

Microvascular obstruction after primary angioplasty: beyond the epicardial artery

Tim Lockie, Sven Plein and Simon Redwood

The Rayne Institute, Department of Cardiology, St Thomas' Hospital, London, UK

Correspondence: Dr Simon Redwood, 6th Floor East Wing, St Thomas' Hospital, London, SE1 7EH.
E-mail: simon.redwood@gstt.nhs.uk

Sponsorship: Dr Lockie is funded by a Clinical Cardiology Research Scholarship (supported by an unrestricted educational grant from Cordis®).

Conflicts of interest: None.

Abstract

Poor tissue perfusion despite removal of the epicardial obstruction remains a problem after primary reperfusion therapies for acute myocardial infarction. It is related to microvascular vessel damage and is associated with poor myocardial recovery and adverse ventricular remodeling. The process is multifactorial and potentially amenable to a variety of treatments that can be administered at the time of reperfusion. Cardiac magnetic resonance has emerged as a safe and highly accurate means of demarcating the region of infarction and identifying areas of microvascular obstruction within. This is useful, not only to help determine the patient's prognosis, but also to test the efficacy of treatments to reduce microvascular damage and improve left ventricular recovery.

■ *Heart Metab.* 2008;40:26–29.

Keywords: Microvascular obstruction, primary angioplasty, acute myocardial infarction, poor recovery, cardiac magnetic resonance imaging

Case report

A 65-year-old white man was brought to St Thomas' Hospital with a 4 h history of chest pain and lateral ST-segment elevation on his ECG (*Figure 1*). He had no prior cardiac history. He had several cardiovascular risk factors, including type 2 diabetes for which he was receiving oral hypoglycemic therapy, systemic hypertension treated with amlodipine, previous smoking, and a strong family history of ischemic heart disease. On arrival in the hospital, the patient was pretreated with aspirin 300 mg and clopidogrel 600 mg, and coronary angiography was performed via the right femoral artery, with a 6-French gauge sheath. Heparin 5000 IU was administered intravenously. Angiography revealed a left dominant coronary system with a large occluded circumflex coronary

artery. There was minor atheroma in the left anterior descending artery; the right coronary artery was not obstructed.

With the use of an Extra Back-up (EBU) 4 guide, the lesion in the circumflex artery was crossed with a Luge™ angioplasty wire (Boston Scientific®). There was a tight stenosis at the point of occlusion, which was then treated with a 2.5 × 15 mm Maverick balloon (Boston Scientific®). This resulted in Thrombolysis In Myocardial Infarction [1] (TIMI) grade 2 flow in the distal vessel. A 3.5 × 20 mm Liberte™ (Boston Scientific®) was deployed across the lesion, with a good angiographic result. Despite this, the flow in the artery remained poor and the patient continued to have chest pain, with persistent elevation of ST-segments. A bolus of the intravenous glycoprotein IIa/IIIb inhibitor, abciximab (ReoPro™, Eli-Lilly®),

Case report

Microvascular obstruction after angioplasty

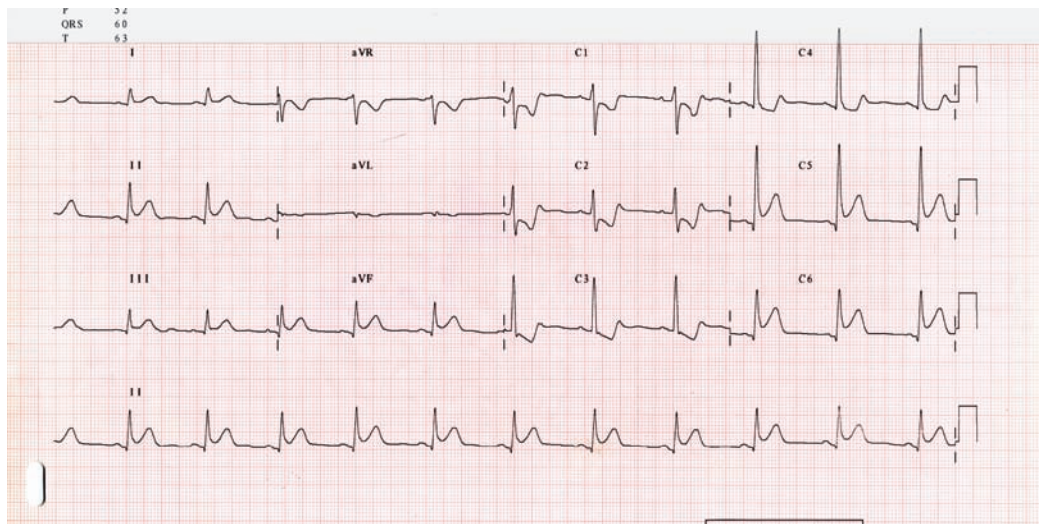


Figure 1. Electrocardiogram showing acute inferolateral myocardial infarction caused by blockage of a dominant circumflex artery, with ST-segment elevation in leads C5, C6, II, III, and aVF, with reciprocal ST-segment depression and T-wave inversion in leads C1–4.

was given and a subsequent infusion commenced. A 1 mg intracoronary injection of isosorbide dinitrate (Isoket™, Schwarz Pharma Limited®) was also administered. Flow remained TIMI 1–2 and the patient continued to suffer chest pain, requiring treatment with intravenous opiates. After 5 min, a further intracoronary bolus of isosorbide dinitrate 1 mg was given, followed by verapamil 20 µg. Eventually, TIMI flow improved to grade 3 and the patient's pain settled. However, myocardial blush grade [2] remained poor, and the ST segments failed to resolve on the surface ECG. The patient remained hemodynamically stable, and was returned to the coronary care unit, where abciximab was continued overnight. The next morning the patient remained well, with no further chest pain. The ECG showed minimal resolution of the ST-segment elevation, with the evolution of significant Q-waves in the lateral leads. The maximum increase in creatinine kinase concentration of 2500 IU/L suggested a moderate/large volume of myocardial infarction.

The patient underwent a contrast-enhanced cardiac magnetic resonance (CMR) study on a Phillips® Intera 1.5 T whole-body system on day 3 after his infarct. First-pass myocardial perfusion was assessed at rest using a novel approach that affords high spatial resolution [3]. Early and late gadolinium-enhanced scans were taken at 2 min and 15 min after intravenous administration of gadolinium-diethylene triamino penta-acetic acid (DTPA) to a total of 0.2 mmol/kg. The perfusion CMR images (Figure 2a) revealed a significant area of hypoenhancement, representing microvascular obstruction at the core of the infarct. This corresponds to the dark areas of non uptake on the late gadolinium-enhanced CMR images, in which

the dense white areas within the myocardium represent infarcted tissue (Figure 2b).

Discussion

Acute myocardial infarction (AMI) and subsequent heart failure constitute a leading cause of death in the UK [4]. Prognosis after AMI is related to the extent of myocardial injury occurring around the time of coronary occlusion [5]. It is known that patients with extensive myocardial infarction are at risk of postinfarction remodeling and heart failure [6]. Early restoration of TIMI 3 blood flow through the infarct-related artery is the main goal of modern treatment [7]. This has led to reduction of infarct size, preservation of left ventricular function, and improved survival [8]. Primary angioplasty is superior to thrombolysis in restoring TIMI 3 flow [9]. Although the restoration of epicardial blood flow does improve the myocardial perfusion of the affected area, the process is not homogenous, and 25–40% of patients have “no-reflow”, with severely impaired perfusion at tissue level despite restoration of TIMI 3 flow in the infarct-related artery [10].

Treatments to reduce microvascular obstruction

Microvascular obstruction is a multifactorial process, and consequently has several potential therapeutic targets. Duration of ischemia is the most important predictor of microvascular obstruction, and therefore prompt revascularization remains the cornerstone of treatment [11]. The release of vasoactive agents such

Case report

Tim Lockie, Sven Plein and Simon Redwood



Figure 2. (a) Cardiac magnetic resonance (CMR) rest perfusion image after contrast injection, showing a lateral wall myocardial perfusion defect (arrow). (b) Late gadolinium-enhanced CMR scan showing corresponding area of microvascular obstruction (dense black area) within the infarct zone (white area).

as serotonin, thromboxane, and leukotrienes, and their resultant coronary vasoconstrictive effects, have been well described [12], and can be partly ameliorated with intracoronary nitrates and calcium-channel blockers [13]. Other intracoronary agents such as adenosine [14] and nicorandil [15] have also been used to improve endothelial function and reduce neutrophil activation. Plugging of arterioles and capillaries with microthromboembolic debris can be treated with heparin and aggressive antiplatelet therapy, including glycoprotein IIb/IIIa inhibitors, which have been shown to improve the likelihood of TIMI 3 flow in patients undergoing primary percutaneous coronary intervention for AMI [16]. The role of distal protection devices and thrombectomy catheters to reduce embolization of debris at the time of percutaneous coronary intervention remains to be determined. Intra-aortic balloon propulsion has also been used to improve flow after percutaneous coronary intervention and is indicated in cases of refractory ischemia or shock [17]. Another area of interest is the concept of “postconditioning”, whereby repeated ischemic stimuli applied in the moments after reperfusion may attenuate reperfusion injury by reproducing the powerful, well established protective effect of ischemic preconditioning. This may improve microvascular function and subsequently reduce infarct size. Large multicenter and outcome trials are awaited, but initial results have been promising [18].

Cardiac magnetic resonance imaging and microvascular obstruction

CMR has emerged as a powerful tool in the assessment of ventricular function, perfusion, and viability in AMI. Its high spatial resolution and reproducibility

make it an excellent tool for assessing ventricular function over time [19]. With the first-pass administration of gadolinium-DTPA, myocardial perfusion can be assessed, both at rest and with stress, in distinct coronary territories and also transmurally within a single coronary territory. Recent advances permit acquisition of myocardial perfusion data with an in-plane spatial resolution of about 1 mm, which allows more detailed delineation of perfusion defects. Hypoenhanced areas in the first few minutes after the gadolinium injection correlate very closely with regions of microvascular obstruction, documented by the use of radioactive microspheres and histological staining of postmortem specimens with thioflavin [20]. Late CMR imaging 10–20 min after gadolinium injection enables precise localization of myocardial infarction (acutely) and scar (chronically) over the full range of infarct size [21].

The pathophysiology of infarct healing and left ventricular remodeling has been studied in a canine model of AMI using gadolinium-enhanced CMR [22]. Infarct healing seemed to be a continuing process, with early infarct expansion followed by infarct resorption, scar formation, and late wall thinning. Necrotic myocytes, interstitial edema, hemorrhage, and inflammatory cells are resorbed and replaced by collagenous scar tissue. In follow-up studies in humans, there was about a 30% reduction in infarct volume at 5 months after primary reperfusion of AMI, with some recovery of function [23]. Segments containing little microvascular obstruction showed good recovery, with improved wall thickening and function. Segments containing microvascular obstruction became thinned and scarred at 5 months, and showed minimal recovery. The presence of severely delayed microvascular reperfusion is predictive of impaired

Case report

Microvascular obstruction after angioplasty

left ventricular systolic function, and is a strong predictor of adverse cardiovascular complications, even after control for infarct size [24].

Summary

Microvascular obstruction after acute myocardial infarction remains a major problem, even after prompt revascularization of the epicardial artery with primary percutaneous coronary intervention. It is associated with poor left ventricular recovery and increased adverse events. There are several potential therapeutic interventions to reduce this damage, but their benefit has been difficult to establish because of the limited techniques available to assess microvascular perfusion and subsequent recovery. With CMR, myocardial scar and microvascular obstruction can be delineated with high spatial definition, using first-pass and delayed gadolinium-enhanced imaging. These methods have emerged as potentially useful imaging techniques with which to investigate the efficacy of both current and novel treatment strategies, and can be used to predict left ventricular recovery after AMI. ■

REFERENCES

1. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med.* 1985; 312:932–936.
2. Gibson CM, Schemig A. Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion. *Circulation.* 2004;109:3096–3105.
3. Plein S, Ryf S, Schwitler J, Radjenovic A, Boesiger P, Kozerke S. Dynamic contrast-enhanced myocardial perfusion MRI accelerated with k-t sense. *Magn Reson Med.* 2007;58:777–785.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet.* 1997;349:1498–1504.
5. Volpi A, De Vita C, Franzosi MG, et al. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation.* 1993;88:416–429.
6. Pfeffer MA, Pfeffer JM, Lamas GA. Development and prevention of congestive heart failure following myocardial infarction. *Circulation.* 1993;87 (5 suppl):IV120–IV125.
7. Simes RJ, Topol EJ, Holmes DR Jr et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation.* 1995;91:1923–1928.
8. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation.* 1992;86:81–90.
9. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med.* 1997; 336:1621–1628.
10. Lincoff AM, Topol EJ. Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation.* 1993;88:1361–1374.
11. Tarantini G, Cacciavillani L, Corbetti F, et al. Duration of ischemia is a major determinant of transmural and severe microvascular obstruction after primary angioplasty: a study performed with contrast-enhanced magnetic resonance. *J Am Coll Cardiol.* 2005;46:1229–1235.
12. Bush LR, Buja LM, Samowitz W, et al. Recovery of left ventricular segmental function after long-term reperfusion following temporary coronary occlusion in conscious dogs. Comparison of 2- and 4-hour occlusions. *Circ Res.* 1983;53: 248–263.
13. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation.* 1994;89:2514–2518.
14. Mahaffey KW, Puma JA, Barbagelata NA, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial. *J Am Coll Cardiol.* 1999;34:1711–1720.
15. Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol.* 1999;33:654–660.
16. Montalescot G, Barragan P, Wittenberg O, et al., for the ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med.* 2001;344:1895–1903.
17. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) – executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation.* 2001; 103:3019–3041.
18. Thibault H, Piot C, Ovize M. Postconditioning in man. *Heart Fail Rev.* 2007;12:245–248.
19. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol.* 2002;90:29–34.
20. Judd RM, Lugo-Olivieri CH, Arai M, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. *Circulation.* 1995;92:1902–1910.
21. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med.* 2000;343:1445–1453.
22. Richard V, Murry CE, Reimer KA. Healing of myocardial infarcts in dogs. Effects of late reperfusion. *Circulation.* 1995;92:1891–1901.
23. Baks T, van Geuns RJ, Biagini E, et al. Effects of primary angioplasty for acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. *J Am Coll Cardiol.* 2006;47:40–44.
24. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation.* 1998;97:765–772.