

# Semiquantitative Analysis of Ischemic Dysfunctional Myocardial Tissue: Comparison of Contrast Enhanced MRI and Myocardial PET

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**Abstract:** Cardiac Positron Emission Tomography (PET) has been demonstrated to be highly specific in differentiating viable from scarred myocardium in patients with ischemic left ventricular dysfunction. The aim of this study was to compare PET imaging with contrast-enhanced magnetic resonance imaging (ceMRI) in patients with ischemic myocardial dysfunction, analysing semiquantitatively the amount of non-viable myocardial tissue.

**Results:** 10 patients with left ventricle ischemic dysfunction underwent myocardial PET with <sup>13</sup>N-ammonia/FDG and delayed sequences of cardiac MRI after injection of gadolinium diethyltriaminepentaacetic acid (Gd-DTPA). PET and MRI images were divided into 17 segments and examined by 2 independent observers. Extent of tissue damage was estimated using a 5-point scoring system. Using PET as gold standard, accuracy in detecting scar tissue was determined for ceMRI. High agreement rate (63% and 69%) between myocardial necrosis in PET and ceMRI was evaluated by Kappa test. Comparison between scores in transmutable extension in PET/ceMRI study with a "0 tolerance" system (that is considering results agreement only if overlap results), the 2 blinded observers demonstrated an agreement rate of 68.9% and 76.5% respectively, with a difference of 7.6% [IC 95% from -2 to 17.1]. With one point of tolerance (considering results agreement even if there was one point of difference), an agreement rate of 93.6 and 95.3% emerged, with a difference of 1.8% [IC 95% from -3.1 to 6.6%].

**Conclusions:** In the identification of non-viable myocardium, semiquantitative analysis of cardiac PET and ceMRI obtained similar accuracy of the two imaging techniques.

**Keywords:** Contrast enhanced MRI, myocardial dysfunction, myocardial positron emission tomography.

## INTRODUCTION

Acute myocardial infarction, which occurs when there is a prolonged occlusion of an epicardial coronary artery without sufficient collateral blood supply, is the most common cause of death and one of the most common causes of morbidity in industrialized nations [1]. For survivors of myocardial infarction, the accurate assessment of damage, as well as the identification of the residual tissue viability in patients with acute myocardial infarction and chronic ischemic heart disease, is crucial in planning future treatment and individual risk stratification [2]. In fact, identification, differentiation and quantification of reversible and irreversible myocardial damage in patients with reduced left ventricular ejection fraction (LVEF) and coronary artery disease are useful in order to predict which patients would obtain profit from revascularization, such as increase of ejection fraction and rate of survival since patients with dysfunctional but viable myocardium profit from revascularization [3, 4] and affects both short-term and long term prognosis [5-8]. Several techniques analyzing the morphologic [9], functional [10], cellular and metabolic [11] integrity of the myocardium have been introduced into clinical medicine. Each of these

methods have specific advantages for the diagnosis of myocardial viability, but none allows direct visualization of the transmural extent of viable and non-viable tissue. Detection of viability based on assessment of myocardial perfusion and glucose metabolism by PET is now considered the reference method [11], and many studies suggest that MRI using gadolinium-based contrast agent (ceMRI) can delineate reversible and irreversible damaged myocardium and can predict areas which will recover functionally after revascularization [12-14] as well as metabolic study by PET. ceMRI of the heart is a non-invasive diagnostic modality with high spatial resolution, an excellent safety profile of the contrast agent, and a lack of radiation exposure, which has recently been proposed as an alternative imaging modality for the assessment of myocardial viability [15]. Among available imaging techniques, ceMRI is one of the favourite applications of both imagers and referring physicians. The so called "late enhancement" concept, also referred to as "delayed enhancement" or "late gadolinium enhancement", has obtained with a T1-weighted imaging of the myocardium in the late equilibrium phase after intravenous administration of gadolinium-based contrast medium. Inversion recovery (IR) sequences have been proved reliable and robust in this respect. Several histological studies have determined a relationship between hyperenhanced myocardium at ceMRI and necrosis [12, 16, 17], and ceMRI permits to distinguish between regions with reversible and irreversible myocardial injury,

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depending on the transmural extent of hyperenhancement, which has been shown to be predictive of recovery of contractile function after myocardial revascularization [18, 19]. The aim of this study was to compare extent and localization of hyperenhancement in Delayed Enhancement (DE) ceMRI with nonviable tissue defined by nuclear metabolic imaging using  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET) in patients with ischemic heart disease and left ventricular dysfunction.

## METHODS

### Patients

From March 2006 to September 2007, patients with coronary artery disease (CAD) proved by coronary angiography and left ventricular systolic dysfunction (LVEF<40%) were included in the study. Myocardial PET and MRI were performed in the same subject within 1 week, without any significant change in clinical status.

### ceMRI

The protocol consisted of contrast-enhanced MRI to determine the extent of delayed contrast enhancement.

Cardiac MRI was performed with a clinical 1.5-T Gyroscan ACS-NT MRI scanner, Philips Medical System, Eindhoven, The Netherlands. A four-element cardiac phased-array receiver surface coil was utilized for signal reception. A breath-hold segmented fast gradient-echo imaging employing steady-state acquisition (Balanced Echo), electrocardiographically triggered sequence was performed to evaluate global left ventricular function using standard parameters. In each patient, a total of nine to 12 short-axis views (depending on left ventricular volumes) and two long-axis views (vertical and horizontal) were acquired with a minimum of 30 cine frames/slices. Delayed sequences were obtained approximately 12 minutes after intravenous injection of 0.2 mmol/kg gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) using a fast field echo sequence (slice thickness 8mm, FOV 360 mm, flip angle 15°, TE 1.3 ms, TR) 4.1 ms. Images were acquired at end-diastole in the same views. Delayed enhancement images were displayed with a grey scale to optimally show normal myocardium and the region of delayed-enhancement myocardium. The scan was analysed according to: a) the left ventricular function (sequences balanced-echo cine MRI) and b) the presence of scar tissue with delayed-enhancement (DE) images.

The extent of hyperenhancement was divided from transmural to subendocardial into 5 steps of a visual scoring system (0-4):

- 0 = no delayed enhancement
- 1 = 1-25% of myocardial wall with hyperenhancement
- 2 = 26-50% of myocardial wall with hyperenhancement
- 3 = 51-75% of myocardial wall with hyperenhancement
- 4 = 76-100% of myocardial wall with hyperenhancement

A myocardial segment end-diastolic wall thickness >6 mm (obtained with a fast gradient-echo sequence) with a visual score>2 was classified as necrotic segment.

### PET Imaging

After an overnight fast, patients were injected with 585 MBq of  $^{13}\text{N}$ -ammonia for the determination of myocardial perfusion at rest. A second PET study was performed in the same day, one hour after the injection of 378 MBq FDG for cell metabolism while the patients were on a euglycemic hyperinsulinemic clamp (see below). PET images were obtained with a GE Discovery LS hybrid PET/CT system (GE Healthcare, Waukesha, Wisconsin). A CT scan was obtained for attenuation correction designed to reduce artefacts of cardiac motion using a helical scan with a rotation time of 1 second and an 11.25 mm/rotation bed speed. In such a way the CT acquisition of the heart was obtained in 27.5 seconds. All the PET studies were performed in 2D mode for scatter reduction. All images were reconstructed with an OSEM 28-subset, 3-iteration method with an in-plane image resolution of 4.8 mm full width at half maximum (FWHM). The reconstruction matrix was 128X128 pixels with a 3.9 mm pixel size.

The FDG/ $\text{NH}_3$  images were evaluated semiquantitatively using a five-point scoring system dividing the left ventricle into 17 segments according to the recommendations of the American Heart Association [8]:

- 0 = normal tracer uptake (from 90 to 100%)
- 1 = important (non transmural) tracer uptake
- 2 = mild tracer uptake
- 3 = severe lack of tracer uptake
- 4 = no tracer uptake

Viable myocardium was identified in myocardial segments with end-diastolic wall thickness >6 mm exhibiting normal or near normal  $^{18}\text{F}$ -FDG accumulation (PET uptake scores ranging from 0-2) with reduced (<2.5) standard deviations (SD) with respect to normal  $^{13}\text{N}$ -ammonia myocardial blood flow (mismatched pattern of imaging). Non-viable myocardium was verified in segments with an end-diastolic wall thickening <6 mm or with severe/absent  $^{18}\text{F}$ -FDG myocardial uptake scores of 3 to 4 with a reduced  $^{13}\text{N}$ -ammonia myocardial blood flow (matched defect).

For each patient, the 17 segments were scored and the sum was calculated.

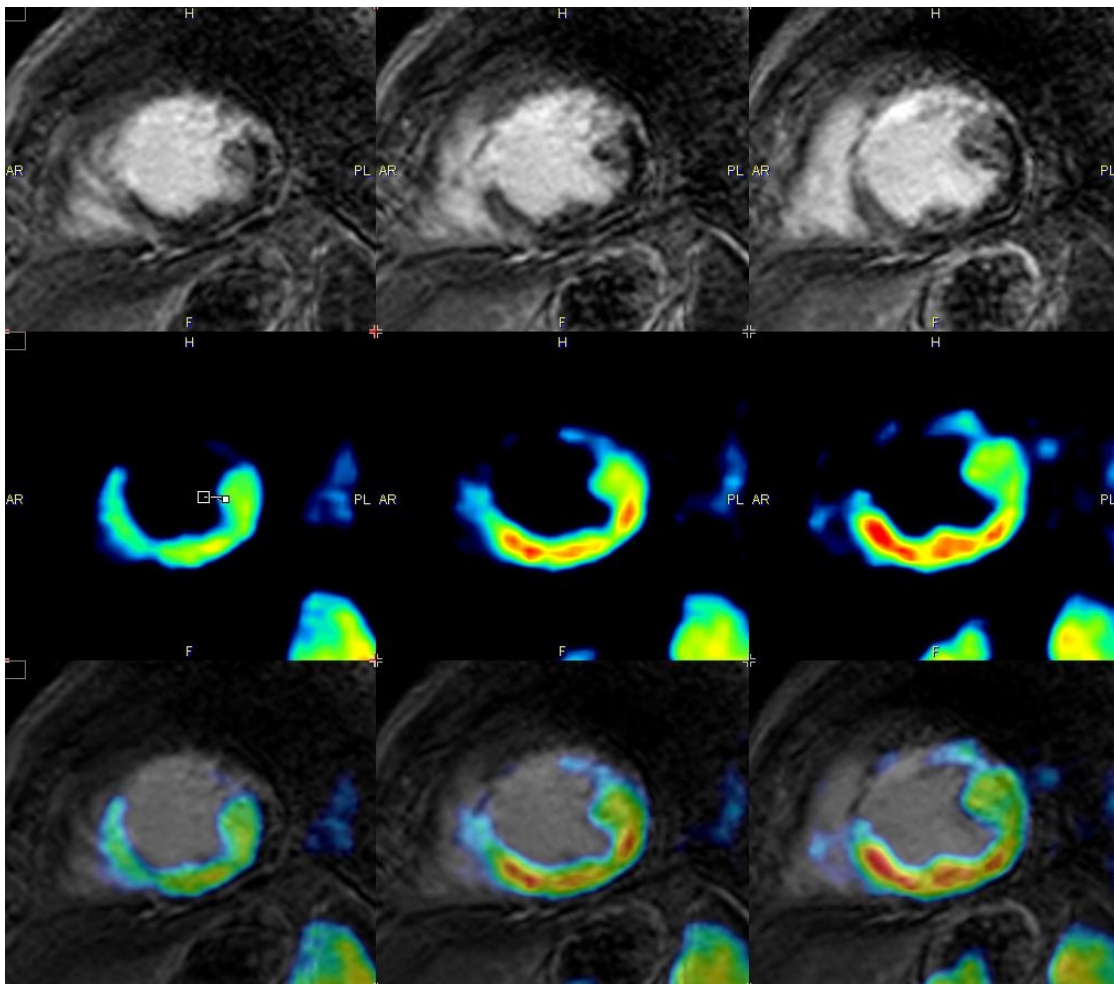
### Images Analysis

The left ventricle was divided into 17 segments using the apex and a representative apical, equatorial and basal short and long-axis view, according to the standards for plane selection proposed by the American Heart Association, the American College of cardiology and Society of Nuclear Medicine [20] (Fig. 1). Images were assessed in both modalities within each segment by 2 independent and blinded observers.

### STATISTICAL ANALYSIS

Images were assessed with the 5-point scoring system for both modalities within each segment by 2 independent observers, blinded to the results of the other observer and the other modality.

Using PET as the gold standard, accuracy in detecting scar tissue was determined for MRI. Inter-modalities agreement was made with both "0 tolerance" system and "1 tolerance"



**Fig. (1).** FDG PET and ceMRI images of one patient with a previous anterior myocardial infarction. The upper images were obtained with ceMRI and represent a short axis of the mid left ventricle. In this image the presence of a transmural delayed hyperenhancement after gadolinium injection in mid ventricular antero-septal and anterior segments emerged; in the mid lateral segment the delayed hyperenhancement was evidenced in the subendocardial tissue. In the middle, an FDG PET scan demonstrated an absence of uptake of the tracer in mid ventricular antero-septal and anterior segment, with a clear reduction of uptake in mid lateral segment. In the lowest image the two images were summed, evidencing the correspondence of the non-viable area.

system, which means that results agreement was established only if results overlap (“tolerance 0” system), or even if there was one point difference between results (“tolerance 1” system), which is considered still clinically acceptable.

Using PET scoring as the gold standard, the 2 observers have given MR images scores using a similar 5-point system, in order to analyze agreement between the 2 studies results, and establish if myocardial territories with no metabolism left in PET, so considered necrotic tissue, were showing scar tissue in MR study. Agreement between myocardial necrosis in PET findings and scar tissue observed in MRI has been evaluated by Kappa test [21]. After analyzing intermodalities agreement, and after comparing the 2 observers results given to globally considered myocardium, scores comparison was performed considering single myocardial territories perfused by different arteries: left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX). This part of the study was performed by 2 observers and using a “tolerance 0” and “tolerance 1” scoring system as well.

After that, still using Kappa test, agreement rate of both observers in giving negative (normal) and positive (pathological) scores in PET and MR studies, considering PET findings as gold standard, was evaluated.

$$K = (P_0 - P_c) / (1 - P_c)$$

where

K = agreement index

$P_0$  = agreement rate observed between true positive and true negative, that is between positive and negative scores both in PET findings and MRI study.  $P_c$  = agreement rate expected between true positive and true negative, that is between positive and negative scores both in PET findings and MRI study.

## RESULTS

Ten patients (9 men, from 46 to 77 years old, mean age  $65 \pm 5$ ) were included in the study after giving informed consent. All the patients had documented a previous

(>6-month) history myocardial infarction (7 anterior, 1 apical, 1 inferior and 1 non-q). All the selected patients had risk factors for ischemic heart disease (past history of nicotine abuse, diabetes mellitus, arterial hypertension, hypercholesterolemia, family history of sudden cardiac death). Coronary angiography assessed that 3 patients had 3-vessel, 5 patients 2-vessel, and 2 patients had 1-vessel disease.

The semiquantitative analysis demonstrated that 72/170 (42.3%) left ventricular segments showed a significant reduction in FDG uptake (score  $\geq 2$ ) whereas in 69/170 (40.6%) segments a delayed hyperenhancement at ceMRI emerged. Comparison between scores in transmural extension of  $^{18}\text{F}$ FDG defect and hyperenhancement in ceMRI study, independently of territories of coronary perfusion, with a “0 tolerance” system (that is considering results agreement only if overlap results) demonstrated an agreement rate of 68.9% and 76.5% respectively, with a difference of 7.6% [IC 95% from -2 to 17.1]. With one point of tolerance (considering results agreement even if there was one point of difference, “1 tolerance” system), the 2 observers had an agreement rate of 93.6 and 95.3%, with a difference of 1.8% [IC 95% from -3.1 to 6.6%] emerging from the comparison between PET and MRI scores.

Therefore the semiquantitative analysis obtained by two blinded observers gained similar results in giving scores of transmural necrosis in PET and MRI studies, underlining that myocardial necrosis observed in PET was confirmed in MRI study, with an overlapping of PET and MRI results with a close relationship between transmural uptake of contrast medium in MRI and uptake of  $^{18}\text{F}$ FDG in PET. There was no significant interobservers variability for MRI and PET studies. About the second part of the study, that is the comparison of scores in different myocardial territories divided into different coronary distribution, analyzing myocardial territories served by left anterior descending artery (LAD), without inserting one point of tolerance (“0 tolerance” system), we have observed that the 2 observers had a concordance between PET and MRI scores of 68.6% and 78.6% respectively, with an interobservers difference rate of 10% [IC 95% from -0.4 to 24%]. With a “1 tolerance” system, agreement between PET and MRI of the 2 observers was 97.1%, with no difference [IC 95% from -5.5 to 5.5].

Agreement analyzing myocardial territories perfused by left circumflex artery (LCX) was 70 and 78%, with an interobservers difference of 8% [IC 95% (from -9 to 25%)] with a “0 tolerance 2 system, and 90 and 92% respectively with a “tolerance 1” system, with a difference of 2% [IC 95% from -9.2 to 13.2].

Results of myocardial territories perfused by right coronary artery (RCA), confirming previous studies trend, have given an agreement rate of PET and MRI scores of 68 and 72%, with a difference of 29.4% [IC 95% from -14 to 22] with a “0 tolerance” system, and a rate of 98 and 96%, with a difference of 4% [IC 95% from -5.3 to 13.3] inserting one point of variability.

Using PET as the gold standard, the agreement rate between scores given by the 2 observers in positive (pathological) and negative about intramyocardial extension of necrosis in PET and MRI studies has been calculated. We have considered true positive scores established positive in

PET and confirmed in ceMRI, true negative scores negative both in PET and MRI, false positive scores positive in MRI but not in PET and false negative scores false in MRI but positive in PET. Comparing rates of agreement observed and expected between the 2 modalities of study by Kappa test, an agreement rate of 63% and 69% emerged. This result has to be considered satisfactorily by Karran system [21], considering very low an agreement rate lower than 20%, low a rate from 20 to 40%, mild a rate from 40 and 60%, elevated from 60 to 80%, and very high when higher than 80%.

## DISCUSSION

An accurate evaluation of viability and the amount of damage in patients surviving myocardial infarction in patients with ischemic left ventricular dysfunction is crucial for the therapeutic decision and for the stratification of the individual risk [22]. Identification, differentiation and quantification of myocardial damage in reversing and irreversible way are useful to predict which patient is potentially able to get benefits by revascularization, improving LVEF and survival [6-8, 23]. In fact, despite the perioperative risk is increased in such patients, the surgical revascularization seemed to improve the left ventricular function and the prognosis. For the identification of the amount of residual viable tissue after an ischemic event numerous techniques of morphological, functional and cellular analysis and of the metabolic integrity of myocardium have been proposed [11, 24]. The non-invasive methods for detecting the presence of myocardial viability include myocardial PET (using  $\text{NH}_3$  for blood flow and  $^{18}\text{F}$ FDG for metabolism) and the stress echocardiography during dobutamine infusion. Recently, ceMRI has been proposed for the quality of images with good correlation with extension, location and the form of the ischemic lesion observed in histological examination. Previous experiences [14-16] showed as the area of myocardial lesion improved the intensity of signal up to 400% superior to the healthy tissue; this characteristic permits the ceMRI to accurately define the transmural extension of infarction and to distinguish among reversible and irreversible myocardium damage, independently from the contractile function of the wall, from the time of ischemic event and the state of perfusion. Furthermore, ceMRI has the incomparable advantage to permit a static and dynamic evaluation of the cardiac muscle in the three views of the space without exposing patient to ionizing radiations. Klein *et al.* [24], comparing the late enhancement in ceMRI and PET in patients with ischemic heart disease, showed that in patients with chronic ischemic left ventricular dysfunction, ceMRI is able to identify the location and the extension of the non-viable tissue with closely agreement with the results of the comparative study of blood flow and metabolism of glucose in PET. Nevertheless, in the evaluation of the infarct size, cardiac ceMRI seemed to underestimate the amount of necrotic tissue in comparison with nuclear technique [25]. This underestimation might be related to the low spatial resolution of nuclear imaging. Moreover, it was postulated that ceMRI may identify subendocardial infarcts, missed by nuclear technique. The quantitative analysis of ceMRI in patients with severe ischemic left ventricular dysfunction, demonstrated a larger extent of hyperenhancement in segments non-viable in PET imaging in comparison with viable segments [26]. Moreover, using a ROC analysis, a cut off value of 37% of

hyperenhancement at ceMRI was identified to differentiate viable from non-viable segments. Finally, Wu *et al.* [27] analysed in 29 patients treated with surgical revascularization a similar value of sensitivity and specificity between ceMRI and myocardial PET in predicting functional recovery. CeMRI predicted well the improvement of LVEF while in subjects with extensive necrotic tissue, myocardial PET was closely related to the poor early functional outcome.

This study compared the reliability of ceMRI and PET <sup>18</sup>FDG in the identification of the amount of myocardial tissue damage in ischemic left ventricular dysfunction. Our results confirmed that the presence of extension of delayed hyperenhancement in ceMRI is negatively correlated with the <sup>18</sup>FDG uptake in PET. The semiquantitative analysis of the two imaging modalities gained a satisfactorily concordance between scores assigned in metabolic PET with <sup>18</sup>FDG and ceMRI. Finally we showed that, in the evaluation of transmural extension of contrast medium in ceMRI and uptake of <sup>18</sup>FDG in PET study in graduated scale of 5 scores (0-4), two experts observes obtained an agreement rate of 63% and 69%. This experience demonstrated that in the visual evaluation of myocardial viability after myocardial infarction, ceMRI is accurate and effective in comparison with myocardial PET. This aspect offers important prospective in cardiological imaging, being MRI, compared to PET, largely diffused, more economical, faster and does not implicate radiological exposure.

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