Adenosine in heart transplants: have we finally found the good indication?

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It is well recognized that donor age is a risk factor for graft failure after cardiac transplantation. Lim et al. [1] have thus addressed a clinically relevant issue in testing the effects of a shot of adenosine given prior to cardioplegic arrest in a syngeneic rat model of heterotopic transplantation. Basically, their results show that, in comparison with control hearts that were arrested by the Celsior solution, those pretreated by adenosine (regardless of the dose: 0.1 or 0.2 mg/kg) arrested and recovered more rapidly after 6 h of cold static preservation, which was associated with a higher myocardial content of high-energy phosphates, a decreased release of biomarkers of myocardial injury, a decreased upregulation of some inflammatory cytokines (assessed by real-time polymerase chain reaction) and a reduced infiltration of macrophages.

The search for the two keywords ‘adenosine’ and ‘myocardial protection’ in PubMed yields a list of 175 papers, of which the oldest dates back to 1975. This clearly illustrates the longstanding interest generated by the use of this compound for reducing the detrimental effects of ischaemia on the myocardium, and adenosine, for example, is considered as a key mediator of preconditioning, which still remains one of the most powerful strategies for mitigating the deleterious effects of ischaemia [2].

The present paper provides additional evidence of these cardioprotective effects of adenosine in the clinically relevant setting of heart transplantation. While the authors demonstrate these benefits on a combination of end points, the mechanism(s) by which adenosine potentiated the effects of Celsior-associated protection still remain elusive. In this context, however, one possible mechanism may have been the ability of adenosine to induce polarized arrest, or at least, to reduce the magnitude of high potassium-triggered depolarization. Membrane depolarization provides a pathway for calcium to enter cells, and calcium overload has long been recognized as a major hallmark of severe ischaemic injury. Indeed, the combination of adenosine and lidocaine has been shown to provide superior protection during an extended period of cold static storage [3], which was largely attributed to maintaining the cell membrane closer to its polarized state. Whether this effect, which was obtained at a higher dose (400 µmol/l) than that used in Lim’s study, was operative in the present experiments cannot be determined because of the lack of electrophysiological measurements, but is nevertheless suggested by the quicker time to arrest displayed by the adenosine-injected hearts prior to cardioplegic arrest. Another protective mechanism of adenosine is a reduction in the inflammatory response [4], which may have been relevant to the present blood-perfused model and is indeed consistent with the finding of a reduced macrophage infiltration along with a decrease in some inflammatory mediators. Another interesting finding of this study is the downregulation of mitogen-activated phosphorylated kinase (MAPK) 38. Activation of this kinase has been linked to ischaemia–reperfusion injury and, comparatively, the present data are consistent with earlier findings that p38 MAPK inhibition improves the preservation of cardiac [5], lung [6] and hepatic [7] transplants. These data are also in line with the reduction of p38 MAPK induced by ischaemic preconditioning [8] as p38 MAPK might induce apoptosis in an isoform-specific fashion. Thus, it is likely that several mechanisms are at play to account for the beneficial effects of adenosine pretreatment seen in these experiments.

As appropriately indicated by the authors, a major limitation of the present experiments is the lack of functional data, which precludes the assessment of whether, and to what extent, the favourable biochemical changes that were observed translated into meaningful haemodynamic improvements. It should, unfortunately, be remembered that clinical trials of adenosine in cardiac surgery have not so far been very successful and that, in particular, the most recent one, which tested the effects of an adenosine-regulating agent (acadesine) in a large patient population, failed to demonstrate a benefit compared with a placebo-injected group [9]. Likewise, a previous phase II trial had primarily demonstrated the safety of giving adenosine as an adjunct to blood cardioplegia, but despite some hints of efficacy, had failed to demonstrate a reduction in dopamine use or overall inotropic use, two of the proposed primary end points [10].

Despite these limitations, the authors should be complimented for bringing to our attention that it may be timely and appropriate to reconsider the use of adenosine in situations where particularly meticulous myocardial protection is made mandatory by the vulnerability of the heart, as occurs when cardiac grafts are harvested from elderly donors. The relevance of using adenosine in this context is strengthened by the fact that a pretreatment in brain-dead donors should be relatively easy to implement. Beyond recommending the drug itself, the merit of this paper lies also in reminding us of the likely benefits of counteracting the potential deleterious effects of hyperpotassic solutions by reducing the extent of the membrane...
depolarization that they trigger and the attendant tissue-damaging calcium overload.

REFERENCES