The prognosis of patients with ST-segment–elevation myocardial infarction (STEMI) has continued to improve significantly since the introduction of the coronary care units in the 1960s. However, despite the widespread use of effective fibrinolytic and antithrombotic drugs, primary percutaneous coronary interventions (PCI), and shorter ischemic times, because of improved emergency transportation, mortality in STEMI patients remains considerable, with estimates of 7% at 1 month and 15% at 1 year.

The incidence of angiographic no reflow (NR) and microvascular obstruction (MVO) at cardiac magnetic resonance is significantly different. The aim of this study was to investigate the occurrence of NR and MVO in a cohort of consecutive patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary interventions.

In this prospective study, 88 consecutive ST-segment–elevation myocardial infarction patients were enrolled within 12 hours from symptoms onset. All patients underwent cardiac magnetic resonance between 2 and 5 days after primary percutaneous coronary interventions. NR was defined as thrombolysis in myocardial infarction flow grade ≤2 and as myocardial blush grade <2. Presence of early or late MVO was assessed 4 and 10 to 15 minutes after gadolinium injection. Thirty-one patients (36%) had evidence of NR, whereas 58 (67%) had MVO. One NR patient did not have MVO. In contrast, NR was present in 30 of 58 MVO patients. MVO patients had higher troponin T peak ($P<0.0001$), larger late gadolinium enhancement area ($P<0.0001$), and lower left ventricular ejection fraction ($P<0.001$) because of an increased end-systolic volume ($P=0.015$). In contrast, patients with NR had higher troponin T peak ($P=0.006$) but similar late gadolinium enhancement area ($P=0.24$) compared with those without NR. Major cardiovascular adverse events–free survival was worse in patients with MVO ($P=0.014$), although it was similar in patients with and without NR ($P=0.33$). The independent predictors of major cardiovascular adverse events were MVO (hazard ratio, 3.418; $P=0.004$) and ischemic time (hazard ratio, 1.016; $P<0.001$). NR was a strong predictor of target lesion revascularization occurrence ($P=0.017$ for log-rank test).

Compared with coronary angiography performed soon after recanalization of the culprit artery, cardiac magnetic resonance performed during index hospitalization provides better prognostic stratification of ST-segment–elevation myocardial infarction patients treated with primary percutaneous coronary interventions. Another novel finding of our study is a significantly increased rate of clinically driven target lesion revascularization in the index event culprit vessel in patients with MVO. (Circ Cardiovasc Imaging. 2017;10:e005841. DOI: 10.1161/CIRCIMAGING.116.005841.)

Key Words: coronary angiography • gadolinium • magnetic resonance imaging • myocardial infarction • prognosis

Identification of High-Risk Patients After ST-Segment–Elevation Myocardial Infarction

Comparison Between Angiographic and Magnetic Resonance Parameters

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The prognosis of patients with ST-segment–elevation myocardial infarction (STEMI) has continued to improve significantly since the introduction of the coronary care units in the 1960s. However, despite the widespread use of effective fibrinolytic and antithrombotic drugs, primary percutaneous coronary interventions (PCI), and shorter ischemic times, because of improved emergency transportation, mortality in STEMI patients remains considerable, with estimates of 7% at 1 month and 15% at 1 year.

Early recanalization of the culprit artery prevents the transmural progression of myocardial necrosis, thus limiting infarct size. However, reperfusion may also be associated with secondary impairment of the coronary microcirculation because of endothelial swelling, luminal obstruction, external compression, and distal embolization. This microvascular damage contributes to the no reflow (NR) phenomenon which consists in the inability of a previously ischemic region, in the territory of a successfully recanalized infarct-related artery, to be effectively reperfused. The incidence of NR in STEMI patients undergoing primary PCI varies between 5% and 50%, depending on the method of assessment. NR can deny the benefits of primary PCI, thus contributing to post-STEMI complications and, eventually, to a worse outcome.

NR is classically diagnosed during coronary angiography using the thrombolysis in myocardial infarction (TIMI)
flow grade, TIMI myocardial blush grade (MBG), and TIMI frame count. Cardiac magnetic resonance (CMR) provides additional information on the effects of NR at a myocardial level, enabling the measurement of microvascular obstruction (MVO) and tissue edema.

The occurrence of NR and MVO is significantly different and might be explained by many factors, including the time of their assessment. Angiographic NR varies between 5% to 10% using TIMI flow grade to around 30% using MBG, whereas MVO at CMR can be observed in >50% of STEMI patients.

Both angiographic NR and MVO at CMR are predictors of worse prognosis.

To our knowledge, no formal comparison of the incidence of NR at angiography and MVO at CMR has been performed in the same STEMI patients. Therefore, the main aim of this study was to investigate the occurrence of NR at angiography and MVO at CMR in a cohort of consecutive patients with STEMI treated with primary PCI.

Methods

Study Population

This prospective observational study was performed at a single center (San Raffaele Hospital, Milan, Italy). The study protocol was approved by the local ethics committees (DO/MS/ER/mm; protocol number 333/11 of March 2, 2011). All patients gave written informed consent to be part of the study and did authorize publication of data. Study population was based on feasibility.

We prospectively enrolled consecutive patients with STEMI within 12 hours from symptoms onset admitted to our hospital from September 2011 to September 2015. Overall, 248 patients were screened, and 88 were enrolled. Exclusion criteria were age <18 and >80, body mass index >35, history of cancer, chronic renal failure with GFR <30 mL min⁻¹ 1.73 m⁻², allergy to gadolinium, claustrophobia, previous known left ventricular (LV) ejection fraction <35%, inability to sign a written informed consent, inability to lay for at least 30 minutes, and cardiogenic shock.

All patients underwent CMR between 2 and 5 days after primary PCI.

Patients’ follow-up visits were performed at a dedicated outpatient clinic. Information about patients’ death was obtained from hospital records, death certificates, or telephone contact with relatives of the patient or referring physician. Major cardiovascular adverse events (MACE) at follow-up were defined as death, cardiac death, nonfatal acute myocardial infarction, unplanned myocardial revascularization (both percutaneous and coronary artery bypass graft) because of persistent angina, clinically driven target lesion revascularization (TLR), admission for heart failure, and implantable cardioverter–defibrillator implantation.

Coronary Angiography and PCI

All patients underwent primary PCI with stent implantation. The same standardized protocol was used for the treatment of STEMI in all patients:

1. Thrombus aspiration with adequate system if high thrombotic burden;
2. Intracoronary or intravenous administration of glycoprotein IIb/IIIa, at the discretion of the operator;
3. PCI with stenting (either bare metal stent, drug-eluting stent, or bioabsorbable vascular scaffold at operator’s discretion); and
4. Selective intracoronary nitropressure (40–120 μg) in case of slow flow, repeatable, possibly with the help of small boluses of epinephrine (0.5–1 mg) to increase blood pressure.

NR was defined as TIMI flow grade ≤2 in the absence of distal embolization and as MBG <2 even in the presence of a TIMI 3 flow grade. TIMI flow grade and TIMI frame count of each vessel were recorded before and after reperfusion, and TIMI MBG was recorded at the end of the procedure.

CMR Technique

CMR imaging was performed on a 1.5-T whole-body scanner (Achieva; Philips Medical System, Best, The Netherlands), using a 5-elements cardiac phased-array coil (SENSE Cardiac, Philips Medical Systems), with respiratory and ECG gating.

All patients underwent short axis (SA), 4- and 2-chamber long-axis Cine, SA T2-weighted short tau inversion recovery turbo spin echo sequence, rest first-pass perfusion (FPP), early gadolinium enhancement (EGE), and late gadolinium enhancement (LGE).

SA Cine imaging used a steady-state–free precession sequence, 10 to 12 slices, 8 mm thickness, 2 mm gap, and 30 phases per cardiac cycle, covering the whole heart in parallel SA slices from base to apex.

SA T2-weighted short tau inversion recovery used a dark blood turbo spin echo sequence, TE 100 ms, TR 1818 ms, FA 90°, 350 cm FOV, and 512 reconstruction matrix, with 10 slices (8 mm thickness, 2 mm gap) covering the entire LV.

Rest FPP was performed simultaneously with the injection of the first peripheral bolus of gadolinium (Gadovist 1.0; Bayer HealthCare Pharmaceuticals, 0.075 mmol/kg; 4 mL/s), using a turbo FFE sequence (TE 0.99 mm, TR 2.1 mm, 330 cm FOV, and 256 reconstruction matrix) with 8 slices (10 mm thickness) covering the entire LV.

A second injection of gadolinium (Gadovist 1.0; Bayer HealthCare Pharmaceuticals, 0.075 mmol/kg; 2.0 mL/s) was performed at the end of FPP to reach the total dose of 0.15 mmol/kg.

SA and 4-chamber EGE images were acquired using a 3-dimensional (3D) inversion recovery TFE T1-weighted sequences, with inversion time individually optimized to null the signal of normal myocardium (TE 1.31 ms, TR 4.4 ms, FA 15°, 300 cm FOV, and 336 reconstruction matrix).

SA and 4-chamber LGE images were acquired 10 minutes after the second injection of gadolinium using the same 3D inversion recovery TFE T1-weighted sequences of EGE.

A semiautomatic software (ViewForum release 4.2, Philips Medical System) was used for all quantitative analysis.

LGE distribution was defined as transmural or subendocardial considering 50% of the wall thickness as cutoff. The extent of LGE in absolute units (mm²) or as % of LV mass was used to compute infarct size. Endocardial and epicardial contours were traced manually for each LGE SA slice. A region of interest was traced in healthy myocardium; regions 5 SD above the signal intensity of the region of interest representing the normal myocardium were considered infarcted. The software then calculates the infarct area as percentage on the total LV myocardium.

MVO was qualitatively recognized as a subendocardial lack of enhancement at FPP sequences and as a hypointense region within the hypointense infarcted area at EGE and LGE sequences. Quantitative analysis of MVO at FPP sequences was obtained tracing a manual region of interest around the involved area, letting the automatic software to obtain a value of MVO as percentage on the total myocardial mass. Quantitative analysis of MVO at EGE and LGE sequences was obtained tracing the endocardial contours, epicardial contours, and a manual region of interest around the involved area for each SA EGE and LGE slice. Once again, the semiautomatic software gave us a quantitative MVO value as a percentage on the total myocardium.

When MVO was present, it was automatically included in the estimation of the infarcted area.

The extent of myocardial edema, that is, signal hyperintensity in the STIR sequences, was assessed in the same way as the infarcted area, but using SA T2 STIR sequences. Oedematous myocardium was defined as the area with signal higher than 2 SD of remote myocardium on LGE sequences. The oedematous area was considered as the area at risk (AAR).

Other CMR parameters were obtained through the semiautomatic analysis of SA cine images. They included end-diastolic and end-systolic LV volume, ejection fraction, and LV mass. Volumes and mass were also normalized for body surface area.

Myocardial salvage index was calculated as the difference between AAR and LGE divided by the AAR itself ([AAR–LGE]/AAR).
Statistical Analyses

Results are reported as mean±SD or as frequency and percentage, as appropriate. The Kolmogorov–Smirnov test was performed to investigate for normality of the distribution. The Wilcoxon rank-sum test was performed to compare continuous variables between patients with and without NR and between patients with and without MVO. Categorical variables were compared by means of the χ² test.

Survival curves for MACE were calculated by the Kaplan–Meier method, and differences between curves were tested by the log-rank test. Survival curves for TLR were also calculated by the Kaplan–Meier method. It was not possible to study the other single events included in the MACE definition because of the low number of events.

Univariate Cox proportional hazard regression models were used to estimate the predictive effect of demographic, clinical, and CMR variables, as well as of NR and of MVO on MACE and TLR. Hazard ratios and 95% confidence intervals of hazard ratio were calculated.

Multivariate Cox proportional hazards regression models were used, including variables with a P value <0.10 at univariate analyses. Both the full model and the model using the forward stepwise selection method were run.

CMR characteristics at 6 months after the index event were compared with CMR characteristics soon after STEMI by means of Wilcoxon paired signed-rank test.

Results

Although we screened 248, only 88 were enrolled in the study because of the presence of exclusion criteria. Most frequent exclusion criteria were refusal of the patient to undergo CMR (85 patients), previous inclusion of the patient in another research trial (24), inability to undergo CMR because of hemodynamic instability (18), and the presence of eGFR <30 (10). Two of the 88 patients enrolled had poor-quality CMR images; thus, their data were discarded. Therefore, the final study population consisted of 86 patients (86% male, mean age 60±10.8 years). All of these patients had at least a 6-month clinical follow-up. Twenty-eight patients (32%) had a follow-up CMR, 196±39 days after the index event. Demographic and clinical characteristics of the study population are shown in Table 1.

Angiographic NR Versus MVO

Overall, 31 patients (36%) had evidence of angiographic NR, whereas 58 patients (67%) had MVO. Among patients with angiographic NR, only 1 did not have MVO. In contrast, NR was present only in 30 of 58 patients with MVO (Table 2).

Differences between patients with and without MVO and those with and without NR are reported in Table 3.

Patients with MVO had higher levels of proBNP (2368±2800 versus 1031±870 pg/mL; P=0.007) and blood glucose level (169±69 versus 140±42 mg/dL; P=0.02) at admission compared with patients without MVO. In contrast, proBNP levels were similar in patients with and without NR (P=0.26), and there was only a trend toward higher blood glucose levels in patients with NR (P=0.07).

Patients with MVO had larger infarct size as assessed by troponin T peak (8985±6250 versus 2834±2168 μg/L; P<0.0001) and LGE area at CMR (34.1±10.4% versus 21.5±10.3%; P=0.0001). Patients with MVO also had significantly lower LV ejection fraction (46.1±9.3% versus 55.4±7.6%; P<0.001), because of an increase in indexed LV end-systolic volume (42.5±13.3 versus 34.7±9.4 mL/m²; P=0.015). In contrast, patients with NR had higher troponin T peak (8888±6416 versus 6018±5611 μg/L; P=0.006), but similar LGE area (32.6±10.4% versus 28.9±12.6%; P=0.24) compared with those without NR.

Myocardial salvage index was significantly better in patients without MVO (0.30±0.25 versus 0.16±0.15; P=0.01), but not in patients without NR (0.23±0.21 versus 0.16±0.16; P=0.16).

Follow-Up

Median clinical follow-up was 464 days (interquartile range [Q1–Q3], 178–818). MACE-free survival was significantly worse in patients with MVO compared with those without MVO (number of events: 25; 44% in MVO+ versus 3; 12% in MVO−, log-rank P=0.014; Figure 1A), although it was similar in patients with and without NR (number of events: 13: 42% in NR+ versus 16; 30% in NR−, log-rank P=0.33; Figure 1B). After Cox regression analysis, the hazard ratio for MVO on MACE-free survival was 3.99 (confidence interval, 1.20–13.23; P=0.023).

Table 2. A 2×2 Table Showing the 2 Factors NR± and MVO±

<table>
<thead>
<tr>
<th></th>
<th>NR−</th>
<th>NR+</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>MVO−</td>
<td>29</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>MVO+</td>
<td>28</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>31</td>
<td>88</td>
</tr>
</tbody>
</table>

MVO indicates microvascular obstruction; and NR, no reflow.
There was an almost significant trend toward a better outcome in patients MVO−/NR− compared with MVO+/NR− and MVO+/NR+, although the prognosis of MVO+/NR+ patients was similar to those MVO+/NR− (number of events: 3; 12% in MVO−/NR− versus 27; 44% in MVO+/NR− versus 13; 43% in MVO+/NR+, log-rank \( P =0.06; \) Figure 2).

In Table 4, results of the multivariate Cox regression analysis are shown: results for the full model and for the model using the forward stepwise selection method are presented. The only independent predictors of MACE-free survival were the presence of MVO (hazard ratio, 3.418; 95% confidence interval, 1.019–11.46; \( P =0.046 \)) and ischemic time (hazard ratio, 1.016; 95% confidence interval, 1.007–1.025 for each 10 minutes increase; \( P <0.001 \)).

In the analysis of the single adverse events occurrence, MVO was a strong predictor of TLR occurrence (number of events: 12; 23% in MVO+ versus 0 in MVO−; log-rank \( P =0.017; \) Figure 3A). The same number of TLR was observed in NR+ and NR− (6; 22% in NR+ versus 6; 12% in NR−; log-rank \( P =0.38; \) Figure 3B).

One patient had acute stent thrombosis that was treated by thrombus aspiration and balloon angioplasty with good final angiographic result. He had MVO at CMR.

Three patients with MVO had maladaptive remodeling of the LV and developed severe LV dysfunction; thus, they had permanent implantable cardioverter–defibrillator implantation for primary prevention.

One patient with MVO had papillary muscle rupture before discharge. He underwent cardiac surgery and survived. However, he developed severe LV dysfunction and underwent subsequent LV assist device implantation.

### Discussion

The results of this study demonstrate that CMR performed during index hospitalization provides better prognostic stratification of STEMI patients treated with primary PCI compared with coronary angiography performed soon after recanalization of the culprit artery. This is an original finding because a formal comparison of these 2 parameters in the same cohort of consecutive patients was not reported previously. The
Incidence of MVO was higher than that of angiographic NR (67% versus 36%), and all but 1 patient with NR had MVO. It has been proposed that, based on the type of changes, that is, structural and functional, at the level of the microcirculation, NR can be either persistent or transient. Therefore, it could be hypothesized that those patients with angiographic NR

**Figure 1.** Classification of the study population according to the presence of microvascular obstruction (MVO; A) and angiographic no reflow (NR; B). MACE indicates major cardiovascular adverse events.

**Figure 2.** Major adverse cardiovascular events (MACE)–free survival in patients with and without microvascular obstruction (MVO) and those with and without no reflow (NR).
NR, but with no evidence of MVO, experienced a transient form of this phenomenon. Furthermore, the damage caused by ischemia and reperfusion varies with time and affects both the vasculature and the myocardium. This in turn has implications for the detection of the damage by angiography and CMR. Coronary angiography performed soon after recanalization of the culprit artery permits the assessment of acute vascular damage, including transient NR. On the other hand, CMR, performed days after the acute event, provides information on the overall consequences of ischemia/reperfusion at the tissue level, more likely consequent to the sustained forms of NR. At variance with our results, previous studies have demonstrated an increase in the number of adverse events in patients with NR.\textsuperscript{18,19} However, in our study, patients with impaired final TIMI flow, but without MVO, did not have any adverse event at follow-up and were thus comparable to patients without NR.

A recent study suggested that the use of the index of microvascular resistance could improve the prognostic value of angiography.\textsuperscript{20} However, the differences in sensitivity and specificity between angiography and CMR are also based on the timing of assessment. It is well known that NR is a dynamic process that evolves over time, thus influencing the accuracy and the diagnostic yield of an early (angiography) versus a late (CMR) examination.

A previous study showed that late MVO is a better predictor of LV recovery compared with angiography and to other CMR criteria.\textsuperscript{21}

In our study, we showed that MVO provides better prognostic stratification of risk after STEMI compared with classical angiographic markers of NR. Interestingly, there was no difference in the prognosis of MVO patients irrespective of the presence or absence of NR, whereas patients without MVO showed a better outcome.

In particular, we demonstrate that MVO occurrence was associated with a significantly higher rate of clinically driven TLR (0% versus 23%), although there was no significant difference in the number of bare metal stents versus drug-eluting stents implantation between the 2 groups. This is an original finding because no study up to now has addressed the impact of NR on in-stent restenosis, although these results must be interpreted with caution because of the small number of events and the fact that the assumptions for the log-rank statistical test are not fulfilled because of crossing lines in

<table>
<thead>
<tr>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA</td>
<td>0.37 (0.009–15.93)</td>
</tr>
<tr>
<td>Ischemia time (per each 10 min)</td>
<td>1.01 (1.009–1.03)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.235 (0.29–5.26)</td>
</tr>
<tr>
<td>Echo EF</td>
<td>0.98 (0.93–1.04)</td>
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<tr>
<td>EF (LV)</td>
<td>0.90 (0.97–1.22)</td>
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<tr>
<td>CO (LV)</td>
<td>0.77 (0.38–1.57)</td>
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<tr>
<td>ESV (LV) index, mL/m²</td>
<td>1.04 (0.97–1.10)</td>
</tr>
<tr>
<td>Myocardial salvage index (AAR%–LGE%)/AAR%</td>
<td>0.07 (0.003–1.49)</td>
</tr>
<tr>
<td>NR+ vs NR−</td>
<td>0.92 (0.37–2.31)</td>
</tr>
<tr>
<td>MVO+ vs MVO−</td>
<td>2.72 (0.65–11.39)</td>
</tr>
</tbody>
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AAR indicates area at risk; BSA, body surface area; EF, ejection fraction; ESV, end-systolic volume; LGE, late gadolinium enhancement; LV, left ventricle; MVO, microvascular obstruction; and NR, no reflow.

Figure 3. Major adverse cardiovascular events (MACE)–free survival in patients stratified according to the presence or absence of microvascular obstruction (MVO; A) and NR (B). Only 1 subject had MVO− and NR−; therefore, the head to head comparison of MACE by Kaplan–Meier curves was performed among NR− and MVO−; NR− and MVO+; NR+ and MVO+. TLR indicates target lesion revascularization. Target lesion revascularization (TLR)–free survival in patients with and without microvascular obstruction (MVO) and no reflow (NR).
the Kaplan–Meier plots. A study by Chan et al.\textsuperscript{22} showed an increased rate of adverse events and target vessel revascularization in patients with NR at 1-month follow-up in a mixed cohort of patients undergoing both elective or primary PCI. However, the composition of the study population and the brevity of follow-up did not permit an accurate assessment of this issue. By contrast, in our study, the rate of unplanned, repeat revascularizations of nonculprit vessels was similar between patients with and without NR. We hypothesize that microvascular dysfunction associated to MVO occurrence can lead to a change in coronary hemodynamics which in turn could favor the progression of in-stent restenosis.

### Study Limitations

Differently from previous reports,\textsuperscript{6,7} we found that patients with angiographic NR had only a nonsignificant trend toward more MACE compared with those without NR. The latter could be explained by the relatively small number of patients enrolled in our study.

Although in all our patients coronary recanalization was technically successful, the effective reperfusion rate, assessed angiographically, may seem rather low (64% of patients had final myocardial reperfusion and 36% of patients presented NR). It is worth noting that we used a definition of NR that included both TIMI flow and MBG. Similar rates of NR have been reported by other authors.\textsuperscript{12,13} Several studies have previously reported that MBG is more sensitive and specific compared with TIMI flow grade in assessing NR, when MVO was used as the gold standard.\textsuperscript{7} Moreover, MBG has been found to be a better prognostic index compared with TIMI flow.\textsuperscript{14}

### Conclusions

Compared with coronary angiography performed soon after recanalization of the culprit artery, CMR performed during index hospitalization provides better prognostic stratification of STEMI patients treated with primary PCI. Another novel finding of our study is a significantly increased rate of clinically driven TLR in the index culprit vessel in patients with MVO.

### Disclosures

Dr Camici is a consultant for Servier and has speaking engagements with MVO. Dr Camici is a consultant for Servier and has speaking engagements with MVO.

### References

The prognosis of patients with ST-segment–elevation myocardial infarction has improved significantly. However, despite the widespread use of effective fibrinolytic and antithrombotic drugs and primary percutaneous coronary interventions, mortality in ST-segment–elevation myocardial infarction patients remains considerable. Early reperfusion is essential to limit infarct size but may adversely affect the coronary microcirculation. This study investigated the occurrence of no reflow and microvascular obstruction in consecutive patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary interventions. We provide evidence that, compared with angiographic parameters in the acute phase, cardiac magnetic resonance performed during index hospitalization provides better prognostic stratification of patients.
Identification of High-Risk Patients After ST-Segment–Elevation Myocardial Infarction: Comparison Between Angiographic and Magnetic Resonance Parameters

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