We thank Dr. Alhan et al. for their constructive and important comment on our study [1]. They highlighted some relevant limitations [2] of this small randomized trial which we aim to address in our response in part. Alhan et al. have correctly asked for some unreported preoperative factors such as the ejection fraction, the pre-OP medication, including angiotensin-converting enzyme inhibitors, and the longevity of diabetes which are reported factors associated with postoperative cognitive dysfunction. We intended to exclude the possible bias by means of the study’s randomized fashion and analysed these factors. The medication, the preoperative ventricular function and EuroSCORE were identical in the two groups. The most important limitation of this trial (as correctly stated by Alhan et al.) is the small size of the cohorts. More important questions with better defined secondary endpoints can only be answered in a bigger randomized multicentre trial. Factors such as the mentioned neurochemical markers, more meaningful values derived from transcutaneous oxygen saturation must be included in a future trial as well as the intermediate and possibly late cognitive outcome measures. We hope that Alhan et al. and other readers will like to participate in the planning and conduction of such a trial. This type of input is crucial to derive more valid knowledge about the association between pressure, microperfusion and postoperative cognitive dysfunction in surgery with the use of cardiopulmonary bypass.

REFERENCES


LETTER TO THE EDITOR

Reviewing α-Gal in valve immunology

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Calcification of bioprosthetic heart valves is an unsolved problem ever since. Lim et al. [1] recently made another attempt to improve tissue performance by applying the novel fixation agent genipin. Numerous efforts of chemical tissue pretreatment have been tested, but up to now, the longevity of biovalves has not substantially increased, especially not in young recipients. Our group has shown that the implantation of biovalves causes an increase in anti-Gal immunoglobulin M and immunoglobulin G (IgG) titters in patients [2, 3]. Thus, we suggested a mechanism of chronic xenograft rejection and consecutive calcification via that anti-Gal response. The α-Gal barrier is known to prevent xenotransplantation from suitable animals to humans, because humans and old world monkeys are the sole mammals which produce anti-Gal antibodies in high titers and lack the α-Gal epitope [4]. Since recently, biovalve researchers perceive the problem of α-Gal antigenicity in glutaraldehyde-fixed biovalves, and α-Gal knockout pigs are proposed as a possible source for valve tissue [5, 6].

Lim et al. [1] delivered a concise report on the use of the cross-linking agent genipin in the pretreatment of bovine pericardium and evaluated calcification in a rabbit intramuscular transplantation model. They proved the superiority of genipin over glutaraldehyde to prevent tissue calcification in a clear sequence of experiments. However, their interpretation of the α-Gal barrier in their setup is disconcerting. They implanted bovine tissue into a rabbit muscle and measured anti-Gal IgG antibodies in plasma before, 12 and 60 days after implantation. Genipin-treated tissue recipients showed significantly lower anti-Gal IgG titers than glutaraldehyde-treated tissue recipients. Furthermore, they showed that decellularization of tissue before implantation abolished this titer increase. But rabbits do not have any α-Gal antibodies, as they express the α-Gal epitope themselves; at least according to the present opinion. How are these results possible then? The authors do not give a clear statement; they indicate an explanation by not correctly citing Macher and Galili [4], saying ‘the differences in the fine specificity of natural anti-Gal in various species may cause the multiple B-cell clones to produce anti-Gal antibodies which have specificities that differ slightly from each other, and thus recognize various facets of the α-Gal epitope in its three-dimensional form’. But Macher and Galili never mention ‘various species’, they merely speak of anti-Gal varieties among individuals. Do the authors suggest differing α-Gal epitopes among different species? This is unlikely, as the sequence homology of α1,3GT is very high among a wide range of species [4]. If uniform Gal epitopes are assumed, one would expect autoimmunologic affection in animals with elevated anti-Gal titers; did the transplanted animals show any signs of systemic inflammation?

Most of the researchers who measure anti-Gal antibodies use self-established ELISAs with internal or no standards. Such ELISAs require extensive titration steps to yield a reliable technique that is suitable for publication. Reevaluation and verification of the results of Lim et al. should be considered.

REFERENCES


LETTER TO THE EDITOR RESPONSE

Reply to Mangold and Ankersmit

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