Nuclear Cardiology and Heart Failure in the Multimodality Arena

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Disclosure: No conflict of interest to declare
Despite improvement in health care systems morbidity and mortality remain high.

The use of imaging techniques for patients with heart failure has evolved substantially over the years. There is a need to identify imaging approaches that have a positive impact on therapy decisions, patient outcomes and costs.
Heart Failure represents the final common pathway for most forms of heart disease.

Question to be answered in a particular patient

- Ischemic vs non-ischemic etiology
- Selection of therapy: Medical, intervention, viability indication for revascularization
- Selection of candidates to device Therapy CRT/ICD
- Risk stratification
Non-invasive cardiac imaging evaluation of patients with chronic systolic heart failure: a report from the European Association of Cardiovascular Imaging (EACVI)

Alessia Gimelli et al. Eur Heart J 2014;35:3417-3425
OBJECTIVES

1) to determine the impact of emerging imaging strategies, on relevant clinical outcomes and decision making in patients with HF

2) to establish standardization quality assurance (QA) measures and central databases in order to achieve reliable outcome driven research

3) to apply this as a platform for evaluation of new and emerging imaging biomarkers in HF.
# The many Faces of Nuclear Cardiology in HF

<table>
<thead>
<tr>
<th>Target mechanism</th>
<th>Method</th>
<th>Clinical goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV function, geometry, dyssynchrony</td>
<td>ECG-gated SPECT &amp; PET (any tracer)</td>
<td>Define HF severity, determine prognosis (guide therapy)</td>
</tr>
<tr>
<td>Perfusion (relative)</td>
<td>SPECT ($^{99m}$Tc-tetrofosmin, $^{99m}$Tc-sesamibi, $^{99m}$Tc-MIBI)</td>
<td>Identify ischemia, determine need for revascularization</td>
</tr>
<tr>
<td>Absolute flow (flow reserve)</td>
<td>PET ($^{13}$NH$_3$, $^{82}$Rb, $^{18}$F-Flurpiridaz)</td>
<td>Identify global disease burden; guide/monitor therapy</td>
</tr>
<tr>
<td>Viability</td>
<td>PET ($^{18}$F-FDG)</td>
<td>Determine revascularization benefit</td>
</tr>
<tr>
<td>Sympathetic innervation</td>
<td>SPECT ($^{23}$MBF)</td>
<td>Risk assessment; guide anti-arrhythmic therapy</td>
</tr>
<tr>
<td>Inflammation</td>
<td>PET ($^{18}$F-FDG with preparation)</td>
<td>Determine cardiac sarcoidosis; guide therapy</td>
</tr>
<tr>
<td>Amyloid deposit</td>
<td>PET ($^{11}$In/$^{99m}$Tc-MDP)</td>
<td>Determin cardiac involvement; (noninvasive biopsy); guide therapy</td>
</tr>
</tbody>
</table>

**Notes:** LV, left ventricular; ECG, electrocardiogram; HF, heart failure; FDG, fluorodesoxyglucose; WBC, white blood cell; MDP, methylendiphosphonate.
Nuclear Cardiology in Heart Failure can be used:

TO DIAGNOSE THE CAUSE OF HF
1. To detect myocardial ischemia/viability
2. To diagnose the severity of LV systolic and diastolic dysfunction in HF
3. Cardiac innervation – mIBG planar and SPECT
4. To assess metabolism with free fatty acid imaging

TO ASSESS OR MONITOR THE IMPACT OF MEDICAL OR INTERVENTIONAL Tx

EMERGING APPLICATIONS OF SPECT-
1. Detection of arrhythmogenic ventricular cardiomyopathy and to guide
2. Resynchronization therapy ands ablation
3. Heart transplantation
4. Myocardial ACE and AT1R imaging
Coronary artery disease is the main cause of heart failure and that reversibility of LV dysfunction depends on the amount of viable tissue.

Pts with ischemic HF have worse prognosis than those of any etiology but may show dramatic improvement with timely revascularization

*Guidelines for Heart Failure JACC 1995;26*
*Felker GM. J Am Coll Cardiol 2002,39,210*
Nuclear perfusion imaging, SPECT

POLAR MAP TO QUANTIFY EXTENT AND SEVERITY OF ISCHEMIA
Is there viability?

- Clinical goal:
  - identify patients:
    - with *dysfunctional* but *viable* tissue
  - with potential to recover function
  - to justify enhanced surgical risk
PET- Viability

- PARR-2
  (PET and Recovery Following revascularization–Phase 2) study, the first large randomized trial using an FDG-PET–guided approach to management of patients with coronary disease and severe left ventricular dysfunction. Event rate 36% with standard care vs 30% with PET guided

Beanlands JACC 2007
Nuklearmedizinische Klinik rechts der Isar

Patient Name: Koch, Horst
Patient ID: 103885
Day of Birth: 1929.09.12

Protocol: PET VIABILITY
Study Desc 1:
Study Desc 2:
Study Date: 2001.12.14
Tracer 1: NH3
Tracer 2: FDG

Viability

NH3
Anterior
Septal Inf
Inferior
Base
Apex

FDG
Anterior
Septal Inf
Inferior
Base
Apex

Regional Distribution in % Territory

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<tr>
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<th>Norm.</th>
<th>Mism.</th>
<th>Scar</th>
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<tr>
<td>LAD</td>
<td>22.5</td>
<td>77.5</td>
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<tr>
<td>RCA</td>
<td>90.0</td>
<td>10.0</td>
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<tr>
<td>LCX</td>
<td>93.8</td>
<td>6.2</td>
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gatedPET:
LVEF 26%

Total Distribution in % LV

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<tbody>
<tr>
<td>Normal</td>
<td>54.8%</td>
</tr>
<tr>
<td>Mismatch</td>
<td>45.2%</td>
</tr>
<tr>
<td>Scar</td>
<td>0.0%</td>
</tr>
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</table>

Courtesy M. Schweiger
**Ischemia on SPECT predicts benefit from revascularisation**

Medical therapy (Medical Rx) as a function of % total myocardium ischemic based on final Cox proportional hazards model. Model, $P<0.0001$; interaction, $P=0.0305$.

“Large ischemia” involving more than 20% of the LV volume
SPECT in Heart Failure can be used:

1. To diagnose the cause of HF
2. To detect myocardial ischemia/viability
3. To diagnose the severity of LV systolic and diastolic dysfunction in HF
4. Molecular tissue function (innervation) MIBG planar/SPECT and PET
5. To assess metabolism with free fatty acid imaging
6. To assess or monitor the impact of medical or interventional treatment
7. Emerging Applications of SPECT-
   - Detection of arrhythmogenic ventricular cardiomyopathy and to guide resynchronization therapy and ablation
   - Heart transplantation
   - Myocardial ACE and AT1R imaging
Assessment of ventricular function in pts with Heart failure

- Selection of patients for coronary artery bypass surgery
- Detection of other causes of HF
- Monitoring of thrombolytic therapy
- Measures cardiotoxic effects of drug treatment e.g. adriamycin
Role of ECG-Gating for Myocardial Perfusion SPECT

Improved diagnostic accuracy for CAD (less equivocal results, identification of attenuation)

Enhanced viability detection (additional regional functional information)

Incremental value for risk assessment (global functional parameters)
Diagnosis and assessment of ventricular aneurysm
SPECT in Heart Failure can be used:

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   - Myocardial ACE and AT1R imaging
Nuclear scintigraphy is the only method currently available!
Υπολογισμός των H/M (heart to mediastinum ratio) και WR (washout rate) με επίπεδες εικόνες MIBG
H/M Ratio of MIBG Uptake: Measure of Specific to Non-specific Uptake

H/M = 2.3  H/M = 1.7  H/M = 1.1

Normal Innervation  NHYA Class II HF  NHYA Class IV HF

Courtesy of Dr. Arnold Jacobson
Evaluation of cardiac innervation by PET

<table>
<thead>
<tr>
<th>Radionuclide tracers</th>
<th>Type of Tracer</th>
<th>Target</th>
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<tbody>
<tr>
<td>11C-meta-hydroxyephedrine</td>
<td>Cat.- Analogue</td>
<td>Sympathetic uptake/storage</td>
</tr>
<tr>
<td>11C-epinephrine</td>
<td>Catecholamine</td>
<td>Sympathetic uptake/storage</td>
</tr>
<tr>
<td>11C-phenylephrine</td>
<td>Catecholamine</td>
<td>Sympathetic washout</td>
</tr>
<tr>
<td>18F-6-fluorodopamine</td>
<td>Catecholamine</td>
<td>Sympathetic uptake/function</td>
</tr>
</tbody>
</table>
ADMIRE-HF   Myocardial 123I-mIBG Imaging in HF. Jacobson et al. JACC 2010.

ADreView Myocardial Imaging for Risk Evaluation in Heart Failure

961 HF failure patients; NYHA II 83%, class III 17%

Ischemic HF 66%, non-ischemic HF 34%

LVEF ≤35%, mean 27% (range 5-35%)

MIBG planar scan; H/M ratio:

H/M ratio ≥1.6 – low risk
H/M ratio <1.6 – high risk
Event rates vs HM ratio
237 cardiac events

ACE Cumulative incidence (%)

0  10  20  30  40

0  6  12  18  24  Months

H/M ratio < 1.60

760 subjects
212 events

H/M ratio ≥ 1.60

201 subjects
25 events

p < 0.0001

AdreView: additional prognostic value for adverse cardiac event risk
Cardiac death vs H/M ratio

53 patients cardiac death

201 subjects
2 cardiac deaths
H/M ratio ≥1.60: 2-year event-free survival 98%

760 subjects
51 cardiac deaths

*p = 0.002 vs H/M ratio ≥1.60
H/M ratio <1.60: 2-year event-free survival 89%

NPV 98% for cardiac death
Regional Myocardial Sympathetic Denervation Predicts the Risk of Sudden Cardiac Arrest in Ischemic Cardiomyopathy - PAREPET
**SPECT in Heart Failure can be used:**

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   - Heart transplantation
   - Myocardial ACE and AT1R imaging
Tracer: I-123 BMIPP (Beta Methyl Iodo Phenyl Pentadecanoic Acid)

Indication: Assess myocardial viability in pts with ischemic cardiomyopathy combined with a perfusion tracer (TL-201), creating miss-math images

Image marker: Uptake and redistribution with long residence time in the myocardium

Metabolic stunning memory: Depicts an ischemic events in the detection of chest pain syndrome in the ER that can be imaged later
SPECT Cardiac Imaging can be used:

1. To diagnose the cause of HF
2. To detect myocardial ischemia/viability
3. To diagnose the severity of LV systolic and diastolic dysfunction in HF
4. Molecular tissue function (innervation) – mIBG planar and SPECT
5. To assess metabolism with free fatty acid imaging
6. F/u post heart transplantation
7. To assess or monitor the impact of medical or interventional treatment
8. Emerging Applications of SPECT- Detection of arrhythmogenic ventricular cardiomyopathy and to guide resynchronization therapy
   • Myocardial ACE and AT1R imaging
   • Image-guided VT ablation
C-11 HED: Reinnervation of Neuronal Fibers that are Cut During Heart Transplantation

CT(left) /SPECT-MIBG (right) imaging of a heterotopic transplant. No uptake in transplanted heart, mild uptake in the native.

KennethSK. J Heart Lung Transplant 2006
Evaluation of sympathetic nerve terminals with 11C-epinephrine (EPI) and 11C-Hydroxyephedrine (HED)

Both tracers showed high selectivity for neuronal uptake in the heart, with a significant reduction in tracer retention in transplant recipients compared with volunteers.

Compared with HED, EPI showed greater retention in volunteers and a lower retention ratio in transplant recipients, suggesting that EPI may be the superior tracer with higher sensitivity to neuronal abnormalities.

Because EPI reflects neuronal uptake, metabolism, and storage, it may be more suitable for the study of neuronal integrity than HED, which primarily traces uptake-1 capacity.

SPECT in Heart Failure can be used:

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   • Detection of arrhythmogenic ventricular cardiomyopathy
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   • Myocardial ACE and AT1R imaging
$^{123}$I-MIBG in congestive heart failure: effect of metoprolol

$^{123}$I-MIBG in congestive heart failure: effect of enalapril

Somsen et al, Heart 1996;76:218-22

before

6 weeks treatment
Impact of β-blockers in children with dilated cardiomyopathy assessed by MIBG

Baseline

Six months

Heart/mediastinum
1.62±26
2.23±49

LV ejection fraction
26±11%
43±17%

Maunoury, EJNMMI 2003;12:1604-1611
SPECT in Heart Failure can be used:

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   • Detection of arrhythmogenic ventricular cardiomyopathy
   • Image-guided VT ablation and resynchronization therapy
   • Myocardial ACE and AT1R imaging
**Arrhythmogenic Right Ventricular Cardiomyopathy**

- The high probability of exercise-induced tachyarrhythmia or sudden cardiac death and its affinity to catecholamine effect constitutes a strong indication of the sympathetic nerve system contribution to the pathophysiology of arrhythmogenesis.

- MIBG - SPECT καπ C-11 HED - PET provide evidence of segmental or global absence (defects) of sympathetic innervation with reduce uptake and storage of catecholamines at pre-synaptic receptors of the left ventricle as well as diminution of beta meta-synaptic receptors.
Delayed contraction area responsible for sustained ventricular tachycardia in an arrhythmogenic right ventricular cardiomyopathy: Demonstration by Fourier analysis of SPECT equilibrium radionuclide angiography

Danielle Casset-Senon, PhD,a Dominique Babuty, PhD, MD,b Daniel Allison, MD,c Laurent Philippe, PhD, MD,a Véronique Eder, MD,a Laurent Fauchier, MD,b and Pierre Cosnay, MDb
Integration of 3-D Scar Models from Thallium SPECT to Guide VT Ablation

3D Voltage Map of LV

Thallium-201 3D SPECT Map

ROC Curve

Results - mIBG Guided Successful Ablation sites

In 13 patients with ICM 40% of patients had successful VT RFA in area of abnormal mIBG innervation despite normal voltage
Myocardial Sympathetic Innervation and Long-Term LV Mechanical Unloading

12 patients with end-stage heart failure who received an LVAD

LVAD-induced ventricular unloading resulted in hemodynamic and clinical improvements that were associated with improved sympathetic innervation.

SPECT/CT Images of Over-expressed Human ACE Mutant Transgenic Rat

Novel Imaging Targets of Local Myocardial Surface RAS for Exploratory Translation

Figure 1: Diagramatic Representation of Myocardial Cell and Potential Targets of Radiotracer Imaging and Mapping of the Surface Renin-Angiotensin System

ACE=angiotensin-converting enzyme; AGT=angiotensinogen; Ang 1=angiotensin I; Ang 2=angiotensin II; AT1R=angiotensin II type 1 receptor; AT2R=angiotensin II type 2 receptor

Schindler TH and Dilsizian V. J Am Coll Cardiol 2012; 60: 2535-8.
Conclusions

- It is fair to say that no one modality at the moment can answer every question we may have in this situation in one sitting.
- Nuclear Cardiology Imaging can be used for the stratification of pts with HF of CAD or CM origin and the assessment of treatment strategies.
- Together with myocardial perfusion, imaging, cardiac sympathetic function, provides information on the extent of regional cardiac denervation which is often larger than that of ischemia/scar.
- Emerging applications such as molecular imaging of SPECT such as detection of arhythmogenic ventricular cardiomyopathy, image-guided VT ablation and resynchronization therapy, heart transplantation programs and myocardial ACE and AT1R imaging is expected to gain more widespread clinical use.
Unsettled issues regarding viability and prognosis

- Does revascularization improve survival in pts with viable myocardium compared to medical therapy?
  
  The annual mortality was significantly lower in those treated with revascularization (3.2%) than those treated medically (16%) irrespective of the diagnostic technique used.

- Does viability assessment improve selection of pts with LV dysfx for revascularization?
  
  Pts with viable myocardium undergoing revascularization the annual mortality rate was 3.2% compared to 7.7% in those without viability. Hence non-invasive evaluation is crucial.

- Is improved outcomes after revascularization related to the improvement of LV fx?
  
  Lack of data addressing link between post-op improved LV fx and improvement in survival. **STICH trial** started 2002 will give the answer in 2008!!..

Bonow R. Ed. JACC 2002;39

Allman KC. JACC 2002;39
STICH and Viability Substudy
Conclusions -- Clinical Implications

- Absence of evidence of benefit is not evidence of lack of benefit, particularly for CABG
- Multiple limitations of viability substudy
- For pts with large viability/dysfunction (>20% LV) matching severe CAD
  Acceptable risk of revascularization
  Shared decision-making
- Need for additional evidence, particularly for PET and MRI

STICH Viability Hypothesis

STICH results:
- Demonstrate a significant association between myocardial viability and outcome, but this association is rendered non-significant when subjected to a multivariable analysis that includes other prognostic variables.
- Fail to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to mortality, whether assessed according to treatment assigned (intention to treat) or to the treatment actually received.

Robert O. Bonow, MD
On behalf of the STICH Trial Investigators
123-I Metaiodobenzylguanidine (123-I MIBG) Imaging

Normal MIBG uptake

PLANAR IMAGING

SPECT IMAGING

HMR = 2.2

Lung apex
Mediastinum ROI
Cardiac ROI
Results – Innervation Defect and Voltage Scar –

<table>
<thead>
<tr>
<th></th>
<th>% MIBG defect</th>
<th>% voltage scar</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Septal</td>
<td>30±5.4</td>
<td>24±9.7</td>
<td>0.202</td>
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<tr>
<td>Inferior</td>
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Results - Successful Ablation sites

90% of successful ablation sites in area of abnormal voltage and innervation defect
<table>
<thead>
<tr>
<th></th>
<th>Echo</th>
<th>CMR</th>
<th>SPECT</th>
<th>PET</th>
<th>CT</th>
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<tr>
<td><strong>CAD</strong></td>
<td></td>
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<tr>
<td>Ischaemia</td>
<td>++</td>
<td>+++</td>
<td>+++++</td>
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<tr>
<td>Hibernation</td>
<td>+++</td>
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<tr>
<td>Necrosis</td>
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<tr>
<td>Anatomy</td>
<td></td>
<td></td>
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<tr>
<td><strong>Valvular</strong></td>
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<tr>
<td>Stenosis</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Regurgitation</td>
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<td><strong>Myocarditis</strong></td>
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<tr>
<td>Sarcoidosis</td>
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<td>Hypertrophic CMP</td>
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<td>HCM</td>
<td>+++</td>
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<td>Amyloidosis</td>
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<td>Iron: haemochromatosis</td>
<td>+</td>
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<tr>
<td>Iron: thalassemia</td>
<td>+</td>
<td>+++</td>
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<td><strong>Restrictive CMP</strong></td>
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<td>Pericarditis</td>
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<td>Endomyocardial fibrosis</td>
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<tr>
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<td>ARVC</td>
<td>++</td>
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What test to perform in HF?

**BIOMARKERS**: ST2 and galectin. Knowledge of the biomarker in general leads to no specific decision and thus is of very limited clinical value

**CTA**: CT-based assessment of FFR is an exciting development for evaluation of CAD, but it has not been studied in the setting of HF and systolic dysfunction, and its correlation with downstream tissue viability—which is what we really need to know—is unknown.

**STRESS ECHO**: The performance of stress echocardiography for detection of CAD in the setting of baseline abnormalities of regional or global function is modest as they point out. Techniques such as strain imaging, while of great interest pathophysiologically from an academic standpoint, have no clear practical implication in HF setting.

**NUCLEAR CARDIOLOGY**: SPECT stress/rest imaging like echocardiography has modest performance for detecting CAD in the setting of HF but has **high negative predictive value to rule out** extensive CAD likely related directly to the cardiomyopathic state. SPECT and PET techniques for assessing viability and potential benefit of revascularization have a solid literature base and have been widely used for that purpose.

**MOLECULAR NUCLEAR IMAGING**: Imaging sympathetic innervation is theoretically attractive to potentially assess arrhythmic risk and perhaps guide ICD decisions as they suggest, but none of the data published to date are adequately powered to enable identification of low risk patients with sufficient confidence to allow a decision not to implant an ICD in someone who otherwise has a clinical indication.
Wessler BS, J Nucl Med 2015;56:20S-4S.
OBJECTIVES

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2) to establish standardization quality assurance (QA) measures and central databases in order to achieve reliable outcome driven research

3) to apply this as a platform for evaluation of new and emerging imaging biomarkers in HF.
Level II Project

ICD: (Scar/Viability), (HED/MIBG)
CRT: (Dysynchrony-Lateral scar-Metabolic reserve)
Is there ischemia?

Systolic wall motion imaging

Perfusion imaging

ECG changes
systolic dysfunction
diastolic dysfunction
hypoperfusion

Time from onset of ischemia

angina

Schinkel et al. EHJ 2003
“More than 50% of Q wave infarct regions on ECG, or of segments with persistent defects on TL-201 scintigraphy or asynergy in ventriculography, have residual metabolic activity indicative of viable myocardium”.

*Brunken R et al. Circulation 73:951, 1986*
Myocardial Viability and Survival in Ischemic Left Ventricular Dysfunction

Robert O. Bonow, MD
On behalf of the STICH Trial Investigators
N Eng J Med 2011

STICH Viability Hypothesis

**STICH results:**
...demonstrate a significant association between myocardial viability and outcome, but this association is rendered non-significant when subjected to a multivariable analysis that includes other prognostic variables.

...fail to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to mortality, whether assessed according to treatment assigned (intention to treat) or to the treatment actually received.
STICH Viability Study
Limitations

- Patient selection—differences in race/EF
- Small percentage (19%) without viability
- ICD in 22%
- High rate of baseline medical therapy
- >25% with single-vessel CAD
- SPECT/Echo parameters not identical
- Multiple SPECT protocols
- No MRI or PET

STICH and Viability Substudy
Conclusions -- Clinical Implications

- Absence of evidence of benefit is not evidence of lack of benefit, particularly for CABG
- Multiple limitations of viability substudy
- For pts with large viability/dysfunction (>20% LV)
  - Matching severe CAD
  - Acceptable risk of revascularization
  - Shared decision-making
- Need for additional evidence, particularly for PET and MRI
So why I-123-mIBG has not gained a more widespread clinical use?

- Referring cardiologists still relatively unaware of clinical value of I-123-mIBG
- Radiation exposure
- Cost of the procedure
- Technical limitations (SPECT images still sub-optimal)
- Alternative, cheaper and easily available biomarkers available
Event-free survival during the follow-up in relation to normal or abnormal MIBG uptake

![Graph showing survival-free of VT/VI (%)](image)

- **MIBG+**
- **MIBG-**

Time (years)

Survival-free of VT/VI (W)

P=NS

Impact of sympathetic innervation on recurrent life-threatening arrhythmias in idiopathic ventricular fibrillation

Presynaptic Innervation (¹²³I-MIBG)

Perfusion (²⁰¹Tl)

Prognostic value of cardiac MIBG imaging in heart failure

FIGURE 4. Survival curve, using life table analysis, with a threshold value of 20% for LVEF. A large difference is seen for survival between patients with a LVEF lower (dotted line) or greater (unbroken line) than 20% (p < 0.001).

FIGURE 5. Survival curve, using life table analysis, with a threshold value of 120% for H/M activity ratio. A striking difference is seen for survival between patients with H/M lower (dotted line) or greater (unbroken line) than 120% (p < 0.001). When compared to Figure 4, this graph shows that survival is much poorer in patients with an H/M below 120% than in those with a LVEF below 20%.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>HCM patients with VT</th>
<th>HCM patients without VT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M—early</td>
<td>1.93 ± 0.34</td>
<td>1.87 ± 0.29</td>
<td>.5635</td>
</tr>
<tr>
<td>H/M—delayed</td>
<td>1.67 ± 0.25</td>
<td>1.85 ± 0.30</td>
<td>.0500</td>
</tr>
<tr>
<td>WR</td>
<td>0.27 ± 0.06</td>
<td>0.17 ± 0.06</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EU dispersion (%)</td>
<td>39.0 ± 9.5</td>
<td>35.6 ± 9.6</td>
<td>.2620</td>
</tr>
<tr>
<td>DU dispersion (%)</td>
<td>41.1 ± 8.0</td>
<td>41.3 ± 8.6</td>
<td>.9178</td>
</tr>
<tr>
<td>WR dispersion (%)</td>
<td>45.3 ± 20.1</td>
<td>52.9 ± 48.2</td>
<td>.5606</td>
</tr>
<tr>
<td>EU—SD (%)</td>
<td>11.1 ± 2.7</td>
<td>10.1 ± 2.9</td>
<td>.2669</td>
</tr>
<tr>
<td>DU—SD (%)</td>
<td>11.7 ± 2.1</td>
<td>11.7 ± 2.6</td>
<td>.9515</td>
</tr>
<tr>
<td>WR—SD (%)</td>
<td>11.9 ± 6.4</td>
<td>13.6 ± 12.8</td>
<td>.6304</td>
</tr>
</tbody>
</table>

H/M, heart/mediastinum uptake ratio; WR, washout rate; EU, early uptake; DU, delayed uptake; EU—SD, SD in regional early uptake; DU—SD, SD in regional delayed uptake; WR—SD, SD in regional washout rate.
Downregulation of beta-adrenergic receptor density (Bmax) in ARV

Reduced beta-receptor density in ARVC (-42%).

Interpretation:
The higher flow corrected k2 in patients with lower Vd argues against a loss of neurons and rather supports a reduced uptake-1 to release ratio.

Conclusion:
ARVC is characterized by increased sympathetic firing rates and consecutively downregulated beta-receptors.

Wichter T et al. Circulation 2000;101:1552-1558
Changes in MIBG imaging parameters predict clinical response to treatment with β-blockers.

Changes in total defect score (TDS) and heart to mediastinum ratio (H/M) are correlated with New York Heart Association (NYHA) class.

Toyama et al. JNM 2003;44:1604-1611
Table 2. Univariate and multivariate linear model between H/M, WR, LVEF, LVMI, and natriuretic peptide

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>R</strong></td>
<td><strong>β-coefficient</strong></td>
<td><strong>R</strong></td>
<td><strong>β-coefficient</strong></td>
</tr>
<tr>
<td>LVEF</td>
<td>−0.28</td>
<td>NS</td>
<td>0.16</td>
</tr>
<tr>
<td>LVMI</td>
<td>0.36</td>
<td>NS</td>
<td>0.25</td>
</tr>
<tr>
<td>ANP</td>
<td>0.48</td>
<td>NS</td>
<td>0.13</td>
</tr>
<tr>
<td>BNP</td>
<td>0.59</td>
<td>−0.001</td>
<td>0.18</td>
</tr>
<tr>
<td>NE</td>
<td>0.43</td>
<td>0.0039</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**P**

<table>
<thead>
<tr>
<th>WR</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
<td><strong>β-coefficient</strong></td>
<td><strong>R</strong></td>
<td><strong>β-coefficient</strong></td>
</tr>
<tr>
<td>HNCM</td>
<td>0.69</td>
<td>0.004</td>
<td>0.30</td>
</tr>
<tr>
<td>HOCM</td>
<td>0.72</td>
<td>0.003</td>
<td>0.30</td>
</tr>
<tr>
<td>APH</td>
<td>0.75</td>
<td>0.001</td>
<td>0.30</td>
</tr>
<tr>
<td>C</td>
<td>0.78</td>
<td>0.0003</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**P**

NS, Not significant.
Figure 2. Early and delayed uptake ratio and washout rate of MIBG in HCM with VT (VT+) and without VT (VT-).
ISCHEMIC CASCADE

What SPECT can do?
Information provided by radionuclide ventriculography studies in pts with heart failure

- Left and right ventricular function
- Volume of ventricular cavities
- Regional wall contraction
Nuclear Cardiology in Heart Failure can be used:

TO DIAGNOSE THE CAUSE OF HF
1. To detect myocardial ischemia/viability
2. To diagnose the severity of LV systolic and diastolic dysfunction in HF
3. Cardiac innervation – mIBG planar and SPECT
4. To asses metabolism with free fatty acid imaging

TO ASSESS OR MONITOR THE IMPACT OF MEDICAL OR INTERVENTIONAL Tx

EMERGING APPLICATIONS OF SPECT-
1. Detection of arrhythmogenic ventricular cardiomyopathy and to guide
2. Resynchronization therapy ands ablation
3. Heart transplantation
4. Myocardial ACE and AT1R imaging
1. Ejection fraction
2. Wall motion abnormalities
3. Volumes
4. Diastolic function indices
5. Dimensions
The Heart Failure Revascularisation Trial (HEART)

Revascularization vs Medical Therapy in Patients with Myocardial Viability

STICH Viability Study
- 1212 patients with EF <33%
- 621 patients with viability studies

Primary endpoint:
All-cause mortality

Secondary endpoints:
CV mortality
Death + CV hospitalization
Differences in pathophysiologic substrate of imaging modalities to detect viability

- **SPECT** imaging reflects intracellular processes, detecting the anatomic and functional integrity of cardiomiocytes membrane which transports kations
- **DES** assesses ventricular contractile reserve
- **PET** images blood flow and metabolism
- **MRI** hyperenhancement identifies scarred myocardium
Myocardial Iodine-123 Meta-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure

Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study

Arnold F. Jacobson, MD, PhD,* Roxy Senior, MD,† Manuel D. Cerqueira, MD,‡ Nathan D. Wong, PhD,§ Gregory S. Thomas, MD, MPH,§ Victor A. Lopez, BS,§ Denis Agostini, MD, PhD,¶ Fred Weinland, MD,¶ Harish Chandna, MD,§ Jagat Narula, MD, PhD,§ on behalf of the ADMIRE-HF Investigators

Table 5

Results of Multivariable Cox Proportional Hazards Analysis of Time to Cardiac Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M</td>
<td>0.36 (0.17–0.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (0.93–0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.48 (1.08–2.02)</td>
<td>0.015</td>
</tr>
<tr>
<td>BNP</td>
<td>1.00 (1.00–1.00)*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Assessment of ventricular function in pts with Heart failure

- Selection of patients for coronary artery bypass surgery
- Monitoring of thrombolytic therapy
- Measures cardiotoxic effects of drug treatment e.g. adriamycin
RNA MEASUREMENTS

1. Ejection fraction
2. Wall motion abnormalities
3. Volumes
4. Diastolic function indices
5. Dimensions
Diagnosis and assessment of ventricular aneurysm
Information provided by radionuclide ventriculography studies in pts with heart failure

- Left and right ventricular function
- Volume of ventricular cavities
- Regional wall contraction
Myocardial Viability and Survival in Ischemic Left Ventricular Dysfunction

Robert O. Bonow, MD
On behalf of the STICH Trial Investigators
MIBG and arrhythmogenic right ventricular cardiomyopathy (ARVC)

Normal early uptake

Structurally normal innervation!

Postsynaptic Cardiac Imaging

- PET or SPECT
  - Beta-receptors
  - Alpha-receptors (Alpha-1, Alpha-2)
  - Adenosine (A2A)
  - Muscarinic (M2)
Postsynaptic Cardiac Imaging

- PET or SPECT
  - Beta-receptors
  - Alpha-receptors (Alpha-1, Alpha-2)
  - Adenosine (A2A)
  - Muscarinic (M2)
Presynaptic Cardiac Imaging

- SPECT
  - I-123 MIBG
- PET
  - C-11-HED
  - F-18-Fluorodopamine
  - F-18-Fluoronorepinephrine
LV Ejection Fraction and Survival in Chronic CAD

Survival During Medical Therapy (%)

- **EF ≥ 50% (n=8640)**
- **EF 35-49% (n=2547)**
- **EF < 35% (n=1200)**

**P<0.001**

*Emond et al. Circulation. 1994;90:2645-57*
Proportion of the population living with Heart Failure

North America
- Canada: 1.5%
- USA: 1.9%

Europe
- France: 2.2%
- UK: 1.3%

Asia
- China: 1.3%
- Japan: ~1%
- Malaysia: 6.7%
- Singapore: 4.5%

Latin America
- No population-based estimates

Africa
- No population-based estimates

Middle East
- Oman: 0.6%

Australasia
- Australia*: 1.3%

*Heart failure: preventing disease and death worldwide
© European Society of Cardiology 2014
Importance of ischemic etiology for HF

• CAD is the primary etiology of LV dysfunction and its identification is of considerable importance in the work-up of HF patients.¹

• Patients with ischemic HF have worse prognosis than those with non-ischemic HF ² but potentially show dramatic improvement with timely revascularization under appropriate situations.

¹. Gheorghiade M, Circulation 1998, 97, 282-9
Non-invasive cardiac imaging evaluation of patients with chronic systolic heart failure: a report from the European Association of Cardiovascular Imaging (EACVI)

Alessia Gimelli et al. Eur Heart J 2014;35:3417-3425
Appropriate use of treatments

ESC – HF Registry
12,440 patients, 211 centres of 21 ESC Countries

Patient disposition

- Total population n. 12785
  - Consent No n. 345
  - Consent Yes n. 12440
    - Hospitalized HF n. 5939 (47.0%)
    - Outpatients CHF n. 7401 (59.5%)
    - De Novo n. 1402
    - Worsening n. 3555
    - Unknown n. 62

Aim: To evaluate how recommendations of European guidelines regarding pharmacological and non-pharmacological treatments for HF are adopted in clinical practice
Appropriate use of Drugs

ESC Registries 2013 - Rate of use and reasons for non use of recommended treatments in HF patients with reduced EF

- Betablockers
  - 92.7% YES 4439 pts
  - 7.3% NO 353 pts

- MRAs
  - 67.0% YES 3209 pts
  - 33.0% NO 1583 pts

Contraindicated
- n. 94 (2.0%)
- Asthma/CFP
- n. 28 (35.9%)
- Bradyarrhythmia
- n. 11 (14.1%)
- Symptomatic hypotension
- n. 11 (14.1%)
- PAD
- n. 9 (3.5%)
- Other
- n. 11 (3.5%)

Not tolerated
- n. 123 (2.6%)
- Bronchoscope
- n. 10 (3.2%)
- Symptomatic hypotension
- n. 7 (1.6%)
- Sleep apnoea
- n. 2 (0.5%)
- Other
- n. 110 (3.2%)

Real undertreatment
- n. 155 (3.2%)

Maggioni APM, et al. Eur J Heart Fail 2013 15, 808-817
Revascularization in chronic HF LVEF< 35%

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG is recommended for patients with significant LM stenosis and LM equivalent with proximal stenosis of both LAD and LCx arteries.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>CABG is recommended for patients with significant LAD artery stenosis and multivessel disease to reduce death and hospitalization for cardiovascular causes.</td>
<td>I</td>
<td>B</td>
<td>112,288</td>
</tr>
<tr>
<td>LV aneurysmectomy during CABG should be considered in patients with a large LV aneurysm, if there is a risk of rupture, large thrombus formation or the aneurysm is the origin of arrhythmias.</td>
<td>Iia</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Myocardial revascularization should be considered in the presence of viable myocardium.</td>
<td>Iia</td>
<td>B</td>
<td>55</td>
</tr>
<tr>
<td>CABG with surgical ventricular restoration may be considered in patients with scarred LAD territory, especially if a post-operative LVESV index &lt;70 mL/m² can be predictably achieved.</td>
<td>Iib</td>
<td>B</td>
<td>291–295</td>
</tr>
<tr>
<td>PCI may be considered if anatomy is suitable, in the presence of viable myocardium, and surgery is not indicated.</td>
<td>Iib</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
**Sudden Cardiac Death Statistics**

One of the most common causes of death in developed countries

<table>
<thead>
<tr>
<th>Incidence (cases/year)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>U.S.</td>
<td>5%</td>
</tr>
<tr>
<td>W. Europe</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

1. Reference
2. Reference
3. Reference
Benefits of ICD therapy

Primary Prevention Post-MI Trials:
Reduction in Mortality with ICD Therapy

% Mortality Reduction w/ ICD Rx

<table>
<thead>
<tr>
<th>Trial</th>
<th>Overall Death</th>
<th>Arrhythmic Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT 1</td>
<td>54%</td>
<td>75%</td>
</tr>
<tr>
<td>27 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUSTT 2</td>
<td>55%</td>
<td>73%</td>
</tr>
<tr>
<td>39 Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-II</td>
<td>31%</td>
<td>61%</td>
</tr>
<tr>
<td>20 Months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Risk Scores to Predict Outcomes in HF

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Reference (from full-text guideline)/Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HF</td>
<td></td>
</tr>
<tr>
<td><em>All patients with chronic HF</em></td>
<td></td>
</tr>
<tr>
<td>Seattle Heart Failure Model</td>
<td>(204) / <a href="http://SeattleHeartFailureModel.org">http://SeattleHeartFailureModel.org</a></td>
</tr>
<tr>
<td>Heart Failure Survival Score</td>
<td>(200) / <a href="http://handheldhofpedia.com/getHealth/CalculatorHFSS-Calc-37354.shtml">http://handheldhofpedia.com/getHealth/CalculatorHFSS-Calc-37354.shtml</a></td>
</tr>
<tr>
<td>CHARM Risk Score</td>
<td>(207)</td>
</tr>
<tr>
<td>CORONA Risk Score</td>
<td>(208)</td>
</tr>
<tr>
<td><strong>Specific to chronic HFpEF</strong></td>
<td></td>
</tr>
<tr>
<td>I-PRESERVE Score</td>
<td>(202)</td>
</tr>
<tr>
<td><strong>Acutely Decompensated HF</strong></td>
<td></td>
</tr>
<tr>
<td>ADHERE Classification and Regression Tree (CART) Model</td>
<td>(201)</td>
</tr>
<tr>
<td>EFFECT Risk Score</td>
<td>(203) / <a href="http://www.CCORT.ca/Research/CHFRiskModel.aspx">http://www.CCORT.ca/Research/CHFRiskModel.aspx</a></td>
</tr>
<tr>
<td>ESCAPE Risk Model and Discharge Score</td>
<td>(215)</td>
</tr>
<tr>
<td>OPTIMIZE HF Risk-Prediction Nomogram</td>
<td>(216)</td>
</tr>
</tbody>
</table>

2013 ACCF/AHA Guideline for the Management of Heart Failure
Relevance of a multidisciplinary approach in heart failure
Projected prevalence of HF in USA

Projected costs of HF in USA

We have a problem!

Dysfunctional Myocardium

- Viable (Recoverable)
  - Remodeled ‘Normal’
  - Stunning
  - Hibernation

Non-viable SCAR
Imaging Modalities to Assist with Guiding Therapy and the Evaluation of Patients with Heart Failure

IMAGE-HF
Overall Objectives of IMAGE-HF

1. Determine the impact of emerging imaging strategies on relevant clinical outcomes, quality of life, cost effectiveness, diagnosis and decision making in patients with HF

2. Establish standardized protocols, quality assurance (QA) and central databases to ensure reliable outcome-driven research

3. Provide a translational platform for the evaluation of imaging biomarkers, and
Level I Projects

Patients presenting with new or worsening symptoms/signs of HF (n=2265)** *
(with one of three clinical questions)

I-A (n=1511)  I-B (n=504)

Unknown Coronary Anatomy
Clinical Question: Is there obstructive CAD?
(n=250)

Known CAD/LVEF <40%
Clinical Question:
Is there ischemia/hibernation?

Known or suspected NICM or HFpEF
Clinical Question:
What is the cause of CM* or HF?
Patients presenting with new or worsening symptoms/signs of HF (n=2,265) (with one of three clinical questions)

Level I Projects

I-A
(n=1511)

Known: CAD/LVEF <45%
Clinical Question:
Is there ischemia/hibernation?

(n=495)

MRI vs PET vs SPECT**
Registry if unable to randomize

Primary Outcome:
Composite Clinical Endpoint

I-B
(n=1,016)

Known or suspected NICM or HFPSE
Clinical Question:
What is the cause of CM* or HF?

(n=504)

Routine MRI vs Echo +/- MRI**

Primary Outcome:
Specific Diagnosis
(Management Decisions)

Follow-up all level one patients

Outcomes: composite clinical endpoints (cardiac death, MI, Arrest, hospitalization), QoL, Cost, resource utilization, safety.
Patients presenting with new or worsening symptoms/signs of HF (n=2,265) (with one of three clinical questions)

Unknown Coronary Anatomy/Etiology
Clinical Question: Is there obstructive CAD?

I-C (n=250)

CTA vs. ICA**

Yes
Consider IA

No

Primary Outcome: Resource utilization

I-A (n=1511)

(n=495)

MRI vs PET vs SPECT**

Registry if unable to randomize

Primary Outcome: Composite Clinical Endpoint

I-B

(n=1016)

Unknown Coronary Anatomy/Etiology
Clinical Question: Is there ischemic "hibernation?"

Follow-up all level one patients

Outcomes: composite clinical endpoints (cardiac death, MI, Arrest, hospitalization), CoL, Cost, resource utilization, safety.

*CM = Cardiomyopathy

STD = Standard care which is: I-A: SPECT perfusion I-B: Echo +/- selective CMR; I-C: coronary angiography
IMAGE HF Level II:
Imaging for ICD / CRT selection? Beyond EF

- ICD
  - Scar / Viability
  - HED / MIBG

- CRT
  - Dysynchrony
  - Lateral Scar, Global Scar
  - Metabolic Reserve? (PREDICT)
Association of fibrosis as assessed by midwall LGE-CMR imaging with mortality and SCD in patients with NICM

(A) All-cause mortality

Log rank P<0.001

(B) Cardiovascular mortality or transplantation

Log rank P<0.001

(C) Sudden cardiac death or aborted sudden cardiac death

Log rank P<0.001

(D) Heart failure death, hospitalization, or transplantation

Log rank P<0.001
FIGURE 2: Level II Projects

Level I patients who do not respond to therapy

Patients excluded from Level I

Candidates for primary Prevention ICD*  No  Excluded

Yes

MRI to define scar**

Primary Outcome:
SCD,VT/VF(appropriate ICD discharge)

Follow-up all Level II patients
Secondary outcomes: composite clinical endpoints (cardiac death, MI, arrest, cardiac hospitalization), ICD discharge, QoL, cost, resource utilization

* Future studies will evaluate roles in other therapies, such as CRT (future project II-B)
** Future studies will evaluate other imaging approaches, such as HE (future project II-C)
Imaging in Heart Failure. What do we know?

- Imaging integral to heart failure Mx – Echo mainstay
- Advanced Imaging and Health Care Costs are increasing
- Ischemia/hibernation predict outcome response to revasc.
  - not needed in all patients / most useful in highest risk patients
  - does advanced imaging with PET or MRI impact outcomes?
- NICM etiology appears important for prognosis
  - does advanced imaging with MRI impact diagnosis, management or outcomes?
- ICD and CRT are effective therapies
  - but may benefit from better patient selection
- Vast array of emerging imaging biomarkers require evaluation for translation
• Serelaxin = recombinant human relaxin-2

• human relaxin-2 is naturally occurring peptide that regulates maternal adaptations to pregnancy

• increases arterial compliance, cardiac output, and renal bloodflow
RELAX-AHF
Effect of serelaxin on dyspnoea

A

B

Dyspnoea Likert scale
- Markedly improved
- Moderately improved
- Minimally improved
- No change
- Minimally worsened
- Markedly worsened

JR Teerlink et al. The Lancet Volume 381, Issue 9869 2012 29 - 39
SERELAX-AHF
Effect of serelaxin on mortality

Serelaxin for AHF got "breakthrough-therapy" path through FDA
Heart failure

2 issues importance

- Myocardial viability
- Risk Stratification
Presynaptic Sympathetic Innervation of the Heart

MIBG (Adreview) visualizes
- cardiac innervation
- cardiac denervation

- behaves as norepinephrine
- tracer is internalized by pre-synaptic nerve endings
Tracing Presynaptic Sympathetic Innervation by MIBG Imaging

\[ ^{123}\text{I} \] METAIODOBENZYL-GUANIDINE (MIBG)

NOREPINEPHRINE

MIBG

BLOOD

CARDIOMYOCYTE

SYMPATHETIC NERVE TERMINAL

Uptake

MIBG
123-I Metaiodobenzylguanidine (123-I MIBG) Imaging

Normal MIBG uptake

**PLANAR IMAGING**

HMR = 2.2

**SPECT IMAGING**
MIBG planar imaging

LVEF 33%

HMR 2.06

LVEF 21%

HMR 1.01
Cardiac 123-I MIBG Imaging for Risk Stratification of Patients with HF

Two-year cardiac event rate for subjects with LVEF ≤35% and LVEF 36-49%, stratified according to H/M ratio

Agostini D, et al. EJNMMI 2008
ADreView Myocardial Imaging for Risk Evaluation in Heart Failure

961 HF failure patients; NYHA II 83%, class III 17%
Ischemic HF 66%, non-ischemic HF 34%
LVEF ≤35%, mean 27% (range 5-35%)
MIBG planar scan; H/M ratio:

H/M ratio ≥1.6 – low risk
H/M ratio <1.6 – high risk
Event rates vs HM ratio

237 cardiac events

ACE Cumulative incidence (%)

0 10 20 30 40

p<0.0001

H/M ratio <1.60

760 subjects 212 events

H/M ratio ≥1.60

201 subjects 25 events

AdreView: additional prognostic value for adverse cardiac event risk
Cardiac death vs H/M ratio

53 patients cardiac death

201 subjects
2 cardiac deaths

H/M ratio ≥ 1.60: 2-year event-free survival 98%

760 subjects
51 cardiac deaths

*p=0.002 vs H/M ratio ≥ 1.60

H/M ratio < 1.60: 2-year event-free survival 89%

NPV 98% for cardiac death
Cardiac death vs H/M ratio

53 patients cardiac death

201 subjects
2 cardiac deaths

H/M ratio ≥ 1.60: 2-year event-free survival 98%

760 subjects
51 cardiac deaths

*p = 0.002 vs H/M ratio ≥ 1.60

H/M ratio ≤ 1.60: 2-year event-free survival 89%

NPV 98% for cardiac death
Severe heart failure – Patient – tailored therapy

LV function and size?

CAD: yes or no?

CAD: ischemia? viability?

Severe MR and LV shape?
LV function and size?

mortality

20 30 40 LVEF (%)
Is there ischemia?
Is there viability?

**PRE-OPERATIVE**
Single Vessel Disease
Occluded L.A.D.

- LVEDV: 123 ml
- LVESV: 81 ml
- LVSV: 47 ml
- LVEF: 0.37

---

**8 MONTHS POST-OPERATIVE**
Patent Coronary Bypass
Graft to L.A.D.

- LVEDV: 104 ml
- LVESV: 25 ml
- LVSV: 75 ml
- LVEF: 0.79

Rahimtoola SH. AHJ 1975
Neurotransmission Imaging in Cardiology

- Cardiac neuronal control is important
  - Autonomic regulation of LV and RV function and perfusion
  - Receptor mediated effects of drugs

Nuclear scintigraphy is the only method currently available!
CAD: yes or no?
Severe heart failure

Medical therapy

Revascularization

Mitral valve repair

LV aneurysmectomy

Individualized therapeutic approach
I-123 mIBG: Imaging Cardiac Innervation in Heart Failure

- Heart failure is characterized by increased sympathetic drive to the myocardium.
- mIBG is an analogue of norepinephrine that can visualize myocardial sympathetic innervation but are neither metabolized nor do they interact with postsynaptic receptors.
- Scintigraphic assessment of myocardial sympathetic innervation by measurement of heart to mediastinum (H/M) ratio of radioactive uptake in patients with NYHA Class II or Class III HF and LVEF ≤35% to help identify those with lower 1- and 2-year mortality risks as indicated by an H/M ratio ≥1.6.
- Limitations: In patients with CHF, mIBG utility has not been established for selecting therapy, monitoring response to therapy, or to identify a patient with high risk of death.
Neurotransmission scintigraphy: Methodology

Most widely used established radiopharmaceuticals

Presynapse

Tyrosine → DOPA → Dopamine → Noradrenaline

uptake-1

β receptor → G proteins → ATP → cAMP

Myocyte

Synaptic cleft

NA NA

Metabolism

18F-dopamine

11C-hydroxyephedrine

123I-MIBG

18F-FDA, 18F-FNE, 11C-EPI, 18F-FMR

13C-CGP 12177

18F-carazolol

123I-MIBG in congestive heart failure

Figure 4

MIBG uptake (cts/voxel)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n=10)</th>
<th>50 mg (n=5)</th>
<th>100 mg (n=9)</th>
<th>150 mg (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^{123}$I-MIBG in congestive heart failure

Somsen, van der Wall, van Vlies et al, Int J Cardiac Imaging 1997;
ΜΕΛΕΤΗ ΣΥΜΠΑΘΗΤΙΚΗΣ ΕΝΝΕΥΡΩΣΗΣ ΤΗΣ ΚΑΡΔΙΑΣ

- Η πρόσληψη επισημασμένων νευροδιαβιβαστών (νορεπινεφρινη-μεταραμινόλη) αντανακλά φυσιολογική δραστηριότητα και τόνο του ΣΝΣ.
- Οι ραδιοισοτοπικές τεχνικές είναι οι μόνες από τις απεικονιστικές τεχνικές με αυτή τη δυνατότητα. Απεικονίζονται με SPECT 123I-metaiodobenzyl gua-nidine (MIBG). Με PET χρησιμοποιούνται 18F-metaraminol και 11C-HED.
- Κλινική εφαρμογή στην πρόγνωση ασθενών με καρδιακή ανεπάρκεια, με κοιλ. Αρρυθμίες/ηλεκτρικό θάνατο, αναδιαμόρφωση αρ. κοιλίας και σε μεταμοσχεύσεις.
SPECT for the detection of viability

Conclusions

- Viability testing does not identify high risk patients subgroups and predicts
  - Respond to b-blockers therapy
  - Response to resynchronization therapy
  - Response to revascularization

- Viability testing should not be considered a prerequisite for decisions regarding medical vs surgical management in patients with ischemic LV dysfunction

- SPECT MPI is a good means to detect and predicts benefit from revascularization
Υπολογισμός των H/M (heart to mediastinum ratio) και WR (washout rate) με επίπεδες εικόνες MIBG
Myocardial Iodine-123
Meta-Iodobenzylguanidine Imaging
and Cardiac Events in Heart Failure

Results of the Prospective ADMIRe-HF (AdreView
Myocardial Imaging for Risk Evaluation in Heart Failure) Study

Arnold F. Jacobson, MD, PhD,* Roxy Senior, MD,† Manuel D. Cerqueira, MD,‡
Nathan D. Wong, PhD,§ Gregory S. Thomas, MD, MPH,§ Victor A. Lopez, BS,§
Denis Agostini, MD, PhD,¶ Fred Weiland, MD,¶ Harish Chandna, MD,# Jagat Narula, MD, PhD,§
on behalf of the ADMIRe-HF Investigators

Table 5: Results of Multivariable Cox Proportional Hazards Analysis of Time to Cardiac Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/M</td>
<td>0.36 (0.17–0.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (0.93–0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.48 (1.08–2.02)</td>
<td>0.015</td>
</tr>
<tr>
<td>BNP</td>
<td>1.00 (1.00–1.00)*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Απεικόνιση της αδρενεργικής νεύρωσης του μυοκαρδίου: Ι-123 MIBG (μετα-ιωδο-βενζυλ-γουανιδίνη)

- Συγγενής της νοραδρεναλίνης
- Καρδιακή ανεπάρκεια —↑NOR—↓MIBG
- ↓MIBG σε EM, μυοκαρδιοπάθειες
- Επιτυχής θεραπεία με α-MEA —↑MIBG (ασχέτως NOR)
- ↑MIBG = ο καλύτερος δείκτης μακροζωίας (!)

![MIBG Chemical Structure](image)
Υπολογισμός των H/M (heart to mediastinum ratio) και WR (washout rate) με επίπεδες εικόνες MIBG
Of 961 HF subjects, 237 (25%) had an adverse cardiac event in the 24 months follow-up.

<table>
<thead>
<tr>
<th></th>
<th>HF Progression</th>
<th>Arrhythmic Event</th>
<th>Cardiac Death</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Event</td>
<td>n=163 (68%)</td>
<td>n=50 (21%)</td>
<td>n=24 (10%)</td>
<td>237</td>
</tr>
</tbody>
</table>

* p<0.0001 vs H/M ≥1.60

2-Year Cardiac Death and All-Cause Mortality vs. H/M

A. Cardiac Death

B. All-cause Mortality

Presynaptic Sympathetic Innervation of the Heart

MIBG (Adreview) visualizes
- cardiac innervation
- cardiac denervation

- behaves as norepinephrine
- tracer is internalized by pre-synaptic nerve endings
Cardiac 123-I MIBG Imaging for Risk Stratification of Patients with HF

Two-year cardiac event rate for subjects with LVEF \( \leq 35\% \) and LVEF 36-49\%, stratified according to H/M ratio

Agostini D, et al. EJNMMI 2008