WHEN MEAT ALLERGY MEETS CARDIAC SURGERY: A DRIVER FOR HUMANIZED BIOPROSTHESIS

To the Editor:

A seemingly impossible relationship between cardiac surgery and meat allergy should have led to the manufacture of gal-deficient valves. Why? In January 2005, over a decade ago, we reported for the first time that recipients of bioprostheses developed an alpha-gal-specific humoral immune response.^{1,2} It was then speculated that the degeneration of the bioprosthesis was associated with the presence of alpha-gal in the valve tissue. This insight was corroborated by multiple groups and, most important, proven in experimental animal work.³⁻⁵ There are limited reports of humans with a hypersensitivity reaction after biovalve implantation.⁶ Is there a possibility that allergy research may have relevance for cardiac surgery? Dr Patts Mills, FRS, from the Asthma and Allergic Disease Center at the Virginia Health System, was the first to report that humans with meat allergies (consumption of red meat that leads to delayed anaphylaxis, angioedema, and urticaria) have developed immunoglobulin (Ig)-E-specific antibodies against alpha-gal.^{7,8} This knowledge was further extended by Kollman and colleagues,⁹ who showed higher levels of alpha-gal-specific IgG1 and IgG3 antibody in a meat allergy cohort compared with nonallergic individuals, an observation that was already shown in recipients of bioprostheses.^{2,9} The link between meat allergy and alpha-gal-specific humoral valve degeneration seems obvious, but until recently was mere conjecture by a limited number of surgeons and allergologists. Hawkins and colleagues,¹⁰ Virginia cardiothoracic surgeons, recently described 2 patients who underwent implantation of a bioprosthetic aortic valve and postoperatively developed a meat allergy associated with a gal-specific IgE immune response. Both patients developed premature degeneration of their bioprosthesis that required reoperation and implantation of a mechanical valve in the aortic position.¹⁰ What can we learn as academic surgeons from this scientific story? (1) Big Pharma has not reacted to academic work to provide more durable gal-deficient bioprosthesis. Cardiac surgeons and cardiologists are continuing to implant valves

that are known to induce a systemic immune response, leading to precocious degeneration. Furthermore, the uncritical lowering of age limits for biovalve replacement has severe consequences.^{11,12} (2) Academic research pertaining to the alpha-gal immune response in cardiac surgery is rather meek: A PubMed search in November 2016 with the key words “alpha-gal” and “valve” brought up only 40 citations. (3) Only the very avant-garde centers, such as the Hannover and Seoul Group, are trying to tackle this important question by means of detergent-based decellularization procedures^{13,14} or by using alpha-galactosidase.¹⁵ Tissue-engineering research is ongoing in most academic centers of relevance, but commercial producers must instigate the manufacture of such “humanized” bioprostheses with potentially longer life spans. The first successful endeavors in that direction have been reported.¹⁶ Allergy and cardiac surgery do not particularly fit together, but in my opinion these “case insights” from patients with meat allergy with valve degeneration will lead to commercially available gal-deficient bioprostheses for future generations of patients with valve disease. Another speculation is that regulatory affairs in the European Union or the Food and Drug Administration in the United States will force the industry to provide such valves, and then ignorance will be overcome. The valve industry takes pride in being innovative at annual cardiac surgery meetings. Will we wait for another decade for action?

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MAMMALIAN MEAT ALLERGY AND ADVANCES IN BIOPROSTHETIC VALVE TECHNOLOGY

Reply to the Editor:

We read with interest the letter to the editor by Ankersmit and colleagues,¹ “When Meat Allergy Meets Cardiac Surgery: A Driver for Humanized Bioprosthesis.” The University of Virginia has led the epidemiologic characterization of the mammalian meat allergy to galactose- α -1,3-galactose (α -gal) believed to arise after inoculation by the Lone Star tick.² We have correlated this to the development of anaphylactic reactions after implantation of bioprosthetic valves in patients who already have the allergy and to the rapid degeneration of bioprosthetic valves in patients who subsequently acquire the allergy.^{3,4} Because all current porcine and bovine bioprosthetic valves contain α -gal, this allergy can be a serious concern for cardiac surgeons and a major consideration in prosthesis selection. In the United States, mammalian meat allergy is primarily concentrated in the

southeast, but cases have been noted throughout the country and internationally. The importance of α -gal, however, is not limited to this specific allergy.

As noted by Ankersmit and colleagues,¹ the link between α -gal and bioprosthetic valves has been known for more than a decade, and the α -gal allergy is likely unmasking immune-related degeneration that is occurring in all patients.⁵ This has been well described and helps explain age-dependent speed of degeneration.⁶⁻⁹ Moreover, immune-related valve degeneration was attenuated in a porcine model deficient of α -gal.¹⁰ Although no α -gal deficient valves are currently available, we disagree that little progress has been made in investigating the impact of and solutions to the problem of α -gal. Ankersmit and colleagues¹ note 2 potential solutions with α -galactosidase and detergent-based decellularization; however, these are certainly not the only options, and might not be the best solutions.

A decade before the discovery of the α -gal-specific humoral response to valve implantation, researchers identified α -gal as one of the main immune targets leading to hyperacute rejection in xenotransplantation.¹¹ Since then, researchers have been trying to sidestep this problem by using α -gal knockout pigs from Revivacor, Inc (Blacksburg, Va). The recent widespread adoption of CRISPR/cas9 genome editing technology has meant rapid genetic modifications that have increased xenograft longevity.¹²

It is to be hoped that recent investment in xenotransplantation will translate to improved and more durable bioprosthetic valves.¹³ As a first step, recent studies demonstrated equivalent physical properties of α -gal-deficient pericardium.^{14,15} The main benefit to CRISPR is the ability to perform multiple genetic manipulations simply and efficiently. Of course, α -gal is not the only immunogenic carbohydrate antigen present in bioprosthetic heart valves, and the next generation of valves should address them all.^{16,17} In this regard, multiple genetic modifications to carbohydrate antigens shows promise in reducing xenograft immunogenicity.¹⁸

Although there is little evidence that device companies are aggressively developing solutions for carbohydrate antigens, the process for bringing these advances to market is long; the Food and Drug Administration regulates not only the new valve but also the genetically modified animal. With 3 potential solutions to alleviate α -gal-related bioprosthetic valve degeneration, we hope that the academic and biotechnology communities can come together to find the best option and bring this to market rapidly. We must work together to continue improving the care of our patients.

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