Applications of 3D printing in cardiovascular diseases

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Abstract | 3D-printed models fabricated from CT, MRI, or echocardiography data provide the advantage of haptic feedback, direct manipulation, and enhanced understanding of cardiovascular anatomy and underlying pathologies. Reported applications of cardiovascular 3D printing span from diagnostic assistance and optimization of management algorithms in complex cardiovascular diseases, to planning and simulating surgical and interventional procedures. The technology has been used in practically the entire range of structural, valvular, and congenital heart diseases, and the added-value of 3D printing is established. Patient-specific implants and custom-made devices can be designed, produced, and tested, thus opening new horizons in personalized patient care and cardiovascular research. Physicians and trainees can better elucidate anatomical abnormalities with the use of 3D-printed models, and communication with patients is markedly improved. Cardiovascular 3D bioprinting and molecular 3D printing, although currently not translated into clinical practice, hold revolutionary potential. 3D printing is expected to have a broad influence in cardiovascular care, and will prove pivotal for the future generation of cardiovascular imagers and care providers. In this Review, we summarize the cardiovascular 3D printing workflow, from image acquisition to the generation of a hand-held model, and discuss the cardiovascular applications and the current status and future perspectives of cardiovascular 3D printing.

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Medical 3D printing refers to the fabrication of anatomical structures from volumetric data sets, typically from imaging, and enables visual inspection and direct manipulation of hand-held models of human anatomy and pathology[1]. Although the technology has been available for >30 years, this decade has heralded exponential growth and interest in the implementation of this new 'modality' into the clinical arena. Many years of technology development and research were followed with anecdotal case reports from which hypotheses were generated. As 3D printing moved from other technology sectors into medicine, cardiovascular 3D printing is beginning to accumulate evidence on applications, following the successes seen in dentistry, maxillofacial interventions, and the musculoskeletal fields[1,2].

Reported applications of 3D printing range from advanced visualization and aid in diagnostic work-up, to guiding treatment strategies[3,4], simulating fully endovascular and surgical procedures[5–7], advancing cardiovascular research[8,9], and improving patient–physician communication[10–12]. These applications largely focus on the clinical benefits of the use of models for education and for planning or simulating interventions, as well as devices that can be implanted. This Review, divided into three parts, summarizes the cardiovascular applications of 3D printing over the past 3 decades. The first part of the Review introduces 3D printing from the perspective of image acquisition, software manipulation of the image data, generation of a hand-held model, and the current cardiovascular 3D printing strategies. The second part highlights cardiovascular 3D printing applications, demonstrating the broad scope of potential applications in cardiovascular care. Finally, we discuss the current status and future perspectives of cardiovascular 3D printing, including cardiovascular 3D bioprinting and molecular 3D printing.

Fundamentals of cardiovascular 3D printing

Generating a 3D-printed model encompasses sequential stages of image acquisition, data postprocessing, and industrial-level manufacturing. Before starting the fabrication of a hand-held model, the clinical appropriateness of the model should be carefully evaluated to

Key points

- Medical 3D printing refers to the fabrication of anatomical structures, typically derived from volumetric medical image data, and enables visual inspection and direct manipulation of hand-held models of human anatomy and pathology
- In cardiovascular 3D printing, advanced modern imaging such CT and MR is combined with dedicated 3D printing software and hardware
- Cardiovascular 3D printing enhances the diagnostic work-up of complex cardiovascular diseases, as well as surgical and interventional procedural planning and simulation
- 3D printing improves patient engagement in understanding their own diseases and participating in their own decision-making, and improves communication with patients and their families
- Widespread adoption of 3D printing is currently limited by the lack of robust evidence that systematically demonstrates effectiveness, and by the high costs and workflow complexity
- Cardiovascular 3D bioprinting and molecular 3D printing — which combine advanced manufacturing, cell biology, molecular biomarkers, and materials science — have not yet translated into clinical practice, but hold great promise for the future

determine the subsequent steps in the 3D printing process. Communication between physicians, imagers, and technologists is paramount to obtain a functional and accurate 3D-printed model. FIG. 1 schematically illustrates the cardiovascular 3D printing workflow and the current strategies employed in early adopting medical centres.

Cardiovascular imaging data acquisition

Cardiovascular 3D printing generally begins with the acquisition of 3D volumetric cardiovascular images in which the anatomy of interest has sufficient signal intensity and contrast — combined with minimal artefact — to be differentiated from surrounding structures. Most models are generated from CT[1,5] or MRI[13,14], but successful 3D-printed models have been also generated from 3D transthoracic or transoesophageal echocardiography (TTE and TEE, respectively)[15,16] and from rotational digital subtraction angiography or 3D rotational angiography[17–19] (FIG. 1). For modelling tissue architecture, data from CT or MRI can be used for the ventricles and the atria, whereas echocardiography images are used to depict valve anatomy[2,20,21]. Conversely, for modelling the vascular lumen — for example, for procedural planning and simulation of intravascular interventions — any 3D angiographic modality can be used, including CT angiography (CTA)[2], magnetic resonance angiography (MRA)[14], and 3D rotational angiography[18].

The quality of the model depends on the quality of the imaging source data. Thin reconstructed images (that is, 0.50–1.25 mm for cardiovascular 3D printing[1,22]) can allow for accurate anatomy delineation, but usually require cumbersome postprocessing. Both cardiac movement and breathing artefacts challenge the accuracy of the subsequent model. Therefore, imaging acquisition incorporates electrocardiography gating, breath-holding, and MRI respiratory gating[2]. 3D printing from CT images should be reconstructed ideally on the order of 1 mm in thickness. Because narrowly reconstructed images have lower signal[23], the use of smoother kernels that make image segmentation easier is often desirable[24]. Standard MRI cardiac sequences can provide images with minimal motion, albeit with rather thick (approximately 1 cm) slabs, which limits the detail of intracardiac anatomy. Routine echocardiography images, although noninvasive, are generated as individual slices with limited field of view and without orientation and, therefore, are not ideal for 3D printing. 3D rotational angiography is useful for 3D printing of the vessel of interest, but this methodology is invasive and not electrocardiography-gated compared with CTA. A summary of representative examples of imaging modalities reported for cardiovascular applications is presented in TABLE 1.

Postprocessing of image data

The second step in the 3D printing workflow is image segmentation, namely, the delineation of the desired tissues by placing regions of interest around them. This process is necessary in order to discriminate between the anatomy of interest and the adjacent tissues, and requires expertise and time[14,21]. Several algorithms are available to perform image segmentation, which often can be tailored towards specific imaging protocols or anatomy. The segmentation process of appropriate regions of interest can be both automated and manual or, more frequently, semi-automated, combining an initial step of automated segmentation followed by manual corrections (FIG. 1).

The boundaries of the regions of interest can be identified on successive 2D images that are subsequently assembled to form a closed surface ‘shell’ of each tissue for which 3D printing is desired. This shell is most commonly a surface mesh composed of small triangles. Although several file formats exist, these data are almost universally stored in standard tessellation language (STL) format. The STL file format is to 3D printers the equivalent of digital imaging and communications in medicine (DICOM) format for radiology and cardiovascular imaging workstations. Similarly to how a 2D workstation interprets the signal values stored in DICOM files to display 3D volume formats on a 2D monitor, a 3D printer interprets data in a STL file to manufacture a physical object[2].

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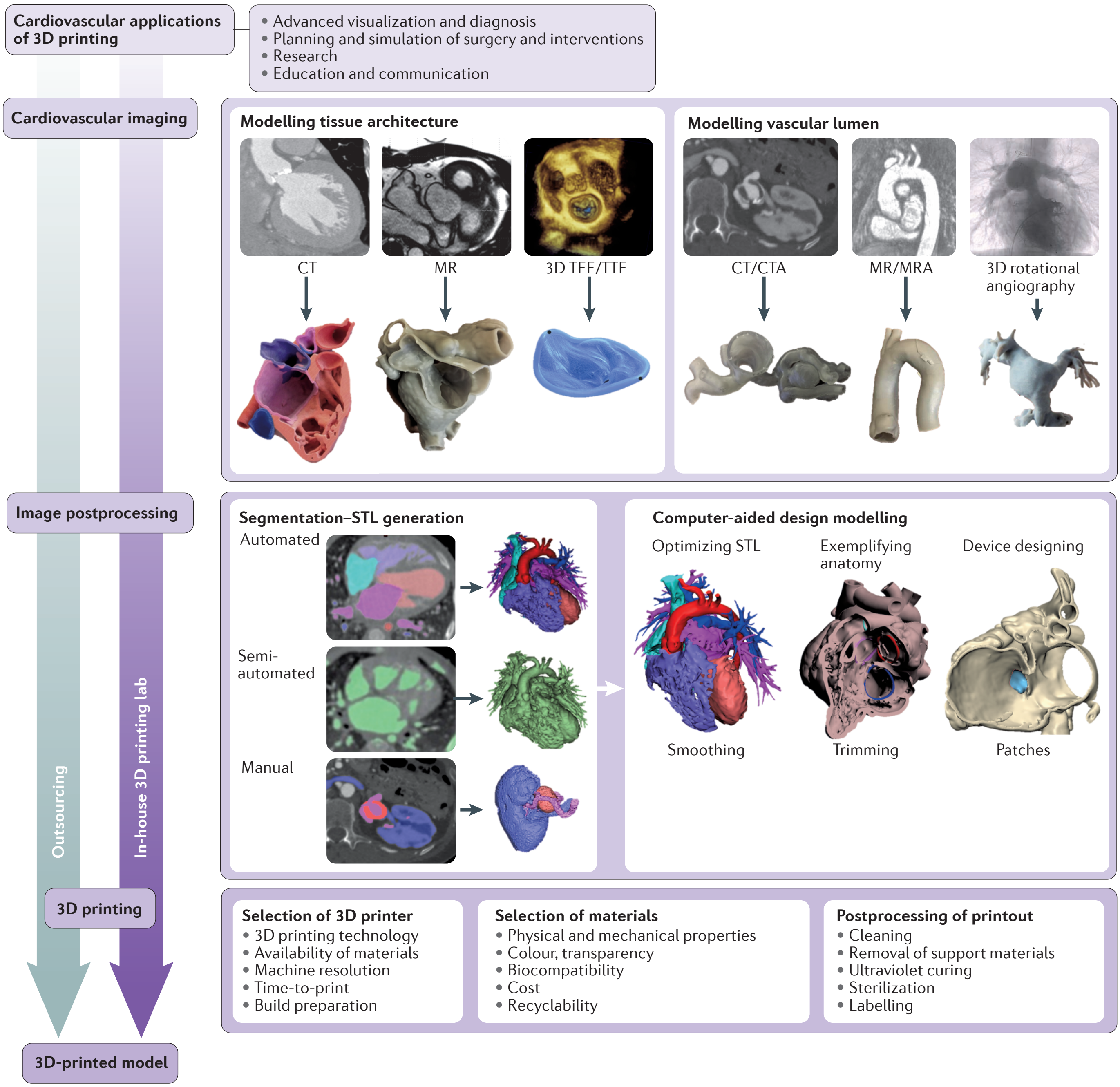

Figure 1 | **Cardiovascular 3D printing workflow.** 3D printing can be completed in-house in a dedicated 3D printing laboratory, or it can be partially or fully outsourced. 3D printing applications include advanced visualization for diagnosis and interventional planning or simulation, research, education, and patient–physician communication. After establishing an appropriate clinical indication, 3D printing typically begins with the acquisition of high-quality volumetric images from CT, CT angiography (CTA), magnetic resonance (MR), MR angiography (MRA), transoesophageal echocardiography (TEE), transthoracic echocardiography (TTE), or 3D rotational angiography. The second step, postprocessing of the image data, includes segmentation or selection of the anatomy of interest in the source images. The anatomical representation is then transformed into a standard tessellation language (STL) file, a file format interpreted by 3D printers. Postprocessing also involves the manipulation of the STL file with the aid of computer-aided design software. Computer-aided design modelling includes, but is not limited to, STL file optimization for printing (smoothing), exemplifying the anatomy of interest (trimming), and device designing (patches). Important considerations for the final step, 3D printing the model, are the selection of the 3D printing hardware, materials, and postprocessing of the physical model. Common examples of considerations at this step are described in the respective boxes. The CT-derived cardiac model is reprinted from Anwar, S. *et al.* 3D printing in complex congenital heart disease: across a spectrum of age, pathology, and imaging techniques. *JACC Cardiovasc. Imaging* http://dx.doi.org/10.1016/j.jcmg.2016.03.013 (2016) with permission from Elsevier. The 3D TEE image and respective 3D-printed model are reprinted from Mahmood, F. *et al.* Three-dimensional printing of mitral valve using echocardiographic data. *JACC Cardiovasc. Imaging* **8**, 227–229 (2015) with permission from Elsevier. The 3D rotational angiography image and respective 3D-printed model are reprinted from Poterucha, J. *et al.* Percutaneous pulmonary valve implantation in a native outflow tract: 3-dimensional DynaCT rotational angiographic reconstruction and 3-dimensional printed model. *JACC Cardiovasc. Interv.* **7**, e151–e152 (2014) with permission from Elsevier.

Table 1 | **Imaging and printing modalities in cardiovascular 3D printing**

Applications of 3D-printed models	Imaging modality	3D printing technology
Structural heart diseases, including valvular diseases		
Advanced visualization and diagnosis	• CT, CTA[59,60] • 3D TTE[15] • 3D TEE[74]	• Material jetting[15,60] • Fused deposition modelling[59,74]
Planning and simulation of surgery and interventions	• CT, CTA[7,61,71]	• Material jetting[7] • Fused deposition modelling[61] • Stereolithography[71]
Education, communication, and research	• CT, CTA[69,87,144] • MRA[26,83]	• Material jetting[69,144] • Fused deposition modelling[26,83]
Paediatric and adult congenital heart diseases		
Advanced visualization and diagnosis	• CTA[36] • MRA[36] • 3D TTE[15]	• Material jetting[15] • Fused deposition modelling[36]
Planning and simulation of surgery and interventions	• MR, MRA[14,110,114,126] • CT, CTA[2,14,111]	• Material jetting[14,111] • Fused deposition modelling[110,114,126] • Selective laser sintering[110] • Stereolithography[2]
Education, communication, and research	• MR, MRA[10,11,14] • CT, CTA[12,14] • 3D rotational angiography[18]	• Material jetting[11,12,14,18] • Selective laser sintering[10]
Coronary arteries and systemic vasculature		
Advanced visualization and diagnosis	• CTA[2,137]	• Fused deposition modelling[137] • Stereolithography[2,137]
Planning and simulation of surgery and interventions	• CTA[129] • MRA[131]	• Selective laser sintering[25] • Fused deposition modelling[129]
Education, communication, and research	• MRA[167] • CTA[1]	• Material jetting[167] • Stereolithography[1]

CTA, computed tomography angiography; MRA, magnetic resonance angiography; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Although a typical STL representation could be 3D printed at this stage, cardiovascular models almost always require a third step in which computer-aided design (CAD) software is used to refine the STL file before printing (FIG. 1). The necessary CAD functions and workflow differ depending on the case and the intended use of the model. For example, CAD software is needed to manipulate STL representations of vessels from which the blood pool has been segmented from a contrast-enhanced angiogram. To simulate a catheter-based procedure, an imputed wall must be generated to surround the blood pool in order to generate a hollow 3D-printed model[25]. Common CAD manipulations include optimizing the STL model for printing (wrapping or smoothing), augmenting the model to exemplify anatomy and pathology (extruding tissues or trimming to reveal anatomical structures), and adding connectors such as cylinders or splints between separate anatomical structures of interest (FIG. 1). Furthermore, 3D printing is also emerging as an idealized method to generate patient-specific devices and implants. These applications differ from models designed to replicate exactly the anatomy data captured in the volumetric imaging. Namely, for devices and implants, the changes to the patient anatomy needed for the management of the disease can be reflected in the model. These steps require CAD software, for example, to match the relevant anatomy precisely, to design a structure for consideration of an intervention, or to perform virtual onscreen testing[26,27].

So far, postprocessing software for medical imaging data has regulations for 3D visualization[28]. However, specific and standardized recommendations and guidelines focused at the necessary steps for 3D printing, whether the model is an exact representation of the anatomy depicted on imaging or whether the model will include modifications intended for patient care, are only now being developed[29]. For the broader adoption of the technology and implementation into daily clinical practice, safety and efficacy are considered paramount in the path to standardization. Simplifying image postprocessing by the use of software platforms that incorporate all the modules (segmentation, STL generation, and CAD modelling) is also needed. Postprocessing simplification probably will be fulfilled by commercial packages offering integrated software platforms that combine ease of use with high-end automated and/or semi-automated segmentation modules and medical 3D printing-geared CAD capabilities. By contrast, the available open-source software, although less costly, has a longer learning curve and has not been vetted by regulatory bodies. Another benefit that comes with standardization is support from other users and vendors, plus generalized opportunities for research.

3D printing process

The final step of 3D printing is the actual manufacturing of the model. The most frequently reported 3D printing technologies in cardiovascular medicine include fused deposition modelling (material extrusion), selective laser sintering (powder bed fusion), stereolithography (vat photopolymerization), and material jetting (BOX 1). Several other 3D printing technologies are available, such as injection moulding, but few have been used in the cardiovascular field.

A wide range of materials are commonly used for medical 3D printing, from plastic (resin) to nylon and metals. The majority of cardiovascular applications reported so far have employed materials with properties that have not been meticulously compared with the cardiovascular tissue they will be mimicking. 3D printing applications for preoperational planning — for example, the simulation of cardiovascular operations and catheter-based interventions — will benefit from materials with physical properties that closely mimic those of the actual tissue. The pliable materials currently available seem to suffice for planning catheter-based interventions. However, these materials do not represent precisely the tissue properties of the myocardium and, therefore, slightly limit the evaluation of tissue response to the surgical procedure or the deployment of medical devices[14]. Material jetting technology can provide new opportunities by combining several materials within the same 3D-printed cast, thereby enabling the fabrication of models of human anatomy and pathology that contain different tissues (such as coronary arteries with calcifications).

The selection of the 3D printing technology for a given cardiovascular application involves multiple considerations. Important parameters include, among others, the time required for the hardware to complete the fabrication of the model, the printer resolution, the need for supporting structures during printing, and the cost of the 3D printer and materials. Factors to deliberate with regard to the cost of the 3D printer and materials are availability and choice of materials, colour capabilities, biocompatibility, sterilization capability, recyclability, and material physical properties. Moreover, one should always consider the need for postprocessing of the final printed model, because postprocessing typically requires additional manipulations, such as removal of support materials, ultraviolet curing, polishing, cleaning, sterilization, and labelling. To assess anatomy, fairly inexpensive technologies can be used (for example, fused deposition modelling). Conversely, multimaterial machines (for example, material jetting), although costly, provide advanced capabilities with regard to materials, time-to-print, throughput, and the quality of the models that can be produced. Representative examples of 3D printing technologies reported in the literature for cardiovascular applications are presented in TABLE 1.

Box 1 | **3D printing technologies in cardiovascular medicine**

Fused deposition modelling (material extrusion). For this technology, the materials are softened, typically with heat, and deposited in successive layers on a built tray by the extrusion head of the printer, followed by rapid solidification. The materials employed for this technique include plastics, such as acrylonitrile butadiene styrene and polylactide, yielding sturdy and durable models, but with lower finish quality. Time-to-print is fairly quick, and allows for multiple printing colours, which is preferable when printing anatomical structures. This is the most frequently used cardiovascular 3D printing hardware, at least in part owing to the relative low cost and shallow learning curve compared with other technologies.

Selective laser sintering (powder bed fusion). An energy source (for example, high-power laser) selectively fuses preheated particles in successive layers on a powder bed surface. A thin bed of powder is applied one layer at a time, and is sintered or melted by the laser in the shape of the 3D object. Rather high cost with regard to both hardware and materials, and requires training for handling and maintenance. Supporting structures are not required, and a variety of materials can be used, such as metal. This technology is ideal for building sterilizable implants.

Stereolithography (vat photopolymerization). For this technology, a high-intensity light source selectively focused in a vat of photosensitive resin is utilized. Successive layers of liquid are exposed to light and solidified as the vat is lowered or raised following the build tray movement. Extra resin is removed and the model is cured with ultraviolet light. Stereolithography models provide a reasonable accuracy–cost ratio, and printed models have high accuracy, with smooth surface finishes. The printing materials are limited to photopolymers that are rather expensive and are not durable over time. Printing characteristics of models enable preoperational simulations and surgical planning.

Material jetting. Material jetting printers jet a liquid photopolymer onto a build tray that is subsequently cured with an ultraviolet light. Gel support material holds together the successive layers of the build polymer sprayed by the printer jet heads. Printers and materials are rather expensive, but characterized by high accuracy, versatility, and multicoloured printing capabilities. Materials include photopolymerizable plastics and polymers (polymethyl methacrylate). Mixing of materials enables the fabrication of models with variable hardness, providing a fair similarity to the physical properties of human anatomical structures.

Cardiovascular 3D printing strategies

For an institution interested in incorporating cardiovascular 3D printing in clinical practice, current options include in-house 3D printing in a 3D printing lab (probably transitioned from the 3D visualization lab[30]) and outsourcing, either through a medical 3D printing dedicated industry or through collaborations and networking. Both viable options have been employed in early adopting centres, each with inherent balances and trade-offs (TABLE 2).

To our knowledge, and according to our own experience, most centres that establish robust in-house 3D printing labs for regular clinical care utilize commercial software that has met regulatory standards for the postprocessing steps, and have acquired at least one higher-end capability 3D printer, commonly multimaterial jetting. Other printing technologies, such as fused deposition modelling and stereolithography, are also frequently part of the laboratory pipeline in centres with in-house 3D printing. This inventory will suffice for the currently reported applications of 3D printing in the cardiovascular field. For advanced surgical or interventional guides, wires or implantable patches, and for prostheses, which have not been yet reported for the cardiovascular field, outsourcing is an alternative option.

Cardiovascular 3D printing applications

Applications of 3D printing in cardiovascular medicine range from the most commonly reported structural heart diseases[7,31–34] and complex paediatric and adult congenital heart diseases[4,14,35,36], to aorta and great vessel pathologies[37,38]. In the same fashion that 3D visualization[30] offered unprecedented illustration and spatial appreciation of cardiovascular structures, 3D printing provides unparalleled tactile perception and true volumetric assessment of complex cardiovascular pathology. 3D-printed models readily enable not only insightful analysis of anatomy and pathology in life-sized models, but, most importantly, these models enable advanced procedural planning, decision-making on device choice and appropriate sizing, and education of cardiologists, surgeons, and patients. The currently reported and expected influence of 3D printing on patients with cardiovascular disease and physicians is summarized in BOX 2.

Structural heart diseases

Structural heart diseases refer to "non-coronary cardiovascular disease processes and related interventions" (REF. 39). The wide range of structural heart diseases, and the need for optimization of structural heart interventions, renders 3D printing a potential game-changer, because adjunct imaging and pre-interventional assessment are highly important in diagnosis and management of these conditions.

Left atrial appendage closure. Exclusion of the left atrial appendage from the systemic circulation in patients with nonvalvular atrial fibrillation is considered an alternative to anticoagulation for the prevention of thromboembolism[40]. A number of percutaneous devices are available

Table 2 | **Current strategies for cardiovascular 3D printing in clinical practice**

Strategy	Advantages	Disadvantages
In-house 3D printing lab	• Ideal option for direct implementation • Enables an optimized clinical collaboration • Time-efficient • Reduction in costs in the long run	• High start-up costs • Fewer hardware and material options are available
Outsourcing	• Expertise and multiple 3D printing technologies • Efficient for surgical guides and implants • Small start-up costs	• Lead times are usually longer • Less clinical collaboration • Difficult for complex cases

for left atrial appendage closure[41], and some of them have been approved for use by the FDA[42] and implemented in practice guidelines in Europe[43]. Planning of left atrial appendage closure usually combines peri-interventional 2D TEE with fluoroscopy guidance and, less frequently, with pre-interventional CT. The variable anatomy of the appendage poses a challenge for accurately sizing the closure device[44], and incomplete occlusion can lead to complications[41].

Patient-specific 3D-printed models of the left atrial appendage can assist in selecting the optimum dimensions of the device and for simulation before the intervention. Different devices have been tested in physical models, enabling the sizing of the closure device and more accurate positioning[6]. Conceptually, models printed with materials that accurately resemble physical tissue properties can facilitate the optimization of the procedure. Models printed using flexible materials have undergone 3D-strain analysis to quantify the interaction between the device and the appendage, thereby avoiding incorrect sizing that would potentially lead to postprocedural pericardial effusion[33] (FIG. 2a–e).

Cardiac aneurysms. Atrial aneurysms (associated with other cardiac abnormalities)[45] and ventricular aneurysms (familial or post-myocardial infarction pseudoaneurysms)[46] can have unpredictable catastrophic complications. The diagnosis of cardiac aneurysms includes echocardiography and CT[45], and management approaches include anticoagulation[47] and, when indicated, either transcatheter occlusion procedures[48] or surgery[49]. For example, in a patient with a fenestrated atrial septal defect accompanied by a large atrial septal aneurysm, a 3D model derived from CT data clearly illustrated both the atrial septal aneurysm and the anatomical relationship to the septal fenestrations[3]. Simulation of the percutaneous procedure with a 3D model enables the proper selection of the occluder device, the diagnostic catheter shapes, and the navigation strategy, thus permitting closure of the atrial septal defect without obstructing the tricuspid valve inflow and the mitral valve annulus. Similarly, 3D printing of models of left ventricular aneurysms has been reported[22]. These models aid in the tactile appreciation of the kinetic rest volume of the left ventricle. With these models, surgeons are able to identify structures at risk, assess ideal resection lines of the aneurysmectomy, and determine the residual shape after the reconstructive procedure.

Hypertrophic obstructive cardiomyopathy. Hypertrophic obstructive cardiomyopathy is a heterogeneous genetic heart disease characterized by eccentric and regional left ventricular hypertrophy[50]. Symptomatic patients with left ventricular outflow tract obstruction are candidates for ventricular septal myectomy to eliminate or markedly reduce the left ventricular outflow tract pressure gradient[51–53]. Although patients who undergo myectomy in experienced centres have low mortality[54], advanced imaging might be necessary for patients with challenging cases of left ventricular outflow tract and anatomical variation in surrounding structures. 3D-printed models, in addition to haptic feedback, offer unparalleled visualization of left ventricular anatomy for idealized surgical planning[55], as shown in FIG. 2f–i. Another example of a 3D-printed model used for myectomy included the left ventricular myocardium, the intraventricular muscle band, the accessory papillary muscle, and the mitral annulus[7]. The model was printed using flexible, coloured materials and enabled preoperative simulation of the surgical myectomy[7]. Flexible materials that simulate better than the currently available ones the systolic anterior motion of the anterior leaflet of the mitral valve would be of value also when planning septal resection or alcohol ablation in cases of hypertrophic obstructive cardiomyopathy.

Cardiac tumours. Although rare, primary cardiac tumours affect mainly young patients, and when the tumour is malignant patients have a poor prognosis[56]. The diagnosis of cardiac tumours relies on multimodality imaging, which is followed by timely surgical resection of the tumour[57]. 3D printing provides advanced understanding of the relationship of the tumour with the surrounding structures, and can facilitate the therapeutic decision-making process. 3D-printed models of primary cardiac neoplasms have been utilized in identifying tumour expansion and structures at risk[22], for selecting the appropriate therapeutic option[58], and for determining surgical approaches[59,60].

Cardiac valves

3D printing of models of valve pathologies, particularly of the aorta and mitral valve, has generated great interest. Physical models derived from CT and echocardiography data are strongly expected to add value for planning and simulation of transcatheter aortic valve repair (TAVR)[32,61] and transcatheter mitral valve repair (TMVR)[27].

Aortic valve. TAVR is considered a safe, and often patient-preferred, alternative to surgical treatment of aortic stenosis in non-operable or high-risk populations[62,63]. Moreover, the indications and the technologies of this procedure are expanding[64]. Potential pivotal improvements in TAVR include better patient selection, tailored prosthesis choice and appropriate sizing, and innovations in valve design[65]. Fairly simple 3D-printed models can assist in pre-interventional identification of potential complications in complex cases[32]. For example, in a study including a large cohort of patients, *ex vivo* simulations of balloon valvuloplasty in physical models of the aortic root that included calcium were used for the identification of risk factors for the need for post-procedural permanent pacemaker implantation[31]. Full heart models provide training opportunities for transapical approaches[66]. Valve-in-valve procedures are particularly challenging, and might become more common in the future. 3D-printed models for planning and simulation of valve-in-valve procedures can aid in identifying risks and selecting optimal prosthesis parameters[67]. In addition, flexible materials can replicate functional properties of severe degenerative aortic valve stenosis[68]. The pathological haemodynamic environment of severely calcified, stenotic aortic valves with minimal leaflet movement can be sufficiently reproduced in these 3D-printed models, and can improve patient-specific TAVR planning[69] (FIG. 3a–e).

Mitral valve. The mitral valve was among the first cardiac structures to be 3D printed[70], with several subsequent successful efforts[16,34,71–73]. 3D-printed models derived from 3D TEE and CT data provide superior clinical information of anatomical relationships before and after repair than standard imaging alone. 3D-printed models of normal and regurgitant mitral valves, including those of ischaemic or myxomatous origin[34], can help to objectively select the annuloplasty ring, and can aid in informing the decisions during mitral valve repair surgery[74] (FIG. 3f–h). Similarly, changes in annular size and shape after the repair procedure can be better appreciated in these 3D models. More advanced image segmentation tools are expected to refine 3D printing of the mitral valve apparatus and, in theory, assist in the optimization of TMVR approaches.

Minimally invasive percutaneous techniques, such as the interventional leaflet repair system MitraClip (Abbott Vascular, USA) and the percutaneous mitral annuloplasty catheter Carillon Mitral Contour System (Cardiac Dimensions, USA), can be an attractive alternative for the treatment of functional mitral regurgitation in high-risk patients[65]. Heart teams have used 3D-printed models to optimize the implantation of a percutaneous annuloplasty system[71]. Similarly, a multi-material model of mitral valve leaflets and subvalvular calcium was employed for percutaneous transseptal placement of the MitraClip[75] (FIG. 3i–l). Accurate sizing of the mitral annulus and avoidance of postprocedural left ventricular outflow tract obstruction are important for uneventful TMVR. Printed heart models provide the opportunity for patient-specific device bench testing, and can help in estimating the risk of left ventricular outflow tract obstruction[27] (FIG. 4a).

Paravalvular leaks. New-generation valves and the improved experience of the operators have reduced the frequency of severe paravalvular leaks following surgical and transcatheter valve replacement[76]. However, mild and moderate paravalvular leaks remain common, and the latter can influence the valve functional benefit and long-term survival[65]. Percutaneous approaches are particularly attractive for the management of paravalvular leaks[77], and 3D printing can assist in the procedure either by pre-interventional prediction of leaks or by enabling treatment optimization. In both instances, 3D-printed models have been demonstrated to be advantageous[3,78]. Flexible 3D-printed models of the aortic root complex that were derived from routine TAVR CT data[79] retrospectively predicted the occurrence of postprocedural paravalvular aortic regurgitation[78]. Similarly, percutaneous closure of periprosthetic mitral valve defects can be simulated in physical models to determine the optimal interventional approach and the appropriate sizing of occluder devices[3].

Pulmonary valve and right ventricular outflow tract. Pulmonary valve disease is rare among adults and presents most frequently in patients with repaired congenital heart diseases[65]. Pulmonary stenosis and pulmonary regurgitation are managed with surgical valve replacement or, less invasively, with percutaneous valve implantation. However, percutaneous valve implantation is not suitable for most patients, and management selection is primarily dictated by the size of the outflow tract in relation to the valve implant. 3D printing can reveal morphological details of the implantation site, and provide insight on the dimensions of the right ventricle outflow tract[80]. Physical models are valuable for planning management, intervention simulation, and device selection[81,82] (FIG. 4b–d). The superiority of 3D-printed models of the right ventricular outflow tract compared with MRI visualization alone for selecting patients and intervention planning was demonstrated in a set of patients evaluated for treatment with percutaneous pulmonary valve implantation or surgical correction[83,84]. Anatomical models of the blood pool in the right ventricular outflow tract were used to assist pulmonary valve implantation[18], and preprocedural 3D modelling is expected to extend this approach to a substantial number of patients[85].

Tricuspid valve. Several studies have demonstrated that 3D-printed models of normal and pathological human tricuspid valves can be generated from 3D TTE data with high accuracy[86]. The feasibility of personalized interventions for tricuspid valve regurgitation was demonstrated in an animal study that employed 3D printing for the development of a braided stent[87]. Additionally, in a patient with secondary tricuspid regurgitation deemed not suitable for isolated tricuspid valve surgery and heart

Box 2 | **Influence of cardiovascular 3D printing**

- Reduction in intraoperative complications, for example, reductions in blood loss, organ ischaemia time, and anaesthesia time
- Reduction in postoperative complications, such as a reduction in the need for follow-up and/or revision procedures
- Reduced operative room time and, potentially, costs
- Enhanced precision of minimally-invasive and open surgeries
- Avoidance of unnecessary surgery, for example, by selecting a more appropriate, tailored treatment
- Improvement in physician–patient communication
- Superior training opportunities for interventionists and surgeons, who can replace expensive and scarce cadaveric materials with 3D-printed models

transplantation, a 3D-printed model of the right atrium–inferior vena cava junction facilitated pre-interventional caval valve sizing and successful implantation[88].

Congenital heart diseases

Moderate and severe congenital heart diseases occur in approximately 6–9 per 1,000 live births[89,90]. Although surgical and medical management of congenital heart diseases has improved over time, mortality remains high[91]. An increased number of patients with congenital heart disease survive owing to advances in surgical treatment and neonatal screening. Therefore, the adult population with congenital heart disease is constantly growing and is expected to continue increasing for the next 4 decades[92]. The heterogeneity of this population, together with the untreated young children with complex congenital heart diseases, makes these patients ideal candidates for personalized, precision management. This personalized management, in turn, explains and supports the widespread adoption of 3D printing in institutions dedicated to the diagnosis and treatment of congenital heart diseases.

Atrial and ventricular septal defects. Atrial septal defects and ventricular septal defects are among the most common congenital heart defects, and can be present either isolated or in combination with complex cardiac

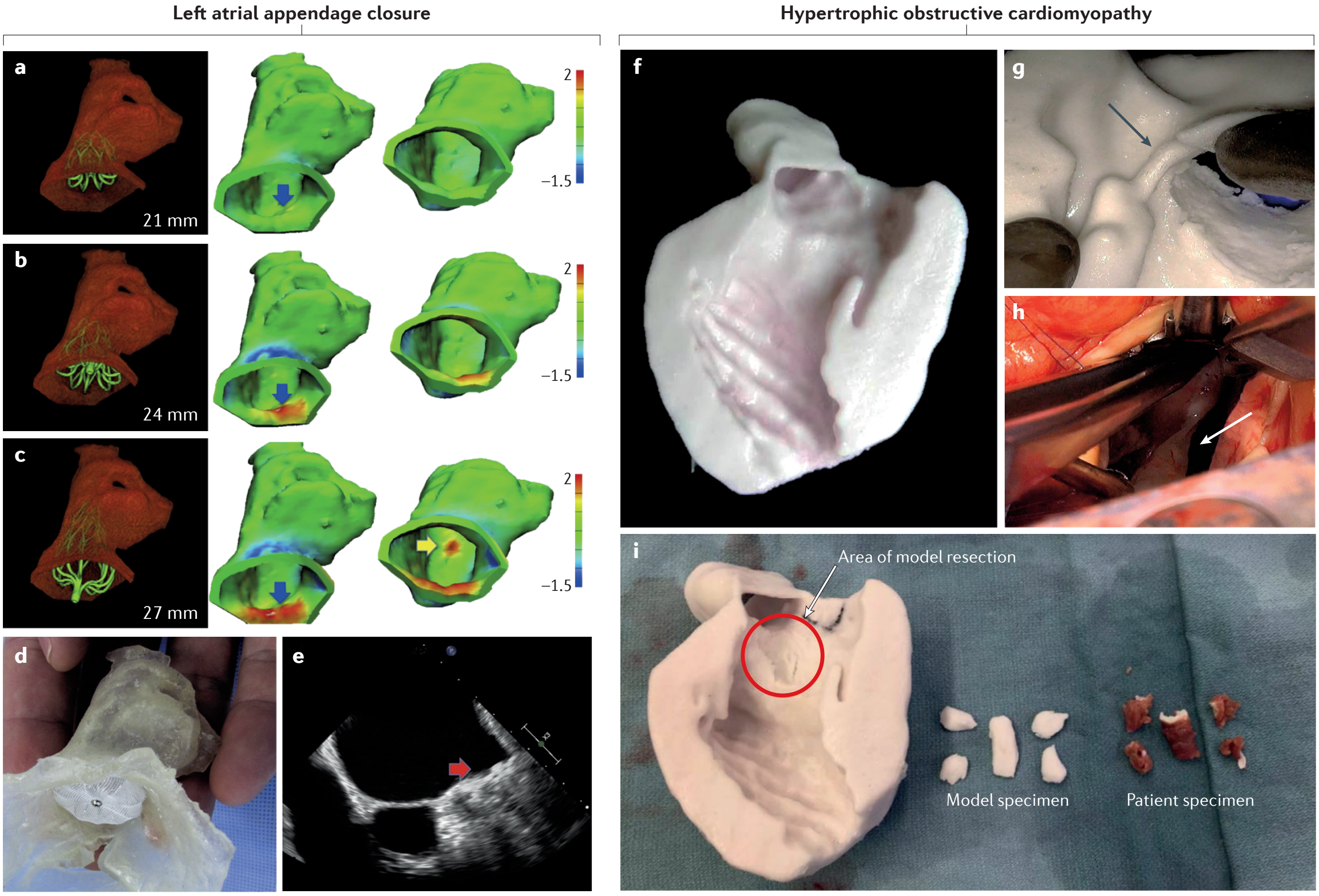

Figure 2 | **3D printing-assisted intervention and surgery planning of structural heart diseases. a–e** | Sizing of a Watchman device (Boston Scientific, USA) for left atrial appendage closure with a patient-specific 3D-printed model. Devices in sizes 21 mm (panel **a**), 24 mm (panel **b**), and 27 mm (panel **c**) were deployed in a flexible atrial model derived from CT images. Anatomical distortion was calculated for each device, creating a 3D map colour-coded according to the degree of deformation produced. The 21-mm device applies minimal radial force at the appendage orifice (blue arrow), whereas the barbs of the 27-mm device apply localized stress to the appendage wall (yellow arrow). Panel **d** shows the Watchman device placed within the flexible 3D-printed model. Transoesophageal echocardiography after the procedure demonstrates complete closure with a 24-mm device (panel **e**, red arrow). **f–i** | 3D printing-assisted septal myectomy in a patient with obstructive hypertrophic cardiomyopathy. A 3D porous scaffold of the anatomy of interest was fabricated and infused with a mixture of silicone and a blend of two hydrogels approximating the consistency of the cardiac muscle (panel **f**). The model was used for preoperative simulation of a transaortic septal myectomy, revealing an abnormality involving the subvalvular mitral apparatus — one papillary muscle inserted directly onto the leaflet (panel **g**, black arrow; view from ventricular side looking out of the left ventricular outflow tract) — that was confirmed during the operation (panel **h**, white arrow; view from aortic side looking into left ventricle). Panel **i** shows the 3D-printed model with resection specimens from the simulated myectomy alongside the actual myectomy specimens from the same patient for comparison. Panels **a–e** are reprinted from Otton, J. M. *et al.* Left atrial appendage closure guided by personalized 3D-printed cardiac reconstruction. *JACC Cardiovasc. Interv.* **8**, 1004–1006 (2015) with permission from Elsevier. Panels **f–i** are reprinted from Hermsen, J. L. *et al.* Scan, plan, print, practice, perform: development and use of a patient-specific 3D printed model in adult cardiac surgery. *J. Thorac. Cardiovasc. Surg.* http://dx.doi.org/10.1016/j.jtcvs.2016.08.007 (2016) with permission from Elsevier.

anomalies[93]. Treatment of these conditions is indicated for large and haemodynamically relevant defects and is generally surgical closure, although percutaneous approaches with closure devices are considered a safe alternative[94–96]. 3D printing has valuably aided in the spatial navigation of occluder devices during the operation and in optimizing patch sizing[3,97,98] (FIG. 5a,b).

Data from CT, MRI, or 3D echocardiography have been used to 3D print anatomical structures of interest, such as the atria and ventricles, and their relationship to neighbouring structures including the great vessels[5,15,36,99–103]. A 3D model of an ostium secundum atrial septal defect that was printed from TEE images provided enhanced 3D visualization of the defect[104].

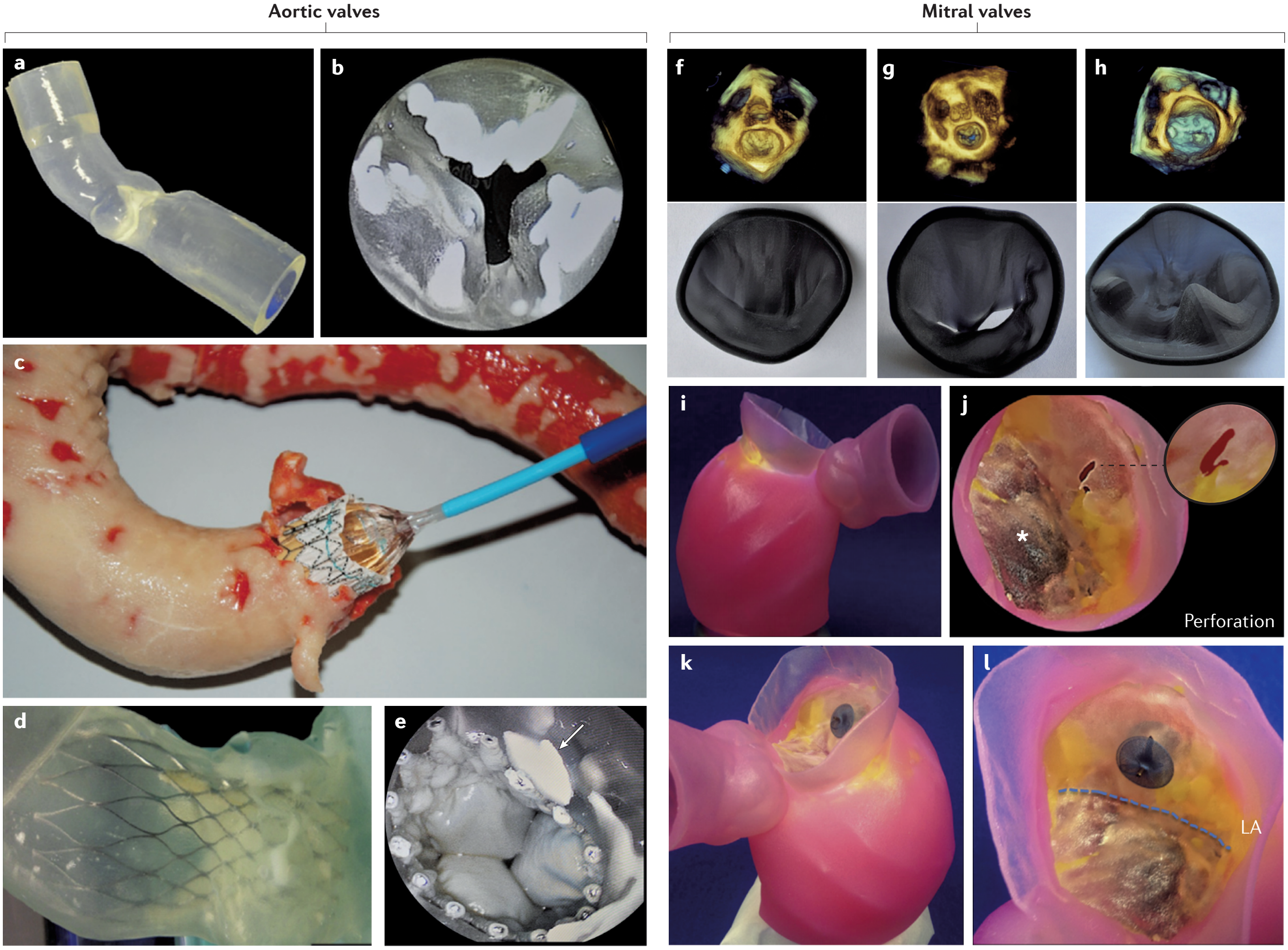

Figure 3 | **3D printing of aortic and mitral valves. a–c** | 3D printing application for aortic valve intervention. Long-axis (panel **a**) and short-axis (panel **b**) views of a 3D-printed model of a calcified, severely stenotic aortic valve derived from CT images. The left ventricular outflow tract, aortic valve, and proximal ascending aorta were printed in pliable material and the calcium was printed in a more rigid material. The model accurately simulated morphological and functional characteristics of the stenosis, as assessed by spectral Doppler. Aortic valve models can be used for simulations of transcatheter aortic valve deployment (panel **c**). **d,e** | Images of a deployed transcatheter valve visible within a 3D-printed model. Long-axis view (panel **d**) and view from the left ventricle (panel **e**) demonstrate regional 'calcific' resistance (white arrow) to a self-expanding nitinol stent frame. These approaches can potentially aid in the development of functional models to predict and improve the acute haemodynamic performance of transcatheter valve treatment strategies. **f–h** | 3D transoesophageal echocardiography views and the respective 3D-printed models of normal (panel **f**) and pathological mitral valves: ischaemic valve with two effective regurgitant orifices at end-systolic frame and incomplete coaptation (panel **g**); and a valve with myxomatous degeneration leading to billowing segments of posterior mitral leaflet (panel **h**). **i–l** | 3D printing application for mitral valve intervention. A multimaterial model of the mitral valve leaflets and the subvalvular calcium deposition (panel **i**) was created from CT images to assist in selection and sizing of an occluder device in a case of severe mitral valve regurgitation with restricted leaflet coaptation and a perforation of the posterior leaflet (panel **j**; the asterisk denotes calcium). An AMPLATZER Duct Occluder II (St. Jude Medical, USA) was placed across the posterior leaflet perforation (panel **k**), and evaluated for potential interaction with the leaflet coaptation zone (panel **l**; superimposed dotted line). LA, left atrium. Panels **a**, **b**, **d**, and **e** are reprinted from Maragiannis, D. *et al.* Functional 3D printed patient-specific modelling of severe aortic stenosis. *J. Am. Coll. Cardiol.* **64**, 1066–1068 (2014) with permission from Elsevier. Panel **c** is reprinted from Schmauss, D. *et al.* Three-dimensional printing of models for preoperative planning and simulation of transcatheter valve replacement. *Ann. Thorac. Surg.* **93**, e31–e33 (2011) with permission from Elsevier. Panels **f–h** are reprinted from Mahmood, F. *et al.* Three-dimensional printing of mitral valve using echocardiographic data. *JACC Cardiovasc. Imaging* **8**, 227–229 (2015) with permission from Elsevier. Panels **i–l** are reprinted from Little, S. H. *et al.* 3D printed modelling for patient-specific mitral valve intervention: repair with a clip and a plug. *JACC Cardiovasc. Interv.* **9**, 973–975 (2016) with permission from Elsevier.

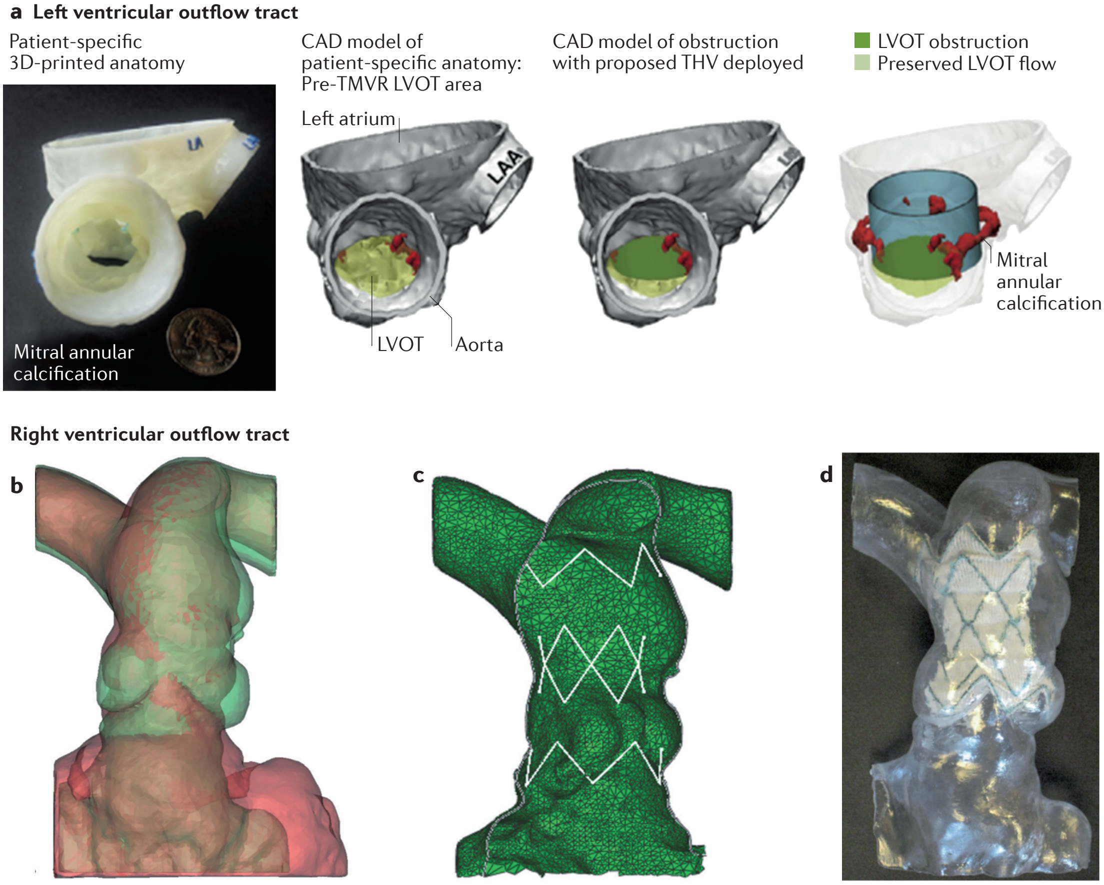

Figure 4 | **3D printing and modelling for transcatheter mitral and pulmonary valve implantation. a** | Fusion of computer-aided design (CAD)-mitral valve models and physical models can be useful in challenging cases of transcatheter heart valve (THV) implantation, such as mitral annular calcifications. Valve implantation can be virtually tested not only on-screen, but also with physical 3D model anatomy to confirm sizing and to estimate risk of left ventricular outflow tract (LVOT) obstruction. **b–d** | Modelling and 3D printing of the right ventricular outflow tract for a patient-specific transcatheter pulmonary valve development. In panel **b**, superimposed diastolic (red) and systolic (green) 3D volume reconstructions show that the pulmonary trunk has maximal dimensions in systole, while the underlying right ventricular outflow tract is at its smallest dimension. Panel **c** shows the finite element model of the contact between the stent graft (white) and the patient anatomy during systole (green). Panel **d** shows a plastic rapid prototype model of the patient anatomy with the final device inserted. TMVR, transcatheter mitral valve replacement. Panel **a** is reprinted from Wang, D. D. *et al.* Predicting LVOT obstruction after TMVR. *JACC Cardiovasc. Imaging* http://dx.doi.org/10.1016/j.jcmg.2016.01.017 (2016) with permission from Elsevier. Panels **b–d** are reprinted from Schievano, S. *et al.* First-in-man implantation of a novel percutaneous valve: a new approach to medical device development. *EuroIntervention* **5**, 745–750 (2010) with permission from Europa Edition.

In patients with ventricular septal defects, long-axis and short-axis measurements obtained from TTE-derived 3D-printed models had high correlation and accuracy with conventional 2D echocardiographic measurements[15]. Notably, the dimensions of the surrounding rim in atrial septal defects have an important role in the selection of occluder devices, because misplacement of the occluder device is associated with complications[97,105]. A physical model can potentially contribute to the pre-operative evaluation of the atrial septal defect, and the performance of an occlusion trial in this model can prevent unnecessary transcatheter closure[97] (FIG. 5a,b). Furthermore, 3D-printed models can be used for occluder device sizing and for the selection of the optimal approach to cross the defect in cases of congenital muscular ventricular septal defects[3].

Incidence of a ventricular septal defect after myocardial infarction is rare, but is associated with a very high mortality[106]. In these cases, the use of percutaneous closure devices might be preferred over high-risk surgical repair[107]. Occluder devices for post-myocardial infarction ventricular septal defects have high rates of failure[108], and bench testing in a 3D-printed model can enable a more accurate selection and successful *in vivo* deployment[109].

Complex paediatric and adult congenital heart diseases. The wide variety of defects associated with congenital heart diseases and the need for precise, personalized care has made this group of patients one of the most studied for 3D printing applications. Given the increasingly good prognosis of these patients,

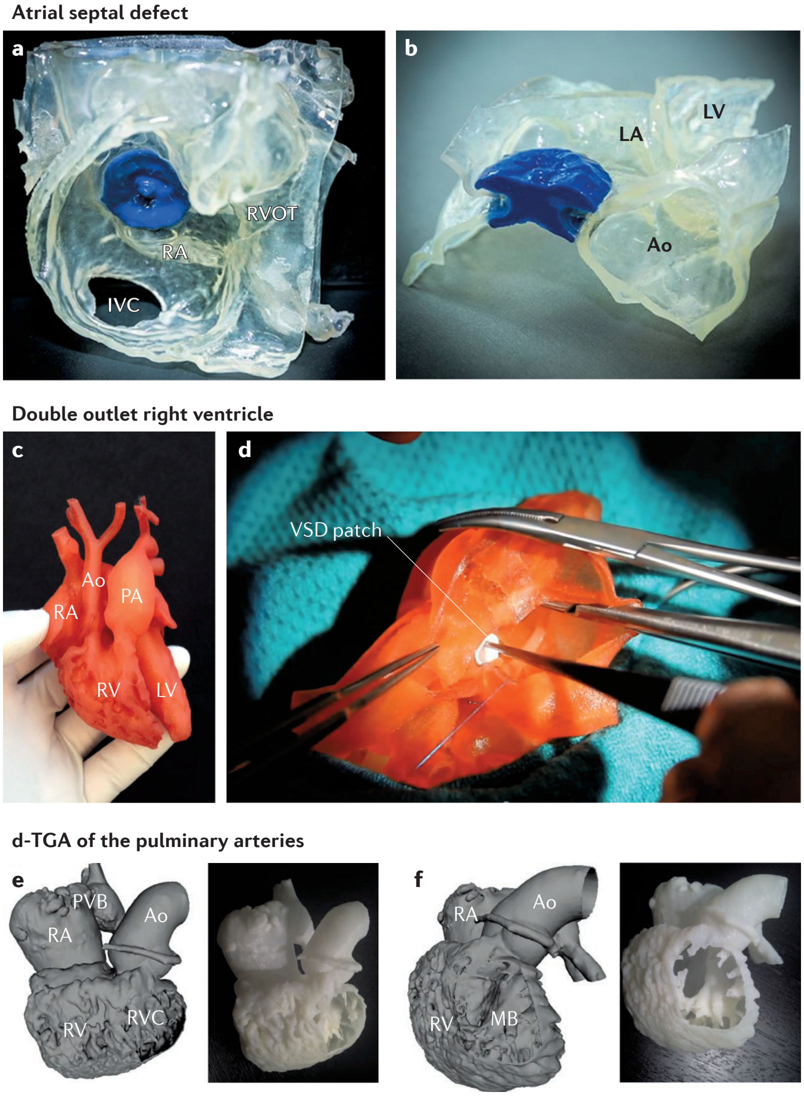

Figure 5 | **3D printing applications for patients with congenital heart disease.** **a,b** | Physical model application in an ostium secundum atrial septal defect. After the implantation of a 17 mm AMPLATZER Septal Occluder (St. Jude Medical, USA), a CT-derived 3D-printed model showed that the occluder adequately filled the atrial septal defect without interfering with the venous inlets, and was perfectly aligned with the interatrial septum (panel **a**). The left-sided countercluder contacted, but did not indent, the aortic wall or the left atrium (LA) roof (panel **b**). **c,d** | Flexible 3D-printed models of hearts from infants with double outlet right ventricle (RV) that enable straightforward appreciation of the anatomical relationships (panel **c**), as well as for hands-on training of the surgical repair of the condition, including suturing of the ventricular septal defect (VSD) patch (panel **d**). **e,f** | 3D models of a patient after Mustard procedure. A 3D virtual model (left) and corresponding printed model (right) of the pulmonary venous baffle (PVB) to the systemic RV in a patient aged 36 years with dextrotransposition of the great arteries (d-TGA) after Mustard procedure in heart failure. The model is viewed from the anterior aspect (panel **e**) and the leftward aspect (panel **f**). The anatomical landmarks of interest — the prominent trabeculations of the systemic RV and the moderator band (MB) — were well reproduced. This procedure enables presurgical planning of cannula placement to avoid possible inflow obstruction as a result of these trabeculations. Ao, aorta; IVC, inferior vena cava; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RVC, right ventricular cavity; RVOT, right ventricular outflow tract. Panels **a** and **b** are reprinted from Bartel, T. *et al.* Three-dimensional printing for quality management in device closure of interatrial communications. *Eur. Heart J. Cardiovasc. Imaging* **17**, 1069–1069 (2016) with permission from Oxford University Press and the ESC. Panels **e** and **f** are reprinted from Farooqi, K. M. *et al.* 3D printing to guide ventricular assist device placement in adults with congenital heart disease and heart failure. *JACC Heart Fail.* **4**, 301–311 (2016) with permission from Elsevier.

cardiologists will face a continuously growing adult population with a surgical history of correction(s). The highly variable anatomy of congenital heart diseases makes diagnosis and treatment options depend on the most accurate structural information for each patient, taking into account their clinical trajectory.

3D-printed models enhance the visuospatial dexterity of the physicians and maximize pre-interventional perception of the anatomy. Several centres have reported the utility of 3D printing for a variety of complex congenital heart diseases[4,24,36,101,110–115], including the prime example of double outlet right ventricle[13,14,116,117]. In double outlet right ventricle, more than half of both great arteries is connected to the right ventricle, and this condition is almost always accompanied by a ventricular septal defect[118]. The variability of the infundibular and intracardiac morphology accounts for diverse clinical manifestations, and necessitates individualized surgical approaches. Entire heart models derived from MRI or CT images and 3D printed in flexible materials aid surgeons to understand the relationship between the ventricular outflow tract, the ventricular septal defects, and the aorta. These models are used to assess and practise the feasibility of intraventricular baffling before the actual biventricular repair[14,119] (FIG. 5c,d).

Infants with tetralogy of Fallot combined with pulmonary atresia can benefit from 3D-printed models that better convey pulmonary vascular anatomy and preoperative identification of major aortopulmonary collaterals without prior cardiac catheterization[4]. 3D-printed models of major aortopulmonary collaterals are a novel, intuitive form of communicating complex pulmonary vascular imaging data that can be referenced during the operation[120]. These models can be advantageous for decreasing fluoroscopy time and contrast exposure, reducing the exposure to general anaesthesia, and reducing cardiopulmonary bypass time. Furthermore, these 3D-printed models can assist in perioperative planning and in visualization during the procedure in infants with failing single-ventricle heart that require cardiac transplantation[113].

A major advance in cardiovascular 3D printing has been the ability to print models in transparent, flexible material. Flexible models can be cut and bent allowing for inspection and assessment of the pathology, and the selection of optimal viewing planes for complicated cases[121]. Simulation of surgical repair before the actual operative procedure has been shown to be feasible in challenging conditions such as hypoplastic left heart syndrome[100,122,123] and transposition of the great vessels[114].

3D printing can aid in the surgical[5] or interventional[2,111] palliation in adults with congenital heart disease treated at a young age[110,111] or not previously diagnosed[112]. 3D-printed models of both the intracardiac volumes and the myocardium walls aided in a complicated case of an adult patient with transposition of the great vessels who had undergone prior surgical interventions[110]. Adults with repaired congenital heart disease frequently develop heart failure[124], experience longer waiting-list times, and have higher waiting-list mortality than other transplantation candidates[125]. Ventricular assist devices that could serve as bridge-to-transplantation or as destination therapy are underutilized in these patients because of the complex anatomy and physiology[126]. 3D printing offers individualized structural models that can potentially enable the planning of cannula and device placement before the procedure[126] (FIG. 5e,f). Likewise, adult survivors of Mustard operation can present with structural issues related to the intra-atrial baffles, including baffle leak or baffle obstruction[127,128]. 3D printing can aid in stent angioplasty[111] or endovascular graft prosthesis placement[2] by increasing procedural efficiency, decreasing radiation exposure, and mitigating procedural complications.

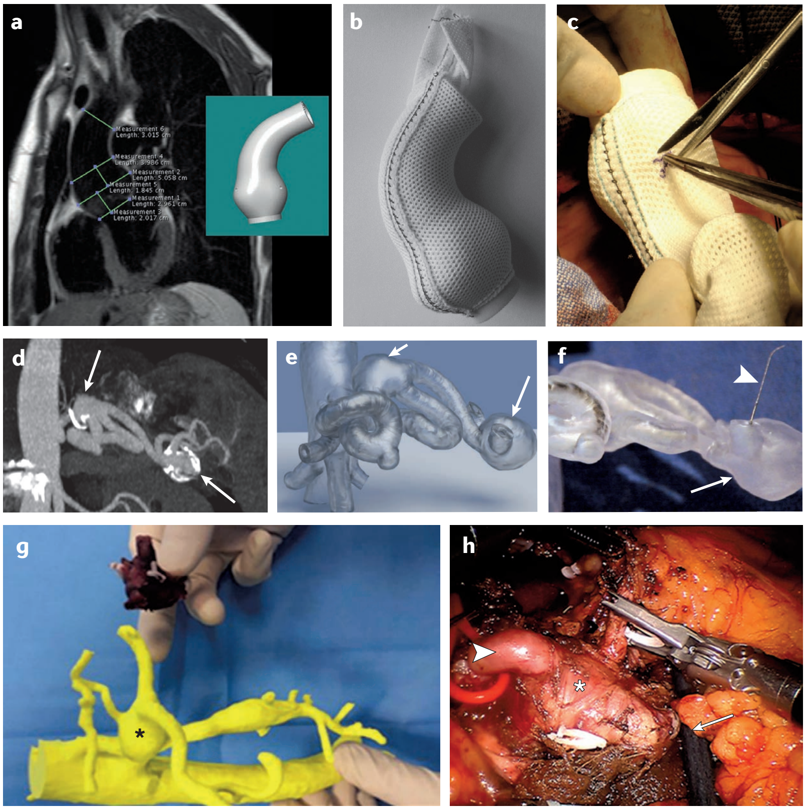

Figure 6 | **3D printing applications for invasive and noninvasive management of vascular pathologies. a–c** | Fabrication and surgical implantation of personalized external aortic root support for conservative approach in patients with Marfan syndrome. MRI or CT images (panel **a**) are used to generate a patient-specific computer-aided design model (inset) of the aortic root that is 3D printed in thermoplastic. The physical model is used as a template for the fabrication of a porous external support from medical-grade polymer mesh fabric (panel **b**). The sterilized support mesh is brought to the operating table, and the location of the exit of the coronary arteries is marked and opened (panel **c**). Finally, the mesh is placed around the aorta from the aortoventricular junction to beyond the brachiocephalic arteries. **d–f** | Utility of 3D printing for planning and guidance during endovascular intervention of splenic artery aneurysms. Panel **d** is a CT angiogram with maximum intensity projection of the splenic artery depicting the two 2-cm splenic artery aneurysms (arrows). Panel **e** shows digital 3D rendering of the hollow splenic artery model that was printed and used for preoperative testing (arrows indicate the two aneurysms). Panel **f** shows the guide catheter in the proximal artery model. The delivery wire for the stent (arrowhead) was successfully navigated past the most distal aneurysm (arrow), and the stent was successfully deployed in the model. **g,h** | Robotically-assisted resection of a coeliac trunk aneurysm (asterisk) guided by 3D printing. The 3D-printed model (panel **g**) enabled the surgeons to reorient the model to the actual intraoperative view (panel **h**; arrowhead is the common hepatic artery; arrow is the splenic artery). Panels **a–c** are reprinted from Pepper, J. *et al.* Implantation of an individually computer-designed and manufactured external support for the Marfan aortic root. *MMCTS* **2013**, mmt004 (2013) with permission from Oxford University Press and the European Association for Cardio-Thoracic Surgery. Panels **d–f** are reprinted from Itagaki, M. W. Using 3D printed models for planning and guidance during endovascular intervention: a technical advance. *Diagn. Interv. Radiol.* **21**, 338–341 (2015) with permission from the Turkish Society of Radiology. Panels **g** and **h** are reprinted from Salloum, C. *et al.* Fusion of Information from 3D printing and surgical robot: an innovative minimally technique illustrated by the resection of a large coeliac trunk aneurysm. *World J. Surg.* **40**, 245–247 (2016) with permission from Springer.

Systemic vasculature

3D printing of models of the systemic vasculature is feasible and beneficial for diagnosis and treatment selection in challenging cases, and for device deployment testing. Clinical advances in 3D-printed models focus mainly on the pathology of great vessels[37,38], with reports in the past 2 years including other vascular beds[25,129]. Models are commonly printed hollow and in flexible materials, enabling tactile perception of the anatomy and pre-interventional simulations.

In patients with Marfan syndrome and aortic root aneurysm, cardiovascular 3D printing has enabled an alternative to aortic root replacement, namely, personalized external aortic root support (PEARS) placement[130,131]. Clinical studies have demonstrated the added value of this procedure[37,132]. 3D-printed aortic models from the annulus to the proximal aortic arch are used to knit a fitting bespoke porous fabric mesh sleeve support. This patient-tailored external support can then be surgically implanted, conserving the aortic root morphology and the natural architecture of the aortic valve[132,133] (FIG. 6a–c). Rigid and flexible 3D-printed models can aid endovascular interventions by enabling the assessment of optimal stent dimensions and positioning in cases of transverse aortic arch hypoplasia[134], as well as the evaluation of single-stage concomitant repair of aortic arch and proximal descending aortic aneurysms (frozen elephant trunk technique) before and after the operation[135]. Furthermore, selecting and sizing of occluder devices with the use of vascular physical models can potentially minimize perioperative morbidity and mortality in cases of anastomotic leaks after replacement of the ascending aorta and the aortic arch[136].

Device selection and stent-graft delivery for endovascular aneurysm repair can be improved by 3D printing, particularly for aneurysms with complex neck and distal anatomy[38,137]. Patient-specific 3D-printed fenestration templates for modification of endovascular grafts in cases of juxtarenal abdominal aorta aneurysms can expedite planning, and theoretically reduce procedural costs[138]. Technical advances have also been reported in 3D printing of smaller-calibre arteries, for example, in the management approach for the selection and optimization of endovascular repair interventions in splenic[25] and renal artery aneurysms[2], as well as robotically-assisted resection of coeliac trunk aneurysms[129] (FIG. 6d–h).

Education, training, and research

Cardiovascular 3D printing is poised to revolutionize the education of patients and their families, as well as the process of decision-making and consent[10,35,102,139].

For example, 3D models of paediatric congenital heart disease have improved engagement with patients, and can enhance physician–parents–patient communication in clinical practice[10]. Medical residents that used 3D models in the critical-care setting showed an enhanced ability to describe and manage postoperative complications in patients with ventricular septal defects[35]. In addition, 3D-printed heart models can enhance communication within multidisciplinary intensive care teams trusted with the management of patients who need congenital cardiac surgery[12].

3D printing will also provide the next incremental step in the training of medical students, residents, and cardiologists who wish to deepen their knowledge of complex anatomy and broaden their horizons in cardiovascular research. Anatomical models are beneficial for medical student education[140], and incorporation of medical 3D models is expected to transform undergraduate medical education[141,142]. 3D models can also reduce the learning curve of inexperienced trainees in endovascular repair procedures of abdominal aortic aneurysms[143]. Direct visual access improves the conceptualization of anatomical volumes and enables direct physical manipulation. This realistic haptic feedback fills a need left by virtual reality simulators by enabling real-life physiology experimentation and testing of devices such as valves[144].

The first step of 3D printing in medical education will be the establishment of local 3D libraries, although more general libraries will soon follow. For example, online 3D model libraries have been developed for congenital heart diseases (see IMIB–CHD, 3D Hope Medical, and NIH 3D Print Exchange), a field in which education is rapidly moving towards the use of 3D models as a central method for learning, practising, or developing new surgical procedures[11,14]. These libraries will be emulated and refined for many more applications, facilitating collaboration and increasing proficiency in the full range of cardiovascular diseases.

Current cardiovascular surgical training is mostly opportunity-based, which limits uniform exposure of the trainees to various procedures. Hands-on surgical training with 3D-printed models will change the traditional opportunity-based education to the requirement-based standardized education. Hands-on courses for surgical training[14] and for teaching cardiovascular 3D printing[102] have now progressed from experimental educational activities to mainstream educational resources.

Patient and public involvement and engagement in research, facilitated by 3D printing, can promote patient-relevant applications and prioritize research topics[145]. Cardiovascular physiology laboratories also benefit from 3D printing. Fabricating custom-designed equipment and creating fully functional experimental setups[146] will probably improve overall lab functionality[9]. Complex, controlled experiments, such as *in vitro* hydrodynamic simulations on benchtop models[147], can be readily realized with 3D printing technology, thereby improving the overall understanding of coronary artery disease, optimizing noninvasive imaging modalities such as CT[1] and flow-encoded MRI[148], and even enhancing biomechanical simulations for coronary bifurcation stenting[149]. Coronary stent delivery techniques can be studied and improved by combining computational fluid dynamic simulations with 3D-printed models[147]. Other vascular research applications include the simulation with 3D-printed silicon models of the haemodynamic milieu of aorta dissection[150,151]. Advances in cardiac valve research include the use of 3D TEE-derived printed models of the mitral valve deployed in a pulse-duplicator chamber, which can provide haemodynamic metrics for functional assessment[8].

The FDA has approved 3D-printed devices within the existing medical device regulations for >1 decade[28]. Models are valuable in preclinical device development[101], as shown in a first-in-human implantation of a purpose-built transcatheter valve into a large native pulmonary tract[26]. Vascular models with nonuniform thickness can be printed in materials adequately mimicking *in vivo* arterial distensibility properties, which can then be used to test devices *in vitro*[152]. 3D-printed-derived silicon cast phantoms have been employed for *ex vivo* stent deployment testing to examine accurate stent graft deployment and potential endoleak[153,154]. Novel, hybrid modelling combining 3D printing and computer simulations can shift the traditional bench-to-bedside development process of using animals before human testing stages towards a more efficient, more relevant, and time-efficient pathway.

3D bioprinting and molecular 3D printing

3D bioprinting refers to the fabrication of 3D functional living constructs with biological and mechanical properties[155]. Utilizing 3D printing technology, cells, cell-scaffolds, biomolecules, and biomaterials are positioned in a layer-by-layer fashion to build 3D structures. 3D bioprinting enables the production of 3D constructs with accurately controlled architecture and different cell types, all in a microenvironment more precisely resembling the natural milieu than that achieved with traditional tissue-engineering techniques[156]. Although the detailed description of the technologies and the bioprinting process of cardiovascular 3D tissues[157] is beyond the scope of this Review, the medical imaging technologies highlighted for 3D printing in previous sections, such as CT and MRI, together with CAD and mathematical modelling provide essential anatomical and functional information of the structures of interest, and can also predict the biomechanical characteristics of the bioprinted tissue constructs[158]. Cardiovascular 3D bioprinting is a field of budding research, although applications have so far not moved outside the wet-lab. Medical, biomedical, and biology experts need to collaborate to expedite progress in the field.

Molecular 3D printing is the next generation in personalized medicine. This technology will enable patient-specific interventions guided by molecular biomarkers, in addition to anatomical (tissue-based and organ-based) biomarkers. This new field integrates anatomy, function, physiology, and also molecular

Box 3 | **Goals for cardiovascular 3D printing**

Short-term goals
- Recognition of available technologies and current cardiovascular clinical applications
- Selection of the optimal 3D printing strategy: national–international collaborations with centres of excellence; in-hospital 3D printing lab; and outsourcing
- Roles and responsibilities of physicians, technologists, and engineers
- Implementation in clinical practice

Long-term goals
- Amalgamation of available case reports
- New studies of specific clinical roles
- New, large-scale, clinical studies
- Demonstration of effectiveness
- Improve costs–outcomes ratio
- Implementation into guidelines and appropriateness criteria
- Worldwide adoption

pathogenesis. 3D-printed models of a patient's diseased organ or tissues can convey specific molecular targets for diagnosis and intervention. Molecular findings that are mapped and integrated on cardiovascular 3D models can guide interventions, and can be used to refine, practise, and teach the interventional procedures. This optimization, in turn, will provide unique opportunities for directed therapies. Cardiovascular molecular 3D printing will require the nexus of advances in multiple disciplines, such as the fusion of imaging modalities (for example, PET and MRI) with 3D printing engineering, together with systems biology, functional genomics and proteomics, molecular target labelling, and clinical expertise.

Current status of cardiovascular 3D printing

Cardiovascular 3D printing in hospitals and medical centres will follow and overcome many of the financial and training obstacles that 3D visualization faced roughly 10–15 years ago[1]. 3D visualization refers to the segmentation and postprocessing of DICOM images with specialized software to represent an anatomical volume (for example, as a multiplanar reformatted image, a maximum intensity projection, or a volume rendering) on a 2D screen. 3D printing is the next frontier for the 3D laboratory. In 3D printing, DICOM images undergo postprocessing to STL (or similar format) files, and are then refined and ultimately 3D printed[102]. The 3D printing lab is the next generation of in-hospital facilities for medical modelling. The main obstacles of the 3D visualization lab — software and hardware costs and the need for training and expertise in image postprocessing — further translate to the 3D printing lab.

With regard to imaging modalities and acquisition protocols, cardiovascular 3D printing requires thin reconstruction images with high signal and contrast. Images that meet these criteria are not always available, particularly in patients with unstable cardiovascular disease and high haemodynamic variability. Experience and time for image segmentation also present challenges. The operator must have dedicated time and training to interpret cardiac anatomy and pathology from the source images; this dedicated time and training can be challenging in multimodality imaging[15,159,160]. Existing image segmentation methods for 3D visualization have improved considerably over the past decade, and are now being recognized as an essential tool for streamlined workflow in cardiovascular 3D printing in particular, and medical 3D printing in general[21,161,162].

The accuracy and reproducibility of clinical 3D-printed models need to be defined and tested, and sufficiently accurate 3D printers have to be incorporated into practice. At present, the accuracy of 3D printers with regard to clinically relevant features is typically <1 mm, and often is less than the voxel size (and hence the spatial resolution) for a particular cardiovascular imaging modality[163]. Several factors can influence the model accuracy during the manufacturing process[164], and probably the most important element is image postprocessing, in particular segmentation[2]. Assessment of intraoperator and interoperator variability is an important future target. The development of robust, automated techniques for each of the postprocessing steps is necessary for studying accuracy and precision of models. Standardization of the source image data acquisition and postprocessing techniques, which is currently lacking, will assist in this objective.

The properties of the materials for 3D printing have great importance for cardiovascular applications. As 3D printing rapidly moves from other industries to medicine, the major gap in the available materials to better emulate human tissues has been recognized. Currently available materials provide models that can be used beyond advanced visualization and patient counselling. However, these materials can be suboptimal for compliant cardiovascular models used for simulations of complex interventional approaches. The planning of the 3D printing of such models should consider the vessel wall thickness, as the thickness might pose a limitation to the resolution of the printer and, consequently, can restrict the distensibility range that can be applied to the vessel[145]. 3D printing material science mandates further research and development in this field. In addition to mimicking cardiovascular tissue, other physical parameters are warranted, such as steadiness, tensile strength, elasticity, and memory capacity, which are intimately related to the pathology[165].

Widespread adoption of 3D printing is currently limited owing to the lack of robust evidence that systematically demonstrates the effectiveness and cost-efficiency of the modality. Other reasons include high costs, complexity of workflow, and narrow awareness that 3D printing can enhance patient care. Medical reimbursement for care providers, whether they are within hospitals or industry-contracted by physicians, will catalyse broad-based improvements for all the limitations noted above; technologies are in-hand or close to development and implementation, and the current challenges can be readily solved with time and money. Because of the investment needed, the implementation of cardiovascular 3D printing in hospitals has been largely limited to large teaching hospitals and research institutions[166].

Future perspectives

Cardiovascular 3D printing has the potential to become a true paradigm shift for the current and future generations of cardiovascular imagers and care providers. Printed models will be incorporated into the standard of care for many cardiovascular applications, akin to the current role that 3D-printed models have in planning interventions for complex congenital heart diseases. The complex process of 3D printing needs to be simplified by improving practicability, efficiency, quality, and ease of use.

Future steps for the research community and the growing body of adopters of cardiovascular 3D printing are summarized in BOX 3. Short-term aims include reduction of costs, identification of appropriate modalities for source images, optimization of the 3D printing workflow, and establishment of roles and responsibilities of technologists and adroit cardiovascular imagers and cardiologists. Dynamically evolving targets and collaborative efforts between academia and industry are warranted in order to accomplish these aims in a timely fashion. In the long run, we recognize that an unmet need exists for the amalgamation of case reports into studies with robust outcomes, an improvement in the cost-to-outcome ratio, the determination of guidelines for appropriateness criteria, and implementation in everyday clinical practice. National and international cardiovascular 3D printing organizations will have a pivotal role in the realization of these targets.

3D printing will have an integral part in the multidisciplinary and collaborative cardiovascular diagnoses and treatment strategies. The feasibility of this technology has been shown for a broad fraction of the cardiovascular disease range. The next step is large patient cohort prospective studies that can lead to large-scale, randomized, clinical trials. A suggested framework for medical and cardiovascular 3D printing trials is presented in FIG. 7. Establishing medical and cardiovascular 3D printing centres of excellence in institutions that can undertake such endeavours is important. From those centres, proper technical recommendations will be determined for each application with respect to image data acquisition, postprocessing, and 3D printing technologies and materials used. Trials designed to investigate the added value of 3D printing for each cardiovascular application will follow, leading to the establishment of appropriateness guidelines and recommendations. As is the case for new technologies and modalities, utilization, user consensus, and incremental technology advances of 3D printing will be fast-paced and will outstrip the ability for methodical patient recruitment in multicentre trials. Nonetheless, such clinical trials are paramount to confirm the growing realization that 3D printing is cost-effective and improves patient outcomes.

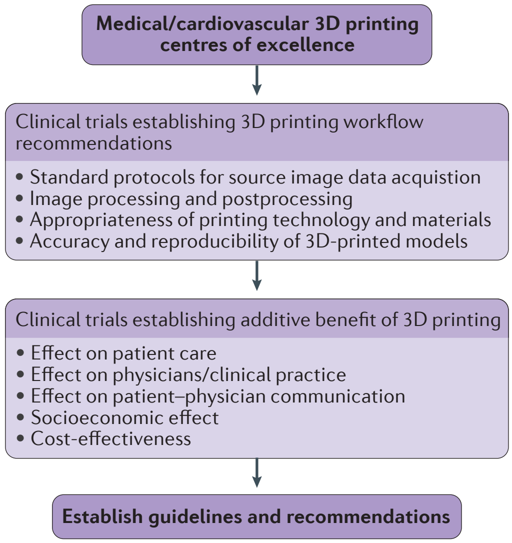

Figure 7 | **Suggested framework for medical and cardiovascular 3D printing clinical trials.** In the proposed medical and cardiovascular 3D printing centres of excellence, technical recommendations stratified by clinical application will be determined regarding the imaging data acquisition, postprocessing, 3D printing technologies, and materials used. The additive benefit of 3D printing for each application under investigation will be established by the effect on patient care, routine clinical practice, patient–physician communication, society, and economy, as well as the cost-effectiveness of the technology. Such clinical trials will potentially lead to the implementation of medical 3D printing in treatment guidelines and recommendations.

From these data, supplemented with expert opinion when data are incomplete, guidelines will come. Guidelines that are needed include specifications for image acquisition and image-quality metrics; a framework detailing image postprocessing — a step at which the greatest differences between the anatomy depicted in the DICOM data and the models produced can be introduced; specifications for the 3D printing hardware; accuracy metrics that compare the 3D-printed model and the anatomy of interest in addition to any modifications to the anatomy, such as in the development of a device; and, finally, definition of clinical scenarios for which 3D printing is considered appropriate for integration into clinical care.

Conclusions

Cardiovascular 3D printing has revolutionized personalized medicine and holds great promise towards patient-tailored cardiovascular practice, physiology research, and development of clinical tools. 3D printing has also greatly advanced the education of physicians and patients. The advent of cardiovascular 3D bioprinting and molecular 3D printing will enable improved precision mapping of pathologies and individual disease aetiologies. The realization of cardiovascular 3D printing in routine clinical practice is poised to be transformative for medicine.

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Competing interests statement

The authors declare no competing interests.

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