Hybrid PET/CT Cardiac Imaging

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Detection of coronary artery disease by PET-CT hybrid imaging

Hybrid device:
PET/ SPECT + 64-rowCT

Comprehensive evaluation of anatomy and function

Gaemperli, Saraste, Knuuti. Eur Heart J Cardiovasc Imaging 2012
Non-invasive coronary CT angiography: Exclusion of obstructive CAD

64-row CT
Prospective gating
Radiation dose: 3-5 mSv
## Multi Center Trials

**ACCURACY Trial – Multi-Center Study in 230 subjects, 16 sites**

<table>
<thead>
<tr>
<th></th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PER PATIENT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50% Stenosis</td>
<td>95%</td>
<td>83%</td>
<td>64%</td>
<td>99%</td>
<td>24%</td>
</tr>
<tr>
<td>&gt; 70% Stenosis</td>
<td>94%</td>
<td>83%</td>
<td>48%</td>
<td>99%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>PER VESSEL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50% Stenosis</td>
<td>84%</td>
<td>90%</td>
<td>51%</td>
<td>99%</td>
<td>10%</td>
</tr>
<tr>
<td>&gt; 70% Stenosis</td>
<td>84%</td>
<td>92%</td>
<td>36%</td>
<td>99%</td>
<td>4%</td>
</tr>
</tbody>
</table>

_Budoff et al, JACC 2008_
Increased utilization of diagnostic tests/invasive coronary angiography after CTA

Meta-analysis of CCTA in chest pain in the ED

UC = Usual care

Hulten E J Am Coll Cardiol 2013
Challenges for CT angiography

- Irregular heart rate and extensive calcifications → Overestimation of stenosis

Schroeder EHJ 2008, Taylor JACC 2010
Challenges for coronary angiography: Anatomy vs. Functional Significance

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

N = 2334

Wijns, de Bruyne, Vanhoenacker, JNC 2007;93:856-61

Hybrid imaging?
Impact of functional significance on prognosis after PCI

A

Survival Free from Major Adverse Cardiac Events (%)

0  60  120  180  240  300  360

Days since Randomization

FFR-guided PCI

Angiography-guided PCI
Revascularization and ischemic burden

Circulation 2003; 107: 2899–2906
PET: Accuracy in the detection of significant CAD

**Table 2** Outline of Results of Meta-Analysis of Rb-82 PET

<table>
<thead>
<tr>
<th>Rb-82 PET Results</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET overall (n = 1,344)</td>
<td>90% (0.88–0.92)</td>
<td>88% (0.85–0.91)</td>
</tr>
</tbody>
</table>

**McArdle, J Am Coll Cardiol 2013**

<table>
<thead>
<tr>
<th>Quantitative</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muzik et al(^{38})</td>
<td>31 with known CAD</td>
<td>93</td>
</tr>
<tr>
<td>Hajjiri et al(^{26})</td>
<td>27 with known or suspected CAD</td>
<td>81</td>
</tr>
<tr>
<td>Kajander et al(^{32})</td>
<td>107 with intermediate likelihood of CAD</td>
<td>95</td>
</tr>
<tr>
<td>Weighed summary</td>
<td>165</td>
<td>93</td>
</tr>
</tbody>
</table>

**Saraste and Knuuti, J Nucl Cardiol 2012**
PET flow quantification = measurement of myocardial perfusion in absolute terms (ml/g/min)

≠ SPECT

Dynamic imaging
→ Kinetic modeling
→ MBF in ml/g/min

Technical improvements
• Count rate performance
  • Data handling
  • Computing power

*Moody et al J Nucl Cardiol 2015*

Combination with clinical protocols
Analysis of PET 15-O-water study

Software packages for myocardial flow quantification:
- Cardiac Vuer
- Munich Heart
- PMOD
- FlowQuant
- Carimas
- Syngo
- Hoquto
- QPET
- UW-QPP
- ImagenQ
- Corridor 4DM

Carimas™ free software developed in Turku PET Centre
The cross-comparison biplots of 10 software packages

When using 1-TCC, the agreement by any SW is good

Complex mathematical modeling, accurate measurement of tracer input and myocardial activity
PET Tracers for Perfusion Quantification

- $^{15}$O-water
- $^{18}$F-flurpiridaz (Nekolla Circulation 2009)
- $^{13}$N-ammonia
- $^{82}$Rb (Lortie EJNMMI 2007, Lautamäki EJNMMI 2009, El Fakhri JNM 2009)
- $^{99m}$Tc-SPECT tracers

Saraste and Knuuti, J Nucl Cardiol 2012
New F-18 labeled PET perfusion tracer (Flurpiridaz)

Good kinetics, image quality and safety

Phase III trial →

Nekolla et al. Circulation 2009

Berman et al. JACC 2013
What is normal myocardial blood flow?

Stress

Range in absolute flow image

Range in tracer uptake

Absolute flow

Normal

Tracer uptake

Abnormal

Measured/modelled flow

Absolute flow (ml/g/min)
Optimal MBF cut-off for the detection of significant epicardial CAD?

330 patients with suspected CAD and O-15 water PET (Turku, Amsterdam, Uppsala)

ICA + FFR in all intermediate (30-90%) stenoses

116 with obstructive CAD

Optimal cutoff for O-15-water
Stress MBF <2.3 ml/g/min
CFR <2.5

Danad et al JACC 2014
Accuracy of quantitative PET perfusion

A

Absolute flow is as good as flow reserve

Danad et al JACC 2014
Accuracy of quantitative PET perfusion

High negative predictive value

Danad et al JACC 2014
Case 1

LAD >50%  
LCX  
RCA >50% IM

CT Acquisition:
Premedication: Metoprolol 12 mg i.v.
HR 60/min
Acquisition: Prospective step-and-shoot protocol 750 mA, 120 kV
Contrast: Iomeron 400mg/ml 90 ml
Radiation dose 8 mSv
Cardiac CTA + PET perfusion protocol

PET- 64 row CT

- CT scan
- PET scan
- Tracer injection
- Contrast injection
Fusion of CTA and PET perfusion?

- A difference image of a heart water study
- The reoriented image
- The ROI definition step
- The polar plot
- The hybrid PET/CT image

Carimas™ free software developed by Turku PET Centre

Nesterov et al EJNMMI 2009
Case 1

CTA and O$^{15}$-water stress perfusion image fusion

Evaluation of haemodynamic significance of stenoses

PET Acquisition:
- Injected Dose: 1100 MBq O-15-water
- Stress: Adenosine 140 µg/min/kg for 6.5 min
- Acquisition: Dynamic 4.5 min
- Radiation dose 0.9 mSv
Case 1

Left coronary artery

RCA

Invasive angiography
Hybrid PET/CT for CAD diagnosis

Figure 2b: Vessel Analysis against ICA+FFR

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDCT</td>
<td>75</td>
<td>95</td>
<td>76</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>PET</td>
<td>94</td>
<td>93</td>
<td>77</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>MDCT-PET hybrid</td>
<td>95</td>
<td>99</td>
<td>96</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>

Kajander et al Circulation 2010

107 patients with intermediate probability of CAD
Challenges and solutions of perfusion imaging

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanced 3 vessel disease</td>
<td>Hybrid imaging/quantitation</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>Hybrid imaging/quantitation</td>
</tr>
<tr>
<td>LM disease</td>
<td>Hybrid imaging</td>
</tr>
<tr>
<td>Anatomical location</td>
<td>Hybrid imaging</td>
</tr>
<tr>
<td>Non-obstructive CAD</td>
<td>Hybrid imaging</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>Hybrid imaging/quantitation</td>
</tr>
</tbody>
</table>

Impact of hybrid imaging in clinical practice?
Advantages of hybrid imaging: Detection of multivessel disease

Adenosine stress $\text{O}^{15}$-water PET perfusion

52-year old female, atypical chest pain
Diffusely reduced stress MBF and 3-vessel obstructive CAD

CTA + Adenosine stress O$^{15}$-water PET perfusion
Example: Different severity of ischemia after quantification with $^{82}$Rb PET

Relative analysis vs. quantification in patients with multivessel disease

- Balanced 3-VD missed in 2 (2%) patients
- Underestimated in 13 (12%) other patients

Regional analysis in patients with intermediate likelihood of CAD, n=104

PET perfusion with O\textsuperscript{15}-water during adenosine stress

24 patients with multivessel CAD (QCA and FFR)

Kajander S et al Circ Cardiovasc Im 2011
Advantages of hybrid imaging: Localization of culprit vessel

Ischemia in the RCA territory
Small LCX
Incremental prognostic value of hybrid CTA-perfusion

Log Rank P-value < 0.005

Event free survival

Follow-up (days)

Van Werkhoven J Am Coll Cardiol 2009
Baseline statin therapy and non-obstructive CAD on coronary CTA

Table 4. Cox Models for All-Cause Mortality in Patients With Nonobstructive CAD

<table>
<thead>
<tr>
<th>Models</th>
<th>Hazard Ratio^ (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=10418)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.52 (0.34–0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>ASA therapy</td>
<td>0.77 (0.53–1.12)</td>
<td>0.173</td>
</tr>
<tr>
<td>Nonobstructive CAD (n=4706)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.39 (0.23–0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA therapy</td>
<td>0.66 (0.42–1.04)</td>
<td>0.070</td>
</tr>
<tr>
<td>No coronary plaque (n=5712)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin therapy</td>
<td>0.64 (0.30–1.37)</td>
<td>0.252</td>
</tr>
<tr>
<td>ASA therapy</td>
<td>0.73 (0.37–1.47)</td>
<td>0.384</td>
</tr>
</tbody>
</table>

Chow ATVB 2014
Advantages of hybrid imaging: Differentiation of epicardial and microvascular dysfunction

Fusion image of 3D coronary anatomy (CTA) and O$^{15}$-water PET perfusion during adenosine stress

65-y old male, risk factors for CAD (smoking, family history), atypical chest pain, >2 mm ST-depression
Hybrid imaging: Differentiation of Epicardial and microvascular disease

$^1{\mathrm{O}}_2$-water PET during adenosine stress

$\text{CFR} = 1.8$

Rest flow:

$\sim 0.9 \text{ ml/g/min}$

Stress flow:

$\sim 1.6 \text{ ml/g/min}$
Improved Cardiac Risk Assessment With Noninvasive Measures of Coronary Flow Reserve

Venkatesh L. Murthy, MD, PhD; Masanao Naya, MD, PhD; Courtney R. Foster, RT; Jon Hainer, BS; Mariya Gaber, MS; Gilda Di Carli; Ron Blankstein, MD; Sharmila Dorbala, MD; Arkadiusz Sitek, PhD; Michael J. Pencina, PhD; Marcelo F. Di Carli, MD

Circulation 2011

2783 patients with suspected CAD, Rb\(^{82}\) rest-stress PET

Prognostic implications of CFR

Ischemia (% of LV)
Implementation of hybrid imaging?

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%)
High probability (>85%)

CT angiography to detect disease and localize stenoses

Hybrid imaging

ICA to confirm disease and final decision of revascularization (if necessary with help of FFR)

Primary prevention
Secondary prevention / Medical therapy
Revascularization and medical therapy

Knuuti and Saraste Eur Heart J 2013
### Open questions with hybrid imaging:

Benefits vs. incremental radiation dose?
Cost effectiveness?
Order of anatomy/functional?
Clinical implementation?

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Duration</th>
<th>Radiation, mSv</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT rest and stress imaging</td>
<td>3-4 h</td>
<td>12</td>
</tr>
<tr>
<td>SPECT/ CAC rest and stress imaging</td>
<td>3-4 h</td>
<td>12</td>
</tr>
<tr>
<td>SPECT/ CTA rest and stress imaging</td>
<td>3-4 h</td>
<td>12</td>
</tr>
<tr>
<td>PET/ CTA stress and rest imaging</td>
<td>1 h</td>
<td>2-5</td>
</tr>
<tr>
<td>SPECT/ CTA stress only imaging</td>
<td>1.5 h</td>
<td>6</td>
</tr>
<tr>
<td>PET/ CTA stress only imaging (quantification)</td>
<td>0.5 h</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Invasive Coronary Angiography: 2.3 – 22.7 (mean 7) mSv
Molecular imaging of myocardial responses to injury

Kiugel et al. Mol Im Biol 2014
$^{18}$F-Galacto-RGD PET of human MI

DeMRI $^{13}$N-ammonia

$^{18}$F-gRGD

4-ch

(A) RA RV LA LV

(B) LV

(C) LV

Relationship to functional recovery?

Makowski Eur Heart J 2008
PET imaging of coronary atherosclerosis and rupture prone plaque?
Clinical nuclear imaging of atherosclerotic plaque inflammation by $^{18}$F-FDG PET-CT

FDG accumulation detected in carotid artery plaques of patients with acute stroke

_Rudd Circulation 2002_
Vascular $^{18}$F-FDG uptake associated with future vascular events

932 cancer patients with prior $^{18}$F-FDG PET study
Mean of TBRs in aorta, carotid and iliac arteries

Prospective trials in non-cancer patients (HRP)

Roeminger JNM 2009
Dual gated $^{18}$F-FDG PET/CT of coronary arteries in ACS patients

- 20 ACS patients
- Dual-gated FDG PET+ CTA
  - $3 \pm 2$ days after onset of symptoms
  - 5 before PCI, 15 after PCI
- Myocardial uptake suppressed by low carbohydrate diet + fasting
  - 19 sufficient for analysis
- 79% of patients visual coronary FDG uptake

Hoppela et al (abstract) ICNC 2011
New PET tracers for atherosclerotic plaque imaging

[¹⁸F] galacto-RGD
HE stain       Autoradiography
Laitinen, Saraste et al. Circ Cardiovasc Imaging 2009

[¹⁸F] Choline
HE stain       Autoradiography
P=Plaque
W=Normal vessel wall
Hellberg, Saraste et al. EAS 2013 (abstract)

[¹⁸F] EF5
HE stain       Autoradiography
Silvola, Saraste et al., ATVB 2011

[¹⁸F] Siglec-9
Silvoa et al., manuscript
Summary: Hybrid PET/CT Cardiac Imaging

- CTA: Exclusion of CAD
- Flow quantification with perfusion PET
- Hybrid imaging: Evaluation of both coronary anatomy and ischemia
  - Functional significance of intermediate stenosis
  - Localization of culprit vessel
  - Detection of multivessel disease
  - Non-obstructive disease
  - Microvascular disease
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