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REVIEW

Imaging-Based, Patient-Specific Three-Dimensional Printing to Plan, Train, and Guide Cardiovascular Interventions: A Systematic Review and Meta-Analysis

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Background To tailor cardiovascular interventions, the use of three-dimensional (3D), patient-specific phantoms (3DPSP) encompasses patient education, training, simulation, procedure planning, and outcome-prediction.

Aim This systematic review and meta-analysis aims to investigate the current and future perspective of 3D printing for cardiovascular interventions.

Methods We systematically screened articles on Medline and EMBASE reporting the prospective use of 3DPSP in cardiovascular interventions by using combined search terms. Studies that compared intervention time depending on 3DPSP utilisation were included into a meta-analysis.

Results We identified 107 studies that prospectively investigated a total of 814 3DPSP in cardiovascular interventions. Most common settings were congenital heart disease (CHD) (38 articles, 6 comparative studies), left atrial appendage (LAA) occlusion (11 articles, 5 comparative, 1 randomised controlled trial [RCT]), and aortic disease (10 articles). All authors described 3DPSP as helpful in assessing complex anatomic conditions, whereas poor tissue mimicry and the non-consideration of physiological properties were cited as limitations. Compared to controls, meta-analysis of six studies showed a significant reduction of intervention time in LAA occlusion (n=3 studies), and surgery due to CHD (n=3) if 3DPSPs were used (Cohen's d=0.54; 95% confidence interval 0.13 to 0.95; p=0.001), however heterogeneity across studies should be taken into account.

Conclusions 3DPSP are helpful to plan, train, and guide interventions in patients with complex cardiovascular anatomy. Benefits for patients include reduced intervention time with the potential for lower radiation exposure and shorter mechanical ventilation times. More evidence and RCTs including clinical endpoints are needed to warrant adoption of 3DPSP into routine clinical practice.

Keywords Patient specific phantoms • 3D printing • Additive manufacturing • Cardiovascular intervention • Personalised medicine

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Introduction

Cardiac imaging using cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (CCT) has undergone a rapid development within the last decades, today depicting cardiac anatomy and physiology with excellent temporal and spatial resolution. Four-dimensional (4D) image datasets, as well as advanced post-processing techniques, have laid the basis for the large number of personalised invasive structural cardiac interventions, available today. Translation of imaging data to patient-specific models is the next frontier in this respect that could facilitate further refinements and patient-specific tailoring of interventions. Three dimensional (3D) printing, also known as rapid prototyping or additive manufacturing, is a promising technology well-established for individualisation of treatment in orthopedic surgery [1], whereas its use in cardiovascular medicine is yet to be defined. Extension in the field of cardiovascular medicine needs to take into consideration varying size of structures according to the cardiac cycle, difficult delineation of soft-tissues and the cardiac valves and the inclusion of functional properties [2]. Patient-specific 3D printed phantoms (3DPSP) meeting these requirements cannot only enhance medical and patient education, but can also be used to plan, train, simulate, and guide cardiovascular interventions. Obtaining accurate 3DPSP of complex anatomic structures allows ex vivo visualisation and delineation of complex spatial relationships in various cardiovascular disease settings [3]. Although the translation of clinically indicated cardiac imaging to 3DPSP does not expose the patient to additional risk, several challenges remain to be overcome before 3D printing will meet widespread clinical acceptance for individualisation of cardiovascular interventions. The scope of this systematic review is to analyse utility of 3D printing in cardiovascular interventions as well as its limitations. Current applications and future directions will be discussed to help interventional cardiologists and surgeons find the ideal targets for 3D printing.

Methods

Two (2) independent reviewers (i.e., authors B.B. and J.I.) conducted a systematic literature query on the databases Medline and EMBASE using the key terms “3D printing,” “3D phantom,” or “additive manufacturing,” plus one of the terms “cardiovascular,” “cardiac,” “aorta,” “aortic-, mitral-, tricuspid-, or pulmonary valve,” “coronary arteries,” “left atrial appendage,” “congenital heart disease,” or “hypertrophic cardiomyopathy” for “All fields” search (Figure 1). All fields search tools also included Medical Subject Headings (MeSH) terms. Any inconsistencies were discussed and reconciled by a third reviewer (i.e., author C.G.). Inclusion criteria were the prospective use of at least one 3DPSP in cardiovascular intervention, published between 1 January 2005 and 1 May 2021, and the investigation of human data as the subject in a peer-reviewed article. Cardiovascular intervention was defined as open surgery or transcatheter intervention of the heart and its structures, the ascending aorta, the aortic arch, and the descending aorta above the coeliac trunk. Studies that printed 3D models for other purposes than personalised medicine (e.g., non-personalised models for validation of imaging modalities) and articles about tissue engineering or bioprinting were excluded, as well as reviews and case reports on applications that had previously been investigated by other studies. Included studies were screened for cross-references fulfilling our inclusion criteria.

Meta-analysis and forest plotting were performed using Meta-Essentials Version 1.5 for Microsoft Excel [4]. Combined effect size is provided by Cohen’s d (mean difference/standard deviation), which was determined by a random-effect model. Weak effects are represented by $d<0.3$; $d=0.3–0.8$ indicates medium effect size, whereas strong effects are mirrored by $d>0.8$. In this model, we included all studies that provided data for mean intervention time and its standard deviation in a group with 3DPSP compared to a control group without 3DPSP. For studies that provided median intervention time and its range, we estimated mean and variance according to Hozo et al. [5]. The extent of heterogeneity was estimated by Q-statistics (“Cochran’s Q” test). I^2 and T^2 were provided to quantify inconsistencies of results across studies as an estimate of the standard deviation of the distribution of effect sizes [6]. Although no clearly defined cut-off exits, $I^2=30\%–60\%$ usually refers to moderate heterogeneity, whereas substantial heterogeneity might be indicated by $I^2>60\%$. Results were considered significant if the two-sided p-value was ≤ 0.05. This review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7], and ethical approval was waived, as no human subjects are involved in this study.

Results

After removing duplicate records, we identified 2,227 articles corresponding to our key search terms, of which a total of 86 articles fulfilled inclusion criteria (Figure 1). Another 21 studies were added via cross-references, resulting in a total of 107 included studies. The number of newly published articles on the use of 3DPSP in cardiovascular intervention has been constantly rising within the last 16 years with approximately half of the identified study being published after 2017 and a trend towards an increase in the number of models obtained in each study using December 2017 as a cutoff (6.4±9.1 vs 8.9±11.8; $p=0.241$) (Figure 2). The included studies with cumulative 814 3DPSP encompass case reports with one patient included (n=38), case series with less than 10 patients (n=38), larger observational and descriptive studies (n=18), comparative studies with a control group with no 3DPSP (n=12), and one randomised controlled trial (Table 1).

Congenital Heart Disease

A total of 38 studies prospectively investigating 3DPSP to guide cardiovascular intervention in congenital heart

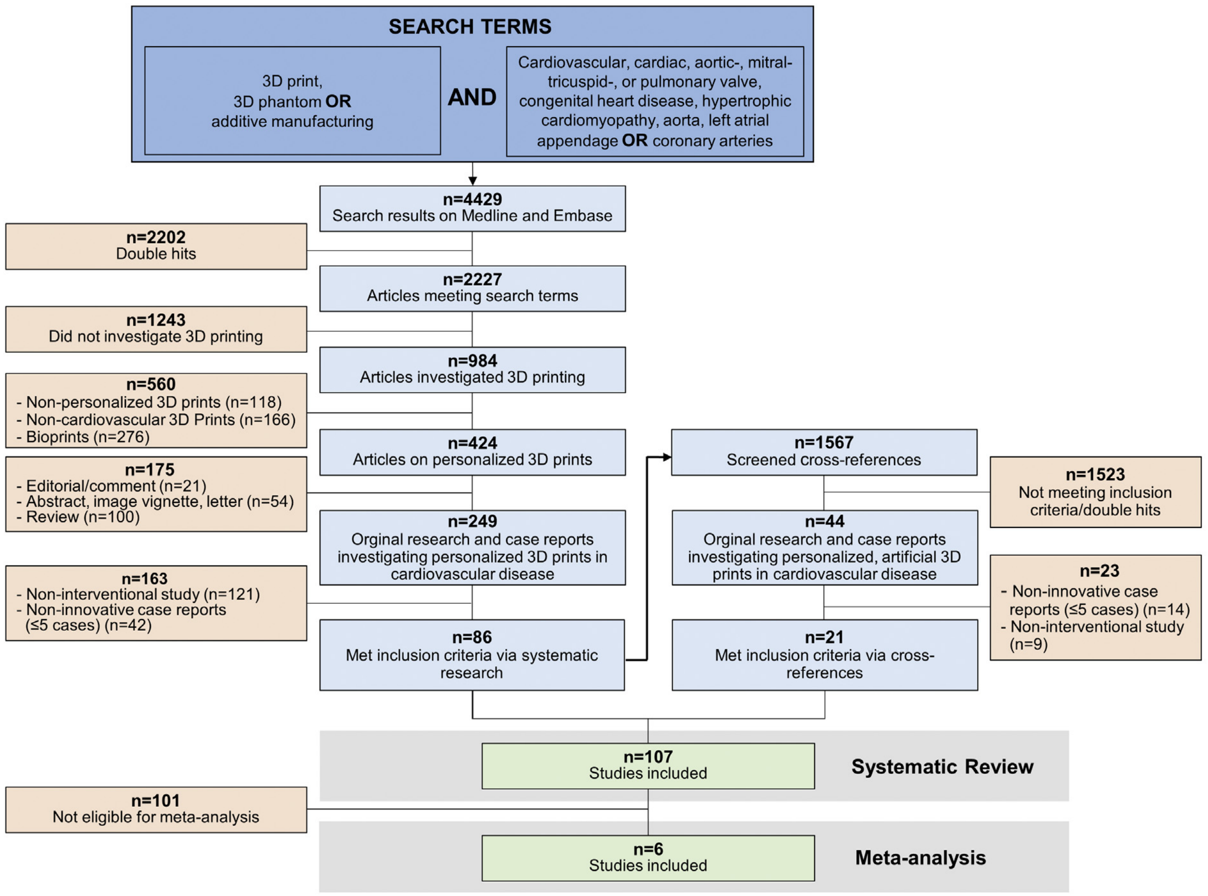

Figure 1 Consort flow of the study selection process. Non-personalised three-dimensional (3D) prints also included animal studies, and articles using personalised 3D models for validation of imaging modalities. Prospective interventional studies were defined by the production and the use of a 3D printed model prior to the intervention. Case reports with less than 5 patients were excluded if larger studies in the same setting existed.

disease (CHD) of which six studies systematically compared 3DPSP to standard therapy and included a control group without 3DPSP. Across all studies, 329 3DPSP were manufactured, rendering CHD the field with the widest application of 3DPSP in cardiovascular interventions. Mottl-Link et al. [8] reported one of the first cases in which a 3DPSP was considered to impact patient management in CHD. A CMR-derived 3DPSP was intraoperatively shown to the surgeon to identify the location of coronary arteries and other structures enabling a complex operation. Valverde et al. [9] extended the use of 3DPSP to the field of transcatheter cardiovascular interventions and reported 3DPSP being a valuable adjunct in planning and simulating endovascular stenting in transverse aortic arch hypoplasia. Following this approach, feasibility of 3DPSP to identify the optimal prosthesis in terms of size for transcatheter closure of atrial septal defect or patent ductus arteriosus was demonstrated [10,11]. Also, 3DPSP can enrich patient counselling [12–14] and affect clinical decision making [15]. In the largest multicentre case-crossover study of CHD to date, decisions on the therapeutic management made by review of imaging data only were compared to decisions based on imaging data and an additional 3DPSP. In nearly half of the included 40 patients (n=19), application of 3DPSP changed the surgical decision and helped to redefine the surgical approach [15]. Compared to standard therapy without 3DPSP, 3DPSP-guided surgery due to CHD might affect operation duration [16,17], aortic cross-clamp time, mechanical ventilation time, and intensive care unit time [11,18]. A benefit of 3DPSP in terms of outcome was reported in a retrospective analysis of 30 patients who underwent device closure for multiple atrial septal defects. Compared to a control group using fluoroscopic guidance, patients treated after previous training on 3DPSP showed lower frequency of occluding device replacement and prevalence of residual shunts, which is also associated with lower costs [19]. Allocation to the use of 3DPSP was in none of the latter studies randomised and results should therefore interpreted with caution. Heterogeneity between studies and the wide spectrum of CHD reduces the generalisability of the findings; nevertheless, CHD is the setting with the largest experience and the broadest body of evidence for the use of 3DPSP in cardiovascular intervention.

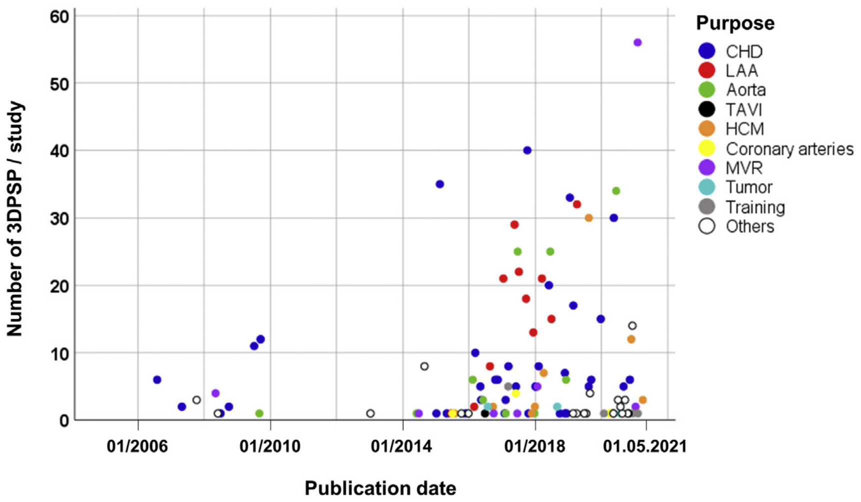

Figure 2 Number and cohort size of articles prospectively investigating 3DPSP in cardiovascular intervention in this review. Abbreviations: 3DPSP, three-dimensional printed patient-specific phantom; CHD, congenital heart disease; HCM, hypertrophic cardiomyopathy; LAA, left atrial appendage; MVR, mitral valve repair or replacement; TAVI, transcatheter aortic valve implantation.

Left Atrial Appendage Closure

The size, shape, and position of the left atrial appendage (LAA) are highly variable, which predisposes utilisation of 3DPSP in the setting of LAA closure. Available evidence from 11 studies, including one RCT demonstrated the value of a total of 182 3DPSP for device sizing and a reduction of intervention time. Liu et al. [20] reported in a case series of eight patients that the device size predicted by the 3DPSP is fully consistent with the device size chosen during the intervention and was able to predict technical challenges during the intervention as well as the presence of peri-device leaks. Additional studies corroborated these findings with high agreement and showed that device sizing by 3DPSP does better predict the final implanted device size (accurate in 95%, 100%, 100%, and 96.9%, respectively) than transoesophageal echocardiography, which underestimated the final size in 10, 4, 7, and 13 cases (45%, 45%, 47%, and 40.6%, respectively) [21–24]. Comparative studies observed a decrease in intervention and fluoroscopy time and an increased likelihood for the absence of peri-device leak if a 3DPSP was considered peri-interventional [22,24,25]. Li et al. [26] performed the only RCT that prospectively investigated 3DPSP in cardiovascular intervention where 42 patients were randomised to undergo LAA occlusion guided by 3DPSP or standard therapy guided by transoesophageal echocardiography and CCT. In the 3DPSP group, no residual shunts occurred and radiation exposure was significantly reduced compared to the control group in which three mild residual shunt cases were observed [26].

Aortic Disease

3DPSP can be applied in the planning and guiding of catheter-based, as well as in surgical treatment of various aortic disease and influence decision-making in planning endovascular aortic repair (EVAR). Review on an additional 3DPSP was reported to change the management decision in 20% of cases compared to review of the CCT images alone in patients with aortic aneurysm [27]. Training residents in EVAR on 3DPSP prior to the intervention was demonstrated to reduce fluoroscopy and intervention time, and lower contrast agent application compared to a control group without training (n=10) [28]. It remains to be determined whether similar associations might have been observed if a non-personalised model had been used. Larger case series evaluated 3DPSP as a valuable instrument in catheter-based, as well as in the surgical treatment of complex aortic disease [29,30]. Tong et al. [31] demonstrated feasibility to fenestrate stent-grafts on 3DPSP before endovascular repair of aortic aneurysm in 34 patients. Before the intervention stents were implanted into a 3DPSP to identify the positions of branches requiring fenestration. With the novel approach, only two branch arteries of 107 fenestrations secured by 102 bridging stent grafts were lost across the intervention.

Available evidence consistently demonstrated safety, reliability, and accuracy of 3DPSP in aortic disease, and paved the way for comparative studies or RCT that could support broader applications of 3DPSP in aortic disease.

Mitral Valve Repair and Replacement

In the included six studies investigating 3DPSP in mitral valve (MV) interventions, 66 3DPSP were evaluated with only one study including more than five cases. Izzo et al. [32] demonstrated the use of a 3DPSP to size the valve prosthesis prior to transcatheter MV replacement. Furthermore, 3DPSP were evaluated for risk assessment of left ventricular outflow tract

Table 1 Studies included in this systematic review.

First Author	Year	n	Type	Imaging Modality	Setting	Comments
Ngan et al. [86]	2006	6	Systematic study	CCT	CHD	3DPSP to plan surgery in pulmonary atresia
Sodian et al. [87]	2007	2	Case series	CCT or CMR	CHD	3DPSP for surgical planning in various settings
Mottl-Link et al. [8]	2008	1	Case report	CMR	CHD	3DPSP to assess intracardiac anatomy in complex CHD
Sodian et al. [76]	2008	1	Case report	CCT	Others	3DPSP to plan SAVR after previous coronary artery bypass
Sodian et al. [88]	2008	2	Case series	CCT or CMR	CHD	3DPSPs to guide heart transplantation due to severe CHD
Jacobs et al. [54]	2008	3	Case series	CCT or CMR	Others	3DPSP in ventricular aneurysm or malignant cardiac tumour
Kim et al. [89]	2008	4	Case series	CCT	CHD	3DPSP guidance on surgical revision of VSD and various other cases
Sodian et al. [90]	2009	1	Case report	CCT	Aorta	3DPSP to guide closure of an anastomotic leak after aortic arch replacement
Riesenkampff et al. [91]	2009	11	Case series	CCT or CMR	CHD	3DPSP to assess intracardiac anatomy in complex CHD prior surgery
Shiraishi et al. [92]	2010	12	Case series	CCT	CHD	Rubber-like urethane 3DPSP to train cutting and suturing prior CHD-surgery
Schmauss et al. [53]	2013	1	Case report	CMR	Others	3DPSP in the resection of a cardiac fibroma
Schmauss et al. [93]	2014	1	Case report	CCT	Aorta	3DPSP for planning surgery in complex aortic arch aneurysm.
Dankowski et al. [94]	2014	1	Case report	CCT	MVR	Production of a 3DPSP prior percutaneous mitral annuloplasty
Farooqi et al. [95]	2015	1	Case report	CMR	CHD	3DPSP for planning in a patient with double outlet right ventricle
Valverde e al. [9]	2015	1	Case report	CMR	CHD	3DPSP to guide stenting of transverse aortic arch hypoplasia
Watanabe et al. [61]	2015	1	Case report	CCT	Others	3DPSP to plan percutaneous coronary intervention in occluded RCA
Yang et al. [36]	2015	1	Case report	CCT	HCM	Guidance of a 3DPSP on septal myectomy
Otton et al. [96]	2015	1	Case report	CCT	LAA	LAA occlusion guiding and occlusion device sizing on 3DPSP
Son et al. [51]	2015	1	Case report	CCT	Others	3DPSP in the resection of a cardiac schwannoma
Fujita et al. [46]	2015	1	Case report	CCT	TAVI	Training of TAVI on a 3DPSP
Lazkani et al. [65]	2015	1	Case report	CCT	Others	3DPSP to guide surgical therapy of a post-infarct VSD
Schmauss et al. [97]	2015	8	Case series	CCT or CMR	Others	3DPSP in perioperative planning in various cardiac disease
Ma et al. [98]	2015	35	Systematic study	CCT	CHD	3DPSP to guide VSD repair
Kiraly et al. [99]	2016	1	Case report	CCT	CHD	3DPSP in surgical repair of Norwood-1 complex aortic arch obstruction
Bharati et al. [100]	2016	1	Case report	CMR	CHD	Planning surgery due to double outlet right ventricle on 3DPSP
Izzo et al. [32]	2016	1	Case report	CCT	MVR	3DPSP for planning of transcatheter MVR

Table 1. **(continued).**

First Author	Year	n	Type	Imaging Modality	Setting	Comments
Al Jabbari et al. [55]	2016	2	Case series	CCT	Others	3DPSP to guide resection of secondary malignant cardiac tumours
Pellegrino et al. [101]	2016	2	Case series	CCT	LAA	LAA occlusion guiding by 3DPSP
Hossien et al. [102]	2016	3	Case series	CCT	Aorta	3DPSP guidance on treatment of type A aortic dissection
Garekar et al. [103]	2016	5	Case series	CCT or CMR	CHD	Evaluation of the accuracy of 3DPSP in complex CHD
Tam et al. [27]	2016	6	Case series	CCT	Aorta	Evaluation the impact of 3DPSP on decision making in EVAR
Wang et al. [10]	2016	6	Case series	CCT	CHD	Planning percutaneous transcatheter closure of ASD on 3DPSP
Liu et al. [20]	2016	8	Case series	3DTOE	LAA	3DPSPs for sizing of LAA occlusion devices
Olivieri et al. [104]	2016	10	Systematic study	CCT or CMR	CHD	3DPSP to enhance postoperative intensive care of patients with CHD
Benke et al. [105]	2017	1	Case report	CCT	Aorta	3DPSP to plan surgery due to aortic pseudoaneurysm
Pluchinotta et al. [106]	2017	1	Case report	CCT	Aorta	Simulated stenting of aortic coarctation on a 3DPSP
Biglino et al. [14]	2017	1	Case report	CCT	CHD	Planning surgery in CHD and educate patients and parents on 3DPSP
Hamatani et al. [37]	2017	1	Case report	CCT	HCM	Training and guidance of a 3DPSP on septal myocardial ablation
Sardari Nia et al. [107]	2017	1	Case report	3DTOE	MVR	3DPSP to plan of endoscopic MV repair
Smith et al. [108]	2017	1	Case report	CCT	CHD	Use of a 3DPSP prior heart transplantation due to severe CHD
Hermsen et al. [35]	2017	2	Case series	CCT	HCM	Guidance of a 3DPSP on septal myectomy
McGovern et al. [109]	2017	3	Case series	CCT	CHD	3DPSP in the management of patients with univentricular circulation
Vodiskar et al. [110]	2017	3	Case series	CCT	CHD	3DPSP in planning surgery for complex CHD
Velasco Forte et al. [60]	2017	4	Case series	CCT or CMR	Others	3DPSP to plan intervention in patients with coronary artery fistulae
Kappanayil et al. [111]	2017	5	Case series	CMR	CHD	3DPSP to plan prior surgery in complex CHD.
Bhatla et al. [112]	2017	6	Case series	CCT or CMR	CHD	3DPSP to guide management decisions in patients with CHD
Hell et al. [21]	2017	22	Comparative study	CCT	LAA	3DPSP to size the occlusion device prior LAA closure
Valverde et al. [15]	2017	40	Comparative study	CCT or CMR	CHD	Multicentre study evaluating the impact of 3DPSP on decision making in CHD
Li et al. [26]	2017	21	RCT	CCT	LAA	RCT evaluating the use of 3DPSP in the setting of LAA occlusion
Yoo et al. [56]	2017	5	Systematic study	CCT or CMR	Training	Hands-on surgical training on 3DPSP of patients with CHD
Olejník et al. [113]	2017	8	Systematic study	CCT	CHD	Evaluation of the accuracy of 3DPSP of patients with CHD
Song et al. [114]	2017	18	Systematic study	3DTOE	LAA	3DPSP to guide LAA occlusion
Torres et al. [28]	2017	25	Systematic study	CCT	Aorta	Training residents on EVAR on 3DPSP

Table 1. **(continued).**

First Author	Year	n	Type	Imaging Modality	Setting	Comments
Goitein et al. [115]	2017	29	Systematic study	CCT	LAA	3DPSP to guide LAA occlusion device sizing
Aroney et al. [116]	2018	1	Case report	CCT	CHD	3DPSP to plan percutaneous closure of a cardiac fistula
Riggs et al. [50]	2018	2	Case series	CCT or CMR	Others	Guidance on pediatric tumour debulking by a 3DPSP
Andrushchuk et al. [39]	2018	2	Case series	CCT	HCM	Combination of virtual simulated myectomy and 3DPSP in HCM
Parimi et al. [117]	2018	5	Case series	Angiography	CHD	Producing 3DPSP from angiography for interventions in CHD
Sun et al. [118]	2018	5	Case series	CCT	CHD	Planning intervention on 3DPSP in patients with Kommerell's diverticulum
Gomes et al. [30]	2018	6	Case series	CCT	Aorta	3DPSP to guide endovascular repair in various aortic disease
Marone et al. [29]	2018	25	Case series	CCT	Aorta	Use of 3DPSP to plan and guide aortic surgery
Zhao et al. [18]	2018	8	Comparative study	CCT	CHD	3DPSP to plan surgery in complex CHD
Obasare et al. [22]	2018	13	Comparative study	CCT	LAA	3DPSPs for sizing of LAA occluders
Ciobotaru et al. [25]	2018	21	Comparative study	CCT	LAA	Comparison of a pro- and retrospective use of 3DPSP in LAA-occlusion
Ryan et al. [17]	2018	33	Comparative study	CCT or CMR	CHD	Comparison of the procedure time of CHD-surgery dependent on 3DPSP use
El Sabbagh et al. [33]	2018	5	Systematic study	CCT	MVR	3DPSP for outcome-prediction and valve sizing in MVR
Guo et al. [38]	2018	7	Systematic study	CCT	HCM	3DPSP for planning and patient educating prior septal myectomy
Hoashi et al. [119]	2018	20	Systematic study	CCT	CHD	3DPSP to guide young consultant surgeons in biventricular repair
Brun et al. [120]	2019	1	Case report	CCT	CHD	Combination of virtual reality and 3DPSP to guide surgery in CHD
Barabás et al. [80]	2019	1	Case report	CCT	Others	LVAD cannula placement with the help of a 3DPSP
Al-Hijji et al. [70]	2019	1	Case report	CCT	Others	3DPSP to guide transapical closure of a LVOT pseudoaneurysm
Mohamed et al. [69]	2019	1	Case report	CCT	Others	Guidance on LV pseudoaneurysm closure by a 3DPSP
Aroney et al. [67]	2019	4	Case series	CCT or CMR	Others	Complex cases of cardiac fistulae repair guided by 3DPSP
Xu et al. [121]	2019	15	Case series	CCT	CHD	3DPSP in planning surgery for anomalous pulmonary venous connection
Xu et al. [122]	2019	17	Case series	CCT	CHD	3DPSP to plan surgery in complex CHD
Han et al. [16]	2019	6	Comparative study	CCT	CHD	Comparison of the procedure time of CHD surgery dependent on 3DPSP use
Matsubara et al. [11]	2019	7	Comparative study	CCT	CHD	3DPSP to guide percutaneous closure of patent ductus arteriosus
Hachulla et al. [23]	2019	15	Comparative study	CCT	LAA	3DPSP for sizing of LAA occlusion devices
Alabbady et al. [123]	2019	1	Case report	CCT	Others	3DPSP to plan repair of an aorto-right ventricular fistula

Table 1. (continued).

First Author	Year	n	Type	Imaging Modality	Setting	Comments
Fan et al. [24]	2019	32	Comparative study	3DTOE	LAA	LAA occlusion guiding and occlusion device sizing on 3DPSP
Andrushchuk et al. [41]	2019	30	Systematic study	CCT	HCM	Combination of virtual simulated myectomy and 3DPSP in HCM
Ali et al. [52]	2020	1	Case report	CCT	Others	Use of a 3DPSP to plan surgical revision of cardiac myxoma
Niizeki et al. [63]	2020	1	Case report	CCT	Others	3DPSP to plan percutaneous coronary intervention in coronary anomaly
Young et al. [62]	2020	1	Case report	CCT	Others	3DPSP for development of a new catheter in occluded RCA
Miller et al. [79]	2020	1	Case report	CCT	Others	3DPSP to simulate LVAD implantation in a failing systemic RV
Kanawati et al. [66]	2020	1	Case report	CCT	Others	Planning CRT-D implantation in complex CHD
Motwani et al. [78]	2020	1	Case report	CCT	Others	Transcatheter closure of paravalvular regurgitation guided by 3DPSP
Spring et al. [73]	2020	1	Case report	CCT	Others	Use of a 3DPSP to plan tricuspid valve-in-valve replacement
Shetty et al. [71]	2020	1	Case report	CMR	Others	3DPSP to guide surgical closure of submitral aneurysm
Basman et al. [47]	2020	1	Case report	CCT	TAVI	3DPSP to achieve a TAVI valve-in-valve procedure
ElGuindy et al. [77]	2020	2	Case series	3DTOE	MVR	Planning paravalvular leak interventions after MVR on 3DPSP
Shearn et al. [72]	2020	2	Case series	CCT	Others	3DPSP to guide Ozaki repair of bicuspid aortic valve
Vukicevic et al. [75]	2020	3	Case series	CCT or 3DTOE	Others	3DPSP for planning Mitraclip implantation
He et al. [124]	2020	5	Case series	CCT	CHD	Closure of multiple ASD guided by a 3DPSP
Perens et al. [125]	2020	6	Case series	CCT or CMR	CHD	3DPSP-guidance on surgical revision of complex CHD
Pizzuto et al. [68]	2020	3	Case series	CCT	Others	Guidance on LV pseudoaneurysm closure by a 3DPSP
Li et al. [19]	2020	30	Comparative study	CCT	CHD	Comparison of 3DPSP- and TOE guided ASD closure to fluoroscopic guidance
Nam et al. [57]	2020	1	Systematic study	CCT	Training	Repetitive training of VSD closure on 3DPSP
Hussein et al. [58]	2020	1	Systematic study	-	Training	Repetitive training of arterial switch procedure on 3DPSP
Hussein et al. [59]	2020	1	Systematic study	-	Training	Repetitive surgical training on 3DPSP of CHD
Wang et al. [40]	2020	12	Systematic study	CCT	HCM	Training septal myectomy on 3DPSP
Borracci et al. [64]	2020	14	Systematic study	-	Others	3DPSP to plan adult cardiovascular surgery
Harb et al. [74]	2020	4	Case series	CCT	Others	3DPSP to tailor surgical tricuspid valve repair
Tong et al. [31]	2020	34	Systematic study	CCT	Aorta	3DPSP to fenestrate stent grafts in aortic disease

Table 1. **(continued).**

First Author	Year	n	Type	Imaging Modality	Setting	Comments
Kim et al. [126]	2021	3	Case series	CCT	HCM	3DPSP in pre-interventional planning and training in HCM
Cen et al. [127]	2021	5	Case series	CCT	CHD	Combination of virtual reality and 3DPSP in pulmonary atresia
Wang et al. [34]	2021	56	Comparative study	CCT	MVR	3DPSP to predicted LVOT obstruction after MVR.

Abbreviations: 3DPSP, three-dimensional printed patient specific phantom; ASD, atrial septum defect; CCT cardiac computed tomography; CHD, congenital heart disease; CMR, cardiac magnetic resonance imaging; CRT-D, cardiac resynchronisation therapy–dual; EVAR, endovascular aortic repair; HCM, hypertrophic cardiomyopathy; LAA, left atrial appendage; LVAD, left ventricular assist device; LVOT, left ventricular outflow tract; MVR, mitral valve replacement/repair; RCA, right coronary artery; RCT, randomised controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TOE, transoesophageal echocardiography; VSD, ventricular septal defect.

obstruction (LVOTO) after MV replacement. Combined with virtual models, it was possible to predict LVOTO by simulation of MV implantation into the 3DPSP [33,34]. Simulated MV replacement on a flexible silicone 3DPSP and testing it in a mock circulatory system was superior in terms of LVOTO-prediction if compared to a digital model, a rigid anatomical 3DPSP made of resin, or the flexible silicone models without dynamic testing [34]. However, the lack of cardiac cycle simulation must be considered as a limitation of 3DPSP in this setting.

Hypertrophic Cardiomyopathy

Eight (8) studies were identified prospectively enrolling patients undergoing 3DPSP guided intervention for hypertrophic cardiomyopathy (HCM). Case reports demonstrated feasibility of 3DPSP to train and guide septal myectomy [35–37] and for patient education prior intervention [38]. Andrushchuk et al. [39] developed an innovative approach in which a 3D print of the severely hypertrophic septum was conducted as a first step. In a second step, computer simulation was used to model the same septum after an optimal virtual myectomy. Thus, the targeted septum, as well as the resected part, were reprinted as 3D model. Both models, the native and the virtually treated one with its resected fragment guided the surgeon during the intervention in two cases. Besides these case reports, three prospective studies including more than five subjects systematically investigated 3DPSP before myectomy [38,40,41]. Authors evaluated them as a helpful tool in the planning of the intervention and for intraoperative guiding to achieve optimal septum thickness, whereas comparative studies are lacking.

Transcatheter Aortic Valve Implantation

Most studies investigating 3DPSPS in transcatheter aortic valve implantation (TAVI) were conducted retrospectively and are not part of this systematic review. They could prove the concept of valve sizing and prediction of paravalvular regurgitation on a 3DPSP [42–45]. Two (2) prospective case reports demonstrated feasibility to train TAVI on a 3DPSP [46,47]. Basman et al. [47] described successful valve-in-valve implantation in a 65-year-old man guided by a 3DPSP. Prior ex vivo implantation of different valves on the model and consecutive seal analysis helped to choose an adequate valve size and lead to a satisfying result in this patient. Further studies on 3DPSP in the setting of TAVI are warranted. The potential of 3DPSP comprises the selection of optimal valve type and size, and the prediction of annulus rupture and coronary artery obstruction (also see Figure 3), particularly in case of valve-in-valve TAVI [48]. 3DPSP of the aortic root and the vascular access may provide further guidance on the feasibility of transfemoral TAVI or if alternative access or surgical aortic valve replacement should be favoured.

Cardiac Tumours

Cardiac and pericardial tumours represent a rare, but large spectrum of different entities with highly variable location, anatomy, and haemodynamic consequences [49]. Involved structures are difficult to delineate and might be anatomically inaccessible which often complicates planning of surgery and defining the optimal extent of tumour debulking. In such settings 3DPSP were applied to guide surgery in pediatric cardiac tumours (n=2) [50], cardiac schwannoma (n=1) [51], cardiac myxoma (n=1) [52], cardiac fibroma (n=1) [53], high-grade sarcoma (n=1) [54], as well as secondary cardiac tumours (n=2) [55]. All authors described an enhancement of the preoperative management of these patients and found 3DSPS helpful in the planning of the optimal interventional approach. However, no comparative study and no case series including more than two patients exists that systematically investigated 3DPSP in the setting of cardiac tumours.

Training of Interventions

Four (4) studies systematically investigated 3DPSP for training of cardiovascular interventions. In the largest study to date, surgeons (n=50) evaluated the quality of the models

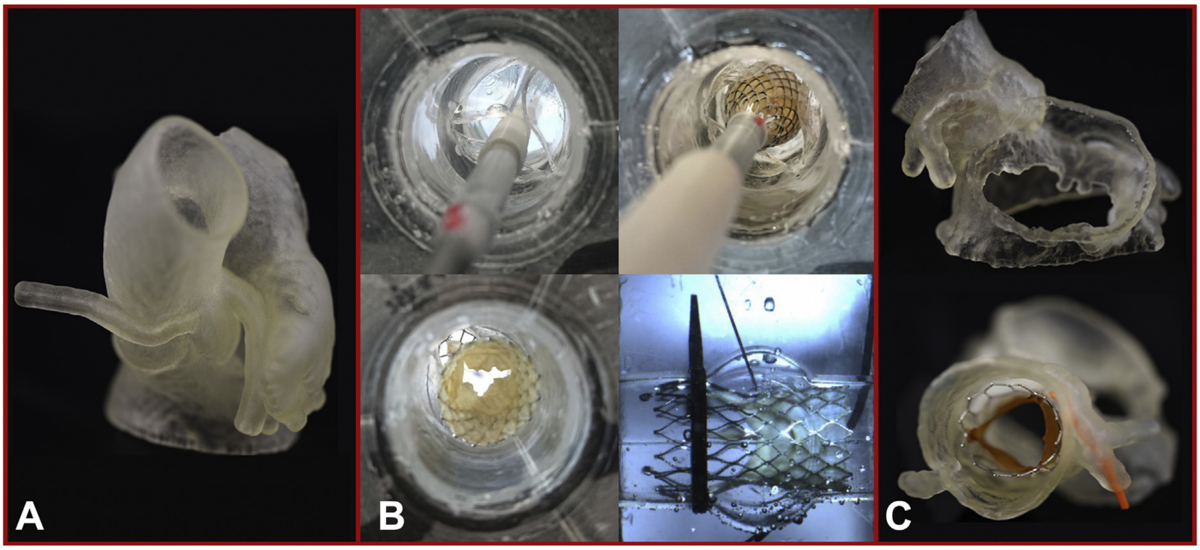

Figure 3 Selected 3DPSP used for the planning of cardiovascular interventions. (A) CCT images of a patient with coronary anomaly translated into a 3D printed phantom (compliant PolyJet 3DPSP) for planning of complex percutaneous coronary artery intervention. (B) Silicone casted aortic root model made from a fused deposition modelling negative used for simulated transcatheter aortic valve implantation and postprocedural testing of paravalvular leakage with dye injection. (C) Compliant multimaterial printed PolyJet 3DPSP aortic root translated from CCT imaging for planning transcatheter aortic valve implantation. Abbreviations: 3DPSP, three-dimensional printed patient-specific phantom; CCT, cardiac computed tomography.

as acceptable (88%) and agreed that the model provided necessary information on the pathology (>85%). However, consistency and elasticity of the materials, especially of valves was mostly rated as different to human tissue [56]. Repetitive training on a 3DPSP led to shorter operation time in a simulated ventricular septal defect (VSD)-closure [57], arterial switch procedure [58], and various other CHD interventions [59].

Other Interventions

Other applications of 3DPSP in cardiovascular interventions have been described in case reports and case series only. Four (4) articles described cumulative seven 3DPSP in coronary artery interventions and evaluated them positively with high impact on decision-making [60–63]. Furthermore, 3DPSP were evaluated as helpful in the planning of adult cardiothoracic surgery [64], post-infarct VSD [65], cardiac resynchronisation device lead implantation [66], or the treatment of complex cardiac fistulae [67]. Other case reports and case series described the emerging role of 3DPSP in left ventricular pseudoaneurysm [68–70] and aneurysm of congenital origin [71]. Successful planning of valve interventions others than CHD, TAVI, and mitral valve repair/replacement (MVR) on 3DPSP were described during Ozaki repairs of the aortic valve [72], tricuspid valve-in-valve replacement [73], surgical tricuspid valve repair [74], and transcatheter tricuspid valve repair by MitraClip (Abbott, Menlo Park, CA, USA) implantation [75]. In the setting of surgical aortic valve replacement (SAVR), 3DPSP was used to plan surgery after previous coronary artery bypass graft [76], or transcatheter closure of paravalvular regurgitation after SAVR [77,78]. Moreover, 3DPSP can be used to simulate left ventricular assist devices implantation [79], and ease left ventricular inflow cannula placement with the help of a 3D printed exoskeleton [80].

Meta-Analysis on the Impact of 3DPSP on Intervention Time

Seven (7) studies reported data about intervention times after 3DPSP application compared to controls without 3DPSP use. One (1) study [11] provided only mean and interquartile range of procedural times and hence was not eligible for inclusion. Among the remaining six studies (Table 2), three investigated 3DPSP in LAA occlusion [19,22,24] and three in surgery due to CHD [16–18]. Taking into account heterogeneity between the settings and the range of intervention times we forwent determining a weighted mean difference and analysed data by the combined effect size instead. Including these studies into a random-effects model, we found a significant association between the use of 3DPSP and a reduction in the intervention time (Cohen's d=0.54; 95% confidence interval 0.13–0.95; p=0.001, I^2 53.3%) (Figure 4).

Discussion

The salient findings of the present analysis can be summarised as follows (Figure 5). There has been increasing interest in applying 3DPSP to cardiovascular interventions during

Table 2 Studies included into meta-analysis.

Authors	Y	Setting	N		Control Arm Imaging	Mean Intervention Time (min±SD)		Mean Difference (min)
			3DPSP	Control		3DPSP	Control	
Zhao et al. [18]	2018	Surgical repair of double outlet right ventricle	8	17	CCT and echocardiography	251.7±35.8	285.1±83.4	-33.4
Obasare et al. [22]	2018	LAA occlusion	13	9	2D TOE	70±20	107±53	-37
Ryan et al. [17]	2018	Surgery due to complex CHD	33	113	CMR or CCT	220±111	229.3±102	-9.3
Han et al. [16]	2019	Surgery due to complex CHD	6	6	CCT	256.3±49.5	304.3±102.4	-48
Fan et al. [24]	2019	LAA occlusion	32	72	3D TOE	41.7±7.2	73.7±37.9	-32
Li et al. [26]	2017	LAA occlusion	21	21	CCT and TOE	96.4±12.5	101.2±13.6	-4.8

Abbreviations: 3DPSP, three-dimensional printed patient specific phantom; CCT, cardiac computed tomography; CHD, congenital heart disease; CMR, cardiac magnetic resonance imaging; LAA, left atrial appendage; TOE, transoesophageal echocardiography.

the last decade, as indicated by a large and increasing number of studies since 2017. All reports consistently evaluated 3DPSP as helpful and enhancing in the planning and guiding of cardiovascular interventions, however no effect on clinical endpoints has been shown. Comparative studies indicate shorter procedure- and fluoroscopy times if the intervention is trained, planned, or guided by 3DPSP. This observation is confirmed by our meta-analysis with regard to intervention time. Only one RCT exists to date, which supports the use of 3DPSP in the setting of LAA closure, confirming previous findings in terms of a decline in radiation exposure.

Despite these encouraging findings, several limitations of 3DPSP require attention. Most studies were of descriptive and observational character and no prospective study exists that included more than 100 patients. No study demonstrated an effect on clinical outcomes including mortality, need for re-intervention, or hospitalisations. 3DPSP can only depict information that was assessed by the imaging modality they are derived from. Hence, the quality of the image acquisition directly affects the anatomic accuracy of 3DPSP, and limits the gain of knowledge they might provide when compared to imaging data alone and virtual 3D models. Poor imitation of tissue characteristics is another important limitation, especially in the setting of direct printing techniques using rigid materials [81]. Depicting of deformations within the cardiac cycle as well as of cardiac valves is often lacking, particularly in single-material models [56]. Furthermore, availability of high-quality 3D printers is limited [82]. High costs for 3D printing, but also for finalised commercially available models, might be a deterrent, in particular for complex multi-material models that might be up to USD$2,500 [83]. Quantification and generalisation of total cost is challenging since most 3D prints are conducted in the research environment in which a quantification of costs is often not possible and also vary greatly due to different

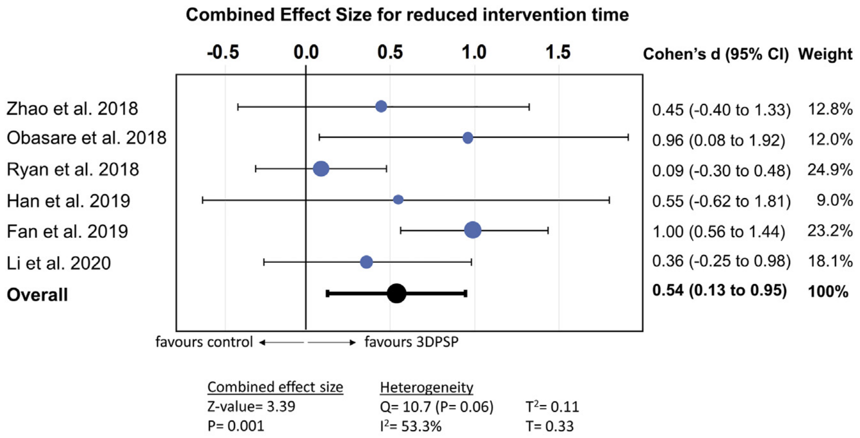

Figure 4 Forest plot for combined effect size on a reduction of intervention time with three-dimensional printed patient-specific phantom (3DPSP).

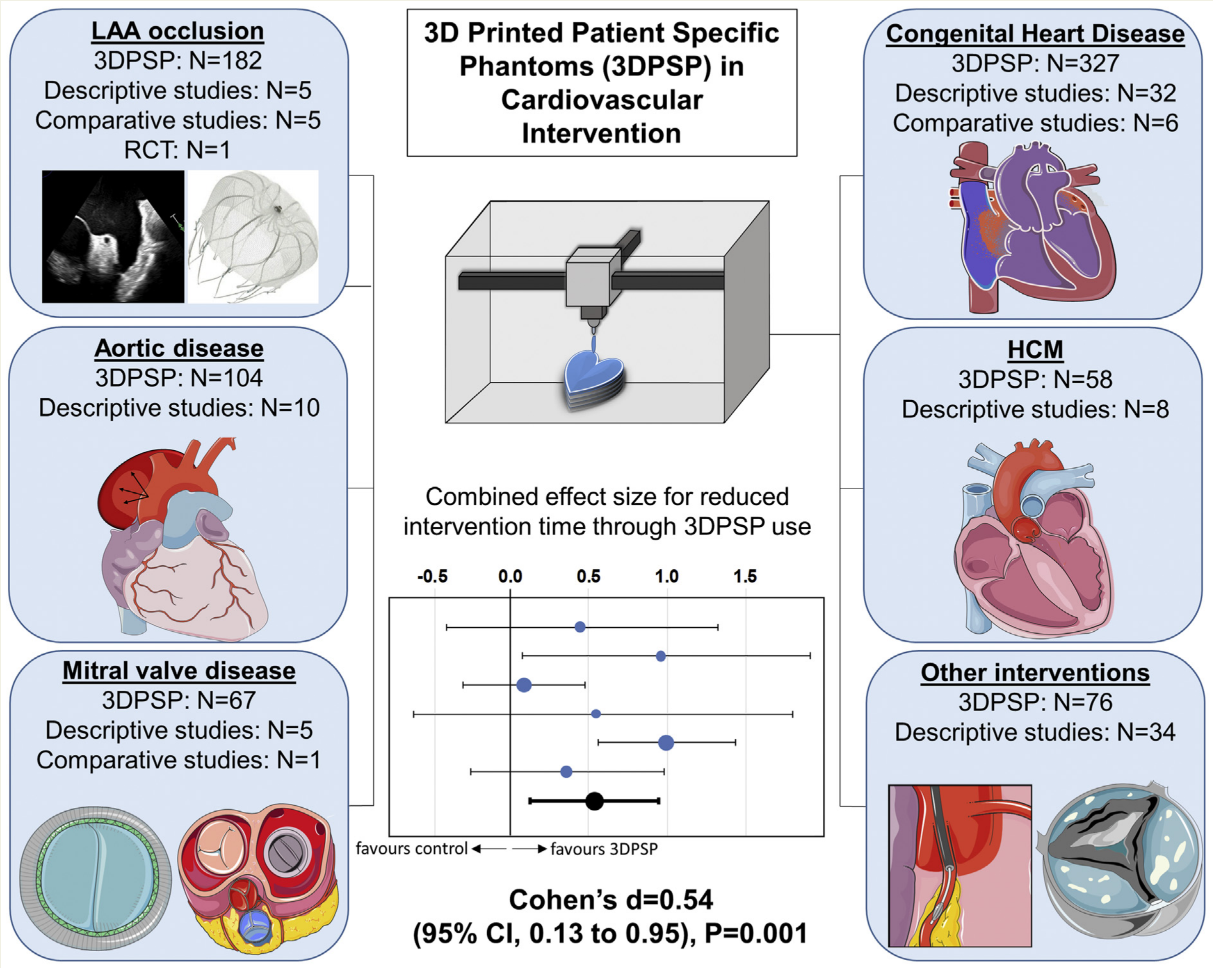

Figure 5 Current applications of prospectively used 3D printed patient-specific phantoms (3DPSP) in cardiovascular intervention.
Abbreviations: HCM, hypertrophic cardiomyopathy; LAA, left atrial appendage. (modified from freely available Servier Medical Art templates, smart.servier.com)

requirements on the finalised models and the experience of the printing team (going along with the time required for printing). Costs for buying 3D printers and segmentation software and also personal costs are the main determinants in the calculation, whereas in comparison, clearly definable costs for printing materials are often negligible. However, also low-cost printed heart models have proven to show excellent correlation to anatomical structures [84].

Irrespective of these limitations, the reviewed studies demonstrate the technical feasibility of 3D printing to plan and guide cardiovascular interventions. Two-dimensional visualisation of 3D models on a screen cannot provide the same information and ease of orientation to understand complex anatomic relationships like a printed model of high quality [85]. Moreover, the opportunity for tactile feedback makes 3DPSP an accessible tool in clinical decision-making in a user-friendly fashion. Becoming familiar with patient-specific conditions in a training or planning process on a 3DPSP prior to intervention speeds up interventional procedures. This might especially apply to interventions with highly variable anatomic structures such as the LAA or in the setting of CHD. The reduction of mechanical ventilation time, aortic cross-clamp time, as well as of fluoroscopy time, and dose might favourably impact on patient outcomes. 3DPSP can be derived from clinically indicated standard imaging not going along with longer scanning time or increased radiation exposure, hence no potential harm is expected for patients. Although the advantage of 3DPSP is difficult to measure and remains subjective in most cases, we conclusively see the strengths of 3DPSP in: I. the simulation of the individual patient anatomy prior cardiovascular intervention thereby improving outcomes and providing safety (i.e., prevention of device embolisation in LAA- or valve interventions or visualisation of rare anatomy in CHD prior surgery); II. device selection and modification (i.e., choosing the optimal type and optimal size of LAA-occluders or prosthetic valves in order to prevent para-valvular leak or size mismatch, or the modification of aortic stent grafts); and III. education and training of fellows in cardiovascular interventions.

Limitations of This Review and Meta-Analysis

The findings of this review should be interpreted in light of several limitations that go beyond the limitations of the individual studies included. Although search terms tried to cover the full spectrum of research on 3DPSP in cardiovascular intervention, rare fields of applications may have been missed by our keywords search. Exclusion of studies that retrospectively investigated 3DPSP in cardiovascular intervention was necessary to reduce the large number of studies meeting our inclusion criteria but might result in missing important findings. Furthermore, a possible publication bias should also be considered. Cases in which manufacturing 3DPSP in an adequate quality has failed or the models were not considered to be helpful might not be published or did not reach significance for acceptance in journals. Our meta-analysis is based on only six studies with a small total number of patients (n=113, 3DPSP vs 238 controls) in different settings (LAA closure and surgery due to CHD), hence heterogeneity should be taken into account and reduces generalisability of our findings to other cardiovascular interventions guided by 3DPSP. Local expertise and volume in imaging and the intervention, as well as operator's experience might bias our findings. Although I^2=53.3% referred to moderate heterogeneity, Cochran's Q was not significant, indicating that the association of 3DSPS to reduced intervention time was consistent across studies.

Conclusions

Three-dimensional patient-specific phantoms is helpful to plan, train, and guide interventions in patients with complex cardiovascular anatomy. Benefits for patients include reduced intervention time, with the potential to lower radiation exposure and shorten mechanical ventilation. More evidence is needed to warrant adoption of 3DPSP into routine clinical practice although future applications are vast.

Conflicts of Interest

Dr. Windecker has received research grants to his institution from Abbott, Amgen, Boston, Biotronik, and St. Jude Medical, he has received no speaker fee. Dr. Pilgrim has received research grants to his institution from Edwards Lifesciences, Symetis, and Biotronik; has received speaker fees from Boston Scientific; and has received reimbursement for travel expenses from St. Jude Medical. Dr. Praz is a consultant for Edwards Lifesciences. Dr. Gräni received research funding from Swiss National Science Foundation and Innosuisse outside of the submitted work. Further Dr. Gräni received travel fees from Amgen and Bayer outside of the submitted work. All other authors report no conflicts.

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