Myocardial Viability

MRI & PET

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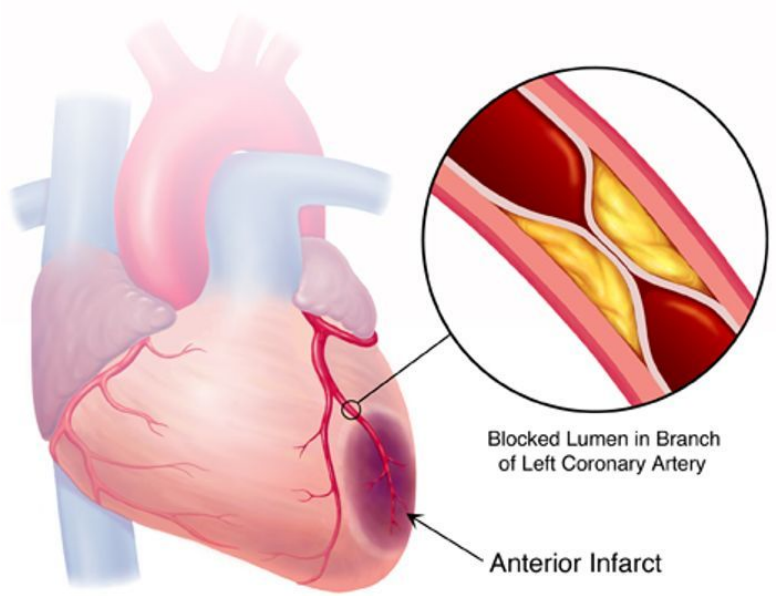
Problem & definitions

- Coronary artery disease (CAD) remains the leading cause of death in the United States and Europe
- CAD is cause by atherosclerosis.The buildup of plaques narrows down the arteries.
- CAD leads to:
  - Inadequate blood flow (ischemia)
  - heart attack (myocardial infarction).
- Myocardial infarction causes cell death and necrosis.



Problem & definitions

- But some of the involved tissue remained **viable**:
  - Pathophysiologically: alive myocardium, with cellular, metabolic, and contractile function.
  - Clinically: dysfunctional myocardium at rest, with a potential for functional recovery on restoration of normal blood supply.

- **Revascularization** is an option to improve ventricular function and long-term survival, compared to taking medications alone.
- However, perioperative mortality and morbidity of patients is high.
- A **myocardial viability** test: determine percentage of nonviable myocardium.
- As the amount of viable myocardium increases above the threshold of 10%, the likelihood of benefit for revascularization increases.

Problem & definitions

Types myocardium (heart tissue):

- Viable

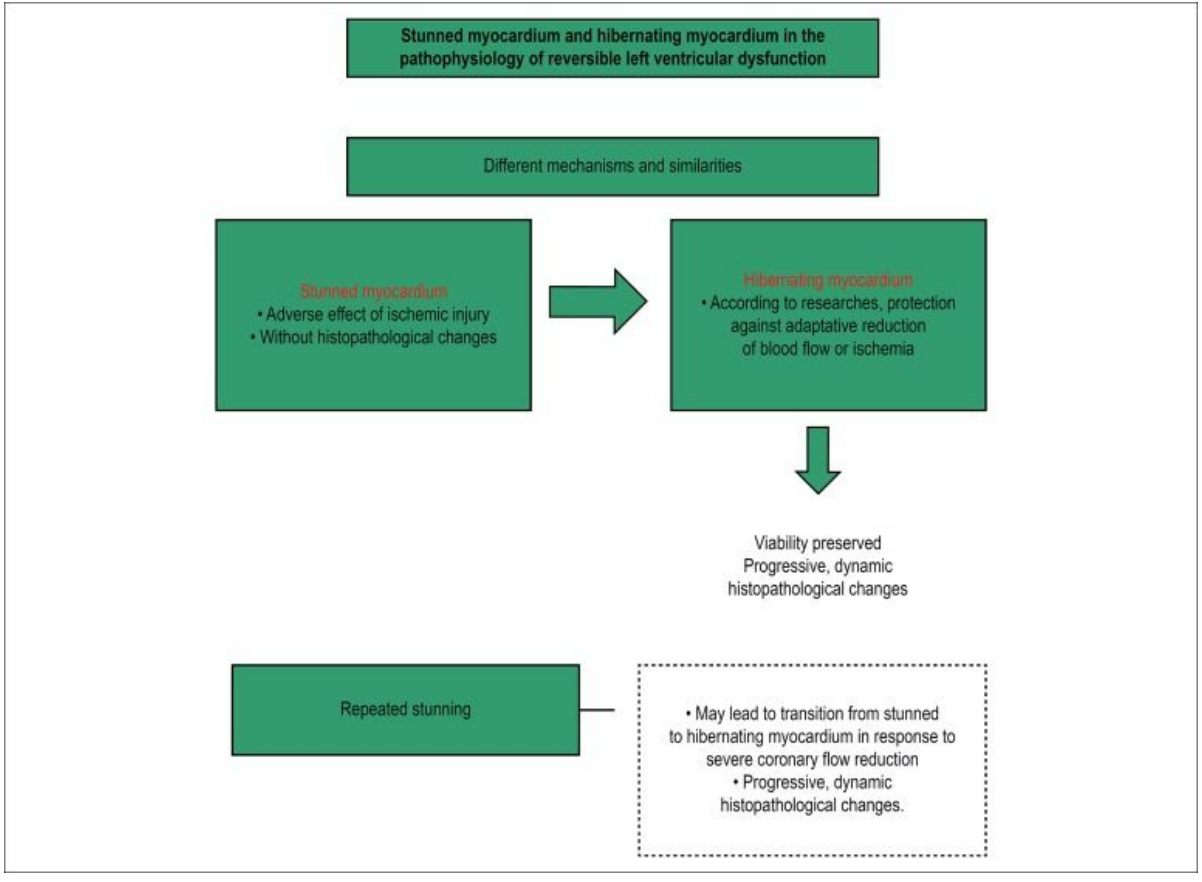
Stunned myocardium:

- short ischemia
  → contractile dysfunction
  → perfusion recovers quickly
- Myocardium may be dysfunctional for several days. Perfusion returns to normal → function is restored
- Most are metabolic changes in myocardium (not structural)
- Electron microscopy of these cells show normal or mildly degenerated cells

Hibernating myocardium:

- prolonged or repetitive reduced perfusion
  → reduced contractile function + intact cell membrane and cell metabolism
- Severe cellular defects and myofibril loss
- Abnormal CFR(coronary flow reserve) and repeated ischemia.
- Reduced perfusion → Reduced contractile function
- chronically dysfunctional but viable myocardium
- Can only restore to normal perfusion after **revascularization**.

Problem & definitions



Problem & definitions

Types myocardium (heart tissue):

- **Non-viable**
  - Myocardial perfusion is not restored
  - Irreversible myocardial cell death

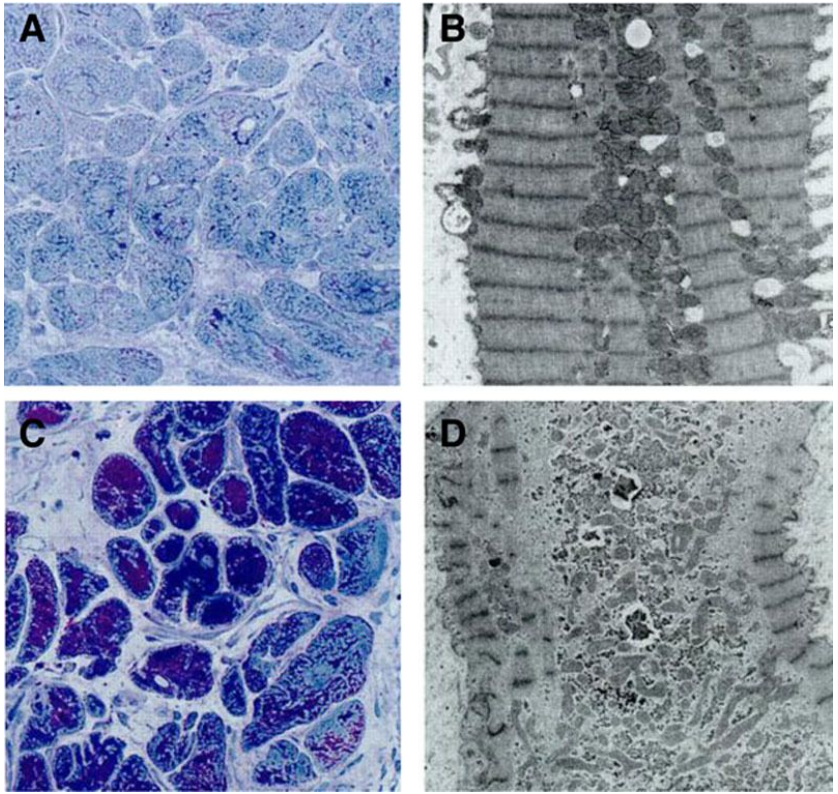
Problem & definitions

A. Normal myocardium (virtually no glycogen, stained in red).

B. A normal cardiac myocyte.

C. Hibernating myocardium. Cardiac myocytes are depleted of their contractile material and filled with glycogen (positive staining).

D. A hibernating cardiac myocyte. Myolytic cytoplasm is devoid of sarcomeres (dark bands) and filled with glycogen.



MRI

a. Principles
b. Performance evaluation
c. Limiting factors
d. Future outlook for this application (comparisons / + other modalities)

MRI for myocardial viability (MV)

Two types of cardiac MRI for MV

- Dobutamine stress magnetic resonance imaging (DSMR)
- Delayed contrast-enhanced cardiac MRI (DE-MRI)

MRI for myocardial viability (MV)

Dobutamine stress magnetic resonance imaging (DSMR):

- use **dobutamine** pharmacological stress
- determine **contractile reserve** of dysfunctional myocardium.
- viable myocardium → **contractile reserve** is present.

MRI for myocardial viability (MV)

Delayed contrast-enhanced cardiac MRI (DE-MRI):

- use **gadolinium-based** contrast agents
- define the **transmural extent of scar**
- On T1 weighted images, the **transmural extent of scar** is visible by regions of increased image intensity.
- As the extent of hyperenhancement increases, amount of non-viable myocardium increases.

MRI - Delayed enhancement

Gadolinium:

- Paramagnetic, shortens the relaxation process of the tissues
- increases the signal in the MRI images.
- an extracellular molecule (cannot enter myocardial cells).

Intravenous injection → arterial microvascular network → flows into the extracellular space (wash-in) and then back into the venous system (wash-out).

If myocyte membranes are damaged (eg, acute MI) or if there is an increase in the extracellular space between myocytes, gadolinium accumulates in the extracellular space, and its washout is delayed after the injection.

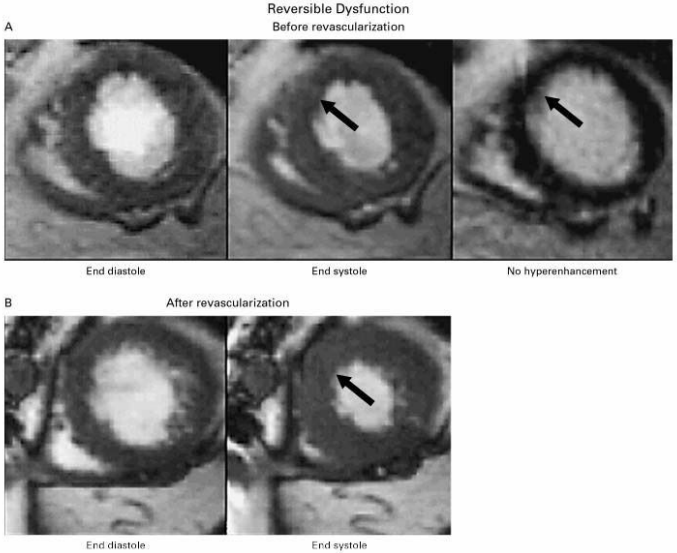
Thus, areas of abnormal myocardium (eg, infarcted, fibrotic, inflamed, or infiltrated myocardium) → bright signal on T1 images.

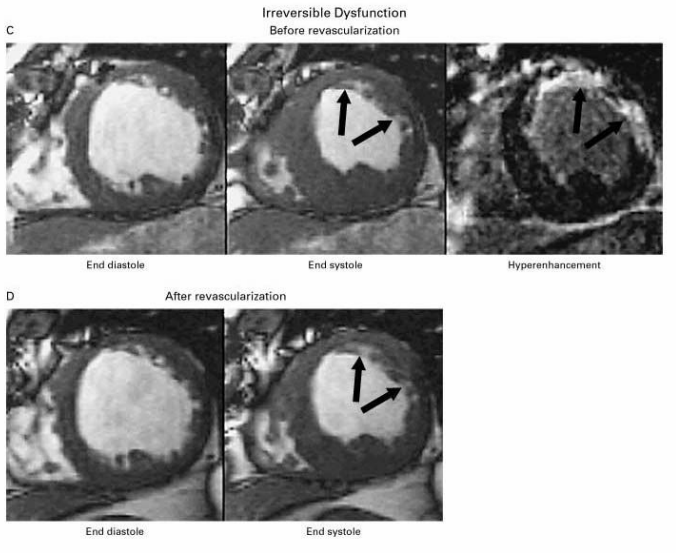
Moreover, signal from normal myocardium is suppressed (nulled) by an inversion recovery preparation pulse.

MRI - Delayed enhancement

Left: The patient with reversible dysfunction had severe hypokinesia of the anteroseptal wall (arrows), and this area was not hyper-enhanced before revascularization. The contractility of the wall improved after revascularization.

Right: The patient with irreversible dysfunction had akinesia of the anterolateral wall (arrows), and this area was hyper-enhanced before revascularization. The contractility of the wall did not improve after revascularization.





MRI - Delayed enhancement

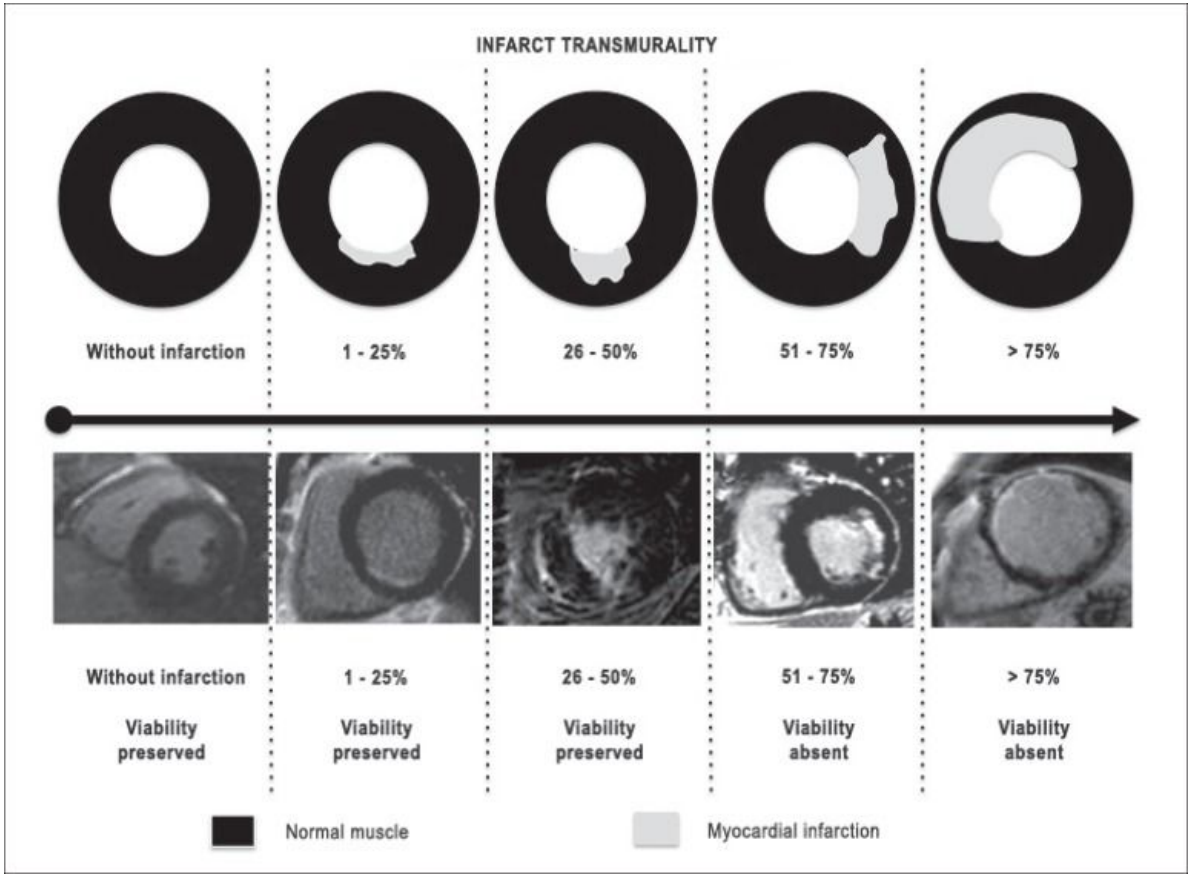
First: NO delayed enhancement → a high probability (around 80%) of contractile improvement after revascularization.

Second: 1 - 25% of the area of the segment with delayed enhancement –> 60% probability of improvement

Third: 26 - 50% of delayed enhancement,~ 40% probability of improvement

Fourth: 51 - 75% of compromised muscle. Revascularization and clinical treatment should be widely discussed.

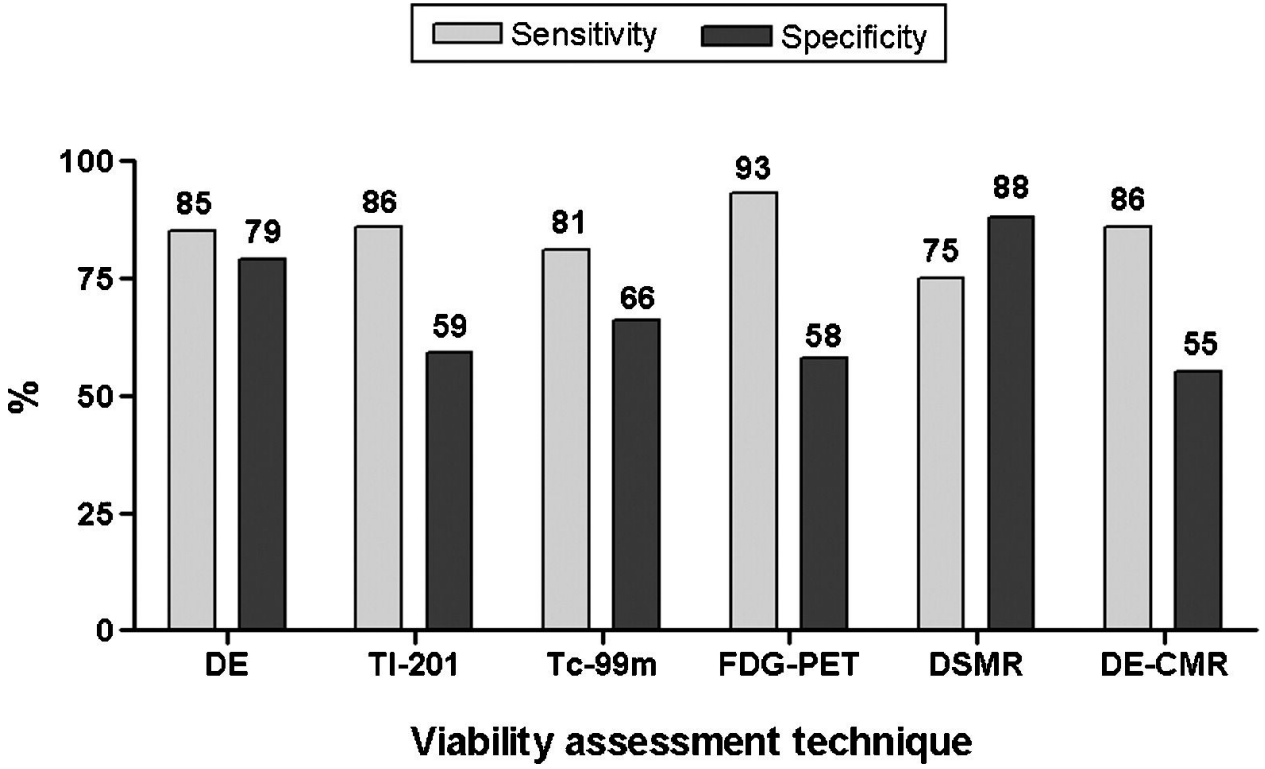
Fifth: More than 75% of the area of the myocardial segment compromised. Potential of contractile recovery of less than 1%.



Performance evaluation

Sensitivity and specificity of methods for assessing myocardial viability

Delayed contrast CMR has **higher** sensitivity.



Outlook

- DE-CMR is **highly accurate** in predicting functional recovery of dysfunctional myocardial segments in patients undergoing revascularization

- A new technique - PET-MR started to be studied, but still has limited availability. The method has the advantage of combining the high spatial resolution of MR with the sensitivity of PET, without excessive ionizing radiation. In contrast to PET-CT, however, the synergism between PET and MR still need to be evaluated.

PET

1. *Principles*
   - Perfusion Imaging
   - Metabolism Imaging
2. *Performance*
   - Protocol
   - Visualization
   - Result
3. *Limiting factors*
4. *Future outlooks*

PET

Traditional 18FDG-PET myocardial viability assessment requires integration of rest perfusion imaging with myocardial glucose metabolism imaging.

PET - *Perfusion Imaging*

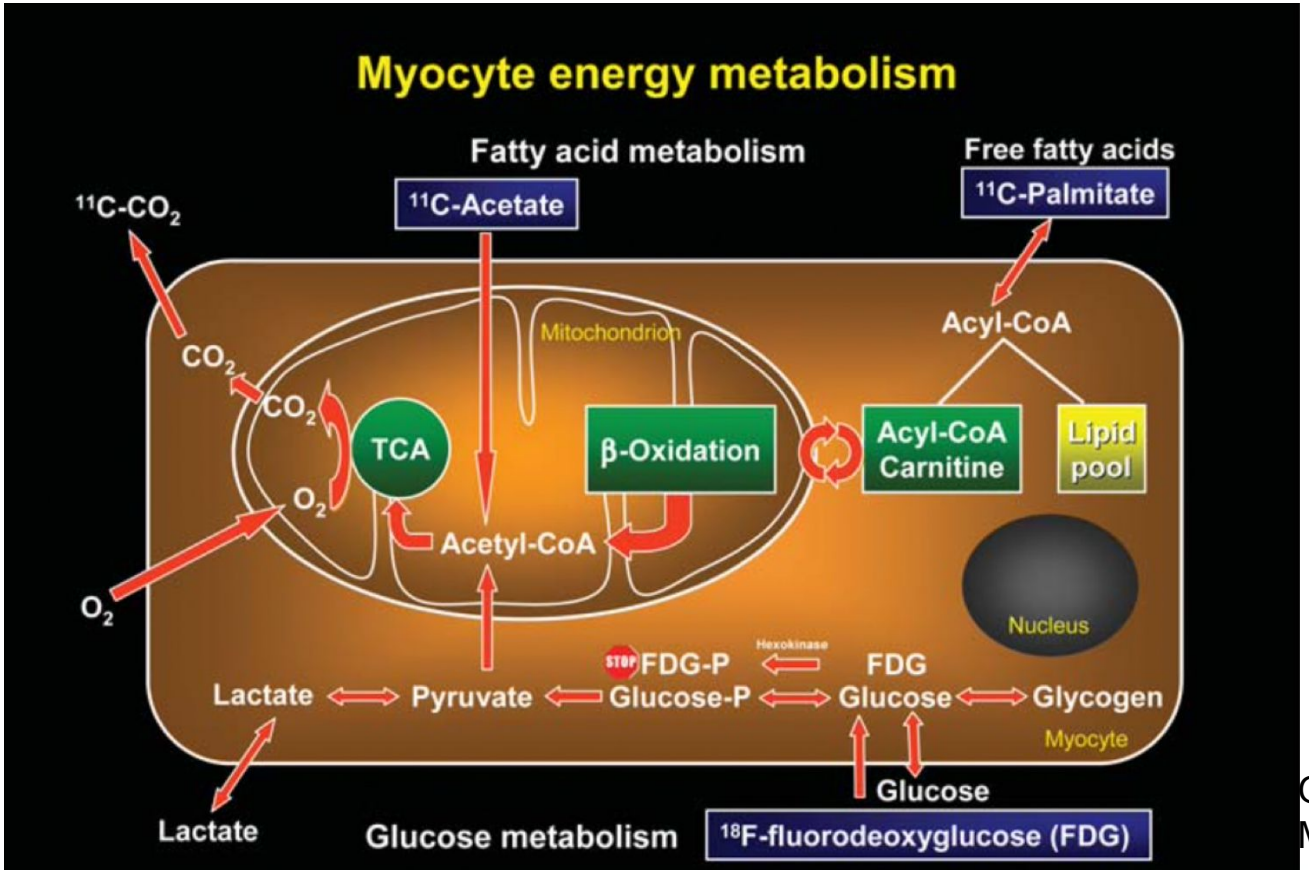
Table 3. Cardiac positron radiopharmaceuticals

Mechanism	Radionuclide	Pharmaceutical	Physical Half-life	Production
Perfusion	Nitrogen-13	Ammonia	10 min	Cyclotron
	Rubidium-82	Rubidium	76 seconds	Generator
	Oxygen-15	Water	110 seconds	Cyclotron
Glucose metabolism	Fluorine-18	Fluorodeoxyglucose	110 minutes	Cyclotron
Fatty acid metabolism	Carbon-11	Acetate	20 minutes	Cyclotron
	Carbon-11	Palmitate	20 minutes	

Perfusion radionuclides are used for detection of acute ischemia (risk area) and myocardial perfusion. The commonly used PET perfusion radionuclides are rubidium-82 (82Rb) and N13-ammonia (13NH3) in North America and 15O- water in Europe. 82Rb is a potassium analogue, which is actively transported into myocytes through the cellular Na-K pump. 13NH3 diffuses freely across cell membranes and is incorporated into glutamine in the myocardium by the enzyme glutamine synthetase. Both these tracers rely on intact cellular function for their uptake and distribution, and their uptake is directly related to myocardial blood flow. 15O-water is freely diffusible with a linear extraction-flow relationship, making it an ideal tracer for flow quantification.

Ghosh et al., “Assessment of Myocardial Ischaemia and Viability.”

PET - *Metabolism Imaging*-Myocyte Metabolism



Shifting Energy Fuel

from fatty acids to glucose.

FDG uptake is a marker for consumption of glucose.

18F-FDG

(18F-fluorodeoxyglucose)

is used as the tracer for metabolic imaging.

Ghosh et al., “Assessment of Myocardial Ischaemia and Viability.”

Energy Cycles (supplement)

Patterns of energy utilization by the myocardium. Positron emission tomography radiotracers that can be used to image myocardial metabolism are boxed. TCA , tricarboxylic acid cycle. The myocardial cell derives its energy from fatty acid and glucose metabolism. Under fasting conditions almost 100% of the energy is gained from oxidation of fatty acids in the mitochondria. This fatty acid utilization can be visualized using radiolabeled ^{11}C-palmitate and can be used to determine myocardial oxygen consumption since this process requires oxygen. After glucose loading or in chronically underperfused myocardium glucose metabolism is turned on inside the cell and can be visualized with the fluorodeoxyglucose tracer. The final common pathway of lipid and glucose metabolism is acetyl-CoA. ^{11}C-acetate enters the tricarboxylic acid cycle and can be used to monitor myocardial oxygen consumption regardless of whether fatty acids or glucose are fueling the cell.

Ghosh et al., “Assessment of Myocardial Ischaemia and Viability.”

Diabetes?

- ***euglycemic hyperinsulinemic clamp*** :the most widely used

a nursing intensive approach that drives glucose uptake via titration of exogenous insulin and close monitoring of glucose levels.

- Once loaded with glucose and enough insulin has been injected (reaching a blood glucose level below 180mg/dl), FDG can be injected.
- The dose varies by the sensitivity of the system and is usually in the range of 5 – 10 mCi.
- The patients should be monitored for an uptake period of 45 – 90 min.
- Myocardial uptake of FDG continues to increase, and blood pool activity to decrease, even after 45 min.
- Waiting 90 min after the injection of FDG may give better signal to nose ratio as the blood pool has less FDG and the myocardial uptake continues to increase, especially in people with diabetes.
- The typical scan duration is typically 10 – 30 min

Khalaf et al.,2019

PET-Radionuclides

Ideally, the physical properties of the PET-isotopes used for the metabolism and perfusion tracers should be comparable. However, this is not the case for 82Rb and 18F-FDG. 82Rb emits high-energy positrons with considerable tissue penetrance, whereas 18F-FDG emits positrons with far lower tissue penetrance.As a result, 82Rb perfusion images are far blurrier around the edges and tend to overestimate the area in which the tracer has been retained. By contrast, the spatial resolution of 18F-FDG is excellent and areas of 18F-FDG uptake will be more precisely co-localized with actual glucose uptake. This effect may be mitigated by heavy post reconstruction filtering on 18F-FDG images to reduce spatial resolution. However, combined 82Rb/18F-FDG viability testing still tend to overestimate the perfused area and underestimate the metabolically active tissue. In this regard, 13N-NH3 is a better perfusion tracer with physical properties of 13N more closely resembling those of 18F.

PET - *Metabolism Imaging*-Mismatch pattern

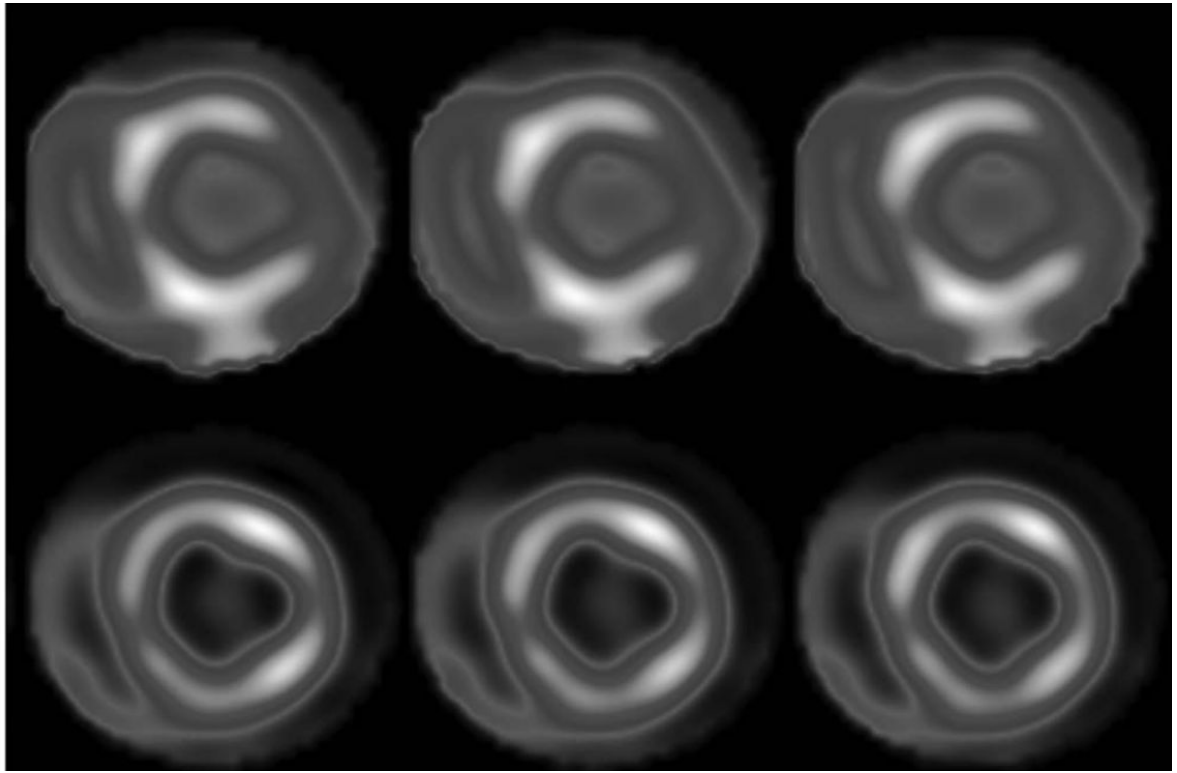
Table 4. Flow-metabolism patterns in dysfunctional myocardium

Blood flow	Glucose metabolism	Definition
+	+	Normal
Diminished	+	Mismatch (viability)
Diminished	Diminished	Match (necrosis)

Demirkol, 2008

Perfusion Images

Metabolic Images



A mismatch defect seen in the lateral wall with reduced perfusion and normal metabolic imaging:a high likelihood of functional recovery following revascularization

Simon et al.,2020

Performance- procedure

- postprandial state receiving glucose and insulin before and during imaging
- attenuation correction
- rest myocardial perfusion imaging with NH3 (740 MBq) was performed
- NH3 decay
- 18F- fluorodeoxyglucose (FDG) (370 MBq) was injected, and data acquisition was initiated 40 minutes after tracer injection
- Transaxial planes were obtained using a whole-body PET
- Attenuation-corrected transaxial images were generated from NH3 and FDG data.
- Data were realigned to generate short- and long-axis views for visual analysis.

Khalaf et al.,2019
Simon et al.,2020

Performance- visualization

1. Purely qualitative eyeballing

Method:the amount of left ventricle scar and hibernation is grouped into the categories “low”, “moderate” or “high.”

Pros:straight forward and can be utilized without commercial or in-house developed software.

Cons:crude estimation of both extent and severity of scar and hibernation.

Simon et al.,2020

Performance- visualization

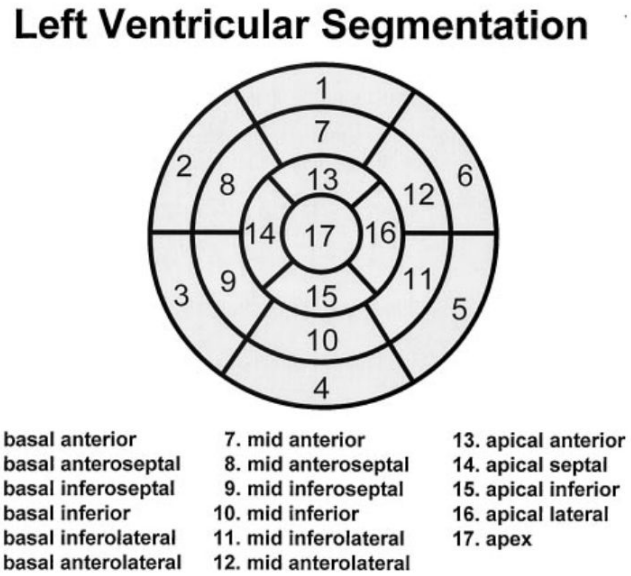
2.Segmentation

Method: Left ventricle is divided into 17 segments with each segment visually assigned a score from 0 to 4 based on relative tracer uptake.

Hibernation score :difference between rest perfusion and 18F-FDG scores (summed rest score-FDG score) for all segments setting any negative difference to 0.

Scar score:positive difference between rest perfusion and viability score (summed rest score—hibernation score).

The total percentage of the myocardium with hibernation or scar can then be calculated by dividing hibernation/scar score with the maximum potential score (17 £ 4 = 68).



Simon et al.,2020

Performance-result

positron emission tomography using ^{18}F-fluorodeoxyglucose (^{18}FDG-PET) is considered as the most sensitive one and holds the advantages of combining high spatial resolution with quantitative measure of myocardial perfusion.The 1- and 5-year follow-up results of PARR-2 study has demonstrated that PET-assisted management benefits patients adhering to imaging-based recommendations.

Liu et al., 2018

Performance-result

For prediction of recovery of regional function after revascularization, a pooled analysis of 24 studies (756 patients) reports a weighted mean sensitivity and specificity of 92% and 63% and a positive predictive value and negative predictive value of 74% and 87%, respectively. There are several observational studies that show increased risk for adverse events in patients with significant hibernating myocardium, who do not undergo timely revascularization, on FDG-PET images.

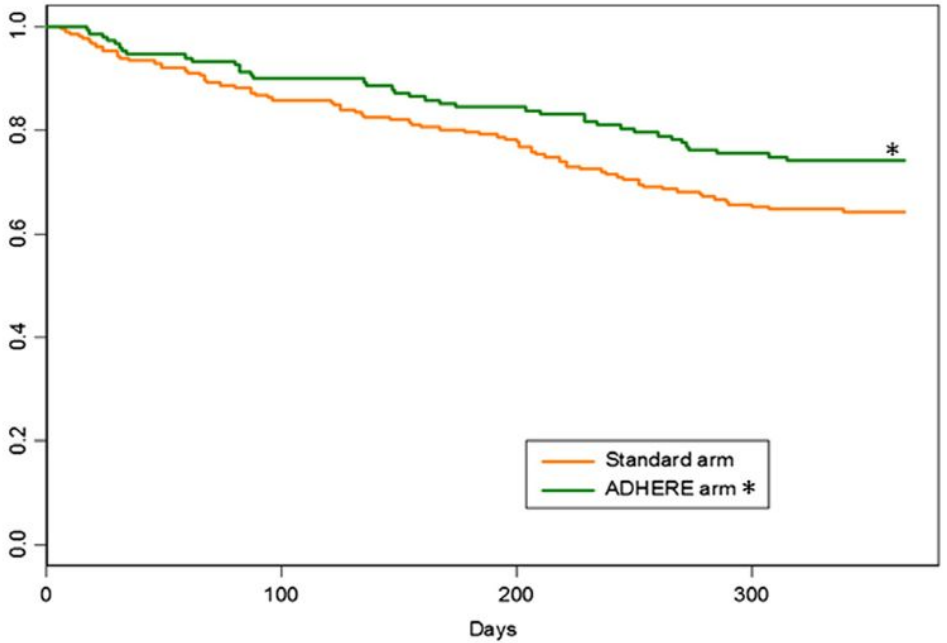


Figure 4 PET adherence group vs standard care arm in determining the clinical effect of ^{18}F-FDG-PET viability studies in the PARR-2 trial. In the post hoc analysis, the ADHERE group that included only PET patients who adhered to the imaging recommendations showed a significant reduction in adverse outcomes when compared with the standard group. The hazard ratio for the ADHERE group was 0.62 (*95% CI: 0.42-0.93, $P = 0.019$). (Reprinted with permission Elsevier and Beanlands et al.[54])

Schinkel et al., “Hibernating Myocardium.”

Highest NPV

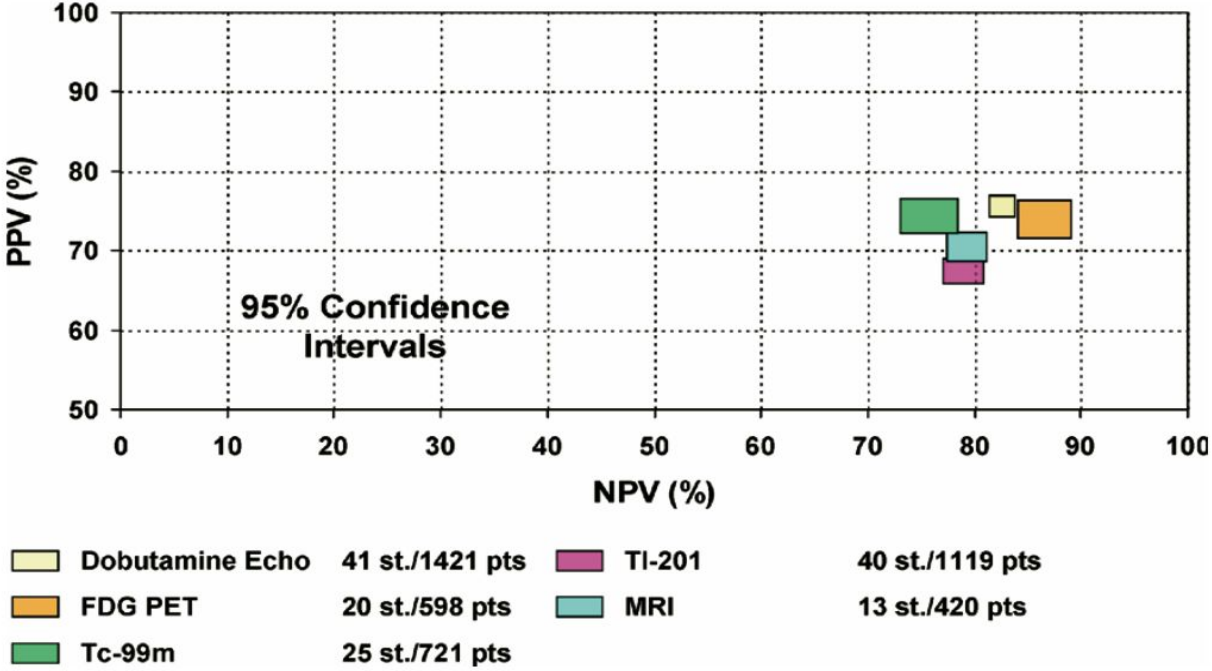


FIG 2. Comparison of positive-predictive values and negative-predictive values with 95% confidence intervals of the various techniques for the prediction of recovery of regional function after revascularization. (Color version of figure is available online.)

Schinkel et al., “Hibernating Myocardium.”

Highest Sensitivity

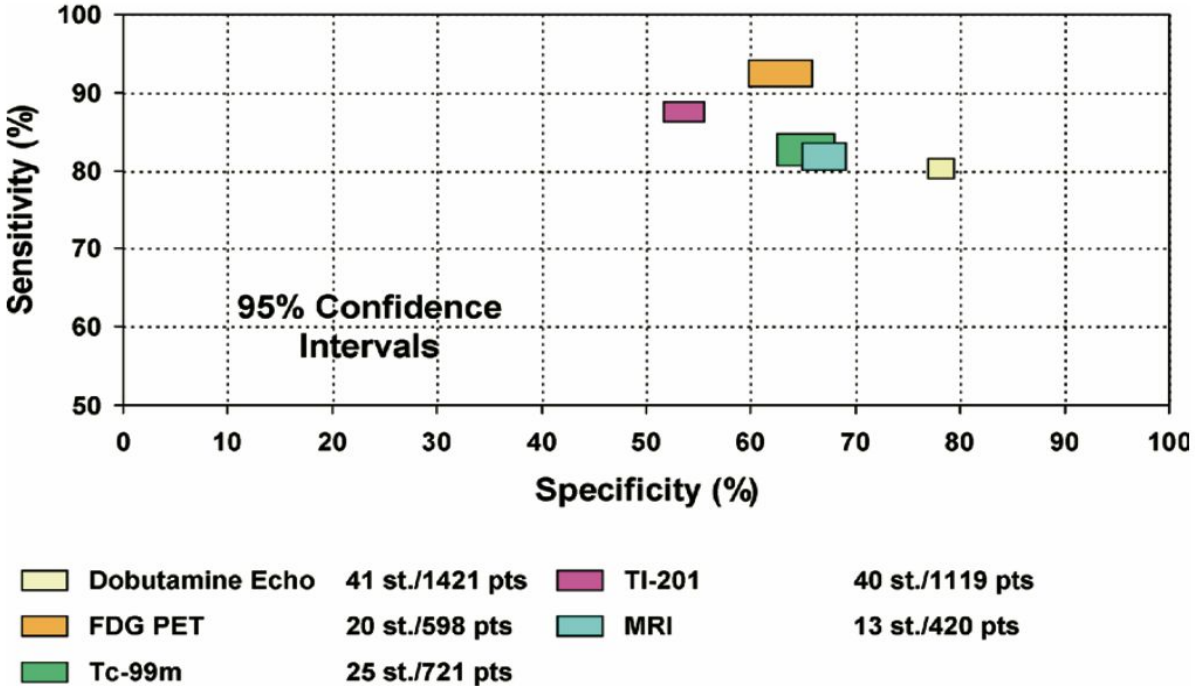


FIG 1. Comparison of sensitivities and specificities with 95% confidence intervals of the various techniques for the prediction of recovery of regional function after revascularization. (Color version of figure is available online.)

Schinkel et al., “Hibernating Myocardium.”

High spatial resolution

Time of flight capability in PET technology enables more accurate localization of the annihilation reaction along the line of detection, hence improving the spatial resolution of FDG- PET imaging.

Conventional PET:Line of response=speed of light*time difference in arrival of two photons/2. Time not precise enough.

In time-of-flight (TOF) PET, the difference in the arrival times of the 2 photons is measured with high precision, which helps localize the emission point along the LOR within a small region of the object

In 2005, early results from a commercial LSO PET system showed that a system timing resolution of 1.2 ns could be achieved with photomultiplier tubes (PMTs) and electronics that were not optimized for TOF imaging

Surti, “Update on Time-of-Flight PET Imaging.”

Limitations

- In patients with substantial myocardial scar burden despite the existence of considerable hibernating myocardium, functional recovery following surgical revascularization is not necessarily translated to survival benefits.
- Time-consuming: Patients need elaborate patient preparations before the conducting the imaging analysis.
- Low availability in clinics because of its high costs.

Rischpler et al., “PET/MRI Early after Myocardial Infarction.”

Outlook

- PET systems manufactured in combination with a CT scanner of variable specification (16, 64, and 128 slice) provide robust attenuation correction, which is particularly useful in imaging obese patients and female patients.
- 3- dimensional PET systems, in which the lead septae that divided the rings of detector crystals in older 2-dimensional systems have been removed, have increased count statistics, allowing for reductions in radiation dose per scan.
- TOF PET may play an important role in situations that require low-dose serial 18F-FDG imaging of patients and im- aging with long-lived radioisotopes for targeted therapy. These applications require low-noise images with reduced counts that are also quantitatively accurate—an area in which TOF PET provides significant advantages.
- the combination of both techniques—LGE MRI and FDG PET

Lim et al., “Myocardial Viability.”
Surti, “Update on Time-of-Flight PET Imaging.”

Open Question

- Why Cardiac Magnetic Resonance Imaging and Positron Emission Tomography imaging with FDG are the most common modalities for assessing myocardial viability?
- Do patients significantly benefit from these imaging modalities?