follow surgical oncologic principles and should be regarded as a bailout procedure and used judiciously.

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WILL THE REAL CULPRIT OF HETEROGRAFT VALVE CALCIFICATION PLEASE STAND UP?

To the Editor:

Sinha and colleagues¹ are not the first to implicate glutaraldehyde as a culprit for tissue valve calcification. Although they are to be commended for their careful methods and the suggestion that glutaraldehyde concentration and exposure times appear to correlate with the degree of calcification, they unfortunately failed to reach far enough back into the literature to recognize that most of their questions had already been answered by others.² A closer look at the literature might also have led these researchers to arrive at a different conclusion; that is, calcific degeneration of heterograft tissues is primarily an immunologic phenomenon.

Alain Carpentier and his wife Sophie, a biochemist, are given credit for the introduction of aldehyde chemistry to the modern manufacture of heterograft tissue valves.³ At the time, they did not advance an argument that aldehyde preservation rendered heterograft tissues nonimmunogenic. That perception belongs to perspicacious marketing departments within the tissue valve industry. The observation that calcific degeneration of heterograft valves is an age-related

phenomenon was an early and important clue to the problem of tissue valve durability.⁴ These issues notwithstanding, the Carpentiers' discovery had already spawned the multibillion dollar industry of heterograft tissue heart valves.

More than 30 years ago, Salgaller and Bajpai⁵ detected both cellular and humoral immune responses to glutaraldehyde-treated and untreated bovine pericardium. Their data provided the first real proof that glutaraldehyde-preserved heterograft tissues are not biologically inert and remain antigenic. The association between a smoldering immune response and tissue valve durability was never widely recognized, however, and glutaraldehyde continued to be the presumed cause of heterograft calcification, leading researchers and companies to search for new tissue treatments designed to retard calcification.

Love and associates⁶ first described the successful use of autologous pericardium briefly treated in 0.6% glutaraldehyde for use as a stent-mounted valve replacement. Since this introduction, multiple investigators have reported wide success with the use of autologous pericardium briefly treated in 0.6% glutaraldehyde for the replacement of semilunar heart valves⁷ and the repair of damaged and shortened mitral valve leaflets.⁸ All these techniques have proved durable, and in none of the published experiences, including those with pediatric or very young patients, has calcific degeneration been considered a limitation.

The more than 20-year clinical experience with autologous pericardium briefly immersed in glutaraldehyde and used for valve reconstruction should finally dispel any perception that aldehydes are directly responsible for calcific degeneration of tissue valves.

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Reply to the Editor:

We thank Mr Love for responding to our article¹ and for emphasizing the importance of immune mechanisms in heterograft calcification. We are in agreement that aldehyde treatment is just one of several factors that can exacerbate calcification of implanted tissues. In the clinical setting of pediatric cardiac surgery, where autologous pericardium is often used and immune mechanisms are presumably not so important, however, it is the factor that can be most readily modified. Unfortunately, our animal model was not suited to autologous pericardium implantation.

We strongly disagree with Mr Love's assertion that calcific degeneration never occurs in the pediatric setting when glutaraldehyde-treated autologous pericardium is used for

valve reconstruction. For example, Bacha and colleagues² described an important incidence of late failure because of calcification in an aortic valve repair with autologous pericardium.

We were surprised by the finding of our study that *shorter* pretreatment duration was associated with greater calcification, suggesting that longer but nevertheless clinically feasible pretreatment times should be used. In the future, we are interested in exploring the efficacy of the many anti-calcification treatments that have been applied to xenograft valves in the hope that they might be effective in reducing the degree of calcification of autologous pericardium in the pediatric setting.

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THE CARDIOPULMONARY BYPASS MODEL IN RATS

To the Editor:

We read with great interest the study for the establishment of a cardiopulmonary bypass (CPB) model in rats titled "Rat model of cardiopulmonary bypass for deep hypothermic circulatory arrest" by Waterbury and colleagues,¹ showing that they had successfully developed a rat CPB model with deep hypothermia circulatory arrest for the research of postoperative neurocognitive function. The authors mentioned

that their model had several innovative elements, including peripheral cannulation, instead of thoracotomy or sternotomy, the lack of a need for tracheal intubation with mechanical ventilation, and so on.

However, some confusion was aroused by these innovations. First, we wonder whether peripheral cannulation, instead of thoracotomy or sternotomy, should be truly called innovative. Logically, to investigate postoperative cognitive function in rats undergoing cardiac surgery or CPB, the experimental rats must be alive after the induced surgical trauma for the subsequent cognitive assessment. Therefore, to date, for all those CPB models in rats that need to survive, thoracotomy or sternotomy is avoided. However, there is an exception. In the research of perioperative myocardium injury in rats using the CPB model from Günzinger and colleagues,² cardioplegic arrest was achieved through cardioplegia injection by direct aortic clamping. To achieve access to the ascending aortic artery for cardioplegia injection, sternotomy was performed, and cannulation and ligation of the bilateral carotid arteries were also performed; thus, theoretically, the survival of the experimental rats was close to impossible.

Second, the authors stressed that the rats undergoing CPB were not intubated and not ventilated, which is fully beyond our knowledge. Without tracheal intubation and mechanical ventilation, how would it be possible to maintain proper anesthesia, because we also know that too deep an anesthesia will compromise the respiration and hemodynamics. However, the rats might move under a light anesthesia. In addition, without supportive ventilation, coming off CPB will undoubtedly be very challenging for the rats buffeted by the sluggish circulation during the rewarming period. More importantly for the CPB model in the research by Waterbury and colleagues,¹ the CPB flow was incomplete, which was about 70% of

normal cardiac output, according to their report. Thus, how to oxygenate the other 30% of the blood? Under such circumstances, desaturation would gradually occur, which was evidenced by the severely reduced pH and base excess in their Table 1 for the physiologically relevant parameters of rats undergoing CPB with deep hypothermia circulatory arrest.

Third, we noted that no vein channel was established for medicine administration. When coming off CPB, the rats might need some inotropes; however, at that time, all the cannulas used for CPB have been extracted and the corresponding vessels ligated.

Finally, bilaterally, the femoral arteries were cannulated and also would have been ligated after surgery, which would produce some difficulties for the motor function of those experimental animals, although the experiment was performed for neurologic evaluation after surgery.

In the Duke Anesthesiology CPB laboratory, the CPB model in rats was instituted at a flow rate of 160 to 180 mL/kg/min, the normal cardiac output of rats. All the experimental rats were also intubated and ventilated for the purposes of both anesthesia and oxygenation. Additionally, thoracotomy or sternotomy was avoided to ensure the survival of the rats. Also, the superficial caudal epigastric artery and vein, instead of the femoral artery and vein, were cannulated for continuous measurement of the mean arterial pressure and for intravenous drug administration to ensure better survival.^{3,4}

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