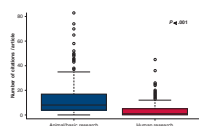


Dr Chambers is co-inventor of the STH-Pol solution. All other authors reported no conflicts of interest.

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REPLY FROM AUTHORS: ARE WE REALLY REDUCING, REFINING, AND REPLACING?

Reply to the Editor:

We read Santer and colleagues' letter on our Commentary regarding their study on St Thomas' Hospital polarized blood cardioplegia in a porcine model.¹



Their reply is both welcome and expected. There is no doubt that animal models have contributed greatly to the field of medicine, and, more specifically, cardiovascular surgery. As we move into a new decade of innovation, however, we must question the clinical relevance of current studies.

As we wrote in our Editorial Commentary, physicians and scientists should not kill, especially for nothing. Although animal research is important, it should be limited to studies with a solid scientific protocol and rationale, as well as very clear clinical implications. To the former point, it is well established that preclinical animal studies are fraught with methodologic inadequacies, and the report by Santer and colleagues is no exception, as highlighted in our commentary.² This has led to poor clinical translation. Although the authors report that up to one third of animal studies translate into clinical trials, we have found otherwise, with just 20% of more than 400 preclinical animal investigations published over the past 10 years being cited in a subsequent human clinical trial (Figure 1).³ Furthermore, less than one half of the studies had solid methodology, and the majority of them provided results that were then contradicted by larger randomized trials (19%) or published findings that were never tested in humans (45%).⁴

Clinical translation is made more difficult by the complexity of the contemporary patient population undergoing cardiac surgery. In a recent publication in the *European Heart Journal*, Cesarovic and colleagues⁵ discuss the need to transition away from single- to multi-disease models, a feat that is becoming increasingly difficult as patients undergoing cardiac surgery become older and have multiple comorbidities. In their

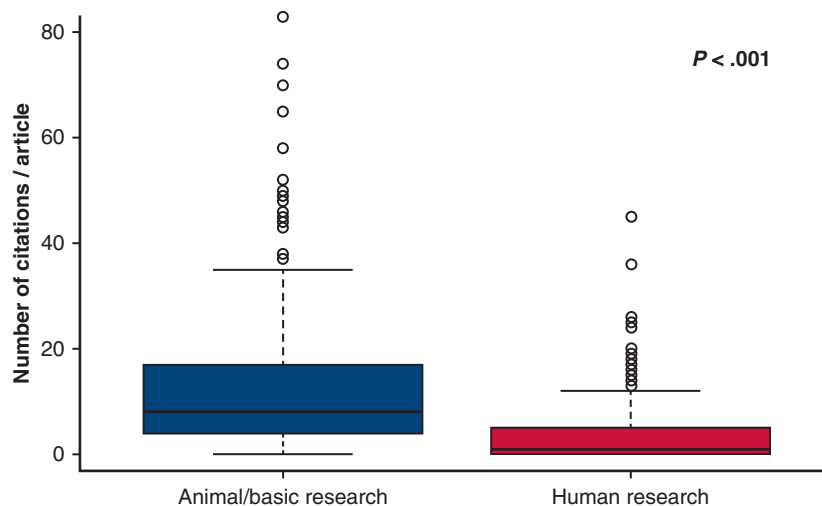


FIGURE 1. In an analysis of 411 studies using surgical animal models published between 2008 and 2018, it was found that the original article was cited a median number of 1 time with a majority of citations in animal/basic science articles (78.6%) and a minority in human/clinical research studies (21.4%). Interpretation: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; thick horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. Circles represent outliers. Adapted from Ruan and colleagues.³

The authors reported no conflicts of interest.

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analysis, Sander and colleagues used an otherwise-healthy porcine model undergoing isolated cardiopulmonary bypass. Are we to interpret these results as indicative of the physiologic response in an elderly patient with diabetes and hypertension undergoing valve replacement with concomitant coronary bypass as the authors state? Probably not.

Finally, we agree with the authors that the 3 Rs (reduce, refine, replace) must be at the forefront for any investigator considering the use of an animal model in the preclinical setting. Even in a well-designed trial, however, we must ask ourselves the key question: will this study change practice? If the answer is no or maybe, then the ethical justification of the study must be questioned. While cardioplegia is vital to cardiac surgery, there exist multiple solutions with very high efficacy

and safety profiles.⁶ Although Santer and colleagues would not want to be subjected to unnecessary research, we do not believe that animals should either.

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