DECLARATION OF CONFLICT OF INTEREST

• Expert for
  – GE Healthcare
  – IBA
  – Bracco imaging
  – AAA
Neurocardiac Imaging
$^{123}\text{I}}$-MIBG Scintigraphy

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Inserm U698
GH Bichat-Claude Bernard, Paris
Noradrenaline concentration in the synaptic cleft is in the picomolar range. PET and SPECT are the only non-invasive techniques with the sensitivity required for imaging this process in vivo.
MIBG Imaging

• MIBG is an analogue of the “false” neurotransmitter guanetidine, a potent neuronblocking agent that acts selectively on sympathetic nerves.
• molecular structure similar to that of noradrenaline and shares the same uptake and storage mechanisms in the sympathetic nerve endings
• In contrast to NA, MIBG undergoes almost no metabolism via enzymes.
• So MIBG is retained in the sympathetic nerve endings and the localization of MIBG relates to the presence of sympathetic nerves.
Decrease of sympathetic innervation in the heart (1)

- Anatomic Factor: denervation
  - Myocyte death, fibrosis
  - Nerve endings lesions
  - heterogeneous sympathetic reinnervation

Cao et al, Circulation 2000

[Immunostaining S100 protein]

Normal

Ischemic VT
Decrease of sympathetic innervation in the heart (2)

- Functional factor: decrease of reuptake and of vesicular storage of NA

*Shannon et al, NEJM 2000*
MIBG Imaging

• Injection of 6 mCi of 123I -MIBG
• Acquisition of planar and SPECT images
  – Early images 15 to 30 min PI,
  – delayed images 4 h PI
• Quantification:
  – heart to mediastinum (H/M) ratio reflects the distribution of cardiac sympathetic nerves and the uptake function at the nerve endings
  – the washout rate is an index of the degree of sympatheticotonia)

• Regional analysis on SPECT images and polar map
MIBG: planar quantification
Global uptake

Normal innervation
H/M ratio: 2.2

NHYA Class II
H/M ratio: 1.7

NYHA Class IV
H/M ratio: 1.1

Heart/mediastinum ratio (H/M), normal value:
* 20 min: 2.3 ± 0.3
* 4 h: 2 ± 0.3

Washout rate calculated from these values; normal: 30 ± 10

Inter-study Reproducibility = 5%
MIBG : SPECT quantification

MIBG summed defect score 38

MIBG summed defect score 4
Discrepancy perfusion/innervation

\[^{99m}\text{Tc-MIBI}\]

Infarct Size

15.2 %LV

\[^{123}\text{I-MIBG}\]

59.3 %LV

perfusion – MIBG mismatch
Prognostic value of MIBG in heart failure

Merlet et al, J Nucl Med 1999
Retrospective studies

<table>
<thead>
<tr>
<th>H/M</th>
<th>Number of patients</th>
<th>Transplants (row %)</th>
<th>SCD and arrhythmic events(^a) (row %)</th>
<th>HF and other cardiac deaths(^b) (row %)</th>
<th>Total MCEs (row %)</th>
<th>2-year event-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.45</td>
<td>71</td>
<td>25 (35)</td>
<td>1 (1)</td>
<td>8 (11)</td>
<td>34 (48)</td>
<td>52</td>
</tr>
<tr>
<td>1.46–1.74</td>
<td>74</td>
<td>12 (16)</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td>21 (28)</td>
<td>72</td>
</tr>
<tr>
<td>1.75–2.17</td>
<td>72</td>
<td>6 (8)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>11 (15)</td>
<td>85</td>
</tr>
<tr>
<td>≥2.18</td>
<td>73</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
<td>44 (15)</td>
<td>10 (3)</td>
<td>13 (8)</td>
<td>67 (23)</td>
<td>–</td>
</tr>
</tbody>
</table>

LVEF ≤35%
NYHA II-III
N=182

13% of ICD candidates

Agostini et al, EJNM 2007
ADMIRE-HF

- Multinational multicentric prospective study
- 96 centres: 35 in Europe, 57 in the US, 4 in Canada, 12 countries in total
- Large patient population of 1095 subjects with 2-year follow-up
- Event determination by an independent adjudication panel of 5 cardiologists

*Jacobson et al, JACC 2010*
Primary objective

• To demonstrate the prognostic value of the H/M ratio of MIBG for identifying subjects at higher risk of an adverse cardiac event

Patients characteristics

• Mean age: 62.4 years; NYHA II/III - 83% class II, 386 subjects had ICDs –

• 66% ischaemic, 34% non-isch. Mean LVEF: 27% (range 5-35%)

• Guidelines-based management

Jacobson et al, JACC 2010
ADMIRE-HF

Composite primary endpoint

• Occurrence of any of the following 3 categories of adverse cardiac events
  
  • Heart failure progression, arrhythmia and cardiac death
  
  • Defined by the time to first event in relation to the H/M ratio

ADMIRE-HF supports a cut-off value for stratifying the risk of an adverse cardiac event

H/M ratio $\geq 1.6$ – low risk
H/M ratio $< 1.6$ – high risk

*Jacobson et al, JACC 2010*
Cardiac Death Event

*\(p=0.002\) vs H/M ≥1.60

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

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

21% of the study population

*\(p=0.002\) vs H/M ≥1.60

Jacobson et al, JACC 2010
Arrhythmic Event

H/M\(\geq\)1.60: 2-year event-free survival 96%

H/M\(<\)1.60: 2-year event-free survival 85%*

*p=0.002 vs H/M \(\geq\)1.60

ADMIRE-HF

Jacobson et al, JACC 2010
Predicting the Need for an Implantable Cardioverter Defibrillator

- 54 ICD-treated pts prospectively followed after assessment of
  - MIBG H/M ratio
  - Plasma BNP concentration
  - LVEF
- 2 groups based on the presence (group A, n=21) or absence (group B, n=33) of appropriate ICD discharge during a 15-mo period

multivariate analysis showed late HMR to be an independent predictor.

N=54 ICD pts

Could MIBG imaging be the gatekeeper for ICD implantation in primary prevention of sudden death?
Study Population (n = 116)

116 consecutive patients referred for ICD implantation based on guidelines for primary prevention

<table>
<thead>
<tr>
<th>Baseline characteristics of the study population (n = 116)</th>
</tr>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
</tr>
<tr>
<td>NYHA functional class</td>
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<tr>
<td>LVEF (%)</td>
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</table>

End points (3 years FU):

Appropriate ICD therapy (prim endpoint)

ICD therapy + Cardiac mortality (sec endpoint)
Predictors for ICD therapy - Imaging variables

<table>
<thead>
<tr>
<th>Imaging variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>123-I MIBG imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early H/M ratio</td>
<td>0.43 (0.05 - 4.11)</td>
<td>0.5</td>
</tr>
<tr>
<td>Late H/M ratio</td>
<td>0.32 (0.04 - 2.81)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cardiac washout rate (%)</td>
<td>1.03 (0.96 - 1.10)</td>
<td>0.5</td>
</tr>
<tr>
<td>Early summed score</td>
<td>1.08 (1.03 - 1.12)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Late summed score</td>
<td>1.15 (1.09 - 1.22)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>$^{99m}$Tc-tetrofosmin GMPS imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summed rest score</td>
<td>1.02 (0.98 - 1.06)</td>
<td>0.4</td>
</tr>
<tr>
<td>Summed stress score</td>
<td>1.03 (0.99 - 1.07)</td>
<td>0.2</td>
</tr>
<tr>
<td>Summed difference score</td>
<td>1.07 (0.98 - 1.16)</td>
<td>0.13*</td>
</tr>
<tr>
<td>123-I MIBG/GMPS mismatch score</td>
<td>1.06 (1.02 - 1.09)</td>
<td>&lt;0.01*</td>
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Predictors for ICD therapy or cardiac death
Imaging variables

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<td>123-I MIBG imaging</td>
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<tr>
<td>Early H/M ratio</td>
<td>0.30 (0.04 - 2.19)</td>
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</tr>
<tr>
<td>Late H/M ratio</td>
<td>0.21 (0.03 - 1.36)</td>
<td>0.10*</td>
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<tr>
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<td>123-I MIBG/GMPS mismatch score</td>
<td>1.05 (1.02 - 1.08)</td>
<td>&lt;0.01*</td>
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Cumulative event rate for ICD therapy in 24 patients (21%)

Population divided according to median MIBG summed defect score (26)

ICD therapy: 2%

Cumulative event rate 52% vs. 5%
3-year follow-up data

52% (n=55)

5% (n=58)
Cumulative event rate for ICD therapy or cardiac death in 32 patients (28%)

Population divided according to mean MIBG summed defect score (26)

Cumulative event rate 57% vs. 10%

3-year follow-up data
75-year old male patient
LVEF 28%

MIBG summed defect score 38

4 episodes of VT with shock on ICD

47-year old male patient
LVEF 31%

MIBG summed defect score 4

No appropriate ICD therapy or cardiac death
MIBG Scintigraphy as a Tool for selecting patients requiring ICD in primary prevention

Peut-on mieux sélectionner les patients insuffisants cardiaques ayant une indication à un défibrillateur automatique implantable (DAI) en prévention primaire ?

Investigateur Coordonnateur: Pr Dominique Le Guludec
(Service de Médecine nucléaire GH Bichat-Claude Bernard, Paris)
Primary objective

To assess the threshold value of heart/mediastinum (MIBG) that would allow to identify a very low risk (<1%/year) of severe ventricular arrhythmias among patients receiving an ICD for primary prevention. NPV +++

Prospective multicentric trial, 18 centers, 330 pts, FU 32 months

Main study endpoint

Occurrence of a VT >160/min or VF diagnosed and treated effectively or not by the ICD
Extent of Cardiac Sympathetic Denervation is far more EXTENSIVE than the infarct size and correlates with the area at risk.

Extent of Cardiac Sympathetic Neuronal Damage Is Determined by the Area of Ischemia in Patients With Acute Coronary Syndromes

- Sympathetic fibers are more sensible to ischemia than cardiomyocytes
- After MI, sympathetic denervation is superimposed to the area at risk

Matsunari, Circulation 2000
Sympathetic Reinnervation 1 Year After Heart Transplantation Assessed Using MIBG Imaging

- MIBG at 2 and 12 months after HT in 45 patients
- showing a 40% incidence of sympathetic reinnervation

**Fig 1.** HMR at 60.18 ± 14.8 days after HT of 1.16 ± 0.10 significantly increased at 373.06 ± 26.19 days, reaching 1.30 ± 0.15.

*Buendia-Fuentes F et al, Transplantation Proceedings, 2011, 43, 2247–2248 (
Sympathetic Reinnervation of Cardiac Allografts Evaluated by $^{123}$I-MIBG Imaging

Correlation between intensity of myocardial 123I MIBG uptake, expressed as HMR and time after heart transplantation (HT). Open squares = patients in whom graft vasculopathy developed.

Cardiac Autonomic Dysfunction in Brugada Syndrome and MIBG Imaging

- 17 pts with Brugada syndrome and 10 age-matched control subjects
- MIBG-SPECT and quantitative 33-segment bull’s-eye analysis.
- Regionally reduced MIBG uptake in 8 (47%) of 17 pts with Brugada syndrome but in none of the control subjects.
- Segmental reduction of MIBG uptake in the inferior and septal LV wall in pts with Brugada syndrome compared with control subjects ($P<0.05$).

Cardiac Autonomic Dysfunction in Brugada Syndrome

MIBG Imaging for Predicting the Development of Atrial Fibrillation

- 98 consecutive pts (age 66 ±13 ys, 63 % male) with idiopathic paroxysmal AF and preserved LVEF (≥50%).
- During 4 ± 3.6 years of FU, the transit to permanent AF was associated with the occurrence of HF (34.3% in 12 of 35 patients with permanent AF vs. 6.3% in 4 of 63 patients without, p <0.0001).
- Lower MIBG uptake and lower LVEF were the independent predictors of the transit to permanent AF.
- These factors and higher BNP concentration were the independent predictors of the occurrence of HF with permanent AF.

Akutsu Y et al., J Am Coll Cardiol Img 2011;4:78–86
Iodine-123 mIBG Imaging for Predicting the Development of Atrial Fibrillation

Figure 3. ROC Curves for Predicting Occurrence of HF With Permanent AF

The receiver-operator characteristics (ROC) curves for predicting occurrence of heart failure (HF) with permanent atrial fibrillation (AF) indicate that the sensitivity of cardiac sympathetic nervous system abnormality (heart/mediastinum ratio ≤2.7) was 83.3% in 10 of 12 patients, and the specificity was 67.4% in 58 of 86 patients. The sensitivity of higher brain natriuretic peptide (BNP) (>75 pg/ml) was 83.3% in 10 of 12 patients, and the specificity was 68.6% in 59 of 86 patients. The sensitivity of lower left ventricular ejection fraction (LVEF) (≤60%) was 75% in 9 of 12 patients, and the specificity was 67.4% in 58 of 86 patients.

Akutsu Y et al, J Am Coll Cardiol Img 2011;4:78–86
LMI1195: a New 18F Benzylguanidine Analog for PET Cardiac Sympathetic Neuronal Imaging

Cardiac imaging in a rat model of HF

Control (LS-5) | HF (HS-5) | Early stage HF
---|---|---
Control (LS-10) | HF (HS-10) | Late stage HF

YU M. et al, JACC 2010,55, 10A
Conclusions

• An accurate tool for evaluation of sympathetic neuromodulation in patients
  – Global neuromodulation
  – Regional
    • Spatial heterogeneity (necrosis, hibernation, Brugada)
    • Perfusion/innervation mismatch

• High negative predictive value for events in patients with heart failure

• Need for worldwide guidelines for standardization

• Still work to understand the respective roles of global and regional abnormalities