function is key to understanding the working mechanisms of SVR and explain the somewhat variable reported success.^{3,4} The pathophysiology of the selected patients, the details of the surgical intervention, such as the amount of volume reduction, the applied additional surgical interventions, and the interactions between these factors, all could “tip the balance.” Identification and quantification of the specific effects of SVR on the various components of cardiovascular function ultimately might help to select optimal candidates and potentially to further optimize this intervention to put more weight on the positive side and lift the negative side.

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CARDIAC XENOTRANSPLANTATION TECHNOLOGY PROVIDES MATERIALS FOR IMPROVED BIOPROSTHETIC HEART VALVES

To the Editor:

In their recent article published in the *Journal*, McGregor and colleagues¹

provide further evidence that bioprosthetic heart valves (BHVs) constructed from wild-type (genetically unmodified) porcine or bovine sources are less than optimal, as previously reported and discussed by others.²⁻⁵ Because of the expression of Gal α 1,3Gal (Gal), and possibly other porcine or bovine antigens, they are susceptible to inflammation, calcification, and failure.

The model used by McGregor and colleagues is not ideal. (1) The pig tissue was implanted into the subcutaneous tissue of the recipient, and therefore was not in direct contact with blood (in which anti-pig antibodies circulate). (2) The pig tissue was coated with anti-Gal antibody before implantation, rather than being continually exposed to anti-pig antibodies (which are continually being produced by a human recipient, which is not the case when a Gal-positive animal, eg, rat or rabbit, is used as the recipient of the graft). (3) The pig graft was exposed only to anti-Gal antibodies and not to other human anti-pig (anti-non-Gal) antibodies. Nevertheless, despite these limitations, the authors clearly demonstrate the detrimental effect of using porcine or bovine tissues that are susceptible to human anti-Gal antibodies and make a strong case that tissues from α 1,3-galactosyltransferase gene-knockout (GT-KO) pigs, which do not express Gal, should be the sources of BHVs, as suggested previously.²⁻⁵

As the authors point out, GT-KO mice and pigs, both of which make anti-Gal antibodies (and therefore mimic humans in this respect), are now readily available for future experimental studies. However, despite the reservations the authors express, the pig-to-nonhuman primate model would clearly be the optimal model. Indeed, studies have already clearly shown that GT-KO porcine tissues elicit a weaker inflammatory response than wild-type (unmodified) pig tissues when implanted into nonhuman primates.⁶

However, why limit clinical trials to the use of tissues from GT-KO pigs, when GT-KO pigs that express one or more complement-regulatory proteins (eg, CD46, CD55) are also available? The expression of a complement-regulatory protein would almost certainly protect the tissues further from immune injury, particularly because there will also be a response to non-Gal antigens. Furthermore, pigs are also becoming available that express human anti-inflammatory or antithrombotic transgenes (eg, CD39 or thrombomodulin), which are likely to provide even greater protection. It can realistically be concluded that survival of BHVs from such genetically engineered pigs would be extended significantly.

The biggest hurdle to the use of genetically engineered pigs as sources of BHVs, despite compelling reasons to do so, would seem to be related to business economics. The cost of genetically engineered pigs would be considerably more than the minimal cost of wild-type pigs. As pointed out previously,⁵ if a BHV from a genetically engineered pig functioned in the patient for a significantly longer period of time, this would clearly be in the patient's interests, but it is unlikely to be to the economic advantage of the company supplying the BHV. The cost of the BHV would be significantly greater, and the need for replacement would be significantly reduced.

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Reply to the Editor:

We thank Manji and colleagues for their comments on our article, "Cardiac xenotransplantation technology provides materials for improved bioprosthetic heart valves." There is growing consensus that ectopic calcification, including calcification of bioprosthetic heart valves, may occur in response to local inflammatory reactions.¹ Our research, which builds on earlier fundamental findings that show glutaraldehyde fixed bioprosthetic materials are not totally immunologically inert,^{2,3} sought to identify a potential clinically relevant mechanism for such inflammation and suggests that anti-Gal antibody binding to bioprosthetic materials may be one such signal. As indicated in the article, our work is consistent with the clinical histopathology of explanted porcine valves derived from left ventricular assist devices and extends the earlier observations that antibody from sensitized serum could accelerate calcification.⁴ This work and our earlier study⁵ using Gal-positive and Gal-deficient fixed porcine pericardium show that natural

preformed anti-Gal antibody is sufficient to accelerate the calcification process in the subcutaneous implant model. This suggests, but does not conclusively prove, that a preformed anti-Gal antibody-mediated inflammatory response may occur soon after implantation and that such an antibody-mediated inflammation may initiate an innate immune response that furthers calcification of the device. The α 1,3-galactosyltransferase gene-knockout (GT-KO) pig, which makes anti-Gal antibody, is an appropriate model to test this hypothesis because implantation of Gal-positive bioprosthetic materials would represent an allogeneic implant that differs from the recipient only by the presence of α Gal sugar. Our results support the use of GT-KO tissues for valve development as a means to debulk the major antigen. It may also be of interest to determine if the early inflammatory response is blocked, whether other clinical modalities that block antibody-induced inflammation could further forestall degeneration of bioprosthetic heart valves.

In their letter, Manji and colleagues suggest that additional genetic modification of bioprosthetic materials, including complement regulatory proteins and antithrombotic functions, might be incorporated to further prevent valve degradation. We agree that incorporation of these functions in living tissues may help to prevent rejection of xenogeneic organs or tissues. The high level of glutaraldehyde fixation used in the preparation of bioprosthetic valves, however, would likely inactivate the function of these proteins, thereby eliminating any potential protection to the bioprosthetic valve.

We agree that under the current regulations the cost of bioprosthetic heart valves from genetically modified sources would likely be increased compared with wild-type pigs. It seems likely that the level of biosecurity, which significantly affects the cost of production, needed for fixed valve tissue would be lower than the high

level of biocontainment required by regulatory agencies to produce live tissues and organs for xenotransplantation. If genetically modified valves have greater durability, then the additional cost of the valve will be offset by the benefit to the patient and use in a potentially expanded younger patient population and might be further offset by future regulatory changes governing the disposition of genetically modified animal tissues.

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