Beyond pharmacology in heart attacks: coronary stents and stem cells

Cheuk-Kit Wong[1], Neal S. Kleiman[2] and Harvey D. White[3]

[1]Dunedin School of Medicine, University of Otago, Otago, New Zealand, [2]Green Lane Cardiovascular Service, Auckland City Hospital, Aukland, New Zealand, and [3]The Methodist DeBakey Heart Center, Section of Cardiology, Houston, Texas and Weill Medical College of Cornell University, New York, New York, USA

Correspondence: Professor Harvey D. White, Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand.
Tel: +64 9 6309992; fax: +64 9 6309915; e-mail: harveyw@adhb.govt.nz

Abstract

The past two decades have been tremendously exciting for clinicians managing patients suffering myocardial infarction, as we defined our understanding of the proximate cause of the thrombotic occlusion of the infarct-related artery, triggered mostly by a ruptured or fissured coronary plaque, with downstream embolism of thrombotic material and resultant myocardial necrosis. This article summarizes developments in non pharmacological therapy with percutaneous coronary artery stenting of the culprit occlusion, and newer approaches in reparative cardiology via stem cell implantation in the infarcted zone. ■ *Heart Metab.* 2007;36:19–23.

Keywords: Myocardial infarction, stem cells, stents

Introduction

The revolution in the management of myocardial infarction in the past two decades can be described by the phrase ''going direct''. The approach that is considered optimal under most circumstances is to proceed as rapidly as possible to direct coronary revascularization, with angioplasty and stenting thus restoring normal coronary perfusion and limiting further damage to the myocardium. However, in many cases, even after reperfusion of the myocardium, recovery of cardiac function is incomplete. As a result, much attention is now focused on ''reparative cardiology'' – that is, trying to reverse myocardial damage through stem cell implantation.

The proximate cause of myocardial infarction is coronary thrombotic occlusion caused by disruption of an unstable (but not necessarily obstructive) atherosclerotic plaque [1]. Complete obstruction of blood flow to the myocardium is usually manifest as ST-segment elevation infarction. When thrombosis is not totally occlusive, or is only temporarily occlusive (ie, non ST-segment elevation acute coronary syndrome), embolization of coronary thrombotic material formed on the ruptured plaque can lead to downstream myocardial cellular damage (*Figure 1*) [2].

The pharmacological management of acute coronary syndromes is fairly well established, but stabilization of the ruptured or eroded plaque requires a mechanical approach. In contrast, regenerating the lost myocardium requires a biological solution.

Evidence favoring percutaneous coronary intervention

In a meta-analysis of 23 randomized trials published in 2003, percutaneous coronary intervention (PCI)

New therapeutic approaches

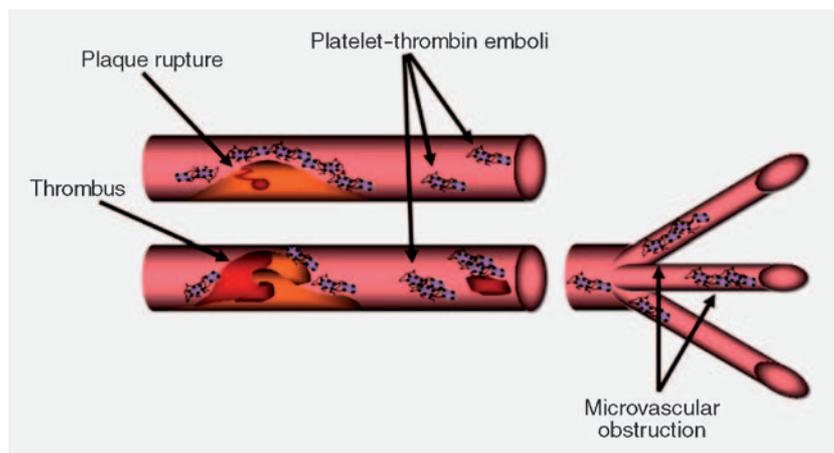*Cheuk-Kit Wong, Neal S. Kleiman, and Harvey D. White*

Figure 1. Plaque rupture with platelet aggregation, thrombus formation, and embolism causing myocardial necrosis. (Adapted from: White [2], with permission.)

was found to be superior to fibrinolysis in treating ST-segment elevation myocardium [3]. A distinct advantage was reduction in recurrent infarction and intracranial hemorrhage. Recurrent infarction after successful fibrinolysis can be interpreted as success of initial reperfusion but failure to maintain patency in the infarct-related lesion. An exception to this paradigm may exist in patients in whom therapy can be started within the first 1 h of the onset of symptoms. In this uncommon situation, the rapidity with which thrombolysis can be started may offer an advantage [4].

The advantage of PCI with stenting is that the plaque material is scaffolded and a wide lumen restored, the latter allowing almost laminar flow, with minimal stasis and turbulence.

It must be emphasized that the symbiosis between the mechanical therapy and the fine-tuning of pharmacological treatments is critically important because, with balloon dilatation and stenting, plaque disruption and exposure of thrombogenic tissue deep within the plaque lead to activation of platelet and coagulation systems. Thus, in the past two decades, we have witnessed an explosion in the development of new medication targeting the different stages of the hemostatic pathway: the glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparins, the direct thrombin inhibitors, and the platelet P2Y12 blockers are the most prominent agents. Of interest, this fine tuning includes managing the balance of risk of bleeding and anti-ischemic efficacy [5]; doses of medications are often the critical factor [6]. Timely performance of primary PCI for ST-segment elevation myocardial infarction is mandatory [7]. The urgency of restoring blood flow to a segment of myocardium that is undergoing necrosis is not present among patients with non ST-segment elevation acute coronary syndromes, but the findings of at least one small study have suggested that earlier implementation of an invasive strategy may result in a more robust reduction in myocardial infarction [8].

Concepts in reparative cardiology

The traditional concept has been that the adult heart is a ''postmitotic organ'' – that is, myocardial growth is accomplished exclusively from hypertrophy of differentiated myocytes, rather than from growth of new myocytes. However, preclinical observations in the past decade have challenged the traditional view and have proposed a new paradigm in which cells in the heart are continuously replaced by newly formed younger populations of myocytes, in addition to replacement by vascular smooth muscle and endothelial cells. Moreover, circulating adult bone marrow cells are able to differentiate into non myelogenous tissue, and may create cardiomyocytes and coronary vessels [9].

Perhaps the seminal observation that challenged the old paradigm was the identification of Y-chromosome-positive myocytes and coronary vessels in female hearts transplanted into male recipients [10]. This finding suggests that circulating cells in the male transplant recipient colonized the female heart and differentiated into myocytes and vascular structures, an important finding consistent with the contention that stem-like cells can migrate to the transplanted heart and give rise to cardiac cell progeny. Subsequent work has led to the identification of a resident pool of cardiac stem cells in the adult heart [11].

Mechanisms of benefit and procedural risks of cellular therapy

Evidence from the clinical trials tends to suggest some degree of efficacy of cellular therapy, although the findings have not been universal across trials, and histologically the question of engraftment of circulating cells versus co-localization of these cells with existing myocytes has not been answered. Two potential lines of benefit from cell therapies exist: contractile capacity

Figure 2. Potential stem cells for cardiovascular repair and regeneration. Cells from various tissues and sources have been used for cardiovascular cell therapy. The contractile and angiogenic capacity and the immunogenicity of these various cells are noted. Endothelial progenitor cells (EP), embryonic stem cells (ES). *Although there are studies demonstrating the persistence of mesenchymal stem cells after infusion into allogeneic or xenogeneic hosts, little is known regarding the host immune response to the recently described multipotential adult progenitor cells. (Adapted from Jolicoeur et al [12], with permission.)

and angiogenic capacity. The latter may be most relevant in patients with severe coronary disease that is not amendable to revascularization, who develop myocardial hibernation. Quite possibly, different progenitor cell types may be better suited to different regenerative tasks, as outlined below (*Figure 2*) [12].

Myocyte regeneration may not be the only or the major mechanism through which contractile function is restored. Animal studies have shown that the bone marrow cells do not engraft into the heart as cardiomyocytes in large numbers, suggesting that such alternative mechanisms as paracrine effects (including secretion of growth factors by transplanted cells, which may stimulate an endogenous repair response), angiogenic effects, or antiapoptotic effects may be operative [12]. Indeed, one hypothesis, the dying stem cell hypothesis, proposed immune modulation as a possible mechanism for the benefit of therapy [13]. In this model, in the setting of cell therapy for acute myocardial infarction, the stem cells that fail to engraft undergo apoptosis and alter the innate and adaptive immunity in the infarcted area, leading to reduced scar formation and reduced myocardial apoptosis.

Recent clinical trials of cell therapies for acute myocardial infarction

Two studies, the Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI) trial [14,15] and the Autologous Stem-Cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial [16], were reported in 2006. Both trials used bone marrow cells delivered through the infarct-related artery to the myocardium. Data from these trials are summarized in *Table I*, together with findings from earlier trials [17].

The discrepant findings between the REPAIR-AMI and ASTAMI trials are intriguing; among other possible explanations are the different number of cells delivered and the different methods of harvesting bone marrow cells. The sensitivity of the different methods for measuring the ejection fraction could also be relevant in explaining the different results, but the absence of a dramatic improvement in ejection fraction in all the studies should be noted.

Future perspectives

Unlike the mechanical treatment of bare-metal coronary stenting, biological stem cell therapy is considerably more complex and requires collaboration between several disciplines, from basic scientists to clinical cardiologists. In the USA, a research network has been established to conduct clinical cell therapy trials. Basic preclinical investigators will collaborate with clinical imaging specialists to measure the efficacy of the technique and to track the fate of cells. It will also be necessary to develop strategies for the application of stem cell therapy in clinical practice, as appropriate.

There remains a considerable lack of understanding about the immunogenicity of stem cells, control of their differentiation, and the best way to introduce them into the damaged heart. However, the use of stem cells has enormous potential for cardiac repair

Table I. Randomized, controlled trials of bone marrow cells for cardiac disease. (Adapted from Rosenzweig A et al [17], with permission.)

Trial or investigator group	Setting	Design	Cells administered in treatment group (No.)	Findings
BOOST [18,19]	PCI after acute myocardial infarction	Randomized trial. 30 patients received BMC; 30 received no infusion. LVEF assessed by MRI	Approximately 2.5×10^9 unfractionated BMC	At 6 months: LVEF 6% greater in BMC group than in control group. At 18 months: no significant difference in LVEF between the two groups
Janssens et al [17,20]	PCI after acute myocardial infarction	Randomized double-blind trial. 33 patients received BMC; 34 received placebo infusion. LVEF assessed by MRI	Approximately 3×10^8 Ficoll-separated BMC	At 4 months: no significant difference in overall LVEF; decreased infarct size and better regional function in BMC group
TOPCARE-CHD [17,21]	Chronic left ventricular dysfunction	Randomized, crossover trial. In the second phase, 24 patients received CPC, 28 received BMC, and 23 received no infusion. LVEF assessed by left ventricular angiography	Approximately 2×10^8 Ficoll-separated BMC or approximately 2×10^7 Ficoll-separated, cultured CPC	At 3 months: greater increase in LVEF (2.9%) in BMC group than in CPC group or control group
ASTAMI [16]	PCI after acute myocardial infarction	Randomized trial. 47 patients received BMC; 50 received no infusion. LVEF assessed by SPECT, echocardiography, and MRI	Approximately 7×10^7 Ficoll-separated BMC	At 6 months: no significant difference in LVEF between the two groups
REPAIR-AMI [14,15]	PCI after acute myocardial infarction	Randomized double-blind trial. 101 patients received BMC; 98 received placebo infusion. LVEF assessed by left ventricular angiography	Approximately 2.4×10^8 Ficoll-separated BMC	At 4 months: greater absolute increase in LVEF in BMC group than in placebo group (5.5% vs 3.0%) At 1 year: reduction in combined adverse clinical events in BMC group compared with placebo group

ASTAMI, Autologous Stem-Cell Transplantation in Acute Myocardial Infarction; BMC, bone marrow cells; BOOST, Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration; CPC, progenitor cells derived from circulating blood; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction; SPECT, single photon emission computed tomography; TOPCARE-CHD, Transplantation of Progenitor Cells and Recovery of LV Function in Patients with Chronic Ischemic Heart Disease.

and regeneration after myocardial infarction, and thus for improvement of patient outcomes. ■

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