Commentary: Do not kill (especially for nothing)

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In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Santer and colleagues compare postcardiopulmonary bypass hemodynamic recovery of pig hearts using polarizing versus depolarizing cardioplegia.¹ After an extensive experimental work, the authors conclude that their results suggest “the noninferiority as well as the potential benefits of a novel hypothermic blood-based polarized St Thomas’ Hospital cardioplegic solution in a clinically relevant model of CPB [cardiopulmonary bypass] in pigs.”

The key problem is the definition of “clinically relevant.” It is unclear how a model on the basis of healthy non-primate hearts undergoing a period of cardiopulmonary bypass and aortic cross-clamping without any surgical intervention (luckily a scenario relatively infrequent in human practice) might be “clinically relevant” for humans with heart disease submitted to surgical repair.

The results of Santer and colleagues¹ are probably “clinically relevant” for surgeons interested in performing cardiac surgery on healthy pigs, but do they have any relevance for humans? Can we learn something applicable to our surgical practice from the complex experimental effort of the Vienna group? In alternative, does this work provide important hypothesis-generating data to be tested in a human trial? The answer to all the questions is a clear no.

The problem of extrapolating animal results to humans is not new. Alexander Pope’s quotation “The proper study of mankind is man” is widely cited.² There is solid evidence that most animal models fail to translate to human clinical research³ (clinical practice is far off). This is true even for surgical animal models.⁴ The key problem is obviously related to the important interspecies differences that make animal results poorly reproducible in humans. In addition, most animal studies are poorly designed and conducted and have major methodological flaws. Santer and associates¹ in the first version on the report did not provide any attempt at sample size calculation and, upon reviewers request, provided an estimate on the basis of a

Is their pain worth it?

Central Message

Animal research rarely benefits humans.

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rat model (adding another interspecies difference to the equation) and on an unsubstantiated definition of superiority. In addition, while presenting a very long list of hemodynamic, biochemical, and histologic outcomes, they do not consider adjusting for multiple testing. It has been argued that animal models must be designed to mimic human disease and treatment as closely as possible.⁵ This was not the case for Santer and colleagues,¹ who studied healthy pigs undergoing isolated cardiopulmonary bypass and aortic clamping.¹

It is known that human clinical trials have been performed despite evidence of harm of the tested intervention in animal models.⁶ This implies that animal data were regarded as irrelevant to inform human clinical research, putting into question why the experiments were performed in the first place.⁶ It is even contended that animal models might be harmful to humans through misleading safety and efficacy results, misdirecting resources away from more effective methods, and potential rejection of useful medical treatments.⁷ With the current immense potential of simulation technology, the use of animal models raise major methodological and ethical questions.

Importantly in fact, although they might be too different to be used in clinical research, animals are very similar to humans in suffering fear, pain, and agony.⁸ Is their pain worth this “science”?

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