Imaging Vulnerable Plaque to Stratify Individual Patient Risk

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Objectives

1. Rationale for detecting vulnerable plaque

2. Methods for detecting vulnerable plaque
Luminal Stenosis
MI arising from a non-obstructive plaque
Majority of MI Arise from Mild or Moderate Lesions on Antecedent Angiography
HR for PCI group, 1.05; 95% CI, 0.87 to 1.27; P=0.62).
Histological Characteristics of the Vulnerable Plaque

Adapted from Vancraeynest et al, JACC 2011

- Inflammation
- Thin Fibrous Cap
- Large Necrotic Core
- Micro-Calcification
- Positive Remodeling
- Neovascularisation

All Potential Imaging Targets
Potential Imaging Targets

- **18F-FDG**
- **11C-PK11195**
- **18F-FMISO (hypoxia)**
- **18F-Fluciclatide PET**
- **18F-FMCH**
- **68Ga-Dotate USPIO MRI**
- **T1 weighted MRI**

Adapted from Vancraeynest et al, JACC 2011
PROSPECT

- 697 patients
- 595 VH-IVUS TcFA identified
- Median follow up 3.4 years
- Only 6 resulted in myocardial infarction

Stone et al. NEJM 2011
Major Limitation of Vulnerable Plaque Strategy

• In retrospective studies vulnerable plaque consistently associated with rupture and MI

• However prospective studies suggest they are relatively common and go on to cause myocardial infarction in only a minority of cases

Arbab-Zadeh, Fuster JACC 2015
Why do Vulnerable Plaques Outnumber Cardiac Events?

- **Inflammation and cell death**
- **VULNERABLE PLAQUE**
- **STABLE PLAQUE**
- **SUBCLINICAL PLAQUE GROWTH**
- **PLAQUE RUPTURE**
- **MYOCARDIAL INFARCTION**

**MYOCARDIAL INFARCTION**

**SUBCLINICAL PLAQUE GROWTH**

**STABLE PLAQUE**

**VULNERABLE PLAQUE**

**PLAQUE RUPTURE**

**Inflammation and cell death**
Why do Vulnerable Plaques Outnumber Cardiac Events?

1) Vulnerable plaques heal and stabilise

2) Even if they do rupture most plaque rupture events are sub-clinical
The Myth of the Vulnerable Plaque?

- If the majority of vulnerable plaques do not themselves go on to cause events how can we justify going on to treat individual lesions?

- We should focus more on identifying the vulnerable patient........
Identification of vulnerable plaque may still be useful at the patient level
Pan Coronary Vulnerability
Vulnerable Plaques to Identify Vulnerable Patients

• Vulnerable plaques do not exist in isolation.

• However patients with active disease tend to develop multiple high risk plaques, increasing that subject’s probability of a clinical rupture event: the vulnerable patient
Methods for Detecting Vulnerable Plaque
Imaging Methods to Identify Vulnerable Plaque

- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET)
Vulnerable Plaques on CT

Positive remodelling and low attenuation plaque (necrotic core)
CT Vulnerable Plaques Identify High Risk Patients

N=3158 patients:
- 294 had high risk plaques
- 2864 did not

ACS 16% patients (n=48)
ACS 1.4% (N=40)

Log-rank p<0.0001
CT Vulnerable Plaques Identify High Risk Patients

Log-rank p<0.0001
Vulnerable Plaques on MRI

- T1-weighted MRI
- High signal due to methaemoglobin
- Marker of acute luminal thrombus or intraplaque haemorrhage
MRI Vulnerable Plaque Identify High Risk Patients

- Single Centre study of 568 patients
- 55 patients had high intensity plaque
- Patients with these plaques had a 9-fold increased risk of future coronary events (HR: 8.93; 95% CI: 3.23 to 24.7; p < 0.001)
Positron Emission Tomography

PET

FUSED PET/CT
18F-FDG

Glucose analogue
Marker of vascular inflammation
FDG Uptake Reflects Macrophage Infiltration In Carotid Atheroma

Tawakol et al JACC 2006
$^{18}$Fluoro-Deoxy Glucose 
Atherosclerosis

Culprit Carotid Plaque Post Stroke /TIA

Contralateral Plaque

Rudd et al. Circulation 2002
Feasibility of FDG Imaging of the Coronary Arteries

Comparison Between Acute Coronary Syndrome and Stable Angina

A

ACS: New Stent

FDG Uptake

Target to Background Ratio (TBR)

ACS Recently Stented
2.61 (IQR=2.27-3.45)

Stable Recently Stented
1.74 (IQR=1.14-2.0)

Stable Remotely Stented
1.43 (IQR=1.09-1.75)

p = 0.02

p = 0.006
Measurement of Coronary 18F-FDG Activity was Difficult

- Not possible in >50% of the coronary vessel territories examined
- No important differences observed between our populations

Joshi, Dweck, Newby. The Lancet. 2014
18F-Fluoromisonidazole
FMISO- HYPOXIA

FIGURE 1 Imaging of Hypoxia in Carotid Atherosclerosis

Joshi, Rudd. JACC 2017
18F-Fluciclatide Angiogenesis

- RGD tracer targeting $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors
Coronary $^{68}$Ga-Dotatate

Somatostatin receptor sub-type 2

Upregulated on the surface of activated macrophages

Localises to culprit and high-risk plaque
18F-Fluoride

Binds preferentially to newly developing microcalcification
18F-Fluoride Predicts Where New Calcium Will Develop

Baseline CT  
Baseline PET/CT  
Repeat CT 2 yrs

Aortic Sclerosis  
Mild AS  
Moderate AS

Jenkins & Vesey JACC 2015
Irkle et al. Nature Communications 2015
Plaque rupture

Micro-calcification

18F-Fluoride

CT

STABILISED PLAQUE

Macro-calcification

Myocardial Infarction

Dweck et al
Circulation Research 2016
18F-Fluoride & Coronary Artery Disease
Different Information from CT

- Computed Tomography
- Positron Emission Tomography
- Fused PET-CT

Supplementary figure 2

Fused PET-CT
18F-Fluoride vs. VH-IVUS
& Histology

HISTOLOGY

VH-IVUS

NaF +ive

NaF -ive
18F-Fluoride Identifies Adverse Plaques

- **Inflammation**
  - NaF Positive: 73%
  - NaF Negative: 21%
  - Positive Remodeling
  - Minimal Luminal Area mm²: 9 (6-14)
  - Plaque Area mm²: 24 (21-29)
  - P<0.001

- **Micro Calcification**
  - NaF Positive: 73%
  - NaF Negative: 21%
  - P<0.001

- **Large Necrotic Core**
  - NaF Positive: 25% (21-29)
  - NaF Negative: 18% (14-22)
  - P<0.001

- **Thin Fibrous Cap**

- **CD68**

- **Cleaved Caspase**

Graphs showing cells per mm² and staining of vessel wall.
Identifies High Risk Patients

Framingham Risk Scores

Dweck JACC 2012
18F-Fluoride post STEMI

Coronary Angiogram (LCA)

Fused 18F-Fluoride PET CT

Joshi, Dweck, Newby. The Lancet. 2014
Coronary Angiogram (RCA)

Fused 18F-Fluoride PET CT

Dweck et al JACC 2012
PET/MR Imaging

<5mSv

Robson, Dweck, Fayad JACC Imaging 2017
Carotid 18F-Fluoride
Carotid 18F-Fluoride

**Figure 1** $^{18}$F-NaF is a Surrogate Marker of Active Calcification in Carotid Plaque

(A) $^{18}$F-sodium fluoride ($^{18}$F-NaF) uptake correlation with hydroxypatite expression; intraplaque clustering is noted (left); fixed-effects model for individual lesion correlations ($r = 0.37, p = 0.006$) (right). (B) $^{18}$F-NaF uptake encompasses a greater region than calcific nodules within plaque (left). CAIN = Canadian Atherosclerosis Imaging Network; CI = confidence interval; CT = computed tomography; df = degrees of freedom; IV = Inverse variance; L = left; PET = positron emission tomography; TBR = tissue-to-blood ratio.
The PRE FFIR Study

Prediction of Recurrent Events with $^{18}$F-Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction
Will 18F-Fluoride Predict Events?

Patients with Myocardial Infarction and Multi-Vessel Disease (n=700)

Baseline $^{18}$F-NaF PET, CTCa$^{2+}$ + CT-Coronary Angiogram <21 days from MI

Telephone follow-up at 12 monthly intervals until study end

CTCa$^{2+}$ + CT-Coronary Angiogram at 2 years

Electronic Health Record Review for 5 years after study end

Disease Progression

Clinical Events (Cardiac Death or MI)
MULTI-MODALITY IMAGING

PET/CT IMAGING

Conclusions

• Plaques that rupture and cause myocardial infarction have certain characteristics that can be identified on imaging “the vulnerable plaque”

• These are actually relatively common and often heal without clinical consequence. Predicting individual lesions that will cause events is unlikely to be successful

• However identifying vulnerable plaques can help identify patients with active disease and an increased risk of events.

• These vulnerable patients could then be targeted with aggressive systemic therapies to prevent events
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Increased Inflammation in Remote Atheroma Post-MI

$^{18}$F-FDG of the Aortae

Joshi et al. JAHA. 2015 In press
Binds to Hydroxyapatite Crystal
Detects newly developing calcium beyond resolution of CT

Calcium on histology  
Micro CT  
Autoradiography  
Micro PET  
Autoradiography

Irkle et al. Nature Communications 2015