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New Technologies for Surgery of the Congenital Cardiac Defect

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ABSTRACT

The surgical repair of complex congenital heart defects frequently requires additional tissue in various forms, such as patches, conduits, and valves. These devices often require replacement over a patient's lifetime because of degeneration, calcification, or lack of growth. The main new technologies in congenital cardiac surgery aim at, on the one hand, avoiding such reoperations and, on the other hand, improving long-term outcomes of devices used to repair or replace diseased structural malformations. These technologies are: 1) new patches: CorMatrix® patches made of decellularized porcine small intestinal submucosa extracellular matrix; 2) new devices: the Melody® valve (for percutaneous pulmonary valve implantation) and tissue-engineered valved conduits (either decellularized scaffolds or polymeric scaffolds); and 3) new emerging fields, such as antenatal corrective cardiac surgery or robotically assisted congenital cardiac surgical procedures. These new technologies for structural malformation surgery are still in their infancy but certainly present great promise for the future. But the translation of these emerging technologies to routine health care and public health policy will also largely depend on economic considerations, value judgments, and political factors.

KEY WORDS: Congenital heart defect, extracellular matrix patch, new technologies, percutaneous valve implantation, robotics, tissue engineering

Abbreviations: ECM, extracellular matrix; FDA, Food and Drug Administration; MSC, marrow stromal cells; P4HB, poly-4-hydroxybutyrate; PA, pulmonary artery; PCL, polycaprolactone; PCLA, poly-L-lactide; PGA, polyglycolic acid; PLA, poly(lactic acid); PLLA, poly-L-lactic acid; RV, right ventricle; RVOT, right ventricular outflow tract; SIS-ECM, small intestinal submucosa extracellular matrix.

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INTRODUCTION

Congenital cardiac surgery frequently requires additional tissue such as patches, conduits, and valves. These prostheses are characterized by a risk of degeneration, calcification, and a lack of growth, and usually need a replacement over a patient's lifetime. The main new technologies in congenital cardiac surgery aim at improving long-term outcomes of these devices and avoiding reoperations.

NEW PATCHES: CORMATRIX® EXTRACELLULAR MATRIX PATCHES

Despite improvements in congenital heart surgery procedural mortality, there remain a substantial number of patients who need multiple reinterventions,[1] because of the lack of growth potential and remodeling of currently used patches (autologous pericardium (with or without glutaraldehyde), preserved xenopericardium, and various prosthetic materials). As a matter of fact, the ideal patch still does not exist. Such an ideal material would not interfere with the patient's growth, would be pliable, soft, resistant to tearing, calcification, and shrinkage, and would possibly not induce remodeling of scar tissue.

Recently, the CorMatrix® (CorMatrix Alpharetta, GA) patch made of decellularized porcine small intestinal submucosa extracellular matrix (SIS-ECM) has been introduced into cardiac surgery. The extracellular matrix (ECM) is the acellular component that surrounds cells in native tissues and is mainly composed of elastin, collagen (structural proteins), glycans (glycosaminoglycans, proteoglycans), and adhesion glycoproteins. These new patches have demonstrated patch remodeling and integration in animal models of cardiac surgery.[2,3] Wainwright et al.[4] showed that right ventricular outflow tract (RVOT) reconstruction with SIS-ECM patches in a rat model resulted in new cardiac tissue formation in the patched areas and the absence of ventricular dilatation, when compared with Dacron reconstructions of the RVOT.

These promising results in experimental studies have then been confirmed in human studies that specifically evaluated the outcomes of SIS-ECM in congenital heart surgery for cardiac and vascular reconstructions.[5–7] Scholl et al.[5] demonstrated in one case of an explanted patch used for augmentation of the tricuspid valve that SIS-ECM was replaced by organized collagen and populated with endothelial-like cells four months after the implant. Quarti et al.[6] showed early encouraging results of these CorMatrix® patches used for vascular repair (pulmonary artery, ascending aorta, aortic arch, and right ventricular outflow tract), but also for valve reconstruction (aortic, tricuspid, mitral, and pulmonary valves) and pericardial closure. Witt et al.[7] demonstrated that SIS-ECM is suitable for the closure of septal defects. But the use of SIS-ECM for the reconstructions of outflow tracts and great vessels in this study carried a small risk of stenosis, especially in patches that form the majority of the vessel circumference. Moreover these studies had rather a short follow-up. Another potential drawback of CorMatrix® ECM patches is the significant variability of the SIS-ECM biomechanical properties between different lots. Contrary to the Surgisis™ trial assessing the clinical use of SIS-ECM for carotid artery repair following endarteriectomy—a study that displayed an increased risk of aneurysm formation—the CorMatrix® lot did not display such a pejorative evolution even when implanted in high-pressure systems. Nevertheless, the limited numbers of patients in studies dealing with the implantation of CorMatrix® in high-pressure systems prevent their authors from speculating regarding the long-term effectiveness of the CorMatrix® in specific high-pressure locations. Long-term outcomes of these ECM patches depend not only on patch biomechanical properties, patch location, and hemodynamic environment, but also on the patient's immune response. Badylak et al.[8] showed that the non-cross-linked SIS-ECM incited an immunoregulatory and proangiogenic macrophage response (leading to remodeling and repopulation of the patch) instead of an inflammatory, scar-forming response (potentially leading to stenosis).

Porcine SIS-ECM is currently approved by the Food and Drug Administration (FDA) for use in humans. Nevertheless, large studies of the growth potential of the porcine SIS-ECM compared to other biomaterials used in cardiac surgery have not been conducted yet.

To summarize, the CorMatrix® ECM displays a lot of potential advantages over other materials currently used in pediatric cardiac surgery, as follows:

- Easily handled and implantable
- Abundant
- Durable (still controversial)
- Minimal scar formation

- Remodeling of the material (no calcification)
- Growth potential (still controversial)

This new biomaterial seems to provide an interim bioscaffold that enables the patient's own cells to repopulate and repair damaged tissues, which is of particular interest in patients with congenital heart diseases, for valve repair, and vascular reconstruction. But the long-term performance of the SIS-ECM in congenital cardiac applications still needs to be assessed through longitudinal studies of greater magnitude.

NEW DEVICES

Percutaneous Pulmonary Valve Implantation: The Melody® Valve

The right ventricle (RV) to main pulmonary artery (PA) conduits that are used to reconstruct the right ventricular outflow tract in congenital heart diseases are prone to develop valvular incompetence and/or obstruction with time. These pejorative evolutions are associated with exercise intolerance, arrhythmias, and an increased risk of sudden death[9] and require multiple open-heart surgeries to replace the pulmonary valve.

Percutaneous pulmonary valve implantation was introduced as a new treatment option in patients with dysfunctional conduits.[10,11] This technological breakthrough aims at prolonging the lifespan of RV to PA conduits and thus postponing open-heart surgery. The trans-catheter pulmonary valve (Melody®; Medtronic, Minneapolis, MN) is composed of a bovine jugular venous valve and a balloon-expandable stent made of a platinum-iridium wire.

The current largely accepted indications for the use of a Melody® valve include[12]:

- A significant RVOT obstruction, defined as RV pressures > 2/3 of systolic blood pressure (SBP) with symptoms, or > 3/4 of SBP without symptoms
- A severe pulmonary regurgitation and RV dysfunction or RV dilatation or impaired exercise capacity
- Along with morphological criteria allowing a safe implantation site: RVOT dimensions < 22 × 22 mm and > 14 × 14 mm

The implantation procedure is standardized and safe, with a procedural mortality < 0.2%. The main complication to avoid during the implantation is coronary compression or occlusion, which can be evaluated by a pre-implantation balloon inflation in the RVOT. Other complications during implantation are the dislodgement of the device when implanted in distensible and dilated RVOTs and the risk of homograft rupture.

Valve implantation significantly reduces the gradient across the outflow tract, RV pressures, and the pulmonary regurgitation,[13] and significantly improves symptoms.

Lurz et al.[13] demonstrated that during a median follow-up of 28 months freedom from reoperation was 93% (±2), 86% (±3), 84% (±4), and 70% (±13), at 10, 30, 50, and 70 months, respectively.

The main complications of the new generation of this innovative technology are late endocarditis and stent fractures in 20%.[14] These stent fractures are silent in the majority of cases and are treated in symptomatic patients with RVOT stenosis by a Melody® valve-in-valve implantation.

Pulmonary valve implantation is becoming the standard procedure in the treatment of dysfunctional conduits. It has been accepted by the regulatory agencies for distribution and use in Europe in 2006 and US Food and Drug Administration in 2010.

By prolonging the lifespan of RV–PA surgically placed conduits, this innovative technology has reduced the number of multiple open heart operations in children and young adults with congenital heart disease, and may improve their life expectancy and life quality.

As with all evolving new technologies, new generations of Melody valves were created in order to reduce current limitations and extend the spectrum of potential clinical indications. Improvements brought to the Melody® valve during the last few years of development or currently in progress include:

- Device design improvements
- Delivery system improvements
- Patient selection improvements using three-dimensional echography and MRI
- Dilatation with high-pressure balloon after implantation (to reduce residual gradients)
- Stent-in-stent implantation
- Structural improvements to extend this technology to patients with native, dilated, and distensible RVOT

These principles of percutaneous valve implantation are currently investigated in other off-label clinical settings. For instance, valves developed for trans-catheter replacement of the aortic valve were implanted in the pulmonary position for patients with larger annulus.[15] A new device allowing the implantation of a pulmonary valve in a RVOT previously repaired with a transannular patch is also currently investigated but not published yet.

Tissue-Engineered Valved Conduits: Decellularized Scaffolds, Polymer Scaffolds, and *in Situ* Regeneration

The ideal RV–PA conduit for reconstruction of the RVOT still does not exist.

Cryopreserved homografts need a revision surgery in 36% and 90% of cases after 10 and 15 years, respectively.[16–18] Hancock conduits need to be replaced after 10 years in 68% of cases, and 50% of Carpentier–Edwards Perimount® (Edwards Lifesciences, Irvine, CA, USA) valves (bioprosthetic stented valve made of bovine pericardium) implanted in children also have to be replaced after 5 years.[19] Children younger than 2 years old operated with a Contegra® Medtronic conduit have to undergo a revision surgery in 67% of cases for failure.[20] The reoperations needed to replace a failing conduit carry a significant risk of mortality (1%–3%) and morbidity: hemorrhagic syndrome, cerebral vascular accident, coronary damage, cardiac rhythm alterations, or infection. These

Table 1. Current Surgical Valved Conduits to Replace the Right Ventricular Outflow Tract.

Current Surgical Devices	Reoperation Rates	Limitations	Ref.
Cryopreserved homografts	6%–58% at 5 years, 36%–90% at 15 years, depending on the diameter, age at surgery, and heart defect	• No growth potential • Immunogenicity and inflammatory response • Calcification • Structural degeneration • Limited availability	18, 22
Stented heterografts (e.g. Hancock® tube: porcine aortic heart valve in a tube made of Dacron®)	19% at 5 years, 68% at 10 years, 95%–100% at 15 years, depending on the diameter, age at surgery, and heart defect	• No growth potential • Early calcification • Structural degeneration • Pannus formation • Excessive stiffness with anatomic compression/distortion	23
Stentless heterografts (e.g. Contegra® tube: bovine jugular vein)	22%–40% at 5 years, depending on the diameter, age at surgery, and heart defect	• No growth potential • Immunogenicity and inflammatory response • Stenosis of the distal anastomosis • Pseudoaneurysm of the proximal anastomosis • Severe conduit regurgitation	24, 25
Stentless heterografts (e.g. Shelhigh® tube: porcine pulmonary heart valve in a tube made of bovine pericardium)	48%–67% at 1 year, depending on the diameter, age at surgery, and heart defect	• **Intimal peel formation at the distal segment** • **No growth potential** • **Immunogenicity** and inflammatory response • Pseudoaneurysm	26
Mechanical valves	Only in older children and adults	• No growth potential • Anticoagulant therapy required • Thromboembolic complications	27

complications translate into prolonged hospitalization and attendant costs. Surgical techniques have improved during the last three decades, but conduit failure and morbidity and mortality still occur (Table 1). Autologous pericardial valved conduits for RVOT reconstruction showed superb properties, but data for long-term follow-up are lacking.[21]

As a consequence of the limited treatment options and the requirements for repeat surgery in children as they grow, new alternatives were investigated to reconstruct the RVOT. The advanced-therapy medicinal products (ATMPs) derived from the concept of regenerative medicine are presently seen as one of the main routes to reduce the above-mentioned risks, with the exception of organ transplantation.

On the basis of these issues, the search for the ideal material to replace the RVOT started. The *in vitro* creation of autologous and living substitute materials by tissue engineering is based on the essential need for growth potential of materials to be used for surgical correction of congenital cardiac defects.

In the last 15 years, different tissue-engineered materials have been proposed to replace the RVOT. Scaffolds were either decellularized allo- or xenogenic biological valved conduits or bioabsorbable prosthetic materials (poly-4-hydroxybutyrate (P4HB), poly-L-lactide (PCLA), polyglycolic acid (PGA)) designed in unvalved patches,[28–32] non-valved tubes,[33–35] or valved tubes.[36–40]

Decellularized scaffolds

Dohmen et al. published an account of the first clinical implantation of a tissue-engineered heart valve in 2000[41]: an *in vitro* seeded decellularized pulmonary allograft was implanted during a Ross operation in an adult patient. The 10-year clinical results of these tissue-engineered heart valves of the same group were promising despite a limited number of patients.[42] Da Costa et al.[43] demonstrated an excellent hemodynamic behavior and a significant decrease in human leukocyte antigen (HLA) class I and II antigens in decellularized allografts compared with standard allografts. Nevertheless pejorative clinical outcomes of this technology were also reported: Simon et al.[44] showed that the Synergraft technology failed in four grafts after 2 days and 1 year post-implantation and that no recellularization of the decellularized grafts was seen at up to 1 year of follow-up. In 2010, Da Costa et al.[45] investigated the outcomes of decellularized aortic homograft implants as an aortic root replacement in 41 patients. No reoperations were performed due to aortic valve dysfunction with a maximal follow-up of 53 months.

Polymer scaffolds and in situ regeneration concept

The literature reports that polymer scaffolds were seeded (or not) with different types of autologous cells: endothelial cells, fibroblasts, myofibroblasts derived from peripheral vessels,[28,32–35,36,37,39] smooth muscle cells derived from aorta or cardiomyocytes.[29] *In vitro* and *in vivo* studies (goats or adult syngenic rats) of these materials implanted in the RVOT demonstrated the biodegradation of the material,[28,29] the endothelialization of the surface of the material,[30,37,38] the synthesis of an extracellular matrix,[28,33,35,37,38,46] the absence of thrombus or stenosis,[36] and a low risk of calcification. In 2006, Hoerstrup et al. proved, in a pioneering work, the growth potential of a bioabsorbable non-valved tube seeded with endothelial cells and fibroblasts implanted on the pulmonary artery in a growing lamb model during 100 weeks.[47] Concomitantly to this biological progress, other synthetic polymers (poly-L-lactic acid (PLLA),[48] poly(epsilon-caprolactone) (PCL),[49] poly(styrene-block-isobutylene-block-styrene) (SIBS),[50] poly(glycerol-sebacate) (PGS)[51]), and other biological materials (fibrin,[52] collagen,[53] 3D cardiac extracellular matrix,[54] or hybrid materials[55,56]) were investigated to create tissue-engineered scaffolds for heart valves. Some polymeric matrices were made "bioactive" through the implantation of growth factors on their surface (transforming growth factor beta, bone morphogenetic protein, and vascular endothelial growth factor).[57,58] Other research groups investigated strategies of "homing" and immobilization of circulating host-derived cells.[59]

Materials designed for RVOT reconstruction by tissue engineering using stem cells were first evaluated *in vitro*.[60] They were bioabsorbable non-valved patches or valved tubes (PGA+/- P4HB or PGA+PLLA). The first stem cells used were human bone-marrow cells that displayed a myofibroblastic differentiation and synthetized an extracellular matrix.[61] In 2007, autologous peripheral blood-derived endothelial progenitor cells and autologous bone-marrow-derived marrow stromal cells (MSC) were seeded on a bioabsorbable non-valved patch on the pulmonary artery of seven goats with a follow-up

of 6 weeks.[62–66] This study showed the development of a living and organized tissue, integrated to the native pulmonary artery. The use of bioreactors for cell culture and maturation in dynamic conditions allowed for the maturation of the tissue-engineered device, the i*n vitro* cell differentiation, and the formation of the extracellular matrix.[67–72] A non-invasive percutaneous method of implantation of tissue-engineered heart valves was described by Dr Hoerstrup's group[73] and by Emmert et al.[74] From 2002, the cells used have been derived from human umbilical cord blood, Wharton's jelly, amniotic liquid, chorial villosities, or induced pluripotent cells seeded on non-valved patches or valved tubes.[75–83] Even periodontal ligament cells cultured under steady flow environments demonstrated potential for use in heart valve tissue engineering.

Materials made of co-polymer of poly(lactic acid) (PLA) and polycaprolactone (PCL), seeded with human bone-marrow cells, were implanted by Shin'oka et al. in 42 patients with congenital heart diseases in Japan between 2001 and 2005.[84,85] The incidence of early stenosis led this group to go back "from bed to bench" to further understand the mechanisms of this type of early failure.[86]

Prototypes of a bioabsorbable valve and valved tube created using PLLA reinforced with non-absorbable polyester (PET) were assessed as tissue-engineered devices to reconstruct the RVOT by the group of Menasché and Kalfa et al. (Figure 1).

Table 2 summarizes the different types of synthetic polymers used in the research field of the right ventricular outflow tract.

The concept of decellularization of tissue-engineered heart valves, initially made of bio-degradable synthetic materials and homologous cells, was then introduced to offer an alternative starter matrix for guided tissue regeneration.[107] This decellularization phase of tissue-engineered heart valves was demonstrated not to alter the collagen structure or tissue strength; it also favored valve performance when compared to their cell-populated counterparts and could provide largely available off-the-shelf homologous scaffolds suitable for reseeding with autologous cells.

Key requirements and properties of those substrates were then discussed in the light of current trends toward designing biologically inspired microenvironments for *in situ* tissue engineering purposes.[108] The concept of *in situ*

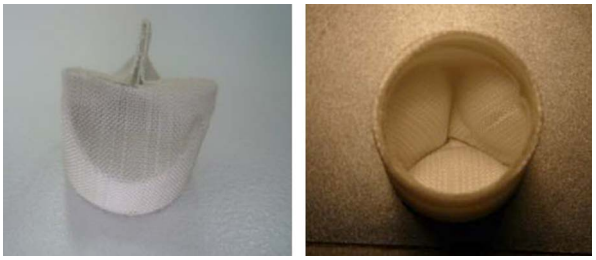

Figure 1. A Global View of a Bioabsorbable Valve Made of Poly-L-lactic acid (PLLA) and Polyester (PET).
Illustrations from D. Kalfa and P. Menasché's group.

tissue engineering, i.e. neotissue regeneration without the use of seeded cells, could solve the disadvantages of using any cell source and achieve a versatile and easier cell-free protocol.[109] The evaluation of *in situ* tissue engineering vasculature (iTEV) by implantation of scaffolds made of polyglycolide knitted fibers and an L-lactide and ε-caprolactone co-polymer sponge in the inferior vena cava of a canine model supported this concept by demonstrating a native tissue-like histological regeneration, with acceptable biomechanical characteristics.[110]

More recently, hundreds of polymers were comprehensively assessed for tissue engineering of cardiac valves, using polymer microarray technology.[111] Biomechanical tests with real-time displacement and strain mapping were also recently reported to quantify biomechanical and biochemical properties of semilunar heart valve tissues, and potentially facilitate the development of tissue-engineered heart valves.[112] The role of substrate stiffness in modulating the gene expression and phenotype of neonatal cardiomyocytes *in vitro*[113] or seeded human bone-marrow stem cells,[114] on the one hand, and in modulating the activation of valvular interstitial cells,[115] on the other hand, demonstrated the importance of the mechanical properties of materials used for valve repair or for engineering valve tissue.[116]

Electrospinning appears in the literature as a promising technology to produce scaffolds for cardiovascular tissue engineering. Amoroso et al. evaluated the effect of processing variables and secondary fiber populations on the microstructure and the tensile and bending mechanics of electrospun biodegradable polyurethane scaffolds for heart valve tissue engineering.[117] Computational tools were developed in order to describe and predict the mechanical behavior of electrospun valve-shaped

Table 2. Different Types of Synthetic Polymers Used in the Research Field of the Right Ventricular Outflow Tract.

n.a.=not applicable

Polymer	Cell Type	Animal Model	Ref.
Poly(ethylene glycol) (PEG)	Human MSC, valvular interstitial cells (VIC)	n.a.	87–91
Poly(glycolic acid) (PGA)/Poly(lactic acid) (PLA)	• Fibroblasts, epithelial cells (EC) and ovine VIC • Human fibroblasts, bovine aortic EC	lambs (2 weeks)	92, 93
PGA/Poly-4-hydroxybutyrate (P4HB)	• Myofibroblasts, ovine EC • Stem cells, endothelial progenitor cells, and ovine valvular endothelial cells (VEC)	lambs (20–100 weeks)	94–98
	• Human amniotic fluid-derived stem cells	sheep (8 weeks)	
Polycaprolactone (PCL)	Human myofibroblasts	n.a.	99
Poly(glycerol sebacate) (PGS)/PCL	Human umbilical vein-derived endothelial cells (HUVEC)	n.a.	100
Poly(ester urea urethane) (PEUU)	Smooth muscle cells (SMC) from rats	n.a.	101–104
Polydioxaneone (PDO)	Ovine MSC	lambs (1, 4, 8 months)	105
Polycarbonate PCU– Polyhedral oligomeric silsesquioxanes (POSS)	n.a.	n.a.	106

scaffolds characterized by different microstructures and showed that a pronounced degree of anisotropy was necessary to reproduce the deformation patterns observed in the native heart valve.[118]

In the emerging field of tissue engineering and regenerative medicine, different design strategies were evaluated to promote the development and evaluation of improved tissue engineering scaffolds. These include mimicking the extracellular matrix, predicting the structural architecture, ensuring adequate initial mechanical integrity, modifying the surface chemistry[109,110,119] and topography[120] to provide cell signaling, and anticipating the material selection so as to predict the required rate of bioresorption.[121] The biofunctionalization of polymeric scaffolds or decellularized native homografts with motifs (such as RGD, SDF-1α, fibronectin, collagen, CD33) led to encouraging results and could be an alternative way to the complex techniques of cell culture and cell seeding.[109,110,122] Prokoph et al. demonstrated that sustained delivery of SDF-1α from proangiogenic hydrogels could effectively attract early endothelial progenitor cells (ePCs), offering a powerful means to trigger endogenous mechanisms of cardiac regeneration.[122]

NEW FIELDS

Antenatal Corrective Cardiac Surgery

Embryology and fetal physiopathology of congenital cardiac defects support the idea that the natural progression of some malformations could be curtailed, or arrested altogether, by an intrauterine intervention on the developing heart. Moreover, prenatal diagnosis is performed more and more widely and precisely. This led to the idea of corrective interventions in the fetus, now regarded as a new frontier in pediatric cardiac surgery. Three types of cardiac surgical procedures have been performed so far in the fetus: aortic valvuloplasty in

hypoplastic left heart syndrome,[123,124] atrial septostomy to prepare surgery of the same syndrome after birth,[125] and pulmonary valvuloplasty for pulmonary atresia and hypoplastic right ventricle. Central to progress in this area is the development of instrumentation specifically designed for minimally invasive cardiac surgery in the fetus, involving experts in microengineering and microrobotics. An "ideal" catheter for minimally invasive, fetal cardiac surgery should therefore be appropriately miniaturized and implemented with sensors and driving systems. Some parts of the ideal "fetal catheter" are already available as a prototype.[126] Such fetal "mechanical" surgical procedures could then be combined with fetal "biological" procedures such as implantation of an appropriate lineage of stem cells or any suitable growth-promoting factor inside the fetal ventricle wall. Collaborations with surgeons, cardiologists, imagers, and engineers will be mandatory to develop such new integrated technologies.

Robotics

Robotically assisted surgical procedures have been introduced into the field of cardiac surgery since the late 1990s. The da Vinci® Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) is the only US FDA-approved system for intracardiac procedures. Robotics was first applied in pediatric cardiac surgery for extracardiac procedures such as patent ductus arteriosus ligation and vascular ring divisions.[127–129] Robotically assisted repairs of atrial septal defect were then performed in children.[131,132] There has also been an on-going interest in developing image-guided techniques to perform the same types of intracardiac repairs currently done as open procedures, but without use of cardiopulmonary bypass. To meet this objective, technical advances need to be achieved in two domains: the creation of instruments and devices providing tactile feedback and steerability, on the one hand,[132] and high-resolution 3D real-time imaging, on the other hand.[133,134] Thus, new catheter-like robotic delivery platforms have been described that facilitate safe navigation and enable complex repairs, such as tissue approximation and fixation, and tissue removal, inside the beating heart.[135]

These new systems combined with enhanced imaging techniques may enable the advancement of the field of beating-heart intracardiac reconstructive interventions currently not feasible with available surgical and catheter-based robotic systems.[136]

CONCLUSION

These new technologies for structural malformation surgery are still in their infancy but certainly present great promise for the future. Further development of these technologies will depend on the collaboration among diverse medical specialties and the contribution from engineers with special skills. But the translation of these emerging technologies to routine health care and public health policy will also largely depend on economic considerations, value judgments, and political factors.

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