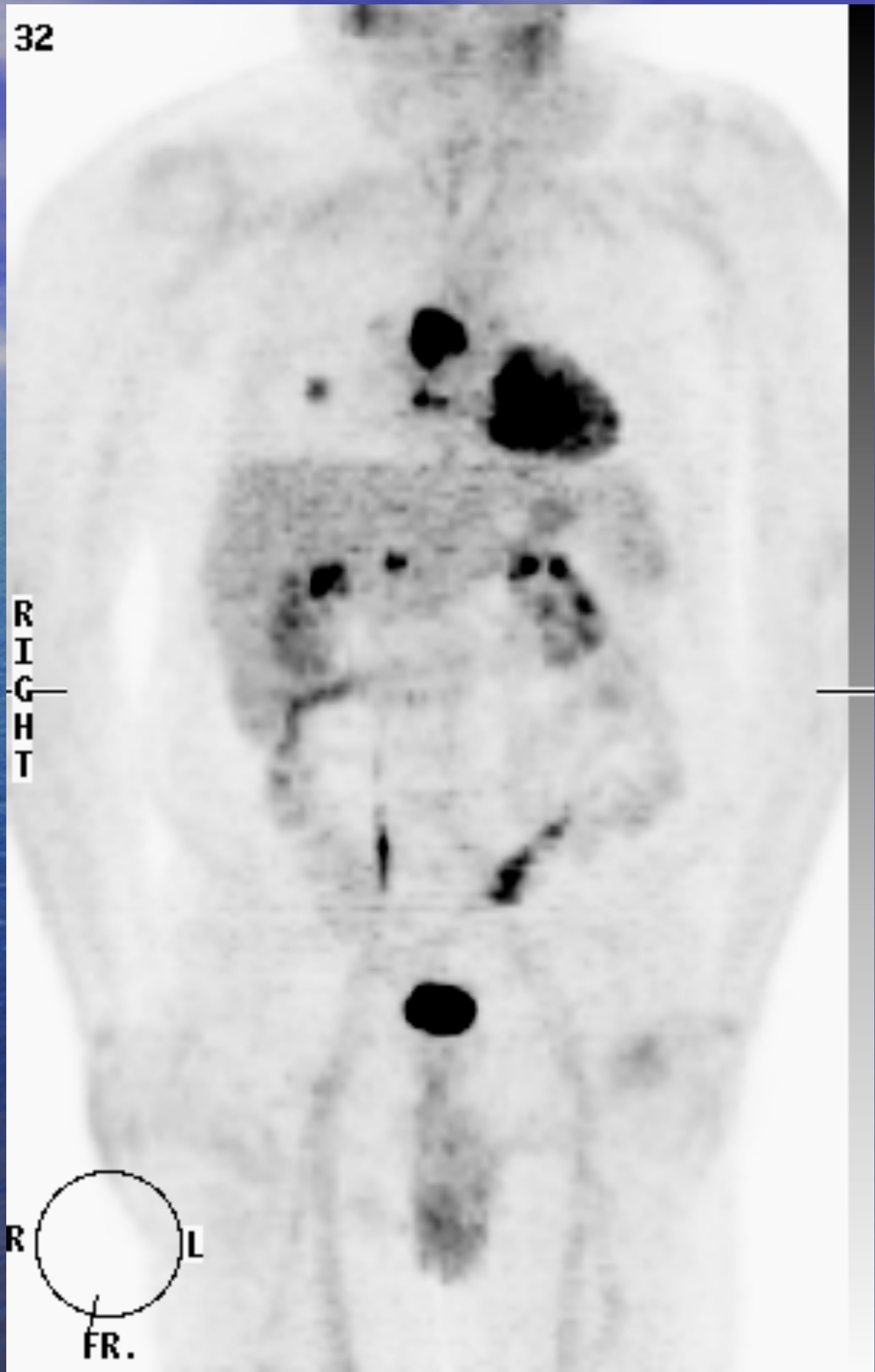
↓ DALCETRAPIB (FAYAD 2011)

↓ PIOGLITAZONE (VUCIC 2011)

- GLIMEPIRIDE (MIZOGUCHI 2011)



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FDG-PET CT STUDY

ADVANTAGES OVER OTHER METABOLIC STUDIES:

- HIGH CONTRAST RESOLUTION
- QUANT. OF PLAQUE VOLUME
- (ASSESS. METABOL. ACTIVITY?)
- DYNAMIC, REAL TIME, IN-VIVO IMAGING
- MINIMAL OPERATOR DEPENDENCE

CORONARY ARTERY ^{18}F-NaF

HIGHER IN CORONARY ATHEROSCLEROSIS vs CO

- CALCIUM SCORE ($r = 0.652$, $p < 0.001$)
- CORRELATES WITH EVENTS ($p = 0.016$)
- FRAMINGHAM SCORE ($p = 0.011$)

CORONARY ARTERY ^{18}F-FDG

- HAMPERED BY MYOCARDIAL ACTIVITY
- NO DIFFERENCE ATHEROSCLEROSIS vs CO

DWECK et al., JACC 59 (2012) 1539 ff

IMAGING METALLOPROTEINASE (MMP) ACTIVITY

^{111}In-DTPA-RP 782

^{99m}Tc-HYNIC-RP 805

MARIMASTAT-ArB(^{18}F)F3

^{123}I-Ho-CGS 27023A

IN EXPERIMENTAL MODELS ONLY

rev. in N. MATUSIAK et al., Curr. Pharm. Des. (2013)

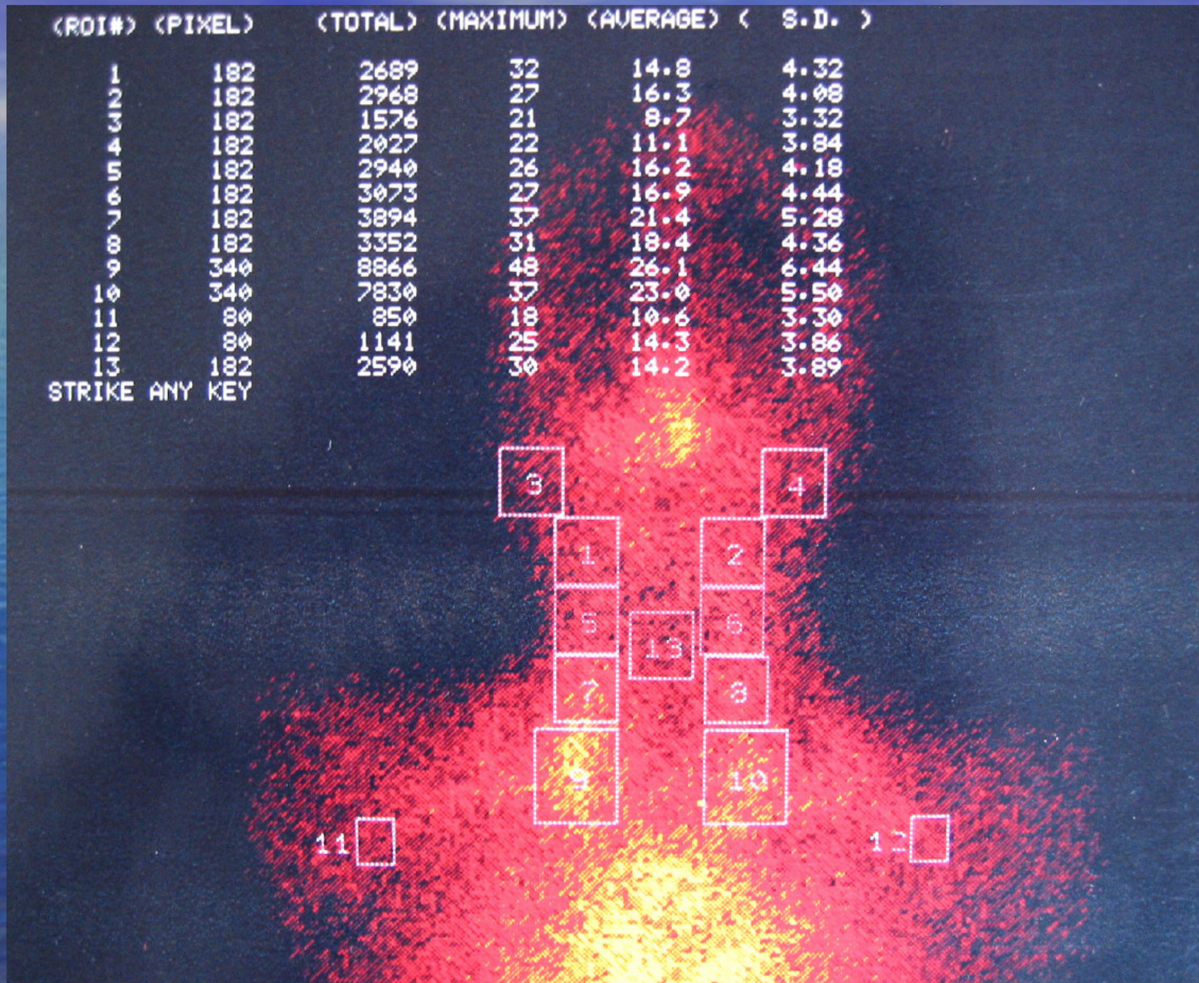
PET/CT TRACERS USED FOR ATHEROSCLEROTIC PLAQUE CHARACTERIZATION

PET radiotracer	Mechanism of action	Uptake suggestive of	Arteries evaluated	Validation in human atherosclerotic plaque
[^{18}F]fluorodeoxyglucose (FDG)[60]	Uptake by metabolically active cells	Macrophage density	Carotid, aorta, coronary, iliac, femoral	Immunohistochemistry and autoradiography
^{11}C-PK11195[97-99]	Selective ligand of the translocator protein (TSPO, 18 kDa), formerly known as peripheral benzodiazepine receptor	Macrophage density	Carotid, aorta (vasculitis)	Immunohistochemistry and autoradiography
^{11}C-choline[101]	Choline enters the cell via specific transport mechanisms, is phosphorylated by choline kinase, metabolized to phosphatidylcholine is incorporated into the cell membrane	Macrophage density, inflammatory infiltrates	Carotid, aorta	No
^{68}Ga-[1,4,7,10-tetraazacyclododecane-*N,N′,N″,N9‴*-tetraaceticacid]-D-Phe1, Tyr3-octreotate (DOTATATE)[100]	Binds to somatostatin receptors of subtype 2 (SSTR2)	Macrophage density	Coronary	No
^{11}C-Acetate[116,]	Fatty acid synthesis in lesions requires acetyl-coenzyme-A, which is produced from acetate	Fatty acid synthesis	Carotid, aorta, iliac	No
[^{18}F]Sodium fluoride[117-119]	Binds to hydroxyapatite molecules by replacing hydroxyl groups	Calcification	Carotid, aorta, iliac, femoral, coronary	No

OTHER PET-TRACERS USED

- ^{11}C-ACETATE – FATTY ACID SYNTHESIS
- ^{68}Ga-MACROPHAGES (CLEARANCE PROBLEM)
- ^{18}F-SODIUM FLUORIDE
- ^{18}F-NaF
- ^{18}F-GALAKTO-RGD
- ^{64}Cu-ANTI-OX-LDL
- ^{18}F-FLUORO-ETHYLCHOLINE

^{111}In-HIG SCINTIGRAPHY



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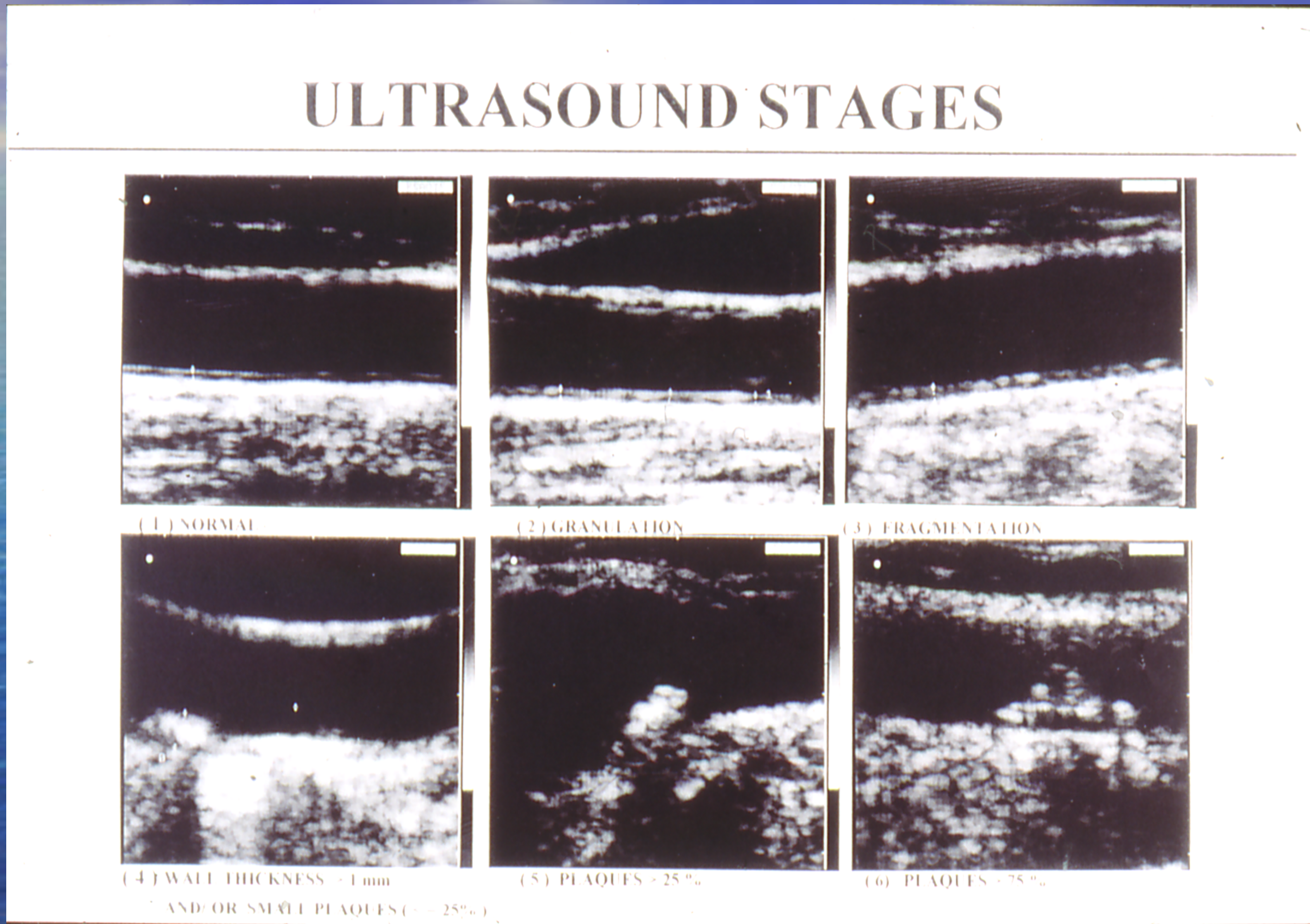
ULTRASOUND STAGES
(1) NORMAL
(2) GRANULATION
(3) FRAGMENTATION
(4) WALL THICKNESS 1 mm
AND/OR SMALL PLAQUES
(5) PLAQUES > 25 %
(6) PLAQUES 75 %

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^{111}In-HIG AND ^{18}F-FDG COLOCALIZE

ACCUMULATE IN

- FOAM CELLS
- LIPID RICH AREAS
- INFLAMMATORY ACTIVE SITES
- HEALING EDGES OF LESIONS
- NOT IN DEENDOTHELIALIZED AREAS

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CORRELATION vs. DIAGNOSIS

^{125}I-LDL – ^{111}IN-MONOCYTES AND ^{18}F-FDG COLOCALIZE

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^{111}In-HIG - SCINTIGRAPHY

Patients characteristics

	n	+	-	m	f	age	CHD (%)	MORTALITY	SEX DISTR.
CVD	100	61	39	61	39	60,6±7,5	62	24 vs 7 **(39,3 vs 17,9%)**	16m/8f vs 4/3
PVD	100	69	31	75	25	64,6±6,9	75	29 vs 5 **(42,0 vs 16,1%)**	20m/9f vs 3/2

NO CORRELATION TO SONOGRAPHY, BUT

PREDICTOR OF EVENTS

(LESIONS vs. INFLAMMATORY PROCESS)

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^{111}IN-HIG vs ^{18}F-FDG

- FDG PREDICTS VASCULAR EVENTS INDEPENDENT OF RISK FACTORS
- ASSOCIATED WITH VASCULAR DISEASE BURDEN
- ARTERIAL SUV vs VENOUS BLOOD-POOL BACKGROUND

MONOCYTE UPTAKE RATIO

^{111}In-MONOCYTES AND ATHEROSCLEROSIS INDEPENDENTLY DESCRIBED1984 BY DU HEYNS AND SINZINGER 1990. NORMOLIPEMICS ALL NORMAL UPTAKE:

LDL-APHERESIS: 1,35±0,07 → 1,19±0,08

NO DIFFERENCE SMOKERS VS. NON-SMOKERS

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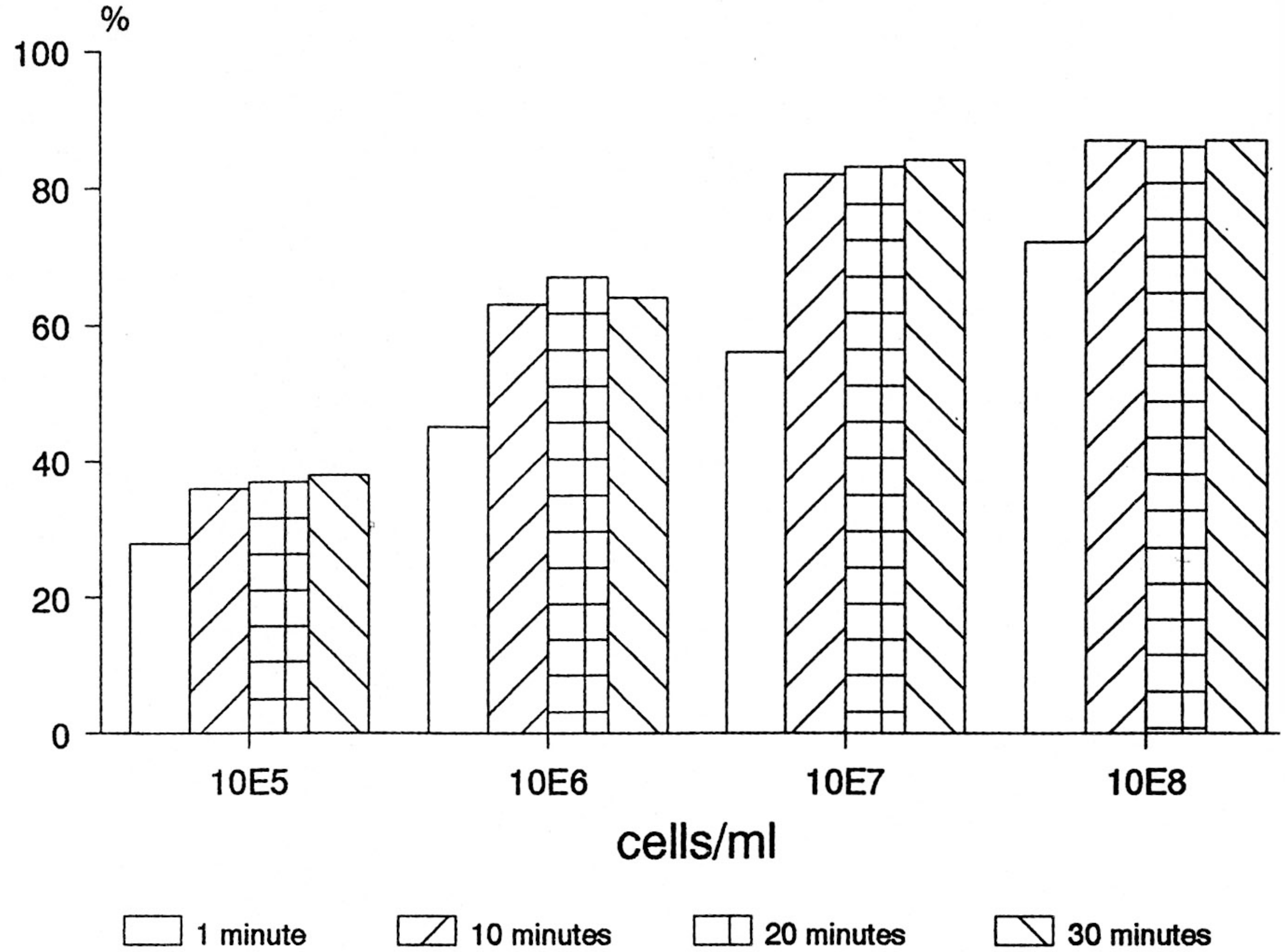
ISORBE and Radiol. Blood El. 1992

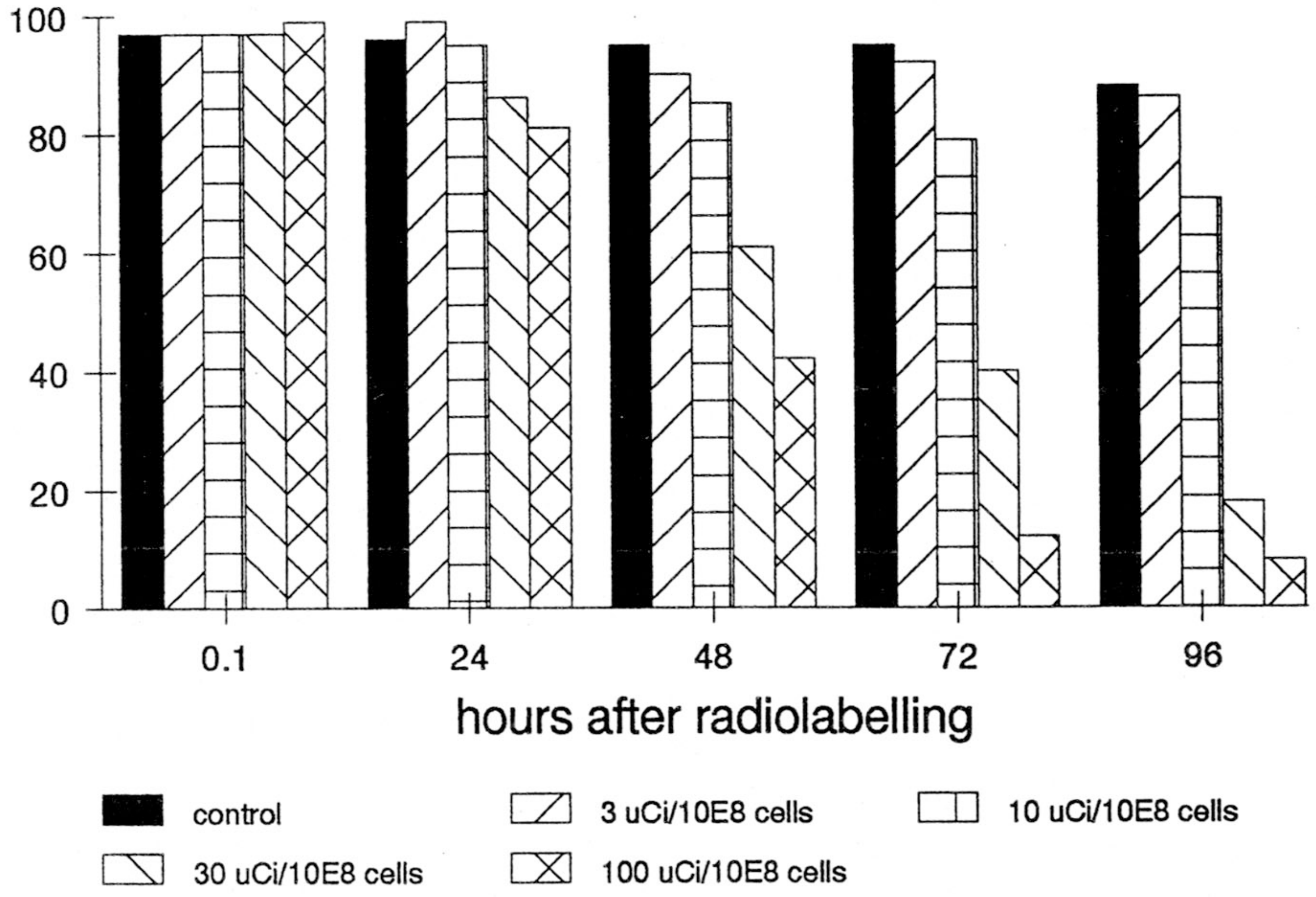
LE VS. MONOCYTE DENSITY



Labelling efficiency determined at different time intervals after labelling at 22°C.

Sinzinger et al 1990

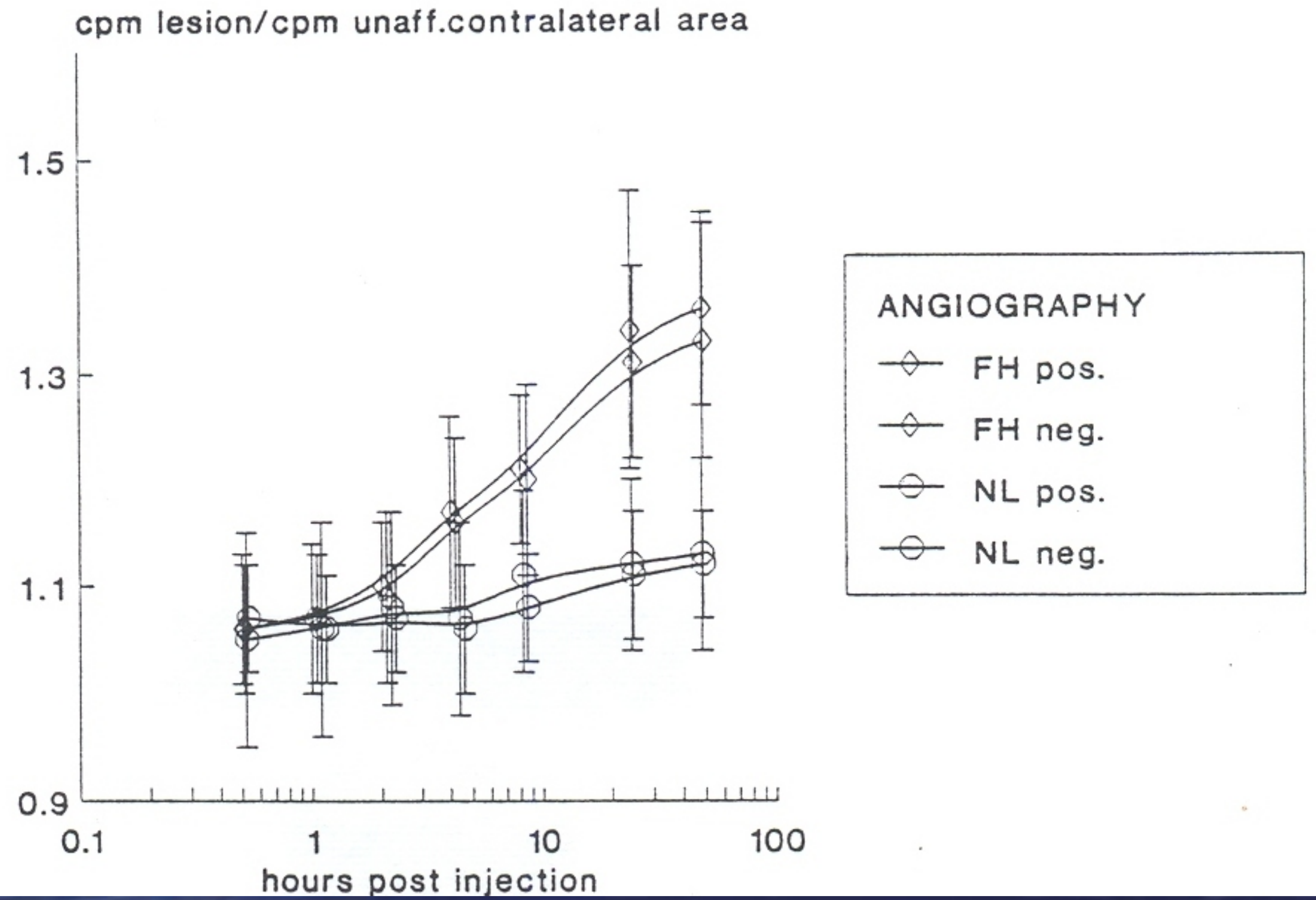
VIABILITY OF RADIOLABELED MONOCYTES



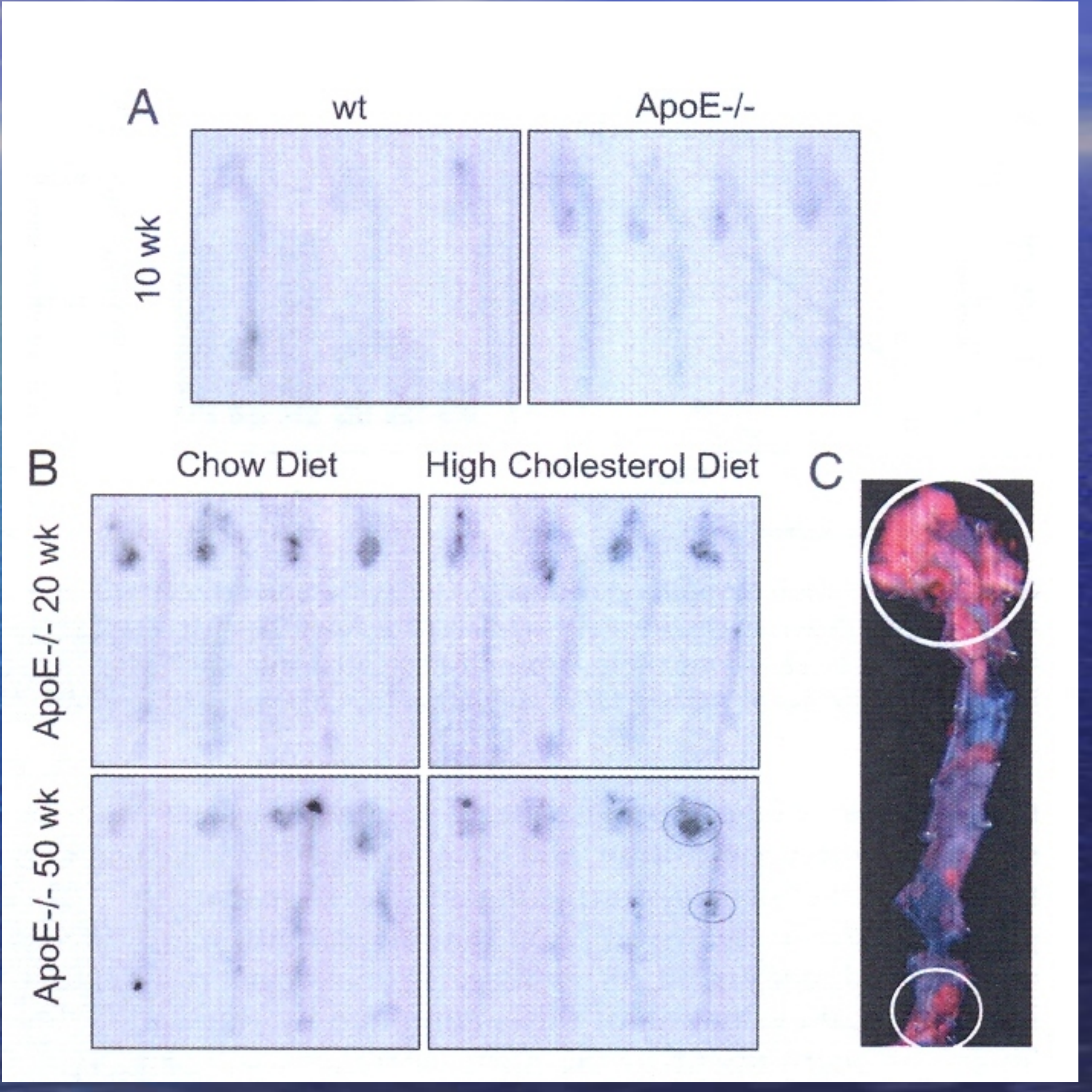
Monocyte viability testet at various intervals after labelling with ^{111}In-oxine.

Sinzinger et al 1990

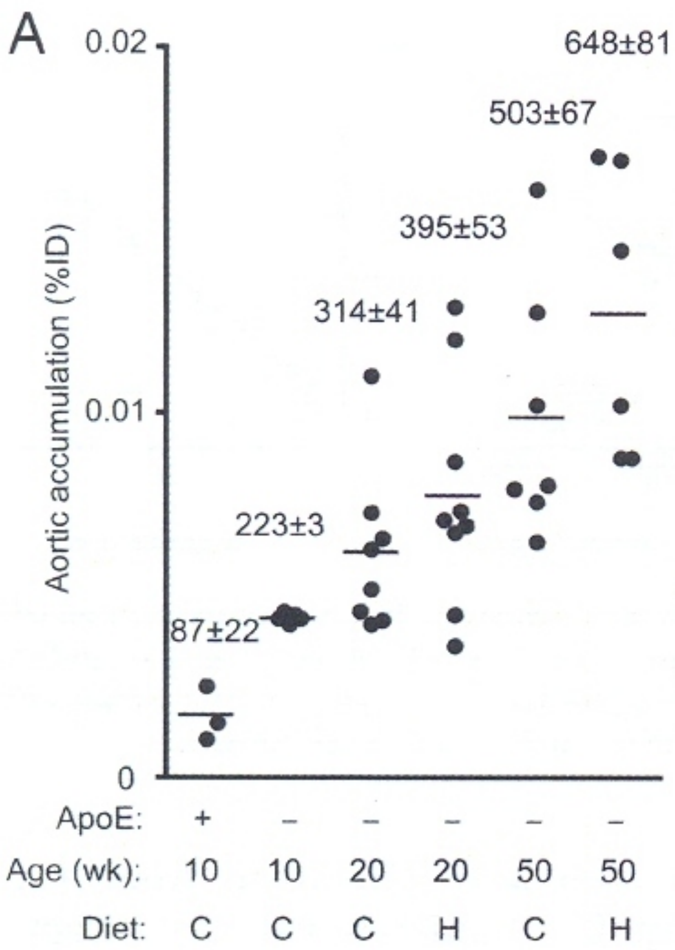
VASCULAR MONOCYTE UPTAKE



^{111}In-oxine MONOCYTES IN MICE



^{111}In-oxine MONOCYTES IN MICE



B

	+ 10 C	– 10 C	– 20 C	– 20 H	– 50 C
– 10 C	>0.05				
– 20 C	>0.05	>0.05			
– 20 H	<0.05	>0.05	>0.05		
– 50 C	<0.01	<0.05	>0.05	>0.05	
– 50 H	<0.001	<0.001	<0.01	<0.05	>0.05

VALUE OF ^{18}F-FDG

n = 15; 64 – 76 a, MALES
NO SINGLE ↑ FDG-UPTAKE
CALCIFICATIONS 14
> 50% LESIONS IN 6 PATIENTS (TOTAL 9)
(SONOGRAPHY) – ONLY 5 VISIBLE

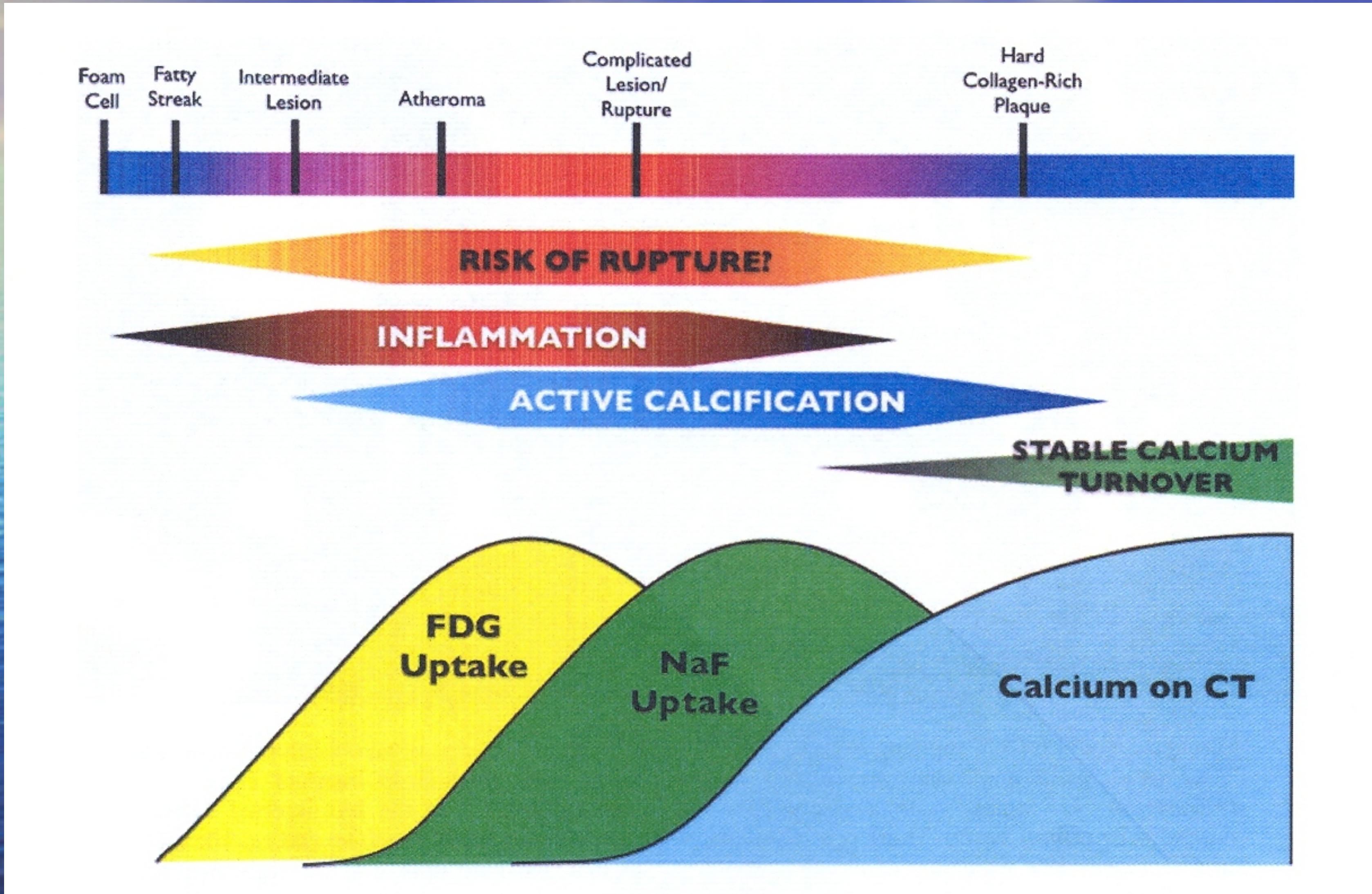
REF: CT DEFINED PLAQUES – NO HIGHER FDG-UPTAKE
MRI DEFINED vs NON-AFFECTED CONTRALATERAL SITE
NO DIFFERENCE

OKANE et al. 2006

^{18}F-FDG – PROSPECTIVE STUDIES IN ATHEROSCLEROSIS

Reference	No. of patients	Circulation time (min)	PET scan type	Method of image analysis
Sakalihasan et al. (*14*)	26	60	PET only	Visual
Rudd et al. (*1*)	8	180	PET only	Net ^{18}F-FDG accumulation rate
Davies et al. (*15*)	12	120	PET only	Uptake ratio > 1.28
Tawakol et al. (*2*)	17	180	PET only	TBR
Okane et al. (*16*)	15	103–158	PET only	TBR
Tahara et al. (*7*)	43	60	PET only	SUV_{max}
Wu et al. (*12*)	47	45 and 150	PET/CT	$SUV_{max} > 2.0$
Lee et al. (*9*)	60	45	PET/CT	Uptake ratio > 1
Arauz et al. (*17*)	13	90	PET only	Visual, $SUV_{max} \geq 2.7$
Rudd et al. (*5*)	11	90	PET/CT	TBR
Tahara et al. (*18*)	216	60	PET only	SUV score
Tahara et al. (*13*)	100	60	PET only	SUV score ≥ 1.60
Kuehl et al. (*19*)	33	60	PET/CT	$SUV_{max} > 2.5$
Paulmier et al. (*20*)	45	60	PET/CT	SUV_{max}
Rudd et al. (*8*)	20	90	PET/CT	TBR
Reeps et al. (*4*)	15	90	PET/CT	SUV_{max}

UNAPPROPRIATE SIMPLIFICATION



WHAT WE NEED

- **A TRACER SPECIFICALLY TAKEN UP BY ONE KEY COMPONENT OF THE VULNERABLE PLAQUE**
- CONCLUSIVE EVIDENCE RATHER THAN MERE CORRELATIONS
- LESION AT RISK, NOT PATIENT AT RISK

MY CLAIM:

FDG WILL NOT SUCCEED IN THIS INDICATION

COMPETING VASCULAR IMAGING MODALITIES

	resolution	sensitivity (vuln.)	limitation	availability
IVUS	100μ	100 (37) %	resolution	+++
Angioscopy	n.a.	100 (25) %	blood free subjectivity	+-
Opt. coherence tom. (OCT)	5μ (!)	90 (75) %	blood free	-
Thermography	500μ	45 (20) %	injury risk	-
Spectroscopy	n.a.	90 (60) %	no structural information	-
Spiral CT	> 500μ	65 (15) %	-	+++
MRI	n.a.	65 (20) %	-	+++
Intravasc. MRI	n.a.	n.a.	Motion, flow, artefacts	+-
Electron beam CT	100μ	calc. 94%, noncalc. 53% vuln. 10%	limited to Ca^{++}	+-

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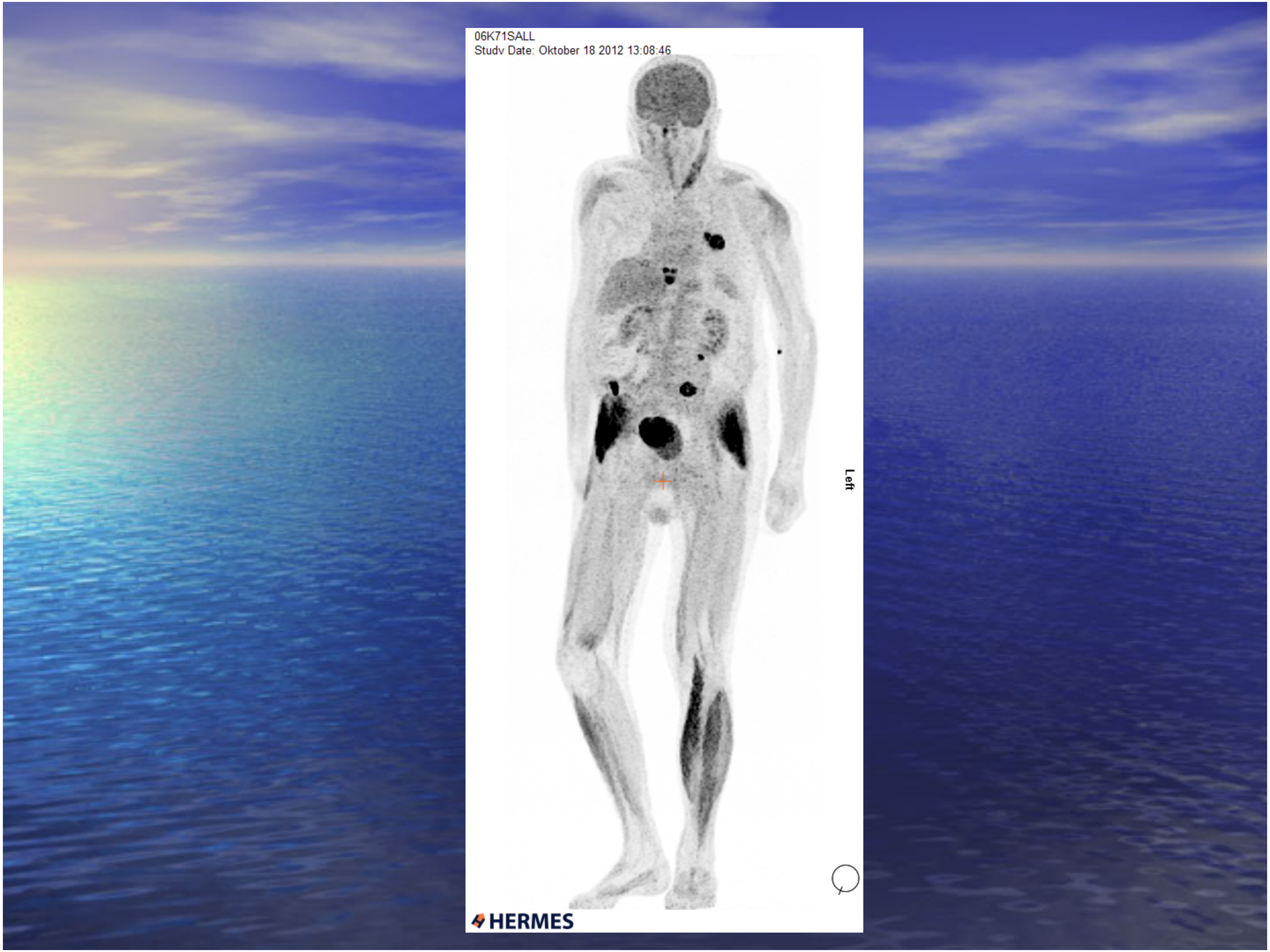
06K71SALL
Study Date: Oktober 18 2012 13:08:46
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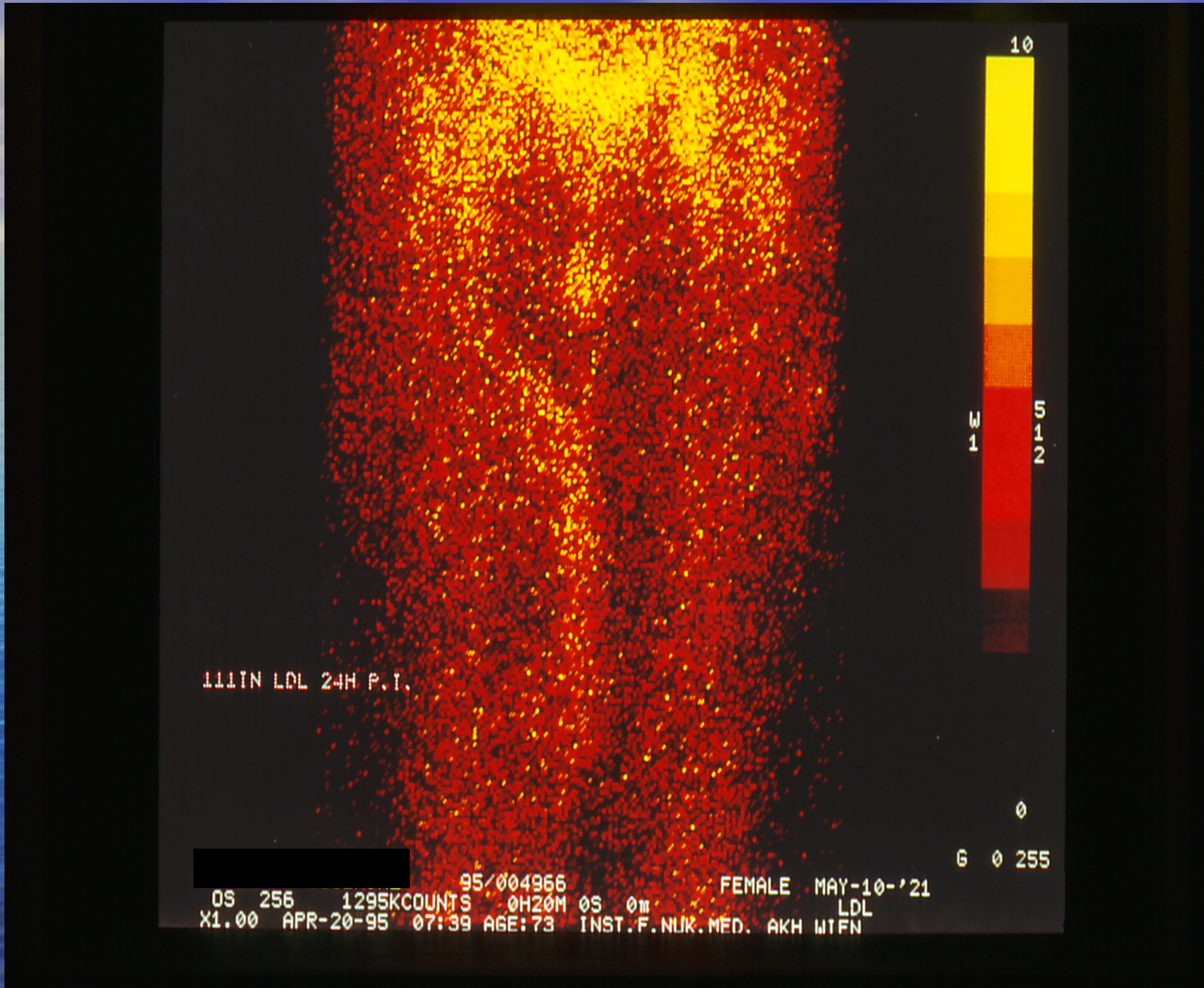
HERMES


Thanks for your attention !



111IN LDL 24H P.I.
10
W 1
512
0
G 0 255
[redacted] 95/004966 FEMALE MAY-10-'21
OS 256 1295KCOUNTS 0H20M 0S 0m LDL
X1.00 APR-20-95 07:39 AGE:73 INST.F.NUK.MED. AKH WIEN

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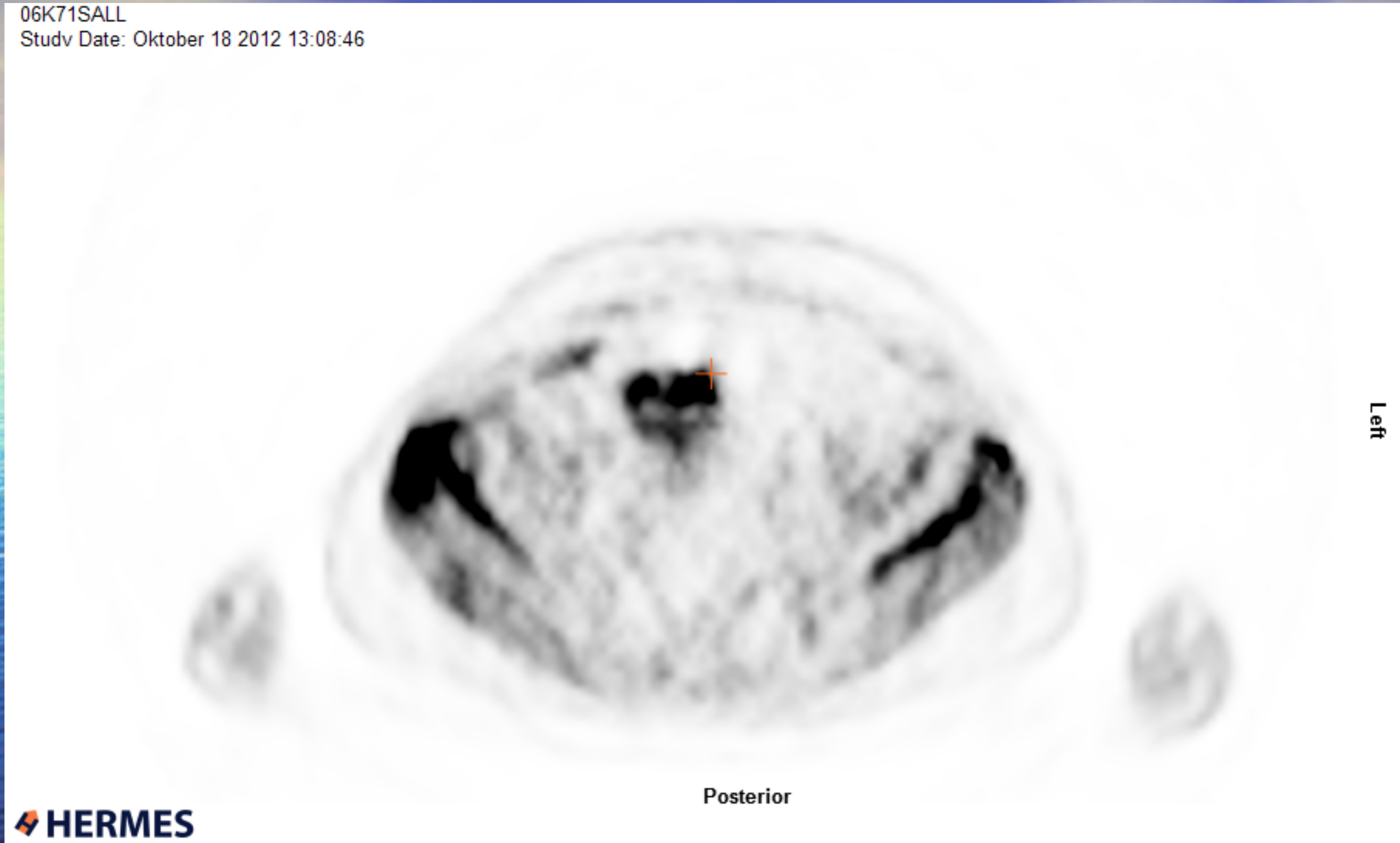
PET-IMAGING

^{64}Cu-ANTI-OX-LDL (MONKEY)

KAMATH et al. (2012)

NO BENEFIT vs. ⊥

VARIOUS ANTIBODIES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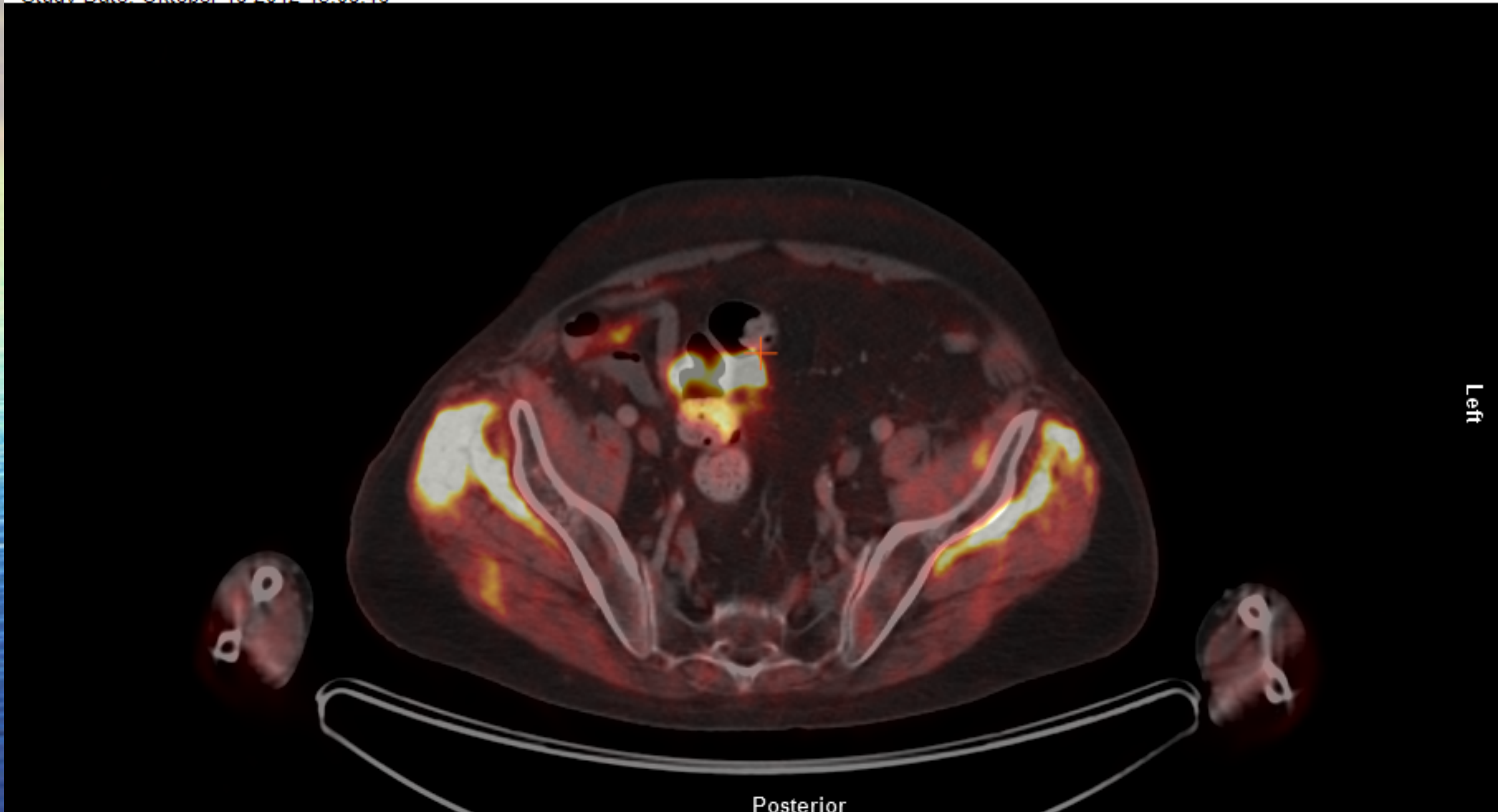

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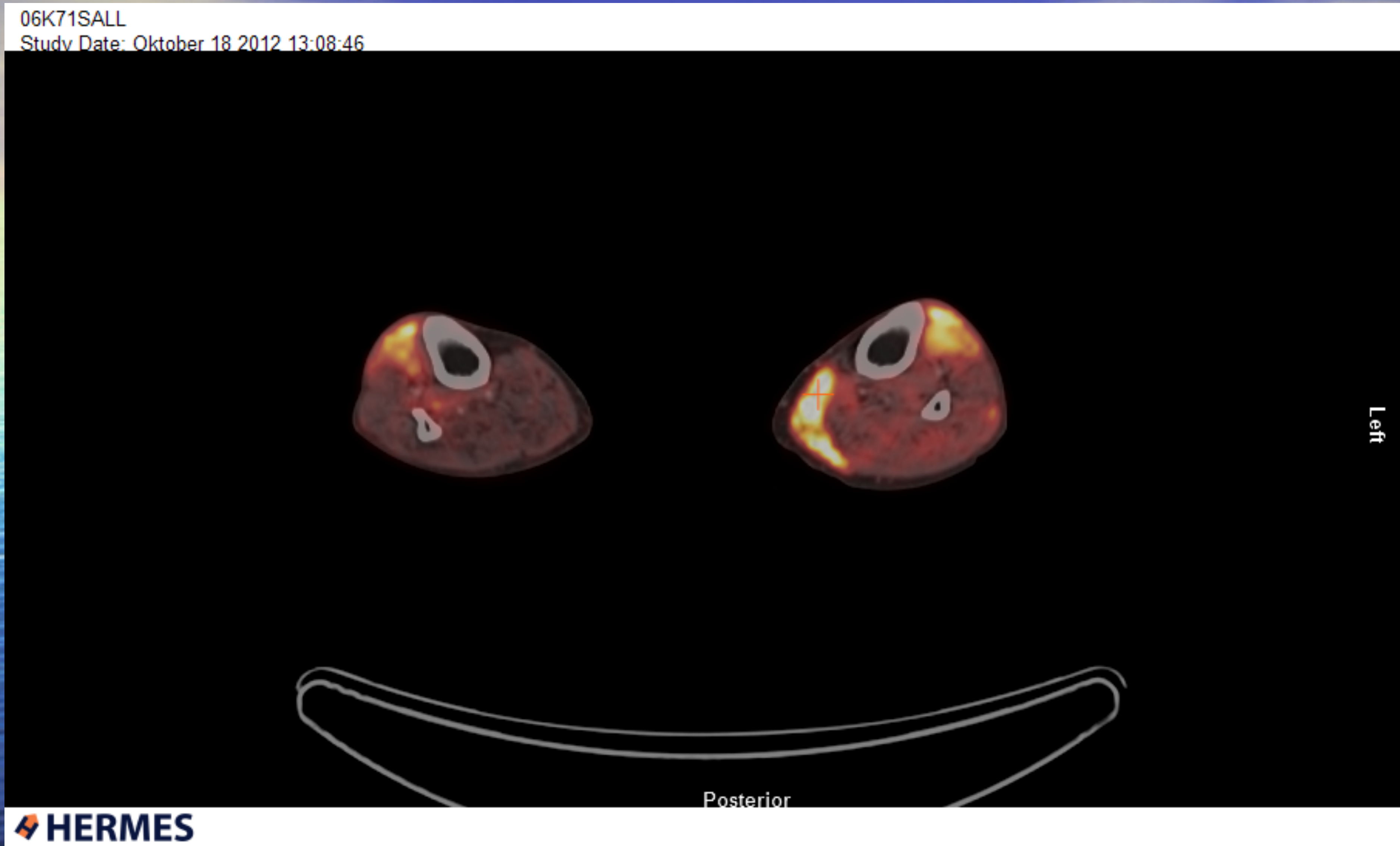
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