Chapter 19

NHE-1 INHIBITORS: POTENTIAL APPLICATION IN CARDIAC SURGERY

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1. INTRODUCTION

A variety of protective strategies are utilized in cardiac surgery to minimize procedure-induced ischemia/reperfusion injury and secondary myocardial dysfunction. This is of particular importance in acute ischemic syndromes where myocardial protection must also encompass resuscitation of the acutely ischemic or infarcting myocardium. Optimal myocardial protection is also of great importance in complex procedures where there is a need for prolonged aortic cross clamping, in the presence of left ventricular hypertrophy or dilatation as is commonly seen with valvular heart disease, or when extensive coronary disease results in inhomogeneous perfusion. Although there is currently increased interest in coronary revascularization without the use of cardiopulmonary bypass, the majority of cardiac procedures continue to be done with bypass, aortic cross clamping and cardioplegic arrest.

A great deal of scientific study has been undertaken to assess various formulations and modes of administration for cardioplegic solutions (1). Such solutions may be crystalloid or blood-based and may be administered at a range of temperatures. A large number of laboratory and clinical studies comparing the efficacy of crystalloid and blood cardioplegia have generally demonstrated advantages with blood cardioplegic solutions (2), although crystalloid solutions continue to be used in many centers with comparable clinical success. The use of systemic and myocardial hypothermia to
maintain cardiac arrest and decrease myocardial metabolic demand was the foundation upon which myocardial preservation techniques were developed. More recent clinical studies have generally demonstrated excellent myocardial preservation with warm blood cardioplegia (3) and warm or "tepid" cardioplegic solutions are now frequently utilized with minimal systemic cooling in routine cases.

Cardioplegic solutions can be administered antegrade into the aortic root, directly into the coronary ostia, or through saphenous vein grafts sequentially as distal anastomoses are completed. Maldistribution of cardioplegic solutions at the cellular level occurs, however, in the presence of occluded vessels with poor collateral and where use of arterial grafts precludes direct graft perfusion. The use of cardioplegia administered retrograde via the coronary sinus is an additional approach developed to permit more uniform cardioplegia distribution.

The ability to control not only the temperature, timing and mode of administration but also the specific formulation of the cardioplegic solution provides the surgeon with a unique opportunity for a direct pharmacologic approach to cardioprotection. A large body of experimental evidence has demonstrated that inhibition of sodium-hydrogen exchange is protective in the setting of myocardial ischemia/reperfusion, and the ability to inhibit the exchanger pharmacologically is a promising new approach to current myocardial preservation techniques.

2. MYOCARDIAL DYSFUNCTION AFTER CARDIAC SURGERY

Myocardial injury in association with cardiac surgery may result in reversible (i.e. myocardial stunning) or irreversible (i.e. myocardial necrosis) damage. Myocardial stunning refers to contractile dysfunction following reperfusion despite the absence of myocardial cellular necrosis. A range of associated reversible abnormalities have been demonstrated in experimental studies including cellular swelling, impaired calcium homoeostasis, increased capillary permeability, impaired endothelial/microvascular function and ATP depletion (4). Studies suggest that the production of toxic oxygen metabolites (5), cellular calcium overload (6) and cardiac troponin I proteolysis (7) are important etiologic factors.

Such reversible dysfunction is known to occur in patients undergoing cardiac surgery. For example, Fremes et al (8) demonstrated a significant improvement in left ventricular function between 6 and 24 hours postoperatively in coronary bypass patients managed with cold crystalloid cardioplegia. This improvement could not be ascribed to alterations in preload, afterload or body temperature. Similarly, Breisblatt et al (9)