Hybrid Cardiac Imaging

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*Juhani Knuuti, M.D.* has financial interests to disclose. Potential conflicts of interest have been resolved.

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ESC guideline for stable CAD 2013

**ALL PATIENTS**

- Assess symptoms
  - Perform clinical examination

**Symptoms consistent with unstable angina**

Follow specific NSTE-ACS guidelines

**Consider comorbidities and QoL**

- ECG
- Bio-Chemistry
- Resting echocardiography
- CXR in selected patients

**Comorbidities or QoL make revascularization unlikely**

Medical therapy

**Cause of chest pain other than CAD?**

- Yes → Treat as appropriate
- No → LVEF <50%?
  - Yes → Typical angina?
    - Yes → Offer ICA if revascularization suitable
    - No → See Fig. 2 for selection of test
  - No → High PTP (>85%)
    - Diagnosis of SCAD established

- No → Assess pre-test-probability (PTP) (see Table 13) for the presence of coronary stenoses
  - Low PTP (<15%) → Investigate other causes
    - Consider functional coronary disease
  - Intermediate PTP, e.g. 15-85% → Non-invasive testing for diagnostic purposes
    - See Fig. 2 for decisions based on non-invasive testing and choice between stress testing and coronary CTA
  - Diagnosis of SCAD established → Proceed to risk stratification (see Fig. 3).
    - In patients with severe symptoms or clinical constellation suggesting high risk coronary anatomy initiate guideline-directed medical therapy and offer ICA
Table 13: Clinical pre-test probabilities in patients with stable chest pain symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30–39</td>
<td>59</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>40–49</td>
<td>69</td>
<td>37</td>
<td>38</td>
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<tr>
<td>50–59</td>
<td>77</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>60–69</td>
<td>84</td>
<td>58</td>
<td>59</td>
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<tr>
<td>70–79</td>
<td>89</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>&gt;80</td>
<td>93</td>
<td>76</td>
<td>78</td>
</tr>
</tbody>
</table>
ESC guideline for stable CAD 2013

Patients with suspected SCAD and intermediate PTP of 15% - 85%

Consider:
- Patient criteria and suitability for given test
- Availability
- Local expertise

Stress testing for ischaemia

PTP 15-65% and LVEF ≥50%

Exercise ECG if feasible - stress imaging testing preferred (echo, CMR, SPECT, PET)
if local expertise and availability permit

Stress imaging (echo, CMR, SPECT, PET); ECG exercise stress testing possible if resources for stress imaging not available

PTP 66-85% or LVEF <50% without typical angina

Coronary CTA in patients at low intermediate PTP (15% - 50%)
- If suitable candidate
- If adequate technology and local expertise available

2nd (imaging) stress test (if not done before)
Coronary CTA in suitable patient (if not done before)
ICA (with FFR when necessary)

Unclear

Determine patient characteristics and preferences

Ischaemia

No ischaemia

No stenosis

Stenosis

Unclear

Consider functional CAD; investigate other causes

Diagnosis SCAD established; further risk stratification (see Fig. 3)

Ischaemia testing using stress imaging if not done before
Cardiac hybrid imaging

- Why hybrid imaging in cardiology?
- Methodological aspects
- Clinical results in coronary heart disease
  - CTA + perfusion
  - Quantitation of myocardial perfusion
- Hybrid imaging in heart failure
- Hybrid imaging in inflammatory cardiac diseases
- Imaging of vulnerable atherosclerotic plaques
Detection of obstructive CAD
Exercise ECG vs imaging

Patient based analysis, ICA as reference standard

![Bar chart showing sensitivity and specificity of different imaging modalities](chart.png)
ESC guideline for stable CAD 2013

Table 12  Characteristics of tests commonly used to diagnose the presence of coronary artery disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis of CAD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>Exercise ECG a, 91, 94, 95</td>
<td>45–50</td>
<td>85–90</td>
</tr>
<tr>
<td>Exercise stress echocardiography96</td>
<td>80–85</td>
<td>80–88</td>
</tr>
<tr>
<td>Exercise stress SPECT96-99</td>
<td>73–92</td>
<td>63–87</td>
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<tr>
<td>Dobutamine stress echocardiography96</td>
<td>79–83</td>
<td>82–86</td>
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<tr>
<td>Dobutamine stress MRI b,100</td>
<td>79–88</td>
<td>81–91</td>
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<tr>
<td>Vasodilator stress echocardiography96</td>
<td>72–79</td>
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<tr>
<td>Vasodilator stress SPECT96, 99</td>
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<td>Coronary CTA c,103-105</td>
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<td>64–83</td>
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<tr>
<td>Vasodilator stress PET 97, 99, 106</td>
<td>81–97</td>
<td>74–91</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; MRI = magnetic resonance imaging; PET = positron emission computed tomography.

a Results without/with minimal referral bias.
b Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.
c Results obtained in populations with low-to-medium prevalence of disease.
The role of imaging in cardiac diseases

- Detection of disease (80’s)
- Risk of disease (90’s)
- Guiding the therapy decisions
Combination of anatomical and functional information in CAD

Wijns, de Bruyne, Vanhoenacker, JNC 2007;93:856-61
Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Survival Free from Major Adverse Cardiac Events (%)

Days since Randomization

FFR-guided PCI

Angiography-guided PCI

Tonino et al. FAME
Anatomical and functional imaging of coronary artery disease

- **Anatomical imaging**
  - Invasive coronary angiography (+IVUS, OCT)
  - Coronary Calcium
  - Coronary CT angiography

- **Functional imaging**
  - Nuclear imaging (SPECT, PET)
  - Stress echocardiography
  - CMR
  - (FFR, invasive pressure gradient)
Cardiac hybrid imaging

- Combination of anatomical and functional imaging
  - Allows detection of non-obstructive CAD
  - Leads more accurate diagnosis of CAD
  - Allows better guidance of CAD therapy
Cardiac hybrid imaging

- Why hybrid imaging in cardiology?
- Methodological aspects
- Clinical results in coronary heart disease
  - CTA + perfusion
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- Hybrid imaging in heart failure
- Hybrid imaging in inflammatory cardiac diseases
- Imaging of vulnerable atherosclerotic plaques
Hybrid imaging protocols

N-13-Ammonia

**Radiation dose**
- CTA: 3-5 mSv
- PET: 1-4 mSv

O-15-Water

**Radiation dose**
- CTA: 3-5 mSv
- PET: 1-4 mSv

Rb-82
Hybrid imaging QC
Simple software tools for hybrid image fusion
Cardiac hybrid imaging

- Why hybrid imaging in cardiology?
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Functional consequences of stenoses by PET/CT
Effects of Coronary Calcium
CAD case

Clinical history

• Male – 69 years old
• Risk factors for CAD
  • Impaired glucose tolerance
• Attacks of anginal pain during previous months and arrhythmias
• Exercise test
  • Moderately reduced exercise capacity (67%)
  • Maximum heart rate 142/min
  • Atypical chest pain with < 1 mm ST-depression in ECG

Case:LP
CT angiography

Curved MPR reconstructions of the major coronary vessels

CT Acquisition:
- Premedication: Metoprolol 10 mg i.v. HR 46/min
- Acquisition: Prospective step-and-shoot protocol, mA 650, 120 kV
- Contrast: Iomeron 400mg/ml 68 ml
- Radiation dose 7.4 mSV

Case: LP

LAD

>50%

LCX

30-40%

RCA

>50%
Invasive angiography QCA

Right

Left

Case: LP

48%

60%

46%
PET perfusion imaging during stress

Displayed as fused volume rendered images scaled to absolute scale 0-3.5 ml/g/min
Normal perfusion: above 2.5 ml/g/min: yellow or red

PET Acquisition:
- Injected Dose: 1100 MBq O-15-water
- Stress: Adenosine 140 µg/min/kg for 6.5 min
- Acquisition time: dynamic 4.5 min
- Radiation dose 0.9 mSV
Invasive angiography + FFR

FFR = Fractional flow reserve – invasive measurement of the stenosis functional gradient during adenosine infusion

Case: LP

Right

48%

FFR: 0.86 (normal)

Left

60%

FFR: 0.92 (normal)

46%

FFR: ?

FFR: 0.86 (normal)
Multivessel disease: What is the culprit lesion?

LAD  |  RCA

C

D

E

F

FFR=0.94

FFR=0.54

FFR=0.63
Multivessel disease: What is the culprit lesion?

Case: stenoses in all major vessels; RCA is culprit
Multislice CT vs. Myocardial Perfusion
Regional comparison in 140 patients

Microvascular disease

Absolute perfusion decreased but no epicardial disease

Relative perfusion

Absolute perfusion
# Challenges and solutions of ischemia imaging

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM disease</td>
<td>Function+anatomy</td>
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<tr>
<td>Balanced 3 vessel disease</td>
<td>Function+anatomy</td>
</tr>
<tr>
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<td>Anatomical location</td>
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</tr>
<tr>
<td>Non-ischemic CAD</td>
<td>Function+anatomy</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>Function+anatomy</td>
</tr>
<tr>
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</table>
Hybrid noninvasive (PET/CT) vs. Hybrid invasive (ICA + FFR)

Vessel analysis in patients with intermediate likelihood of CAD, N=107

<table>
<thead>
<tr>
<th></th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
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<tr>
<td>MDCT</td>
<td>76</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>PET</td>
<td>77</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>MDCT-PET hybrid</td>
<td>96</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Kajander et al Circulation 2010
Hybrid imaging

Per patient

Per vessel

Prognosis and combined MDCT and perfusion imaging

Prognosis and combined MDCT and perfusion imaging

335 consecutive patients undergoing a 1-day stress/rest (99m)Tc-tetrofosmin SPECT and a CCTA

Impact of hybrid imaging on downstream resource utilization

- Revascularisations
  - CATH rate: 45%
  - CAD yield Per CATH: 39% (NEJM 2010 USA N=400'000)
  - REVASC Per CATH: 36% (GER N=840'000)

p<0.001

Impact of hybrid imaging on treatment decisions

Table 2  Treatment decisions for all patients categorised for the necessity of revascularisation

<table>
<thead>
<tr>
<th></th>
<th>Revascularisation</th>
<th>No revascularisation</th>
<th>Percentage agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPECT and CA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisation</td>
<td>50</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>No revascularisation</td>
<td>4</td>
<td>48</td>
<td></td>
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<tr>
<td><strong>Treatment decisions categorised for necessity of revascularisation (N=107)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hybrid SPECT/CCTA</td>
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<td>50</td>
<td>5</td>
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</tr>
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<td>4</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment decisions on type of revascularisation (N=50)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hybrid SPECT/CCTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>18</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>CABG</td>
<td>3</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Agreement tables for panel decisions based on hybrid SPECT/CCTA and SPECT and CA in all patients. (A) Decisions on the necessity of revascularisation (no revascularisation versus PCI or CABG) in all patients. Percentage agreement was 92% (95% CI 85 to 96). (B) Decisions on the type of revascularisation (PCI versus CABG) in the group of patients indicated for revascularisation based on hybrid SPECT/CCTA. Percentage agreement was 74% (95% CI 60 to 84).

CA, coronary angiogram; CABG, coronary artery bypass grafting; CCTA, CT coronary angiography; PCI, percutaneous coronary intervention; SPECT, single photon emission CT.

Hybrid imaging: Turku registry
n=1963 patients

CT angiography finding

PET perfusion finding

273 patients

707 patients with CTA
Downstream referral: ICA

Invasive coronary angiography

<table>
<thead>
<tr>
<th>Normal perfusion</th>
<th>Reduced perfusion AND corresponding stenosis in CTA</th>
<th>Reduced perfusion NO corresponding stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 10 20 30 40 50 60
Downstream referral: PCI

<table>
<thead>
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<th>Normal perfusion</th>
<th>Reduced perfusion AND corresponding stenosis in CTA</th>
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</tr>
</thead>
</table>

Percutaneous coronary intervention
Downstream referral: CABG

- Normal perfusion
- Reduced perfusion AND corresponding stenosis in CTA
- Reduced perfusion NO corresponding stenosis

Coronary artery by-pass grafting
MDCT findings in patients with normal (SPECT) perfusion imaging result

Paradigm shift 2: From ischemic to CAD cascade

Preclinical atherosclerosis
Non-obstructive CAD
hypoperfusion
metabolic alterations
diastolic dysfunction
systolic dysfunction
ECG-Changes
angina

Myocardial perfusion

Signs of ischaemia
Concerns on sequential / hybrid imaging for CAD

- Sequential: Complicated for patients
- Hybrid: Logistic challenges
- Higher work load
- Non-standardized image analysis
- Higher radiation burden
- Less evidence
- Cost-effectiveness
CTA helps in identifying potential stenoses that can be then visualised using coronary TTE

CTA (62% diam. stenosis)  Color-Doppler view  Flow velocity profiles

Maximal (2.1 m/s)

Pre-stenotic (0.3 m/s)

Case 0046

Joutsiniemi et al EHJ Cardiovascular Imaging 2012
Functional consequences of stenoses by CT?

Multi-detector computed tomography myocardial perfusion imaging in a canine model of left anterior descending artery stenosis during atenolol infusion. The image on the right is a multiplanar reconstruction of the heart in the cardiac short axis. Note the perfusion deficit in the anteroseptal, anterior, and anterolateral walls. The image on the right is a color-coded map of the myocardial attenuation densities with the range shown below in Hounsfield units. Note the dark blue area in the anteroseptal, anterior, and anterolateral walls.

Courtesy of George RT and Lardo AC, Johns Hopkins University, Baltimore, MD, U.S.A.
Classic diagnostic path in patients with suspected CAD

Symptomatic patients with suspected CAD
Estimation of pretest probability of CAD using clinical history and exercise ECG when available

Low probability (<15%)

Intermediate probability (15-85%)
Stress imaging (ischemia) or CT angiography (in lower range of intermediate probability group)

High probability (>85%)
ICA to detect the disease and decide about revascularization (if necessary with help of FFR)

Ischemia – (or CTA -)
Low risk ischemia (or mild CAD in CTA)
Primary prevention

Ischemia + (or CAD + in CTA)
Secondary prevention / Medical therapy

Knuuti and Saraste. Eur Heart J 2013
Proposed diagnostic path in patients with suspected CAD

Symptomatic patients with suspected CAD
Estimation of pretest probability of CAD using clinical history and exercise ECG when available

Low probability (<15%)
- Secondary prevention / Medical therapy
  - Revascularization and medical therapy

Intermediate probability (15-85%)
- Hybrid imaging
  - CT angiography to detect disease and localize stenoses
  - CAD -
  - CAD +
    - Stress imaging (ischemia)
      - Ischemia -
        - CAD +
      - Ischemia +
        - CAD +

High probability (>85%)
- ICA to confirm disease and final decision of revascularization (if necessary with help of FFR)
- Revascularization and medical therapy

Primary prevention
Secondary prevention / Medical therapy
Knuuti and Saraste. Eur Heart J 2013
Challenges and solutions of ishchemia imaging

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<td>Quantification</td>
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<td>Quantification/</td>
</tr>
<tr>
<td></td>
<td>Function+anatomy</td>
</tr>
</tbody>
</table>
Quantification of perfusion?

- Tracer
- Imaging protocol
- Data analysis
- Implementation of quantitative results into clinical reading
- Understanding the limitations
- Convince the clinician that quantitative results are useful and reliable
Analysis of dynamic study

Published softwares for myocardial perfusion quantification:

- Munich Heart
- PMOD
- FlowQuant
- Carimas
- Siemens SW
Analysis of dynamic PET scan

Report of

Name
ID
Gender
Height
Weight
Study Description
Institute
Radiopharmaceutical
Isotope

Model name
Input function
Camaras
Date
9-4-2013 11:45:10

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<thead>
<tr>
<th>Modelling Results</th>
<th>Flow (mllg/min)</th>
<th>PIF (mllg/ml)</th>
<th>Ve (mllg/ml)</th>
<th>STD (mg/ml)</th>
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<tr>
<td>GLOBAL</td>
<td>1.88349</td>
<td>0.77595</td>
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<tr>
<td>LAD</td>
<td>1.56021</td>
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<tr>
<td>LCX</td>
<td>2.33669</td>
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<td>1.36435</td>
<td>0.63421</td>
<td>0.19997</td>
<td>6592.48457</td>
</tr>
</tbody>
</table>

Turku PET Centre
Absolute myocardial blood flow: Interpretation criteria need to be revised

Stress

Range in absolute flow image

Range in tracer uptake

Absolute flow

Normal

Tracer uptake

Abnormal
12 unselected examples of relative vs quantitative analysis

<table>
<thead>
<tr>
<th>Relative</th>
<th>Absolute</th>
<th>Relative</th>
<th>Absolute</th>
<th>Relative</th>
<th>Absolute</th>
</tr>
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Quantification of myocardial perfusion

Which patients will benefit?

- Balanced 3 vessel or multivessel disease
- Culprit lesion vs. non-culprit lesion in multi vessel disease
- Early changes in coronary dysfunction
Results: patients with multi-vessel disease

106 patients with 30-70% pretest likelihood of CAD. Quantitative hybrid PET/CT imaging vs. invasive angiography with FFR

The estimated probability of significant CAD (stenosis+reduced FFR) by O-15 water PET stress flow

Joutsiniemi et al Circulation 2011
Absolute flow is as good as flow reserve!
330 patients from Turku, Amsterdam and Uppsala

\[
\begin{align*}
\text{AUC hyperemic MBF} &= 0.90 \ (0.86 - 0.94) \\
\text{AUC CFR} &= 0.85 \ (0.81 - 0.90) \\
\text{AUC CFR}_{\text{corr}} &= 0.85 \ (0.81 - 0.90) \\
\text{AUC baseline MBF} &= 0.61 \ (0.54 - 0.68)
\end{align*}
\]

Danad et al (submitted)
The estimated probability of significant CAD (stenosis+reduced FFR) by O-15 water PET stress flow in 330 patients with suspected CAD

Danad et al (submitted)
Cardiac death  
(6,037 patients, 169 cardiac deaths)

All-cause death  
(7,061 patients, 570 all-cause deaths)
Prognostic value of CFR by PET

2783 patients

Murthy et al Circulation 2012
Problematic patient groups with quantification of perfusion

If no anatomical information is available

- Patients with heart failure
- Patients with advanced atherosclerosis but no epicardial obstructive disease
- Microvascular disease
Molecular imaging of vulnerable atherosclerotic coronary plaque

- **Cardiac hybrid PET-CT:**
  - Coronary CT angiography
  - Dual-gated $^{18}$F-FDG-PET

- **Non-invasive visualization of $^{18}$F-FDG uptake in inflammatory coronary atherosclerotic plaque in a patient with acute coronary syndrome (ACS)**
Dual gated $^{18}\text{F}-\text{FDG}$ PET/CT of coronary arteries in ACS patients

- 39 year old man
- Risk factors of CAD:
  - Smoking
  - Family history +
- 5 days of UAP
- ECG: lateral T-inversion
- LCX subtotal occlusion stented

Preliminary results
- 20 ACS (non-STEMI or UAP) patients
- Dual-gated FDG PET/CT
- 80% of patients visual coronary FDG uptake
- TBR $3.2\pm1.3$ (range 1.8-5.4)

Lankinen EHJ 2011 (abstract)
Turku PET Centre, Finland
CTA + CMR PERFUSION
Viability hybrid imaging: CTA and FDG

Hybrid scanner: 64-detector CT-PET

Case LJ
Extended transmural uptake in the late enhancement image in MR
Fused FDG PET shows preserved viability in this area

Courtesy: O Ratib, R Nkoulou and T Schindler, University Hospital Geneva
PET/MRI for DE CMR, perfusion and angiogenesis ($^{18}$F-Galacto-RGD)

Makowski Eur Heart J 2008
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