MIBG Imaging in Heart Failure Management

Manuel D. Cerqueira, MD
Professor of Radiology and Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Chairman, Department of Nuclear Medicine,
Imaging Institute
Staff Cardiologist, Heart and Vascular
Institute
Cleveland Clinic
All Disclosures/Conflicts
Manuel D. Cerqueira (4/2017)

Consultant/Advisory Board
– Astellas Pharma USA

Research Grants
– Perceptive Informatics, Inc.

Speakers Bureau
– Astellas Pharma USA

None
– Stock options, royalties, ownership or software revenues
Which HF Patient Has Highest Risk?

**Subject 11**
- 76 y/o male
- NYHA class II Ischemic
- Meds: Carvedilol, Irbesartan, Lasix, Amlodipine, Atorvastatin, Digoxin
- Core lab echo LVEF: 27%
- BNP: 250
- ICD: Yes

**Subject 02**
- 71 y/o male
- NYHA class II Ischemic
- Meds: Metoprolol, Lisinopril, Amlodipine, Atorvastatin
- Core lab MPI LVEF: 33%
- BNP: 484
- ICD: Yes
Pathophysiology of HF With Reduced EF

MI

Virus, Toxin, HTN

Myocardial Injury

CO, BP

Neurohumoral Activation

BP, blood pressure; CO, cardiac output; EF, ejection fraction; HF, heart failure; HTN, hypertension, MI, myocardial infarction.

Risk Stratification in HF

- LV ejection fraction (LVEF)
- Non-sustained VT (NSVT)
- NYHA class
- Microvolt T-wave alternans (MTWA)
- Measures of cardiac autonomic tone
- QT-interval duration and QT dispersion
- Signal averaged ECG (SAECG)
- Electrophysiology study (EPS)
- Biomarkers
- Imaging
Risk Stratification in HF-Imaging Options

• Echocardiography-essential and basic to all HF

• SPECT and PET
  • Exclusion of ischemia, scar size and hibernation

• Cardiac MR
  • Viability assessment, structure

• Cardiac CT-Role to be defined

• Coronary angiography-definitive for revascularization
Neurohormonal Activation in HF: SOLVD

Median Plasma Norepinephrine (pg/mL)

- Control
- ALVD
- Heart Failure

Median Plasma ANF (pg/mL)

- Control
- ALVD
- Heart Failure

Median Plasma AVP (pg/mL)

- Control
- ALVD
- Heart Failure

Median Plasma Renin Activity (pg/mL)

- Control
- ALVD
- Heart Failure

ALVD, asymptomatic left ventricular dysfunction; ANF, atrial natriuretic factor; AVP, plasma arginine vasopressin; SOLVD, Studies of Left Ventricular Dysfunction. Francis GS, et al. Circulation 1990;82;1724-1729.
Prognostic Significance of Neurohormonal Activation

CONSENSUS Trial

**Plasma Norepinephrine**
- Above median
- Below median
- $P<0.05$

**Angiotensin II**
- Above median
- Below median
- $P<0.01$

**Aldosterone**
- Above median
- Below median
- $P<0.05$

**ANP**
- Above median
- Below median
- n.s.

ANP, atrial natriuretic peptide.
Norepinephrine Levels and Mortality

V-HeFT II
Baseline Plasma Norepinephrine (pg/mL)
(Cumulative Mortality by Risk Category)

Cumulative Mortality (%)

- PNE > 900 pg/mL
- PNE > 600 and < 900 pg/mL
- PNE ≤ 600 pg/mL

Two Year
Overall

P < 0.0001
P < 0.0001
### b-adrenergic Neuroeffector Abnormalities in the Failing Human Heart

<table>
<thead>
<tr>
<th>Group</th>
<th>Total $\beta$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>ICY P $K_D$</th>
<th>$% \beta_1$</th>
<th>$% \beta_2$</th>
<th>$\alpha_1$ receptor density</th>
<th>IBE-2254 $K_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A (Nonfailing, $n = 12$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>87.7±7.4</td>
<td>68.0±6.4</td>
<td>19.6±2.3</td>
<td>11.9±2.7</td>
<td>77.0±2.3</td>
<td>22.9±2.2</td>
<td>8.8±1.2</td>
<td>39.5±12.1</td>
</tr>
<tr>
<td>RV</td>
<td>102.1±9.2</td>
<td>81.2±10.0</td>
<td>18.0±2.7</td>
<td>12.3±3.0</td>
<td>80.0±3.0</td>
<td>19.9±2.9</td>
<td>6.8±4.0</td>
<td>27.4±20.0</td>
</tr>
<tr>
<td><strong>B (Biventricular failure, $n = 54$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>51.1±1.9*</td>
<td>32.8±1.6*</td>
<td>18.2±0.9</td>
<td>15.3±1.8</td>
<td>63.4±1.5*</td>
<td>36.1±1.4*</td>
<td>17.6±3.3</td>
<td>41.9±5.3</td>
</tr>
<tr>
<td>RV</td>
<td>47.8±2.6*</td>
<td>33.9±2.5*</td>
<td>17.1±1.1</td>
<td>15.2±2.2</td>
<td>65.6±2.2*</td>
<td>34.4±2.0*</td>
<td>15.9±3.2</td>
<td>38.9±7.3</td>
</tr>
<tr>
<td><strong>C (PPH, isolated RVF, $n = 12$)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>85.4±6.1†</td>
<td>62.1±4.2†</td>
<td>24.9±3.4†</td>
<td>9.4±1.6</td>
<td>72.0±2.5†</td>
<td>28.2±2.2†</td>
<td>16.4±2.7</td>
<td>39.3±11.7</td>
</tr>
<tr>
<td>RV</td>
<td>41.9±4.0*†</td>
<td>23.2±2.6*†</td>
<td>19.6±3.7</td>
<td>10.2±2.5</td>
<td>56.0±5.6*†</td>
<td>41.5±4.6*†</td>
<td>14.6±2.8</td>
<td>34.0±10.7</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. Abbreviations: LV, left ventricle; RV, right ventricle. * $P < 0.05$ vs. respective chamber in A. † $P < 0.05$ vs. respective chamber in B. ‡ $P < 0.05$ vs. LV.
Mechanisms of Receptor Downregulation
Iobenguane I 123: Chemical Structure

\[
\begin{align*}
\text{123I} & & \text{Iodine atom} \\
\text{123I-meta-iodobenzylguanidine (123I-mIBG)} & & \text{Iobenguane I-123} \\
\text{Norepinephrine} & & \\
\end{align*}
\]
Evidence suggests that mIBG employs the same uptake and storage mechanisms as NE but it is not metabolized by MAO or COMT which results in it being localized in a high concentration in the presynaptic neuron.
Imaging Considerations

I-123:
  – $T_{1/2}$: 13.2 hours
  – Gamma emission (principal emission): $159$ keV

Dosage: 10 mCi (370 MBq)

Absorbed radiation dose: $\sim 5$ mSv

Collimator: low energy, high-resolution

Matrix: 128 x 128 for planar image

Camera
  – Image must include mediastinum and heart
Iobenguane I 123 Imaging Protocol

Energy window: 159 ± 20%

Camera positioning: include the entire heart and as much of the upper chest as possible within the field of view

Imaging: Anterior planar view of the chest at 4 hours following administration of AdreView
– Optional:
  • SPECT imaging should be done after the planar imaging at 4 hours
Estimation of the H/M Ratio

Step 1: Visual examination of the location, pattern and intensity of cardiac radioactivity uptake to guide quantitative assessment

Step 2: Quantitative assessment of radioactivity uptake using H/M ratio on anterior planar images of the chest
Step 1: Visual Assessment of Anterior Planar Image

Normal
Distinct visualization of the left ventricular myocardium in the left lower chest, with greater uptake in the heart than in the adjacent lungs and mediastinum

Abnormal
Decreased cardiac uptake (homo- or heterogeneous) with indistinct/absent LV visualization
A: Cardiac activity: usually less than that of adjacent left lung
B: In extreme cases, little or no cardiac AdreView uptake seen

LV, left ventricle. AdreView PI.
Quantitating I-123 Cardiac Uptake

**Steps**

1. Draw ROI defining epicardial LV border

2. Draw horizontal line to mark estimated location of lung apices

3. Draw vertical line ~equidistant from medial aspects of right and left lung
Quantitating I-123 Cardiac Uptake

Steps

1. Examine the counts for the 12 pixels along the vertical line starting 4 pixels below the intersection point with the horizontal line determined in Step 2, and identify the pixels with the lowest counts. If more than one pixel has this same number of counts, choose the most superiorly located pixel and then draw 7x7 pixel ROI around pixel on line 3 with lowest counts.

2. H/M ratio = counts/pixel in the total myocardium. ROI determined in Step 1 divided by counts/pixel in the 7x7 pixel mediastinal ROI determined in Step 4.
I-123 MIBG Imaging: Specific Patient Considerations

Patients at risk for thyroid accumulation:
  – Administer Potassium Iodide Oral Solution or Lugol’s Solution at least 1 hour before administration of AdreView

Patients with prior reactions to iodine
  – Consider expected benefits vs risk of potential hypersensitivity

Patients with conditions affecting the sympathetic nervous system, eg, Parkinson’s disease
  – May show decreased cardiac uptake of AdreView independent of heart disease
I-123 MIBG: Use of Concomitant Medications

Medications with potential to interfere with MIBG Imaging
- Risk of unreliable imaging results

If MIBG imaging is essential, physicians must consider if they can safely withdraw the following categories of medications

<table>
<thead>
<tr>
<th>Category of medication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives that deplete NE stores or inhibit reuptake</td>
<td>Reserpine, labetalol</td>
</tr>
<tr>
<td>Antidepressants that inhibit NE transporter function</td>
<td>Amitriptyline and derivatives, imipramine and derivatives, SSRIs</td>
</tr>
<tr>
<td>Sympathomimetic amines</td>
<td>Phenylephrine, phenylpropanolamine, pseudoephedrine, ephedrine</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
</tr>
</tbody>
</table>

NE, norepinephrine; SSRIs, selective serotonin reuptake inhibitors.
I-123 MIBG: Use of Concomitant Medications

Period of time necessary to discontinue any specific medication prior to AdreView dosing has not been established

Clinical studies have not determined:
- Which specific drugs may cause false-negative imaging results
- Whether all drugs in any specific pharmacologic class have the same potential to produce the negative imaging results

Increasing AdreView dose will not overcome any potential uptake limiting effect of these drugs

Before AdreView administration, discontinue (for ≥5 biological half-lives) drugs known or expected to reduce NE uptake, as clinically tolerated
Calculation of late H/M ratio

Healthy individual without heart disease (H/M = 2.40)

Heart failure patient with moderately reduced cardiac uptake (H/M = 1.34)
Prediction of HF vs Arrhythmic Death

Representative ADMIRE-HF Patients

On the basis of the H/M ratios, 2-year cardiac mortality risk for patient 1 is 10 times that of patient 3.

1

65 y/o M
NYHA 2
LVEF = 25%
H/M = 0.96

Died at 8 mo
HF progression

2

51 y/o M
NYHA 2
LVEF = 33%
H/M = 1.38

Died at 8 mo,
SCD
(No ICD)

3

64 y/o M
NYHA 2
LVEF = 30%
H/M = 1.67

No event

Jacobson A. Late-Breaking Clinical Trials. ACC 2009.
Iobenguane I 123: Use of Concomitant Medications

Period of time necessary to discontinue any specific medication prior to AdreView dosing has not been established.

Clinical studies have not determined:

- Which specific drugs may cause false-negative imaging results.
- Whether all drugs in any specific pharmacologic class have the same potential to produce the negative imaging results.

Increasing AdreView dose will not overcome any potential uptake limiting effect of these drugs.

Before AdreView administration, discontinue (for $\geq 5$ biological half-lives) drugs known or expected to reduce NE uptake, as clinically tolerated.
Feasibility for SPECT Imaging

4-hour delayed images in patient with planar H/M = 2.4

Normal

Abnormal
$^{123}$I-mIBG: Normal SPECT Imaging

Images provided by A. Jacobson, MD of GE Healthcare
Abnormal $^{123}$I-mIBG SPECT

Quantitative Analysis

$^{123}$I-mIBG/ rest Myoview with matched basal Inferolateral infarct and a larger peri-infarct area of dennervation on $^{123}$I-mIBG.

Images provided by A. Jacobson, MD of GE Healthcare
Anterior and apical infarct. Global reduction of mIBG uptake results in poor quality SPECT and underestimation of disease severity on bullseye plot.

Images provided by A. Jacobson, MD of GE Healthcare
Impact of Effective HF Therapy on $^{123}$I-\textit{m}IBG Imaging

Pre-therapy: H/M=1.11

Post-therapy: H/M=1.62

Agostini D J Nucl Med 2000;41:845
Sudden Cardiac Death (SCD)

Most common cause of death in the United States
More than 350,000 deaths per year
Claims more lives than stroke, lung cancer, breast cancer, and AIDS combined
### Relationship of SCD to NYHA Class

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Annual Mortality (%)</th>
<th>Sudden Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>5-15</td>
<td>50-80</td>
</tr>
<tr>
<td>III</td>
<td>20-50</td>
<td>30-50</td>
</tr>
<tr>
<td>IV</td>
<td>30-70</td>
<td>5-30</td>
</tr>
</tbody>
</table>

Goals of SCD Risk Stratification

Identify low-risk patients in high-risk populations

Identify high-risk patients in low-risk populations
Limitations of Current Risk Stratification for ICD Implantation

Low Incidence of Appropriate Shocks

MADIT-II

SCD-HeFT

21% appropriate shocks at approx 4 years

10 million in US qualify for prophylactic ICD

$200 billion to healthcare costs

LVEF

- LVEF is the most consistent and one of the strongest predictors of all-cause mortality in patients with ischemic and nonischemic cardiomyopathy
- LVEF lacks specificity as a predictor of arrhythmic events
- LVEF alone is not enough!
Predicting ICD Discharge With MIBG and HRV

17 patients w ICDs
10 with history of ICD discharge, 7 without
MIBG + HRV analysis

Those with ICD discharge: Lower H/M ratio, greater MIBG defect, multiple decreased HRV variables

Combined MIBG and HRV analysis identified patients with appropriate shocks and those with no shocks/no arrhythmia

Prognosis in HF and Sympathetic Innervation by MIBG: ADMIRE-HF

N = 961 patients with HF and LVD

EVENT = HF prog, arrhythmic event, or cardiac death

*P < .0001 vs H/M ≥ 1.6

H/M ≥ 1.6: 2-year event-free survival 85%

H/M < 1.6: 2-year event-free survival 63%*

ADMIRe-HF: Composite Primary Endpoint

Heart Failure Progression

Arrhythmic Event

Cardiac Death

All-Cause Mortality

Patient Selection for ICD Placement

Extent of myocardial scar/fibrosis


- Rest perfusion defect size not predictive of cardiac events in the ADMIRE-HF study
Can assessment of sympathetic nervous system activity by $^{123}$I-MIBG predict which patients will have appropriate therapy from an ICD?
86 of 961 (9%) patients had arrhythmic events
- 63 nonfatal events (sustained VT, aborted cardiac arrest, ICD firing)
- 23 SCDs

Multivariable predictors:
1) LVEF ($P < .001$)
2) H/M ratio < 1.60 ($P = .017$)
SCD Stratified by H/M Ratio

![Bar chart showing SCD rates stratified by H/M ratio.]

- H/M < 1.3: 6 cases
- H/M 1.3 - 1.59: 16 cases
- H/M ≥ 1.6: 1 case

*P < .05*

ADMIRE-HF study, data courtesy of Arnold Jacobson, MD, PhD.
Seattle Heart Failure Model (SHFM)

- Multivariate predictor of survival from 1 to 5 years and life expectancy

- **SHFM includes**: (Circulation 2009;120:835)
  - Demographic (age, gender, ischemic etiology)
  - Clinical markers (SBP, EF, NYHA)
  - Lab variables - Na, Cr, Hgb, % Lymphs
  - Medications - ACEI/ARB, Beta-blocker, Dig, Statin, Diuretic
  - Devices - ICD, CRT, CRT-D

- Widely validated in tens of thousands of subjects
Addition of Late H/M Ratio to SHFM and Predicted Annual Mortality
### Which Patient Has Highest Risk?

<table>
<thead>
<tr>
<th>Subject 11</th>
<th>Subject 02</th>
</tr>
</thead>
<tbody>
<tr>
<td>76 y/o male, NYHA class II Ischemic</td>
<td>71 y/o male, NYHA class II Ischemic</td>
</tr>
<tr>
<td>Meds: Carvedilol, Irbesartan, Lasix, Amlodipine, Atorvastatin, Digoxin</td>
<td>Meds: Metoprolol, Lisinopril, Amlodipine, Atorvastatin</td>
</tr>
<tr>
<td>Core lab echo LVEF: 27%</td>
<td>Core lab MPI LVEF: 33%</td>
</tr>
<tr>
<td>BNP: 250</td>
<td>BNP: 484</td>
</tr>
<tr>
<td>ICD: Yes</td>
<td>ICD: Yes</td>
</tr>
</tbody>
</table>
MIBG Ratios

Subject 11

Event: Resuscitated cardiac arrest day 484

Subject 02

Event: None
Can Sympathetic Innervation Imaging Help in Patient Selection for ICD?

**PATIENTS AT RISK**

- **LVEF > 35%**
  - High Clinical Risk: NSVT, Symptoms, Large Perfusion Defect
    - **H/M < 1.6** → ? ICD
    - **H/M ≥ 1.6** → NO ICD

- **LVEF ≤ 35%**
  - **H/M < 1.6** → NO ICD
  - **H/M ≥ 1.6, < 2% arrh. events/yr** → ICD

Is ICD cost-effective?