HEART

Editorial

Detection and prevention of myocardial damage during open heart surgery

Perioperative myocardial injury is a major cause of morbidity and mortality after open heart surgery. Advances in myocardial protection and a greater understanding of the mechanisms of cellular damage have been central to the improving results of adult and paediatric cardiac surgery. The development of reliable methods to quantify the degree of perioperative myocardial injury is of particular importance for the evaluation of different cardioprotective, operative, anaesthetic, and perfusion strategies.

Assessment of myocardial damage
A range of different methods of assessing myocardial injury are available, each with individual advantages and limitations. Clinical end points such as myocardial infarction or death are of paramount importance and differences in these are most likely to influence clinical practice. However, their infrequent occurrence means that power calculations for clinical studies indicate a requirement for large study populations. This limits their practical use in routine low risk patients.

A number of indicators of myocardial damage can be used as surrogate markers of clinical outcome. These include measures of cardiac dysfunction derived from haemodynamic data obtained using pulmonary artery catheters or by transoesophageal echocardiography. Alternatively, the measurement of biochemical markers such as creatine kinase MB isoform or cardiac troponin T or I offer methods which can be used to "quantify" the severity of myocardial injury. Sophisticated research laboratory based end points have also been used, including changes in cellular ultrastructure, high energy phosphate levels, and membrane degradation products. Care is required, however, when the results obtained from these surrogate measures are extrapolated to changes in clinical practice: statistically significant differences are not necessarily clinically important or relevant differences.[1]

Biochemical markers
Biochemical markers to quantify myocardial injury have been widely used in cardiological and cardiac surgical practice. Their sensitivity and specificity are affected by a number of factors including molecular size, cellular location, solubility, release ratio, clearance, ease of detection, and specificity for irreversible myocardial injury. In the surgical patient, the relative cross reactivity with either identical markers or their isoforms released from damaged skeletal muscle severely limits the application of many of them because of the subsequent lack of specificity that results.

More recently, serum troponin assays have been identified as specific and sensitive markers of both clinical and subclinical myocardial cell injury.[2] The troponins (T, I, and C) are a group of intimately related regulatory proteins located in striated muscle. In cardiac muscle, they are tightly bound to the contractile apparatus and plasma concentrations are therefore extremely low. With acute myocardial injury, there is a biphasic release of troponin into the serum. Troponin in the cell cytoplasm is released within three to five hours after loss of membrane function. A late phase of continued release of troponin for five days or more is associated with destruction of the contractile apparatus and cell death. The sensitivity of the troponins for the evaluation of myocardial injury is greater than that of CK-MB because of the wide diagnostic window that they possess. More impressive than this is the specificity of these proteins for myocardial injury even in the face of skeletal muscle injury. It is known that sternotomy alone does not produce a detectable increase in troponin T.[3] Although there is some cross reactivity between the myocardial and skeletal isoforms of troponin T, modern monoclonal assays are able to reduce this to less than 1%.[4]

Current trends in myocardial protection
A number of techniques are currently in clinical use for protecting the heart during cardiac surgery. Most surgeons use high potassium cardioplegic solutions to arrest the heart, though a few continue to use intermittent periods of ischaemia with fibrillation, particularly for coronary artery surgery. The proponents of particular methods provide scientific data to suggest superior performance of one technique over another by comparing various surrogate end points, but consistently fail to demonstrate improvements in major clinical end points for the reasons alluded to earlier. However, the studies of Buckberg and associates in Los Angeles serve as a beacon to investigators in this area because they demonstrate the application of basic science and clinical studies to the advancement of clinical practice.[5 6] Based on these persuasive studies there has been a shift from the use of cold crystalloid cardioplegia administered at intervals via the aortic root during the ischaemic period to more complex techniques using blood cardioplegia administered anterogradely and retrogradely via the coronary sinus with both warm and cold solutions with, when indicated, additives such as amino acids to act as energy substrates and agents to ameliorate reperfusion injury.[5 6]

The realisation that electromechanical arrest reduces the oxygen demands of the myocardium by up to 90%, with only a small further reduction[7] produced by hypothermia, has led to a reversal in the concept that cooling the heart is necessary for safe myocardial preservation. Continuous normothermic cardioplegic arrest with blood avoids the potentially damaging effects of hypothermia on

cellular integrity, and has been shown to be at least as safe as hypothermic regimens.[8] Inadequate delivery, related to the presence of coronary stenoses remains a concern, which is partially alleviated by concurrent retrograde administration of cardioplegia. However, there is scope for further definition of the scientific basis of this method.

There is increasing recognition that ongoing ischaemia, particularly in unstable patients, may be associated with evidence of myocardial damage immediately before surgery. This critical period for potential intervention is often neglected by surgeons who rely upon the expertise of their anaesthetic colleagues to minimise the oxygen requirements of the heart, by the avoidance of stress induced catecholamine release, arterial hypertension, and tachycardia. The study by Boldt *et al* on page 207 of this issue of the journal identifies, on the basis of changes observed in a number of biochemical markers including troponin T, the potential cardioprotective effects of prophylactic infusion of enoximone and enalaprilat before cardiopulmonary bypass in patients undergoing coronary revascularisation. The inclusion of patients with clinical evidence of perioperative infarction in the control and clonidine groups creates some difficulties since the release of troponin in established infarction is comparatively so great that the data are inevitably skewed in the groups containing such patients. The incidence of perioperative infarction after coronary artery surgery is multifactorial and although randomisation should distribute these influences equally between the groups, small population sizes do not allow for this. Therefore, while serum troponin measurements can be used in the assessment of subclinical myocardial damage and in the diagnosis of established infarction, analysis of the results in both groups of patients must be undertaken separately. Although the findings of the study do not provide a platform for the alteration of clinical practice, a number of agents with potentially cardioprotective actions are being evaluated and further developments in this area are awaited with interest.[9]

A second study, also in this issue (page 214), exploits the value of serum troponin assays as markers of myocardial injury in association with paediatric cardiac surgery. Taggart *et al* measured serum myoglobin, CK-MB, and troponin T and I in a group of patients undergoing paediatric cardiac surgical procedures of varying complexity and in controls undergoing thoracotomy only. This study confirms the specificity of the cardiac troponins as markers for the presence of myocardial injury, with the largest increases being observed in patients undergoing the arterial switch operation or repair of ventricular septal defects. The values are much higher than those reported in other studies in adults,[10] although they are similar to the concentrations reported in a paediatric population.[11] Taggart *et al*'s conclusion, based on these findings, that paediatric myocardium exhibits reduced tolerance to ischaemia may be somewhat premature and comparisons with adult patients undergoing coronary artery surgery may be inappropriate. Little is also known about how the distribution and cellular kinetics of troponin in paediatric myocardium differs from that of adult myocytes. Immature myocardial cells differ considerably from adult cells both in terms of their physiological adaptation to adverse conditions, but also in their contractile architecture. Whether or not these differences in cellular morphology have an important effect upon the magnitude of troponin release is not known.

Data obtained from animal studies suggest that the normal paediatric myocardium, with its initial dependence on glycogen and its facility for anaerobic metabolism possesses some increased resistance to perioperative ischaemia and reperfusion compared with the mature cell.[12] Under these conditions, improved calcium exchange and high energy phosphate production, improved mechanical function,[13] and more efficient glycolysis and transamination of amino acids occurs.[14] However, children undergoing paediatric cardiac surgery have abnormal myocardial physiology. The presence of cyanosis accelerates the damaging effects of myocardial ischaemia[15] and is associated with an abnormal coronary collateral circulation which results in increased cardioplegia washout. In addition, depending on the procedure, the use of profound hypothermia and circulatory arrest and variation in the amount of direct myocardial excision or manipulation may increase the degree of myocardial injury.

In summary, there are a number of ways of assessing myocardial damage during open heart surgery and both cardiac troponin T and I have emerged as highly sensitive and specific markers of even subtle degrees of injury. The practical clinical importance of such differences is still being defined. Problems can arise with data interpretation in subjects with coronary artery disease when studies designed to evaluate subclinical injury are complicated by patients with overt infarction and its associated massive release of such biochemical markers. Investigators using these markers need to temper their enthusiasm with a clear understanding of not only the potential value, but also the pitfalls and limitations of their application and extrapolation to clinical practice.

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