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EDITORIAL COMMENT

Computer Modeling of Valve Disease

A New Old Technique to Understand and Predict Outcomes*

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Digital twins are virtual computational models designed to replicate the behavior of physical objects or simulate processes; they are increasingly used in engineering as well as in health care, because they allow for an understanding of complex scenarios and promote knowledge and innovation. In cardiovascular diseases, models are used to mimic the performance of a diseased organ or tissue and to simulate diverse treatments to guide or reinforce surgical planning and clinical decision making. They allow for an understanding of the effect of surgical modification on the (fluid)mechanics of the diseased apparatus, the sizing and landing position of a device, and the effect of drugs on the organ/system physiology. The main advantage of computer models over standard clinical experimentation is the possibility of testing hypotheses in a controlled environment, according to a reductionist approach, isolating the target of the investigation from the surrounding potential confounding clinical factors. Thirty years ago, models were typically paradigmatic, based on simplified morphologies replicating the average patient; nowadays, models are obtained from 3-dimensional imaging data sets and reproduce the anatomy of the specific patient with unprecedented precision.

The paper by Dabiri et al[1] in this issue of *JACC: Advances* presents a model integrating fluid dynamics and tissue mechanics of the mitral structures to analyze the effects of number and location of transcatheter edge-to-edge repair (TEER) with a MitraClip (Abbott) implant. The approach of the authors opens the perspective for patient-specific periprocedural planning and strategy optimization of TEER. By simplifying assumptions in terms of leaflet geometry, chordae tendinea, and MitraClip device, as well as in terms of fluid-dynamics modeling, their model allows the replication of an ample number of pathological cases and can simulate diverse corrections in a way and with a detail not attainable in clinics.

Transcatheter correction with the MitraClip is the evolution of the edge-to-edge technique developed by Alfieri et al[2] about 30 years ago. The technique relies on a very simple method of correcting mitral regurgitation by the suture of the leaflets at the site of regurgitation. This method, although simple, has a major limitation: although it efficiently corrects regurgitation independent of the underlying mechanism, it reduces the valve opening to a variable extent, depending on the location and the length of the suture.

In the late 1990s, the Alfieri technique was progressively used as an alternative for surgical valve repair in the context of complex anatomies. Questions related to the hemodynamic performance of a "nonphysiological" valve conformation were raised and challenged the widespread use of the edge-to-edge technique.

We needed immediate answers on very important questions: What is the influence of a double orifice configuration on valve hemodynamics? Does a symmetric vs an asymmetric configuration determine different outcomes? What is the stress applied to the leaflets and the risk of limited durability? Can we use the standard Doppler echocardiography methods to evaluate valve hemodynamics? A clinical trial to answer these questions would delay the possibility of

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applying of a promising technique associated with excellent short-term results in challenging patients. Therefore, we applied a computer model approach to help our clinical decisions. All of the previous questions have been answered using a combination of finite element and fluid dynamic models of increasing complexity and therefore fidelity.[3]

The first relieving answer was that the hemodynamics of a mitral valve are not influenced by a double-orifice configuration, and the valve behaves like a single-orifice valve with an area equal to the sum of the 2 valves. Obviously, the suture of the valve edges reduces the overall valve opening, but diastolic gradients are acceptable if the cumulative valve area is larger than 2.5 cm^2. This answer, based on simple fluid dynamic models, gave us a very simple rule during valve repairs: if 1 of the 2 orifices accepts an 18-mm sizer (corresponding to a surface of 2.5434 cm^2), the opening is compatible with acceptable diastolic function.

The second question was: in a valve with 2 orifices of different sizes, are the velocities equal in both orifices? Which 1 of the 2 orifices should we probe to obtain the velocities to calculate transvalvular gradients? The fluid element model demonstrated that the velocity in the middle of the 2 orifices was equal for both orifices, independent from the double orifice configuration (symmetric vs asymmetric). This feedback was key to validate the use of conventional echo-Doppler standard measurements to assess transvalvular gradients noninvasively.

Finally, the last and important question was related to durability. Although we rarely observed suture tears in our experience, we addressed the risk of disruption of the suture bridge, as well as the impact of the stress acting on the leaflets in the long-term function of the valve repair. A finite element model demonstrated that the stress acting on the leaflets is related to the length of the suture and to the size of the annulus. Longer suture and smaller annular sizes are associated with smaller stresses on sutures and leaflets. This answer has been applied in practice, with a standardized approach using an annuloplasty device in all cases and extending the suture length to reduce the risk of tears, but carefully avoiding too long of a suture to prevent stenosis. The same concepts are applied today in our current practice with MitraClip procedures.[4] The latest-generation MitraClip includes larger devices to reduce the risk of leaflet adverse events and to be more efficient.

Several models have been developed since then, mostly focused on improving the physics and/or the realism of the digital twins, rather than to support clinical decisions. However, one lesson learned in this journey is that the clinical value of a model is more in the weight of the questions than on the sophistication of the simulation. In our experience, simulation-based investigations have been able to answer questions in a relatively short time, as opposed to clinical trials, which would last longer and would be highly confounded by the complex clinical scenario and the diversity of the patients.

The paper by Dabiri et al[1] shows how a model can be used to predict the hemodynamic behavior of the valve with different TEER strategies. The model, based on a very complex and advanced fluid-structure interaction, integrates all aspects of valve function and provides a very intuitive output. Blood flow is represented as particles describing valve fluid dynamics under different valve configurations, starting from different anatomies and mechanisms of regurgitation, and applying different TEER strategies. The model has some limits. Above all, the posterior leaflet is handled as a single unit, whereas we know how much the indentations and the variable anatomy of the underlying subvalvular apparatus play a role in the effects of TEER.[5] It is common experience that a central (A2-P2) TEER is usually very predictable, whereas implanting devices outside of the chordal free zone can be challenging because of the more complex subvalvular apparatus and the configuration of the posterior leaflet. Also, TEER outcomes are highly dependent on the symmetry of implantation, a parameter that was not introduced in the model.

Not all issues can be solved with the current modeling options. It is common for expert operators to be confronted with unexpected behavior of the valve during TEER and need for “on-the-spot” change in the repair strategy. The support of artificial intelligence tools could be very helpful both before and during the procedures to improve the prediction of the result of a TEER strategy before attempting a device implant.

Artificial intelligence can be successfully applied to improve the segmentation process of medical images in terms of accuracy, robustness, and speediness to provide a means to introduce uncertainties in models as in real patients, to augment the number of virtual patients through data augmentation methods. In other worlds, artificial intelligence is a strategic tool to enhance in silico trials, building more sophisticated models that can be challenged against testing hypotheses beyond the simple mechanistic approach. More recently, the ability of these models to digest and analyze big data has been used to develop a new era of precision medicine, in which patient-specific models can be used to develop personalized care.[6]

Without a doubt, in the future, computer simulations will become more and more embedded in our decision pathways, improving the safety and efficacy of procedures.

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