Future of CV Medicine: Transformations in Clinical Practice and Drug Discovery

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The potential of computer-aided design and 3D printing, physiomimetics, and in silico modeling to transform clinical practice and drug discovery were highlighted in this session on the future of cardiovascular (CV) medicine.

PERSONALIZED PROSTHETIC HEART VALVES

The success of transcatheter aortic valve replacement and the advent of transcatheter mitral valve replacement are driving the need for strategies to create valves that are perfectly sized for each patient to eliminate postprocedure regurgitation, which currently occurs in about 70% of patients and is known to increase heart failure hospitalization and reduce survival [Hayashida K et al. *JACC Cardiovasc Interv.* 2012]. Such personalized valves are possible by using computer-aided design and 3D printing, according to work by Dee Dee Wang, MD, and colleagues at the Henry Ford Health System, Detroit, Michigan, USA.

The limitations with current methodologies to determine the size of the aortic valve include the lack of a gold standard to measure the aortic annulus on computed tomography (CT) imaging and the limited number of sizes of commercially available prosthetic aortic valves. Further, the aortic annulus is a virtual ring as compared with a true physical structure [Piazza N et al. *Circ Cardiovasc Interv.* 2008]; thus, accurate, reproducible measurement of this asymmetrical area is currently challenging. The presence of calcium will cause a gap because a prosthetic valve cannot conform to this bony structure. For transcatheter mitral valve replacement, determining the height and dimensions of the mitral valve for its correct landing location are required, for which CT is insufficient, in part because the presence of calcium interferes with identifying the correct location to measure.

Computer-aided design adds a dimensional analysis of the aortic and mitral valve areas, but its accuracy depends on the accuracy of the CT imaging. Software programs assist with determining the size of the prosthetic valve and provide visualization of the potential fit, but this is unreliable because it does not account for the possible presence of calcium. To address these limitations, Dr Wang and colleagues are developing proprietary methods to evaluate the permanent anterior motion of the mitral leaflet and are combining this with 3D printing to create the prosthetic valve that is sized to the specific mitral anatomy of a patient. It provides the correct sizing to personalize structural heart interventions.

The first transcatheter caval valve implantation combined CT and 3D printing, along with transesophageal echocardiography, to evaluate the caval valve and create the prosthetic valve [O'Neill B et al. *J Am Coll Cardiol.* 2015]. The patient was discharged 1 week after the successful procedure and was doing well at 4 months.

PHYSIOMIMETICS: MODERNIZING DRUG DISCOVERY

Physiomimetics is a new strategy to improve the efficiency of the drug discovery process. Such strategies are being developed to address the declining productivity in the pharmaceutical industry, with a decreasing number of drugs approved annually despite the increasing costs for research and development, according to Ashutosh Agarwal, PhD, University of Miami, Miami, Florida, USA.

Physiomimetic microsystems are intended to be models that mimic native tissue microenvironments, use human (rather than animal) cells, and collect functional outputs, while having a high throughput and being inexpensive. These microsystems will mimic the physiology and hopefully

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pathophysiology of different organs, and would replace the currently used static cultures and animal models. An "organ on a chip" is a new platform to study disease and screen drugs in healthy and diseased tissue.

Borrowing a standard nanotechnology process from the electronic industry called photolithography that creates the chips for phones and computers, Agarwal and colleagues have created a heart on a chip. Scalable, standardized, and reproducible fabrication of such chips is possible with a benchtop CO_2 laser engraving system.

In 2 different proof-of-principle studies with a heart chip, this group showed it was possible to measure the dose response to isoproterenol to evaluate cardiac contractility [Agarwal A et al. *Lab Chip*. 2013], to more sensitively detect toxicity to doxorubicin, and to evaluate the impact of doxorubicin on the QT interval and twitch stress. In another study, they created a patient-specific heart chip with patient-derived induced pluripotent stem cells that revealed insights into the mechanisms of a rare genetic disorder, Barth syndrome [Wang G et al. *Nat Med.* 2014].

Among challenges to be addressed are methods to capture organ-organ interactions, determining the cells or culture to use, how to scale organs to one another, and how to scale the drug response for small engineered pieces of tissue to an organism or organ.

IN SILICO MODELING: MODERNIZING CLINICAL CARDIOLOGY

Computer models and simulation, called in silico modeling, are well known in engineering and are bringing a modern revolution in clinical cardiology, stated Paul Morris, MBChB, University of Sheffield, Sheffield, England, United Kingdom. It has been used for research and development in the medical device industry, for example, to test prosthetic heart valves and coronary stents to analyze mechanical stress to determine their design and safety.

CV in silico modeling can be 0-, 1-, or 3D or multiscale (which combines models of different dimensions, times, or lengths); and can use imaging and segmentation. One clinical tool is virtual fractional flow reserve (FFR). FFR is an invasive procedure known to improve outcomes and reduce costs when used to guide therapy, but it is underused. A simulation of the geometry of the vessel and blood flow and pressure gradients across the stenosis can provide for virtual FFR.

The virtual FFR is less invasive, analyzes a large section of the epicardial circulation, and can simulate the physiological impact of a therapy, which allows for planning and optimizing the treatment plan. Reductions in the risk for patients and in health care costs are also advantages of such in silico modeling.

System models or models that represent the entire human physiome, that is, a Virtual Physiological Human, are possible by integrating models of different lengths and time scales. The Virtual Physiological Human is a major focus of coordinated research in Europe. According to Dr Morris, clinical tools are available now to model virtual FFR and the risk of aneurysm rupture, and within 10 years there will be less-invasive, interactive diagnostic tools, virtual intervention suites, and clinical risk estimators. Beyond 10 years, there will be integrated, multiscale system models and in silico trials.