# 3D Modeling: A Future of Cardiovascular Medicine

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<th>Journal:</th>
<th><em>Canadian Journal of Physiology and Pharmacology</em></th>
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<td>Manuscript ID</td>
<td>cjpp-2018-0472.R1</td>
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<td>Manuscript Type:</td>
<td>Review</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>11-Sep-2018</td>
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<tr>
<td>Complete List of Authors:</td>
<td>Garner, Kaley; University of Central Florida</td>
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<tr>
<td>Is the invited manuscript for consideration in a Special Issue:</td>
<td>Made in Canada</td>
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<tr>
<td>Keyword:</td>
<td>Three-dimensional, Cardiovascular Disease, Cardiac Modeling, Surgical Simulation, Medical Education</td>
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3D Modeling: A Future of Cardiovascular Medicine

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Running Title: 3D Modeling in Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) resulting from atypical cardiac structures continues to be a leading health concern despite advancements in diagnostic imaging and surgical techniques. However, the ability to visualize spatial relationships using current technologies remains a challenge. Therefore, 3D modeling has gained significant interest to understand complex and atypical cardiovascular disorders. Moreover, 3D modeling can be personalized and patient-specific. 3D models have been demonstrated to aid surgical planning and simulation, enhance communication among surgeons and patients, optimize medical device design, and can be used as a potential teaching tool in medical schools. In this review, we discuss the key components needed to generate cardiac 3D models. We highlight prevalent structural conditions that have utilized 3D modeling in pre-operative planning. Furthermore, we discuss the current limitations of routine use of 3D models in the clinic as well as future directions for utilization of this technology in the cardiovascular field.

Keywords: Three-dimensional, Cardiovascular Disease, Cardiac Modeling, Patient-specific, Pre-operative Planning, Surgical Simulation, Medical Education
Introduction

3D disease modeling has recently demonstrated significant potential in pre-operative evaluation and interventional care of cardiovascular disease (CVD). Treatment of CVD presents a major clinical challenge due to high incidence (Benjamin et al. 2018; Smith et al. 2017), increased risk for co-morbidities (Cohen et al. 2013; Gerardin and Earing 2018; Rushton and Kadam 2014), and the potential need for long-term care (DiBardino and Jacobs 2014). Many factors are attributable to the development and progression of acquired forms of CVD, including hyperlipidemia, hypertension, and metabolic syndrome (Lee et al. 2012; Thayer et al. 2010). However, conditions related to cardiac structural abnormalities are also a source of CVD (Dankowski et al. 2014; Lau et al. 2018).

Structure-related CVD is diagnosed in approximately 40,000 newborns each year with nearly 25% requiring invasive corrective care (Benjamin et al. 2018). Congenital heart disease (CHD) and valvular disease are two common structure-related CVDs (Dankowski et al. 2014). These diseases can arise when cardiac structures fail to properly form during development, leading to conditions such as atrial septal defects (ASD), ventricular septal defects (VSD), reversed great vessels, underdeveloped heart chambers, and valve regurgitation (Lau et al. 2018). While these conditions are variable in their severity, they can be life-threatening and require surgical intervention to correct (Pouch et al. 2017).

The management of structure-related CVD requires four main components: diagnostic imaging, evaluation of pathology, pre-operative planning, and surgery. Current diagnostic imaging methods include: magnetic resonance imaging (MRI),
computed tomography (CT), and echocardiography. While these imaging data sets are effective in diagnosing and treating straightforward cardiac cases, they are restricted in their ability to depict 3D spatial relationships needed for pre-operative planning in complex cases of CVD (Valverde 2017). As a result of the challenges associated with this process, 3D printed disease modeling has recently emerged as an innovative method to produce physical replicas of patient anatomy from diagnostic images (Farooqi and Sengupta 2015). The clinical utility of 3D printed CVD models is multifold and has been demonstrated in pre-operative planning (Dankowski et al. 2014; Mendez et al. 2018; Olejnik et al. 2017; Smith et al. 2017; Valverde 2017; Valverde et al. 2017), communication between physicians and the interventional care team (Biglino et al. 2017), surgical simulation and training (Chen et al. 2018; Hoashi et al. 2018; Olivieri et al. 2016; Yoo et al. 2017), as well as in the design of patient-specific medical devices (Hachulla et al., 2018).

This review discusses the methodology used to generate 3D CVD models with detailed descriptions of techniques and practices to optimize the three major components of model production: diagnostic imaging, digital modeling, and 3D printing. Furthermore, we highlight the clinical utility of 3D modeling in CVD by presenting four complex structural pathologies: double-outlet right ventricle (DORV), hypoplastic left heart syndrome (HLHS), transposition of the great arteries (TGA), and valvular disease.

**Principles of 3D Cardiovascular Disease Modeling**

Figure 1 shows the three major steps used to create 3D disease models: 1) acquisition of diagnostic images (MRI, CT, and echocardiography), 2) digital modeling, and 3) 3D printing. Acquisition of diagnostic images encompasses the techniques of...
MRI, CT and echocardiography. Using specialized software, targeted regions of interest (ROI) within these image sets can be defined and converted into 3D digital models that can be 3D printed (Farooqi et al. 2016b). 3D disease models have several benefits in the treatment of CVD, such as simulating surgical procedures in effort to reduce surgery time and costs as well as improve patient outcomes through improved planning (Zhao et al. 2018).

The following sections will discuss the technical aspects of each of these major steps in CVD modeling with an emphasis on presenting the current standards and techniques to optimize each component.

**Acquisition of Diagnostic Images (MRI, CT, and Echocardiography)**

Diagnostic images are acquired to assist in planning of CVD disorders and interventional therapy (Grigoratos et al. 2018). Several specific features of these diagnostic image sets make them unique and suitable for 3D disease modeling: 1) 2D images are acquired in all three dimensions ($x$, $y$, and $z$) resulting in a volumetric data set (Otton et al. 2017), 2) images are displayed in a spectrum of greyscale (GS) which allows targeted image structures to be isolated and further processed with digital modeling software (Farooqi et al. 2016a), and 3) a unique file format in the form of DICOM (Digital Imaging and Communication in Medicine) is generated that can be universally used in digital modeling software (Marro et al. 2016).

In diagnostic imaging, when 2D images ($x$ and $y$) are acquired throughout a volume of space adding depth ($z$), it allows volumetric image sets to be obtained and processed in 3D modeling software to develop a volumetric 3D digital object (Otton et al. 2017). However, there are concerns in this process that can influence the 3D models accuracy and the ability to depict pathology. Optimal diagnostic image sets are
isotropic and have high spatial resolution (Greil et al. 2007; Valverde 2017). Isotropic image sets have equal distances between sequential planes in all three dimensions (Valverde 2017). If one dimension of the scan (for example, x) is larger than the other two (y and z), then the model will have poorer spatial resolution and result in substandard model production as a result of the inability to capture details of cardiac structures between imaging planes (Otton et al. 2017). High spatial resolution is achieved through smaller distances between planes (Greil et al. 2007). 0.3 mm$^3$ to 1.25 mm$^3$ and 1.5 mm$^3$ to 1.8 mm$^3$ is optimal for model production from CT and MRI, respectively (Valverde 2017; Valverde et al. 2017). Diagnostic images must also display targeted cardiac tissue with a high degree of contrast relative to the surrounding structures in order for a GS range to be designated and specific cardiac structures to be isolated (Yoo et al. 2015). Moreover, diagnostic scans are exported in the DICOM format, which is the industry standard for storing and transferring medical image sets (Wang et al. 2018). These images can be used directly with 3D modeling software without the need for file type conversion (Mitsouras et al. 2015).

Optimization of image acquisition settings can significantly increase the efficiency of the model production process by reducing the time required for each step (Otton et al. 2017). Ideal images have high contrast between structures, low noise, and high spatial resolution (Giannopoulos et al. 2016). Therefore, it is important to evaluate the capabilities and limitations of each imaging modality prior to acquiring patient images for 3D modeling. A systematic review by Byrne et al. (2016) determined that CT and MRI are both commonly used to model intracardiac (atria and ventricles) and extracardiac
structures (great vessels) (Byrne et al. 2016). However, echocardiography data sets are more commonly used for modeling valvular anatomy (Byrne et al. 2016).

**Magnetic Resonance Imaging**

MRIs are acquired based on the way protons in the body move when subjected to a strong magnetic field (Bonnichsen and Ammash 2016). In a study by (Kappanayil et al. 2017), 3D models constructed from MRI significantly improved surgical decision-making and pre-operative planning of CHD. MRI is particularly useful when other imaging techniques fail to adequately capture a condition (Samyn 2004). MRI typically compliments diagnosis founded on echocardiography (Fratz et al. 2013). For example, MRI can be used to improve visualization of the right ventricle, which is limited in echocardiography (Samyn 2004). MRI can also provide information about blood flow, valvular regurgitation, and structural characteristics in complex CHD via phase contrast imaging (Bonnichsen and Ammash 2016; Samyn 2004). Gadolinium can be used to enhance visualization of the aorta, pulmonary arteries and veins in magnetic resonance angiography, which can optimize efficiency in model production of these structures (Bonnichsen and Ammash 2016). However, MRI is limited in patients with implanted devices, such as pacemakers, stents, or artificial valves due to the potential of artifacts that prevent adequate cardiac visualization and model production (Bonnichsen and Ammash 2016). Other limitations of MRI include low sensitivity compared with CT and echocardiography, long acquisition time, and high costs are factors that limit its ability to serve as the primary imaging technique in CVD (Dydynski et al. 2016; Luijnenburg et al. 2010).

**Computed Tomography**
CT has been reported to be one of the most sensitive and widely used imaging techniques for cardiac disease modeling (Mitsouras et al. 2015). A major advantage to CT is that small details can be resolved that are not easily observed in other imaging modalities such as MRI and echocardiography (Gosnell et al. 2016). Therefore, when modeling structures such as the coronary arteries, vessel stenosis, and extracardiac anatomy, CT is an advantageous option (Bonnichsen and Ammash 2016; Gosnell et al. 2016). Dydynski et al. (2016) demonstrated success in creating 3D models from CT angiography for patients in which transthoracic echocardiography failed to clearly show the position of the VSD in relation to the pulmonary and aortic outflow tracts (Dydynski et al. 2016). However, the major limitation of CT use is the exposure to radiation caused by the emission of x-rays, which has been correlated with increased risk of cancer (Brenner and Hall 2007). This is a major concern when considering imaging for CHDs in children to generate 3D printed cardiac models (Hill et al. 2017).

**Echocardiography**

Echocardiography is the most common form of imaging in CHD (Farooqi and Mahmood 2018). By correlating absorbance of sound waves with tissue density, structural and hemodynamic information can be obtained (Ginty et al. 2018). In recent years, advancements in this technology have resulted in 3D echocardiography, which has been valuable in visualizing atrioventricular and semilunar valves over 2D echocardiography (Witschey et al. 2014). However, the ability to perform quantitative analysis of these structures and interact with a computerized rendering is often time-consuming and dependent on significant user-input within 3D echocardiography analysis software (Vegas 2016; Witschey et al. 2014). Several groups have successfully used 3D echocardiography in combination with 3D printing to overcome these
limitations and model cardiac valves (Ginty et al. 2018; Scanlan et al. 2018; Witschey et al. 2014). Mitral valve replacement is often the preferred therapeutic approach over mitral valve repair due to the challenges associated with valve imaging and a highly technical repair procedure (Witschey et al. 2014). Witschey et al. (2014) demonstrated that 3D echocardiography could be used to capture mitral valve morphology from mid-systolic and diastolic image frames and converted into a physical model using 3D printing in order to improve surgical repair technique (Witschey et al. 2014). Moreover, Ginty et al. (2018) and Scanlan et al. (2018) reported using 3D echocardiography to generate patient-specific dynamic mitral valve models for surgical simulation (Ginty et al. 2018; Scanlan et al. 2018). While 3D echocardiography is a valuable tool to 3D model cardiac valves, it is limited in visualization of extracardiac structures, such as the aorta and pulmonary arteries (Shah 2013).

**Digital Modeling**

The process of segmentation allows for the isolation and extraction of specified structures from DICOM images so that 3D models can be made with anatomical accuracy (Otton et al. 2017). Segmentation software can be used to defined GS values corresponding to the cardiac tissue as the ROI which is overlaid with a mask (Dankowski et al. 2014; Lau et al. 2018; Yoo and van Arsdell 2017). As a result, the masks created on each image in the stack can be merged together to form a 3D digital model (Giannopoulos et al. 2015; Lau et al. 2018; Olejnik et al. 2017).

Currently, there are several commercially available segmentation packages that have successfully been used to create 3D models of cardiovascular disease. The two most commonly used are Mimics® (Materialise NV, Leuven, Belgium, 1992–2015) (Reynisson et al. 2015) and Simpleware® (Simpleware, Exeter, UK)(Rodrigues et al. 2014).
2009); however, other non-commercial options are available, such as ITK-SNAP® (http://itksnap.org) (Yushkevich et al. 2006), 3DSlicer® (http://www.slicer.org) (Calon et al. 2017), and OsiriX® (https://www.osirix-viewer.com) (Reynisson et al. 2015).

Following segmentation, the digital model undergoes post-processing to orient the model for the optimal view of the condition (Dankowski et al. 2014). The segmented digital model is exported out in the .STL file type, which is the industry standard for 3D objects and 3D printing software (Otton et al. 2017).

**3D Printing**

3D Printing, also known as additive manufacturing, is a method of creating physical objects from digital 3D designs by stacking many 2D layers of materials in overlapping patterns (Farooqi and Mahmood 2018; Rengier et al. 2010; Ripley et al. 2017). 3D technology was initially established in the manufacturing and engineering industries as a method to rapidly create prototypes (Farooqi and Mahmood 2018). However, in recent years it has demonstrated promising applications in medicine. Dental and orthopedic specialties were among the first to begin incorporating 3D printing as a technique to create patient-specific implants and prosthesis (Farooqi and Mahmood 2018; Ripley et al. 2017). The ability to create multiple variations of a prototype promoted its dissemination into other medical specialties, such as CVD (Mitsouras et al. 2015).

Several types of 3D printers are used in medical printing, such as fused deposition modeling (FDM) (Faletti et al. 2018; Witschey et al. 2014), stereolithography (SLA) (Dankowski et al. 2014), and binder jetting (Jacobs et al. 2008; Smith et al. 2017). Selection of printer type and material is heavily influenced by the desired characteristics of the printed 3D model (Mitsouras et al. 2015). Features such as size, desired color
and flexibility, layer resolution, and cost are key variables of consideration (Farooqi and Mahmood 2018). FDM works by extruding heated thermosensitive plastics, such as acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA), in successive layers that bond together as they cool to room temperature (Rengier et al. 2010). It is both an economical and widely available option; however, its low layer resolution makes its use limited for medical applications where precision is needed (Meier et al. 2017; Mitsouras et al. 2015). Conversely, SLA is a highly precise option that uses photopolymers that solidify upon exposure to UV light (Medero et al. 2017). In this system, a mechanical stage is lowered into a vat of photosensitive resin where a pattern is formed with UV light causing the material to harden. As the stage incrementally increases in height, subsequent layers can be formed. However, materials are often costly and require significant use of support materials (Mitsouras et al. 2015; Revilla-Leon and Ozcan 2018). Binder jetting is a technique in which a layer of powder is deposited in a defined shape and is subsequently bonded by the addition of an adhesive liquid (Rengier et al. 2010). This process is typically used for its ability to create models of multiple colors which can be used to highlight specific anatomical structures (Smith et al. 2017).

While the majority of these 3D printers produce rigid 3D models, materials that are flexible can provide distinct advantages in CVD (Kappanayil et al. 2017). Recently, new materials mimicking properties of human tissue have been introduced (Hoashi et al. 2018; Kappanayil et al. 2017). Flexible materials can provide valuable educational benefits in applications such as surgical simulation by allowing young surgeons to practice complicated procedures without risk to the patient (Hoashi et al. 2018; Yoo et al. 2017). For example, flexible materials such as HeartPrint® (Materialise Leuven,
Belgium) has been reported to provide realistic flexibility and tensile strength (Gosnell et al. 2016; Samuel et al. 2015).

**Clinical Applications of Patient-Specific Models**

CHD and valvular disease are prevalent conditions that arise from malformation of cardiac chambers (Farooqi et al. 2016b), vasculature (Hoashi et al. 2018; Loke et al. 2017; Ma et al. 2015) and incompetent valves (Birbara et al. 2017; Ripley et al. 2016; Scanlan et al. 2018; Vukicevic et al. 2017b; Witschey et al. 2014). The complex geometries and patient-specificity in these conditions make surgical planning, visualization of intracardiac spatial relationships, and optimal fitting of medical devices a challenge (Dankowski et al. 2014; Olivieri et al. 2014). DORV, HLHS, TGA, and valvular diseases are examples of conditions that benefit from 3D patient-specific models. A summary of case studies using 3D modeling in each of these conditions is shown in Figures 2 and 3.

**Double Outlet Right Ventricle**

DORV is a type of complex CHD that results from a VSD which causes the aorta and pulmonary arteries to connect to the right ventricle (Yoo and van Arsdell 2017; Zhao et al. 2018). The variability in position of the great arteries, location of the VSD, and presence of right ventricular outflow tract obstruction make surgical planning a significant challenge (Pang et al. 2017; Pushparajah et al. 2013). 3D models have shown improvement over 2D visualization on a computer screen in relaying a comprehensive understanding of DORV pathology (Yoo and van Arsdell 2017). In a study by Zhao et al. 3D models of DORV patients decreased surgical time, cardiopulmonary bypass time, mechanical ventilation time, and time in post-operative intensive care relative to a control group without 3D models (Zhao et al. 2018).
Moreover, models provided clear visualization of the VSD size, location of the main pulmonary artery, and aorta which improved the surgeon’s ability to determine appropriate baffle placement (Zhao et al. 2018). Farooqi et al. (2016) reported that sixteen 2D cardiac MRI images were needed to visualize the same ventriculo-arterial relationship as a single 3D model, providing evidence that 3D models are effective tools in CVD (Farooqi et al. 2016b). Therefore, 3D models are valuable in DORV pathology as evidenced by their ability to demonstrate complex connections between the great arteries and right ventricle, as well as reduce time associated with surgery (Riesenkampff et al. 2009; Zhao et al. 2018).

Hypoplastic Left Heart Syndrome

HLHS is fatal without surgical intervention (Pouch et al. 2017). This condition results from mitral and aortic valve narrowing and undersized left atrium and/or ventricle (Chen et al. 2018; Pouch et al. 2017). Corrective surgery is performed in three stages: the Norwood procedure (performed immediately following birth), the Glenn procedure (at approximately 6 months of age), and the Fontan procedure (performed between 18 months to 3 years of age) (Chen et al. 2018). Following each of these interventions, changes in the hemodynamics within the aorta and competence of the tricuspid valve can determine a patient’s prognosis (Chen et al. 2018; Pouch et al. 2017). 3D modeling is commonly used in the Norwood procedure which requires reconstruction of the aorta, as it can increase the susceptibility for valve regurgitation, coarctation, stenosis, and hypertension (Arbia et al. 2015; Chen et al. 2018). In a study by Chen et al. (2018), 3D models were used to simulate aortic arch reconstruction surgery and understand how arch morphology influences post-operative hemodynamics (Chen et al. 2018). Models provided a method to appropriately size patches and optimize surgical technique (Chen
et al. 2018). As a result, 3D modeling was shown to have potential in reducing costs and time associated with HLHS operations (Chen et al. 2018). Kiraly et al. (2016) further demonstrated the efficacy of 3D models in pre-operative simulation (Kiraly et al. 2016). 3D modeling of a patient that previously received a neonatal modified Norwood-1 procedure resulted in clear visualization of multiple obstructions to the descending aorta and innominate artery as well as provided exact dimensions to perform arch augmentation without excess patch material (Kiraly et al. 2016).

Furthermore, HLHS has been associated with dysfunction of the tricuspid valve, leading to regurgitation (Pouch et al. 2017). Therefore understanding of valve morphology can provide a foundation for surgical techniques that promote valve competence and patient survival (Pouch et al. 2017). Pouch et al. (2017) demonstrated that 3D modeling of the tricuspid valve using semi-automated segmentation could reliably be used for 3D visualization and quantitative assessment (Pouch et al. 2017). Specifically, 3D models were used to quantify the annular bending angle of the tricuspid valve, which has been associated with tricuspid failure in HLHS (Pouch et al. 2017).

**Transposition of the Great Arteries**

In patients with TGA, the aorta abnormally connects to the right ventricle while the pulmonary artery abnormally connect to the left ventricle resulting in circulation of oxygen depleted blood to the body (Files and Arya 2015). In most patients, the arterial switch operation is recommended to reverse these connections and achieve normal anatomy (Chapron et al. 2013). However, occurrence of baffle obstruction and poor post-operative hemodynamics can cause cyanosis and dyspnea (Olivieri et al. 2014; Poterucha et al. 2017; Xie et al. 2017; Yang et al. 2018). Olivieri et al. (2014) created a 3D model from CT scans of a patient diagnosed with dextro-TGA that had undergone
surgical correction via the Mustard procedure (Olivieri et al. 2014). In this patient, a transthoracic echocardiogram showed a pulmonary venous baffle obstruction that required implantation of a stent to alleviate symptoms of dyspnea (Olivieri et al. 2014). Complicated cardiac structure can make surgical planning necessary to determine the appropriate stent sizing and deployment route (Olivieri et al. 2014; Olivieri et al. 2016). Simulation on the 3D model provided insight into sizing, placement and relationship to intracardiac structures (Olivieri et al. 2014). Additionally, Chapron et al. (2013) demonstrated that 3D models created from patient CT scans of a two year old male diagnosed with D-TGA, ASDs, and patent ductus arteriosus could be used to refine surgical technique of the mustard operation in order to improve post-operative hemodynamics (Chapron et al. 2013). Inspection of chamber size and shape provided by the 3D models added valuable information about pre- and post- operative cardiac morphology (Chapron et al. 2013). In a study by Hoashi et al. (2018), twenty patient-specific models of CHD, including 7 with TGA, were printed in a flexible material for surgical simulation (Hoashi et al. 2018). The models were beneficial in learning about TGA anatomy and facilitated physical simulation of surgical repair (Hoashi et al. 2018).

Valvular Disease

The cardiac cycle is regulated by the highly dynamic flow of blood through the hearts valves (Ayoub et al. 2016). In valvular disease, defective geometry of valve structure prevents proper function, resulting in altered hemodynamics (Witschey et al. 2014). Percutaneous catheter-based approaches, such as transcatheter aortic valve replacement (TAVR), can be used as corrective therapy (Ripley et al. 2016). Two of the major challenges associated with this approach is the need to precisely fit prosthetic valves within variable cardiac structure, and once placed, form an adequate seal to
prevent paravalvular aortic regurgitation (PAR) (Hahn et al. 2018; Ripley et al. 2016). 3D models have been used for this purpose to simulate surgical procedures and determine precise dimensions needed for proper valve fit (Ripley et al. 2016). Ripley et al. (2016) used 3D models constructed from CT images to visualize the aortic root anatomy so that proper TAVR device placement could be assessed (Ripley et al. 2016). Fit of valve prosthetics on the 3D printed model was able to accurately predict the development of PAR following TAVR (Ripley et al. 2016). Dankowski et al. (2014) reported using 3D models to simulate and plan a percutaneous mitral annuloplasty and information gained from this simulation optimized the valve delivery technique and placement (Dankowski et al. 2014). Furthermore, 3D models have been shown to provide quantitative information of cardiac function, specifically the left ventricular end diastolic diameter and height (Dankowski et al. 2014). Witschey et al. (2014) created 3D models of severe forms of mitral valve regurgitation (Witschey et al. 2014). Visual inspection of printed models derived from 3D echocardiography data demonstrated distorted valve geometry commonly associated with valvular disease (Witschey et al. 2014).

Limitations

The current state of 3D disease modeling for routine clinical use is hindered by several factors: 1) production time, 2) costs of modeling, 3) requirement of technical expertise, 4) depiction of a static cardiovascular system, and 5) limited quantitative evidence of clinical utility (Lau et al. 2018). The process to convert patient scans into 3D models requires extensive user-input and time (Cantinotti et al. 2017). While this is influenced by the complexity of the pathology depicted by the model and the technical
ability of the user, the average time required for segmentation alone can range from two to twenty hours (Cantinotti et al. 2017; Giannopoulos et al. 2016). Additionally, high costs associated with segmentation software, the 3D printer, and material can present additional challenges. On average, model production costs range from several hundred dollars to several thousand dollars (Chen et al. 2018; Farooqi and Sengupta 2015; Kurenov et al. 2015; Werner et al. 2010). Although several open-sourced options exist and are free to download, commercial segmentation software can cost between $500 to as much as $10,000 (Kurenov et al. 2015). Moreover, knowledge of cardiac pathology, the ability to interpret diagnostic images, and training on specialized software are prerequisites of model production, all of which require high-level technical expertise (Byrne et al. 2016). Additionally, current models are often static depictions of pathology printed in rigid materials that are derived from a single imaging modality. These are limited in the ability to demonstrate certain conditions, such as hemodynamics (Mitsouras et al. 2015). Several groups have recently begun addressing this by developing dynamic cardiac models using flexible materials (Markert et al. 2007; Ripley et al. 2016). The elasticity of these models coupled to specialized electronics allows simulation of in vivo hemodynamics with tissue-like properties (Maragiannis et al. 2014; Markert et al. 2007; Ripley et al. 2016). Furthermore, reports of evidence supporting clinical benefit has primarily been qualitative, with conclusions founded on questionnaires and case-studies (Bhatla et al. 2017; Kappanayil et al. 2017; Riesenkampff et al. 2009; Shiraishi et al. 2010; Valverde et al. 2017). Several groups have begun moving towards quantitative assessment by creating custom rating systems in which clinical utility can be established (Garekar et al. 2016). However, with the diversity among patients with CVD
and the numerous approaches to modeling, creating a universal analysis method presents a challenge (Cantinotti et al. 2017). In this regard, establishing a universal procedure to perform segmentation and determine accuracy is needed. Several groups have proposed measuring specific features in the diagnostic scan and correlating them with the 3D model and/or structures in vivo (Farooqi et al. 2016b; Hammon et al. 2017; Olejnik et al. 2017; Olivieri et al. 2016). However, these studies are limited in sample size and condition diversity; therefore, this challenges the use of the technology widely.

**Future Perspectives**

In addition to the reported clinical utility, education and biomedical engineering are two major applications that may also benefit from 3D printed CVD models. Current methods of teaching cardiac pathology rely on diagrams and pictorial representations or the use of cadavers that are often costly, inaccessible, and subject to ethical considerations (Costello et al. 2014). Implementation of 3D modeling in education has been shown to improve conceptualization and communication while benefiting students through simulation training (Costello et al. 2015; Kim et al. 2008). Further, 3D modeling also presents opportunities to improve the process of designing novel medical devices. Computerized 3D reconstructions of patient anatomy from diagnostic data sets have become more common; however, they remain limited in their ability to be used interactively (Kurup et al. 2015). 3D disease models can bridge this gap by physically integrating devices with patient-specific models in order to ensure optimal fit (Hachulla et al. 2018; Little et al. 2016) and post-operative function (Vukicevic et al. 2017a).

While several challenges preclude routine clinical use presently, the evidence supports 3D disease modeling as a beneficial approach to personalized treatment of
CVD. Future technological advancements in diagnostic imaging, optimization of software algorithms for segmentation, and advanced printing technologies will make disease modeling more efficient and more likely to be integrated into clinical practice (Cantinotti et al. 2017). In conclusion, 3D disease modeling is an up and coming tool which has the ability to improve care of cardiovascular patients and medical education.
Acknowledgements

The authors would like to thank Jessica Hellein for technical assistance in preparing the manuscript.
Conflicts of Interest

D. K. Singla is an associate editor for the Canadian Journal of Physiology and Pharmacology.
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**Figure Legend**

**Figure 1: Generalized Methodology for 3D Disease Model Production.** This flowchart shows the workflow of generating a 3D disease model from diagnostic image acquisition to 3D model production. This also briefly describes the clinical applications of this technology.

**Figure 2: Case studies of DORV and HLHS.** Information presented summarizes the current research on the use of 3D disease modeling in DORV and HLHS. (DORV: Double Outlet Right Ventricle, HLHS: Hypoplastic Left Heart Syndrome, VSD: Ventricular Septal Defect, MRI: Magnetic Resonance Imaging, CT: Computed Tomography)

**Figure 3: Case studies of TGA and Valvular Disease.** Information presented summarizes the current research on the use of 3D disease modeling in TGA and Valvular disease. (TGA: Transposition of Great Arteries, ccTGA: Congenitally Corrected Transposition of Great Arteries, DORV: Double Outlet Right Ventricle, D-TGA: Dextro-Transposition of Great Arteries, PAR: Paravalvular Aortic Regurgitation, TAVR: transcatheter aortic valve replacement)
Acquisition of Diagnostic Images
MRI, CT, US

Digital Modeling
Thresholding and Segmentation

3D Printing
Fused Deposition Modeling, Stereolithographic, and Binder Jetting

Clinical Applications

Pre-Operative Planning and Communication
Medical Device Design
Clinical Education

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<th>Condition</th>
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<th>Study Objective</th>
<th>Imaging Modality</th>
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<td>Hyperplastic Left Heart Syndrome (HLHS)</td>
<td>One Patient: • HLHS with aortic and mitral valve stenosis, Previously underwent Norwood-1 operation Fifteen Pediatric Patients (Age 4d to 15y): • Fontan correction prior to modeling</td>
<td>Understand the feasibility of using 3D modeling to quantitatively assess valve morphology post-operatively.</td>
<td>Transesophageal 3D echocardiography/3D platform (Philips Medical Systems, Andover, MA)</td>
<td>Segmentation: Custom method using deformable modeling</td>
<td>Not reported</td>
<td>• Preoperative model was consistent with intraoperative findings • Provided information about patch material sizing that allowed arch augmentation</td>
<td>Kiraly et al., 2016</td>
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<tr>
<td>Double Outlet Right Ventricle (DORV)</td>
<td>Six Patients (Age: 2-29y) • DORV with remote VSD and normal ventricles</td>
<td>• Evaluate model on 11 parameters and assign scores relative to MR/CT (-2 to 2) -2(inconsistent with MR/CT anatomy), 0 (no extra information), +2(model added information)</td>
<td>3T MRI scanner (Philips Healthcare)</td>
<td>Not reported</td>
<td>• Printer: 3D Systems (Materialise, Belgium) • Material: Sandstone (3D Systems)</td>
<td>• Models can aid pre-surgical planning • models provided additional information over MRI/CT • Facilitated enhanced communication • Increased confidence in surgical decisions</td>
<td>Garekar et al., 2016</td>
</tr>
<tr>
<td></td>
<td>Five Patients (Age: 2-11y) • DORV with remote VSD and normal ventricles</td>
<td>• DORV with remote VSD</td>
<td>64-detector CT scanner (Philips Healthcare)</td>
<td></td>
<td>• Medical Imaging and Interaction Toolkit • Printer: ZPrinter 310 (Z Corporation, Burlington, MA) • Material: Not reported</td>
<td>• Improved understanding of DORV pathology • Give information about position, size, and relationship of structural anomalies</td>
<td>Farooqi et al., 2016</td>
</tr>
<tr>
<td></td>
<td>Two Patients: • Patient 1: (Age:20M) Female with DORV, prior pulmonary trunk banding aortic coarctation • Patient 2: (Age:11M) Female with DORV, multiple VSDs and valvar pulmonary stenosis</td>
<td>• Assess the feasibility of biventricular repair</td>
<td>1.5 Tesla system using the sense-cardia coil (Philips, The Netherlands)</td>
<td></td>
<td>N/A: Virtual Model</td>
<td>• Improved understanding of DORV pathology</td>
<td>Riesenmann et al., 2009</td>
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</tbody>
</table>

**Figure 2**

Garner and Singla

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### Transposition of the Great Arteries (TGA)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patient Pathology</th>
<th>Study Objective</th>
<th>Imaging Modality</th>
<th>Software</th>
<th>Printer Type and Material</th>
<th>Result</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Patients (Age: 7.6Mo to 3Y)</td>
<td>• ccTGA w/ DORV: 3M, 1F  • ccTGA: 1F  • TGA: 1M  • TGA w/ Tricuspid atresia: 1F</td>
<td>• Preoperative surgical simulation</td>
<td>Multislice computed tomography (details not specified)</td>
<td>• Not reported</td>
<td>• Custom technology using stereolithography followed by vacuum casting technology</td>
<td>3D models sufficiently aided in simulating surgical procedures</td>
<td>Hoashi et al., 2018</td>
</tr>
<tr>
<td>1 Patient (Age: 2Y, Male)</td>
<td>• D-TGA with atrial septal defects and small patent ductus arteriosus</td>
<td>• Understand pre- and post-operative hemodynamics to refine surgical technique of the Mustard operation</td>
<td>CT scans were obtained via a Siemens Definition Flash with a slice thickness of 0.6 mm and a slice increment of 0.3 mm</td>
<td>• Segmentation: Mimics software (Materialise, Belgium)  • Post-processing: 3-matic software</td>
<td>• Printer: Fortus 400mc (Stratasys)  • Material: Not specified</td>
<td>Aid in follow-up procedures  • Useful in monitoring the size and shape of chambers and blood flow pattern before and after surgery</td>
<td>Chapron et al., 2013</td>
</tr>
<tr>
<td>1 Patient (Age: 30Y, Male)</td>
<td>• D-TGA post Mustard</td>
<td>• Use 3D model to assess placement of cardiac catheter</td>
<td>Contrast-enhanced ECG gated cardiac CTA on a 320-detector row system (Toshiba Aquilion One Vision, Tochigi-ken, Japan)</td>
<td>• Segmentation: Mimics software (Materialise, Belgium)  • Post-processing: not reported</td>
<td>• Printer: Objet500 Connex Polyjet printer (Stratasys, Eden Prairie, MN)  • Material: Not specified</td>
<td>Demonstrated clinical utility for surgical planning  • Provided insight on appropriate catheter size and placement</td>
<td>Olivieri et al., 2014</td>
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### Valvular Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patient Pathology</th>
<th>Study Objective</th>
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<th>Result</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 Patients (Age: not reported)</td>
<td>• 8 patients diagnosed with paravalvular aortic regurgitation (PAR)  • 8 control patients w/o PAR</td>
<td>• Determine if CT derived models can be used to print the aortic root complex for TAVR planning</td>
<td>Pre-procedural cardiac CT  • Toshiba Aquilion One Dynamic Volume CT (Tochigi-ken, Japan)  • Post-procedural TTE</td>
<td>• Segmentation: Vitrea6.7 (Vital Images)  • Post-processing: 3-matic software</td>
<td>• Printer: Form 1 plus, (Formlabs, Cambridge, MA)  • Material: clear flexible resin (Formlabs)</td>
<td>3D models assist visualization of aortic root anatomy  • Models provided the opportunity to plan TAVR device placement in situ  • Have potential to aid prediction of PAR following TAVR</td>
<td>Ripley et al., 2016</td>
</tr>
<tr>
<td>1 Patient (Age: 41Y, Male)</td>
<td>• Heart failure due to dilated cardiomyopathy, atrial fibrillations and mitral valve regurgitation</td>
<td>• Determine the feasibility of using heart modeling to plan percutaneous structural heart procedures</td>
<td>Retrospectively gated, contrast enhanced, multi-slice CT with slice thickness of .625mm</td>
<td>• Segmentation: Not reported  • Post-processing: not reported</td>
<td>• Printer: Commercial SLA printer (details not reported)  • Material: Photopolymer resin (details not reported)</td>
<td>The 3D model allowed:  • Understanding of the location, quantity and size of papillary muscles which is necessary to optimize crossing wire placement  • Quantitative assessment of the Left ventricular end diastolic diameter and left ventricular height  • Provided understanding of the positioning of the catheters under the mitral valve</td>
<td>Dankowski et al., 2014</td>
</tr>
<tr>
<td>4 Patients (Age: not reported)</td>
<td>• 2 patients with severe ischemic mitral regurgitation (IMR)  • 1 patient with severe myxomatous mitral regurgitation (MMR)  • 1 patient with normal mitral valve</td>
<td>• Evaluate the potential of 3D modeling as a guide in surgical repair of mitral valve disease</td>
<td>2D, m-mode, spectral and color Doppler and 3D echocardiographic data was collected with an ultrasound platform (iE33 Model, Philips Medical Systems, Andover, MA) equipped with an 11L probe transesophageal matrix-array transducer</td>
<td>• Segmentation: Custom process (based on continuous medial representation algorithm)  • Post-processing: CatalystEX (CADimensions)</td>
<td>• Printer: Dimensions Elite  • Material: ABS (Layer thickness: .254mm)</td>
<td>Demonstrated the potential of 3D modeling in surgical simulation of mitral valve repair which is underutilized as a result of significant expertise required  • Models demonstrated the distorted valve geometry associated with IMR and MMR</td>
<td>Witschey et al., 2014</td>
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