Infarct angioplasty: beyond stents and glycoprotein IIb/IIIa inhibitors

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The primary goal of treatment in acute myocardial infarction is to salvage jeopardised myocardium, preserve ventricular function, and improve long term survival.[1] Since de Wood's landmark observations ushered in the modern reperfusion era, the main focus of treatment in this field has been on methods to restore blood flow to the ischaemic myocardium. With contemporary angioplasty techniques, normal epicardial coronary flow can be achieved in most patients, and for this reason catheter based reperfusion is now widely accepted as the preferred treatment for acute myocardial infarction (AMI). Despite these advances, however, many patients have relatively poor recovery of ventricular function in the infarct zone, attributable to suboptimal restoration of flow at a tissue level. Mechanisms contributing to this ''myocardial no reflow'' phenomenon are not well understood, but are thought to include ischaemia induced microvascular damage, distal embolisation, and reperfusion injury.[2–6] Studies utilising sensitive measures of myocardial perfusion such as ST segment resolution, contrast echocardiography, and cardiac magnetic resonance imaging have demonstrated worse clinical outcomes in patients with poor tissue level flow.[7–10] These observations have prompted the search for new pharmacologic and mechanical approaches to enhance tissue level perfusion and improve myocardial salvage during reperfusion treatment.

MYOCARDIAL PROTECTION (MECHANICAL)

Systemic hypothermia

Myocardial temperature is an important factor influencing the extent of necrosis after coronary artery occlusion.[11 12] In experimental studies, mild hypothermia has been shown to significantly reduce infarct size (fig 1).[13–15] Cooling appears to protect the myocardium by lowering metabolic demand in the risk region, as well as reducing myocyte apoptosis and increasing production of heat shock proteins. Several innovative endovascular cooling systems have been developed, in which a catheter in placed in the inferior vena cava via the femoral vein to cool the patient centrally.[16] Compared with surface cooling techniques, these systems are advantageous because they permit rapid induction of hypothermia and precise control of core body temperature. In the COOL-MI trial, 395 patients with AMI (< 6 hours from symptom onset) were assigned to undergo primary percutaneous coronary intervention (PCI) with or without adjunctive hypothermia, induced using the Reprieve Temperature Therapy System (Radiant Medical, Inc, Redwood City, California, USA).[18] Cooling was initiated before primary angioplasty (target temperature 33.0 ±0.3°C). Cooling was found to be safe and well tolerated, however the final infarct size at 30 days was similar in both study groups. This result appears to have been related to the fact that most patients in the hypothermia arm received only partial cooling before reperfusion (Δ1.1°C compared to baseline). In secondary analysis, there was a significant reduction in infarct size in patients with anterior wall infarction who were adequately cooled at the time of first balloon inflation. Similar results were found in the multicentre ICE-IT trial.[19] Overall these findings suggest that the heart needs to be cooled optimally before reperfusion for hypothermia to have a cardioprotective effect (table 1). A further study evaluating this novel treatment is currently in progress (COOL-MI II).

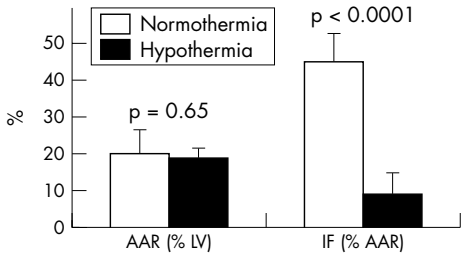

Figure 1 Infarct size in hypothermic pigs and normothermic controls after coronary occlusion and reperfusion. The size of the area-at-risk (AAR) was comparable in both groups, however infarct size (IF) was significantly reduced in the hypothermia group.[15]

Hyperoxaemic reperfusion

Hyperbaric oxygen reduces injury and improves healing in a range of tissues when administered during ischaemia–reperfusion. This therapy was first investigated as a method to limit myocardial necrosis over 40 years ago, but until now has been impractical to implement in patients with acute myocardial infarction. Recently, an innovative system has been developed to deliver hyperbaric levels of oxygen to

Abbreviations: AIMI, AngioJet in acute myocardial infarction; AMIHOT, acute myocardial infarction with hyperoxemic therapy; BOOST, bone marrow transfer to enhance ST-elevation infarct regeneration; CASTEMI, caldaret in ST elevation myocardial infarction; COMMA, complement inhibition in myocardial infarction treated with angioplasty; COOL MI, cooling as an adjunctive therapy to percutaneous coronary intervention in patients with acute myocardial infarction; CREATE-ECLA, clinical trial of metabolic modulation in acute myocardial infarction treatment evaluation-Estudios Cardiológicos Latinoamérica; EMERALD, enhanced myocardial efficacy and removal by aspiration of liberated debris; EVOLVE, a prospective, randomized trial of IV MCC-135 in acute myocardial infarction; ICE-IT, intravascular cooling adjunctive to percutaneous coronary intervention; LOW TEMP, lowering adverse outcomes with temperature regulation; MAGIC, a randomized trial of intracoronary infusion of peripheral blood stem-cells mobilized with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis; NICAMI, non-invasive surface cooling thermoregulator system to induce mild hypothermia in acute myocardial infarction; POZNAN, percutaneous transvenous transplantation of autologous myoblasts in the treatment of postinfarction heart failure; RESEARCH, rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital; TOPCARE-AMI, transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction; XAMINE-ST, X-Sizer in acute myocardial infarction patients for negligible embolization and optimal ST resolution

Table 1 Clinical trials of hypothermia during acute myocardial infarction

Study acronym	Design	Inclusion criteria	Cooling system	No. of patients	Target temperature	Duration of cooling	Primary end point
COOL-MI Pilot[16]	Randomised pilot study	MI <6 h	Reprieve Temperature Therapy System	42	33˚C	3 h	MACE
LOW TEMP[17]	Registry	MI <6 h	Coolgard Temperature Management System	20	32-34˚C	4 h	Infarct size
NICAMI	Registry	MI <6 h	Artic Sun Temperature Management System	11	34˚C	3 h	MACE
COOL-MI[18]	Randomised, multicentre	MI <6 h	Reprieve Temperature Therapy System	412	33˚C	3 h	Infarct size
ICE-IT[19]	Randomised, multicentre	MI <6 h	Celsius Control System	228	33˚C	6 h	Infarct size
COOL-MI II	Non-randomised, multicentre	Anterior MI <6 h	Reprieve Temperature Therapy System	150	33˚C	3 h	Infarct size

MACE, major adverse cardiac events; MI, myocardial infarction.

ischaemic tissue on a regional basis utilising a small extracorporeal circuit (TherOx AO System, TherOx, Inc, Irvine, California, USA) (fig 2).[20] The TherOx System produces Aqueous Oxygen (AO), a physiologic solution of saline and oxygen, which is mixed with the patient's blood to achieve a pO_2 of 600–800 mm Hg.[21] Hyperoxemic blood is then delivered into the infarct related artery via a sub-selective infusion catheter. In animal models of myocardial infarction, hyperoxemic treatment after coronary reperfusion has been associated with less myocardial injury and preservation of ventricular function.[22] Promising results were seen in an observational study at Centro Cardiologica Monzino, Milan, Italy.[23] Consecutive patients with anterior wall infarction were treated with a 90 minute infusion of AO after stenting of the left anterior descending coronary artery. Compared with historical controls, patients treated with AO were found to have an earlier peak creatine kinase, more complete ST segment resolution, and greater improvement in left ventricular function at six months.

The AMIHOT trial was designed to evaluate whether hyperoxemic reperfusion with Aqueous Oxygen would improve ventricular function or limit infarct size after primary PCI for AMI.[24] Two hundred and sixty nine patients presenting within 24 hours of symptom onset were randomised after successful stenting of the infarct vessel to standard care or a 90 minute intracoronary infusion of hyperoxemic blood. The primary study end points were regional wall motion by serial echocardiography, infarct size (SPECT imaging) and ST segment resolution. Hyperoxemic reperfusion was safe and well tolerated, however there was no significant difference in the primary study end points with Aqueous Oxygen therapy. In secondary analysis, there did appear to be a significant treatment benefit in patients presenting within six hours of symptom onset, as well as in

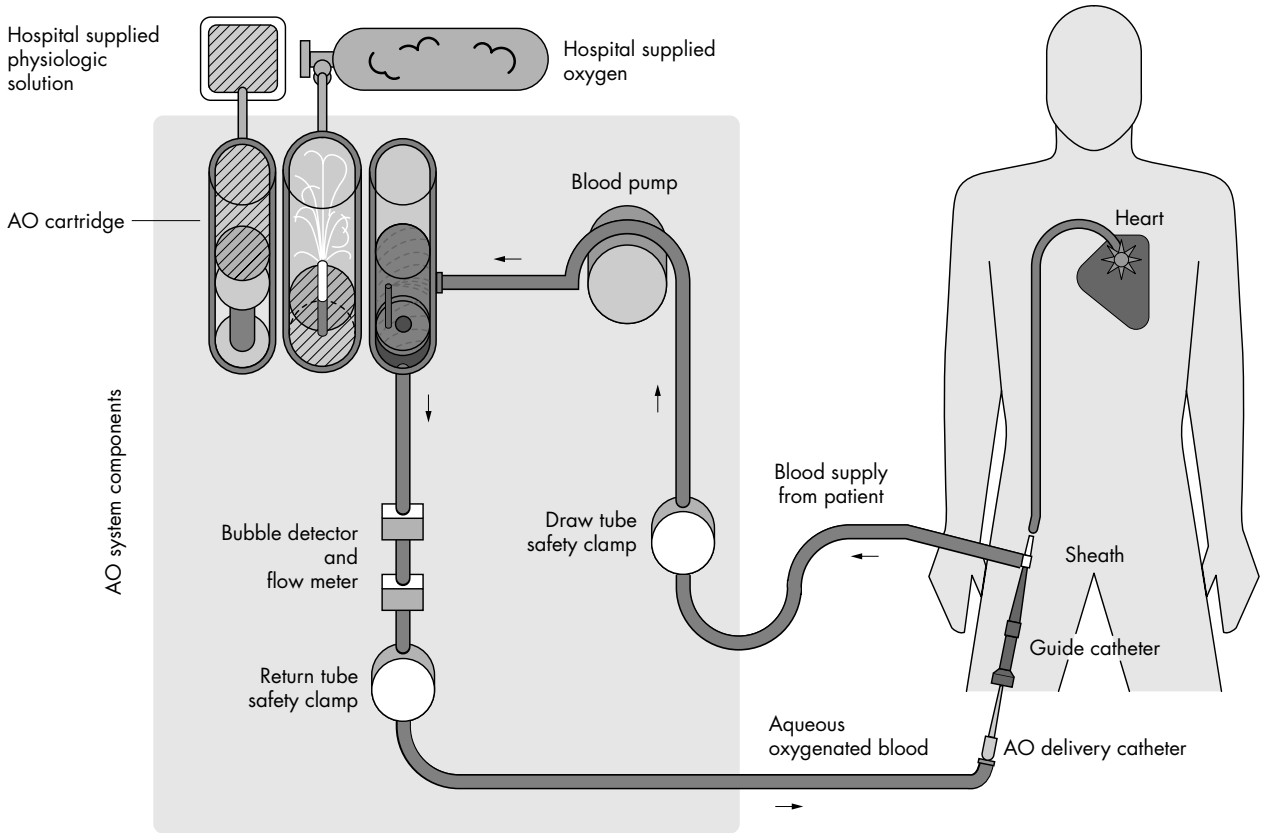

Figure 2 Schematic diagram of the TherOx® Aqueous Oxygen (AO) System.[18]

patients with anterior infarction. A further trial is being planned to confirm these observations.

MYOCARDIAL PROTECTION (PHARMACOLOGIC)

Complement inhibition

Complement activation is an important mediator of inflammatory damage, which is believed to contribute to the reperfusion injury phenomenon. The COMMA trial was performed to determine the effect of pexelizumab, a monoclonal antibody against C5 complement, on infarct size in patients undergoing mechanical reperfusion.[25] In the active treatment arms, two dosing regimens were tested: bolus alone, and bolus plus infusion. The primary end point—infarct size by area under the curve—was similar in each study group. However, there was an intriguing and significant reduction in 90 day mortality in the pexelizumab bolus plus infusion group compared with the bolus alone or placebo group, suggesting that pexelizumab may be beneficial in this setting. A definitive mortality trial (APEX MI) has been initiated to further investigate the effect of this agent in patients with AMI.

Glucose–insulin–potassium

There has been interest in protecting the ischaemic myocardium via metabolic modulation with glucose–insulin–potassium (GIK) treatment. This treatment has a number of beneficial effects at a cellular and biochemical level, including shift of myocardial metabolism from free fatty acids to glucose oxidation and increased adenosine triphosphate synthesis. Prior clinical trials of GIK have had mixed results, in part due to marked heterogeneity in study design, dosing regimens, and reperfusion modality. In a trial conducted by the Zwolle group, 940 patients with AMI undergoing primary angioplasty were randomised to receive a GIK infusion for 8–12 hours or no infusion.[26] Overall, there was no difference in 30 day mortality (the primary end point) between study groups, however there was a significant improvement in survival with GIK in the 856 patients who presented without signs of heart failure (Killip class 1) (1.2% *v* 4.2%, $p < 0.01$). Conversely, a higher mortality was observed in the GIK group in those with heart failure, possibly due to the high volume of the GIK infusion. However, results of the recently presented CREATE-ECLA trial have now settled the question of whether GIK improves mortality in AMI patients.[27] In this trial, the largest study of GIK treatment, 20 201 patients with STEMI presenting within 12 hours from symptom onset were randomised to receive high dose GIK infusion for 24 hours or usual care. Approximately 1800 patients in the trial were treated with primary PCI. At 30 days, there was no difference in all cause mortality (control 9.7% *v* GIK 10.0%, $p = 0.45$), or any secondary outcome measures including cardiac arrest, cardiogenic shock, or reinfarction.

Modulation of intracellular calcium

During myocardial infarction, intracellular calcium overload is thought to play a major role in reperfusion injury. Caldaret (MCC-135) is a novel compound that reduces intracellular calcium concentrations by inhibiting the sodium–calcium exchanger and increasing uptake into the sarcoplasmic reticulum. The CASTEMI trial was performed to determine whether intravenous caldaret would reduce infarct size in patients with ST elevation AMI undergoing primary PCI.[28] In this trial, 387 patients were randomised to either low dose caldaret (57.5 mg), high dose caldaret (172.5 mg), or placebo infusion. At seven days there was no difference in myocardial infarct size or left ventricular function, except in anterior MI patients with TIMI 0 or 1 flow, who were treated with high dose caldaret. A larger clinical trial evaluating caldaret is currently in progress in the USA (EVOLVE).

DISTAL EMBOLISATION

Embolisation of thrombus and atherosclerotic plaque occurs frequently during mechanical reperfusion for AMI, especially in vessels with a large clot burden. Plugging of the distal microvasculature causes mechanical obstruction of flow, but also induces a secondary inflammatory response in the injured myocardium. Accordingly, several techniques have been developed to limit the effects of distal embolisation, including the use of thrombectomy devices and distal protection systems (table 2).

Adjunctive thrombectomy

Two small, randomised studies have demonstrated that adjunctive thrombectomy, using the X-Sizer device, may be beneficial during percutaneous intervention for AMI.[29 30] The X-Sizer device (ev3, White Bear Lake, Minnesota, USA) consists of a catheter with a helical shaped cutter at the distal tip to extract thrombus and soft atheromatous material. In these trials, thrombectomy performed before stent implantation was associated with a lower incidence of angiographic complications such as no reflow, and improved myocardial perfusion assessed by the degree of ST segment resolution or TIMI myocardial perfusion grade.

In the larger AIMI trial, patients were randomised to primary PCI with or without rheolytic thrombectomy using the AngioJet device (Possis Medical Inc, Minneapolis, Minnesota) before stent implantation.[31] Surprisingly, the primary end point (infarct size by SPECT imaging) was higher in the thrombectomy group (12.5% *v* 9.8%, $p < 0.02$) and there was no difference in final TIMI flow, myocardial blush, TIMI frame count, or ST segment resolution between study groups. Moreover, there was a significantly higher incidence of major adverse cardiac events at 30 days in the thrombectomy arm (6.7% *v* 1.7%, $p < 0.01$). These data suggest that routine use of the AngioJet thrombectomy device does not add incremental benefit during mechanical reperfusion. Whether the device is useful in patients with a large thrombus burden needs further investigation.

Embolic protection devices

The introduction of embolic protection devices has been a major advance in interventional cardiology, particularly for the treatment of saphenous vein graft disease. Based on these observations, embolic protection was felt to be a promising strategy to improve outcomes during percutaneous treatment of AMI. In the EMERALD trial, 501 STEMI patients were randomised to primary PCI with or without the 0.028 inch GuardWire balloon occlusion system (Medtronic).[32] The co-primary efficacy end points of the trial were infarct size (measured by ^{99m}Tc-sestamibi imaging) and complete ($> 70\%$) ST segment resolution. Overall, the GuardWire device performed well and visible debris was removed in $> 70\%$ of patients. However, there was no difference in infarct size, degree of ST segment resolution, myocardial blush, or clinical outcomes between the study arms. Given the frequency of distal embolisation in myocardial infarction, these findings were unexpected and have raised questions about the pathophysiologic importance of this phenomenon during mechanical reperfusion. It is unclear whether filters will offer any advantage over balloon occlusion systems, although observational data suggest these devices may be helpful.[33]

DRUG ELUTING STENTS

Although routine stent implantation improves angiographic and clinical outcomes in patients with AMI, restenosis develops in a significant proportion of patients often necessitating repeat revascularisation of the target vessel. Drug eluting stents have been shown to virtually abolish

Table 2 Trials of devices designed to limit distal embolisation during mechanical reperfusion for acute myocardial infarction

	Study design	No. of patients	Primary study end point	Principal results
Adjunctive thrombectomy				
Napodano[29]	AMI <12 h, angiographic thrombus, and TIMI flow ⩽2. Randomised to thrombectomy with stenting or stenting alone	92	Post-procedural TMPG-3	Higher incidence of normal myocardial perfusion after stenting in thrombectomy group (TMPG-3 71.7% *v* 36.0%, p=0.006).
XAMINE-ST[30]	AMI <12 h. TIMI 0 or 1 flow at baseline. Randomised to stenting with or without thrombectomy using the X-Sizer device	201	ST segment resolution	More complete ST segment resolution and lower incidence of distal embolisation in the X-Sizer group
AIMI[31]	AMI <12 h. Randomised to PCI with or without thrombectomy using the AngioJet catheter	480	Infarct size (day 14–28)	Larger infarct size in thrombectomy group (12.5% *v* 9.8%, p<0.02). No difference in final TIMI flow, cTFC, TMPG, or ST resolution. Higher mortality in thrombectomy group
Embolic protection				
EMERALD[32]	AMI <6 h. Randomised to PCI with or without the GuardWire Plus System	501	ST resolution 30 minutes after last angiogram Infarct size (day 5–14)	No difference in ST segment resolution (63.3% GuardWire *v* 61.9% control) or infarct size (median 12.0% GuardWire *v* 9.5% control) between study groups
Limbruno[33]	AMI <6 h and TIMI flow grade <3 undergoing PCI with FilterWire device. Case matched comparison	100	Safety and feasibility of adjunctive FilterWire use	Use of FilterWire safe during PCI. Lower cTFC and higher TMPG after PCI in FilterWire group

AMI, acute myocardial infarction; cTFC, corrected TIMI frame count; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; TMPG, TIMI myocardial perfusion grade.

restenosis in patients with stable de novo coronary lesions, however patients with thrombotic lesions and AMI were excluded from these trials. One of the theoretical concerns about using drug eluting stents in this setting has been the risk of late stent thrombosis. However, recent observational data from the RESEARCH registry suggest that sirolimus eluting stents are safe and also improve clinical outcomes in myocardial infarction.[34 35] At present no data are available with paclitaxel or other drug eluting stent systems. Further studies are required before we can recommend routine use of drug eluting stents in myocardial infarction.

CELLULAR THERAPY

Among newer approaches for myocardial infarction, cell based therapy has generated immense interest as a means of repairing infarcted myocardium. This is based on the notion that circulating bone marrow derived stem cells may home into areas of myocardial injury and differentiate into new cardiomyocytes and vascular tissue. Initial clinical studies evaluated direct intramyocardial injection of autologous skeletal myoblasts during coronary bypass surgery; however, enthusiasm for this approach has been tempered by a high incidence of ventricular arrhythmia. On the other hand, preliminary investigation with bone marrow derived or blood derived stem cells suggest this strategy is safe and feasible after AMI, and may improve left ventricular function (table 3).[36–41] The ideal route of cell administration is unclear, however recent studies have favoured direct intracoronary infusion of the progenitor cells. Mobilisation of peripheral blood stem cells with granulocyte colony stimulating factor (G-CSF) is an attractive alternative to bone marrow cell collection, but observations from one study suggest that G-CSF therapy may aggravate in-stent restenosis.[38] Other important questions that have been raised include the optimal type of stem cells to deliver, quantity and concentration of cells, timing of delivery after injury, and long term safety effects. Although these initial studies have demonstrated some improvement in cardiac function, larger randomised clinical trials will be required to evaluate the efficacy of stem cell therapy in myocardial infarction.

CONCLUSION

Although extraordinary advances have been made in the treatment of AMI, new approaches are required, beyond stents and glycoprotein IIb/IIIa inhibitors, to improve clinical outcome for these patients. At present, the major focus of

Table 3 Initial human experience with stem cell therapy following acute myocardial infarction

Study	Design	No. of patients	Cell type	Delivery	Results
TOPCARE (2002)[36]	Primary PCI for AMI Randomised to BMSC or PBSC	20	BMSC & PBSC	Intracoronary infusion	Stem cell infusion was safe and feasible. Compared to historical controls, patients treated with cell infusion had improved EF and regional wall motion in the infarct zone
Strauer (2002)[37]	Primary PCI for AMI Cell transplant 5–9 days after PCI	10	BMSC	Intracoronary infusion	Intracoronary infusion safe. Compared to non-randomised controls, patients receiving cell infusion had improved cardiac function in the infarct zone
MAGIC (2004)[38]	Primary PCI for AMI Randomised to 3 groups: cell infusion; G-CSF alone; control	27	PBSC after G-CSF mobilisation	Intracoronary infusion	Improved myocardial perfusion, EF, and exercise capacity in patients who received cell infusion, but high rate of in-stent restenosis in patients who received G-CSF
BOOST (2004)[39]	Primary PCI for AMI Randomised to BMSC or control	60	BMSC	Intracoronary infusion	At 6 months, improved EF in bone marrow cell group (6.7% change *v* 0.7% change in controls, p=0.0026). No difference in risk of restenosis, arrhythmia, or adverse clinical events
POZNAN (2004)[40]	Phase I trial of percutaneous delivery of autologous skeletal myoblasts	10	Autologous myoblasts	Intramyocardial injection from cardiac veins	Percutaneous cell delivery safe and feasible

AMI, acute myocardial infarction; BMSC, bone marrow derived stem cell; EF, ejection fraction; G-CSF, granulocyte colony stimulating factor; PBSC, peripheral blood derived stem cell; PCI, percutaneous coronary intervention.

clinical research is adjunct therapies and devices designed to enhance tissue level perfusion and augment myocardial salvage. Therapeutic targets include modulation of myocyte metabolism, and prevention of reperfusion injury or distal embolisation. Several pharmacologic and mechanical strategies have shown promise in clinical trials and are the subject of ongoing investigation. For those patients with irreversible myocardial injury, cell based cardiac repair and regeneration has emerged as a fascinating potential option, which may revolutionise our approach to treatment of heart disease and expand the benefit of catheter based reperfusion.

No conflict of interest to disclose

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