Changes in the intracellular concentration of myocardial glutamine in patients undergoing coronary artery bypass surgery using crystalloid and blood cardioplegia

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Recent years have witnessed an increased interest in the role of myocardial intracellular free glutamine pool and its transport across the sarcolemma [e.g. 1-4]. In other tissues, including skeletal muscle, glutamine has a plethora of functions which include donating nitrogen for the biosynthesis of a number of important compounds such as nucleotides and amino acids [1,5] and an anabolic effect as demonstrated by regulating protein and glycogen metabolism [1,2,6]. Furthermore studies with several cell lines have shown that glutamine is an essential requirement for optimal proliferation and a major source of energy for cultured cells [7-9].

The intracellular concentration of glutamine in mammalian heart cells is different in different species. In both guinea-pig and ferret hearts, glutamine constitutes approximately 10% of the total free amino acid pool [3 and Suleiman et al. unpublished data] whilst in the hearts of patients with ischaemic disease, glutamine makes up more than 25% of the pool [4]. In isolated Langendorff guinea-pig hearts, intracellular glutamine levels are influenced by different experimental conditions and its efflux is faster than efflux of other amino acids [10]. The changes in glutamine may be the net result of changes in metabolism, transport and in the rate of protein synthesis and degradation. Mounting evidence, however, suggests a Na-dependent transport mechanism is responsible [3,4,10 and Suleiman et al. unpublished data].

During coronary artery bypass surgery, where the heart is arrested using cold crystalloid cardioplegia i.e. conditions that render the heart both ischaemic and hypothermic, a rise in intracellular Na+ concentration is likely to occur [4]. Under these conditions the left ventricles of patients show a fall in intracellular glutamine concentration [4]. This fall was attributed to a Na+-dependent symport mechanism. In this study we compared the effects of cold blood and cold crystalloid cardioplegia on intracellular glutamine concentration in ventricular biopsies taken from patients undergoing coronary artery bypass surgery.

Patients were randomised to one of two accepted techniques of myocardial protection: antegrade cold (4°C) crystalloid St Thomas' 1 cardioplegic solution (20 mM K+) or cold (4°C) blood cardioplegic solution (20 mM K+) containing blood and St Thomas' 1 cardioplegic solution (4 blood : 1 crystalloid).

Cardioplegia was administered as a 1 litre bolus at the beginning of the ischaemic period. Infusions were repeated at 30 min intervals or earlier if electrical activity resumed. Preoperative and intraoperative variables for the two groups were comparable. Myocardial biopsy specimens (4-10 mg wet weight) were taken from the apex of the left ventricle using a "Trucut" needle. The first biopsy was taken immediately (approx. 5 min) after institution of cardiopulmonary bypass and a second biopsy was taken after 30 min of ischaemia. The study was approved by the hospital ethics committee and patients informed consent obtained. Glutamine levels in tissue and plasma were determined as described elsewhere [11]. Although tissue concentration was expressed per wet weight, a similar trend was also obtained when values were expressed per protein concentration.

The resting levels of glutamine measured in the first biopsy was 8.5±0.5 mmol/kg wet weight (n=18) and 8.3±0.5 mmol/kg wet weight (n=12) for crystalloid and blood groups respectively. The concentration of glutamine in the plasma was 0.42±0.02 mM for crystalloid and 0.44±0.02 mM for blood cardioplegia. This provides a resting concentration gradient of approximately 20 fold across the sarcolemma. In an earlier study [4] we have shown that ischaemic arrest with cold crystalloid cardioplegia provoked a fall in glutamine intracellular concentration in ventricular biopsies collected after periods exceeding 40 min. In this study we show a significant fall only after 30 min of hypothermic ischaemia using crystalloid cardioplegia (Figure 1). In contrast to crystalloid cardioplegia, ischaemic arrest using blood cardioplegia did not induce a significant fall in intracellular glutamine concentration (Figure 1). In a small number of patients, when the ischaemic period was extended beyond 40 min, a third biopsy was collected (data not shown). In these biopsies the fall in crystalloid group was maintained whilst in the blood group there was a small insignificant fall. Blood cardioplegia contains glutamine which would oppose the amino acid efflux. This suggests that the fall in glutamine is due to efflux induced by the absence of glutamine from the crystalloid cardioplegia. However we have recently studied the effect of the two myocardial protection techniques on ATP levels (Suleiman et al. unpublished data). A significant fall in ATP was only seen in the crystalloid group. The fall in ATP will result in a rise in intracellular Na+ concentration by way of inhibiting the Na-pump. This work suggests that the fall in myocardial intracellular glutamine concentration during arrest using cold crystalloid cardioplegia is due to efflux provoked by the absence of the amino acid from the crystalloid solution and by a rise in intracellular Na+ concentration. This fall was prevented with cold blood cardioplegia as the presence of extracellular glutamine and a reduced rise in intracellular Na+ concentration will oppose glutamine efflux.

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Figure 1. Changes in glutamine intracellular concentration, measured using an HPLC, in biopsies taken from the ventricles of patients undergoing coronary bypass surgery using cold crystalloid (n=18) or blood cardioplegia (n=12). The first biopsy was taken before ischaemia and the second taken after 30 min of ischaemia.

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