Non-Oncologic Applications for PET/MR: Neuro, Cardiac, Rheumatologic, and Orthopedic Indications

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Disclosures

- No financial disclosures

- We do not have a PET/MRI scanner
Objectives

• To discuss non–oncologic applications of PET/MRI

• To review both FDG and non-FDG PET tracers and the potential for use in PET/MRI

• To appreciate the role of PET/MRI in diagnosis and management of non-oncologic diseases
• **Inflammatory/rheumatologic disease**
  – JRA, JIA, TMJ

• **Musculoskeletal/orthopedic indications**
  – Chronic pain, e.g. low back pain, osteoid osteoma, etc

• **Cardiovascular applications**
  – Congenital heart disease
  – Myocardial ischemia
  – Infection

• **Neurologic applications**
  – Epilepsy

• **Trauma**
  – Non-accidental trauma
  – Concussive traumatic brain injury
• Why PET/MRI
  – Need/opportunity for functional information
    • PET
      – Metabolism
      – Active bone turnover
      – Perfusion
    • MRI
      – Dynamic cardiac function
      – Neuro (DTI, F-MRI)
  – Complementary structural/anatomic information
  – Quantitative changes associating structure and function, e.g. dynamic $^{18}$F-PET, bone fat/water content and risk of fracture in metabolic/osteoporotic bone disease
PET for Monitoring of Inflammatory States

- **FDG uptake correlates with disease activity**
  - Swelling, tenderness, synovial thickening (US)
  - More sensitive than clinical Sx
  - Neither MRI nor FDG/PET changes have not yet been found to correlate with treatment outcome

- **FDG Monitoring of disease activity on therapy**
  - Infliximab Rx: FDG correlated with response
  - Early response (change in $SUV_{\text{mean}}$ after 2 weeks of Rx) predicted changes in disease activity
    - May predict clinical outcome

- **Currently insufficient data to support routine use (e.g. reimbursement) for diagnosis or therapy evaluation**

Radiotracers

- $^{18}$F-FDG
  - non-specific, sensitive for detecting sites of active inflammation
- $^{18}$F-NaF
  - $^{18}$F ions exchange with –OH on the surface of bone hydroxyapatite $\rightarrow$ $^{18}$F-fluoroapatite
  - Uptake function of blood flow and remodeling
  - Rapid uptake/clearance $\rightarrow$ Imaging in 15-30 min.
- $^{18}$F-NaF dosimetry (compared to MDP)
  - 250 keV positron energy, 511 keV photons vs 140 keV gamma and different half-lives
  - Overall dose is similar (bone surface $>$ MDP; bladder wall $>$ $^{18}$F)

13 yo with joint pain and hypercalcemia

• Active disease:
  - Synovial enhancement
  - Sub-chondral edema
  - FDG uptake
  - Joint fluid

• Inactive disease:
  - Sub-chondral cysts
  - Lack of enhancement
  - No FDG uptake
Temporomandibular Joint Disease

- **Condylar hyperplasia**
- **Rheumatoid arthritis**
  - Synovial enhancement
    - Precursor to bony change
    - Not part of grading system
  - MRI grading
    - Edema, joint space narrowing, erosions, bone destruction
- **JIA**
  - TMJ disease
    - young age, disease duration, polyarticular or systemic dz
    - Often asymptomatic
• No imaging studies evaluating role of FDG and/or $^{18}$F-Na
  – Studies in other joints show degree of FDG uptake correlates with disease activity
• One study comparing $^{18}$F-Na to MDP: superior diagnostic ability and quantitation for $^{18}$F-PET  
  Lee et al. Dentomaxillofac Radiol: (2013) 42, 29292350
PET/MRI and Musculoskeletal Disease

• **Low back pain**
  - Non-specific, common in young athletes
  - CT shows pars defects in ~ 50% of patients with focal uptake on $^{18}$F-PET
  - MRI may provide better correlation
  - Compression fractures & associated injuries
  - Absence of $^{18}$F uptake at site of pars defect may exclude this as a cause of pain
  - $^{18}$F uptake may reveal other causes for pain
13 yo female athlete with low back pain after injury

20 yo chronic neuromuscular scoliosis with progressive L>R back pain
17 year old left handed pitcher with right sided pain upon extension
18F-Na PET/MRI and Osteoid Osteoma

14 yo with hip pain and concern for osteoid osteoma. 18F-PET to localize activity relative to joint cartilage
• **Osteoarthritis**
  - Increased bone remodeling marker of OA progression
  - $^{18}$F-Na uptake marker of pain
    • Severity correlates with SUV
  - Evaluation of both articular cartilage (MRI) and sub-chondral bone ($^{18}$F-Na)

• **OA in Children**
  - Hip dysplasia
  - Legg-Calve-Perthes
  - Physical trauma
    • Hips, knees, spine
  - Genetic mutations
    • Cartilage/physeal abnl

Opportunities for PET/MRI in CHD

- **Myocardial ischemia**
  - Suitability for revascularization

- **Structure/function correlates**
  - Wall motion abnormalities
    - Scar tissue vs ischemic
  - Single ventricle pts
  - Cardiomyopathies

- **Myocardial perfusion imaging**
  - Coronary flow reserve

- **Infection**
  - Endocarditis with conduits and valves
  - Requires preparation with high glycemic load diet
Opportunities for PET/MRI in CHD

- **Radiotracers**
  - $^{82}\text{Rb}$; generator
    - $t_{1/2} = 78\text{s}$, 60% extraction; non-linear myocardial uptake
  - $^{13}\text{N-NH}_4^+$; cyclotron
    - $t_{1/2} = 9.8\text{ min}$, 80% extraction
    - Relatively long biologic half-life ($^{13}\text{N-glutamine}$)
    - Excellent for MPI
  - $^{18}\text{F-FDG}$; cyclotron
    - $t_{1/2} = 110\text{ min}$
    - Myocardial viability
  - $^{15}\text{O-H}_2\text{O}$; cyclotron
    - $t_{1/2} = 2.4\text{ min}$; short biological half-life, poor count density

Myocardial Ischemia in CHD

- CHD survivors with atherosclerosis
- Coronary reimplantation
  - TGA, ALCAPA, AV disease, Aortic root aneurysms
- Systemic RV’s
  - Hypoplastic left heart
  - Corrected TGA
- Syndromic patients
  - Williams Syndrome: coronary artery narrowing
  - Other vasculopathies
Fixed and Reversible Defects

42 yo former Tetralogy of Fallot patient, s/p RV/PA conduit, presenting with typical angina: $^{13}$N-NH$_3$ PET

Partington et al. J Nuc Cardiol (2016) 23: 45-63
Fixed and Reversible Defects

20 yo TGA, s/p ASO with chest pain: $^{82}$Rb PET, showing apical and anterolateral reversible defects

Partington et al. J Nuc Cardiol (2016) 23: 45-63
Myocardial Flow Reserve

- Time activity curve fitting
- 2 compartment model
- Estimates of MBF in ml/g/min
- MFR = Stress MBF / Rest MBF

List mode or Multi-frame/Dynamic Acquisition: $^{82}$Rb or $^{13}$NH$_4^+$

Myocardial Flow Reserve

List mode or Multi-frame/Dynamic Acquisition: $^{82}\text{Rb}$ or $^{13}\text{NH}_4^+$

$^{13}$NH$_4^+$ PET/CT in diabetic patient with hypertension and risk of ischemic heart disease: LAD

Myocardial Flow Reserve

Patients with Normal Regional Perfusion

- Associated with worse outcome in CAD
  - A non-specific variable
- In CHD, being studied:
  - TGA
    - Variable reductions in MFR depending on repair
  - ALCAPA
    - Reductions in LCA territory MFR vs RCA
  - Fontan
    - Reduced MFR in systemic RV
  - Cyanotic Heart Disease

5-yo D-TGA, VSD and PS, s/p attempted Rastelli with ligation of the LAD; subsequent BTS and BDG. Assess myocardial perfusion and LV viability

\[ ^{13}\text{N-NH}_4^+ \text{ PET/CT with Adenosine stress} \]
\( ^{18} \text{F-FDG} \) and endocarditis

- **Prosthetic valves, stents & conduits**
  - Predisposed to infection
  - Difficult to evaluate by MRI, CT or echo
  - High sensitivity but potential for false +
  - Dietary prep with ketogenic (high fat/low carb) diet
    - Shifting myocardium to FA metabolism
    - Reduce background

10 mo later, after Abx Rx
Radionuclide Imaging in Epilepsy

- Pre-surgical epilepsy evaluation
- Opportunity for shortening the imaging & sedation
- Role for non-FDG PET tracers
54 children with refractory epilepsy

- EEG, MRI, FDG-PET, Ictal/Interictal SPECT, SISCOM
- Concordance with clinical epileptogenic zone:
  - MRI: 21/54 (39%)
  - SISCOM: 36/54 (67%)
  - \(^{18}\)F-FDG PET: 31/54 (57%)
  - FDG PET + SISCOM: 41/54 (76%)
  - In 2/3 of MRI failures either PET or SISCOM localized

- SISCOM and \(^{18}\)F-FDG PET: complementary pre-op data matching EEG/clinical data in \(\frac{3}{4}\) of patients

- *Note challenge of obtaining interictal and ictal SPECT*

MRI, PET and Epilepsy

- Greater severity of pre-op hypometabolism correlated with better post-op seizure control
- Ipsilateral temporal lobe hypometabolism 86% predictive of good post-op outcome
- Functional deficit zone: Brain region with abnormal function during interictal period
  - Extratemporal hypometabolism in TLE has worse outcome
- Need for additional tracers
Tracers for Targeted Epilepsy PET Imaging

- $^{11}$C flumazenil (FMZ)
  - GABA antagonist
  - More sensitive and accurate than FDG-PET
- $^{11}$C-carfentanil (CFN)
  - Opioid receptor (delta) agonist
- $^{18}$F-MPPF
  - Serotonin 5-HT1A antagonist
- $^{11}$C-alpha-methyl-L-Tryptophan (AMT)
  - Increased uptake in TSC and in some FCD pts
Reduced $^{18}$F-FMZ uptake in right temporal lobe in MTS, more precisely localizing epileptogenic focus than FDG.

$^{11}$C-AMT uptake localizing the epileptogenic left parietal tuber.

Kumar & Chugani. JNMT (2017) 45: 22
Integrating PET and MRI

Complex MRI, DTI, MEG and EEG analysis characterizing epileptogenic tubers in TSC patient

18F-NaF PET, MRI and non-Accidental Trauma

MRI:
- Soft tissues
- Brain
- 18F-NaF Bone PET
- Occult lesions
- Distribution
wb MRI in Suspected Infant Abuse

- **167 fractures**
  - 27% both SS and MRI
  - 41% by wbMRI
  - 32% by skeletal survey
- **wbMRI: low sensitivity for detecting CML (31%)**
- **wbMRI: low sensitivity for muscle injury near rib fx**
- **Conclusion:**
  - Insensitive for detecting high specificity lesions

\(^{18}\)F-NaF PET & Skeletal Trauma in Child Abuse

- 22 pts, 114 bone locations with fracture
- \(^{18}\)F-PET sensitivity vs skeletal survey
  - 18\% higher for all fractures
  - 35\% higher for thoracic fractures
  - 27\% higher for posterior rib fractures
  - 18\% lower for CML’s
  - Similar specificity, expect posterior rib fractures, where skeletal survey was 99\% specific vs 93\%

18F-NaF PET & Skeletal Trauma in Child Abuse

18F-NaF PET showing additional lesions in thorax and spine in 2 patients with multiple fractures

Tau PET imaging in Traumatic Brain Injury

- Severity based on clinical Symptoms
- MRI
  - fMRI, DTI, DWI
  - FA, RD, AD
- $^{18}$F-Flubetapir
  - amyloid plaques
- $^{18}$F-SV-1451
  - tau protein aggregates
- TBI associated with increased tau deposition

Saint-Aubert et al. Mol Neurodeg (2017)

$^{18}$F-SV-1451 PET in Human TBI

Wooten et al. JNM (2017) 58: 484

Courtesy of N. Kwatra, MD
• Reviewed non–oncologic applications of PET/MRI

• To review both FDG and non-FDG PET tracers and the potential for use in PET/MRI
  – $^{18}$F-Na
  – $^{13}$N-NH$_4^+$, $^{82}$Rb
  – $^{11}$C-alpha-methyl-L-Tryptophan (AMT)
  – $^{18}$F-SV-1451 for tau imaging

• To appreciate the potential role of PET/MRI in diagnosis and management of non-oncologic diseases