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# Impaired coronary flow reserve after a recent myocardial infarction: Correlation with infarct size and extent of microvascular obstruction

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ABSTRACT

*Background:* The exact relationship between the coronary flow reserve (CFR) and infarct size remains unknown. In this prospective study the relationship between the CFR both in the infarcted and remote myocardium and infarct size was investigated. Furthermore, the diagnostic value of the CFR to predict the extent of microvascular obstruction (MO) was evaluated.

*Methods:* In thirty patients the CFR was measured with a Doppler guide wire 6 ± 3 days after a first myocardial infarction (MI) in the infarct related and in a reference coronary artery. MO and infarct size were determined with magnetic resonance imaging.

*Results:* The CFR was inversely related to infarct size in the infarcted and remote myocardium (respectively, $r = -0.60$, $p<0.01$ and $r = -0.62$, $p<0.01$).

In the infarcted myocardium the extent of MO was strongly related to the infarct size and was in a multivariate analysis the single significant determinant of the CFR and the hyperaemic flow.

In the remote myocardium no relationship was present between infarct size and hyperaemic flow, but the baseline flow increased as the infarct size became larger ($r = 0.58$, $p<0.01$).

In a receiver operator characteristic (ROC) analysis, a CFR value ≤ 2 in the infarct related coronary artery offered the best sensitivity (65%) and specificity (71%) to detect the presence of MO ($p<0.05$).

*Conclusions:* After MI, the CFR both in the infarcted and remote myocardium is inversely related to infarct size. In the infarcted myocardium, a CFR value ≤ 2 predicts the presence of MO with moderate sensitivity and specificity.



## 1. Introduction

Reperfusion therapy for myocardial infarction (MI) aims to restore myocardial perfusion in order to limit infarct size and ultimately to improve the prognosis of the patient [1]. In numerous investigations the strong predictive value of both infarct size and absence of reperfusion in the core of the infarct territory for recovery of function and even left ventricular (LV) remodeling has been shown [2–5]. Magnetic resonance imaging (MRI) has been established as a reliable technique to assess these structural alterations [6–8].

A functional impairment of the coronary microcirculation has also been demonstrated after MI. The coronary flow reserve (CFR) is decreased in the infarcted myocardium and this parameter has been related to the recovery of myocardial function [9]. A relationship between infarct size and perfusion can therefore be assumed, but it remains unclear whether the CFR can be used to assess the extent of necrosis in the infarct territory.

The CFR has been reported to be also impaired in the non-infarcted, remote myocardium [10]. Neurohormonal activation, increased filling pressures or alterations in systolic function could all affect the CFR in the remote myocardium. The exact relationship between the CFR and infarct size remains however unknown.

In this study, we examined the relationship between coronary microcirculatory reactivity, assessed invasively with a Doppler crystal-tipped guide wire, and infarct size. We hypothesized that the CFR in the infarcted myocardium would be related to extent of necrosis, determined with delayed contrast-enhanced MRI. In addition, the diagnostic value of the CFR for the prediction of presence of microvascular obstruction (MO) was evaluated. Furthermore, in order to investigate the relationship between infarct size and coronary haemodynamics in the remote myocardium, the CFR was also measured in a reference vessel.

## 2. Materials and methods

### 2.1. Patient selection

Thirty consecutive patients with single vessel disease, who were referred for elective coronary intervention following thrombolytic therapy for a recent first MI (range

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3–12 days), were prospectively included in this study. MI was defined as 1) an episode of thoracic pain > 30 min, 2) ST-elevation on ECG and 3) rise of troponin values [11]. Exclusion criteria included 1) previous heart surgery, 2) severe valvular dysfunction, 3) electrocardiographic signs of hypertrophy, 4) visible collateral circulation on angiography, 5) cardiogenic shock, 6) total occlusions and 7) contraindications for MRI.

The study complied with the Declaration of Helsinki. All patients gave written informed consent and the protocol was approved by the ethics committee of the Antwerp University Hospital.

### 2.2. Coronary perfusion

All patients were treated with intravenous heparin and a continuous infusion of nitrates was started before the catheterization procedure. Balloon angioplasty and subsequent stenting were performed following standard procedures until an optimal angiographic result was obtained (diameter stenosis < 25%).

Coronary flow velocities were measured with a Doppler crystal-tipped angioplasty guide wire (Flowire, Volcano Therapeutics, Inc., Rancho Cordova, USA) after intracoronary bolus administration of isosorbide dinitrate (1 mg). The tip of the wire was positioned 1 cm behind the stented lesion in the infarct related vessel. Subsequently, the wire was placed in an epicardial vessel without stenosis perfusing remote, non-infarcted myocardium. Flow velocity measurements were performed in baseline conditions and during hyperaemia after an intracoronary bolus injection of 40 μg of adenosine. The coronary artery diameter at the site of the Doppler sample volume was determined by quantitative methods (Quantitative Coronary Angiography, GE Medical Systems, Buc, France).

The CFR was defined as the ratio of the average peak velocities (APV) in hyperaemic and baseline conditions. The rate pressure product was calculated as heart rate × systolic blood pressure. The left ventricular end diastolic pressure (LVEDP) was determined with a fluid filled catheter.

The relation between actual coronary flow and perfusion velocity is degraded in the presence of diffuse atherosclerosis [12]. The actual coronary flow (ml/min/g) was therefore calculated as 0.5 × average peak velocity × cross sectional area of the epicardial vessel divided by the perfusion bed mass [12]. In order to determine the myocardial perfusion bed mass, total LV mass was determined with MRI and a recently validated angiographic territory score based on the number of terminal branches of the epicardial vessels and their relative length on coronary angiography, was calculated [13–15]. Briefly, each terminal vessel that supplied the left ventricular myocardium was graded with a score of 3, 2, 1 or 0, corresponding to large, medium, small or absent. The sum of the scores of the vessels downstream of the tip of the guide wire were summed and divided by the sum of the scores of all the terminal vessels supplying the LV. The regional LV mass distal to the tip of the guide wire was determined by multiplying the total LV mass with this fraction. Determination of the territory scores was performed by two independent observers blinded to the MRI data. The intraclass correlation coefficients for intra-observer and the inter-observer agreement were both 0.9.

### 2.3. Magnetic resonance imaging

MRI was performed on a 1.5-T scanner (Siemens Sonata, Erlangen, Germany) utilizing a 12 channel body array surface coil. All patients were examined in the supine position. An intravenous catheter was placed in an antecubital vein for injection of contrast material.

Scout images were obtained to determine the exact position and axis of the left ventricle. Cardiac cine images were made from base to apex in the short axis direction using a steady state free precession sequence. Typical imaging parameters were a 380 × 320 mm² FOV, a 256 × 159 matrix, 8 mm slice thickness, 2 mm slice gap, 70° flip angle, 1.51 ms echo time and 45.15 ms repetition time.

Six short-axis slices were chosen at equal distances along the left ventricle long-axis for first-pass perfusion imaging with an electrocardiographically triggered saturation recovery ultra-fast gradient echo sequence (repetition time/echo time/inversion time, 188 ms/0.96 ms/100 ms; flip angle, 15°). A 96 × 128 matrix, an 8 mm slice thickness and a 309 × 380 mm² field of view were used. A bolus of gadopentetate dimeglumine (Gd-DTPA, Magnevist, Schering, Germany) in a dose of 0.1 mmol/kg of body weight was injected intravenously at a flow rate of 3 ml/s and flushed with 20 ml of normal saline by using a MRI compatible power injector (Medrad, Indianola, USA). Immediately after first-pass imaging, a second bolus of Gd-DTPA (0.1 mmol/kg of body weight) was administered.

Delayed contrast-enhanced images covering the left ventricle from base to apex in the short-axis view (slice thickness 8 mm, gap 2 mm) were acquired 15 min after perfusion imaging with the use of a breath-hold, phase sensitive inversion recovery steady state free precession sequence with a repetition time and echo time of 680 ms and 1.26 ms, respectively and a flip angle of 45°. Typical imaging parameters were a 308 × 340 mm² field of view and 184 × 256 matrix.

### 2.4. Magnetic resonance image and data analysis

End diastolic volume, end systolic volume and ejection fraction (EF) were determined from the cine images using the MASS software package (Medis, Leiden, The Netherlands).

Areas of MO were defined as zones of hypoenhancement during first-pass perfusion imaging [16]. These zones presented as a dark rim along the endocardial border during the first pass of the contrast agent. Each short axis slice was divided in 12 segments, in which the presence of hypoenhancement was visually assessed. The total extent of MO was expressed as percentage of the total endocardial border length [5]. Time-myocardium intensity plots were constructed with the MASS software package to confirm the presence of hypoenhancement [16].

Infarct size was determined from delayed enhancement short-axis slices [17]. Each slice was divided in 12 segments, except for the apical slice, which was divided in 4 segments. Transmurality of the hyperenhancement was scored in each segment on a 5-point scale (0: 0% left ventricular wall thickness, 1: 1–25%, 2: 26–50%, 3: 51–75%, 4: 76–100%) [17]. Infarct size for each slice was calculated as

$$\text{Infarct size of slice(g)} = (\textstyle\sum \text{scores}/n) \times \text{mass of slice(g)} (n = 48, \text{ except for the apical slice : } n = 4)$$

Total infarct size expressed as percentage of LV mass was calculated by the formula:

$$\text{Total infarct size(\% LV mass)} = \frac{\sum \text{Infarct size of slice(g)} \times 100\%}{\sum \text{Mass of slice(g)}}$$

Measurements of LV ejection fraction, extent of MO and infarct size were performed by two independent observers blinded to the invasive measurements. The intraclass correlation coefficients for intra-observer and the inter-observer agreement for these parameters were all above 0.9.

### 2.5. Statistics

All data are presented as mean ± standard deviation. Perfusion parameters of the infarcted and the remote myocardium and haemodynamic variables at baseline and hyperaemia were compared with a paired *t*-test. Stepwise regression analysis was performed to identify the most important determinants of the CFR and the hyperaemic flow in the infarcted myocardium (F to enter > 4). Pearson's correlation coefficients were calculated for the relation between infarct size and the perfusion parameters. Receiver operator characteristic (ROC) analysis was used to determine the diagnostic accuracy of the CFR to predict the presence of necrosis. A p value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Patients' characteristics

Percutaneous coronary intervention was successfully completed in all 30 patients. The mean time between the acute MI and the invasive assessment of coronary perfusion was 6 ± 3 days. Patients' characteristics are presented in Table 1.

**Table 1**
Patient characteristics (n = 30).

| | |
|---|---|
| Age (years) | 56.9 ± 11.0 |
| BMI (kg/m²) | 27.2 ± 3.9 |
| Male/female (n) | 26/4 |
| Hypercholesterolemia (n) | 24 (80%) |
| Smoking (n) | 19 (63.3%) |
| Diabetes mellitus (n) | 3 (10%) |
| Arterial hypertension (n) | 11 (36.7%) |
| Familial history (n) | 17 (56.7%) |
| ACE-inhibitors (n) | 21 (70%) |
| Beta-adrenergic receptor antagonist (n) | 28 (93.3%) |
| Statins (n) | 28 (93.3%) |
| Reference artery | |
| LAD (n) | 5 |
| LCX (n) | 14 |
| Treated artery | |
| LAD (n) | 20 (66.7%) |
| LCX (n) | 3 (10%) |
| RCA (n) | 7 (23.3%) |
| Diameter stenosis after stenting (%) | 9.3 ± 5.5 |
| LVEDP (mm Hg) | 28.1 ± 8.0 |
| MR imaging | |
| LV end diastolic volume (ml) | 177.5 ± 44.8 |
| LV end systolic volume (ml) | 104.9 ± 41.2 |
| Ejection fraction (%) | 42.2 ± 10.4 |
| LV mass (g) | 162.8 ± 39.6 |
| Infarct size (% LV mass) | 27.2 ± 11.5 |
| MO (% endocardial border) | 14.1 ± 12.1 |

BMI = body mass index, LAD = left anterior descending artery, LCX = left circumflex artery, MO = microvascular obstruction, RCA = right coronary artery, LV = left ventricular, LVEDP = left ventricular end diastolic pressure.