Recent and Future Developments of PET Viability Imaging

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Definition of Viable Myocardium

- **Prospectively**
  - **Myocardium without scarring due to ischemia/infarct**
  - **Dysfunction having potential functional recovery**
  - **Viability**

- **Retrospectively**
  - **Recovery of function after successful revascularization**
  - **Prevention of cardiac remodeling/risk**
  - **Hibernation**

Shah BN et al. *Eur Heart J* 2013

Viable Myocardium as we learned

- Terminology
  - Stunning: in 1975 (Heyndrickx et al. *J Clin Invest*) – canine
    - Prolonged dysfunction after relief of ischemia
    - Acute event of ischemia
  - Hibernation: in 1978 (Diamond et al. *Am Heart J*) – human
    - Persistent dysfunction due to reduced blood flow
    - Chronic hypoperfusion
- Pathogenesis
  - Stunning: reactive oxygen species due to reperfusion
    - Decreased sensitivity to Ca^{2+}
  - Hibernation: change in cell structure
    - Sarcomere loss, glycogen storage, disarray of mitochondria

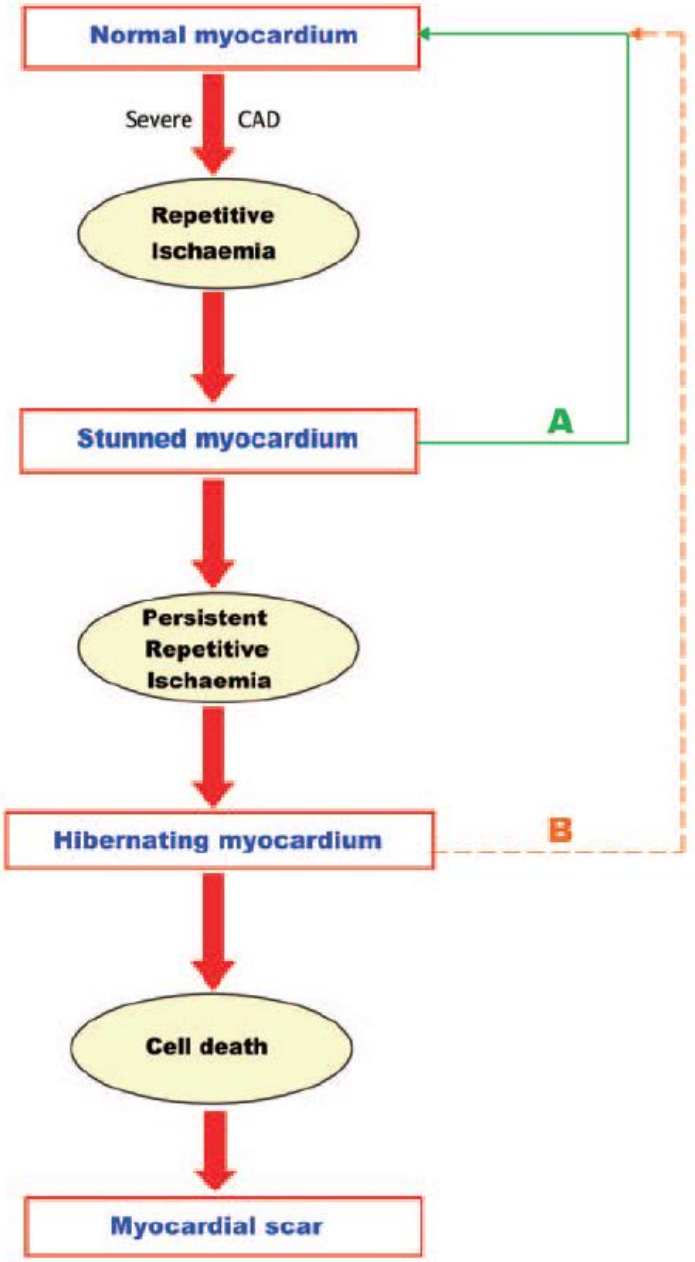
Spectrum of Myocardial Dysfunction

CFR	CR	PERF	MET	SCAR
✓	✓	✓	✓	X

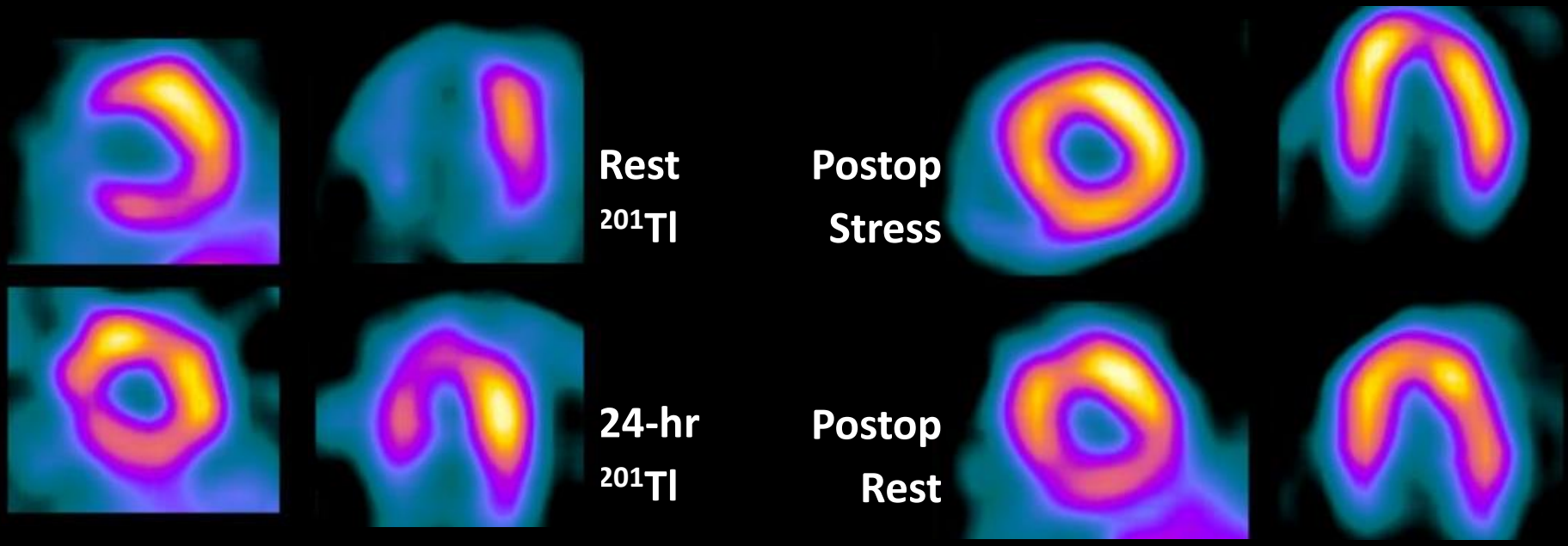
CFR	CR	PERF	MET	SCAR
↓	✓	✓	✓	X

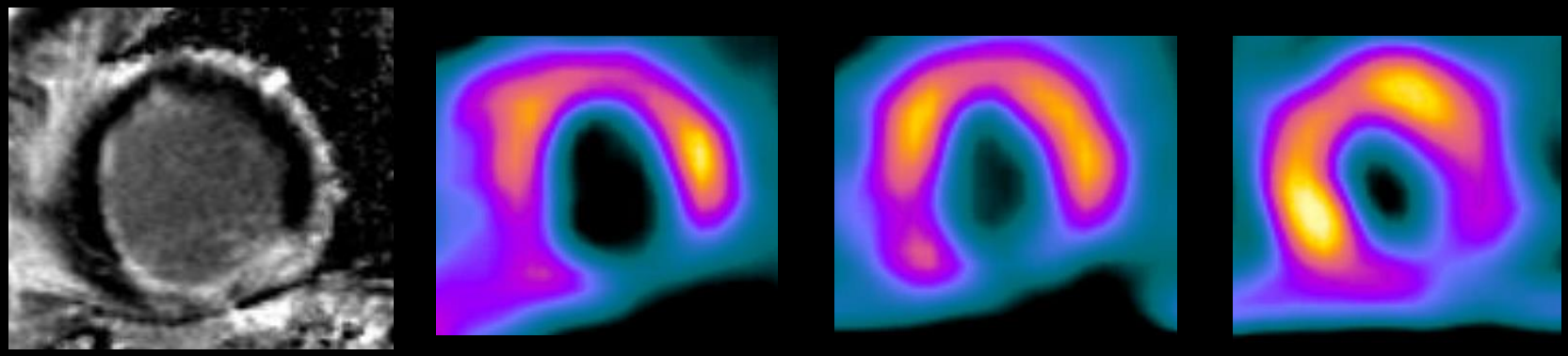
CFR	CR	PERF	MET	SCAR
↓ ↓	↔	↔	✓	X

CFR	CR	PERF	MET	SCAR
↓ ↓ ↓	X	X	X	✓

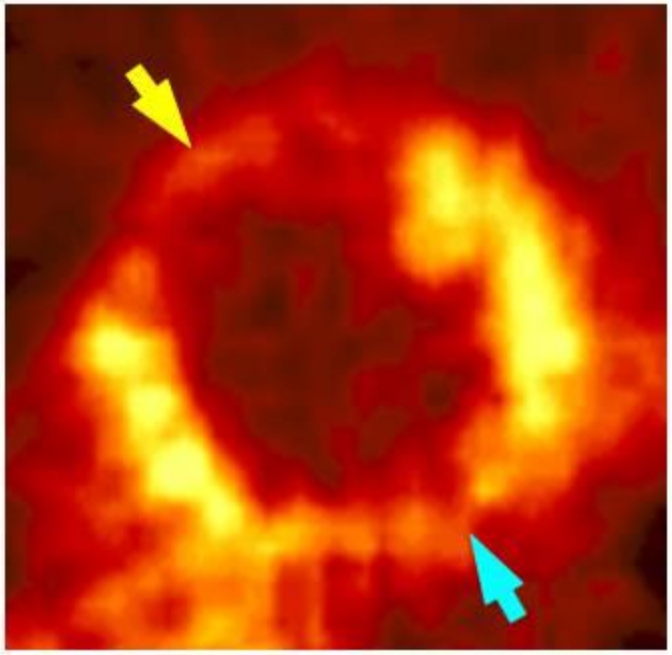


Shah BN et al. *Eur Heart J* 2013

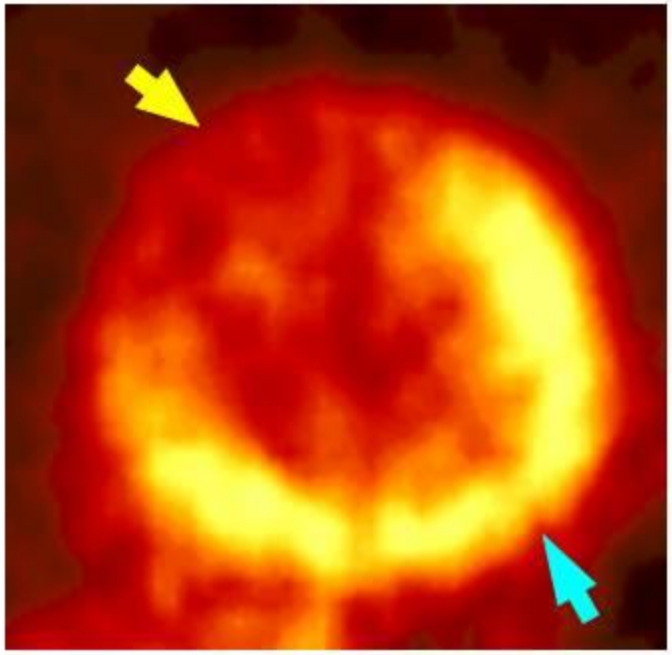

Rest
201Tl
Postop
Stress
24-hr
201Tl
Postop
Rest


MRI
Stress MIBI
Rest Tl
Delayed Tl

Q/M Match vs. Mismatch

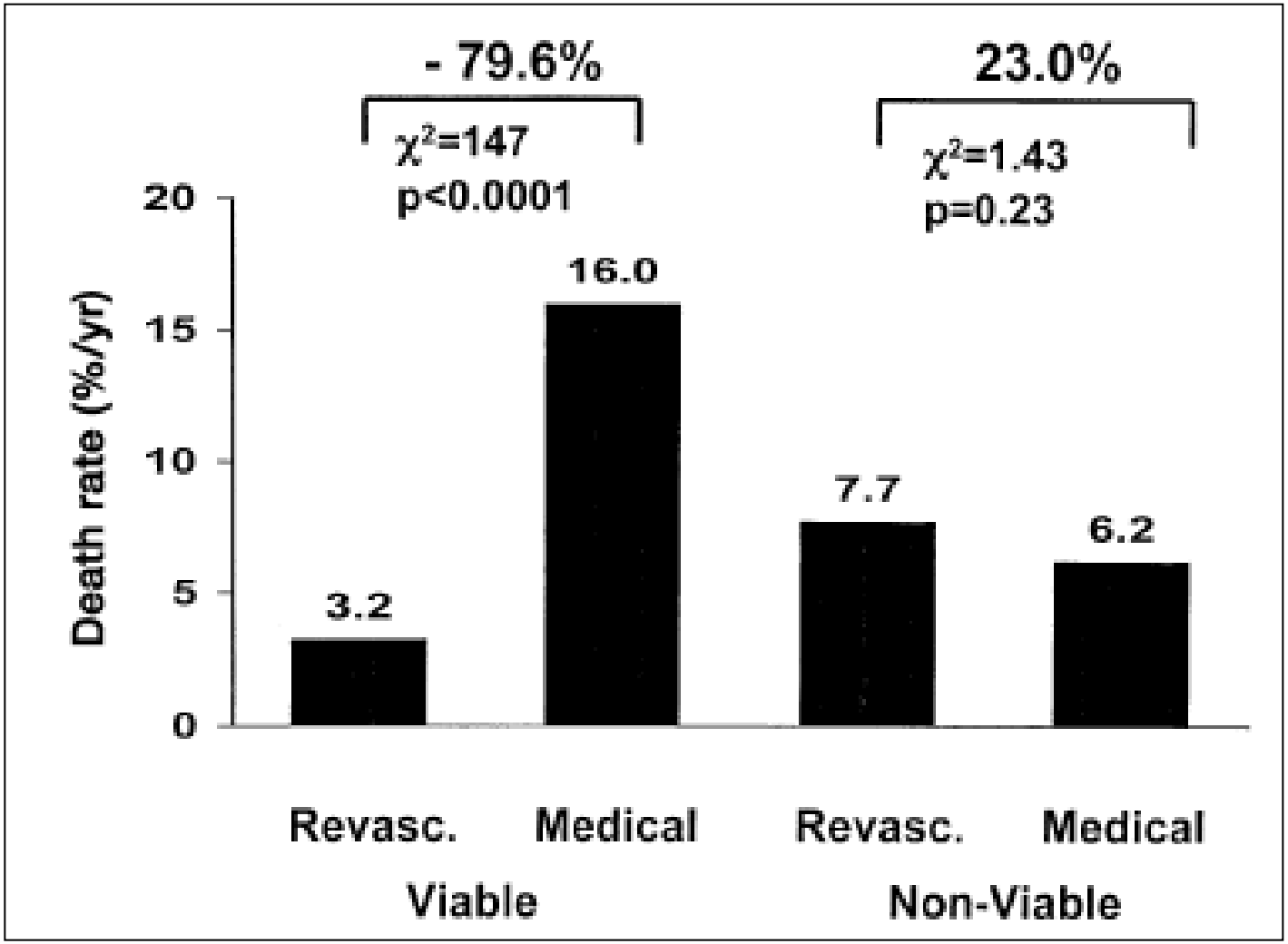


$^{13}NH_3$ - PET



^{18}FDG - PET

Viable Myocardium : Impact of Revascularization



Allman, *J Am Coll Cardiol* 2002

Clinical Viability Assessment

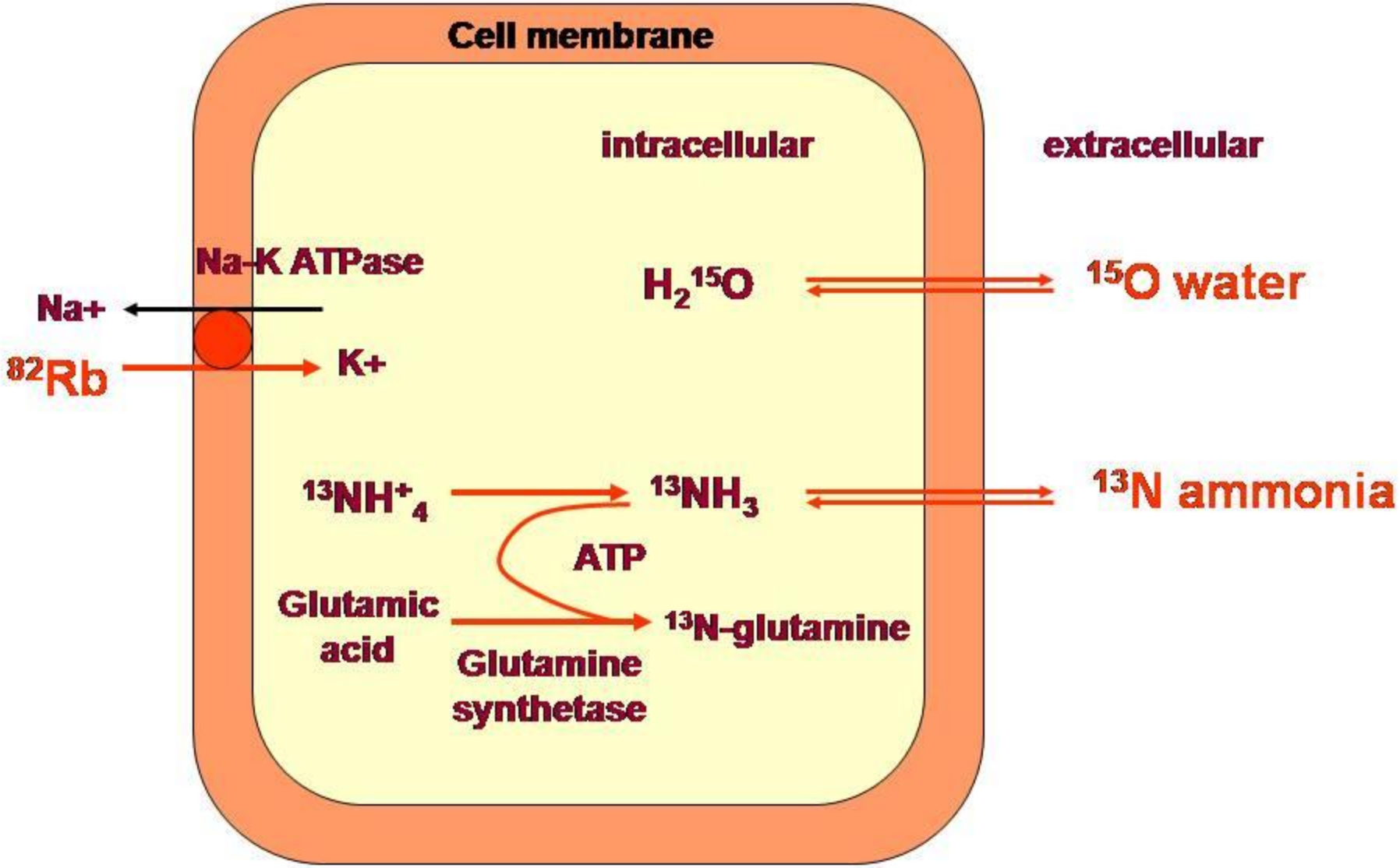
- Diagnostic Points
  - Contractile reserve
  - Perfusion, perfusion reserve
  - Energy metabolism
  - Structure: cell intactness, fibrosis
  - Dobutamine Echo
  - Perfusion SPECT/PET
  - FDG/FFA PET
  - MRI

	(Chronic) Stunning	Transition Phase	Chronic Hibernation	Infarction
Rest Flow	Normal	Normal	↓ ↓	↓ ↓ ↓
Flow Reserve	↓	↓ ↓	↓ ↓ ↓	↓ ↓ ↓
Inotropic Reserve	+	+	±	–
Energy Metabolism	+	+	+	–
Structural Change	–	Mild	More	Fibrosis
Function Recovery	+	+	+ (delayed)	–

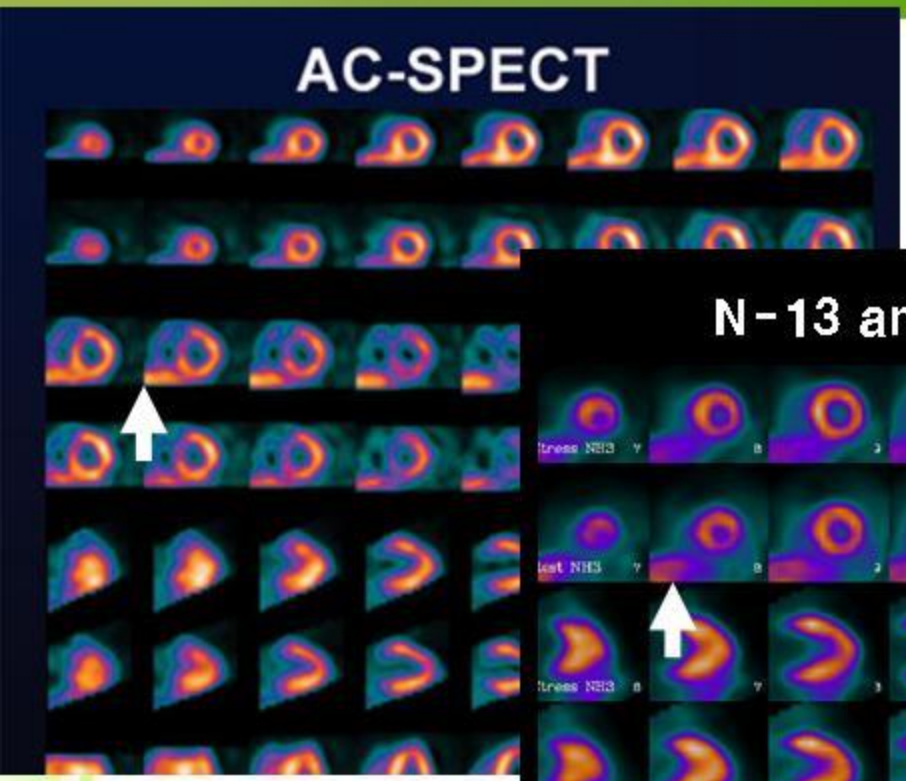
Viability Assessment with perfusion SPECT

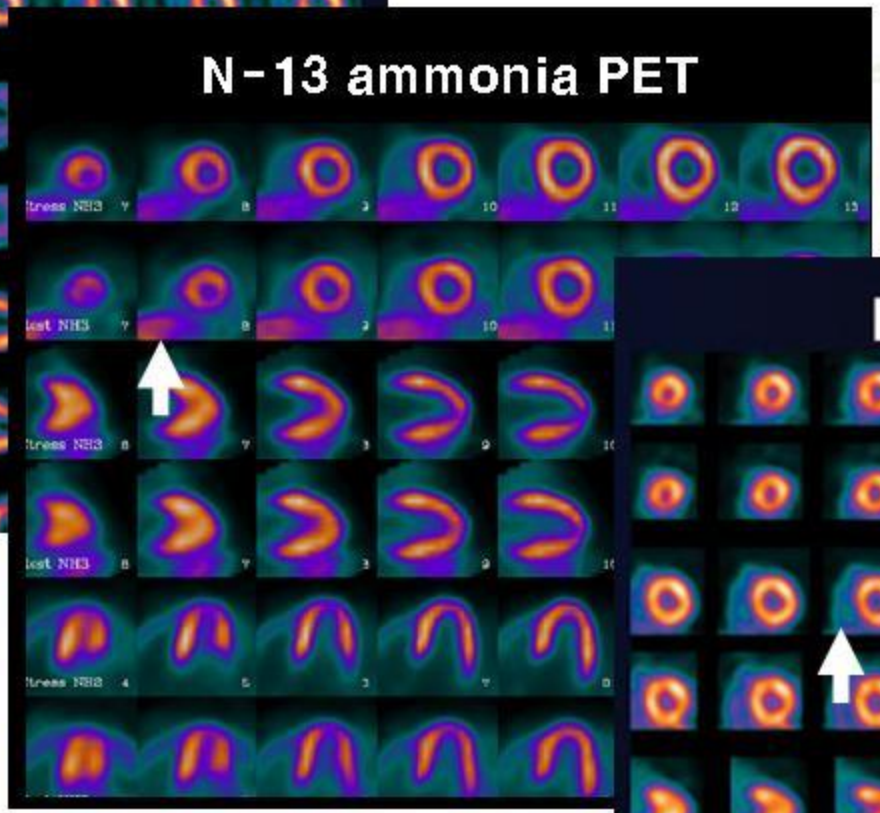
- **Rest Perfusion**
  - **Uptake mechanism of perfusion tracer**
    - **^{99m}Tc-MIBI: binding to mitochondrial membrane**
    - **^{201}Tl: ion-entrapment (like K^+) in intact cells**
  - **Determining factor of uptake**
    - **Perfusion**
    - **Preserved cell intactness**
  - **Stunning rather than hibernation ?**

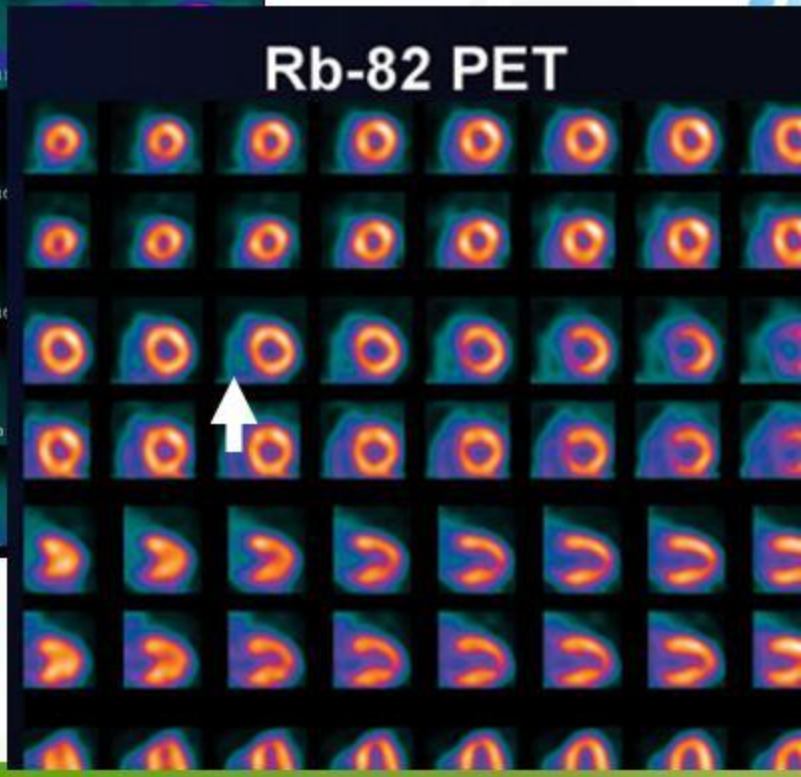
PET radiotracers for myocardial perfusion



Cardiac PET vs SPECT



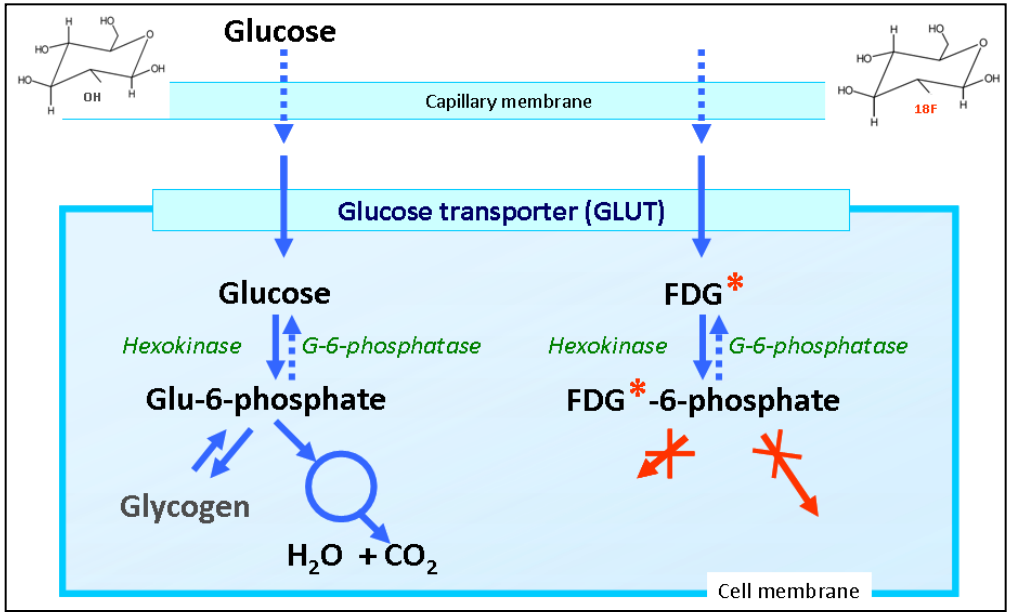


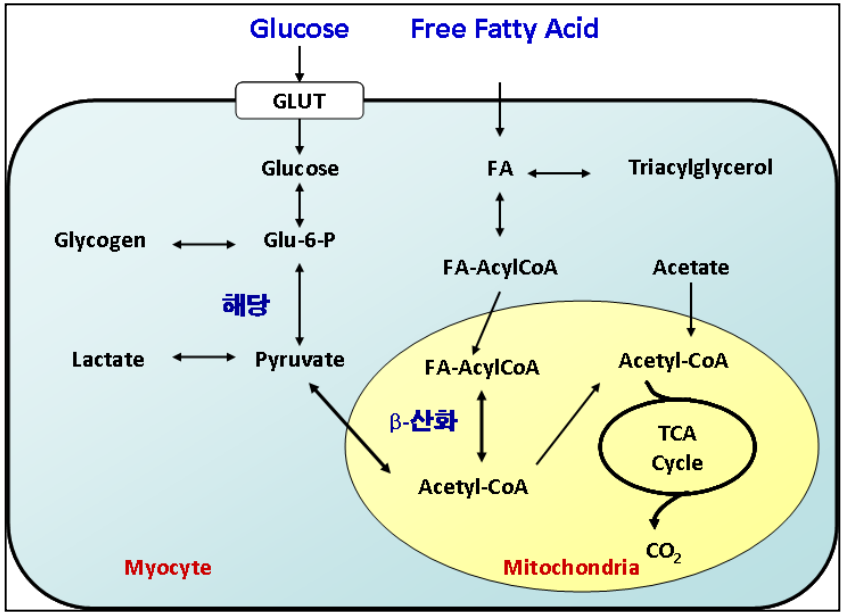


Subdiaphragmatic tracer uptake

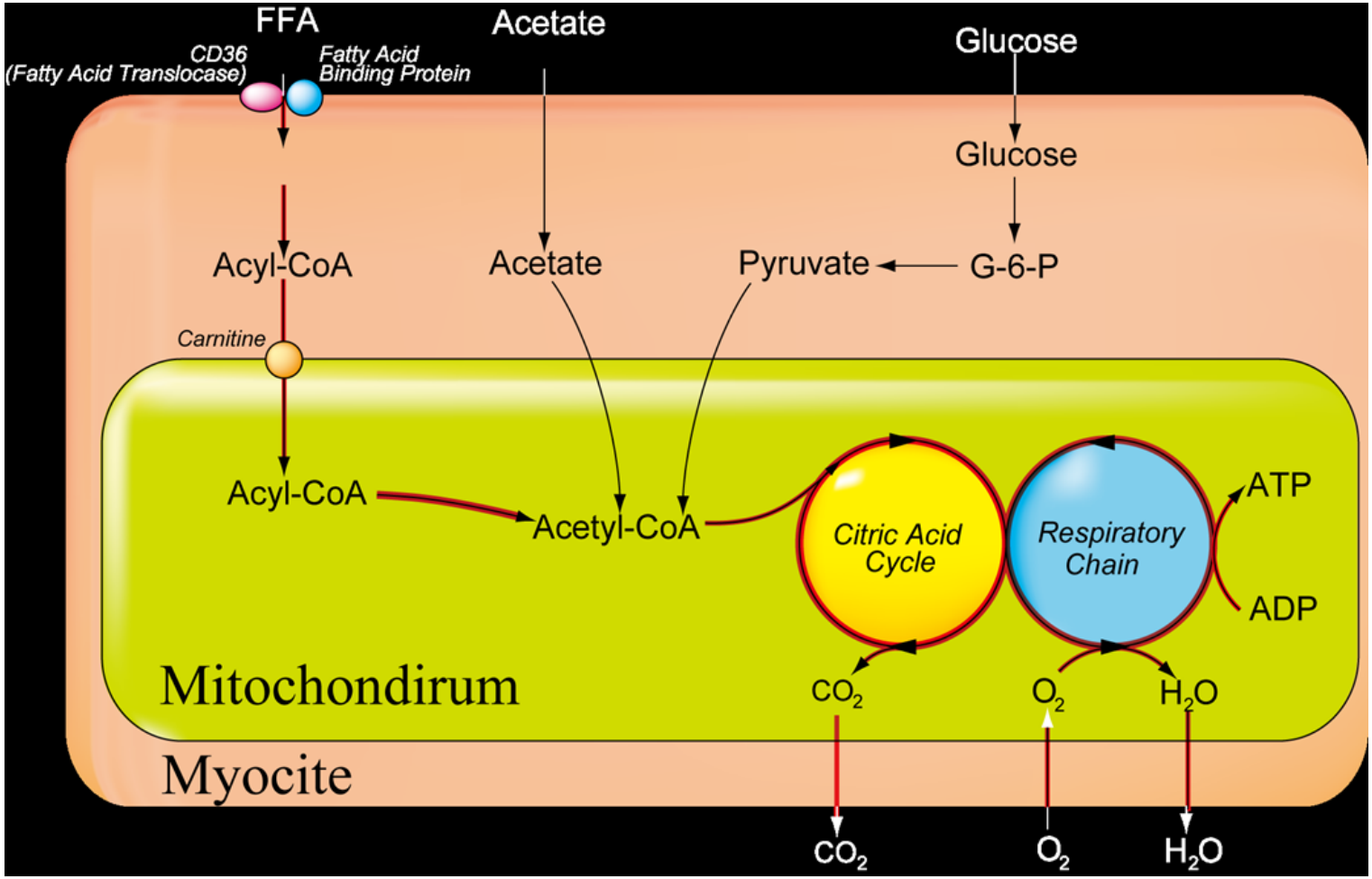
Viability Assessment with Metabolism

- Energy Metabolism
  - Preserved glucose metabolism in hypoxic myocardium
  - Perfusion-metabolism mismatch
  - ^{18}F-FDG PET with glucose challenge or insulin clamp

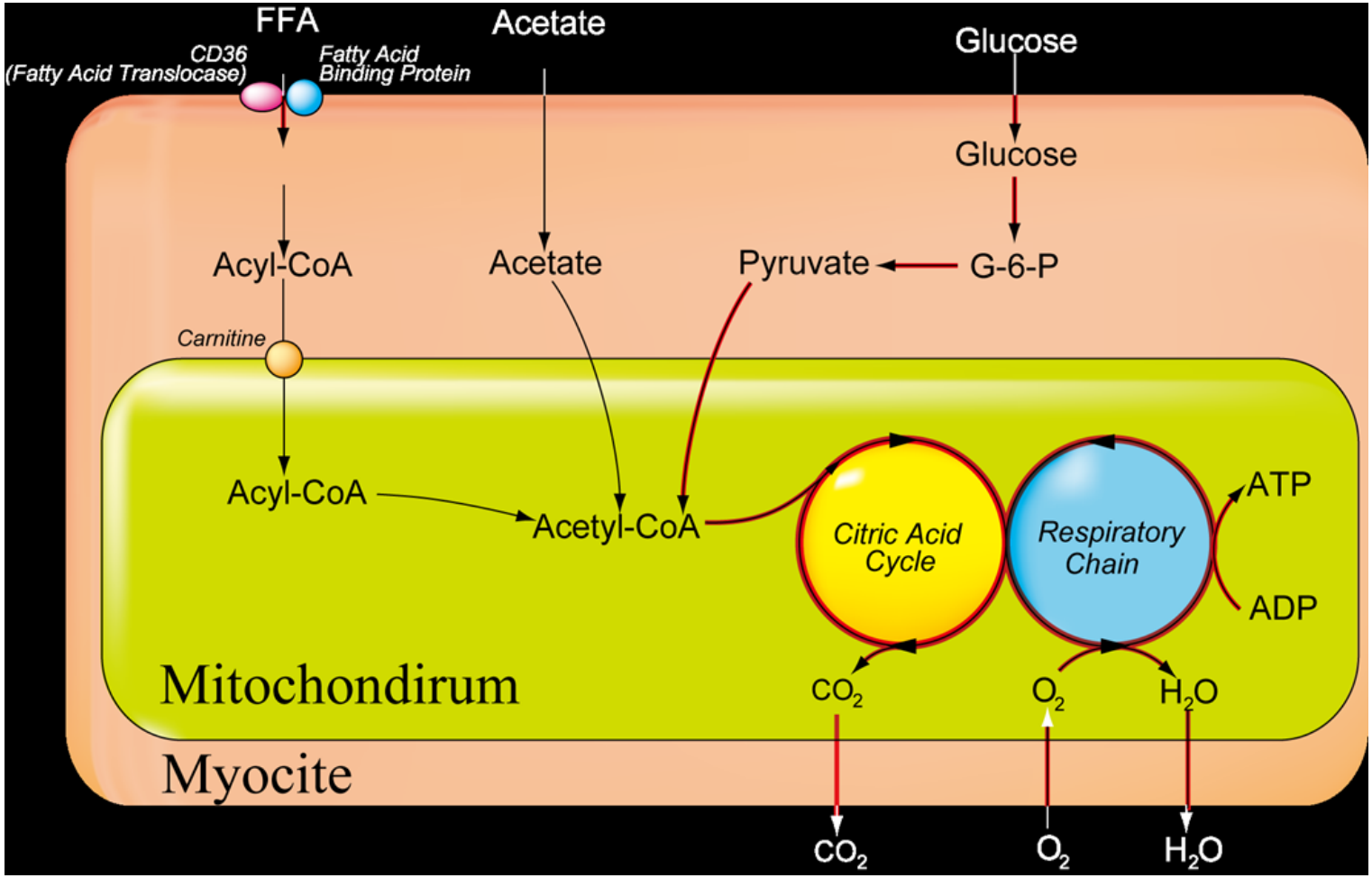




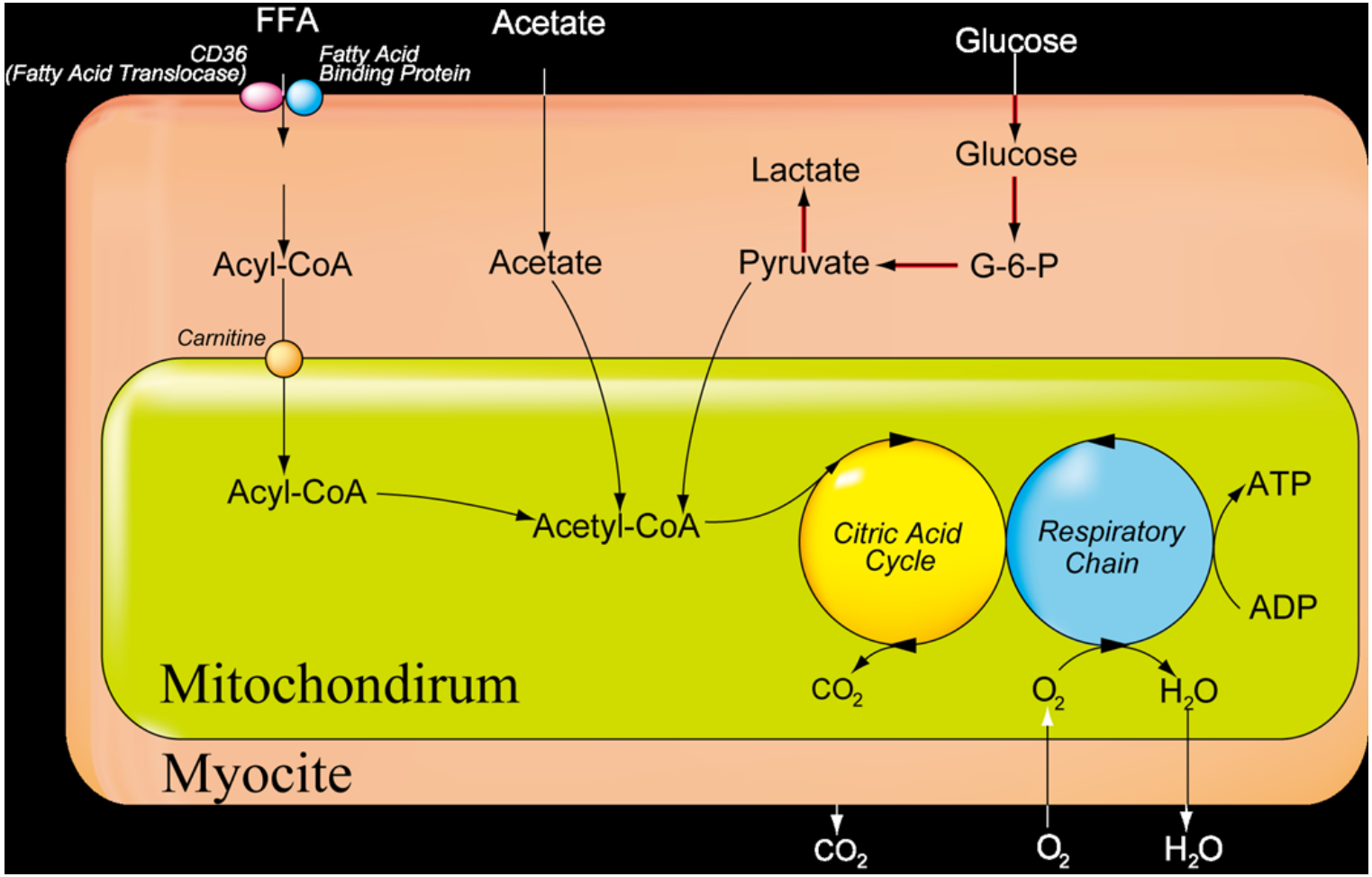
Under Fasting



Under Carbohydrate Load



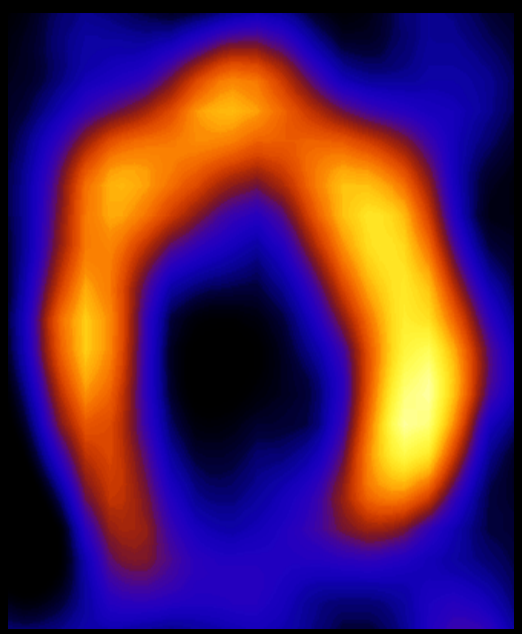
During Ischemia

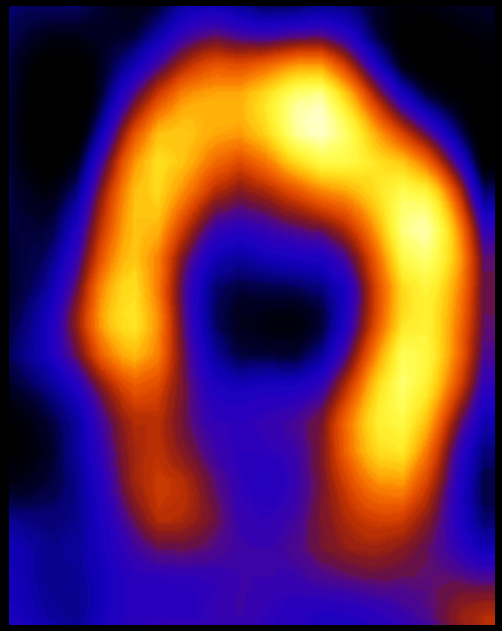


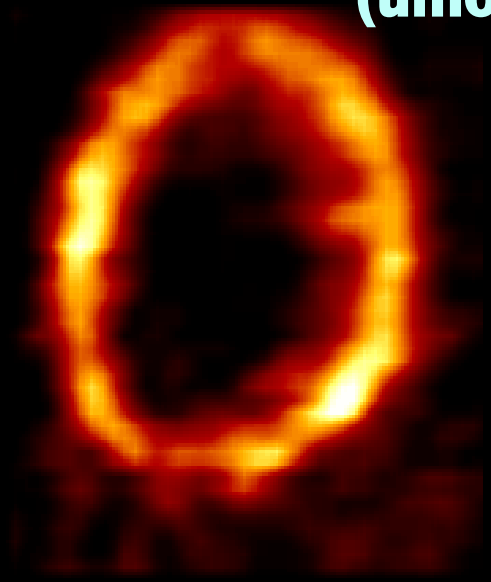
Hibernating Myocardium : Classic Mismatch

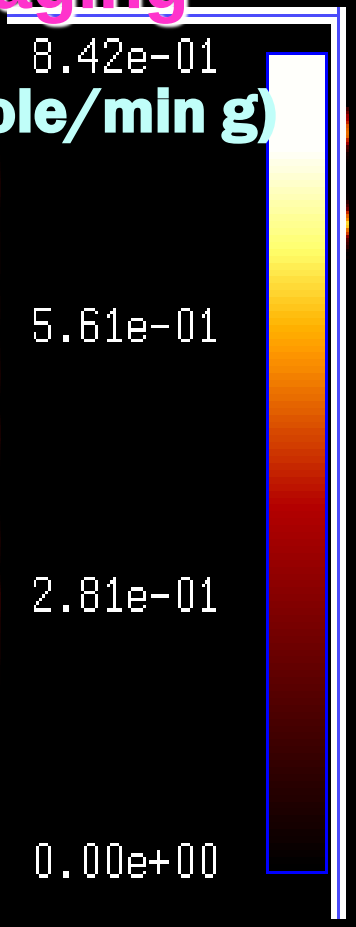
Perfusion Imaging

Metabolic Imaging





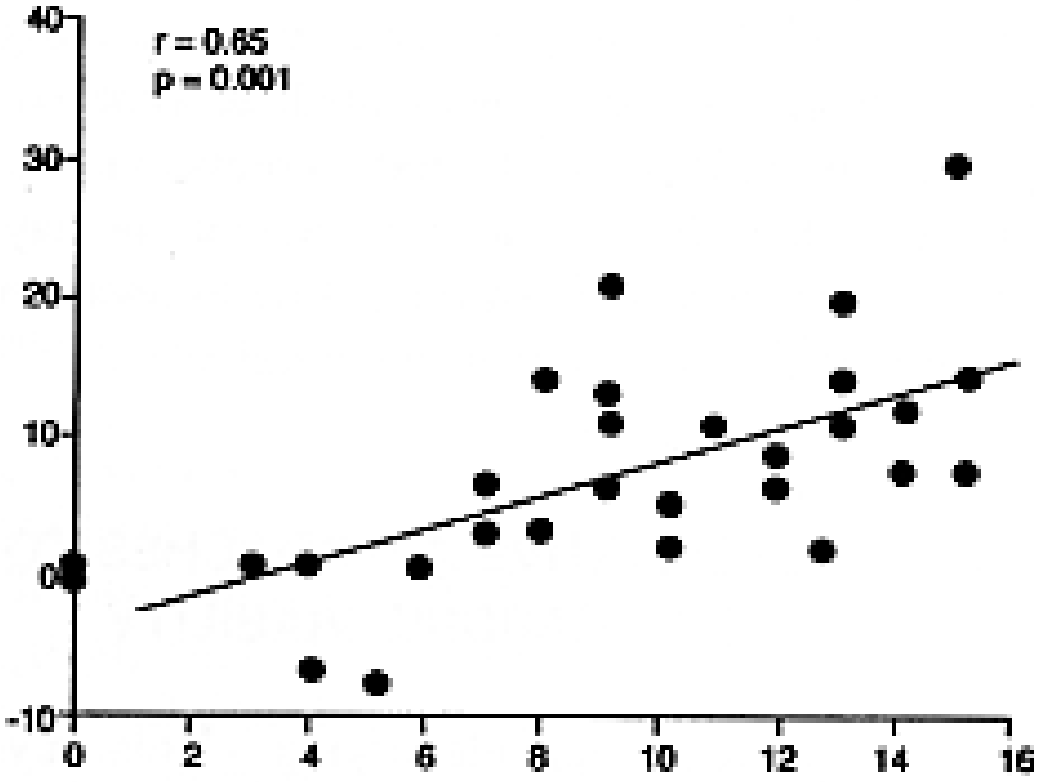




Rest Tl-201 24 hour delay $MMR_{glucose}$

(Partial redistribution)

LVEF changes after TX with PET findings

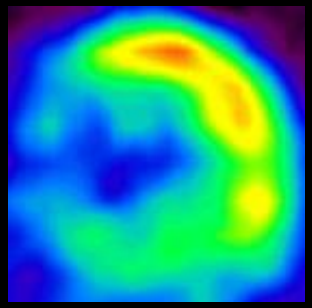
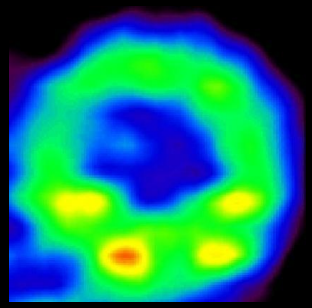
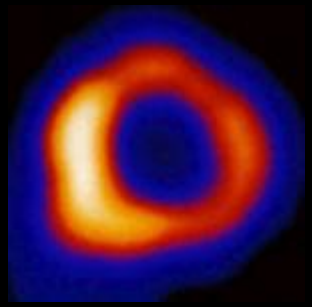
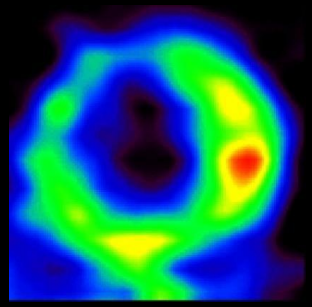


R= 0.65

P= 0.001

Schelbert HR. Semin Nucl Med 32: 60-69, 2002

Two kinds of patients preparation

Fasting	*Glucose Load*
	
F-18 FDG	F-18 FDG
	
Tl-SPECT	NH_3 PET

FDG: gold standard for viability

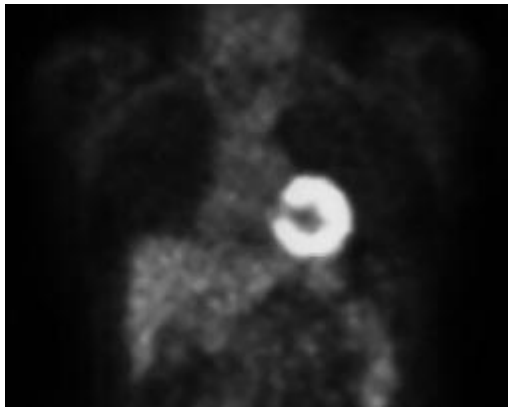
- **No uptake of FDG = No metabolism, Not viable**
  - **High sensitivity and low specificity**

	Sensitivity	Specificity	
Tillisch J et al. NEJM 1986	95	80	Glucose load
Tamaki N et al. Am J Cardiol 1989	78	78	Fasting

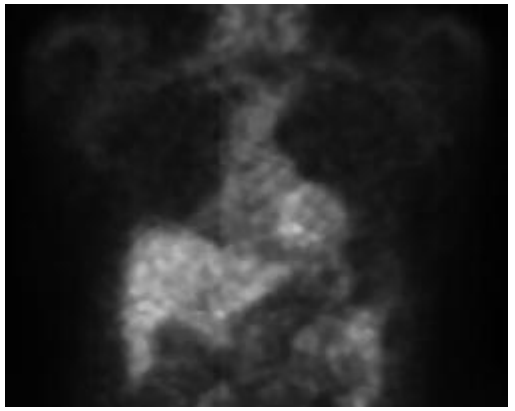
  - **AHA/ACC/ASNC guideline; Class I, Level of evidence B**

FDG PET: How to interpret

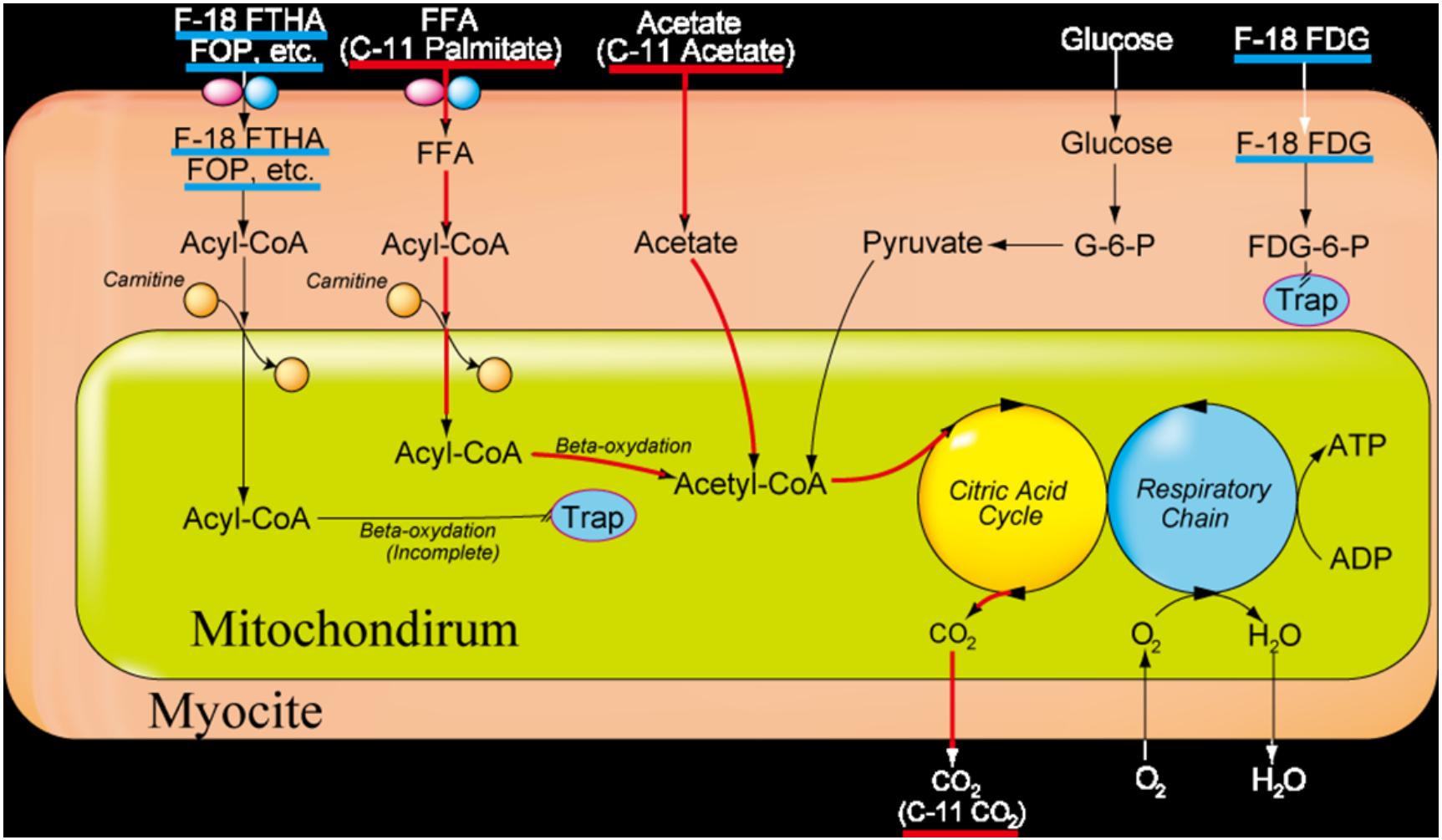
- **Flow/metabolism Mismatch**
  - **Always requires perfusion images**
- **% Uptake of FDG**
  - **Requires FDG image only**
  - **Ratio to normal area (% uptake) > 50~60%**
- **Metabolic rate of glucose**
  - **Absolute measurement of metabolism**
  - **Threshold is around 0.25 uMol/min/g**
  - **Inter-individual variation**



Fasting 4 h

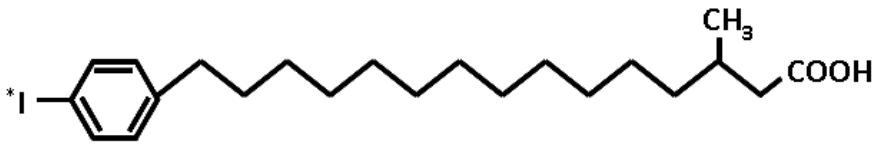


Fasting 8 h

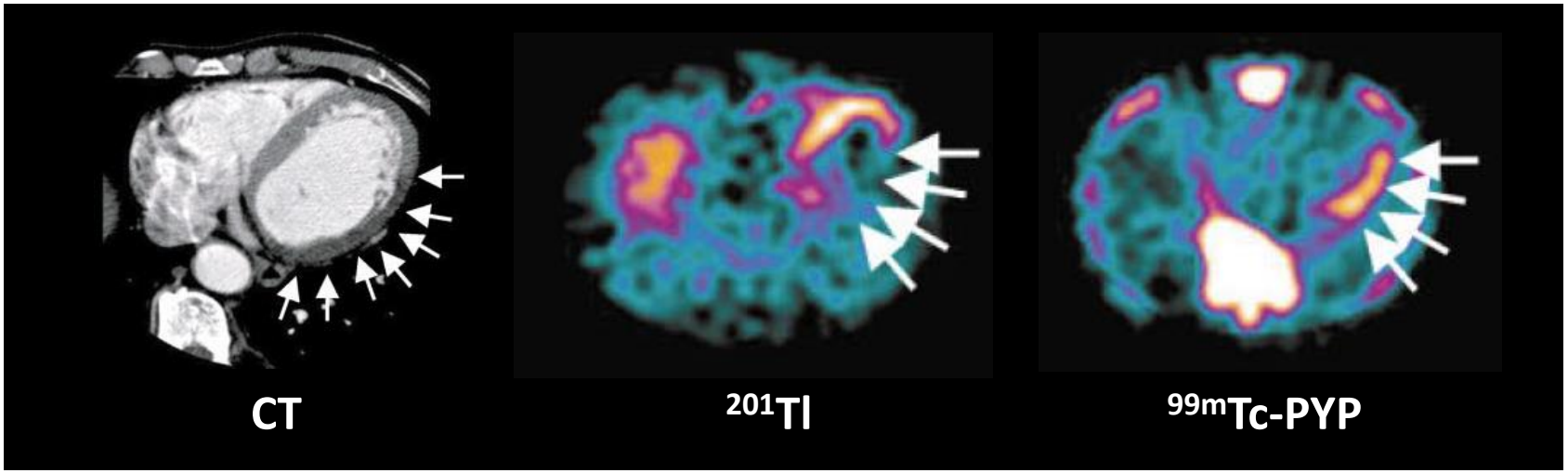

F-18 FTHA
FOP, etc.
FFA
(C-11 Palmitate)
Acetate
(C-11 Acetate)
Glucose
F-18 FDG
F-18 FTHA
FOP, etc.
FFA
Glucose
F-18 FDG
Acyl-CoA
Acyl-CoA
Acetate
Pyruvate
G-6-P
FDG-6-P
Carnitine
Carnitine
Trap
Acyl-CoA
Beta-oxydation
Acetyl-CoA
Citric Acid
Cycle
Respiratory
Chain
ATP
ADP
Acyl-CoA
Beta-oxydation
(Incomplete)
Trap
Mitochondirum
Myocite
CO2
O2
H2O
CO2
(C-11 CO2)
O2
H2O

Viability Assessment with SPECT

- **Others**
  - ^{99m}Tc-Pyrophosphate (PYP)
    - Uptake in Ca^{2+} deposit area of infarct tissue
  - ^{123}I-BMIPP
    - Fatty acid metabolism



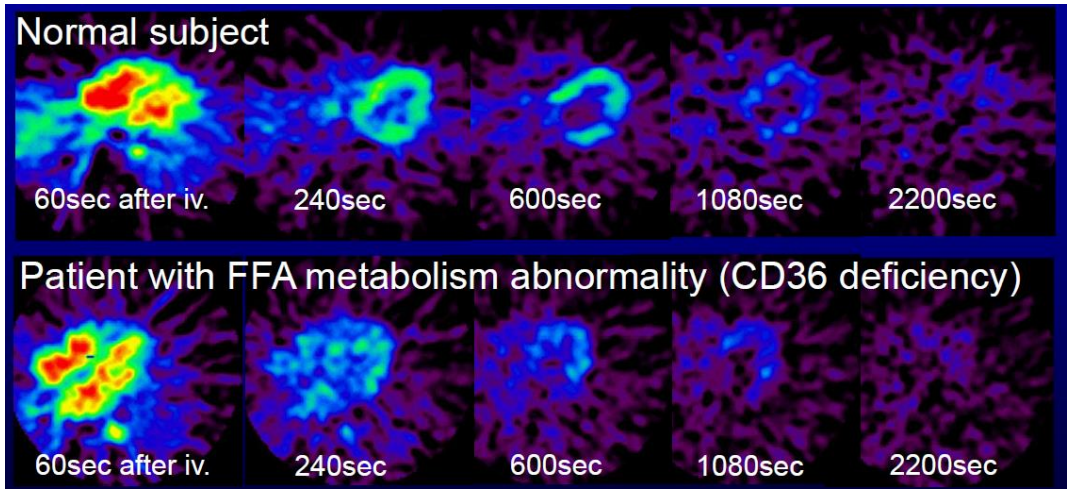
15-(*p*-iodophenyl)-3-(R,S)-methylpentadecanoic acid



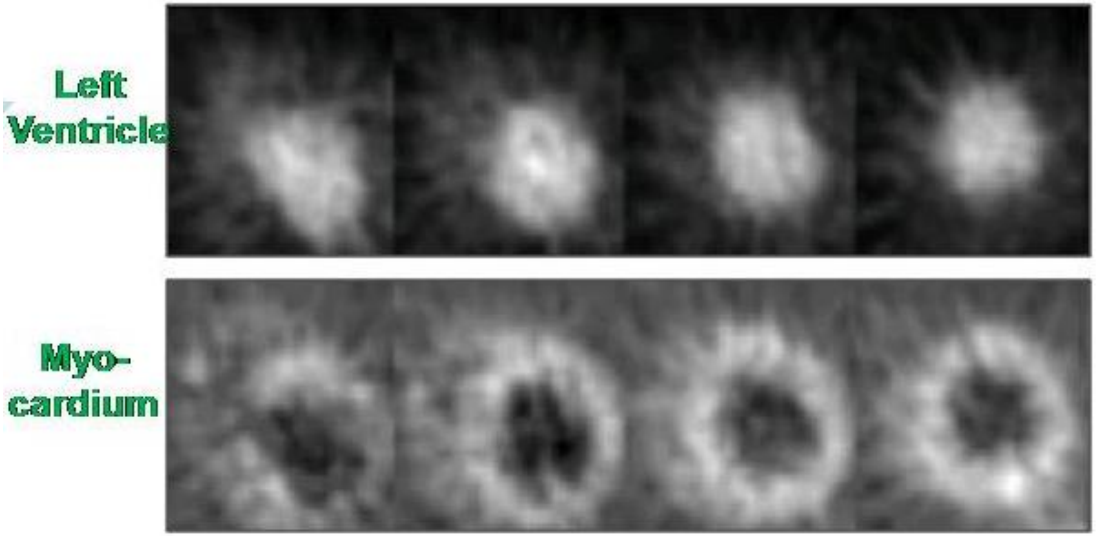
Koyama et al. *J MRI* 2004

Viability Assessment with PET

C-11 Palmitate PET



O-15 water PET



Detecting Hibernating Myocardium

- Comparison of Modalities

Technique	No. of studies	No. of patients	Mean EF (%)	Sensitivity (%)	Specificity (%)
Dobutamine echocardiography—total	41	1421	25–48	80	78
Low-dose DbE	33	1121	25–48	79	78
High-dose DbE	8	290	29–38	83	79
Myocardial contrast echocardiography— total	10	268	29–38	87	50
Thallium scintigraphy— total	40	1119	23–45	87	54
Tl-201 rest-redistribution	28	776	23–45	87	56
Tl-201 re-injection	12	343	31–49	87	50
Technetium scintigraphy—Total	25	721	23–54	83	65
Without nitrates protocol	17	516	23–52	83	57
With nitrates protocol	8	205	35–54	81	69
Positron emission tomography—total	24	756	23–53	92	63
Cardiovascular magnetic resonance— total	14	450	24–53	80	70
Low-dose dobutamine protocol	9	272	24–53	74	82
Late gadolinium-enhancement protocol	5	178	32–52	84	63

Shah BN et al. *Eur Heart J* 2013

Comparison of Modalities

- General Concepts on Relative Performance
  - Dobutamine Echo: low sensitivity / high specificity
  - ^{201}Tl SPECT: high sensitivity / low specificity
  - ^{18}F-FDG PET: higher sensitivity / low specificity
  - DE CMR: high sensitivity / low specificity

Modality	Sensitivity	Specificity	Accuracy
^{99m}Tc-MIBI	79	58	69
Redistribution ^{201}Tl	86	58	73
^{18}F-FDG PET	92	57	76
Dobutamine Echo	81	80	81
DE CMR	> 90%	26-68%	-

Zaret, *Clinical Nuclear Cardiology* 2005/ Saraste, *J Nucl Cardiol* 2008

Diagnostic Criteria

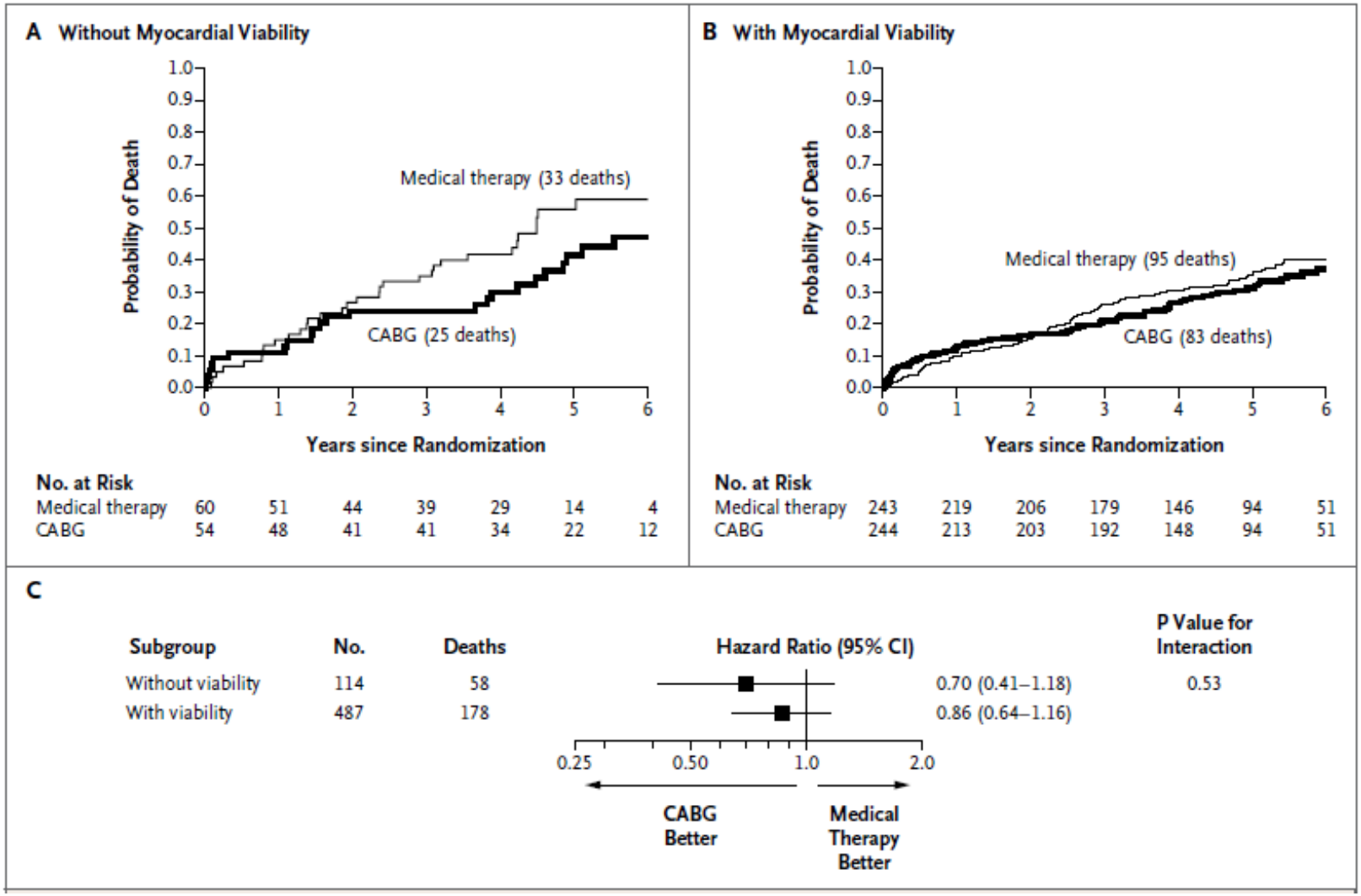
- **Usual Cutoff for Viability**
  - **^{201}Tl Delayed SPECT: 50% of normal myocardium**
  - **^{18}F-FDG PET: 50% of normal myocardium**
  - **DE CMR: transmurality 25–50%**

Characteristic	Imaging modality	Markers of viability
Perfusion/intact cell membrane	Thallium-201 SPECT	Tracer activity >50% Redistribution >10% (Δ)
Perfusion/intact mitochondria	Technetium-99m TF/MIBI SPECT	Tracer activity >50%
Glucose metabolism	FDG imaging (PET or SPECT)	Improved tracer uptake after nitrates Tracer activity >50% Preserved perfusion/FDG uptake Perfusion-metabolism mismatch
Free fatty acid metabolism	BMIPP SPECT	Tracer activity >50% Perfusion-BMIPP mismatch
Contractile reserve	Dobutamine echo/MRI Dobutamine gated SPECT	Improved contraction Infusion of low dose dobutamine

Bax, *Heart* 2004

Surgical Treatment for Ischemic Heart Failure (STICH)

NEJM 2011

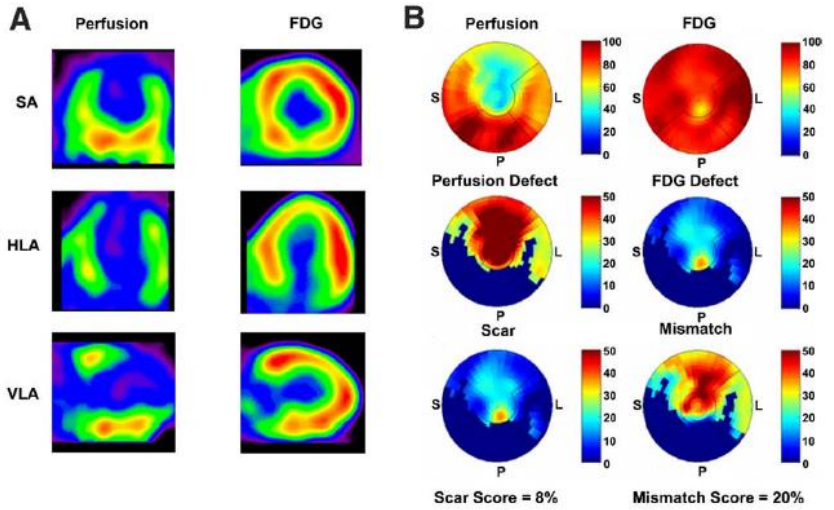


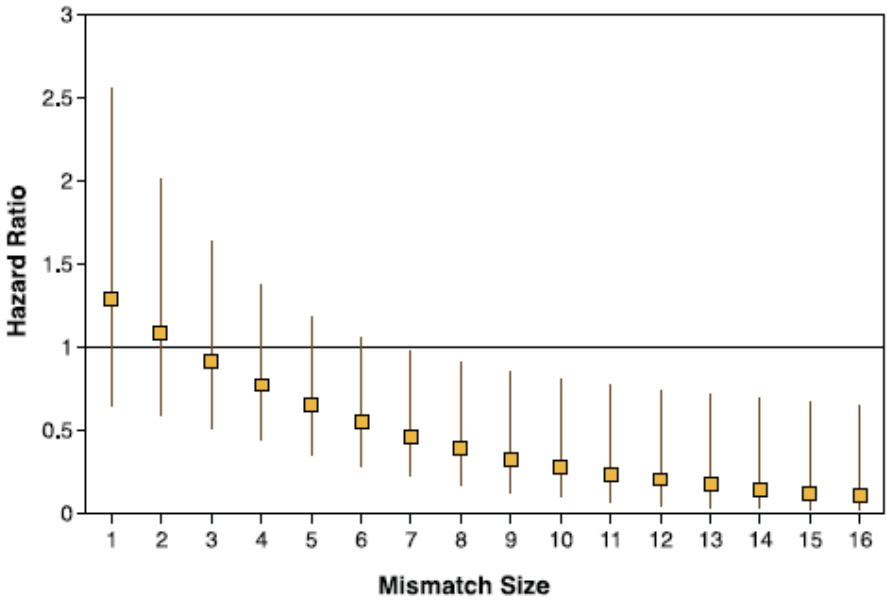
A Substudy of PARR-2 trial

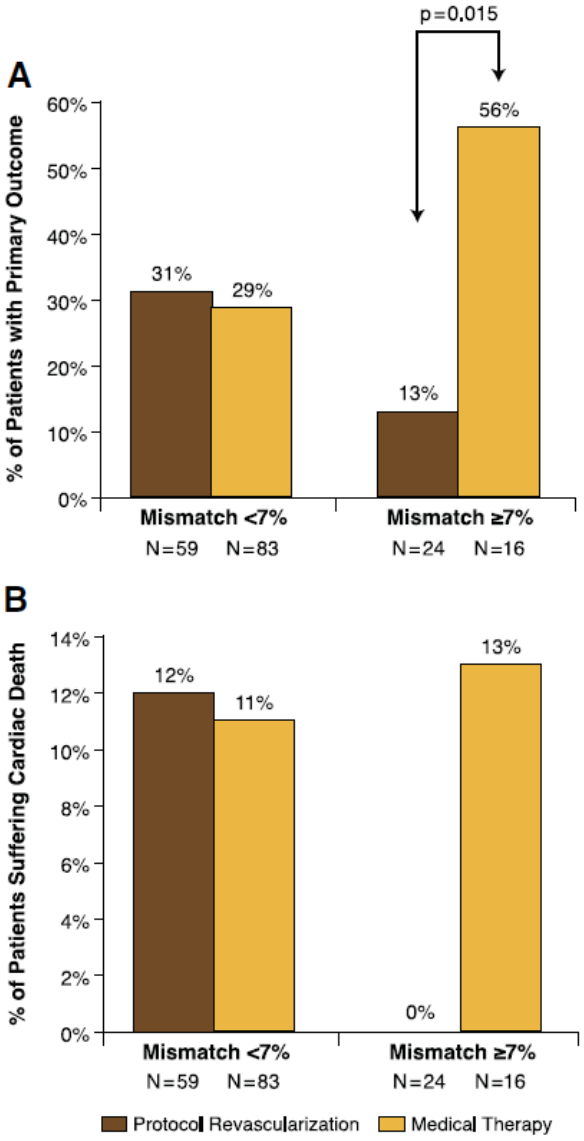
- A Substudy of PET and Recovery following Revascularization – 2 trial

JACC 2007

JACC Img 2009







What is needed in viability test on PET

- Assessing Prognosis and Patient management
  - Prediction of improvement of symptom, exercise capacity, and QOL
- Easy availability
  - Cardiac study dedicated scanner or cyclotron
- Hybrid system (PET/CT vs PET/MR)
  - Transmural vs non-transmural
- Automatic and quantitative and reproducible methods
  - Optimal cut-off
  - Serial monitoring

^{15}O-Dedicated Cyclotron System

d ⇒ $^{16}O_2$ in N_2

⇓

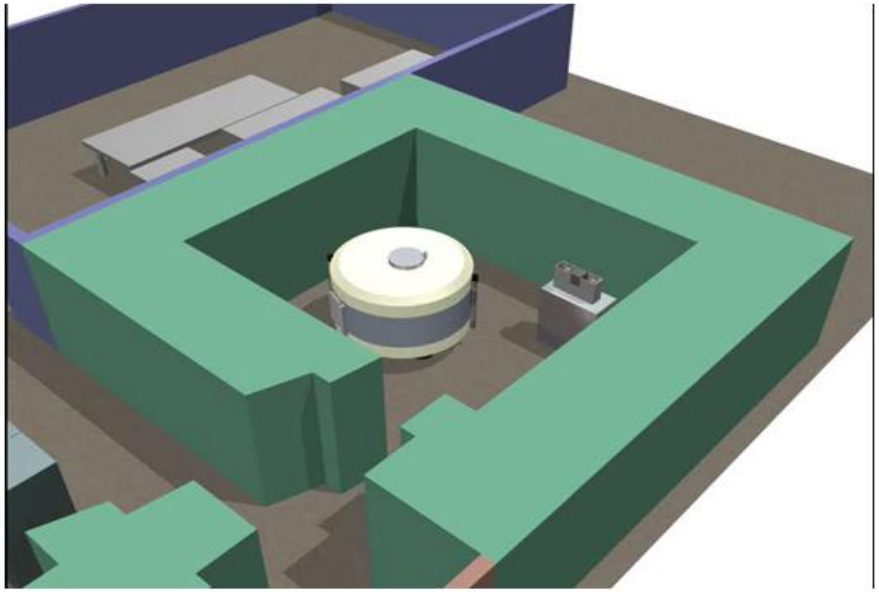
^{15}O-^{16}O (^{15}O-oxygen)

$^{14}N(d,n)^{15}O$

E>3.0 MeV

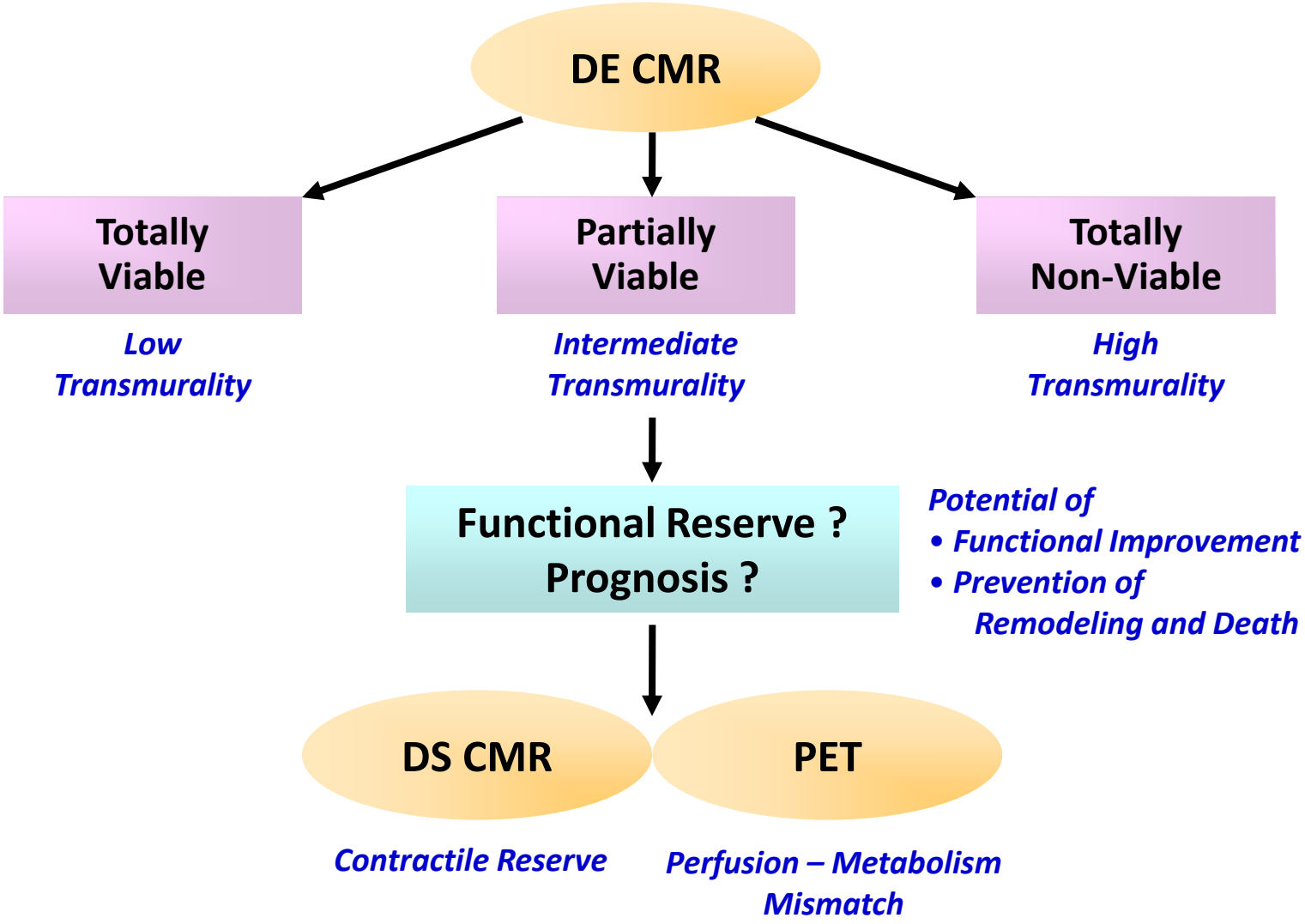
Proton at 18 MeV
Deuteron at 9 MeV

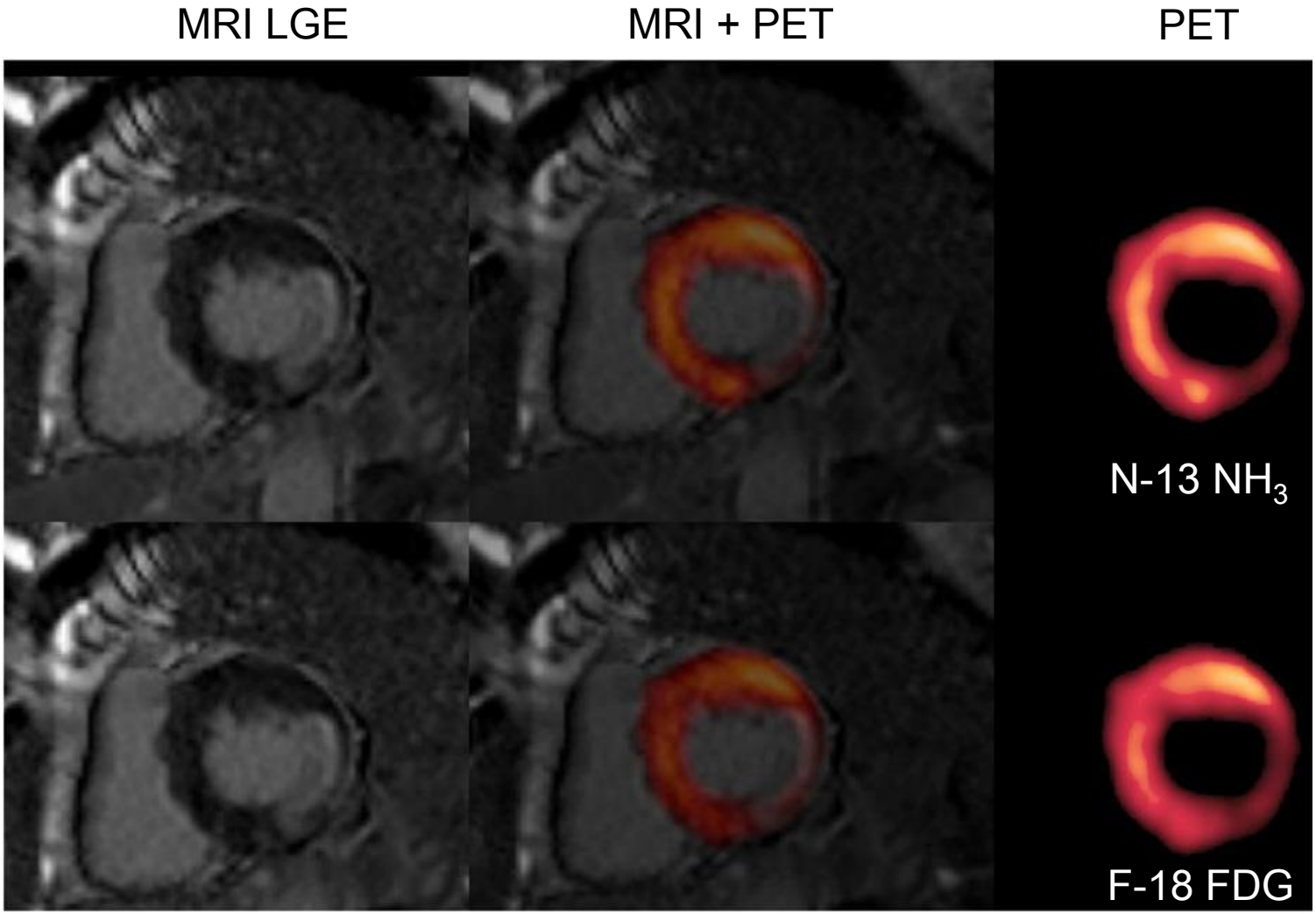
Deuteron at 3.5 MeV



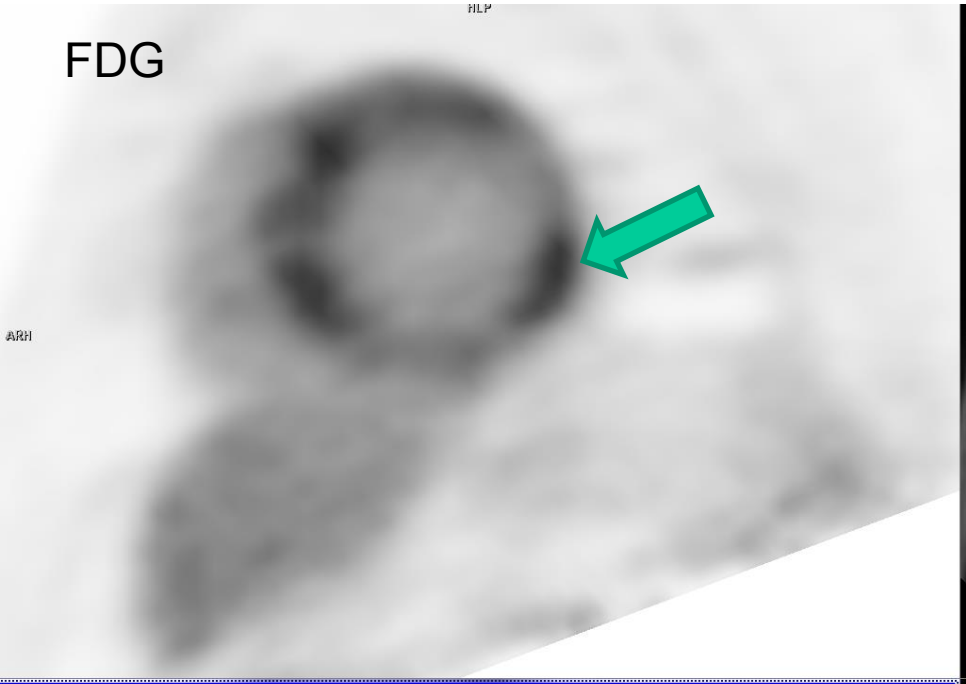
National Cerebral & Cardiovascular Center, Japan

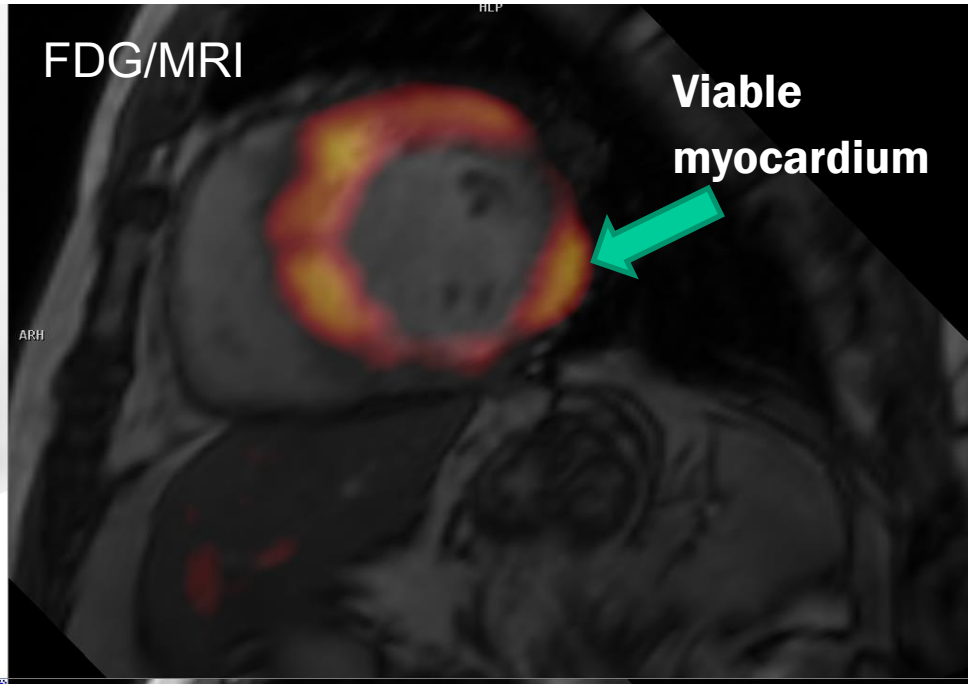
DE CMR with Stunning & Hibernation

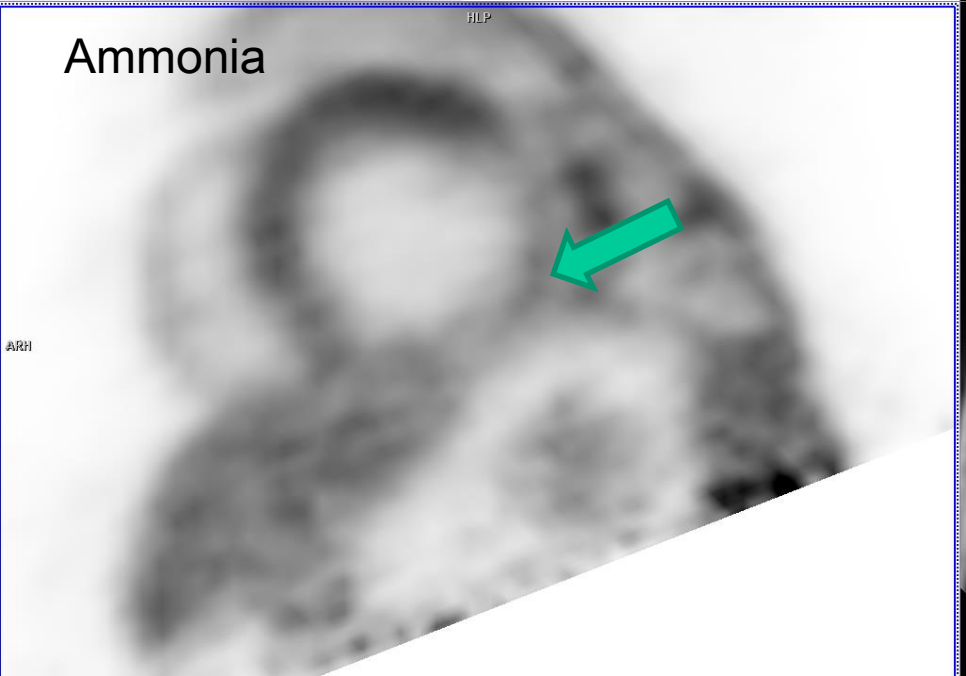


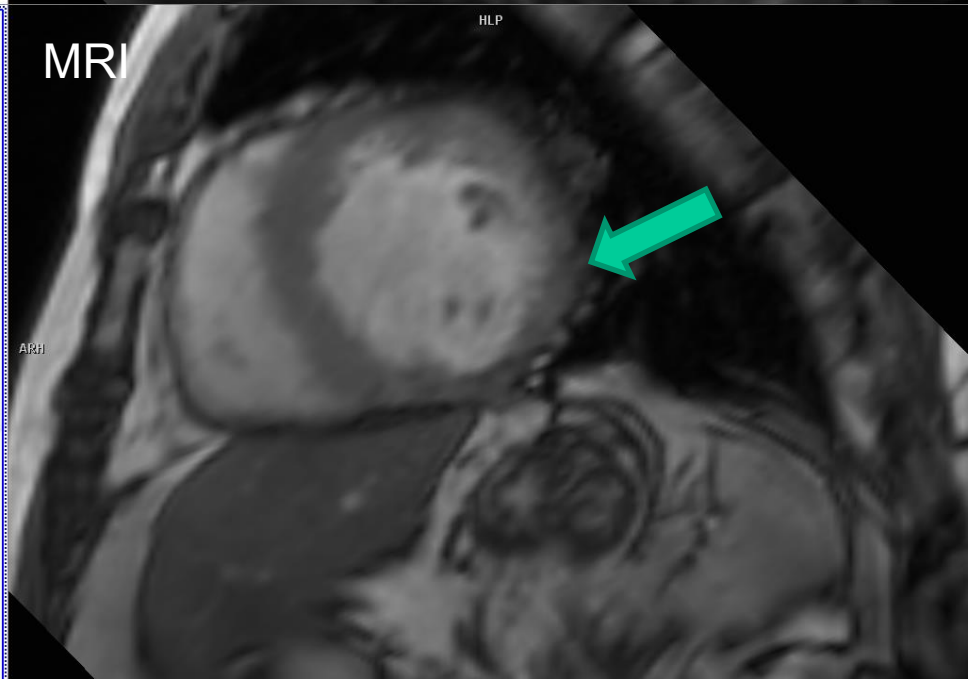


Anagnostopouos et al. Int J Cardiol 2013

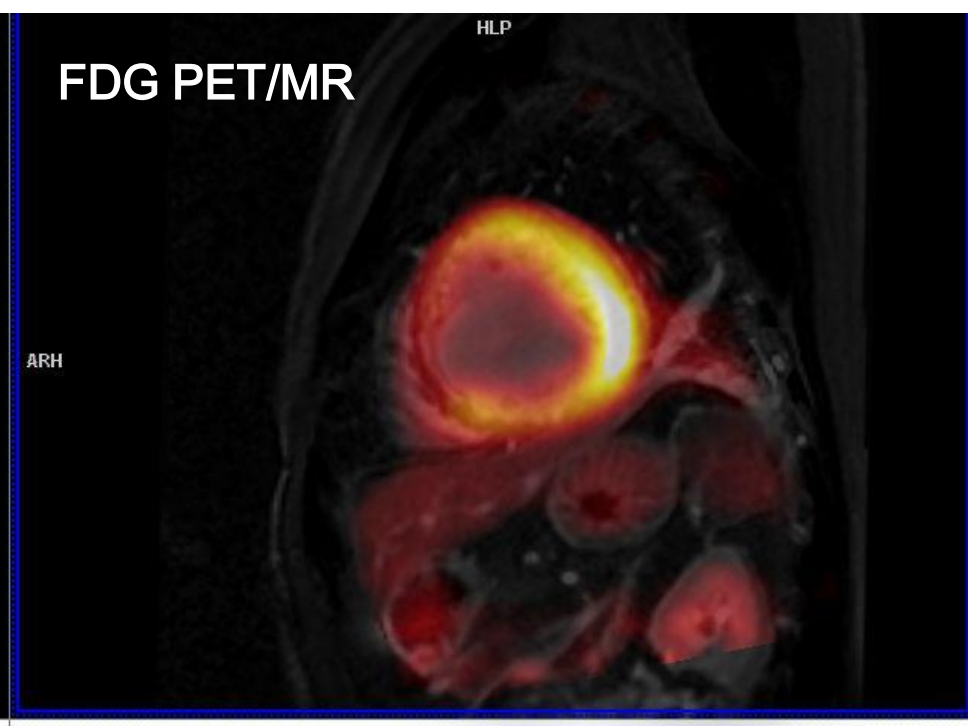




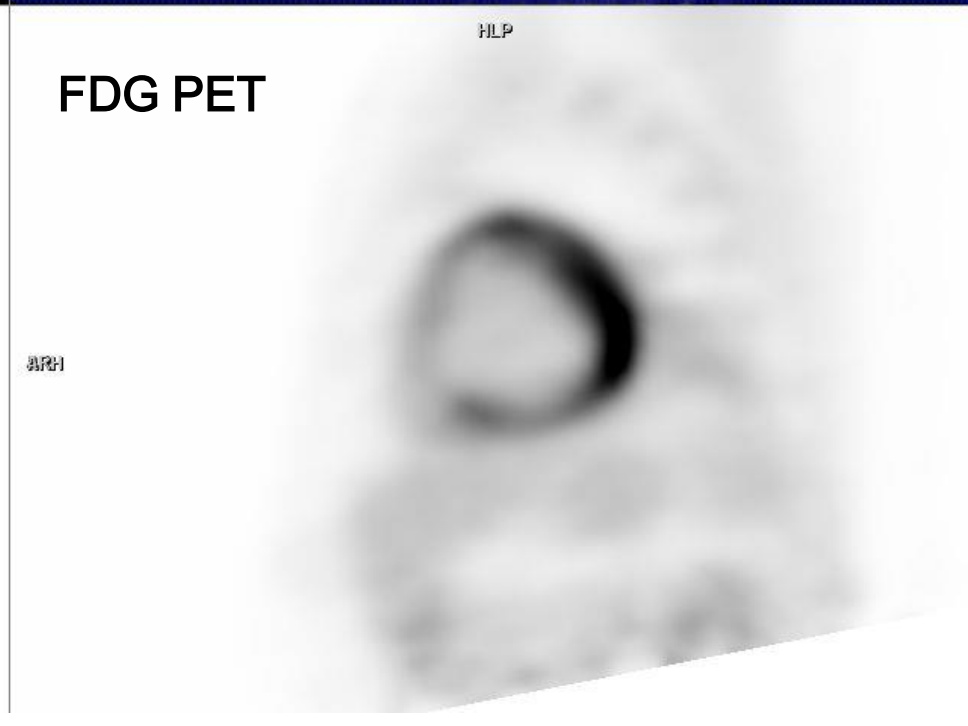




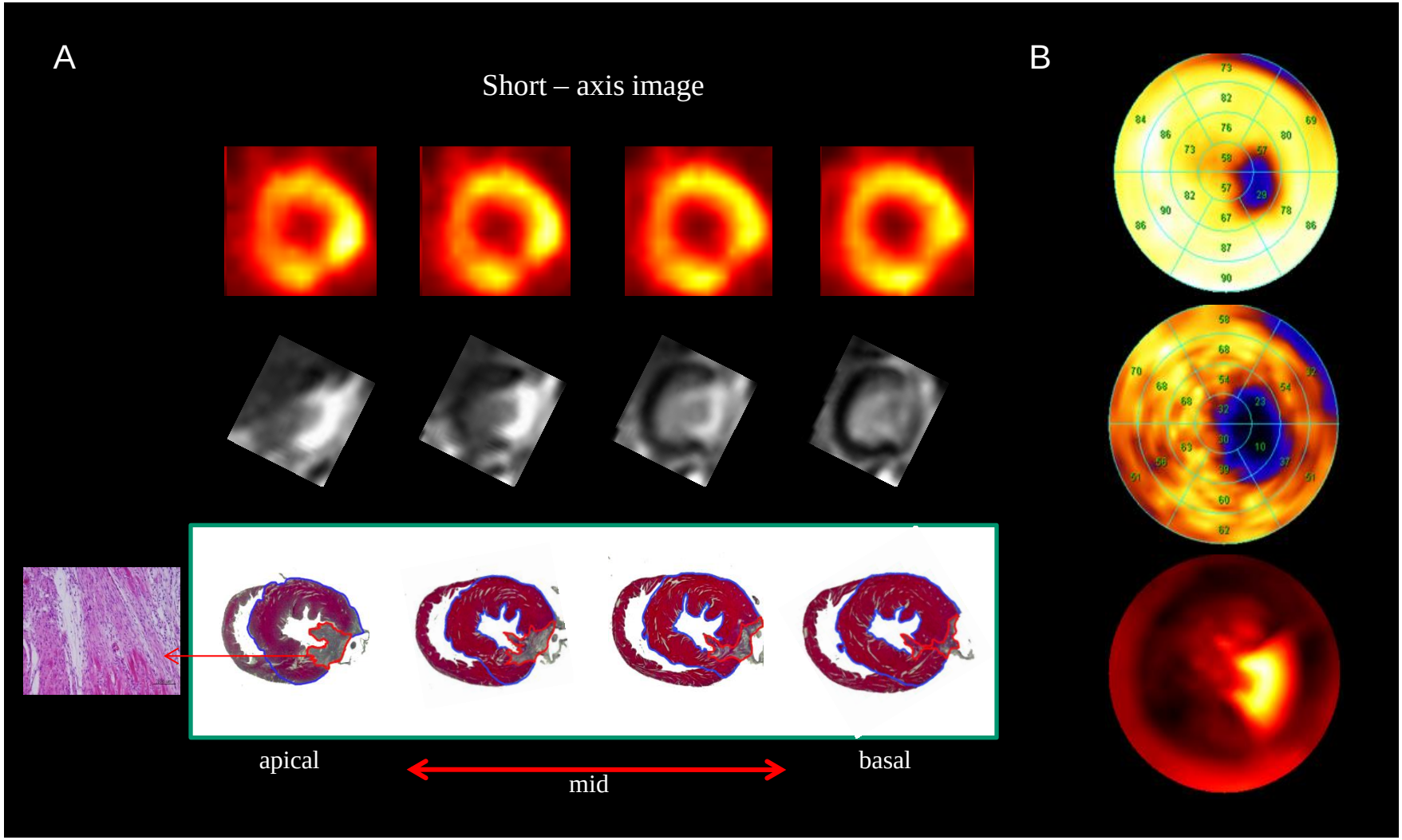

MR_delayed enhancement
HLP
ARH


FDG PET/MR
HLP
ARH


FDG PET MIP
H
RA

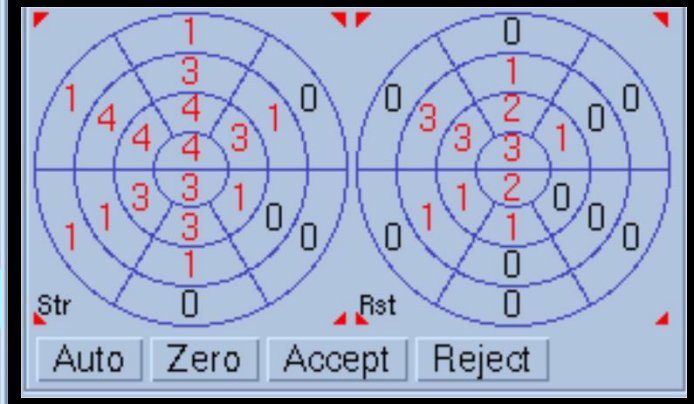

FDG PET
HLP
ARH

Automatic quantitative assessment of MI size by MGMM



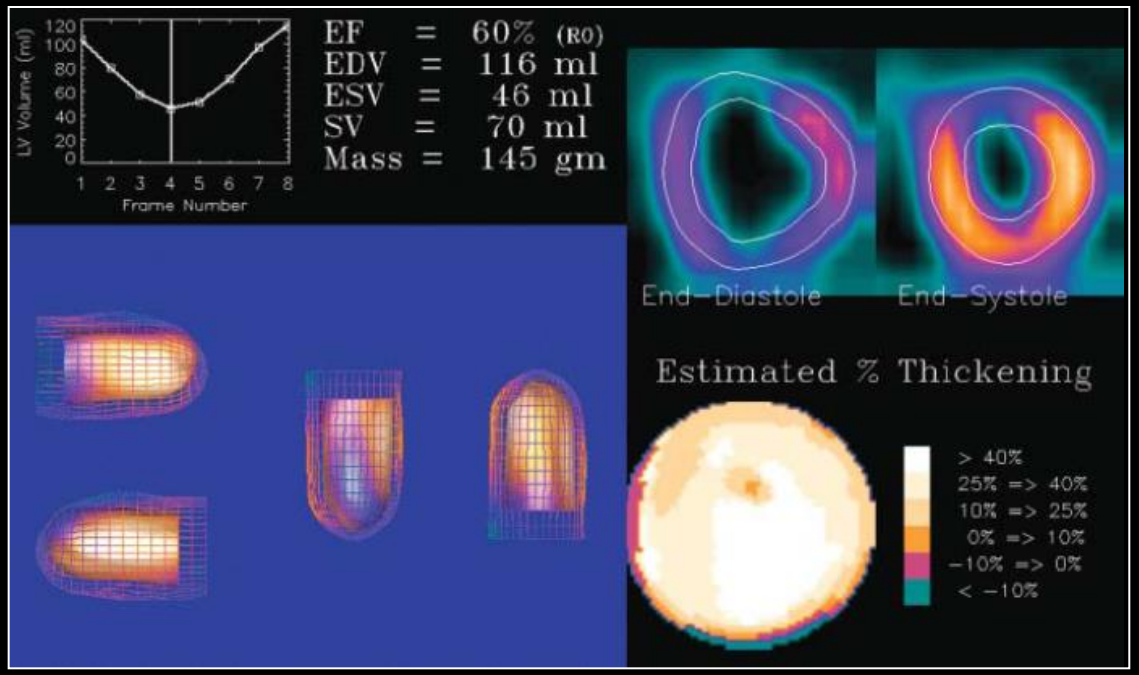
JACC Img 2013, *submitted*

AutoQUANT



SSS 17	SRS 12	SDS 4
SS% 21	SR% 15	SD% 5
Volume	85ml	
Wall	148ml	
Defect	40ml	
Extent	27%	
TPD	21%	

EC Toolbox



Summary

- Pathophysiology of Viability
  - Stunning/hibernation
- Viability Assessment Using Nuclear Imaging
  - ^{18}F-FDG PET: useful tool for viability assessment
    - Usually acquired under glucose loading state
  - ^{201}Tl redistribution/reinjection by SPECT
  - FFA, acetate can be used on cardiac PET study
- Combination of Structure & Physiology
  - Transmurality-adjusted FDG uptake (or Tl redistribution)
- Viability Assessment with Extended Concept Needed
  - More than functional improvement