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Who is who in this storm?

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Please submit your article's Central Message here. The text box will limit you to 200 characters, spaces included	Translational research are becoming popular even in the field of cardiac surgery, but can a bench-based model change our clinical practice?
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Who is who in this storm?

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiac surgery is an effective, evidence-based clinical practice built on decades of research spanning from basic science to rigorous large animal studies and randomized controlled trials (RCTs) in patients. This translational approach has benefited patients enormously[1]. More recently, we are witnessing a surge of different research methods from bench-based simulation to overnight observational studies from registries and meta-analysis that are raising questions and debates[2]. Concomitantly, in the era of innovation, we witness a crisis in research reproducibility[3], limited reporting of registered RCTs[4] and a call to re-surface rigorous large animal research[5]. One is left wondering if these are signs of a perfect storm. At these new times, the typical cardiac surgeon looks like a passive passenger on the boat of innovation, struggling to keep the rudder straight while sailing across the troubled waters of intellectual property, commercialization, conflict of interests, harm[6] lack of evidence[7], visibility, patient interest and evidence-based medicine. Who is who in this storm? Paulsen and colleagues[8] have reported a bench-based model using a 3D-printed heart simulator designed to test the long-term efficacy of two routinely used aortic conduits for valve sparing procedures. This is despite thousands of patients have already received these two conduits. The novelty of this report is that it tries to address an important clinical question on the long-term durability of the conduits using a bench-based simulator. The simulator is ingenious, modelling physiological waveforms and mechanical activities of the heart. Porcine aortic root/valves were sutured in the two conduits followed by implanting silicone tubes as mock coronary buttons. A long shot. At first look, few conflicting questions come to mind: is this simulator reliable? Can it really predict long-term durability by running for few hours? Where is the rigorous confirmatory trial in large animals? Yet, we must respect this methodological approach as modern computational

modelling has been shown to be effective in predicting health outcome[9]. Based on the evidence arising from this simulation, the authors conclude that while the Valsalva Graft accurately reflect the aortic root geometry longitudinally, its radial displacement of the valve commissures triggers abnormal forces on the leaflets affecting their long-term durability. A strong conclusion, with not a single patient operated and not a drop of blood lost! With the only variable in this simulator being the type of conduit used, it might be that the highlighted difference is genuine. Who knows? In a traditional translational research pathway, this would trigger an immediate need for in-vivo validation in a relevant large animal model. However, the simulation has several limitations. The whole system looks too artificial as opposed to a typical in-vivo model. The lack of vascular elasticity in the system is an issue. Sub-optimal surgical expertise and/or mismatch between variable sizes of porcine valve used and the fixed diameter of the conduits selected might have affected the radial displacement of the leaflets. Finally, the simulation was conducted with normal saline solution and not with blood, using a fluid with different viscosity, hence affecting dynamics. These are the practical immediate criticisms that we can raise. Translational large animal models with advanced longitudinal in-vivo imaging would provide confirmatory knowledge of the pathophysiological, mechanistic and dynamic issues associated by this study with the Valsalva Graft surgical procedure. This, in turn, would have more robust implications on the clinical scenario, possibly warranting a call for a comparative RCT? The study by Paulsen and colleagues[8] also highlights that undertaking isolated bench-based simulation, no matter how good it can be, does not help much in moving the field forward. This is because real translation occurs across a pipeline in which bench simulation represents only the first step. This illustrates the key learning

point that bench-based modelling needs to go hand-to-hand with advanced in-vivo preclinical validation in relevant models[10], to facilitate translation to bedside. Translating valuable basic science into patients requires time, funding, appropriate surgical skills, translational biomedical knowledge and high experimental reproducibility. A gap in translation seems to be the main limitation of this process. Rigorous in-vivo validation in relevant preclinical models may represent an effective way to bridge the gap between bench-based science and bed side across the storm. Like a bridge over troubled waters.

References

1. Drolet BC, Lorenzi NM. Translational research: Understanding the continuum from bench to bedside. Transl Res. 2011;157(1):1-5. doi:10.1016/j.trsl.2010.10.002.

2. Packer M. Are Meta-Analyses a Form of Medical Fake News. Circulation. 2017;136:2097-2099. doi:10.1161/CIRCULATIONAHA.117.030209.

3. Baker M. Is there a reproducibility crisis? Nature. 2016;533:452-454. doi:10.1038/533452A.

4. Who is not sharing their trial results? https://trialstracker.ebmdatalab.net/#/. Accessed November 27, 2018.

5. Wadman M. A trans-Atlantic transparency gap on animal experiments. Science (80-). 2017;357(6347):119-120.

6. Alemzadeh H, Raman J, Leveson N et al. Adverse Events in Robotic Surgery : A Retrospective Study of 14 Years of FDA Data. PLoS One. 2016;104:1-20. doi:10.1371/journal.pone.0151470.

7. Medical device rules need “drastic change” to protect patients. https://www.bbc.co.uk/news/health-46337937. Accessed November 27, 2018.

8. Paulsen, MJ; Kasinpila P; Imbrie-Moore AM; et al. Modeling conduit choice for valve-sparing aortic root replacement on biomechanics with a 3D-printed heart simulator. J Thorac Cardiovasc Surg. 2018.

9. Morris PD, Narracott A, Von Tengg-Kobligk H, et al. Computational fluid dynamics modelling in cardiovascular medicine. Heart. 2016;102(1):18-28.

doi:10.1136/heartjnl-2015-308044.

10. Doenst, T; Schlensak, C; Schibilsky, D et al. Do we need Basic Research in Cardiac Surgery. Thorac Cardiovasc Surg. 2018;66(1):2-6.

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