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REVIEW ARTICLE

Patient-specific 3D Valve Modeling for Structural Intervention

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ABSTRACT
Three-dimensional (3D) printing is an advanced manufacturing technique, recently introduced in the medical field to convert clinical imaging information of anatomical features into physical replicas built through digitally guided deposition of successive layers of material. This novel clinical instrument has emerged as a confluence of advances in imaging technology, 3D printing techniques, and structural heart interventions. Both digital and physical 3D modeling are now used to better visualize patient-specific anatomic features prior to catheter-based valve intervention. This review discusses common structural heart valve problems and the imaging challenges associated with catheter-based interventions. We highlight how 3D printed modeling can be used as a tool to overcome certain limitations of 2D visualization and how such modeling can be used to plan, practice, and predict success for increasingly complex catheter-based structural heart valve interventions. An overview of current 3D modeling techniques and advances are presented, including their limitations and future directions.

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Introduction

Structural heart disorders and interventions

Structural heart diseases represent the non-coronary heart conditions, including congenital and acquired defects of heart valve function. Traditional treatment of these defects has relied on open heart surgery, but with the development of improved imaging, innovation of medical devices, and catheter-based techniques, less invasive interventional treatments are becoming viable options to treat complex structural heart diseases. As catheter-based interventions become increasingly available, new challenges are being recognized. Such challenges include the visualization and conceptual presentation of complex anatomic structures that are no longer necessarily viewed directly during surgery. In addition, for most percutaneous procedures the native diseased valve anatomy is not removed, which increases the complexity in predicting device interaction and deformation during deployment within a beating heart. As such, the prediction of the new functional construct (native and prosthetic) is difficult and highly variable between patients.

Discussion

3D printed modeling

3D printed modeling is a process in which patient-specific anatomical models are generated from clinical images such as computed tomography (CT), magnetic resonance imaging (MRI) or echocardiography. It represents a confluence of novel technologies in clinical imaging, advanced image processing software platforms, and 3D rapid prototyping (printing). A series of steps are required to generate accurate replicas of cardiac valve structures (Figure 1). The first step is the imaging data acquisition and its conversion into Digital Imaging and Communication in Medicine (DICOM) standard format. This image data then undergoes digital image processing, which includes identification of the target geometry (a step commonly referred to as image segmentation), and 3D volume rendering. A Stereolithography file (STL) file is a file that contains a special description of a segmentation/volume rendering that can be interpreted by 3D printers.[1] A life-size physical model is then fabricated using 3D printing techniques that can blend different print materials and colors to produce increasingly sophisticated replicas of normal and pathologic heart valve components.

Structural heart interventions

Increasingly complicated structural heart interventions now require the visualization of complex 3D anatomy to plan and perform specific procedures. A brief summary of some of the current procedural challenges are highlighted.

Aortic valve replacement

Trans-catheter aortic valve replacement (TAVR) provides urgent relief of severe symptomatic aortic valve stenosis and is a lifesaving procedure for patients deemed high risk for surgical treatment. TAVR device sizing is performed using CT imaging,

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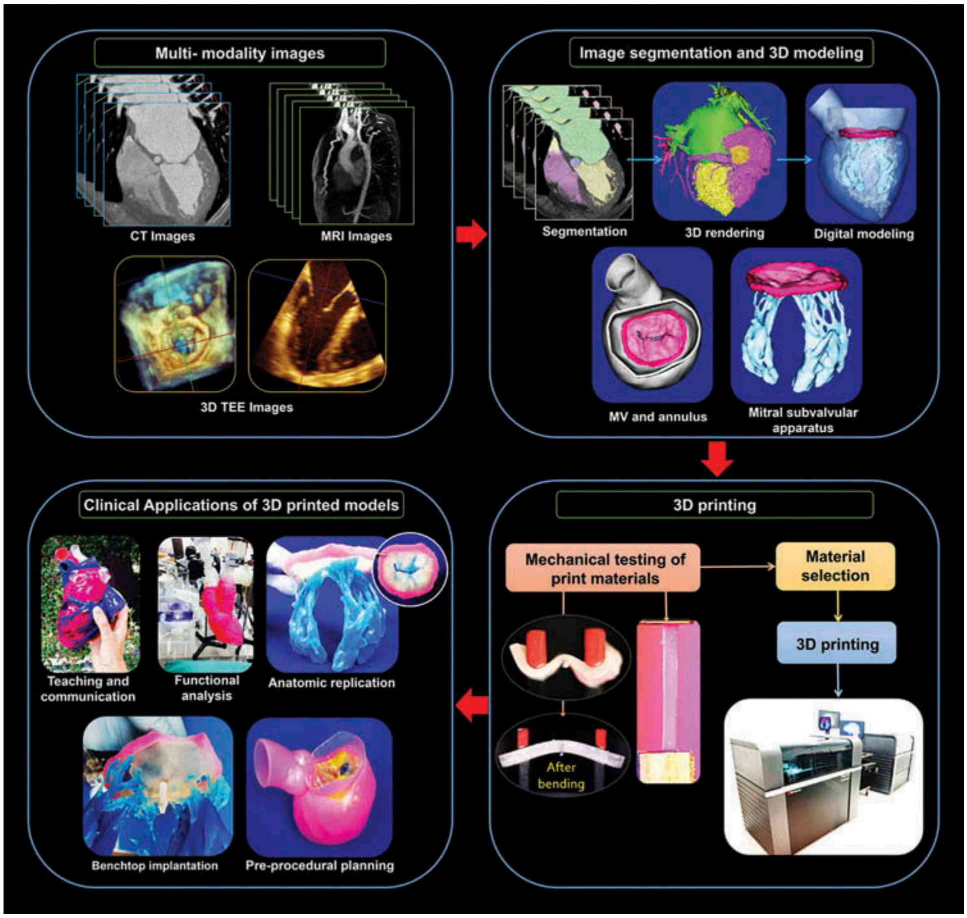

Figure 1. 3D printed modeling workflow. 3D printed modeling begins with clinical imaging acquisition—CT, magnetic resonance images and 3D TEE (top, left). DICOM images are then exported into image processing software for segmentation and digital modeling. Digital STL file of patient-specific models is exported for 3D printing (top, right). 3D print materials are preselected based on mechanical parameters (bottom, right). Applications of 3D printed models are shown (bottom, left).

while fluoroscopy is primarily used for intraoperative guidance, supported by echocardiographic imaging. Although TAVR outcomes have consistently improved,[2,3] the principal complication of this procedure is still paravalvular regurgitation. When paravalvular regurgitation severity is assessed by Doppler echocardiography as moderate or greater, this complication is associated with significant morbidity and increased mortality.[4] It is generally accepted that the occurrence of paravalvular regurgitation is related to transcatheter heart valve sizing (especially under sizing), device implant depth, and patient-specific regional calcium deposition within the aortic root complex.

Additionally, the relatively common complication of new cardiac conduction delay as well as the rare complications of coronary artery obstruction and aortic root rupture are all secondary to patient-specific aortic root geometry. These potential procedural outcomes must all be considered by TAVR teams when deciding upon a specific transcatheter heart valve design and size.

Mitral valve repair

Severe mitral valve (MV) regurgitation is associated with progressive left heart dysfunction, congestive heart failure, and death.[5] Percutaneous MV repair with a MitraClip (Abbott, California, USA) device is now available to treat patients with severe MV regurgitation and increased surgical risk. The MitraClip system is a catheter-based procedure for mitral leaflet repair that approximates the anterior and posterior leaflets using a fabric covered clip. Post-procedural success is generally based on the color Doppler quantification of residual regurgitation severity. However, the accurate quantification of residual mitral regurgitation is challenging due to the common occurrence of more than one mitral regurgitation jet and the local ultrasound artefact or shadow caused by the implanted prosthetic material. Thus, patient-specific mitral regurgitation simulation could provide a reference standard for flow measurements and their associated regurgitant flow volumes.

Adequate leaflet grasping is also crucial for the success of percutaneous MV repair. In addition, complex MV geometry (including extensive leaflet and annulus calcification, deep leaflet scallops and clefts, and myxomatous disease involving medial or lateral scallops) can represent a significant challenge to effective grasping and successful deployment of the MitraClip. Thus, comprehensive replication of mitral anatomy and personalized planning of possible intraoperative complications using patient-specific 3D printed modeling and procedural simulation prior to the clinical procedure may be of significant benefit for selected patients.

Patients with structural and functional abnormalities of MV geometry are increasingly being evaluated for Trans-catheter Mitral Valve Replacement (TMVR) procedures.[6,7] However the deployment of a TMVR device requires the successful navigation of several anatomic and functional obstacles. The large bulk of current devices create challenges for trans-septal delivery. The mitral annulus size, variable annular calcification, and dynamic motion throughout the cardiac cycle may all impact decisions about TMVR device size. Device design variations address the problem of TMVR device anchoring in different ways using anchors, tabs, apical tethering, leaflet barbs, and self-centering cork-like strut frame design.[7] However, individual patient anatomic variation in mitral leaflet length, chordae tendineae position and thickness, aorto-mitral annular angle, and left ventricular outflow tract (LVOT) flow area may limit the delivery and successful performance of a TMVR device.

Tricuspid valve repair

Disorders of the tricuspid valve, such as annular dilatation or leaflet tethering can create significant tricuspid regurgitation. These functional disorders are generally a consequence of right ventricle remodeling due to pressure or volume overload.[8] Advanced stage tricuspid regurgitation is associated with a poor prognosis and, although surgical repair represents a gold standard for tricuspid regurgitation treatment, the mortality rate is higher than with other surgical valve repair procedures.[9,10] As an alternative, tricuspid regurgitation repair options using catheter-based models are being explored, including central occluder devices (e.g. Forma device; Edwards Lifesciences, Irvine, CA, USA)[11], leaflet coaptation devices (e.g. MitraClip),[12–14] annular reshaping methods (e.g. Trialign; Mitralign, Inc., Tewksbury, MA, USA)[10], and even the implant of stented transcatheter heart valves within the inferior or superior vena cava (e.g. Tric Valve: Vertriebs GmbH, Vienna, Austria).[15,16] In addition to being more difficult to image via echocardiographic or CT methods, the tricuspid valve leaflet anatomy, as well as the subvalvular apparatus, is more variable than the MV. Furthermore, the right ventricle geometry, large myocardial tendon (moderator band), and the thinner right ventricle myocardial wall adds complexity to the performance of catheter-based devices used for tricuspid valve repair or replacement.

Pulmonary valve implantation

Percutaneous pulmonary valve implantation is a catheter-based procedure developed to treat right ventricular to pulmonary artery stenosis and pulmonary valve regurgitation.[17] Although the procedure has been widely accepted, the success of the procedure is highly dependent on the geometry and function of the right ventricle outflow tract (RVOT), pulmonary trunk, and pulmonary artery branch sizes, all of which vary from patient to patient.[17,18] Hence, a detailed pre-procedural anatomy assessment using multi-modality imaging is essential. Echocardiography represents a key imaging modality for the evaluation of RVOT gradient and quantification of pulmonary regurgitation, as well as for the assessment of right ventricle pressures.[17,18] However, echocardiographic acquisition is challenging in patients who have had multiple operations.[18] MRI is commonly used for the assessment of right ventricle volume and patient-selection for percutaneous pulmonary valve implantation.[17] Additional challenges include device migration and fractures of the stent frame,[17–19] as well as the potential for coronary artery compression. The limitation of available device sizes may also be an obstacle for percutaneous pulmonary valve deployment in dilated RVOT geometries.[20]

Modeling methods

3D computational modeling

Computational modeling is a collection of numerical methods and mathematical equations used to describe the biomechanical and hemodynamic behavior of heart valves before and after structural interventions. In recent years, significant efforts have been made to develop computational models that accurately simulate and analyze valve mechanics,[21,22] complex fluid dynamics and the comprehensive fluid structure interactions at play in normal and diseased heart valves.[23] Such computational methods have been used to model interactions with percutaneously implanted devices.[24–26] In general, this vast area of purely computational 3D modeling is currently not used clinically and exceeds the scope of this review.

In contrast, much simpler computer modeling which involves the use of clinical images and digital-devices, has become available to aid in patient selection for structural heart procedures. Commercial software can be used to visualize patient-specific geometric data with an overlay of a structural heart device onto the digital anatomy.[27] In general, the device (e.g. TAVR, or TMVR) used for the digital overlay would be a generic shape unless the device manufacturer provides the end-user with the specific (often proprietary) device STL file.[27] This form of computer modeling could accurately be referred to as "computer rendering" or "augmented 3D visualization." These methods are useful for sizing a prospective device prior to implantation and predicting gross structural mismatches such as marked LVOT obstruction. The main benefit of this novel computational imaging method is to provide superior visualization of multiple anatomic elements and device components within a digital environment. This permits free-rotation of the imaging perspective and some ability to measure novel geometry such as the "neo-LVOT" created by the overlay of a device upon a patient-specific anatomy.[28] However, the main limitations of this digital modeling approach are that tissue deformation caused by an implanted device is not adequately simulated, and any deformation of the device by the cardiac tissue is not simulated at all. This two-way device/tissue deformation may be the most important element of the model to simulate when specific structural complications, such as aortic root rupture in TAVR or TMVR device sizing, are the main concerns for a specific planned intervention. A physical 3D print of the same structures may provide more robust modeling of any device/tissue deformation—provided that the model is structurally accurate and replicates (or at least approximates) the tissue properties of the valve structure, and that blood pressure and flow effects (which are lacking from most 3D printed models) are negligible influences on the specific deformation being modeled.

Patient-specific 3D printing

Imaging acquisition

Clinical imaging tools continue to play a key role in structural heart interventions. CT images generally produce excellent spatial resolution and good temporal resolution to evaluate heart valve structures and function. CT is extremely useful for anatomical reconstruction in patients with a large amount of calcification around the aortic root complex, mitral annulus, or subvalvular mitral apparatus. CT images are also more convenient for screening very sick patients or those with pacemakers and pacemaker leads that limit the use of magnetic resonance imaging. However, MRI datasets can be used for modeling congenital heart defects or intra-cardiac tumors and can provide a reproducible differentiation of soft tissue without radiation or use of contrast. Although MRI and CT images are commonly used for 3D print modeling, the evolution of 3D volumetric echocardiography with improved spatial and temporal resolution have made this imaging modality common in all catheter-based structural heart interventions. Thus, 3D echo has become an appealing imaging modality for the 3D reconstruction of dynamic and anatomically challenging heart valves.[29–31]

Image segmentation

Patient-specific reconstruction of cardiovascular structures requires the identification of target geometries and their delineation (segmentation) within the 2D projected planes of volumetric images (coronal, axial, and sagittal planes) or other manually selected 2D multi-planar reformatted planes. Most segmentation software platforms offer automatic or semiautomatic segmentation of cardiac chambers, while the complete and detailed segmentation of heart valves and subvalvular apparatus elements usually require manual identification (Figure 1). Software selection depends on the available budget and on the complexity of the desired modeling goals. The time required for this segmentation step is highly dependent upon imaging quality and complexity of the segmented elements. Some cardiac structures, such as the aortic root, can be reconstructed in minutes using high quality CT images. In contrast, the highly complex MV apparatus with chordae and papillary muscles may require segmentation in different imaging planes, which can take several hours to complete.

Models can be generated from different imaging modalities or from different imaging phases within a single imaging modality, provided that each image dataset contains some common anatomic landmark (e.g. unique calcification or prosthetic feature). When necessary, digital models of different cardiac elements can be derived from different imaging modalities (3D transesophageal echocardiography [TEE] combined with CT)[32] or the same image modality (3D TEE mid-esophageal view combined with a 3DTEE trans-gastric view; Figure 2) then co-registered into an integral hybrid model. Whether from a single origin dataset or from the co-registration of multiple datasets, the 3D digital model is saved as STL files within computer-aided design software.[30]

Within this design software environment additional model modifications are possible, including but not limited to the addition of a display base if the model is intended to be a teaching tool, or the addition of vascular connectors to permit patient-specific *in vitro* functional flow modeling studies. After segmenting the anatomic image dataset, and after performing any required modification, the final step is to assign print color and material properties to each anatomic element prior to 3D printing.

Print material selection

Novel 3D printing technologies offer a wide range of options in both quality and complexity. Selection of the appropriate print material is important for accurate replication of the physiological behavior of native cardiac tissues. The chosen materials (and associated physical properties) influence the type of printer to be employed, as well as the time and cost of model production. For simple models used for teaching or demonstration purposes, a rigid, transparent, or monochrome patient-specific model is often created. For such models, a blend of two or more materials is effective to highlight specific pathologies such as calcification (Figure 3) or to mimic dichotomous material properties such as calcified and non-calcified aortic root tissues (Figures 1 and 3). PolyJet technology offers hundreds of material options that can be blended to fabricate very complex models, with an expanding range of colors and textures. Material is preselected with the purpose of replicating previously characterized mechanical properties of tissues.

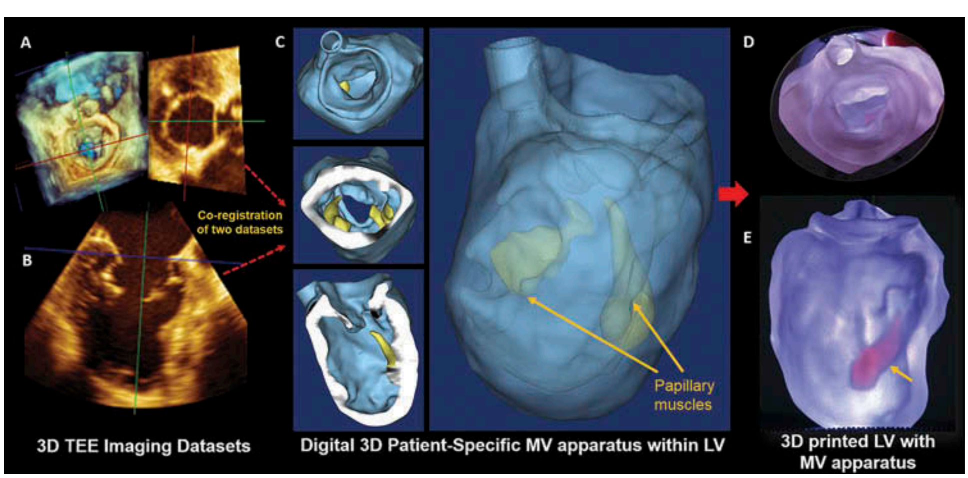

Figure 2. Reconstruction of patient-specific left heart model using multiple 3D TEE datasets and co-registration technique. (A) En-face 3D TEE images used for reconstruction of mitral valve annulus and leaflets. (B) Long-axis 3D TEE dataset used for reconstruction of papillary muscles, left ventricle and LVOT. (C) Digital, patient-specific model created by co-registration of the short-axis and long-axis echo data sets. (D) Atrial view of 3D printed mitral valve model. (E) Multi-material 3D printed patient-specific model with soft left ventricle with stiffer papillary muscles (assigned with yellow arrow). Image is adapted from Vukicevic et al.[30]

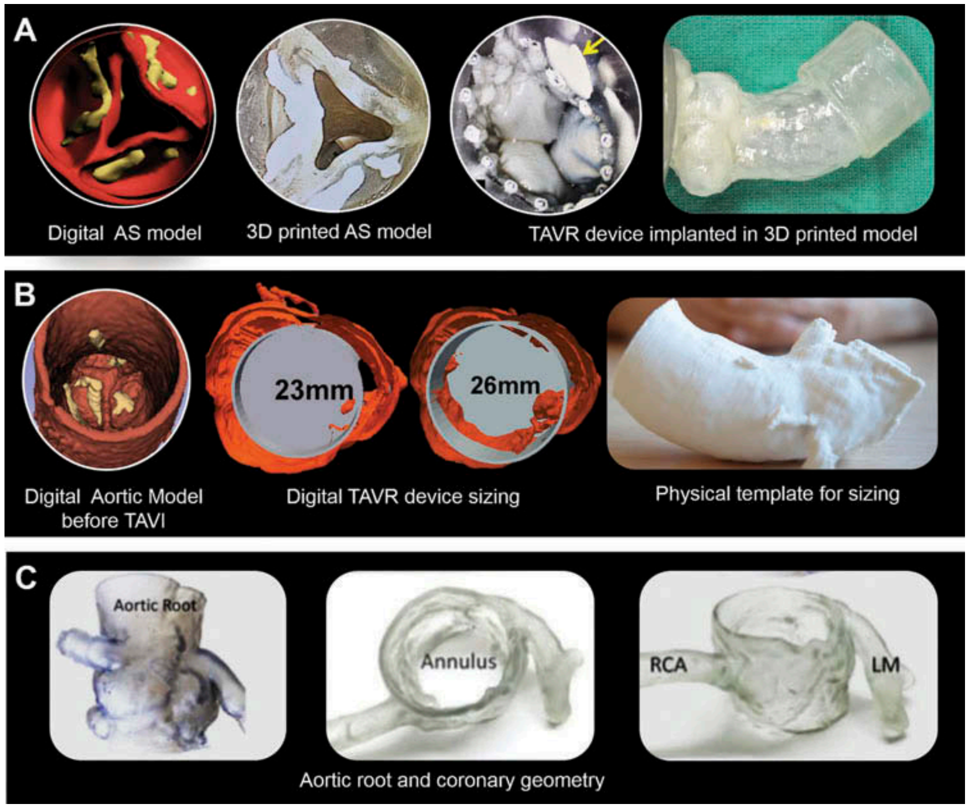

Figure 3. Aortic stenosis and pre TAVR models. (A) Digital and 3D printed multi-material, patient-specific aortic stenosis model with soft aortic cusps and rigid calcium within the aortic root, used for the functional evaluation of patient-specific hemodynamic parameters (adapted from Maragiannis et al.[33]). The aortic stenosis model is used for implantation and evaluation of the TAVR device, showing the deformation and conformation of the TAVR stent to the aortic root anatomy and calcified segments (yellow arrow) (adapted from Maragiannis et al.[34]). (B) Digital aortic models used for digital sizing of a TAVR device (left), then 3D printed, and the valve sizing is performed by visual inspection (adapted from Hernandez-Enriques et al.[35]). (C) 3D printed models of aortic root used for the anatomical observation and the evaluation of aortic arch geometry (adapted from Ripley et al.[36]).

Although material selection and properties have dramatically improved in recent years, replication of the dynamic and layered cardiac structural elements such as mitral leaflets or chordae still represent one of the biggest challenges in 3D printed modeling. Mitral leaflet layers consist of the highly extensible elastic fiber-rich atrialis, the lubricating inner glycosaminoglycan- and proteoglycan-rich spongiosa, and the load-bearing, dense collagen-rich fibrosa.[37] The chordae tendineae contain cylindrical collagen and elastic fibers. The material properties of these native leaflet regions also change in stiffness during the cardiac cycle, with the apparent stiffness increasing during contraction and decreasing during relaxation.[38] These heterogeneous biomechanics are attributed to collagen fiber dynamics, as well as regional differences in leaflet thickness and extracellular matrix composition, particularly between clear and rough zones of the anterior leaflet.[39] To approximate the complex tissue structure, rubber-like materials, for example the TangoPlus materials family, are often used with PolyJet technology for 3D print replication as they have been shown to approximate the mechanical properties of cardiac tissue under relatively small mechanical deformations.[30,40] However, it has been reported that layered and patterned printed blends of dual-materials may more closely mimic the mechanical behavior of native valve tissues. Wang and colleagues integrated spiral, helical, and chain patterns of harder materials into the base of flexible materials in an attempt to replicate the stress-strain curve of native cardiac valve tissue, as shown in Figure 4.[40,41] Most recently, Qian and colleagues have developed 3D printed models of the aortic root and valve cusps to quantitatively predict the occurrence and site of paravalvular regurgitation after TAVR.[42]

Because MV material properties are a result of its unique layered structure, printing layered composites of materials with different stiffness, including a less stiff inner layer, may more accurately mimic the true mechanical behavior of leaflets *in vivo* (Figure 4). Vukicevic and co-workers tested a series of 3D print materials and their composites arranged in bilayer and three-layer structures and compared their mechanical properties with those of explanted animal mitral tissues.[30] They created 3D printed mitral leaflets that were fabricated using two different material textures and stiffness (Figure 4) to allow for functional and structural testing of various repair and replacement devices. Comparison figures of stress-strain relations in the mitral anterior and posterior leaflets, as well as in a series of 3D printed material composites, showed that 3D printed materials replicate well the biomechanical behavior of leaflets in the normal physiological range of MV function (<10% strain, yellow frame in Figure 4F), corresponding to the fiber uncrimping phase.[43,44] It remains difficult to accurately replicate the transitional and linear regions of the native valve leaflet stress-strain curve as depicted in Figure 5F (>15% strain). In the transitional region, mitral leaflet collagen fibers are recruited and tissue stiffness increases under the applied stress (transitional region, blue framed area in Figure 4F). As the collagen becomes fully uncrimped and begins

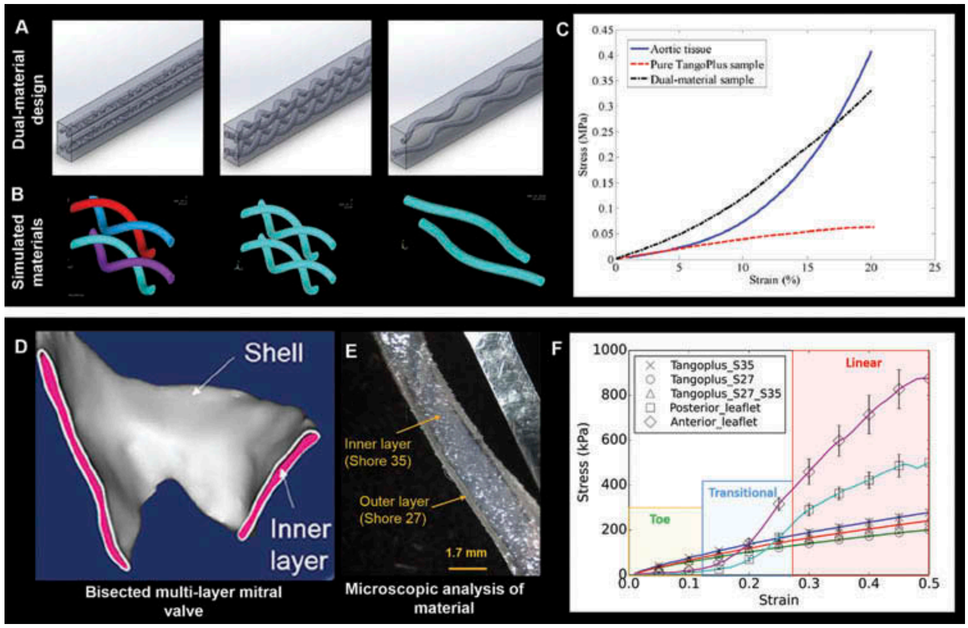

Figure 4. Print material selection, patterning, and mechanical testing. (A) Three-different dual material patterned blend modeled to approximate mechanical behavior of cardiac tissues. (B) Simulation of dual materials. (C) Stress-strain curve of the aortic tissue, pure TangoPlus and dual materials sample under strain up to 25% (adapted from Wang et al.[40,41]). (D) Digital bi-layer bisected mitral valve showing layered structure. (E) 3D printed leaflet cross-section under microscopic analysis, showing inner and outer layers of materials with different stiffness. (F) Stress-strain curve of the mitral tissue and TangoPlus materials (adapted from Vukicevic et al.[30]).

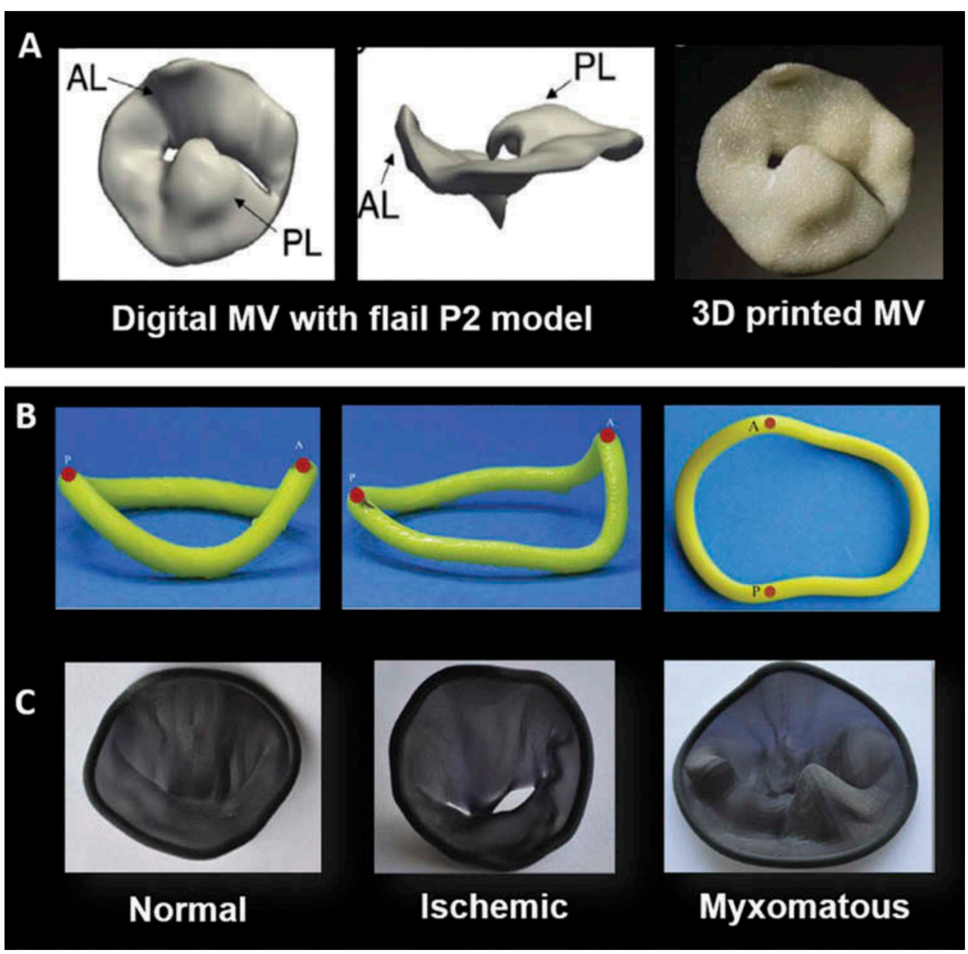

Figure 5. Echo-based patient-specific mitral valve modeling. (A) Digital and 3D printed model of patient with severe regurgitation and flail P2 leaflet reconstructed from 3D TEE images (adapted from Witschey at al.[45]). (B) Patient-specific models of (normal, ischemic remodeled and myxomatous) mitral annuli (panel B adapted from Mahmood et al.[48]). (C) annuli with leaflets (panel C adapted from Mahmood et al.[29]).

bearing the applied load, the tissue experiences maximum stiffness (linear region, red framed area in Figure 4F). In summary, these results show that the blend of 3D print materials investigated improved the stress-strain relation of 3D printed samples, approximating more closely the mechanical behavior of mitral valves within the toe region of the graph (representing the physiologic range of MV leaflet performance).

3D printing process

The process of 3D printing was first introduced by James Hull in 1986[46] as a form of stereolithography and was initially developed for faster industrial manufacturing and fabrication of prototypes. With an increasing need for volumetric replicas in the medical field, 3D printing technology was first applied for personalized implants in dental and orthopedic medicine, but has since been extended to surgical and cardiovascular medicine. 3D printing techniques have evolved and several methods are commonly used for manufacturing anatomical replicas, including stereolithography, selective laser sintering, fused deposition modeling, and PolyJet technology. Stereolithography is the oldest 3D printing technique. It builds solid 3D objects through polymerization of liquid photopolymer resins using a laser beam to solidify and build layer upon layer of the object. It is a quick, accurate and reasonably cost effective technique. Selective laser sintering creates 3D objects through a fusion of polymer powder. This method is relatively fast, and its use is ideal for 3D models that do not require a complex support architecture. Fused deposition modeling uses polymer filaments extruded through a heated nozzle. This technique is capable of printing durable and mechanically functional objects using multiple different materials, however the range of available materials is limited. PolyJet printers spray very thin layers of photopolymer, curing each layer using ultra violet light. This technology allows the digital mixing of hundreds of different materials and colors, which is ideal for the fabrication of intricate anatomically accurate models.

Applications for structural heart diseases

The cardiovascular applications for 3D printed modeling fall into four broad categories.

(1) *Training*: models used for teaching medical team members about the patient-specific pathology, or to communicate more visually with patients and their families.
(2) *Planning*: to consider or refine a certain surgical or interventional procedure based on interaction with a physical model.
(3) *Functional evaluation*: Incorporating a patient-specific environment to evaluate performance measures or imaging characteristics.
(4) *Device development*: Iterative adjustments to devise design or materials based on physical interaction with 3D printed patient-specific (or pathology-specific) models.

The following section describes some of the published experiences in 3D printed modeling for specific valve disorders and highlights their applications within the above categories.

Aortic valve modeling

3D printed anatomical replicas can be useful within clinical practice. Several authors have used clinical images to generate cardiac structures, including aortic stenosis and aortic regurgitation models, showing the usefulness of 3D printed replicas. Maragiannis and co-workers created multi-material 3D printed patient-specific models to focus on functional evaluation of native aortic valve stenosis.[33] By blending soft and hard materials, they aimed to replicate the dual-material properties of a heavily calcified aortic root complex (Figure 3A). In addition, they subjected these valve models to patient-specific hemodynamic pressures and flow conditions within a flow loop and evaluated the performance of each valve model against the clinical echocardiographic features of the patient.[33,34] This research group also performed benchtop implantation of a TAVR device inside a patient-specific, multi-material model of aortic stenosis to demonstrate how 3D patient-specific replicas can be employed to simulate transcatheter heart valve stent deformation within specific aortic root configurations (Figure 3). Unlike digital-only 3D models that fail to incorporate any simulation of device deformation, transcatheter heart valve stent deformation caused by patient-specific calcification may be accurately replicated using 3D printed materials that approximate the physical properties of the diseased tissues being modeled.

Hernandez-Enriquez and co-workers developed a patient-specific 3D aortic root model for procedural planning and device evaluation of TAVR device sizing and for the estimation of paravalvular aortic regurgitation using both digital-only implantation of the TAVR device, as well as inspection of the device implanted within a 3D printed model.[35] As shown in Figure 3B, digital sizing of the ideal valve stent within the aortic model did not replicate stent deformation or the conformal changes to the aortic root geometry. However, the interventional team that performed a visual inspection of 3D model found it useful for accurate transcatheter heart valve device sizing. In a similar fashion, Gallo and colleagues developed a 3D printed model of the aortic valve complex to plan TAVR. This complex aortic model replicated a surgically revised aortic aneurysm repaired with Dacron graft and the branchiocephalic trunk re-implanted proximal to the aortic annulus.[47] The 3D printed model was used to evaluate the risk of vascular occlusion, and the heart team successfully performed the TAVR using a self-expandable device.

Ripley and colleagues used CT images to generate aortic root models for procedure planning and functional evaluation. They replicated the aortic root with coronary arteries to visualize patient-specific anatomies before TAVR procedures and examined the feasibility of using these models to predict paravalvular aortic regurgitation (see Figure 3C).[36] By implanting TAVR devices of varying sizes (23 mm, 26 mm, 29 mm) into 3D printed aortic roots, they estimated paravalvular aortic regurgitation by projecting a light source through the LVOT. When the valve fitted the aortic root perfectly, the light was completely blocked, but when the valve did not occupy the entire aortic annulus area the light was transmitted through the gaps and was interpreted as potential risk areas for paravalvular aortic regurgitation after TAVR.

Mitral valve modeling

Initial efforts in 3D printed modeling of mitral features were focused on the extraction of anatomical information from volumetric echocardiographic data. Consequently, 3D TEE imaging datasets were used to reconstruct normal and pathological mitral annuli, both before and after surgical procedures (Figure 5).[48,49] Initially, those simple anatomical replicas were fabricated of rigid materials using stereolithographic techniques and proved useful in providing more detailed information for sizing surgical annular rings and for detecting anatomic abnormalities and changes.[48,49]

Significantly increased clinical interest in percutaneous MV treatments, combined with vast improvements in modeling methodologies and image-processing technologies, fueled the need for a more detailed definition of MV anatomical features. Consequently, the next generation of MV models comprised complete patient-specific 3D printed models of MV leaflets that were developed using 3D TEE images (Figure 5).[29,45] Those proof-of-concept MV replicas served for surgical guidance and as visual anatomical education tools.[45] However, the closed coaptation lines and static leaflets inherent in this generation of models were not appropriate for the benchtop implantation of medical devices.

With the continuing advancement of 3D printing technologies and the emergence of a variety of digital materials and material composites, 3D printed MV models have become increasingly sophisticated. The current generation of MV models allow for the creation of a MV apparatus with all functional elements, including the mitral annulus, leaflets, chordae tendineae and papillary muscles (Figures 1 and 6).[31] Each MV element can be fabricated utilizing a range of flexible materials with different stiffness values. This allows for an anatomic replication of mitral elements with approximated mechanical performance which is useful for benchtop implantation of MV repair and replacement devices. These multi-material MV apparatus models have been created to address specific patient repair challenges such as deployment of an occluder device into a perforated native mitral leaflet.[50] When the model is life-sized and appropriately

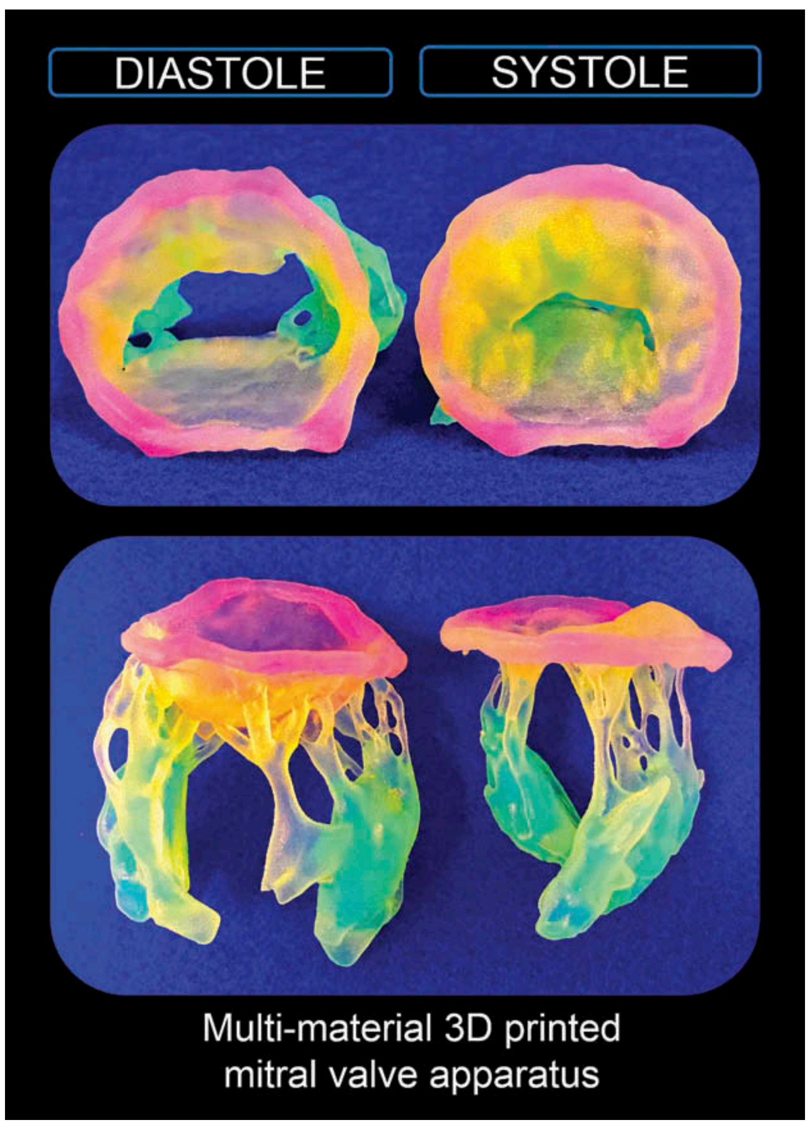

Figure 6. Multi-material 3D printed model of a patient-specific mitral valve apparatus. Segmented from a single CT image dataset. Enface images (top) and long-axis images (bottom) depict the color choices used to print the mitral annulus (pink), leaflets (clear), chordae tendinaea (yellow) and papillary muscles (green). Within the enface images, regions of the clear mitral leaflets appear yellow due to insertions of the yellow chordae tendinaea.

deformable, it may be invaluable in facilitating device positioning and predicting interaction with native tissue.[31] The advent of deformable, patient-specific models makes them suitable for benchtop implantation of MV repair devices and instrumental in selection of the most appropriate repair strategy, as well as device selection and sizing.[30,50]

Unlike open heart surgeries, less invasive TMVR procedures permit neither direct observation of the mitral apparatus geometry, nor any staged evaluation of the biological interaction with the implanted TMVR device. Due to intra-procedural challenges and frequent post-procedural complications following early TMVR interventions, the use of 3D modeling (both virtual and 3D printed) to visualize, simulate, and train before performing a TMVR procedure has gained increasing support and research momentum.[31,51–54] While it has been demonstrated that the virtual (digital only) implantation of a TMVR stent frame can provide a rough estimation of LVOT obstruction,[51,52,54] the estimation of the virtual neo-LVOT in post-TMVR constructs does not include the interaction of TMVR devices with surrounding tissues or the anterior leaflet deflection that contributes to additional LVOT obstruction risk (Figure 7).[31,51] In contrast, patient-specific 3D printed models may allow for device-tissue interaction and deformation to better predict structural and functional challenges encountered during and after a TMVR procedure.[31,53,55] The combination of image processing and advanced multi-material 3D printing technologies allow for an accurate and realistic replication of MV geometries (including even heavily calcified regions) and are being evaluated as a means to improve TMVR patient selection and clinical outcomes. Utilization of current 3D models under pressurized conditions in the pulse duplicator is an ongoing area of exploration and may soon provide a more complete patient-specific anatomic and functional model environment to evaluate these highly complex and individualized valve interventions.[54,55]

Tricuspid and pulmonic valve modeling

Several investigators have recently demonstrated the feasibility of creating 3D models of the tricuspid valve from 3D TEE image data.[56,57] A recent proof-of-concept deformable valve model was created to plan the repair of tricuspid regurgitation using the MitraClip repair system.[57] Schievano and colleagues retrospectively used magnetic resonance images to reconstruct a series of

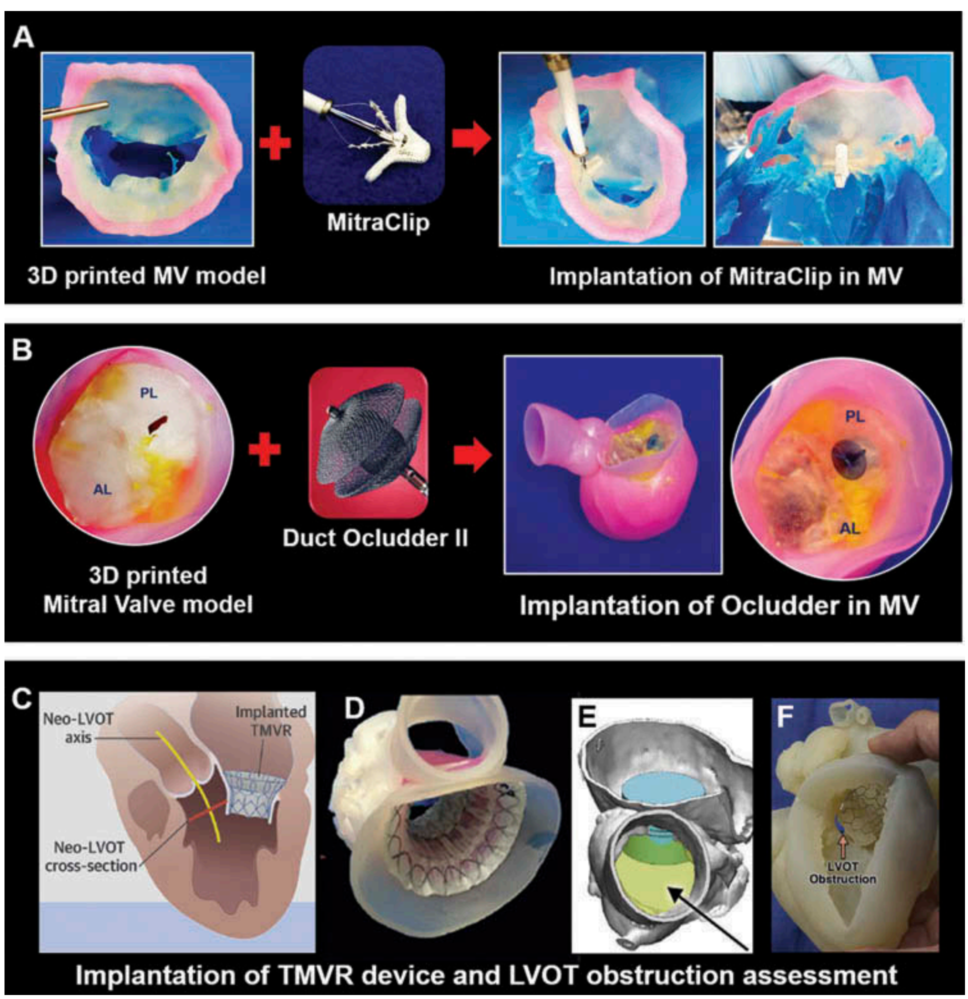

Figure 7. Interventions in mitral valve models. (A) Benchtop implantation of MitraClip device in patient-specific 3D printed mitral valve apparatus. (B) Procedural planning, simulation and device selection for native mitral valve perforation repair (adapted from Little et al.[50]). (C) TMVR procedural planning and LVOT risk assessments (adapted from Vukicevic et al.[31]). (D) TMVR device implanted into patient-specific mitral valve model with anterior mitral leaflet (pink) visible within the LVOT (image top); (adapted from Vukicevic et al.[31]). (E) Digital implantation of TMVR device into the patient-specific digital model (adapted from Wang et al.[52]). (F) 3D printed model to assess predicted LVOT area following TMVR (adapted from Eleid et al.[53]).

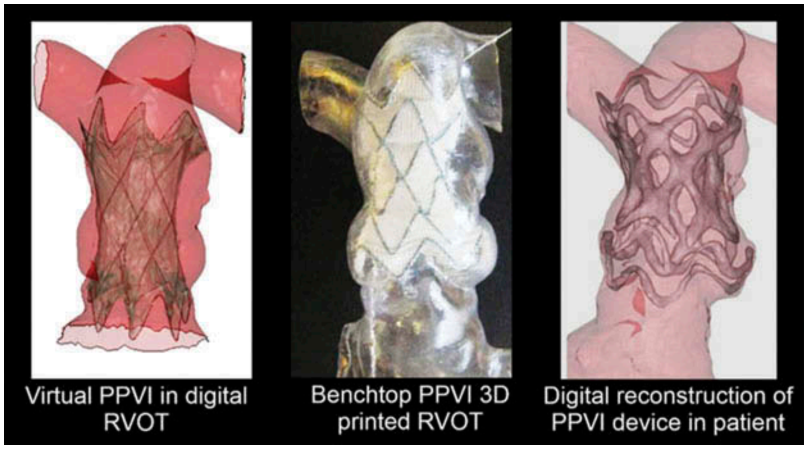

Figure 8. Modeling RVOT for percutaneous pulmonary valve implantation evaluation. Virtual implantation of novel percutaneous pulmonary valve stent (left), benchtop implantation of pulmonary valve stent within the patient-specific RVOT model showing the deformation of device (middle). Digital reconstruction from a clinical CT study of the percutaneous pulmonary valve implantation device after implantation into the patient (right), showing stent frame deformation as seen in the 3D printed construct (middle panel). Figure adapted from Chung at al.[18].

patient-specific right ventricle geometries of patients who have undergone percutaneous pulmonary valve implantation.[58] They found that 3D printed patient-specific models can introduce additional information, compared to magnetic resonance images alone[58] and used a patient-specific 3D model to plan a first-in-man implantation of a new generation of percutaneous pulmonary valve implantation devices (Figure 8).[59] For this application, they examined the feasibility of implanting a novel device into the RVOT using either the right pulmonary artery or the left pulmonary artery for device staging and positioning. After benchtop testing of both pathways, they determined that the percutaneous pulmonary valve implantation procedure was not possible within the right pulmonary artery, while the implantation via the left pulmonary artery and pullback through the pulmonary trunk was successful. Accordingly, the first-in-man percutaneous pulmonary valve implantation was performed after refining the device delivery methods in a 3D printed model (Figure 8).

Current challenges

A rate-limiting step for 3D printed modeling is the time and expertise required to segment a large clinical image dataset into a focused digital model of the region of interest. Within this smaller dataset, the anatomic tissues of interest must be identified, "tagged," and then assigned a specific color or material for printing. As this process becomes increasingly automated, the time and cost required for 3D printed modeling is expected to decrease.

A current limitation to 3D functional modeling is that the normal mechanical properties of cardiac tissues across the age spectrum is not known. Animal models and cadaveric human reports have provided some guidance, but individual anatomic variations in pathologic tissue fibrosis and calcification patterns will continue to limit the precise replication of patient-specific tissue properties using 3D printed methods. However, as has already been demonstrated [30,50] for many considerations, only an approximate replication of tissue properties (e.g. soft, medium, and hard) is required. Ongoing collaboration between materials scientists and 3D printed material manufacturers will undoubtedly continue the pace of rapid advances within this field.

Although the costs of printers and materials are decreasing, the cost of patient-specific anatomical models remains a significant barrier to the wider adoption of such programs. Since both the printer technology and the supporting software applications are rapidly evolving, a solution for many institutions may be to outsource this activity to a third-party vendor of rapid prototyping services. The authors of this review have found this to be the most practical approach to contain costs and to ensure uninterrupted access to high quality 3D printed models whenever required.

The clinical application of 3D print modeling is new to the Structural Heart Disease (SHD) field so several important questions remain unanswered. Will more advanced computer simulators make 3D printing obsolete? This is entirely possible, however a robust computer simulation of the deformation of patient-specific pathologic cardiac tissue by an implanted device is a very challenging problem. So far, a solution to this problem has not yet been reported. Who will benefit from a 3D printing program? The SHD imager will benefit from enhanced appreciation of the spatial volume—sometimes viewed from an image perspective never before seen or used by the imager. The interventionalist may benefit from a more comprehensive understanding of the target anatomy and possible consequences of an adverse deployment of the device. And the patient should benefit from having a more informed and better-prepared implant team. Will the benefit justify the cost? This answer may depend upon who is asking the question. The perspective of a successfully treated patient may differ from that of an institutional administrator, or regional care authority. A unifying answer may require a multi-institutional registry to objectively define the clinical benefit and programmatic costs of a 3D printing program to treat patients with structural heart disorders.

Conclusion

Future directions

3D bioprinting is a collection of techniques that use biocompatible materials, cells, and supporting components to fabricate living tissues within a desired 3D structural architecture.[60] Recently, techniques have been developed to bioprint heart valves using biological materials, including hyaluronic acid, alginate, and gelatin, along with encapsulated valvular interstitial cells.[61,62] This emergent field of bioprinting has been previously reviewed.[63,64] Although there is increasing interest in using 3D bioprinting methods to fabricate replacement heart valves, this approach is not yet a clinical option for the treatment of patients with structural heart disorders.

Patient-specific 3D printed, multi-material models of complex valve constructs have the potential to significantly impact the teaching, planning, and performance of structural heart interventions. Future efforts must focus on continued technical improvements in image data management, anatomic segmentation, and 3D printed material selection protocols. In addition, those involved in structural heart interventions and modeling must begin to gather data regarding the impact of such modeling on clinical patient outcomes. Only after quantification of the broader impact of patient-specific modeling can we expect to see sustainable and widely adopted mechanisms to fund 3D print programs for cardiovascular care.

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