


Deutsche Gesellschaft für Nuklearmedizin e.V.

SUMMER SCHOOL
2016
August 25-27, 2016 - Oberwolfach

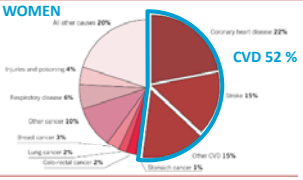
**Molecular Imaging in
Preclinical Cardiovascular Research**

Lisa Honold
European Institute for Molecular Imaging, Münster



Models Imaging Visualization Perfusion Viability Inflammation Translation


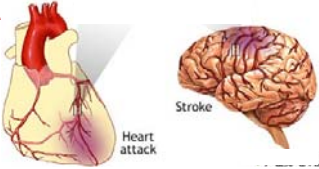
Cardiovascular Disease – A Challenge Worldwide



WOMEN
All other cancers 20%
Prostate and colon 4%
Respiratory disease 4%
Other cancer 10%
Brain cancer 3%
Long cancer 2%
Gastrointestinal cancer 2%
Bladder cancer 1%
Ovarian cancer 1%

Coronary heart disease 22%
Stroke 19%
Other CVD 13%
Breast cancer 1%

CVD 52 %

Heart attack Stroke


European Heart Network 2012

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Cardiovascular Disease Models

Small animals do typically **not present**
with cardiovascular diseases




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Models Imaging Visualization Perfusion Viability Inflammation Translation

Animal Models of Atherosclerosis

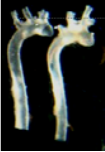
ApolipoproteinE^{-/-} mouse



ApoE^{-/-}

Cholesterol_{plasma}

Genotype	standard chow (mg/dl)	HFC (mg/dl)
WT	~200	~250
ApoE ^{-/-}	~500	~2800

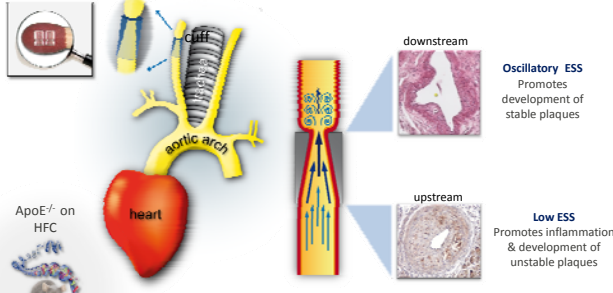


Nakashima, ATVB 1994

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Cuff Model – shear-stress induced local atherosclerosis



ApoE^{-/-} on HFC

heart

aortic arch

Cuff

downstream

upstream

Oscillatory ESS
Promotes development of stable plaques

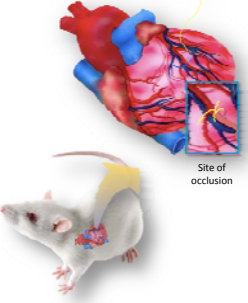
Low ESS
Promotes inflammation & development of unstable plaques

Kuhlmann et al., JoVE 2011

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Induction of Myocardial Infarction



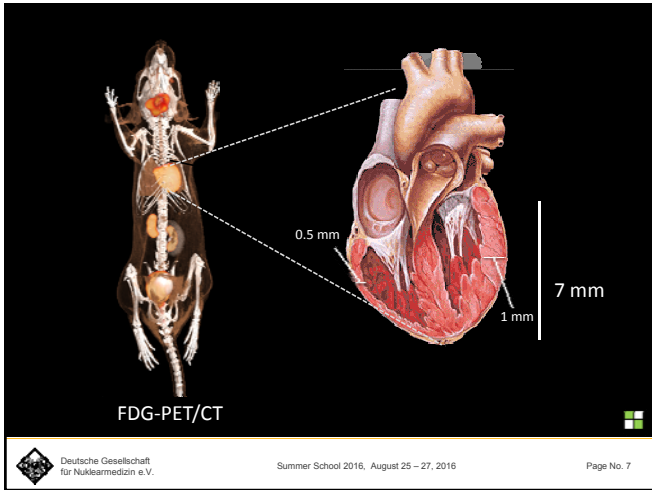
scar formation
3 weeks after induction of MI

Site of occlusion

30 min ischemia

perm. ligation

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Imaging: Monitoring of bio signals

eye ointment
cover
i.v. line resp probe anesthesia
ECG

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Imaging: Movement Correction

Mouse: 26 g, heart rate, ~ 500 bpm Reconstructed Gates: 8

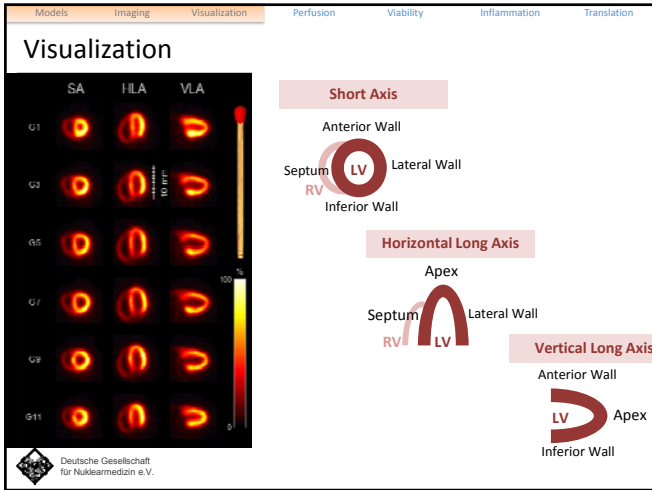
resp probe
ECG

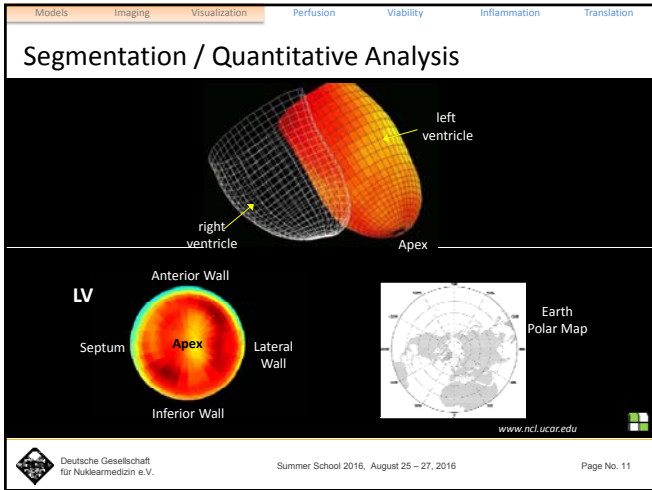
cardiac resp.

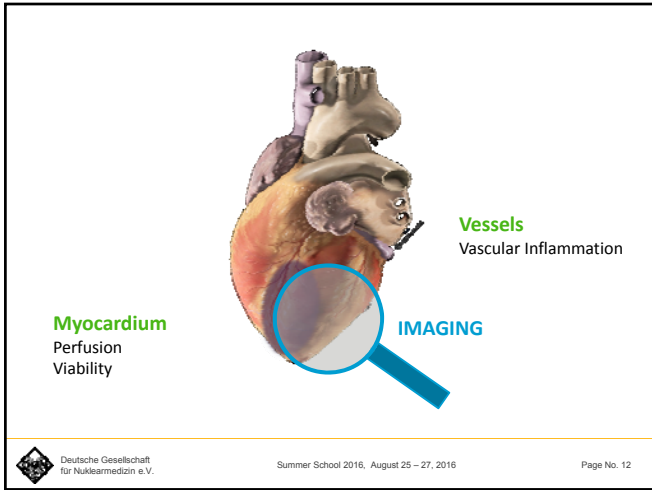
List mode acquisition:
60-90 min p.i. 12 MBq F-18-FDG

Schäfers K, Z Med Phys 2006

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Myocardial Perfusion Imaging

Blood **Cardiomyocyte**

Coronary blood flow (ml/min/g)

Theor uptake (normal)

Rest Exercise Pharmacologic vasodilation

Sagbein, Biomed Res Int. 2014

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Myocardial Perfusion Imaging

Healthy mouse, 26g

RV LV SA

RV LV HLA

RV LV VLA

time after injection →

Vrachimis A, EJNMMI Res. 2012

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Myocardial Perfusion Imaging

Mouse, 24g Ischemia !

ant

RV LV lat

inf

apex

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Models Imaging Visualization Perfusion **Viability** Inflammation Translation

Perfusion Imaging: Application

Monocyte migration

axial coronal

myocardial perfusion

^{125}I -CD11b labeled monocytes: SPECT / CT

day 1 post cells day 2 post cells

infarct remote

Honold L, Gran S, Roth J, Schäfers M, in preparation

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Models Imaging Visualization Perfusion **Viability** Inflammation Translation

Viability

Mouse, 24g, permanent MI ^{18}F -FDG-PET ultrasound

SA HLA VLA PM Scar [%]

FF [%]:

Time Point	SA	HLA	VLA	PM	Scar [%]	FF [%]
baseline					na	43
day 1					34	25
day 14					34	15

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Models Imaging Visualization Perfusion **Viability** Inflammation Translation

Influence of anesthesia on cardiac ^{18}F -FDG uptake

healthy 3d post MI $\sim 8\text{MBq}$ FDG i.v. Acq. 50-60min p.i.

Anesthesia	Healthy	3d post MI
Standard Isoflurane		
Conscious Injection/Uptake		
Conscious Fasting		
Conscious Fasting, Heparin		
Ketamine/Xylazine		

Thackeray et al., EINMMI 2015

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Atherosclerosis – targets

Vrachimis et al. QJNM 2016

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Models Imaging Visualization Perfusion Viability Inflammation Translation

FDG-PET/CT in Carotid Cuff Model

Wenning et al., Atherosclerosis 2014

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Models Imaging Visualization Perfusion Viability Inflammation Translation

FDG-PET in patients

→ FDG signal correlates with macrophage density in excised carotid samples

But: true nature of FDG signal is still unclear (macrophages vs. surrounding fat vs. ???)

Tawakol et al. J.Am.Coll.Cardiol. 2006

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Atherosclerosis – targets

Vrachimis et al. QJNM 2016

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Models Imaging Visualization Perfusion Viability Inflammation Translation

MMP Imaging

bright field only fused FRI

diet

0 weeks

6 weeks

12 weeks

Cy5.5-MMPI

Faust A. Bioconjug Chem 2008
Faust A. Contrast Media Mol Imaging 2013

Waschkau B

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Models Imaging Visualization Perfusion Viability Inflammation Translation

MMP Imaging

ApoE^{-/-}, 8 week high cholesterol diet

in vivo

F-18-MMPI

MMP2/9

Waschkau B

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Translational MMP Imaging in MS

Gerwien H, Hermann S, Schäfers M, Sorkin L, in revision

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Translational MMP Imaging in MS

¹⁸F-MMPI-PET and Gd-T1-MRI of patient with acute attack of relapsing remitting MS at baseline and 35 days after treatment (methylprednisolone)

30-60 min p.i. of 250 MBq MMP radiotracer ¹⁸F-BR351

Gerwien H, Hermann S, Schäfers M, Sorkin L, in revision

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Models Imaging Visualization Perfusion Viability Inflammation Translation

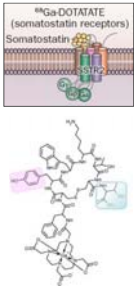
Atherosclerosis – targets

Vrachimis et al. QJNM 2016

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Models Imaging Visualization Perfusion Viability Inflammation Translation

Somatostatin-receptor imaging with DOTATATE



Somatostatin (SST): Circulating peptide with neuroendocrine, immunomodulatory and cell-regulatory functions

SSTRs: Overexpressed in a number of diseases, particularly neuroendocrine tumors

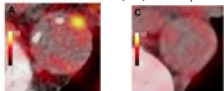

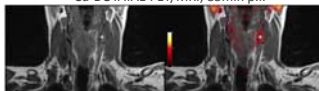
DOTATATE: SST analog with SSTR2 specificity
⁶⁸Ga or ⁶⁴Cu labeled

Tarkin et al. Nat. Reviews Card., 2014

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Models Imaging Visualization Perfusion Viability Inflammation Translation

DOTATATE PET in patients

Several retrospective studies report DOTATATE PET (⁶⁸Ga or ⁶⁴Cu) signal to correlate with presence of plaques and cardiovascular risk factors

Strong correlation between *in vivo* signal and *ex vivo* markers of activated macrophages (CD163)

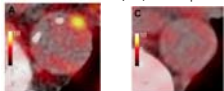
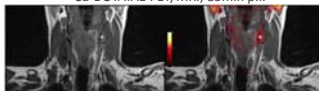
→ Detection of vulnerable plaques?

Rominger et al. 2010, JNM; Li et al. 2012, EJNMMI; Malmberg et al. JNM 2015 *Pedersen et al. Arterioscl. Throm. Vas. 2015*

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Models Imaging Visualization Perfusion Viability Inflammation Translation

DOTATATE PET in patients

VISION study
(Vascular Inflammation imaging using Somatostatin receptor positron emissIOn tomography)

50 subjects with atherosclerosis, sequential PET/CT imaging with ⁶⁸Ga-DOTATATE and ¹⁸F-FDG, contrast angiography of carotid and coronary arteries, autoradiography and immunohistochemistry of excised carotid plaques

US National Library of Medicine. ClinicalTrials.gov, <http://clinicaltrials.gov/show/NCT02021188> (2013)

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Models Imaging Visualization Perfusion Viability Inflammation Translation

SSTR2 imaging – bedside to bench - to bedside?

Specific tracer uptake on tissue level? What cells in the plaque express SSTR2?

Digested aorta from ApoE^{-/-} > 60% of monocytes/macrophages

> 28% of T-cells > 95% of endothelial cells

Li et al. Atheroscl., 2013

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Models Imaging Visualization Perfusion Viability Inflammation Translation

SSTR2 imaging – bedside to bench - to bedside?

⁶⁴Ga-DOTANOC

Tracer improvements?

Rinne et al. MOL IMAGING BIOL, 2016

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Mouse Imaging Workshop 14-18 November 2016

Topics

- **Animal handling:** i.v./i.p. injection, tail vein catheter, anaesthesia, surgery
- **μ PET/ μ SPECT:** static and dynamic scanning, CT fusion
- **μ CT:** in vivo scans +/- contrast agents, respiratory gating
- **μ MRI:** in vivo scans +/- contrast agents, cardiac & respiratory gating
- **Ultrasound:** hands-on scanning +/- contrast agents
- **Optical imaging:** fluorescence, bioluminescence
- **Multimodal imaging:** PET/CT, PET/MRI, SPECT/CT
- **Image analysis:** methods, coregistration, quantification (VisualLab)



<http://www.uni-muenster.de/EIMI/teaching/mia/>