The integrative value of myocardial perfusion-function imaging with 13N-ammonia positron emission tomography
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Myocardial perfusion reserve in spared myocardium: correlation with infarct size and left ventricular ejection fraction


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ABSTRACT

**Purpose.** Left ventricular ejection fraction (LVEF) after myocardial infarction is considered to be determined by the size of the infarction and residual function of the spared myocardium. Myocardial perfusion reserve (MPR) has been shown to be a strong prognostic factor in patients with ischemic heart failure, even stronger than LVEF. In the present study, the interrelationship between MPR, LVEF and infarct size was investigated.

**Methods.** In total, 102 patients with a prior history of myocardial infarction were included. All underwent rest and stress $^{13}$N-ammonia and gated $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) for evaluation of myocardial ischemia and viability. FDG polar maps were used to determine the size of the infarction. The LVEF was obtained by gated $^{18}$F-FDG PET or another available method within 3 months of the PET scan. MPR was obtained per segment in the spared myocardium.

**Results.** The mean age of the subjects was $68\pm 12$ years. Global MPR was $1.63\pm 0.51$. The mean LVEF was $36\pm 10\%$ and mean infarct size $23.72\pm 14.8\%$. A linear regression model was applied for the analysis considering the LVEF as a dependent variable. All risk factors, mean stress flow, infarct size and MPR were entered as variables. The infarct size ($p<0.001$) and MPR ($p=0.04$) reached statistical significance. In a multivariate model MPR had a stronger correlation with LVEF than infarct size.

**Conclusion.** In patients with a prior history of myocardial infarction, LVEF is not just related to infarct size but also to MPR in the spared myocardium.
INTRODUCTION

In the past few decades, substantial improvement of treatment strategies for patients with myocardial infarction (MI) has been achieved. Although this has greatly reduced the rate of early mortality, post-MI induced heart failure remains a major cause of MI-associated morbidity and late mortality (1). After MI, spared myocardium should compensate for tissue fibrosis due to MI. Two important determinants of functional outcome are the amount of remaining myocardial tissue and the myocardial perfusion dynamics of the spared myocardium.

Cardiac positron emission tomography (PET) myocardial perfusion imaging accurately diagnoses coronary artery disease (CAD) and provides well-established risk and prognostic variables (2). The relationship between myocardial perfusion and (regional) left ventricular (LV) function in heart failure patients (3,4) was described previously. The importance of myocardial perfusion and further development of heart failure as a result of this phenomenon has also been proposed (5,6). In heart failure patients with CAD, the decision on whether or not to revascularize depends at present on infarction size and residual viability. However, there are limitations of the many cohort studies that have fuelled the enthusiasm for viability testing as a prerequisite for referral of patients for myocardial revascularization.

Recently, it has been demonstrated that myocardial perfusion reserve (MPR) constitutes a strong prognostic factor for cardiac death; moreover, the same study concluded that MPR has greater sensitivity for this matter than left ventricular ejection fraction (LVEF) or the extent of viable myocardium (7). MPR is calculated by dividing the stress perfusion by the rest perfusion. MPR was also of prognostic value in cases of revascularization based on the PET scan results (2). MPR depends on coronary artery supply and on microvascular components, but the latter can be hampered by endothelial dysfunction (ED) (3). Impaired subendocardial coronary reserve can be caused by hypertrophy but also by haemodynamic changes (8,9) and may lead to heart failure. The value of MPR in the spared myocardium in relation to infarction size and LV function outcome is unknown. Patients with comparable infarction sizes demonstrate a wide spectrum of LVEF values during follow-up, especially in small infarction sizes (10). MPR in spared myocardium may be related to LVEF after MI. MPR may be of better value than viability assessment to estimate which patient needs therapy to reduce
heart failure risk in the future.

In the present study, the interrelationship between MPR, LVEF and infarct size was investigated, using $^{13}$N-ammonia and $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET.

**MATERIALS AND METHODS**

**Patients and study design**

This study prospectively included, with retrospective analysis, 102 patients who underwent rest–dipyridamole stress $^{13}$N-ammonia and gated $^{18}$F-FDG PET, between 2002 and 2009 at the Department of Nuclear Medicine and Molecular Imaging of the University Medical Center Groningen, for evaluation of stress-induced ischemia and myocardial viability. Patients with an MI and known LVEF were included. However, a quick data analysis of the available CAD data of patients revealed 40 patients (39%) had single-vessel disease and 82 patients (61%) had multi-vessel disease (MVD). Patient data were collected from the hospital’s patient files and information system.

**PET acquisition**

The patients underwent dynamic rest $^{13}$N-ammonia (400 MBq), dipyridamole stress $^{13}$N-ammonia (400 MBq) and gated $^{18}$F-FDG (200 MBq) PET using a 1-day protocol. Briefly, PET studies were performed after the patients had discontinued vasoactive medication for 5 plasma half-lives and had refrained from caffeinated beverages for a minimum of 12 h. Imaging was performed with the patient supine on an ECAT HR+ PET camera (Siemens Medical Systems, Knoxville, TN, USA). A transmission scan for further attenuation correction was done for 5 min using an external ring source filled with $^{68}$Ge/$^{68}$Ga. Accidental coincidence and dead time were automatically corrected. Myocardial perfusion imaging at rest was started 2 min after injection of 400 MBq of $^{13}$N-ammonia and continued for 15 min. The same protocol was used 6 min after intravenous injection of dipyridamole to acquire the stress myocardial perfusion image. A parametric polar map was generated from the PET data. These data were corrected for partial volume effect and activity spillover from the blood pool. Regional (stress and rest) myocardial blood flow was calculated. Segmental MPR was calculated by
Myocardial perfusion reserve in spared myocardium

dividing dipyridamole stress $^{13}$N-ammonia PET result by rate-pressure product normalized rest $^{13}$N-ammonia on each segment.

To stimulate $^{18}$F-FDG uptake, patients were given 75 g of glucose orally just before scanning or were given 500 mg of acipimox (Nedios, Byk Pharmaceuticals, Zwanenburg, The Netherlands) orally 90 min before scanning to lower circulating free fatty acids (11). To prevent side effects of acipimox (e.g. skin rash), 250 mg of aspirin was administered orally 5 min before acipimox. In diabetic patients, $^{18}$F-FDG imaging was done with hyperinsulinaemic euglycaemic glucose clamping (12). After the $^{13}$N-ammonia data had been acquired, 200 MBq of $^{18}$F-FDG was injected intravenously, followed by a PET dynamic acquisition. The total $^{18}$F-FDG PET acquisition time was 40 min, with the last 20 min acquired in gated mode with 16 frames per cardiac cycle. The length of each gate was based on the current R-R interval. The R-R interval was allowed to vary by 10%. Data were corrected for attenuation using the transmission scan and were reconstructed using filtered backprojection (Hann filter, 0.5 pixels/cycle).

Kinetic models and data analysis

Dynamic parametric polar maps were constructed from the PET data (13). PET perfusion data at rest were corrected for rate-pressure product. Myocardial blood flow data were corrected for partial volume effect and spillover and quantified by the model of Hutchins et al. (14). Briefly, myocardial and blood time-activity curves derived from regions of interest (ROIs) over the heart and ventricular chamber are fitted using a three-compartment model for $^{13}$N-ammonia, yielding rate constants for tracer uptake and retention. The perfusion flow reserve (dipyridamole-to-rest ratio) was calculated by dividing the dipyridamole $^{13}$N-ammonia stress study by the $^{13}$N-ammonia rest study. Data analysis of $^{18}$F-FDG was performed with Patlak analysis (15). Mismatch was quantified by first normalizing the $^{18}$F-FDG uptake polar map and the dipyridamole blood flow polar map to their means. Then, a difference polar map was created by subtracting the normalized dipyridamole blood flow polar map from the normalized $^{18}$F-FDG uptake polar map. Mismatch was calculated as the percentage myocardium above the 95% confidence interval of the normal age- and sex-matched database, and results were expressed as percentage of the total myocardium. Similarly, matching areas were quantified by constructing a product polar map; the normalized dipyridamole blood flow polar map was
multiplied by the normalized $^{18}$F-FDG uptake polar map. Match was defined as the percentage myocardium below the 95% confidence interval. The extent of mismatching areas (viable myocardium) and matching areas (non-viable myocardium) was calculated from these data as previously described (13). Based on the matching defects the area of infarction (AOI) was determined by planimetry. Using only the stress perfusion images for comparison with $^{18}$F-FDG uptake allows identification of jeopardized myocardium but does not allow differentiation between hibernation and ischemia. From a practical point of view, however, this differentiation may not be that important, because both hibernation and ischemia need to undergo revascularization. The last frames (20-min acquisition time) of the dynamic gated $^{18}$F-FDG PET studies were summed and transformed into static studies and used for further data analysis with the help of the quantitative gated single photon emission computed tomography (SPECT) program (16). LVEF was computed using the gated $^{18}$F-FDG images.

The $^{18}$F-FDG polar map was taken as reference for infarction size. Each $^{18}$F-FDG polar map consisted of 480 small regions and was analyzed by drawing ROIs to determine the extent of the MI as a percentage of the total myocardial surface assessed by the scan. Regional $^{18}$F-FDG distribution was considered as infarcted when a threshold uptake of <50% of the peak was calculated and used as overlay for the $^{13}$N-ammonia polar maps. The mean rest and mean stress $^{13}$N-ammonia was calculated in these ROIs of infarcted myocardium. MPR was also calculated for these ROIs, as described previously. In the same way, MPR was calculated for the areas of spared myocardium after subtracting the ROI of infarction in the polar map. The LVEF was derived from the gated $^{18}$F-FDG PET scan on the same day or assessed by another validated imaging method such as multiple gated acquisition (MUGA), cardiac magnetic resonance imaging (cMRI) or echocardiogram within an interval of 3 months of the PET scan acquisition.

**Statistical analysis**

Descriptive statistics are expressed as mean ± SD. Categorical measurements are presented as frequencies with percentages. Linear regression analysis was performed considering LVEF as the dependent variable. The global spared tissue MPR, stress perfusion and the infarction size were considered as the independent variables. Important parameters such as age, gender, hypercholesterolemia, smoking, diabetes mellitus,
hypertension and family history were included in the stepwise multivariate analysis. Student’s t test was used to compare MPR in spared myocardium between patients with single-vessel disease and MVD. Analyses were performed with SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). A p-value<0.05 was considered statistically significant.

RESULTS

Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±12</td>
</tr>
<tr>
<td>Sex, F/M (n)</td>
<td>20/82</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>42</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>43</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>36</td>
</tr>
<tr>
<td>Family history (%)</td>
<td>31</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36±10.1</td>
</tr>
<tr>
<td>Mean area of MI (%)</td>
<td>23.7±14.7</td>
</tr>
<tr>
<td>Mean myocardial perfusion at rest in spared myocardium (ml/min per 100 g)</td>
<td>66.3±36.2</td>
</tr>
<tr>
<td>Mean myocardial perfusion at stress in spared myocardium (ml/min per 100 g)</td>
<td>103.3±60.6</td>
</tr>
</tbody>
</table>

Abbreviations: LVEF, left ventricular ejection fraction; MI, myocardial infarction

Between 2002 and 2009, 102 patients were included who had a previous history of MI; 45% of the patients had an infarction in the left anterior descending territory, 38% in the right coronary artery territory and 27% in the circumflex territory, 55% of the patients underwent percutaneous coronary intervention (PCI), 23% underwent coronary artery bypass grafting (CABG), while 22% did not undergo an intervention within 3 months after MI. In all patients rest $^{13}$N-ammonia, dipyridamole stress $^{13}$N-ammonia and gated $^{18}$F-FDG PET scan were performed. The patient characteristics are shown in Table 1. There were 82 men and 20 women; the mean age for men was 68±12 years and 71±11 years for women ($p$=ns). Among the men 38% had hypercholesterolemia, 34% hypertension, 10% diabetes mellitus, 48% were
smokers and 30% had a family history of cardiovascular disease. Among the women 60% had hypercholesterolaemia, 45% hypertension, 10% diabetes mellitus, 25% were smokers and 35% had a family history of cardiovascular disease. The mean LVEF was 36±10% and the mean AOI was 23.7±14.7%. The global MPR in the spared myocardium was 1.63±0.51. Single-vessel disease was directly related to the infarction area. Spared myocardium in patients with MVD was supplied by stenotic as well as non-stenotic (treated) coronaries. The preserved MPR in spared myocardium in patients with single-vessel disease was 1.32±0.54 and for patients with MVD 1.25±0.52 and was significantly different ($p=0.048$). In the regression analysis for LVEF the AOI ($p<0.001$) as well as MPR ($p=0.04$) reached statistical significance. At the same time only diabetes mellitus ($p=0.03$) showed a statistically significant correlation with LVEF. Neither stress perfusion nor any of the other cardiovascular risk factors reached statistical significance.

As shown in Figure 1, regarding the correlation between the AOI and the corresponding LVEF, there is an inverse correlation between the measurements; a larger AOI results in a lower LVEF.

Figure 1. Linear regression graph for the AOI and LVEF showing a significant decrease in ventricular function in patients with a smaller AOI. AOI, area of infarction; LVEF, left ventricular ejection fraction.

Figure 2 shows the correlation between MPR in the spared myocardium and the LVEF. LVEF is higher in patients with a higher MPR in the spared ventricular myocardium.
Figure 3 shows an inverse, although weak, correlation between the spared myocardium MPR and the AOI. The higher the AOI, the lower the preserved MPR in spared myocardium. The correlation between stress perfusion with LVEF and MPR was not significant (\(p=ns\)).

In a multivariate model the relationship between LVEF and AOI and MPR was analyzed (Figure 4). Both AOI and MPR remained significantly correlated to LVEF. Remarkably, MPR had a stronger relationship (\(r=0.046\), range: 0.013 – 0.079; \(p=0.006\)) than the AOI (\(r=-0.002\), range: -0.003 – -0.001; \(p=0.001\)) (Figure 5).

**DISCUSSION**

In the present study we evaluated the relationship between regional perfusion reserve in spared myocardial tissue, infarction size and LVEF outcome after a previous MI. The main finding of this study is that besides infarct size, MPR in the spared myocardium is related to LVEF outcome in these patients.

Congestive heart failure is the leading cause of MI-associated mortality and morbidity. The influence of myocardial perfusion and microvascular conditions on myocardial contractility has been evaluated in several studies.
Chapter 4

Figure 4. Bar graph expressing mean LVEF and MPR in spared myocardium that were compared after grouping the patients with evidence of larger and smaller MI according to the PET scan (AOI>20% and AOI<20%). This difference proved to be statistically significant with a $p=0.004$ for LVEF and a $p=0.040$ for MPR between the groups. AOI, area of infarction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MPR, myocardial perfusion reserve.

Figure 3. Linear regression graph for MPR in spared tissue and AOI showing a lower MPR in patients with a more extended AOI. AOI, area of infarction; MPR, myocardial perfusion reserve.
in non-ischemic heart failure patients (3,17,18).

The fate of myocardial remodeling in response to functional loss after an MI depends on sufficient perfusion and oxygen supply. Reduced MPR and stress perfusion PET values as were found in the deteriorated segments may imply insufficient oxygen supply as a cause of deterioration. Reduced coronary reserve is also one of the hallmarks of ventricular hypertrophy (8). Although this reduced coronary reserve may not affect baseline LV function, it could be of greater importance during periods of stress such as occurs during exercise where increased metabolic demands induced by the stress may not be fully met by increases in coronary blood flow. The impaired subendocardial coronary reserve is caused not only by the hypertrophy but also by the haemodynamic changes, e.g. the LV subendocardial wall stress, which increases markedly upon exercise (8).

It is hypothesized that at reduced subendocardial perfusion in spared, hypertrophic myocardium it becomes severe enough to induce myocyte necrosis and replacement fibrosis. Furthermore, myocardial ischemia and LV fibrosis as well as the altered loading conditions may result in impaired diastolic function, which in turn diminishes systolic function and will finally lead to remodeling of the left ventricle (9).

Improvement of segmental function may on the one hand relate to recovery after myocardial stunning or on the other hand reflect the compensation of the healthy/spared myocardial in order to compensate for the loss of infarcted tissue. The prognostic role of regional and global MPR in patients with hypertrophic cardiomyopathy (17,19), idiopathic LV dysfunction (20) and ischemic heart disease (2,21) has been shown in previous studies. The present study did not evaluate the prognostic value of myocardial perfusion measurement but focused on the relationship between LV function after MI and perfusion dynamics in the spared myocardium. These data do however further elaborate on MPR and stress perfusion PET values in a well-characterized group of patients with a previous MI. An important study, however, the Surgical Treatment of Ischemic Heart Failure (STICH) trial, failed to demonstrate a significant interaction between myocardial viability and medical vs surgical treatment (22). The STICH data indicate that in patients with CAD and severe LV dysfunction due to MI assessment of myocardial viability does not identify patients who will have the greatest survival benefit from adding CABG to aggressive medical therapy. This confirms the potential value of MPR to evaluate the preserved
**Figure 5.** a) A 64-year-old man with a distal anterior, apical infarction (matched rest and adenosine stress flow and FDG defect) with a preserved MPR (2.1) of the spared myocardium and moderately reduced LVEF (40%). b) A 57-year-old man with distal, apical infarction (matched rest and adenosine stress flow and FDG defect) with a reduced MPR (1.7) of the spared myocardium and severely reduced LVEF (33%). LVEF, left ventricular ejection fraction; MI, myocardial infarction.
perfusion function of the left ventricle after MI.

In a previous MI study with Doppler flow assessment of flow reserve, microvascular function appeared to be a strong predictor for LV functional recovery (23). It has also been shown that despite aggressive upfront antiplatelet and/or thrombolytic therapy post-procedural angiographic and microcirculatory variables were unaffected (24). These studies underscore the importance of microvascular function after MI. Our results are in line with these observations.

A limitation of this study is that long-term outcomes are not available, but need to be collected in future studies. These data are of importance to estimate if MPR PET is still linked in the long run with LV contractility patterns after MI. LVEF was assessed by different imaging techniques. This could have caused a small bias in estimation of LVEF between these different methods. Different therapy (CABG, PCI) protocols may have influenced the MPR and LVEF in the patients.

**CONCLUSION**

Myocardial perfusion PET is a powerful tool to evaluate the relationship between myocardial perfusion (reserve) and LVEF after MI. The observation that a reduced LVEF is accompanied by a reduced perfusion reserve further emphasizes the relationship between sufficient oxygen supply and cardiac remodeling after MI. Future research should establish whether prognostic evaluation of perfusion reserve could further identify patients at risk of developing heart failure.
REFERENCES


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