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From Reperfusion to Regeneration and Beyond

Review Article

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Abstract

The pathophysiology of AMI is a thrombotic occlusion of coronary artery leading to death of heart muscles. The treatment therefore aims at restoration of the blood supply by reopening the artery that can be achieved pharmacologically as well as mechanically. Done in a timely manner these techniques are able to salvage at best only 2-4% of the myocardium at 6 months. The notion of repairing or regenerating lost myocardium via cell based therapies is highly appealing. At present the important tasks ahead of us are efforts to reduce the myocardial perfusion injury as well as regenerate myocardium which may revolutionize the treatment of AMI. This not only will decrease the mortality but also improve long term survival and quality of life.

Introduction

Reperfusion: A First Step towards Survival

In 1912, James Herrick proposed that acute myocardial infarction (AMI) was due to thrombotic occlusion of the coronary artery [1,2]. The experimental evidence however was obtained from a landmark study in 1980 by Marcus DeWood and colleagues who performed coronary angiography in the early hours of AMI and found coronary occlusion to be present in 87% of patients studied within 4 hours of symptom onset [3,4]. The nature of occlusion was shown to be thrombotic at emergency CABG.

Herrick's hypothesis of coronary thrombosis in acute MI, presented investigators with the theory that thrombolytic agents could potentially prevent or limit the extent of myocardial damage. The treatment of acute MI based on fibrinolysis was proposed in 1958 by Hume R et al. [5]. A basis of reperfusion therapy was laid by the late 1970s in the classical studies by Reimer, Jennings and colleagues [6,7]. In their classical experiments in a canine model of coronary occlusion, myocardial cell death began within 15 minutes of occlusion and proceeded rapidly in a wave front from endocardium to epicardium. Myocardial salvage could be achieved by releasing the occlusion within a narrow time frame (<3-6 hrs). The degree of salvage was inversely proportional to the duration of ischemia and occurred in a reverse wave front from epicardium to endocardium. The extent of necrosis could be modified by changing metabolic demands and varying collateral blood supply as well as the duration of occlusion.

This phase of reperfusion was initiated in 1975 by Chazov et al. who lysed coronary thrombi by infusing streptokinase directly into the blocked coronary arteries of patients with AMI [8]. It was then demonstrated that timely reperfusion actually salvaged severely ischemic myocardium [9]. Although intracoronary fibrinolysis became routine in a few cardiac centers, it was not suitable for widespread adoption for logistical reasons. In 1986, the GISSI investigators, in one of the first cardiac mega-trials, demonstrated a reduction in mortality by streptokinase infused intravenously [10].

The use of fibrinolytic therapy has since been studied extensively in more than 200,000 patients in randomised clinical trials. A pooled analysis of 58 studies (N=14214 angiographic observations) formed the basis for an overall profile of patency rates of several commonly used reperfusion regimens [11]. In the absence of thrombolytic therapy, spontaneous perfusion was observed early after ST elevated MI in 15-21 % of patients at 60-90 minutes after study entry. No further increases were observed within the first day. All thrombolytic regimens improved early patency rates although the speed of thrombolysis varied. Combination therapy with reduced dose of tissue plasminogen activator (tPA) and abciximab improved patency rates further up to 91%. In contrast to varying early patency

with different regimens, patency rates at 3-24 hours and beyond were found to be similar. Reocclusion rates were generally higher after fibrin specific therapy than after nonfibrin agents (13%vs 8%) especially in the absence of optimal concurrent IV heparin [12]. The importance of concomitant heparin for maximising the effect of tPA was demonstrated in an angiographic study by the Heparin and Aspirin reperfusion therapy (HART) investigators [13]. The validity of these composite patency rates generated from many studies of varying design and size including ours [14] was confirmed by a single large GUSTO angiographic study [15]. In this study, rates of complete (TIMI 3) perfusion at 90 minutes were 54% with accelerated tPA, 29% with streptokinase plus subcutaneous heparin and 31 % with streptokinase and IV heparin. Mortality at 30 days was lowest with TIMI 3 flow [4.4%]; highest 8.9% among those with absent flow and intermediate in those with partial. [TIMI 2] flow [7.4%]. GUSTO 1 convincingly demonstrated that the potential of fibrinolytic agents to save myocardium and lives depended primarily on their ability to induce early (90 minutes), complete (TIMI 3 flow) and sustained coronary artery recanalization.

However reperfusion by thrombolysis is an "illusion" created by the imperfect barometer of the static 90 minute angiographic view of coronary patency. Clinical and experimental data clearly demonstrate a sobering deterioration of benefit derived from coronary recanalisation that is not early, nor rapid with incomplete reflow, with critical residual stenosis, decreased tissue level reperfusion, diminished by cyclical patency or frank re-occlusion or possibly negated by reperfusion injury. Relative and absolute contraindications to thrombolytic therapy are also frequently noted e.g. severe hypertension, recent cerebrovascular accident, recent surgery or history of gastrointestinal haemorrhage. Thus appreciation of the limitations of current thrombolytic regimens created a new window of opportunity to enhance the quality of reperfusion therapy for acute MI.

The concept of catheter based reperfusion for STEMI did not truly emerge until Gru¨ntzig's first description [16] of percutaneous transluminal coronary angioplasty (PTCA) followed by pilot experience of Rentrop and colleagues in 1979 with balloon angioplasty to open the occluded infarct artery in 7 patients [17]. The field of catheter based reperfusion for STEMI was subsequently developed through a series of observations and reports from multiple centres as well as randomised trials and was quickly adopted in hospitals worldwide [18]. The trials of catheter based reperfusion compared with fibrinolysis showed the advantage of angioplasty and stenting over pharmacological therapy, even accounting for delays encountered in transporting the patients to PCI facilities. For many years there has been an active debate as to which reperfusion therapy is better. Cumulatively 23 randomised trials in 7739 patients showed an advantage for primary angioplasty in terms of short term reduction of mortality, reinfarction and stroke [19]. Angioplasty saved 20 more lives /1000 as compared to thrombolytic therapy clearly showing the superiority of the treatment. The vast majority of these patients underwent balloon angioplasty, but in recent years the use of stenting has largely replaced balloon angiolplasty. The 1990s brought the development of novel percutaneous coronary interventions (PCIs), particularly the introduction of coronary stents, initially bare metal and later drug-eluting stents following intracoronary balloon inflation to overcome restenosis. As summarised in pooled data of nine trials for primary stenting, the results were better for reduction of reinfarction and repeat target vessel revascularisation [20]. Primary angioplasty may be the preferred approach in patients with extensive MI who have immediate access to a cardiac catheterisation laboratory with experienced personnel. Patients having 1] contraindication to thrombolytic therapy 2] cardiogenic shock 3] prior coronary bypass surgery or 4] stuttering onset of pain are candidates only for primary angioplasty. Poor candidates are those in whom undue delays in access to catheterisation laboratories facilities would be expected or those with complex coronary artery disease including left main disease or a small MI.

Boersma et al. [21] have shown in a systematic evaluation of fibrinolytic therapy that when applied within the first hour of symptom onset, 65/1000 patients treated were saved as compared to only 29 lives saved when given 3 hours or more after infarct onset. Similar results were seen in the GISSI -I trial. [10]. Regrettably, the same studies showed that only a small fraction (3-5%) of patients presented within this golden hour. In contrast, mechanical reperfusion restores flow almost simultaneously with its successful application. Recently, investigators in the stent versus thrombolysis for occluded coronary arteries in patients with AMI (STOP AMI) trial demonstrated that myocardial salvage index was significantly higher for angioplasty than for lysis at any interval from symptom onset and particularly so after the initial 3 hours [22].

Besides early administration of therapy, complete reperfusion (TIMI III) flow in the infarct artery at 90 minutes is also an important predictor of improved outcomes. Even when brisk flow is achieved with lytic therapy, substantial attrition of the benefit occurs because of intermittent patency (25%), reocclusion (13%) and impaired microvascular flow or no Re-flow (23%). This concept of "illusion of reperfusion" reflects our overestimation of the actual rate of complete reperfusion induced by lytic therapy which probably occurs in only 25% of those treated. Because as compared to lytic treatment primary angioplasty is capable of achieving TIMI III flow in at least 15-35 % more patients, it is reasonable to assume that this difference in the patency rates will translate into clinical benefits [23]. In a pooled analysis of 4 PAMI trials Stone et al have shown that mortality at 6 months post angioplasty with TIMI III flow was 2.6 % versus 6.1% with TIMI II flow and 22.2% with TIMI I flow [24]. Further pre angioplasty flow had a significant impact on the ability to achieve successful reperfusion as well as 6 months mortality after angioplasty wherein success rate was 98.1% for TIMI III flow as compared to 91.5% if there was TIMI 0 flow before intervention [25]. This observation becomes very important in considering strategies to facilitate primary angioplasty. Now that we have entered third decade in reperfusion therapy we can expect iterative improvements in all aspects and finally optimal outcomes and reduction in fatality and morbidity and improvement of long term survival of AMI.

Reperfusion injury

Myocardial reperfusion reduces ischemic cell death but it can also injure the surviving myocardium. In the 1960s, well before the first human reperfusion studies were carried out, Jennings RB et al. [26]

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and Krug et al. [27] demonstrated impaired reperfusion after release of a temporary coronary occlusion. Kloner RA et al. [28] reported that reperfusion caused microvascular damage with swelling of capillary endothelial cells and of myocytes, leading to what was termed the 'no reflow phenomenon. Areas of no-reflow have been found to be associated with infarct expansion in animals and a high mortality in patients [29]. Myocardial reperfusion is often accompanied by myocardial injury, commonly known as lethal reperfusion injury. Indeed, in 1985, myocardial reperfusion was referred as 'a double-edged sword [30].

During the past decade, three paradoxes have been incriminated as playing a role in lethal myocardial reperfusion injury [31]. (1) The calcium paradox, which raises intracytoplasmic calcium concentration, (2) the oxygen paradox, in which reperfusion raises myocardial pO2, causing the formation of toxic reactive oxidants and (3) the pH paradox, in which a physiologic pH is suddenly restored in the ischemic zone in which the pH had declined. It has been postulated that these paradoxes are involved in opening a channel in the inner mitochondrial membrane, the so-called mitochondrial permeability transition pore, and that the resultant rapid influx of calcium and reactive oxygen species through these pores damages mitochondria, which in turn fail to synthesize high energy phosphate, thereby leading to myocyte death.

Prevention of lethal myocardial reperfusion injury

The clinical value of ischemic preconditioning local or remote is useful only when the timing of the prolonged ischemia, such as that induced by cardiac surgery or a PCI is known. It is not applicable to patients with the usual AMI in whom the time when the coronary occlusion will occur is of course not known. Many interventions to prevent or diminish lethal myocardial reperfusion injury have been studied [32]. Two are particularly interesting and have shown some promise, both in preclinical studies as well as in small, but intriguing proof of principle clinical trials. The first is an extension of the principle of cardiac preconditioning, in which brief cycles of alternating ischemia and reflow prior to a sustained occlusion reduce the size of the subsequent infarct [33]. It has been observed that this cyclic ischemia can be induced in an organ or tissue other than the heart, yet remain cardioprotective, an intervention termed 'remote ischemic preconditioning [34,35]. The second is pharmacologic conditioning, in which cyclosporin A was infused intravenously just prior to balloon inflation. Following encouraging preclinical studies by Griffiths and Halestrap [36,37] who conducted a three-center clinical trial and showed that Cyclosporin A reduced infarct size. However, 'postconditioning' in which the cyclic periods of ischemia and reflow are begun immediately after the prolonged occlusion is relieved - has also been shown to reduce ischemic injury [38] and it too can be effective when carried out remotely [39]. Conditioning can also be begun during the occlusion and it is then referred to as 'perconditioning' [40]. Most recently aspiration thrombectomy prior to coronary stenting to overcome reperfusion injury has also been implemented [41,42]. The mechanism of protection afforded by these different forms of conditioning appears to be prevention of opening of the above-mentioned mitochondrial permeability transition pore [31]. It has been estimated that timely reperfusion can salvage approximately 50% of severely ischemic myocardium [43] and that prevention of lethal myocardial reperfusion injury should prevent the necrosis of an additional 40%. If the latter is successful, it would further substantially reduce the mortality from AMI [31].

Salvage of Myocardium

The goal of reperfusion therapy is to restore the full nutritive flow and salvage myocardium. However after the introduction of these two modalities of the reperfusion almost 20 years ago, there is very little evidence in the reduction of long term mortality with the current established reperfusion therapies. Rapid reperfusion of the occluded arteries is of great importance in salvaging ischaemic myocardium and limiting the size of infarct. Unfortunately, myocardial necrosis starts rapidly and the "damage is done" largely before patients reach the hospital and before myocardial reperfusion at the tissue level is achieved. Congestive heart failure is the commonest cause of frequent hospitalisation after MI with 50% of the patients dying within 5 years of diagnosis. Despite optimal pharmacotherapy and mechanical devices, the morbidity and mortality remains high. Left Ventricular (LV) function is the single important determinant factor for improved long term survival after an AMI. Contemporary reperfusion strategies using percutaneous interventions are shown to be associated with only modest improvements in global LV function as evidenced by 2% to 4% increase in the ejection fraction (EF) at six months after an AMI [24]. Cardiac transplant seems to be an ideal option for a vast number of these patients, but due to lack of donor hearts cannot meet even a partial demand of it. Other measures like heart assist devices and pacemakers have shown not to prolong the survival and are not cost effective. Various strategies like thrombectomies and distal protection devices have been tried to improve the microvascular dysfunction that occurs after the reperfusion of myocardium but have failed to salvage the myocardium [25]. A host of pharmacotherapies have failed miserably except perhaps high dose adenosine, the story for which is not completely closed. Other modalities like COOl MI, HOT MI, APEX MI and post-conditioning of MI [41,44], have not held any promise as shown by the studies. Given the less than ideal results of salvaging ischemic myocardium so far, recently a great interest has emerged in myocardial regeneration or replacement therapy.

Regeneration: Towards New Life

The dogma that the heart is a terminally differentiated organ incapable of self renewal has been challenged. Although the cells derived from resident cardiomyocytes or circulating cells have regenerating capacity, their ability to minimize the deleterious effects of ventricular myocardial remodeling is limited. The surviving cardiomyocytes bordering the infarct zone becomes hypertrophied as part of adaptive mechanism to compensate for the loss of myocardium. However the normal angiogenesis after the myocardial infarction is insufficient to meet the greater demands for oxygen and nutrients to prevent the apoptosis of the hypertrophied cardiomyocytes. Therefore increasing the perfusion to infarcted myocardium to enhance oxygen and nutrients through the formation of new vessels has the potential to improve the cardiac function. Thus reversal of heart failure would require not only restoration of blood supply but also replacement of myocytes. This can be achieved collectively by stem cells which will increase neoangiogenesis and also replace the

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lost cardiomyocytes by transdifferentiation. Since early reports in experimental models less than 10 years ago [45-50], the stem cell field has made enormous advances in moving towards clinically applicable treatment options, and we are now at the dawn of a new era. These positive results gave way to clinical trials on human beings wherein transplantation of bone marrow cells (BMCs) into the target coronary artery was carried out [51-54]. The results from small clinical studies suggest that therapy with adult bone marrow derived cells reduces infarct size and improves left ventricular functions and perfusion. An extensive meta analysis by Abdel Latiff A et al. [55] on eighteen eligible studies (N=999 patients) involving adult bone marrow cells such as bone marrow nuclear cells, bone marrow mesenchymal cells and bone marrow derived circulating progenitor cells measuring the same outcomes, demonstrated that as compared to controls, bone marrow transplantation improved left ventricular ejection fraction (LVEF) (pooled difference of 3.66%; 95% confidence interval. [CI], 1.93% to 5.4%, P<0.001); reduced infarct scar size (-5.49%; 95%CI: -9.1% to -1.8%; P=0.003); and reduced left ventricular end-systolic volume (LVESV) (-4.8%ml; 95% CI-8.2 to -1.41ml; P=0.006). Further steps required were to carry out multi-centeric randomized large trials targeted to address the impact of intracoronary cell therapy on important outcomes and long term event free survival as compared to the conventional therapy. With this aim Leistener et al. [56] in one of the TOPCARE interim reports and Moccetti et al. [57] in a single-center, open-labelled study have reported that the improvement seen at 6 months in LV functions in ABMSC group was sustained at 24 months including our report [54]. Cardiac regenerative medicine is promising, and a number of clinical trials in humans have already shown its indisputable safety. However, many factors remain unresolved, such as cell type (bone marrow, adipose tissue-derived progenitors, induced pluripotent (iPS) cells, cardiac resident progenitors, or embryonic stem cells), the route of administration (intramyocardial, transendocardial, or intracoronary), and the time of optimal delivery after MI. Several multi-centre trials are on-going in an attempt to answer some of these questions and to prove true benefit in clinical and functional parameters [58,59].

Tissue engineering is also emerging as an option for cardiac regeneration [60]. However, the challenges are enormous, including, selection of the optimal cell source, developing engineered matrices (biological or non-biological; biocompatible or not), establishing the cellular electromechanical coupling, promoting an efficient and stable contractile function, and ensuring functional vascularization [61]. A majority of these experimental processes have only been tested in small animal models. The transposition of a fat flap over the ischemic myocardium has recently been proposed, with promising results in the swine preclinical model of MI [62,63].

Finally, a new avenue being explored is gene therapy, an emerging multidisciplinary field that identifies key signalling pathways, and creates new technologies and novel vector constructs [62,63]. Different routes of administration and viral vectors have been tested in small and large animal models with encouraging results [64]. Preliminary clinical trials have been conducted for delivering AAV1-SERCA2 [65] or AD-HGF [66] through intracoronary infusion, and have reported benefits in patients with severe heart failure.

While current strategies are not enough to salvage the myocardium physicians will have to come out of their mind set of restricting their use to reperfusion modalities and increased use of antithrombotic, anticoagulants and devices to improve the salvage of myocardium. They have to revolutionary think about newer ways which has been elusive in the last twenty years. Every attempt must be made to optimize reperfusion, prevent reperfusion injuries and work on various fronts for regenerating the new myocardium.

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