The Heart Surgery Forum Supplement #2000-03493
4 (Supp 1):S40–S42, 2001

Online address: www.hsforum.com/vol4/supp1/2000-03493.html

Ischemia and Reperfusion Injury of the Myocardium

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(#2000-03493)

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INTRODUCTION

Prolonged interruption of coronary blood flow during heart surgery results in irreversible myocardial cell damage. Interventions such as thrombolysis, emergency percutaneous coronary angioplasty and coronary artery bypass surgery can restore blood flow to affected myocardial tissue. However, restoration of coronary blood flow following acute disruption is also accompanied by a further injurious phenomenon known as myocardial reperfusion injury. This article seeks to highlight the elements involved in this process and possible interventions to reduce its effects.

MYOCARDIAL ISCHEMIA & REPERFUSION INJURY

Myocardial Damage

When myocardial ischemia is limited to periods of less than approximately 20 minutes, reperfusion of the affected tissue will lead to recovery following transient changes in cellular structure, function and metabolism. These changes are manifested functionally as depressed myocardial contractility, which may persist for a variable period. This particular condition is not associated with myocyte necrosis and is often referred to as "myocardial stunning" [Park 1999].

Myocardial reperfusion injury occurs when blood flow is restored after ischemic periods of more than 20 minutes. The end result of this process is myocardial cell death, the extent of which is directly proportional to the duration of the ischemic insult. The histological changes are characterized by explosive cell swelling, calcium deposition, and contraction band formation [Piper 1999]. The release of toxic oxygen species from ischemic tissue on restoration of coronary blood flow, accompanied by alterations in intracellular calcium homeostasis, constitute the most important factors in the production of this phenomenon [Gross 1999]. Other processes involved in the pathogenesis of reperfusion injury include activation of the complement system, as well as neutrophil and endothelial cell activation. Endogenous mediators such as adenosine, nitric oxide, superoxide dismutase, ATP-sensitive potassium channels and the sodium-hydrogen antiport aid in ameliorating the effects of these injurious agents [Mizuno 1997, Vinten-Johansen 1999].

Oxygen radicals are generated at an increased rate in reperfused formerly ischemic myocardium. Species such as superoxide anions, hydroxyl, and peroxynitrite radicals are produced upon introduction of molecular oxygen to ischemic tissue [Ronson 1999]. The subsequent interaction between these molecules and cell membrane components leads to myocardial cell damage and depressed contractile function. This seemingly deleterious effect of restoration of oxygen to ischemic tissue is referred to as the "oxygen paradox" [Park 1999]. The presence of contraction-band necrosis on histological examination is a strong indicator of oxygen paradox injury [Piper 1999].

Myocyte calcium levels have been observed to increase upon reperfusion of ischemic myocardium. Damage to the cell membrane and sarcoplasmic reticulum, possibly by free radical species, results in a net increase in the concentration of intracellular calcium. This results in relative insensitivity of contractile elements to calcium with subsequent depression of myocyte contractility. This phenomenon is known as the "calcium paradox" [Gross 1999, Park 1999].

Immune System Activation

During myocardial ischemia and reperfusion, the immune system is activated through various mechanisms.

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One of the most important is activation of complement pathways, a process that also provides chemotactic stimuli for endothelial adhesion and recruitment of neutrophils to areas of inflammation. Myocardial cell damage follows the release of enzymes and toxic oxygen species from activated neutrophils, as well as complement-mediated cell lysis [Jordan 1999].

Endothelial Dysfunction

The vascular endothelium also plays an important role in the evolution of reperfusion injury. In areas of myocardial damage, increased permeability of the dysfunctional endothelium leads to exudation of capillary fluid with consequent increased blood viscosity and relative stasis of flow. Nitric oxide formation is also significantly reduced in dysfunctional endothelium, resulting in localized vasospasm and disturbed flow distribution [Boyle 1996]. Neutrophils marginate to the periphery of the capillary lumen and adhere loosely to the endothelium via an interaction with endothelial selectins. After rolling along the endothelial surface, neutrophils become more strongly adhered through an interaction between neutrophil integrins and endothelial cell intercellular adhesion molecules (ICAMs). Following neutrophil adhesion, the endothelium serves to provide an initial chemotactic concentration gradient for neutrophils to migrate along toward the inflammatory focus [Asimakopoulos 2000]. The concept of endothelial stunning has been elaborated recently by Buckberg [Mizuno 1997, Buckberg 2000].

THERAPEUTIC PROCEDURES

Since the introduction of cardiopulmonary bypass to cardiac surgery, a variety of procedures have become possible that achieve excellent clinical results. Despite the many advantages gained with this technique, though, significant morbidity has been attributed to the inflammatory response produced. Multiple advances in anesthetic, surgical and perfusion techniques have been implemented in order to protect the heart and the patient from these deleterious effects.

The inflammatory response after coronary artery bypass grafting with the assistance of extracorporeal circulation is primarily due to induced regional ischemia, reperfusion injury to the myocardium and interactions between the patient's blood and the foreign surface of the bypass circuit and the oxygenator [Taylor 1996]. The systemic inflammatory response produced profoundly affects the postoperative recovery of the patient. Systemic changes such as hypotension, renal insufficiency, acute respiratory distress syndrome, leucocytosis, fluid retention, postoperative bleeding and thromboembolic events all occur with increased frequency in patients who have been placed on cardiopulmonary bypass [Ascione 2000]. This in part may also be a reflection of the type of patients being considered for these procedures, as older patients and patients with other co-morbidities are accepted for surgical treatment.

Agents That Reduce Inflammatory Response

Many strategies targeting the main culprits involved in producing the post-bypass inflammatory response have been promoted in order to reduce post-operative morbidity and mortality. Cardioplegic solutions, which were initially employed purely to arrest the heart, are now supplemented with blood, amino acids and other substrates. The addition of intravenous dexamethasone following the induction of anesthesia is used in several centers to diminish the post-operative inflammatory response [Yared 2000]. Adenosine, used as an adjunct to cardioplegic solutions, is now widely considered to have a cardioprotective effect by producing arrest through hyperpolarization of myocardium via KATP channel activation as well as interfering with leukocyte-endothelial cell interactions [Vinten-Johansen 1999]. Heparin-coated circuits have been advocated to reduce the production of inflammatory cytokines, as well as to diminish leukocyte activation and preserve platelet function [Wan 1998]. Aprotinin, a serine protease inhibitor, is thought to exert an anti-inflammatory effect through interfering with leukocyte integrin expression as well as blocking complement and fibrinolytic pathways [Royston 1996, Asimakopolous 2000]. Leukocyte filtration has also been employed as a means of depleting circulating granulocytes, whose role is central in the production of myocyte damage and the systemic inflammatory response [Roth 2000]. Delivery of nitric oxide, or its precursor L-arginine, has been shown to reduce both endothelial and myocyte damage, as well as limit vasospasm in the coronary microcirculation [Mizuno 1997].

Gene Therapy

Gene therapy is currently being evaluated as another possible mechanism for reducing the inflammatory response to cardiac surgery [Boyle 1999]. Organ-specific genetic manipulation allows for local control of mediators within the inflammatory process while incurring minimal systemic effects. Some consideration has been given to these manipulations in order to preserve the myocardium during reperfusion [Allen 1999].

Cardiac Preconditioning

The concept of cardiac preconditioning has been advocated as a further protective measure, where brief periods of ischemia are induced followed by reperfusion, with the aim of increasing production of endogenous inflammatory mediators prior to the more prolonged ischemic periods accompanying coronary revascularization [Perrault 1999]. Preconditioning can be accomplished mechanically with various surgical maneuvers such as intermittent aortic cross-clamping or coronary occlusion. Myocardium can also be preconditioned pharmacologically through the use of such agents as adenosine infused prior to the establishment of cardiopulmonary bypass or as an intra-coronary injection prior to percutaneous coronary angioplasty [Chilian 1999, Vinten-Johansen 1999, Zhao 1999].

Off-pump Surgery

Coronary artery bypass surgery performed without the use of cardiopulmonary bypass has become increasingly popular in recent years. The elimination of the bypass circuit and performing anastomoses on the beating heart has been shown to be associated with a marked decrease in the systemic inflammatory response and its attendant morbidity [Ascione 2000]. Although temporary occlusion of coronary vessels and regional ischemia followed by reperfusion is required, provocation of various inflammatory cascades is greatly diminished by obviating the need for extra-corporeal circulation. Off-pump surgery combined with ischemic preconditioning may significantly reduce operative morbidity and mortality.

Minimally Invasive Procedures

Cardiac procedures performed through less invasive approaches have also demonstrated a reduction in systemic inflammatory response when compared to conventional surgical maneuvers. Minimal direct coronary artery bypass using small thoracotomy incisions and partial sternotomy have been shown to provoke a much smaller inflammatory reaction compared to standard median sternotomy [Czerny 2000]. These alternative procedures, combined with off-pump revascularization, may well represent a future direction in cardiac surgery, particularly in these times of need for shorter lengths of hospital stay and budget constraints.

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