Letters to the Editor

RE: Gregoric ID, Frazier OH, Tamez D, et al: Thrombogenicity of Mechanical Aortic Valves in an Animal Model: Site Specific Testing is Crucial. ASAIO J 50: 376-380, 2004.

Dear Editor:

I am writing this letter concerning the article "Thrombogenicity of mechanical aortic valves in an animal model: Site specific testing is crucial," published in the July–August issue of the *Journal*.[1] Gregoric, et al. discuss that "The physiologic extremes present in the bovine model are ideal for preclinical valve testing, especially of mechanical aortic prostheses."[1] We believe to the contrary, that an animal model that presents the so-called "worst case" scenario is not appropriate for the preclinical testing of mechanical heart valves designed for human use. The choice of an animal model for preclinical testing should be consistent with Institutional Animal Care and Use Committee (IACUC) as well as International Standard Organization (ISO) guidelines.

Justification for animal use by an investigator requires sufficient evidence that the anatomic and physiologic features of an animal make it desirable for the model. The authors present that the rapid growth, strong myocardial contractility, and high cardiac output are desirable characteristics of the bovine model. However, these physiologic characteristics are not compatible with a human-sized aortic valve. In fact, the authors reveal that two of three calves were prematurely euthanized because the valve's effective orifice area was too small for the animal model.

Choosing the calf as a model for chronic valve testing is not in the best interest of general animal care and use because the physiologic characteristics of the calf model are not consistent with the specific aim of the investigators: "Site Specific Testing is Crucial." The authors report difficulties with thombogenicity of a first evolution mechanical trileaflet valve (TV1) when placed in the aortic position. When the investigators then retested the valve after a computerized valve study redesign, there was decreased mortality. From this, the authors conclude that the calf model was a superior animal model for studying thrombogenicity in the aortic position without an adequate comparison with other animal models. The research laboratory of the authors is quite familiar with the bovine model and has used it in the application of mechanical circulatory assist devices for more than 20 years. However, the use of the bovine model in assist devices is typically chosen because the mediastinum of the calf is greater in size compared to the dog, sheep, pig, and goat. Regrettably, it is all too common that researchers rely upon a model that is familiar, rather than one that is appropriate for the research question.

The ISO's principal objective for preclinical *in vivo* evaluation of prosthetic heart valves is to test the function of the replacement heart valve in a biologic environment with the closest compatibility to human conditions.[2] The *in vivo* evaluation is the final investigational step before human implantation. It is specifically performed to assure that the replacement heart valve will perform as least as well as currently used replacement valves. As yet, there is no ideal animal model for this purpose. However, the model should be selected with the closest degree of human compatibility as possible. This includes testing in the anatomic position for which it is intended.

Fortunately, the authors' detailed computational fluid dynamic studies identified the origin of the problem to be flow separation and turbulence behind the hinge windows in the TV1 valve. The subsequent valve (TV2) was again tested in a calf model with a significant decrease in thrombus formation. Although the authors do not report the cardiac output in the article, at 159 days (mean survival TV2), it would be estimated to be 18 L/min. This is approximately triple that of human cardiac output. In summary, the calf model is not an ideal model for the preclinical testing of prosthetic heart valves. It is rather a model of patient prosthesis mismatch.

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References

1. Gregoric ID, Frazier OH, Tamez D, *et al*: Thrombogenicity of mechanical aortic valves in an animal model: Site specific testing is crucial. *ASAIO J* 50: 376–380, 2004.
2. Association for the Advancement of Medical Instrumentation. *Cardiovascular Implants: Cardiac Valve Prostheses*. ISO 5840:200X, 4th edition. Arlington, VA, 2004. Richard W. Bianco

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