Hyphaemic microvascular resistance is not increased in viable myocardium after chronic myocardial infarction

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Aims The present study compared microvascular resistance (MR) of viable myocardium in infarct areas with those in reference areas in patients with chronic myocardial infarction (MI).

Methods and results In 27 patients, MR (ratio distal coronary pressure and flow) of reference and viable infarct areas was calculated at baseline and during hyperaemia. H215O positron emission tomography (PET) was used to provide myocardial blood flow measurements. In infarct regions, H215O PET solely measures flow in viable myocardium, excluding flow in scar tissue. Distal coronary pressure was measured with a pressure wire in the infarct-related and reference artery. The average time between PET study and infarction was 3.3 + 4.4 years. Mean hyperaemic distal coronary pressure was significantly lower in the infarct-related artery. MR varied considerably between patients and was significantly higher in infarct areas at baseline (135 ± 38 vs. 118 ± 29 mmHg mL min/mL; P, 0.05), but not during hyperaemia (39 ± 18 vs. 35 ± 11 mmHg mL min/mL). The correlation between MR in infarct and reference areas was significant.

Conclusion To determine MR, distal coronary pressure measurements should be used. Hyphaemic MR in viable myocardium within the infarcted area is not higher when compared with the reference area. This supports the application of the established fractional flow reserve cut-off value in the setting of chronic MI.

KEYWORDS Microcirculation; Physiology; Infraction; Regional myocardial blood flow

Introduction Recently, there has been an increasing interest in the assessment of myocardial microvascular function. Impairment of microvascular function has been demonstrated in the absence of coronary artery disease (CAD) and myocardial disease, in the presence of myocardial disease, in the presence of obstructive CAD, and due to coronary intervention.1–5 Within the context of acute and subacute myocardial infarction (MI), several diagnostic strategies have evolved to study microcirculatory function, including myocardial contrast echocardiography, nuclear scintigraphy, magnetic resonance imaging, positron emission tomography (PET), TIMI frame counting, TIMI myocardial perfusion grading, and Doppler flow wire studies. These techniques provide (semi-)quantitative information on coronary or myocardial blood flow (MBF) and it is implicitly assumed that these flow measurements are inversely proportional to microvascular resistance (MR) in the infarcted myocardium.6–17 However, none of the above-mentioned flow measurements corrects for epicardial resistance and therefore provides information on total (epicardial plus microcirculatory) vascular resistance only.

To specifically study microcirculatory function in patients with obstructive CAD, MR has to be determined. This can be realized by combining distal coronary pressure and myocardial flow measurements. MR can then be calculated as the ratio of distal coronary pressure and regional flow. Data on MR are available only in patients without MI or in the subacute phase of MI.18–22 To the best of our knowledge, MR data in patients with chronic MI are absent.

H215O PET is a technique that provides quantitative information on regional blood flow in the myocardium.23 In infarct regions, H215O PET measures flow in viable myocardium only; perfusion of scar tissue is not included in H215O PET data.24 As H215O PET data provide flow measurements per millilitre (viable) myocardium, the smaller amount of viable myocardium within an infarct region can be accounted for, when comparing flow measurements in infarct and reference areas.
The aim of the present study is to compare MR in chronic MI areas with a reference myocardial area, using a pressure wire to measure distal coronary pressure and $\text{H}_2\text{O}$ PET to measure MBF.

Methods

Study population

The study population consisted of 27 patients. Patients were included if they had stable angina pectoris, no signs of heart failure, documented single MI (a more than three-fold increase over the normal value for serum creatine kinase) more than 2 months before the study, and at least one normal non-infarct-related artery (non-IRA) at angiography. Patients with previous coronary artery bypass grafting were excluded. In all patients, recent information was available on the extent and localization of the infarct area by echocardiography and/or 2-methoxy isobutyl isonitrile (MIBI) perfusion scintigraphy. In 22 patients, the PET study and coronary pressure measurements were performed on the same day; in the other five patients, the interval between these two procedures was less than 1 week. All cardiac medication continued during both studies, except for diuretics, which was stopped prior to angiography and pressure measurement. In all patients, written informed consent was obtained, and the study was approved by the medical Ethics Committee of the VU University Medical Centre.

Positron emission tomography

All scans were performed in two-dimensional mode, using ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA). Subjects were monitored with a single-lead electrocardiogram; blood pressure was monitored with an arm cuff. Transmission images were acquired as previously described. Following this baseline study, hyperaemia was induced by intravenous infusion of adenosine (140 pg/kg/min) and a second $\text{H}_2\text{O}$ scan was performed. Subsequently, blood pool imaging was performed using C$^{15}$O. Emission data were corrected for physical decay of $\text{C}^{15}$O, dead time, scatter, randoms, and photon attenuation. Reconstruction of the $\text{H}_2\text{O}$ emission sinograms was performed using filtered back projection (FBP) with a Hanning filter at 0.5 of the Nyquist frequency. Transmission and C$^{15}$O sinograms were iteratively reconstructed using ordered subset expectation maximization (OSEM, CTI version 7.1.1; two iterations, 16 subsets), followed by 5 mm Gaussian post-smoothing to ensure identical resolution of FBP and OSEM reconstructed images.

Positron emission tomography data analysis

Anatomical tissue fraction (ATF) images were generated by subtracting the blood pool from the transmission images. Transaxial ATF images of the left ventricle were re-oriented according to the anatomical axis of the heart and displayed as short-axis slices. The same reslicing parameters were applied to the dynamic $\text{H}_2\text{O}$ images. Regions of interest (ROIs) were defined manually on the ATF images at the basal, midventricular, and apical levels. Each basal and midventricular slice was divided in six equidistant sectors, starting from the posterior insertion of the right ventricular free wall to the left ventricle. Corresponding ROIs from a variable number of slices were grouped in each patient to generate 13 volumes of interest (six basal, six midventricular and one apical). Additional ROIs were defined in the left and right ventricular chambers. This latter set of ROIs was projected onto the dynamic $\text{H}_2\text{O}$ images, to generate image-derived input functions. Using the standard single-tissue compartment model, together with these input functions, MBF (mL/min/mL of perfusable tissue) was determined, including intrinsic corrections for spillover from both left and right ventricles.

Pressure measurement

After intracoronary administration of 0.2 mg isosorbide dinitrate, angiograms of the IRA and reference coronary artery were made in two orthogonal views. Quantitative coronary angiography of the IRA and reference coronary artery was performed off-line using the CAAS II system (CAAS System; Pie Medical Data, Maastricht, The Netherlands). The sensor of the pressure wire (WaveWire, Volcano Therapeutics, Rancho Cordoba, CA, USA) was advanced to the tip of the guiding catheter. At this point, it was verified that both pressure measurements were identical. Then, the pressure wire was positioned distal into the IRA. Hyperaemia was induced by intracoronary administration of 40 $\mu$g of adenosine, and proximal and distal pressures at maximal hyperaemia were recorded. Next, the pressure wire was advanced distally in a contralateral reference coronary artery with normal appearance at angiography. Again, hyperaemia was induced and proximal and distal pressures were measured.

Calculation of microvascular resistance

A 13-segment model was used for echocardiography, MIBI scintigraphy, and PET. Segments with wall motion abnormalities (WMAs) at echocardiography and/or baseline perfusion defects at MIBI SPECT were defined as infarct area. The reference myocardial area was defined as segments within the perfusion area of an angiographically normal coronary artery, without WMA or perfusion defects. In both the infarct and the reference segments, MBF was determined. MBF was defined as the ratio of mean distal coronary pressure to MBF. MBF was calculated in the IRA and reference coronary artery, at baseline and at maximal hyperaemia.

Statistics

All data are presented as mean $\pm$ SD. The paired sample t-test was used to compare measurements in infarct and reference areas. A value of $P$ less than 0.05 was considered significant.

Results

Clinical characteristics of the patients are summarized in Table 1. Most patients had a Q-wave MI and the infarction was predominantly located in the anterior wall. The left ventricular ejection fraction was considerably impaired. The mean diameter stenosis and hyperaemic distal coronary pressure in the IRA differed significantly from the reference coronary artery. Mean blood pressure and rate pressure product at hyperaemia were not significantly different between PET study and cardiac catheterization.

Results of pressure and PET MBF measurements are given in Table 2. The mean hyperaemic distal coronary pressure was significantly lower in the IRA. Baseline and hyperaemic flow were lower in the infarct area. When compared with the reference area, MBF in viable myocardium in the infarct area was significantly higher only at baseline.

The relation between MR in reference and infarct areas at hyperaemia and at baseline in individual patients is shown in Figure 1. In both conditions, a significant relation was found.

Discussion

In the present study, MR in viable myocardium in infarct areas was compared with that in reference areas in patients with stable CAD and a chronic MI. MR at baseline, but not at maximal hyperaemia, was higher in the infarct area. In individual patients, there was a significant correlation between MR in infarct and reference areas, both at baseline and during hyperaemia.
H₂¹⁵O positron emission tomography to measure myocardial blood flow in infarcted areas

H₂¹⁵O PET provides blood flow data, in that part of the myocardium is capable of exchanging water rapidly, i.e. viable myocardium. In patients with an MI, H₂¹⁵O PET MBF data have been shown to successfully predict recovery of contractile function after revascularization in both acute and chronic settings. 27–29 The distribution of water-perfusable myocardium estimated by H₂¹⁵O and PET corresponded well with the location of the histochemically proven non-infarct myocardial tissue in an animal model of old MI. 24 In another animal study, a good correlation was found between H₂¹⁵O PET MBF and microsphere estimates of MBF within the infarcted area. 30 These findings imply that perfusion of the scar tissue within an infarct area is very low (no microspheres are seen) and is not measured by H₂¹⁵O PET. If one should account for the blood flow in the scar tissue within an infarct area, average total blood flow (scar tissue and viable myocardium) in an infarct area would be much lower and MR would be much higher. However, assessment of only viable myocardium in an infarct area seems more relevant from a clinical point of view.

As the H₂¹⁵O PET technique provides values of flow per millilitre of perfusable tissue (viable myocardium) and not per millilitre of total tissue in the infarct area, MR in equivalent amounts of viable myocardium in infarct and reference myocardial areas can be compared. In contrast, when using a Doppler guide wire or electromagnetic flow probe to

Table 1 Clinical characteristics, angiographic, and haemodynamic data (n = 27)

| Age (years) | 56 ± 9 |
| Sex, M/F    | 23/4  |
| Coronary risk factors, n (%) |
| Diabetes mellitus | 2 (7) |
| Hypertension   | 9 (33) |
| Hyperlipidaemia | 17 (63) |
| Smoking        | 15 (56) |
| Infarct-related artery, n |
| LAD/LCx/RCA   | 17/3/7 |
| Q-wave/non-Q-wave MI, n | 22/5 |
| Left ventricular ejection fraction (%) | 44 ± 15 |
| Time interval MI and PET study (years) | 3.3 ± 4.4 |
| Reference diameter (mm) |
| Reference vessel | 3.03 ± 0.49 |
| IRA           | 2.86 ± 0.66 |
| DS (%) |
| Reference vessel | 8 ± 9* |
| IRA           | 54 ± 25 |
| Hyperaemic mean BP during PET (mmHg) | 93 ± 9 |
| Hyperaemic mean pAo during cag (mmHg) | 96 ± 13 |
| hRPP during PET (b.p.m. mmHg) | 8479 ± 1805 |
| hRPP during cag (b.p.m. mmHg) | 7849 ± 1587 |

BP, blood pressure; cag, coronary angiography; DS, diameter stenosis; hRPP, hyperaemic rate pressure product; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; MI, myocardial infarction; pAo, aortic pressure; RCA, right coronary artery.

*P < 0.0001 reference vessel vs. IRA.

Table 2 Pressure measurements, positron emission tomography myocardial blood flow data, and microvascular resistance

<table>
<thead>
<tr>
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<th>Infarct area</th>
<th>Reference area</th>
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<tbody>
<tr>
<td>bPao during cag (mmHg)</td>
<td>104 ± 18</td>
<td>104 ± 17</td>
</tr>
<tr>
<td>bPd during cag (mmHg)</td>
<td>93 ± 23</td>
<td>102 ± 18</td>
</tr>
<tr>
<td>hPao during cag (mmHg)</td>
<td>97 ± 17</td>
<td>98 ± 14</td>
</tr>
<tr>
<td>hPd during cag (mmHg)</td>
<td>72 ± 18*</td>
<td>94 ± 15</td>
</tr>
<tr>
<td>FFR</td>
<td>0.75 ± 0.16*</td>
<td>0.96 ± 0.04</td>
</tr>
<tr>
<td>Baseline MBF (mL/mL/min)</td>
<td>0.72 ± 0.23</td>
<td>0.90 ± 0.21*</td>
</tr>
<tr>
<td>Hyperaemic MBF (mL/mL/min)</td>
<td>2.10 ± 0.92</td>
<td>2.98 ± 1.12*</td>
</tr>
<tr>
<td>bMR (mmHg mL min/mL)</td>
<td>135 ± 38</td>
<td>118 ± 29**</td>
</tr>
<tr>
<td>hMR (mmHg mL min/mL)</td>
<td>39 ± 18</td>
<td>35 ± 11</td>
</tr>
<tr>
<td>bMR/hMR</td>
<td>3.9 ± 1.5</td>
<td>3.6 ± 0.8</td>
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bPao, aortic pressure at baseline; bPd, distal coronary pressure at baseline; bMR, baseline microvascular resistance; cag, coronary angiography; hRPP, hyperaemic rate pressure product; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; MI, myocardial infarction; pAo, aortic pressure; RCA, right coronary artery.

*P < 0.0001 reference vs. IRA.

**P < 0.05 reference vs. IRA area.

Figure 1 Correlation between microvascular resistance in reference and infarct areas (A) during hyperaemia (hMR) and (B) at baseline (bMR). Regression lines and 95% confidence limits are given.
compare maximal coronary flow in an IRA and a reference vessel, no correction is made for the smaller mass of viable myocardium perfused by the IRA. Therefore, assessment of MR based on these techniques cannot distinguish whether a lower maximal flow velocity (which results in a higher MR calculation) within an IRA is caused by a truly augmented MR or by a decreased perfusion bed because of the infarction.31

In contrast to prior studies, infarct location and MBF were determined in a 13-segment model in our study.32 This approach allows for more precise delineation of the infarct area and, therefore, allows for the assessment of MR within the infarct area only. MBF data of segments with MIBI perfusion defects or WMA at baseline were only used.

Distal coronary pressure to assess microvascular resistance

In patients with obstructive CAD, due to a transstenotic pressure gradient, distal coronary pressure is lower than aortic pressure and, therefore, MR cannot be calculated using aortic pressure. This fact is not always accounted for.32 Furthermore, coronary arteries without focal stenosis at angiography generally are considered non-flow limiting. However, atherosclerosis is a diffuse process that can remain invisible at angiography and can cause a graded, continuous pressure fall along the arterial length.33,34 In the present study, coronary pressure was measured in the most distal parts of IRA, thus avoiding the above-mentioned pitfalls. These measurements showed large variation in hyperaemic transstenotic pressure gradients in the IRA. This is also reflected in widely varying fractional flow reserve (FFR) values. In the contralateral coronary artery, which had a normal angiographic aspect, the hyperaemic distal pressure was 0–5 mmHg lower than the aortic pressure, underscoring the fact that occult atherosclerosis can result in a detectable epicardial resistance.

Microvascular resistance in chronic myocardial infarction

Currently, few data are available on MR, only in patients without prior infarction. Studies have shown that MR is heterogeneous both within and between normal controls.35 In patients with an intermediate coronary stenosis, spatial heterogeneity of MR was found at hyperaemia.21 In myocardial areas perfused by a severely narrowed coronary artery, it has been reported that hyperaemic MR is augmented and that MR normalizes after successful coronary angioplasty.20,22 However, when accounting for collateral flow, minimal MR was found to be independent of the severity of an epicardial stenosis.39

In an animal study with microspheres, Vanhaecke et al.36 found that the hyperaemic flow in the viable, reperfused myocardium was transiently diminished, but did recover after 1 week. In the irreversibly damaged myocardium, however, the decrease in the peak hyperaemic flow was very substantial and permanent. In the present study, we found that MR in the infarct areas was elevated only at baseline, but not during hyperaemia. The microcirculatory vasodilator reserve in the infarct area was not inferior when compared with the reference area, similar to the animal study mentioned earlier. This suggests that, in patients with a patent IRA, microcirculatory function within the viable myocardium of an infarct zone is not hampered in the chronic phase of an MI. A prerequisite for adequate microcirculatory function is an appropriate number, functionally intact capillaries for the amount of myocardial tissue to be perfused. In a histopathological study of chronic MIs, an inverse relation between reduction in capillary density and transmurality of the infarct scar has been demonstrated; the lowest density was found in patients with ventricular aneurysms and an occluded IRA. The amount of viable myocardial tissue within an infarct area correlated with the number of (surviving) capillaries.37

In the present study, variability of MR in the reference area was large. This corresponds with the findings of previous studies in healthy humans and patients and reflects a physiological phenomenon.21,35,38

Clinical implications

Nuclear perfusion scans, used to assess the haemodynamic significance of an epicardial stenosis, are based on the comparison of flow in the area of interest and a reference segment. These tests assume that MR is the same in both areas. As illustrated in Figure 1A, for most patients, a good correlation between both MRs was found, suggesting that these perfusion studies can be used in patients with chronic MI to assess a coronary stenosis in the IRA. An important prerequisite to determine FFR is that measurements are performed under conditions of minimal myocardial resistance. To use the cut-off value for FFR (established in patients without infarction) in an IRA, the MR in infarcted and non-infarcted myocardial areas should be comparable. The findings of the present study support the application of FFR measurements in an IRA, in the setting of a chronic MI. This is in line with studies of FFR in the subacute phase of MI, in which the established FFR cut-off value for non-infarct myocardial areas proved to be valid also in infarct areas.18,39,40

Limitations

PET and pressure measurements were not performed simultaneously. Hence, the data might have been acquired under different haemodynamic conditions. However, no difference in rate pressure products between both procedures was observed. Furthermore, hyperaemia during PET scanning and pressure measurements was induced by intravenous and intracoronary adenosine administration, respectively. Studies have shown, however, that there is no difference in the level of hyperaemic flow following intracoronary or intravenous administration of adenosine.41

Collateral flow probably does not affect the measurements of MR. Regional PET data are the summation, at the myocardial level, of antegrade and collateral coronary flow. If present, collateral flow is also reflected in the distal coronary pressure measurement.42 Therefore, both PET flow and pressure data completely incorporate the contribution of collateral flow; hence, this effect should cancel out in the estimation of MR.

In patients with a critical coronary stenosis, the microcirculation may become dysfunctional.43 In the present study, most of the patients had only a minimal or intermediate coronary stenosis and, therefore, the effects on the results are likely to be small.
Conclusion
In patients with CAD, distal coronary pressure often is lower than aortic pressure and, therefore, aortic pressure cannot be used to determine MR. Hyperaemic MR in viable myocardium within the infarct area is not higher when compared with the reference area. This finding supports the use of non-invasive stress tests or the established FFR cut-off value (0.75) in the assessment of coronary stenoses in patients with a chronic MI.

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References


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**Multiple sirolimus eluting stent fractures**

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A 73-year-old woman was admitted with a history of previous myocardial infarction and a nuclear perfusion scan showed an area of ischaemia in the inferior wall. Coronary angiography revealed a total occlusion of the proximal right coronary artery (RCA); percutaneous coronary intervention was performed and two sirolimus eluting stents (Cypher 3.0–33 mm, Cypher 3.0–28 mm, and Cordis) were deployed (in overlapping) at 16 atm with a good angiographic result. No gap between the two stents (Panel A) was evident at fluoroscopic images. The full metal jacket distended the normal tortuosity of the vessel. Twenty-eight months later, the patient returned to our emergency department for unstable angina.

Repeat angiography showed the patency of the vessel with multiple sites of angiographically non-significant in-stent neointimal proliferation; the fluoroscopic images revealed complete stent fracture and misalignment located in the proximal (moderate angulation) and middle segments (site of overlapping and hinge points) of the RCA (Panel B, arrows). The vessel had regained its physiological tortuosity.

Intravascular ultrasonography (Galaxy, Boston Scientific) confirmed the absence of metallic struts in the site of circumferential fracture with neointimal hyperplasia at the strut-free segments (Panels C–F).

Clinical vignette

Vessel tortuosity and the use of overlapping stents may contribute to these complications.