Review paper

Advancements in the treatment of Congenital Heart Disease

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Abstract

Congenital Heart Disease (CHD) is the most common congenital disorder in new-borns. This literature review aims to discuss several forms of CHD, including truncus arteriosus, tetralogy of Fallot, Ebstein's Anomaly, ventricular septal defect and aortic coarctation, with a specific focus upon the recent advancements in the treatment of CHD, especially surgical advancements. Although several of these novel treatment options have improved patient outcomes, the complication rates still remain high and emphasis should be placed upon further research to be conducted enabling the development of better treatment strategies for CHD patients. There is a need for data standardization across single center trials and/or multicenter large studies with sufficient follow-up time to evaluate long-term outcomes in patients with CHD. Among others, this review includes the description of the following treatment options: endovascular techniques, complete surgical repair, and hybrid techniques.

Keywords

Congenital heart disease, Truncus arteriosus, Tetralogy of Fallot, Ebstein's anomaly, Ventricular septal defect, Aortic coarctation, CHD, Endovascular technique, Surgical, Pulse oximetry

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Introduction

Congenital Heart Disease

Congenital heart disease (CHD) comprises structural defects of the heart and/or blood vessels, which affects approximately 0.8-1.2% of livebirths worldwide (1). It is the most common congenital disorder in new-borns, and it may negatively impact the heart function and circulation (1, 2). Over the last few decades, the surgical repair and treatment of CHD have made significant progress due to advancements in technology, which has resulted in improved patient outcomes, reduced morbidities as well as decreased mortality, with more than 90% of children with CHD surviving into adulthood due to advancements in disease recognition and improved medical and surgical management, (3) with the survival of paediatric patients with CHD over the past few decades significantly increasing (4, 5). Due to advancements in perioperative care, the rate of brain injury in CHD has been significantly reduced. In a study where 270 term new-borns with complex CHD were enrolled in pre- and post-operative MRIs between 2001 and 2021, it was found that while the preoperative rates did not change, the postoperative rates for white matter injury (WMI) declined by 18.7% (6). These aspects are further explored throughout this literature review.

CHD encompasses a multitude of structural defects, including atrial septal defect (ASD), ventricular septal defect (VSD), tetralogy of Fallot (TOF), truncus arteriosus (TA), coarctation of the aorta (CoA), transposition of the great arteries (TGA), as well as others. Each of these CHD forms has different severity and occurrence rates.

Although no specific cause of CHD has yet been isolated, there are several genetic and environmental factors linked to its manifestation. CHD can be caused by either genetic (~ 40% of cases) or environmental factors ~ 2-10% of cases, with various maternal illnesses including diabetes, obesity and nutritional deficiencies such as vitamin A, vitamin D, as well as the combination of both (3, 7, 8). Some of these genetic factors can include chromosomal abnormalities, gene mutations, familial predisposition, while some environmental factors may include maternal infections, maternal diabetes as well as maternal exposure to specific toxins and/or medications (9).

Genetic Testing of CHD with more advanced methodologies, such as chromosomal microarray (CMA) or exome sequencing have established genetic predisposition, thereby enabling better prediction and consequent management of CHD, and allowing for screening of family members. Furthermore, these techniques have enabled perinatal management, allowing for a better understanding of long-term event free survival, growth, neurodevelopmental performance and ventricular function, hence leading to improved clinical outcomes (10).

Although genomic factors play an importance in CHD manifestation, detailed information is largely unknown. Regardless, some aspects of CHD which are associated with a phenotype could benefit from genomic editing. Some of these CHD phenotypes that have been considered for CRISPR-Cas9 intervention include DiGeorge's Syndrome and Barth Syndrome; among others (11-13). Genome editing using CRISPR-Cas9 for treating genetic conditions like

cardiomyopathy requires precise and efficient techniques to ensure safety (14). Although recent successes have shown promise in correcting specific mutations, concerns about reproducibility, off-target effects, and delivery challenges need to be addressed before considering its further application in patients with CHD (15).

Epigenetic modification is another aspect that is being researched, which affects the spatiotemporal pattern of gene expression (16). The best known examples of the epigenetic process include DNA methylation, histone modifications and non-coding RNA activity, the most common being DNA methylation. DNA methylation refers to the process of adding methyl group(s) to DNA molecules (17, 18). Several studies have investigated the association between DNA methylation and CHD (19). DNA methylation profiles differ between different stages of embryonic development, neonates, and adults, as well as between healthy individuals and patients with heart disease (20). Changes in DNA methylation during cardiac development can affect the expression of genes involved in heart development and myofibril gene expression (21). Further research is needed to better understand the complex relationship between DNA methylation, environmental factors, and the development of CHD.

Discussion

Congenital Heart Disease

Various screening methods can be utilized to diagnose CHD, including prenatal ultrasound, clinical observation, and postnatal pulse oximetry testing. Pulse oximetry screening is performed within 24 hours of birth and involves measuring pre- and post-ductal oxygen saturations using a pulse oximeter, with one placed on the right hand and the other on either foot. The sensitivity of pulse oximetry screening to detect critical CHD is 38%, making it a satisfactory initial screening tool. However, using other tests, such as ultrasound, can narrow the diagnosis. Infants with critical CHD requiring surgery may have better short-term outcomes and long-term survival when diagnosed prior to or at the neonatal cardiac screen. Nevertheless, a retrospective chart review and registry study found no significant difference in survival rates between those diagnosed during screening and those diagnosed at a later stage. Further research is required to evaluate the effectiveness of different screening methods and to determine the best approach for detecting and diagnosing CHD in new-borns (22).

The treatment of CHD involves a multitude of methods including medical and surgical interventions. Medication may be prescribed for patients in order to manage their symptoms, prevent complications and improve overall heart function. Another technique is surgical intervention, which is a more common route, since CHD is a structural defect. Surgery utilised for each patient depends on the specific type of CHD. However, surgical intervention is associated with more risks, including bleeding, infection or other heart and lung complications. Numerous advances in the treatment of CHD have allowed for the development of open-heart surgery, minimally invasive surgery, endovascular procedures, and hybrid procedures. Additionally, to improve patient outcomes, long-term follow-up care of patients diagnosed with CHD is vital. The

follow-up care typically includes regular monitoring and examination to timely detect and access complications, if and when these arise. This allows for optimal heart function and a lower re-operation rate, which varies depending on the specific type of CHD detect as well as the surgical technique first utilised (23).

The utilisation of surgical simulation incorporated in the teaching of congenital heart surgery through three-dimensional (3D) printed models or silicone moulding technology, allows for instant feedback from the teacher and decreasing the risk to patients. Due to the rarity of the disease and the multitude of natures of CHD, this procedure is demanding as it is, hence innovative and realistic simulation teaching tools are needed. Additionally, there is no agreed consensus on the duration and nature of the training prior to certification, varying significantly between countries, hence there is a possibility of a shortage of cardiothoracic surgeons in the future in this field (24). Teaching by simulation platforms is expected to bring uniformity of procedure and skill-sets. Through repeated simulations future surgeons are expected to be able to retain and improve skills, as well as decrease the procedural time (25). There is a vast variety of simulation platforms, some include virtual reality simulators, beating heart simulators, isolated biological heart simulators, 3D replica human simulators etc. Currently, the most commonly utilised is low-fidelity simulators, for learning cutting, suturing and other basic skills (26). However, an advancement has been the hands-on surgical training (HOST) model which uses 3D printing or silicone moulds, first introduced in 2015. Training using the model demonstrated improvement in surgical time and technical performance at the second HOST attempt for the arterial switch operation and Norwood operations (27, 28).

Another treatment of CHD to be considered is stem cell therapy, which can be supplemented alongside surgery and has been shown to have favourable outcomes, providing benefits to cardiac function, quality of life and somatic growth. However, stem cell therapy should only be performed in the context of well-planned clinical trials, and more studies and research into this field will help to clearly determine the efficacy. Umbilical cord cells, endothelial progenitor cells, mesenchymal stem cells, cardiac stem cells and bone-marrow derived progenitor cells have been used in CHD clinical trials (29, 30). Wehman et al. conducted preclinical studies on pigs with right ventricular pressure overload, utilising mesenchymal stem cells through intramyocardial delivery, enabling right ventricular function preservation and attenuation of remodelling. Unfortunately, there have been limited stem cell studies conducted on children with CHD (31, 32) .

Additionally, another regenerative technique utilised increasingly is to use biological scaffolds, categorised as homografts and xenografts, which have been shown to improve patients' quality of life, however, these necessitate subsequent prophylactic anticoagulant therapy (33). Homografts, either from the patient's body or tissue from a human donor, possess traits such as manipulability, capacity for growth and repair due to cellular infiltration, however, some can evidently stimulate an immune response hence are best required to undergo fixation or decellularization. The pericardium is a commonly utilised autologous biological

graft for pulmonic valve correction, however, it has a tendency to degenerate due to endothelial stress. A particular option for homograft that has shown promise as a scaffold material is decellularized Extracellular Matrix (dECM), which promotes wound healing and tissue regeneration through its anti-bacterial activity, due to the presence of structural proteins and glycoproteins which positivity impact wound healing (34-36). For CHD surgical replacement though, a homograft represents the preferred option, due to the more accurate matching of tissue, and the perception that they are more durable and less immunogenic. However, their availability is limited for clinical CHD scenarios, representing a significant challenge, necessitating surgeons to use xenografts from bovine or porcine sources, which include Matrix P valves (MPV), Matrix P plus® valves (MP+V), urinary bladder matrix (UBM), Proxicor®, and dECM hydrogels (36).

In summary, the surgical treatment of CHD has advanced significantly in recent years, enabling improved outcomes and reduced complications for patients. Novel surgical techniques have improved the efficiency and quality of treatment. However, for optimal patient care, the management of CHD does require a multidisciplinary team approach and ongoing follow-up to ensure minimal complications.

Truncus Arteriosus

Truncus Arteriosus (TA) is a critical form of congenital heart disease (CHD) characterised by the existence of a single arterial trunk, which fails to separate into systemic and pulmonary circulatory branches during embryonic development. While TA constitutes less than 3% of all CHD diagnoses (37), the severity and elevated mortality rate of TA necessitate neonatal or early infancy surgical repair. A delay in surgery beyond 3 months of age causes an increase in the likelihood of cardio-pulmonary decompensation as well as hypertensive disease (37).

Multiple surgical techniques have been developed to treat TA. One clinical study conducted at the King Abdulaziz Cardiac Center with a sample size of 64 patients diagnosed with TA between 2001 and 2021 found that early surgical repair (within 3 months of age) resulted in complete resolution of pulmonary hypertension in the majority of patients after 61.8 ± 58 months of follow-up (38). In contrast, the late repair group showed a 37% prevalence of persistent pulmonary hypertension with a mean follow-up of 41.5 ± 68.2 months, requiring ongoing medication for management. However, the early repair group also had a higher rate of reinterventions at 36%, compared to the group that underwent surgery after three months of age, with a rate of 6% (38).

In another study evaluating the outcomes of TA surgical repair, re-intervention was necessitated for 36% of the total of 23 patients post-surgery. However, notably, the patients that underwent surgery prior to the age of 3 months had a significantly higher prevalence of reinterventions (48%) in comparison to the group that underwent surgery after 3 months of age (6%). The average time to first reintervention was greater for the early-repair group: at 38 months for the early-repair group and 24 months for the late-repair group. The

majority (87.5%) of patients survived over an average follow-up period of 56.7 months, with no significant difference in overall mortality rate between the two groups (12.5%). The primary cause of mortality was pulmonary hypertension complications, with respiratory infections being a contributing factor, within both groups (37). These findings highlight the increased importance of continued surveillance and management of patients post-surgery in order to timely detect and manage complications.

Despite the improvement in patient outcomes over time, there still remain significant complications associated with these surgical procedures. For example, these complications include the need for additional surgical interventions and the presence of persistent pulmonary hypertension post-surgery. Furthermore, the sobering fact remains that the surgical mortality rates are 10.8% for neonatal patients, and 9.2% for children (37). Hence, there is still a need for the development of newer and more efficient techniques. The most commonly used techniques are the modified Blalock-Taussig shunt (in for example, the Norwood procedure) and the right ventricle to pulmonary artery conduit, which can be used alongside three-dimensional technologies (39). A study reported that the integration of three-dimensional printing technology and imaging technology in the surgical planning for TA has improved the accuracy and precision of the procedure, leading to improved outcomes and reduced complication rates, as well as reduced morbidities. Additionally, it is more cost-effective, which makes it suitable for lower-income countries (40). These developments highlight the ongoing evolution of surgical options for TA and the significance of continued research and innovation in this field.

However, one of the drawbacks with the Blalock-Taussig shunt is its inability to accommodate physical growth. Another study addressed this inability, by using a geometrically tunable, hydrogel lined blood shunt, allowing for modulation to prevent growth related mismatch from arising when blood shunt diameter is either too narrow or too wide in patients. The hydrogel lining internally, with a fixed outer diameter sheath, enables for the hydrogel to swell and shrink based on crosslinks, hence controlling the blood flow. In a study by Garven et al. through experimental and simulation analysis, this hydro-gel lined shunt was shown to increase the diameter through increasing crosslinking by 15-18% (which was within the design requirement), increasing uniformly in contrast to other options, including external plungers, balloons, and ductal stenting, thereby reducing the risk of thrombus formation (39, 41-42), This study demonstrated the feasibility of using this growth adaptive shunt in the future, however, further research and innovation is required for eventual use in humans through clinical trials.

In conclusion, TA is a rare but critical congenital heart defect that requires early surgical intervention to mitigate the high risk of cardiopulmonary decompensation and hypertensive disease. Advances in surgical repair methods have been made, with the majority of patients in early repair groups experiencing complete resolution of pulmonary hypertension after follow-up. However, there remain significant

complications, including the need for reinterventions, persistent pulmonary hypertension, and early or late mortality. Further research is needed to improve the outcomes and success rate of surgical repair for TA.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is a form of congenital heart disease (CHD) that involves four structural anomalies, including a ventricular septal defect (VSD), an overriding aorta, pulmonic stenosis, and right ventricular hypertrophy. It is the most common cause of cyanotic CHD, with an estimated prevalence of 7-10% with congenital heart disease (43). The structural defects present in TOF lead to the mixing of systemic and pulmonary blood, which results in decreased oxygenation of the body and a characteristic blue discolouration of the skin and mucous membranes (cyanosis).

For TOF, there are various predisposing factors that include both environmental and genetic aspects. Some environmental aspects include maternal exposure to alcohol, tobacco smoke as well as certain chemicals. Although genetic predisposition is rare, this has also been implicated in the development of TOF, and has been shown with an increased risk of death. These can include chromosomal aberrations, such as DiGeorge's Syndrome, and mutations in genes that are involved in heart development: GATA4, JAG1, NKX-5 (44).

Complete surgical repair is one of the techniques to treat TOF. This technique aims to correct all of the four defects that are associated with TOF and allows for the restoration of normal hemodynamics. This procedure involves the closure of the ventricular septal defect, the resection of the right ventricular outflow tract obstruction (RVOTO), as well as the placement of a transannular patch to increase the diameter of the right ventricular outflow tract (RVOT) (43). This technique is considered an optimal option for treatment for TOF surgically and has consistently been shown to have favourable long-term patient outcomes with low mortality and reduced reoperation rates (44, 45). During the surgery of TOF, unfortunately, residual RVOTOs are very common, as well as incredibly undesirable, to the point where surgeons consider reintervention favourable (46). Surgical techniques used to correct RVOTO have fortunately advanced. The traditional surgical approach for this component of the TOF defect has been a complete repair, which entails removing the obstruction and reconstructing the right ventricular outflow tract. In recent years, partial repair techniques that involve preserving a portion of the right ventricular outflow tract obstruction have been developed.

The surgical repair of TOF can be supplemented through teaching with 3D printing models as simulation to enhance surgical skills among inexperienced cardiothoracic surgeons. This is shown within a study by Nam et al. aiming to assess the effectiveness of utilising a 3D-printed model for surgical training in congenital heart disease, utilising a life-size model of a 6-month-old patient with TOF and complex pulmonary stenosis was printed using a Stratasys Object500 Connex2 printer (47). The suitability of different composite materials was evaluated by cardiothoracic surgeons, and Tango 27 was ultimately

selected as the final model. Six inexperienced cardiothoracic surgeons performed three simulation surgeries individually. The time required to perform certain surgical procedures and the surgical proficiency were measured and evaluated. Hence, results showed that the surgeons' performance significantly improved over the three simulation surgeries. The median time for applying VSD and RVOT patches decreased, and the surgical proficiency scores increased. However, it was noted that the 3D-printed model had limitations, such as it fully replicate an actual human heart, and certain structures were simplified or not visualized. The choice of printing materials was limited, and further diversification of materials is necessary for improved surgical simulation (47).

Furthermore, Endovascular techniques reduce invasiveness of surgical procedures, which enables faster recovery times for patients, as well as reduced risk of complications. The transcatheter valve technologies currently available include the Melody Valve as well as the SAPIEN XT, both which have shown favourable outcomes, but require monitoring to prevent complications like endocarditis. This technique has been found to be safe and effective in the treatment of small to moderate sized ventricular septal defects, and has also shown to improve clinical outcomes (48).

Another advancement in the surgical treatment of TOF is the utilisation of a cardiopulmonary bypass (CPB) alongside with biventricular support. CPB with biventricular support involves the usage of a mechanical device to assist both ventricles during the repair process. This enables better blood flow throughout the repair, which decreases the risk of ischemic injury to the heart. Biventricular support has been shown to improve clinical outcomes, including reduced postoperative morbidity, and reduced risk of low cardiac output syndrome. However, a longer time on the CPB machine is considered a risk factor for arrythmias in the postoperative period (43).

Furthermore, another development within regenerative medicine has shown promise in the therapeutic treatment of CHD (and more specifically TOF and VSDs). MicroRNAs are small, non-coding RNAs which regulate gene expression, required for the normal development of the cardiac muscle, revealed by a specific tissue deletion in mice (49). O'Brien et al. studied MicroRNAs and expression patterns of 16 infants of mean age 276 days with non-syndromic TOF and 8 infants with normal cardiac development, discovering that 61 MicroRNAs 135 small nucleolar RNAs (snoRNAs) were dysregulated with children with TOF, and there was a negative correlation with 33 MicroRNAs (50). Furthermore, 51% of the 44 genes involved with cardiac network were mediated by snoRNAs, alluding that impaired expression of these may lead to TOF development (49, 50).

Within recent years, there has also been a shift towards utilising autologous tissue for the surgical repair of TOF. Autologous tissue has been shown to have reduced complications in comparison to synthetic materials, however it has also been shown to have limited durability. (51) Additionally, the use of autologous tissue has been shown to require shorter hospital stays, reduced risk of pulmonary insufficiency and other immune-

related complications, which are common with synthetic materials (51). More research is needed to evaluate if the autologous materials within the valve are viable long-term (51).

Re-operation rate after complete repair of TOF although low, is still not ideal. The most common reason for re-operation was the development of residual defects, such as a residual ventricular septal defect or residual right ventricular outflow tract obstruction (43). The long-term outcomes after complete repair of TOF were found to be excellent, with high survival rates and good functional status (44).

Overall, the modern advancements in surgical treatment of TOF have highly improved clinical outcomes for patients. This is through the increased usage of minimally invasive techniques, biventricular support, and autologous tissue as well as improved imaging technology. Together, these reduced the risk of complications and improved the quality of life.

Ventricular Septal Defect

Ventricular septal defect (VSD) is one of the most common congenital heart diseases occurring in infants and children. It represents 20% of all congenital heart defects, which makes it a major public health issue (52). It is primarily characterized by a hole in the septum, which separates the two ventricles of the heart, resulting in blood flowing from the left ventricle to the right ventricle, bypassing the lungs, as shown in Figure 1. This causes an increased workload on the heart and lungs, which leads to an increased risk of heart failure as well as respiratory complications.

Several MicroRNAs have been shown to lead to the development of VSDs, some include miR-1, miR-195 among others (53, 54). The results from the studies on the role of Micro-RNAs in the development of CHDs indicate that their therapeutic regulation may improve clinical outcomes post-surgical intervention, two of the major strategies currently being inhibition of MicroRNA activity by oligonucleotides and restoration of MicroRNA function using viral-vector based expression (49).

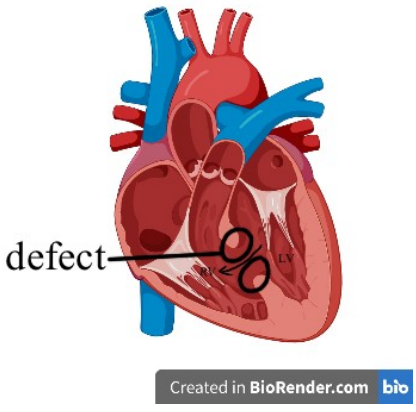

Figure 1: Anatomy of a heart with VSD

With the advancement of surgical techniques, the management and treatment of VSDs have become more efficient, leading to improved patient outcomes. Some of these surgical techniques include open heart surgery, transcatheter closure, patch closure, and percutaneous closure as well as minimally invasive surgery. However, the primary focus for the more advanced surgical techniques is minimally invasive surgery. These techniques have several advantages including reduced surgical time, smaller incisions, decreased pain and scaring in comparison to traditional open-heart surgery (52).

Open-heart surgery is the traditional surgical technique typically used to treat VSDs. This technique involves a full sternotomy, which allows the surgeon to directly access the heart and hence, repair the defect. Open heart surgery is often reserved for patients with larger or more complex VSDs, or for those who are unable to undergo a percutaneous or minimally invasive procedure. In terms of patient outcomes, open heart surgery has been shown to be highly effective in repairing VSDs.

Minimally invasive surgery, such as percutaneous closure and minimally invasive cardiac surgery, is a safe and effective surgical technique used to treat ventricular septal defects (VSDs) without the need for a full sternotomy or thoracotomy. This technique utilizes catheter-based devices and can be performed under local or general anaesthesia. A study by Xu et. al. reported that 94.9% of patients had VSDs that were successfully occluded using the symmetric or asymmetric occluder, with them being able to insert an occluder within the VSD and open it, to confirm the absence of residual shunt and tricuspid regurgitation, with a low rate of re-operation and no mortalities (55). The rest of the patients were converted into a VSD Repair. It was shown that minimally invasive procedures with VSD repair demonstrated better short-term outcomes, in comparison to open repair (56). In a study by Chen et. al. comparing percutaneous device occlusion with minimally invasive surgical repair, the success rate for percutaneous device occlusion was 93%, while that for minimally invasive surgery was 98.3%. Minimally invasive surgery was shown also be cheaper as compared to percutaneous device occlusion, making it useful in low-income countries (57). However, significantly more residual shunts were observed within the minimally invasive surgical approach. These were typically resolved on their own, with only 1 patient of 113 requiring reintervention. Four other patients in the minimally invasive surgery group needed reoperation due to postoperative bleeding or a large residual shunt. In the minimally invasive surgery group, 4 patients developed major complications, and 37 presented with minor complications. The percutaneous occlusion group consisted of 80 patients, 1 patient had a major complication, while 27 patients had minor complications (57). Major complications in this case included endocarditis, reoperations, death due to the procedure, thromboembolism, complete atrioventricular block requiring a pacemaker, valvular regurgitation resulting from the procedure requiring surgical intervention and device embolization requiring surgical removal. Minor complications included wound complications which required interventions, groin hematoma, device embolization, cardiac arrhythmia, new or increased valvular regurgitation of 2 grades

or less, haemodialysis requiring only medication, pericardial or pleural effusion, pneumothorax, pneumopericardium and pneumoderma which required a chest tube or aspiration.

Advances in imaging technology have greatly improved surgical outcomes for patients with VSDs. 3D echocardiography and magnetic resonance imaging (MRI) have allowed for better visualization of the heart prior to and during surgery. This has resulted in improved surgical planning and reduced the risk of complications. The use of 3D visualised operative procedure during surgery significantly decreased the median time on the cardiopulmonary bypass surgery (CPB), as well as a decreased rates of early mortality: 27.3% of patients experienced early mortality within the conventional group, while none experienced early mortality within the 3D group (58).

The Nit-OccludÒ-Leˆ VSD coil device is a recent advancement within the surgical treatment of VSDs without the need for traditional open-heart surgery. A study published by Haas et. al. reported that the device had been successfully implanted in 91.9% of patients, while it failed in 8.1% of patients, with the reasons for failure being the inability to advance delivery sheath through patient and or defect being too large for the device (59). Within the 91.9% of patients with successful implantation, there was a 95% complete closure rate after 6 months, with 1.8% of patients having severe complications which included embolization and a severe hemolysis. The study followed patients for a median of 31.1 months and found that the device was well-tolerated, with minimal complications and no reported deaths. The device's minimally invasive nature and high success rate makes it an attractive option for patients who are seeking; or need; a less invasive surgical option. Additionally, the reduced need for reoperation and the improved outcomes observed in patients make the Nit-OccludÒ-Leˆ VSD coil device a highly promising development in the field of VSD surgery. It is important to note that the studies cited here are relatively small and more large-scale, long-term studies are needed to fully evaluate the safety and effectiveness of this device. However, the results of these studies provide strong initial evidence for the device's efficacy in treating VSDs and suggest that it may become a widely used surgical option in the future (59).

Ebstein's Anomaly

Ebstein's Anomaly is a relatively rare form of congenital heart disease that is characterised by a malformation of the tricuspid valve as well as the right ventricle of the heart. The primary function of the tricuspid valve is to control the flow of blood from the right atrium to the right ventricle. It is displaced towards the apex of the right ventricle and thus can be completely or partially incorporated within the ventricular wall. As a result, the effective area of the valve decreases, resulting in regurgitation and potentially elevated right atrial pressure. The first presentation of Ebstein's Anomaly can be detected during the prenatal period, due to the onset of cyanosis caused by increased RV end-diastolic pressure, with plasma volume increasing by 30-50% during the third trimester (60).

Although the precise causes of Ebstein's Anomaly are not yet established, both

environmental and genetic factors may contribute to its manifestation. Genetic mutations and chromosomal abnormalities have been linked to the disease, but no particular environmental risk factors have been found (60). Ebstein's Anomaly is thought to occur in 1 in 200000 live births (61), however, a completely accurate prevalence is unknown due to the disease's variable severity and at times, its difficult detection.

In the past, surgical treatment for Ebstein's Anomaly was quite limited including for example, palliative procedures with a focus on alleviating the symptoms of the disease, such as relieving right atrial pressure or reducing regurgitation. However, in recent years, surgical repair of Ebstein's Anomaly has become increasingly successful, and there have been various advancements in surgical techniques for treating the disease, improving patient outcomes.

The success of surgical treatment for Ebstein's Anomaly depends on several factors, some of which include the size as well as the location of the tricuspid valve, the degree of regurgitation, and the presence of other associated cardiac defects. In general, patients with mild to moderate Ebstein's Anomaly who undergo surgical repair typically have favourable long-term outcomes, with low rates of regurgitation and satisfactory functional outcomes. However, patients with severe Ebstein's Anomaly may require multiple surgeries and may have a higher risk of long-term complications, such as heart failure and arrhythmias.

The Cone Repair, which is a modification of the Carpentier Repair, is used to correct tricuspid regurgitation (TR) in patients with Ebstein's anomaly. This involves the detachment of the anterior and posterior leaflets of the tricuspid valve, then dividing any abnormal papillary muscles and tissue in between the leaflets and the corresponding right ventricular valve; thus, preserving attachments between the leaflet-free edges. This allows for the delamination of the leaflets, leaving only the normal attachment of the anterior leaflet to the true tricuspid annulus and the sub valvular apparatus in place. The posterior leaflet-free edge is then, rotated clockwise and sutured to the anterior leaflet edge, forming a new tricuspid valve that resembles a 'cone'. With this procedure, several studies have shown no significant tricuspid valve stenosis, as well as the reduction of TR, reduction in the RV size, as well as a lower mortality following repair. However, some studies have also reported a decline in the RV function in 32% of cases, with some improvement post late-follow up (60, 62)

Another recent advancement in the surgical treatment of Ebstein's Anomaly is the implantation of a bioprosthetic valve, which is a mechanical valve, that is essentially covered with tissue, hence mimicking the natural valve. This procedure involves the replacement of the tricuspid valve with a bioprosthetic valve and is considered to be a simpler and less technically challenging surgical procedure in comparison to the valve-sparing repair. The bioprosthetic valve has been previously shown to have good short-term outcomes, satisfactory durability as well as low chronic anticoagulation medication needs, but the long-term outcomes of this procedure are still being evaluated (63).

Aortic Coarctation

Aortic coarctation (CoA) is a structural defect (as shown in Figure 2), that is characterized by the narrowing of the aorta. Therefore, this leads to increased blood pressure within the upper extremities and a decrease within the lower extremities. CoA is a relatively common congenital heart defect, comprising 5-7% of all congenital heart diseases (64). While the exact cause of aortic coarctation is unknown, there are several environmental and genetic aspects that have been shown to contribute to the manifestation of CoA. These include maternal smoking, as well as alcohol consumption during pregnancy. Furthermore, CoA is more common in males than females and is often associated with other heart defects such as bicuspid aortic valve, VSD, or patent ductus arteriosus (64).While some patients with CoA are asymptomatic, the majority tend to experience symptoms such as shortness of breath, atypical chest pain, and exertional headaches. If CoA is left untreated, patients may not survive after the fifth decade of life due to hypertensive complications. Hence, surgical intervention is necessary.

The primary treatment for the correction of CoA is a surgical repair. Primary surgical techniques include direct repair, extra-anatomic bypass, hybrid procedures, aortoplasty, reverse artery perforator graft (RAPG) and endovascular stenting.

Direct repair can be performed both with or without a cardiopulmonary bypass (CPB). This surgical technique entails the removal of the narrowed section of the aorta and then connecting the two healthy ends. Total CPB, in conjunction with hypothermic circulatory arrest (HCA) has been utilised to reduce the risk of neurological damage post procedures. A recent study showed that direct repair with a total CPB and HCA resulted in excellent outcomes, with no in-hospital deaths, as well as no evidence of recurrent coarctation during the follow-up period (65).

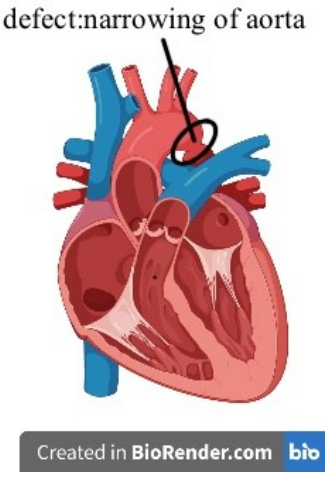

Figure 2: Anatomy of a heart with Aortic Coarctation

Another advancement in the treatment of CoA is an extra-anatomic bypass, which essentially bypasses the narrowed sections of the aorta by creating a bypass between the healthy sections of the aorta. This procedure can be performed through either the chest or the abdomen. Extra-anatomic bypass was associated with a low mortality rate, as well as a low rate of reoperation in patients. However, it is associated with a risk of bypass graft thrombosis and is not suitable for patients with aneurysm (66, 67).

Endovascular stenting has lower morbidity and mortality rates than open surgery, making it a viable option for certain patients who do not have an aneurysm. Balloon angioplasty, another endovascular technique, which uses a balloon to widen the narrowed portion of the aorta, is another option for endovascular repair. Despite the high initial success rate, complications such as restenosis and aneurysm formation occured in 15% and 5-35% of patients, respectively (67). Endovascular repair using balloon angioplasty and stenting can also result in procedural complications such as stent migration and restenosis. However, in cases of focal dissection or short aneurysm, covered stents demonstrated comparable complication and reintervention rates as bare metal stents. Despite the risks of endovascular stenting, the procedure has been shown to reduce the rate of restenosis to less than 10%, which is comparable to the rate observed with open surgery. In a single-centre study, aortic reintervention for restenosis was observed in 12% of stenting patients and 5% of open-surgery patients (67). Overall, endovascular stenting is a promising alternative to open surgery for patients who do not have an aneurysm, but careful patient selection and follow-up monitoring are required to manage potential complications (67).

Conclusion and Analysis

With advancements in technology, the surgical treatment of CHD has resulted in improved patient outcomes. For example, the studies on the VSD surgical treatment have shown that minimally invasive surgery is the optimum choice as it reduces patient recovery time, allows for smaller incisions and decreased pain. Additionally, the surgical treatment of VSD has been shown to benefit from imaging technology, giving surgeons a better understanding of the defect structure. Therefore, these imaging devices should be utilized more, and need to become more affordable and accessible to enhance patient outcomes.

Despite all of these improvements, there is still a need to find better treatment options, as patients still face numerous complications post-surgery. There is still a gap in the literature about the etiology of CHD with only 15% of CHD cases being traced to primary sources (1). Therefore, identifying the primary cause of CHD will lead to more personalised treatment options for patients. Additionally, multiple studies described in this article represent single center analyses, which could be further improved by expanding the patient population (22). For example, when comparing late and early surgical repair in truncus arteriosus, the data originated from a single center examining the outcomes in 64 patients (38). Birth weight and gestational time were not recorded in the study, which may have an effect on patient outcomes and need for reinterventions. In another study describing truncus arteriosus,

there were only 20 patients with the median follow-up time of only 8 months (40). Such short follow-up time does not allow for an accurate estimate or understanding of the long-term effects of surgical repair on truncus arteriosus. Given the paucity of funding or coordination, even single center analysis results can be pooled together if data sampling and recording procedures were to be standardized across multiple centers. Thus, there is a need for data standardization across single center trials and/or multicentre large studies with sufficient follow-up time to evaluate long-term outcomes in patients with CHD. Moreover, with greater number of CHD patients surviving to adult age, it is important to further investigate the need for CHD management and interventions in the adult population.

Congenital heart defects, such as aortic coarctation, tetralogy of Fallot, ventricular septal defect, truncus arteriosus, and Ebstein's anomaly, are significant malformations that require a multidisciplinary approach for optimal patient care. Recent advancements in surgical techniques, such as open-heart surgery, minimally invasive surgery, hybrid procedures, and catheter-based procedures, have improved patient outcomes and reduced complications. However, careful patient selection and follow-up monitoring are necessary to manage potential complications. Regular monitoring and examination of patients with CHD are vital to detect complications timely and ensure optimal heart function. Continued research and innovation in this field are needed to improve outcomes and success rates of surgical repair for these congenital heart defects. Additionally, the integration of three-dimensional printing and imaging technology in surgical planning has shown promise in improving accuracy, precision, and in reducing complication and re-intervention rates. While the mortality rate has decreased over time, further improvements are needed to increase long-term survival rates and decrease complications associated with surgical procedures.

References

1. Wu W, He J, Shao X. Incidence and mortality trend of congenital heart disease at the global, regional, and national level, 1990-2017. *Medicine (Baltimore)*. Jun 05 2020;99(23):e20593. http://doi.org/10.1097/MD.0000000000020593

2. Bouma BJ, Mulder BJ. Changing Landscape of Congenital Heart Disease. *Circ Res*. Mar 17 2017;120(6):908-922. http://doi.org/10.1161/CIRCRESAHA.116.309302

3. Yasuhara J, Garg V. Genetics of congenital heart disease: a narrative review of recent advances and clinical implications. *Transl Pediatr*. Sep 2021;10(9):2366-2386. http://doi.org/10.21037/tp-21-297

4. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation. Jan 16 2007;115(2):163-72. http://doi.org/10.1161/CIRCULATIONAHA.106.627224

5. Moons P, Engelfriet P, Kaemmerer H, et al. Delivery of care for adult patients with congenital heart disease in Europe: results from the Euro Heart Survey. Eur Heart J. Jun 2006;27(11):1324-30. http://doi.org/10.1093/eurheartj/ehi858

6. Peyvandi S, Xu D, Barkovich AJ, et al. Declining Incidence of Postoperative Neonatal Brain Injury in Congenital Heart Disease. J Am Coll Cardiol. Jan 24 2023;81(3):253-266. http://doi.org/10.1016/j.jacc.2022.10.029

7. Lage K, Greenway SC, Rosenfeld JA, et al. Genetic and environmental risk factors in congenital heart disease functionally converge in protein networks driving heart development. Proc Natl Acad Sci U S A. Aug 28 2012;109(35):14035-40. http://doi.org/10.1073/pnas.1210730109

8. Kuciene R, Dulskiene V. Selected environmental risk factors and congenital heart defects. Medicina (Kaunas). 2008;44(11):827-32. https://pubmed.ncbi.nlm.nih.gov/19124958/ .

9. Sun R, Liu M, Lu L, Zheng Y, Zhang P. Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments. *Cell Biochem Biophys*. Jul 2015;72(3):857-60. http://doi.org/10.1007/s12013-015-0551-6

10. Russell MW, Chung WK, Kaltman JR, Miller TA. Advances in the Understanding of the Genetic Determinants of Congenital Heart Disease and Their Impact on Clinical Outcomes. J Am Heart Assoc. Mar 09 2018;7(6) http://doi.org/10.1161/JAHA.117.006906

11. Spencer CT, Bryant RM, Day J, et al. Cardiac and clinical phenotype in Barth syndrome. Pediatrics. Aug 2006;118(2):e337-46. http://doi.org/10.1542/peds.2005-2667

12. Nguyen Q, Lim KRQ, Yokota T. Genome Editing for the Understanding and Treatment of Inherited Cardiomyopathies. Int J Mol Sci. Jan 22 2020;21(3) https://pubmed.ncbi.nlm.nih.gov/19124958/

13. Moerman P, Goddeeris P, Lauwerijns J, Van der Hauwaert LG. Cardiovascular malformations in DiGeorge syndrome (congenital absence of hypoplasia of the thymus). Br Heart J. Oct 1980;44(4):452-9. http://doi.org/10.1136/hrt.44.4.452

14. Porteus MH, Baltimore D. Chimeric nucleases stimulate gene targeting in human cells. Science. May 02 2003;300(5620):763. http://doi.org/10.1126/science.1078395

15. Seok H, Deng R, Cowan DB, Wang DZ. Application of CRISPR-Cas9 gene editing for congenital heart disease. Clin Exp Pediatr. Jun 2021;64(6):269-279. http://doi.org/10.3345/cep.2020.02096

16. Szyf M. The early life social environment and DNA methylation: DNA methylation mediating the long-term impact of social environments early in life. Epigenetics. Aug 2011;6(8):971-8. http://doi.org/10.4161/epi.6.8.16793

17. Shipony Z, Mukamel Z, Cohen NM, et al. Dynamic and static maintenance of epigenetic memory in pluripotent and somatic cells. Nature. Sep 04 2014;513(7516):115-9. http://doi.org/10.1038/nature13458

18. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev. Jan 01 2002;16(1):6-21. http://doi.org/10.1101/gad.947102

19. Cao J, Wu Q, Huang Y, Wang L, Su Z, Ye H. The role of DNA methylation in syndromic and non-syndromic congenital heart disease. Clin Epigenetics. Apr 26 2021;13(1):93. http://doi.org/10.1186/s13148-021-01077-7

20. Fulka H, Mrazek M, Tepla O, Fulka J. DNA methylation pattern in human zygotes and developing embryos. Reproduction. Dec 2004;128(6):703-8. http://doi.org/10.1530/rep.1.00217

21. Chamberlain AA, Lin M, Lister RL, et al. DNA methylation is developmentally regulated for genes essential for cardiogenesis. J Am Heart Assoc. Jun 19 2014;3(3):e000976. http://doi.org/10.1161/JAHA.114.000976

22. Miller R, Martens T, Jodhka U, Tran J, Lion R, Bock MJ. Effects of universal critical CHD screening of neonates at a mid-sized California congenital cardiac surgery centre. *Cardiol Young*. Feb 2022;32(2):236-243. http://doi.org/10.1017/S1047951121001797

23. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol*. Jan 2011;8(1):50-60. http://doi.org/10.1038/nrcardio.2010.166

24. Moffatt-Bruce SD, Ross P, Williams TE. American Board of Thoracic Surgery examination: fewer graduates, more failures. J Thorac Cardiovasc Surg. May 2014;147(5):1464-69. http://doi.org/10.1016/j.jtcvs.2014.01.003

25. Burkhart HM. Simulation in congenital cardiac surgical education: We have arrived. J Thorac Cardiovasc Surg. Jun 2017;153(6):1528-1529. http://doi.org/10.1016/j.jtcvs.2017.03.012

26. Fann JI, Sullivan ME, Skeff KM, et al. Teaching behaviors in the cardiac surgery simulation environment. J Thorac Cardiovasc Surg. Jan 2013;145(1):45-53. http://doi.org/10.1016/j.jtcvs.2012.07.111

27. Hussein N, Honjo O, Haller C, et al. Quantitative assessment of technical performance during hands-on surgical training of the arterial switch operation using 3-dimensional printed heart models. J Thorac Cardiovasc Surg. Oct 2020;160(4):1035-1042. http://doi.org/10.1016/j.jtcvs.2019.11.123

28. Yoo SJ, Hussein N, Barron DJ. Congenital Heart Surgery Skill Training Using Simulation Models: Not an Option but a Necessity. J Korean Med Sci. Oct 03 2022;37(38):e293. http://doi.org/10.3346/jkms.2022.37.e293

29. Tarui S, Ishigami S, Ousaka D, et al. Transcoronary infusion of cardiac progenitor cells in hypoplastic left heart syndrome: Three-year follow-up of the Transcoronary Infusion of Cardiac Progenitor Cells in Patients With Single-Ventricle Physiology (TICAP) trial. J Thorac Cardiovasc Surg. Nov 2015;150(5):1198-1207, 1208.e1-2. http://doi.org/10.1016/j.jtcvs.2015.06.076

30. Burkhart HM, Qureshi MY, Peral SC, et al. Regenerative therapy for hypoplastic left heart syndrome: first report of intraoperative intramyocardial injection of autologous umbilical-cord blood-derived cells. J Thorac Cardiovasc Surg. Mar 2015;149(3):e35-7. http://doi.org/10.1016/j.jtcvs.2014.10.093

31. Tsilimigras DI, Oikonomou EK, Moris D, Schizas D, Economopoulos KP, Mylonas KS. Stem Cell Therapy for Congenital Heart Disease: A Systematic Review. Circulation. Dec 12 2017;136(24):2373-2385. http://doi.org/10.1161/CIRCULATIONAHA.117.029607

32. Wehman B, Sharma S, Pietris N, et al. Mesenchymal stem cells preserve neonatal right ventricular function in a porcine model of pressure overload. Am J Physiol Heart Circ Physiol. Jun 01 2016;310(11):H1816-26. http://doi.org/10.1152/ajpheart.00955.2015

33. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J. Sep 2010;31(17):2124-32. http://doi.org/10.1093/eurheartj/ehq200

34. Arrizabalaga JH, Nollert MU. Human Amniotic Membrane: A Versatile Scaffold for Tissue Engineering. ACS Biomater Sci Eng. Jul 09 2018;4(7):2226-2236. http://doi.org/10.1021/acsbiomaterials.8b00015

35. Leal-Marin S, Kern T, Hofmann N, et al. Human Amniotic Membrane: A review on tissue engineering, application, and storage. J Biomed Mater Res B Appl Biomater. Aug 2021;109(8):1198-1215. http://doi.org/10.1002/jbm.b.34782

36. Harris AG, Salih T, Ghorbel MT, Caputo M, Biglino G, Carrabba M. Biological Scaffolds for Congenital Heart Disease. Bioengineering (Basel). Jan 02 2023;10(1)http://doi.org/10.3390/bioengineering10010057

37. Alamri RM, Dohain AM, Arafat AA, et al. Surgical repair for persistent truncus arteriosus in neonates and older children. *J Cardiothorac Surg*. May 11 2020;15(1):83. http://doi.org/10.1186/s13019-020-01114-1

38. Hrfi A, Ismail M, Mohammed MHA, et al. Outcome of truncus arteriosus repair: 20 years of single-center experience comparing early versus late surgical repair. *Cardiol Young*. Aug 2022;32(8):1289-1295. http://doi.org/10.1017/S104795112100408X

39. Garven E, Rodell CB, Shema K, et al. Tunable Blood Shunt for Neonates With Complex Congenital Heart Defects. Front Bioeng Biotechnol. 2021;9:734310. http://doi.org/10.3389/fbioe.2021.734310

40. Yacoub MH, Hosny H, Afifi A, et al. Novel concepts and early results of repairing common arterial trunk. *Eur J Cardiothorac Surg*. Feb 18 2022;61(3):562-571. http://doi.org/10.1093/ejcts/ezab336

41. Motohashi Y, Shimada R, Sasaki T, et al. Development of a simple device enabling percutaneous flow regulation for a small vascular graft for a Blalock–Taussig shunt capable of flow regulation: complete translation of an original article originally published in Pediatric Cardiology and Cardiac Surgery (154–159, 2016: vol. 32). Gen Thorac Cardiovasc Surg. Mar 2018;66(3):145-149. http://doi.org/10.1007/s11748-017-0860-3

42. Douglas WI, Moore KB, Resig PP, Mohiuddin MW. The adjustable systemic-pulmonary artery shunt provides precise control of flow in vivo. ASAIO J. 2010;56(1):73-6. http://doi.org/10.1097/MAT.0b013e3181c83965

43. Forman J, Beech R, Slugantz L, Donnellan A. A Review of Tetralogy of Fallot and Postoperative Management. *Crit Care Nurs Clin North Am*. Sep 2019;31(3):315-328. http://doi.org/10.1016/j.cnc.2019.05.003

44. Smith CA, McCracken C, Thomas AS, et al. Long-term Outcomes of Tetralogy of Fallot: A Study From the Pediatric Cardiac Care Consortium. *JAMA Cardiol*. Jan 01 2019;4(1):34-41. http://doi.org/10.1001/jamacardio.2018.4255

45. Barron DJ, Jegatheeswaran A. How and When Should Tetralogy of Fallot be Palliated Prior to Complete Repair? *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2021;24:77-84. http://doi.org/10.1053/j.pcsu.2021.02.002

46. Karl TR. Tetralogy of fallot: a surgical perspective. *Korean J Thorac Cardiovasc Surg*. Aug 2012;45(4):213-24. http://doi.org/10.5090/kjtcs.2012.45.4.213

47. Nam JG, Lee W, Jeong B, et al. Three-Dimensional Printing of Congenital Heart Disease Models for Cardiac Surgery Simulation: Evaluation of Surgical Skill Improvement among Inexperienced Cardiothoracic Surgeons. Korean J Radiol. May 2021;22(5):706-713. http://doi.org/10.3348/kjr.2020.0682

48. Balzer D. Pulmonary Valve Replacement for Tetralogy of Fallot. *Methodist Debakey Cardiovasc J*. 2019;15(2):122-132. http://doi.org/10.14797/mdcj-15-2-122

49. Hoelscher SC, Doppler SA, Dreßen M, Lahm H, Lange R, Krane M. MicroRNAs: pleiotropic players in congenital heart disease and regeneration. J Thorac Dis. Mar 2017;9(Suppl 1):S64-S81. http://doi.org/10.21037/jtd.2017.03.149

50. O'Brien JE, Kibiryeva N, Zhou XG, et al. Noncoding RNA expression in myocardium from infants with tetralogy of Fallot. Circ Cardiovasc Genet. Jun 2012;5(3):279-86. http://doi.org/10.1161/CIRCGENETICS.111.961474

51. Amirghofran A, Edraki F, Edraki M, et al. Surgical repair of tetralogy of Fallot using autologous right atrial appendages: short- to mid-term results. *Eur J Cardiothorac Surg*. Apr 13 2021;59(3):697-704. http://doi.org/10.1093/ejcts/ezaa374

52. Morray BH. Ventricular Septal Defect Closure Devices, Techniques, and Outcomes. *Interv Cardiol Clin*. Jan 2019;8(1):1-10. http://doi.org/10.1016/j.iccl.2018.08.002

53. Porrello ER, Johnson BA, Aurora AB, et al. MiR-15 family regulates postnatal mitotic arrest of cardiomyocytes. Circ Res. Sep 02 2011;109(6):670-9. http://doi.org/10.1161/CIRCRESAHA.111.248880

54. Zhao Y, Samal E, Srivastava D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. Nature. Jul 14 2005;436(7048):214-20. http://doi.org/10.1038/nature03817

55. Xu HS, Inamdar KY, Firoj KM, Zhao WZ. Perventricular device closure of ventricular defects in 235 young children: a single-center experience. *J Thorac Cardiovasc Surg*. Dec 2013;146(6):1551-3. http://doi.org/10.1016/j.jtcvs.2013.08.004

56. Adan A, Eleyan L, Zaidi M, Ashry A, Dhannapuneni R, Harky A. Ventricular septal defect: diagnosis and treatments in the neonates: a systematic review. *Cardiol Young*. May 2021;31(5):756-761. http://doi.org/10.1017/S1047951120004576

57. Chen ZY, Lin BR, Chen WH, et al. Percutaneous device occlusion and minimally invasive surgical repair for perimembranous ventricular septal defect. *Ann Thorac Surg*. Apr 2014;97(4):1400-6. http://doi.org/10.1016/j.athoracsur.2013.12.027

58. Qiu H, Wen S, Ji E, et al. A Novel 3D Visualized Operative Procedure in the Single-Stage Complete Repair With Unifocalization of Pulmonary Atresia With Ventricular Septal Defect and Major Aortopulmonary Collateral Arteries. *Front Cardiovasc Med*. 2022;9:836200. http://doi.org/10.3389/fcvm.2022.836200

59. Haas NA, Kock L, Bertram H, et al. Interventional VSD-Closure with the Nit-Occlud. *Pediatr Cardiol*. Feb 2017;38(2):215-227. http://doi.org/10.1007/s00246-016-1502-8

60. Ramcharan TKW, Goff DA, Greenleaf CE, Shebani SO, Salazar JD, Corno AF. Ebstein's Anomaly: From Fetus to Adult-Literature Review and Pathway for Patient Care. *Pediatr Cardiol*. Oct 2022;43(7):1409-1428. http://doi.org/10.1007/s00246-022-02908-x

61. Attenhofer Jost CH, Connolly HM, Dearani JA, Edwards WD, Danielson GK. Ebstein's anomaly. *Circulation*. Jan 16 2007;115(2):277-85. http://doi.org/10.1161/CIRCULATIONAHA.106.619338

62. Sainathan S, da Fonseca da Silva L, da Silva JP. Ebstein's anomaly: contemporary management strategies. *J Thorac Dis*. Mar 2020;12(3):1161-1173. http://doi.org/10.21037/jtd.2020.01.18

63. Holst KA, Connolly HM, Dearani JA. Ebstein's Anomaly. *Methodist Debakey Cardiovasc J*. 2019;15(2):138-144. http://doi.org/10.14797/mdcj-15-2-138

64. Shih MC, Tholpady A, Kramer CM, Sydnor MK, Hagspiel KD. Surgical and endovascular repair of aortic coarctation: normal findings and appearance of complications on CT angiography and MR angiography. *AJR Am J Roentgenol*. Sep 2006;187(3):W302-12. http://doi.org/10.2214/AJR.05.0424

65. Kouchoukos NT, Scharff JR, Castner CF. Repair of primary or complicated aortic coarctation in the adult with cardiopulmonary bypass and hypothermic circulatory arrest. *J Thorac Cardiovasc Surg*. Feb 2015;149(2 Suppl):S83-5. http://doi.org/10.1016/j.jtcvs.2014.07.071

66. Yousif A, Kloppenburg G, Morshuis WJ, Heijmen R. Repair of adult aortic coarctation by resection and interposition grafting. *Interact Cardiovasc Thorac Surg*. Oct 2016;23(4):526-30. http://doi.org/10.1093/icvts/ivw206

67. Charlton-Ouw KM, Codreanu ME, Leake SS, et al. Open repair of adult aortic coarctation mostly by a resection and graft replacement technique. *J Vasc Surg*. Jan 2015;61(1):66-72. http://doi.org/10.1016/j.jvs.2014.06.010