MHIF FEATURED STUDY:
AEGIS 2

• DESCRIPTION:
  CSL112 is being developed for use in patients with ACS (diagnosed with either STEMI or NSTEMI and exclusive of unstable angina) to reduce the risk of CV death, MI, and stroke upon delivery of CSL112.
  Evidence from the Apo-I Event Reducing in Ischemic Syndromes-I (AEGIS-I) study has demonstrated that administration of apoA-I increases cholesterol efflux in MI patients.

• CRITERIA LIST/QUALIFICATIONS:
  Inclusion
  Positive Troponin with at least 50% stenosis on > 1 epicardial artery or prior cath with at least 50% stenosis on > 1 epicardial artery or prior CABG
  Additional risk factor: DM, > 65 y.o., prior hx of MI or PAD

  Exclusion
  • EF < 30%  Body weight < 50 kg
  • ALT > 3 x ULN  Allergy to soy beans or peanuts
  • GFR< 30  Plan for CABG
Liquid Drano for Coronary Arteries

Apolipoprotein A-I (apoA-I) is the primary component of HDL

CSL 112 is apoA-I, purified from human plasma
Role of HDL in Reverse Cholesterol Transport
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CONDITION: Acute Coronary Syndrome
PI: Thomas Knickelbine, MD
RESEARCH CONTACT: Stephanie Ebnet
SPONSOR: CSL Behring

OPEN AND ENROLLING:
Please Refer Patients to Steph!
Nuclear Cardiology: Beyond perfusion imaging

• Nuclear cardiology is a “mature” technology
• Used mainly for stress perfusion imaging
• LV systolic function
• Newer detector technology, processing, SPECT alternatives (PET), novel radiotracers
Overview

- Myocardial viability
- Coronary blood flow measurement
- Cardiac sarcoidosis
- Cardiac amyloidosis
- Inflammatory disorders
  - Vasculitis
  - Device infections
  - Endocarditis
Assessing myocardial viability

• Ischemic cardiomyopathy is the most common cardiomyopathy in developed countries
• These patients are at high risk for complications during revascularization
• Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF, who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind. (Level of Evidence: C)
• Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD. (Level of Evidence: B)

Viability testing and impact of revascularization on prognosis

- 79.6% 23.0%
χ²=147 χ²=1.43
p<0.0001 p=0.23

Death rate (%/yr)

<table>
<thead>
<tr>
<th></th>
<th>Revasc.</th>
<th>Medical</th>
<th>Revasc.</th>
<th>Medical</th>
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<tbody>
<tr>
<td>Viable</td>
<td>3.2</td>
<td>16.0</td>
<td>7.7</td>
<td>6.2</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2002;39:1151-9
Methods for assessing myocardial viability

• Thallium scan
• DSE
• CMR
• FDG-PET

Hibernating myocardium

• Characterized by impaired function (loss of contractility)
• Can regain function with resolution of ischemia/hypoxia
• Hibernating myocardial cells exhibit altered metabolic pathways
Cardiac myocyte metabolism

Myocyte energy metabolism

- Fatty acid metabolism
  - TCA cycle
  - Acyl-CoA
  - Carnitine
  - Lactic acid
  - Pyruvate
  - Glucose-P
  - Glycogen
  - Glucose-6-P
  - FDG-P

- Free fatty acids metabolism
  - \(^{15}C\)-Palmitate

Myocyte Response to Ischemia

- Normal function
- Early recovery
- Partial or delayed recovery
- Coronary flow reserve
- Revascularization

- Adaptive down-regulation
  - Decreased flow
  - Metabolic alterations
  - Activation of cell survival genes
  - Structural changes
    - Glycogen storage
    - Contractile proteins
    - Mitochondria
    - Apoptosis
    - Collagen matrix deposition
    - Hypertrophy

- Repetitive ischemia
  - Repetitively damaged (normal perfusion)
  - Functional hibernation (increased perfusion)
  - Structural hibernation (decreased perfusion)

- Cell death
  - DE \(\rightarrow\) FDG \(\leftrightarrow\) SCAR

Myocardial Substrate Use

- Fasting state: higher FFA, lower glucose
- Fed state: lower FFA, higher glucose
- Glucose uptake is increased during hypoxia and mild-moderate ischemia and decreased with severe ischemia
- FFA uptake is decreased during all levels of ischemia
- Acipimox is used in Europe, but not available in the US
18FDG

- Radioactive glucose analog
- Half life of 110 min
- Phosphorylated, then needs to decay before it can be metabolized further
- Produced by cyclotron

Myocardial FDG uptake can be nonuniform

Temporal and spatial variability in myocardial FDG uptake

Patterns of FDG uptake in patients “without” CV disease

a) No uptake
b) Diffuse uptake
c) Focal uptake
d) Focal on diffuse uptake

Nose H, et al. J. Medical Inv 2014 16:53-58
Glucose manipulation for viability

- Oral loading
  - Inadequate uptake in 10% of patients
- Euglycemic hyperinsulinemic clamp
  - Laborious and impractical
- Simplified IV loading with insulin and glucose
  - Too high a glucose level (>150 mg/dL) can result in poor images

Patterns of FDG-PET uptake

<table>
<thead>
<tr>
<th>Perfusion</th>
<th>FDG</th>
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<tbody>
<tr>
<td>Preserved</td>
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<tr>
<td>Reduced</td>
<td>Normal</td>
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<tr>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Preserved</td>
<td>Reduced</td>
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</table>
Functional recovery after revascularization depends on the amount of viable myocardium.
A higher mismatch size derives greater benefit from revascularization

**STICH**

- Evaluated the effectiveness of CABG in patients with CAD and LV systolic dysfunction (EF ≤35%)
- Patients randomized to CABG or medical therapy
- Viability substudy included 601 patients (not randomized)
- SPECT or DSE was used for viability assessment
- No difference in mortality in viability substudy
STICH

- SPECT viability: “...patients with viability were defined as those with 11 or more viable segments on the basis of relative tracer activity.”
- DSE viability: “...patients with viability were defined as those with 5 or more segments with abnormal resting systolic function but manifesting contractile reserve during dobutamine administration.”
- “We also did not incorporate other approaches, such as positron-emission tomography (PET) or contrast-enhanced magnetic resonance imaging (MRI).”
- Viability testing not obtained randomly- selection was based only on the physician’s discretion -> possible selection bias
PARR-2

- Assessed the effectiveness of FDG-PET-assisted management of patients with severe LV dysfunction (EF <35%) and CAD
- Randomized 430 patients: 218 PET, 212 standard care
- F/U one year
- No difference in outcomes

Ottawa FIVE subsubstudy

- 18F-FDG PET Imaging of Myocardial Viability in an Experienced Center with Access to 18F-FDG and Integration with Clinical Management Teams
- 111 patients: 56 PET-guided therapy, 55 standard therapy
25% of patients in original study deviated from PET-recommended therapy

Long term beneficial effect of revascularization
Other factors that determine functional recovery

- Baseline LVEF
- Amount of infarcted myocardium
- Degree of myocardial remodeling/LV size
- Time to revascularization
Coronary blood flow measurement

- The percent stenosis on angiography does not reliably predict coronary flow reserve (anatomy ≠ physiology)
- Flow-guided revascularization appears to reduce subsequent coronary events when compared to percent stenosis-guided revascularization
- Nuclear stress tests are not reliable at predicting the extent of disease
- “balanced ischemia”
- Transplant vasculopathy
- Coronary vasomotor abnormalities- microvascular disease
- CFR- coronary flow reserve= stress flow/rest flow

How bad is the stenosis?
How bad is the stenosis?

Percent stenosis does not always correlate with flow
CF measurements with cardiac PET

- Do not involve another injection - performed with standard stress test protocol
- No additional radiation
- Values can be mapped to the standard myocardial segments/territories

CF measurements with cardiac PET

- Obtained by analyzing time-activity curves from dynamic acquisition of myocardial tracer uptake
- Tracer kinetic models and corrections for partial volume and myocardial spillover are applied to obtain CBF in mL/min/g
Time activity curves

Radiotracers used for CBF measurements
CBF by PET correlates well with MS flow

Similar perfusion patterns with different CFR results
Flow reserve aids to improve diagnostic accuracy

![Graph showing flow reserve](J_Nuc_Cardiol_2004_11_440-49)

![Images of cardiac studies](Journal_of_Nuclear_Med_2018_59_Feb_2018)
Flow reserve gives additional prognostic information

Flow reserve gives additional prognostic information
CFR measurement by PET may aid in assessing for transplant vasculopathy
Cardiac sarcoidosis

• Myocardial involvement is present in 20-76% of patients with sarcoidosis
• Patients with cardiac involvement typically die of CV complications
• Isolated cardiac sarcoidosis is not uncommon - difficult to diagnose

Cardiac sarcoidosis - diagnosis

<table>
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<tr>
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<th>Japanese</th>
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<tbody>
<tr>
<td>Histologic dx</td>
<td>+EMBx</td>
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<tr>
<td>Clinical dx</td>
<td>Biopsy-proven extra cardiac sarcoid AND 1 or more of: - steroid/immunosuppressant responsive CM or HB - Unexplained low EF (&lt;40%) - Unexplained VT - Mobitz type II or 3rd degree HB - Patchy uptake on cardiac PET - DE on CMR - +gallium scan AND Other causes have been excluded</td>
</tr>
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<td>“Probable” CS</td>
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• Active areas of sarcoidosis are glucose-avid
• Unaffected myocardium should be FFA-avid
• Pt is instructed to eat a high protein, high fat, and low carbohydrate diet
• No strenuous exercise for 24h prior to test
• Active myocardial inflammation (e.g. active myocarditis) can also cause preferential glucose uptake

Diet for sarcoid scan

• Please fast (no food) for at least 12 hours prior to this procedure.
• Plan to eat dinner between 5:00 and 6:00 p.m. the evening before your procedure.
• Follow a high protein, high fat, low carbohydrate diet for dinner.
• Eat a high fat, low carbohydrate meal for breakfast.
• Drink plenty of liquids so you stay well hydrated.
• Forbidden foods:
  • Sugar in any form is strictly forbidden (including natural sugars in fruit)
  • No pastas, breads, cereals, rice
  • No candy or gum
  • Processed products such as deli meats are discouraged. These products often contain hidden sugars.
  • Starchy vegetables are not permitted (potatoes, etc.)
  • Corn, peas, carrots, most legumes, grains are not permitted.
Uptake in CS is typically heterogeneous

PET pattern in CS

FDG uptake and perfusion abnormalities suggest poorer prognosis
RV uptake of FDG gives poorer prognosis

![Survival Free of Death/VT graph](J.Am.Coll.Cardiol.2014.03.391.png)
Treatment can alter FDG uptake pattern


Treatment can improve LV systolic function

Association of Change in SUV Volume Above 4.1 g/mL with LVEF Change

Association of Change in SUV Maximum with LVEF Change
Use of FDG PET to evaluate for cardiac sarcoidosis

- Patients with histologic evidence of extra-CS, and abnormal scarring for CS, defined as one or more of following:
  - Abnormal electrocardiographic findings of complete left or right bundle branch block or presence of unexplained pathologic Q waves in two or more leads
  - Echocardiographic findings of regional wall motion abnormality, wall aneurysm, basal septum thinning, or LVFP > 50%
  - Holter findings of sustained or nonsustained ventricular tachycardia
  - Cardiac MRI findings suggestive of CS
  - Unexplained palpitations or syncope
  - Young patients (≤ 65 y) with unexplained, new onset, significant conduction system disease (i.e., sustained second- or third-degree atrioventricular block)
  - Patients with idiopathic sustained ventricular tachycardia, defined as not fulfilling any of the following criteria:
    - Typical outflow tract ventricular tachycardia
    - Fascicular ventricular tachycardia
    - Ventricular tachycardia secondary to other structural heart disease (coronary artery disease or any cardiomyopathy other than idiopathic)
  - Patients with proven CS as adjunct to follow response to treatment

J Nucl Med. 2017;58:1341-1353
Amyloidosis

• Caused by extra or intracellular deposition of amyloid protein
• Aggregates of misfolded proteins that are produced by cells at the site of deposition or originate from a distant location and precipitate locally
• Other constituents include glycosaminoglycans, apolipoprotein-E, and serum amyloid P-component

Amyloidosis- pathology

• HE staining-amorphous eosinophilic staining
• Apple green birefringence on Congo red staining
• Beta-pleated sheet structure on x-ray diffraction
Systemic amyloidoses

- A amyloidosis (AA)
- Light chain amyloidosis (AL)
- Heavy chain amyloidosis (AH)
- Transthyretin amyloidosis (TTR)
- Beta2-macroglubulin amyloidosis
- Cryopyrin-associated amyloidosis
Cardiac amyloidosis

- **EKG**
  - Low voltage, arrhythmia, conduction abnormalities
- **Echo**
  - LVH
  - Restrictive diastolic function
  - Systolic dysfunction
- **CMR**
- **Definitive diagnosis requires EMBx?**
- **nuclear imaging**
Nuclear radiotracers used for cardiac amyloid

- $^{99m}$Tc-DPD
- $^{99m}$Tc-MDP
- $^{99m}$Tc-PYP
- $^{1}$I-123 SAP
- $^{18}$F florbetapir
- $^{18}$F florbetapen
- $^{11}$C Pittsburgh B compound

99m Tc RNI grading

- Scan interpretation
- Grade 0- absent cardiac uptake
- Grade 1- mild uptake less than bone
- Grade 2- moderate uptake equal to bone
- Grade 3- high uptake with less or no bone uptake
99m Tc-PYP uptake is less in AL than ATTR


99m Tc-PYP uptake is less in AL than in ATTR

99m Tc-PYP images

Examples of Tc99-PYP scans
Sensitivity and specificity of RNI for ATTR

Gillmore, JD et al. Circulation. 2016;133:2404-2412

Proposed diagnostic algorithm

Gillmore, JD et al. Circulation. 2016;133:2404-2412
F18 florbetapir

- FDA-approved for brain imaging for amyloid
- Binds to amyloid protein


- Taken up by both AL and ATTR amyloid in the heart
F18 florbetapen

<table>
<thead>
<tr>
<th>AL amyloid</th>
<th>ATTR amyloid</th>
<th>Control</th>
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<tr>
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<td><img src="image2" alt="ATTR amyloid images" /></td>
<td><img src="image3" alt="Control images" /></td>
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F-18 florbetapen

![Box plot comparison](image4)

New treatments for ATTR are on the horizon

- Tafamidis is a transthyretin stabilizer that has been shown to slow the progression in TTR polyneuropathy
- Inoteresen and Palisiran improve symptoms of polyneuropathy in patients with hereditary ATTR
Tafamidis improves outcomes in patients with ATTR cardiomyopathy

FDG PET for device infection

- ~240,000 implants were performed in the US in 2003
- Incidence of PPM/ICD infections is 1.9 cases/1000 implants/yr
- Infections can be associated with endocarditis (leads) or just the generator pocket
- ~70% of patients present with signs of pocket infection
- Lead extraction results in ~2% morbidity and ~0.8 % mortality rates
- Diagnostic delays can result in poorer outcomes
A negative PET can help rule out infection

26 pts with possible infection
12 extracted
12/12 +PET

14 not extracted
1/13 +PET

20 pts with definite infection
All extracted
17 with +PET

Pocket infection

J Am Coll Cardiol 2012;59:1616–2
Epicardial lead infection

Negative FDG PET for CIED infection
FDG PET and device infections

FDG PET may help in patients with possible CIED infection
FDG uptake is greater in patients who underwent extraction

Proposed algorithms for CIED diagnosis
Large vessel vasculitis

Endocarditis
Take home points

• Myocardial viability assessment by FDG-PET has been validated and may improve outcomes
• Myocardial blood flow data from cardiac PET may aid in identifying targets for revascularization and also aid in the identification and prognosis for patients with MVD and CAV
• FDG-PET is useful in the treatment algorithm for cardiac sarcoidosis
• PYP scans can make the diagnosis of cardiac ATTR without the need for EMBx
• FDG-PET may also aid in the diagnosis of some inflammatory conditions (including infection)

Nuclear cardiology

• Wendy Beasley, CNMT
• Kelli Lemke, CNMT
• Joel Graham, CNMT
• Xao Lor, CNMT
• Jake Boerboom, CNMT
• Carol Carron, CNMT
• Miranda Weaver, CNMT
Thanks!