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REVIEW ARTICLE

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Tricuspid atresia: Where are we now?

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Abstract

Tricuspid atresia (TA) is a complex congenital heart disease that presents with cyanosis in the neonatal period. It is invariably fatal if left untreated and requires multiple stages of palliation. Early recognition and timely surgical intervention are therefore pivotal in the management of these infants. This literature review considers the pathophysiology, presentation, investigations, and classification of TA. Moreover, it discusses the evidence upon which the latest medical and surgical treatments are based, as well as numerous recent case reports. Further work is needed to elucidate the etiology of TA, clarify the role of pharmacotherapy, and optimize the surgical management that these patients receive.

KEYWORDS

congenital heart disease, management, palliation, tricuspid atresia

1 | INTRODUCTION

Tricuspid atresia (TA) is a cyanotic congenital heart disease (CHD) characterized by total agenesis of the tricuspid valve. It accounts for approximately 1% of all cases of CHD and its incidence, which is similar in both males and females,[1] is reported as ~0.1 per 1000 individuals.[2] This places it as the fourth most common cyanotic CHD after tetralogy of Fallot, transposition of the great arteries (TGA), and hypoplastic left heart syndrome.[2] Risk factors for TA include Down syndrome, poorly controlled diabetes, excess alcohol consumption during pregnancy, and a family history of CHD.[3]

TA is associated with high mortality without early intervention.[4] It is, therefore, important to recognize its presentations, order the relevant investigations, and initiate swift surgical management. This review discusses the pathogenesis, presentation, workup and management of patients with TA. In particular, the different surgical options and intraoperative techniques are described in detail.

2 | PATHOGENESIS

Although the underlying etiology of TA is poorly understood, it is known to arise due to a disruption of tricuspid valvulogenesis.[5] Physiological atrioventricular (AV) valvulogenesis is a multistep process involving the Wnt/β-catenin, bone morphogenetic protein/transforming growth factor-β, and Ras/extracellular-signal-regulated kinase (ERK) pathways.[6] Genetic mutations in these pathways have been proposed to underline certain cases of TA, such as a germline homozygous missense mutation in *RASA1*, which encodes a protein that regulates the Ras/ERK cascade.[5] Compound heterozygous missense mutations in the *NFATC1* gene, whose protein acts further downstream in the Ras/ERK pathway, have also been reported.[7] The familial recurrence of TA is thought to be extremely low,[8] although an autosomal recessive pattern of inheritance has been described in some cases.[9] Further research is required to elucidate the complex genetic control of valvulogenesis and how this is dysregulated in TA.

To best understand how these patients present, it is necessary to briefly describe the most common route of blood flow through a

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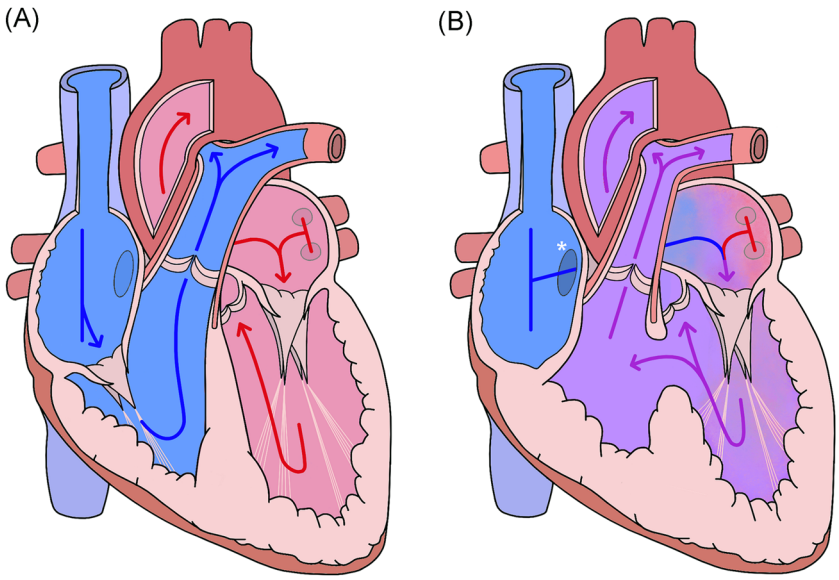

FIGURE 1 Blood flow in tricuspid atresia. A, Normal. B, TA. *Patent foramen ovale or ASD. ASD, atrial septal defect; TA, tricuspid atresia

heart with TA (Figure 1). In TA, the right atrium is separated from the hypoplastic right ventricle. This means that a patent foramen ovale or atrial septal defect (ASD) is required to enable deoxygenated blood from the systemic venous circulation to mix with oxygenated blood returning from the lungs.[10] Usually, this occurs in the left atrium, and the resultant partially oxygenated blood is then pumped out of the aorta by the left ventricle. To reach the right-sided outflow tract, this partially oxygenated blood can be shunted from left-to-right across a ventricular septal defect (VSD). It then leaves through the pulmonary trunk, which may or may not be stenosed at its entrance, or entirely hypoplastic. In some cases where a VSD is not present or there is significant pulmonary obstruction, the patient is reliant on a patent ductus arteriosus (PDA) to enable blood flow into the pulmonary circulation. While the cardiac output is mixed in TA, it may still provide sufficient oxygenation to minimize cyanosis if it contains a great enough proportion of oxygenated pulmonary venous return. The degree of pulmonary blood flow (PBF) is, therefore, the main determinant of cyanosis in these infants. This, in itself, is determined by the extent of pulmonary obstruction, the existence and size of a VSD, the relationship of the great arteries, and the presence of a PDA.[11]

3 | PRESENTATION

Around 50% of individuals with TA present with symptoms on the first day of life, with 80% being symptomatic by the first month.[4] Generally, two distinct presentations are observed. The first group of patients have high PBF due to left-to-right shunting across a VSD, a lack of pulmonary obstruction, and if present, TGA. They present with minimal cyanosis initially but go on to develop right-heart strain and cardiac failure in the first few weeks of neonatal life.[4] Patients typically exhibit fatigue, difficulties in feeding, failure to thrive, and recurrent respiratory tract infections. On examination, one may find tachypnea, tachycardia, hepatomegaly, and prominent neck venous pulsations. Splitting of the S2 heart sound and an S3 at the cardiac apex may also be heard, in addition to a variety of murmurs as described below.[11] Coarctation of the aorta commonly occurs in this subset of patients and may predispose to early heart failure.[4] In these cases, decreased femoral pulses may also be palpated.[11]

The second group of patients consists of those with reduced PBF and accounts for the majority of infants with TA.[12] This is usually due to pulmonary obstruction and/or a small or absent VSD.[4] These patients exhibit central cyanosis, tachypnoea and hyperpnoea within the first few days of life.[4] Clinically, their condition may be exacerbated by the closure of the ductus arteriosus, as this is an important means by which these infants get blood flow to their lungs. On examination, patients may have an attenuated right ventricular impulse and an "a" wave in their jugular venous pressure; however, no hepatomegaly or clinical signs of heart failure are observed at this stage.[4]

In both groups, murmurs are usually heard on auscultation of the precordium. At the lower left sternal border, a holosystolic murmur is often appreciated. This represents the underlying VSD and its intensity is inversely related to its size. For this reason, this murmur may not be heard in patients with a large VSD. At the pulmonic position, a continuous "machinery" murmur signifies a PDA, and at the upper left sternal border, infants with pulmonary stenosis may also have a systolic ejection murmur.[11] Careful and precise auscultation is, therefore, required to differentiate the mix of sounds that may be heard on examination.

4 | INVESTIGATIONS

Advancements in antenatal cardiac screening have resulted in as many as 67% of TA cases being diagnosed before birth in Wales (UK), though this may be up to 100% in other countries such as Italy.[13] However, in some places without national screening policies and limited health care resources, this figure may be comparatively lower.[13] The National

Health Service in the UK offers a routine fetal ultrasound scan between 18 and 22 weeks of gestation to detect congenital abnormalities.[14] If this is suggestive of CHD, a fetal echocardiogram can be used for subsequent diagnosis.[14] Antenatal diagnosis of CHD has been instrumental in reducing the mortality rates from cardiac compromise before scheduled neonatal cardiac surgery.[15]

If the TA is not identified during antenatal screening, it may be diagnosed shortly after birth. In the UK, newborns are routinely examined within 72 hours of birth for signs such as cyanosis and cardiac murmurs.[14] This involves pulse oximetry, which estimates systemic arterial oxygen saturations and provides a rapid, highly specific and moderately sensitive method of detecting critical CHDs, even in asymptomatic newborns.[16] Cyanotic CHD can also be distinguished from respiratory causes of cyanosis using high-flow oxygen. In addition, arterial blood gas analysis can provide information regarding ventilatory and metabolic status. This is particularly important in patients that present with severe disease, as it may identify hypercapnia and acidosis.[4] A full blood count, including hematocrit and hemoglobin, is also required to check for long-standing hypoxaemia.[17]

In TA, an electrocardiogram (ECG) typically shows left axis deviation in the frontal plane.[12] This is less commonly seen in TA patients with accompanying TGA.[12] There may also be tall and peaked P waves in lead II and the right chest leads (due to right atrial enlargement), increased amplitude of S waves in leads V1-2 and R waves in leads V5-6 (due to left ventricular hypertrophy), and decreased R waves in leads V1-2 and S waves in leads V5-6 (due to diminished right ventricular forces).[4] While these ECG features may not always be present, when they are identified in a patient with cyanotic CHD, they are virtually diagnostic of TA.[4]

Chest radiographs are routinely used in the workup of CHD. In TA, radiography can be used to categorize patients into groups of high or low PBF. Those with pulmonary oligemia often show a normal-sized heart, increased concavity in the region of the pulmonary artery segment, and a prominent right atrial shadow.[12] Conversely, those with increased PBF show cardiomegaly and prominent pulmonary vasculature.[12] Crucially, the distinction between increased and decreased pulmonary vasculature markings on chest radiographs, in addition to history-taking, physical examination and ECG, may be sufficient to diagnose TA.[12]

Generally, the definitive test in CHD diagnosis is echocardiography,[17] though the aforementioned investigations may be sufficient in some cases of TA. Two-dimensional echocardiography classically shows enlargements of the atria and left ventricle, a hypoplastic right ventricle, an atretic tricuspid valve, as well as ASDs, VSDs, and occasionally, TGA and/or aortic coarctation.[12] Doppler echocardiography can reveal shunting across septal defects and the presence of an obstructive pulmonary outflow tract, in addition to estimating pulmonary artery pressures.[12]

5 | CLASSIFICATION

Multiple classification systems have been described for TA based on valve morphology,[18] the radiographic appearance of pulmonary vascular markings,[19] and the great-artery relationships.[20] However, due to a lack of consistency between methods, a unified classification system was later proposed (Figure 2).[22] While the principle grouping is still based on the interrelationships of the great arteries, all categories are further subdivided according to the presence of other cardiac defects. Specifically, type III TA describes great-artery abnormalities other than dextro-TGA, including levo-TGA (L-TGA, subtype 1), double outlet right ventricle (subtype 2), double outlet left ventricle (subtype 3), anatomically corrected dextro-malposition of the great arteries (subtype 4), and anatomically corrected levo-malposition of the great arteries (subtype 5). In addition, all main types and subtypes can be described as "a," "b," or "c," referring to pulmonary atresia, pulmonary stenosis (or hypoplasia), or no pulmonary stenosis, respectively. Following this, the integrity of the ventricular septum is considered and other malformations may be described.[22] An example could therefore be written as type Ia TA with a large VSD.

6 | MANAGEMENT

6.1 | Initial management

Patients with TA require multiple cardiac surgeries to maximize longevity. These take a significant amount of time and resources to organize. Prostaglandin E1 (PGE1) can therefore be given in the meantime to maintain a PDA.[23] This is a potentially life-saving intervention in cases of TA with reduced PBF, as these infants rely on a PDA for the pulmonary and systemic circulations to mix.[24] Without prostaglandins, the ductus arteriosus typically closes within 2 to 3 days of birth, leading to a worsening of symptoms. However, a recent systematic review published by the Cochrane Database has highlighted the lack of randomized controlled trials (RCTs) focusing on the safety and efficacy of PGE1 in neonates with ductal-dependent cardiac lesions.[24] In addition, the use of PGE1 in newborns has been associated with numerous adverse effects, such as fever (which could delay surgical management),[25] hypokalemia, hypotension,[26] apnea, and gastric outlet syndrome.[23] However, many of these side effects are manageable and should not deter clinicians from using PGE1 in newborns with CHD.[23]

In cases of TA with reduced PBF and cyanosis, patients may also undergo surgery to have a polytetrafluoroethylene conduit fitted between the right subclavian artery and right pulmonary artery.[27] This is known as a modified Blalock-Thomas-Taussig shunt (MBTS) and like PGE1, it also enables temporary mixing of the systemic and pulmonary circulations. The MBTS shunt differs from its predecessor, the original Blalock-Taussig shunt, as it uses a synthetic connection rather than a direct anastomosis between arteries.[28] Although the MBTS is commonly used in the treatment of CHD and has been validated in TA, it is associated with high in-hospital mortality, especially in patients less than 3 kg.[29] Reports of refractory cardiac arrest following shunt insertion have even been described.[27] Ductal stenting is a reasonable alternative to the MBTS, as it is associated with similar or improved pulmonary artery growth, fewer complications, a shorter length of stay, and improved survival.[30]

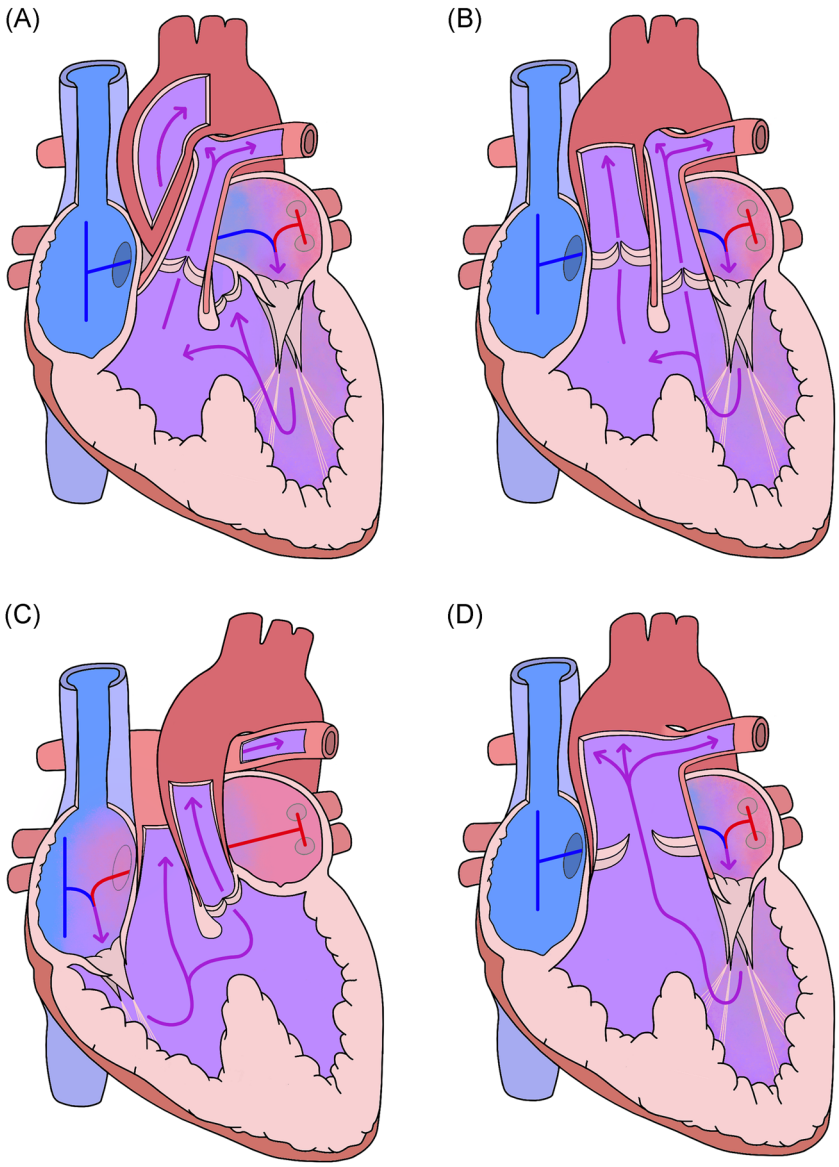

FIGURE 2 Classification of tricuspid atresia. A, TA with normal great arteries (69%). B, TA with D-TGA (28%). C, TA with great-artery position other than dextro-transposition. L-TGA (subtype 1) is shown (3%). D, TA with persistent truncus arteriosus. Data from Eidmen et al.[21]. D-TGA, dextro-transposition of the great arteries; L-TGA, levo-transposition of the great arteries; TA, tricuspid atresia

Conversely, patients with TA and high PBF may benefit from pulmonary artery banding (PAB) to reduce blood flow to the lungs.[31] This may help us to prevent pulmonary plethora, right-heart strain, and subsequent cardiac failure. Initially, this was carried out using a Gore-Tex (non-stretchable) band. However, as the circulation underwent rapid and unpredictable growth, this often became too tight before the intended removal surgery.[32] Dilatable alternatives have therefore been developed.[32] Absorbable pulmonary bands have also been described in the literature, with one case reporting complete absorption within 5 months.[33] By this time, the patient's VSD had narrowed, therefore sustaining this reduction in PBF and avoiding a second operation or the need for pulmonary arterioplasty.[33] It should be noted, however, that variable rates of resorption may result in unpredictable PBF.[34] This may make preparations for definitive management less adequate. Similarly, subaortic stenosis and subsequent aortic arch obstruction after PAB may also complicate further procedures.[31] In cases with a persistent truncus arteriosus, either bilateral PAB,[35] or unifocalization of the pulmonary arteries and the placement of a BTS shunt can be used.[36]

Another subgroup to be aware of is those suffering from both TA and TGA. These patients commonly develop subaortic stenosis and outflow tract obstruction, which may require VSD enlargement and resection of the subaortic conus.[37] However, as this can result in complications such as heart block, an alternative method known as the Damus-Kaye-Stansel (DKS) procedure is often used.[37] This involves an end-to-side anastomosis between the main pulmonary artery and ascending aorta.[38] More recently, a double-barrel variant of the DKS procedure has emerged, in which the main pulmonary artery and initial aortic segment lead into a single ascending aorta.[38] This technique has been shown to be superior over its predecessor in reducing the amount of pulmonary regurgitation before definitive management.[38]

6.2 | Definitive management

6.2.1 | Preparing for the Fontan procedure

The Fontan procedure is a method of redirecting systemic venous blood directly into the pulmonary arteries without passing through the right ventricle. This is a palliative procedure that bypasses the atretic tricuspid valve. However, establishing a Fontan circulation usually involves multiple stages of repair.

The first stage, known as the bidirectional Glenn procedure, is carried out between 4 and 6 months of life.[39] It involves the separation of the superior vena cava (SVC) from the right atrium and the formation of an end-to-side anastomosis between the SVC and right pulmonary artery. The proximal pulmonary trunk is also divided or ligated to prevent retrograde blood flow down the outflow tract.[40] This arrangement allows blood to flow down the SVC and bidirectionally into both lungs, hence the name of this procedure (Figure 3A).[41] This distinguishes the bidirectional Glenn from its predecessor, the original Glenn procedure, which is based on unidirectional flow.[42] The resultant circulation bypasses the right side of the heart, therefore reducing ventricular load, myocardial work, and offsetting heart failure.[42] The bidirectional Glenn is not without its risks though; case studies have reported pulmonary vein stenosis and in the context of main pulmonary artery ligation, massive aneurysm of the right ventricular outflow tract.[40,43]

Another method of creating this cavopulmonary anastomosis is the hemi-Fontan procedure. This is similar to the bidirectional Glenn method but the connection between the SVC and right atrium is maintained and instead, a homograft is sewn at the SVC-right atrium connection, thereby reducing systemic blood flow to the right atrium.[41] Following either of these approaches, the Fontan procedure can be attempted.

It should be noted though that most deaths in TA occur during the periods between operations.[27] This is increased for infants with a low weight at the time of their first cardiac surgery.[44] A greater emphasis on identifying other risk factors for increased mortality during this time is required to improve interstage outcomes.

6.2.2 | Performing the Fontan procedure

The final surgical step is the Fontan procedure, which completes the Fontan circulation and allows for improved PBF. This is usually carried out between 18 and 36 months of age.[39] Completing the Fontan circulation reduces volume overload, preserves ventricular functioning, and reduces the degree of atrial dilatation.[45,46] It is well known that performing this surgery post-hemi-Fontan reduces mortality rates in neonates.[47]

Originally, the Fontan operation involved correcting the ASD and creating an anastomosis between the proximal end of the right pulmonary artery and right atrial appendage. This allowed blood to flow from the inferior vena cava (IVC) directly to the lungs via the right atrium (Figure 3B).[48] It has since been modified and there are two common variants used in practice today. The intracardiac lateral tunnel technique involves using a prosthetic patch to create a channel from the IVC, through the right atrium, through the distal part of the SVC and into the right pulmonary artery (Figure 3C).[49] Another method uses an extracardiac conduit to directly connect the IVC and the right pulmonary artery (Figure 3D).[49] The outcomes of these techniques are generally similar, with a recent systematic review concluding that there are no significant differences in the short-term incidence of post-Fontan arrhythmias between the lateral tunnel and extracardiac conduit.[50] However, the authors note that the latter may be preferred and has the potential to "significantly lower the risk of late arrhythmias after Fontan surgery".[50] It can also minimize the need for cardiopulmonary bypass or remove it completely, which may help us to preserve ventricular and pulmonary function.[51] Khairy and Poirier[49] point out that these benefits are theoretical and remain to be proven by clinical trials.

6.2.3 | Outcomes after the Fontan procedure

Survival after the Fontan procedure for TA has been reported as 90% at the age of 1 month, 81% at 1 year, 70% at 10 years, and 60% at 20 years.[52] This is in comparison to survival rates of 74% at 1 month, 58% at 1 year, and 52% at 4 years for hypoplastic left heart syndrome.[53] However, while the Fontan procedure can help us to extend the lives of patients with TA, it is a palliative operation and results in a nonphysiological circulation. It is performed with the intent of normalizing PBF, but in some cases, it can actually result in increased PBF, increased pulmonary vascular resistance, and ventricular dysfunction.[54] A recent meta-analysis has shown that the overall mortality rate across all variants of the Fontan procedure is 8.3% at a mean follow-up time of 8.9 years.[55] Schwartz et al[55] also found that patients treated by the original Fontan method had significantly higher mortality rates at this same endpoint. To reduce the likelihood of this occurring, a fenestrated atrial baffle can be used to alleviate the increased pulmonary pressures, especially in those with pulmonary stenosis or abnormal pulmonary anatomy (Figure 3D).[45,54]

It should be noted that survival following the Fontan procedure has improved over the last 30 years due to surgical advancements, patient selection, and staging of the Fontan circulation.[51] The average life expectancy of patients is now 35 to 40 years, although this is still in contrast to 70 to 80 years in the general population.[56] As a result of post-Fontan patients living longer, late complications are becoming increasingly appreciated.[57] These include protein-losing enteropathy,[57] thromboembolism, and arrhythmias, with the latter being a major risk factor for morbidity.[51] Eventually, many of these patients require cardiac transplantation. In fact, 70% to 80% of patients transplanted for CHDs are those with univentricular systems such as TA.[58] This results in similar long-term survival compared to those transplanted for other reasons.[58]

It is important that clinicians fully explain the outcomes of the Fontan procedure, as this may influence the parent's decision to consent to this operation. It has been reported that due to the

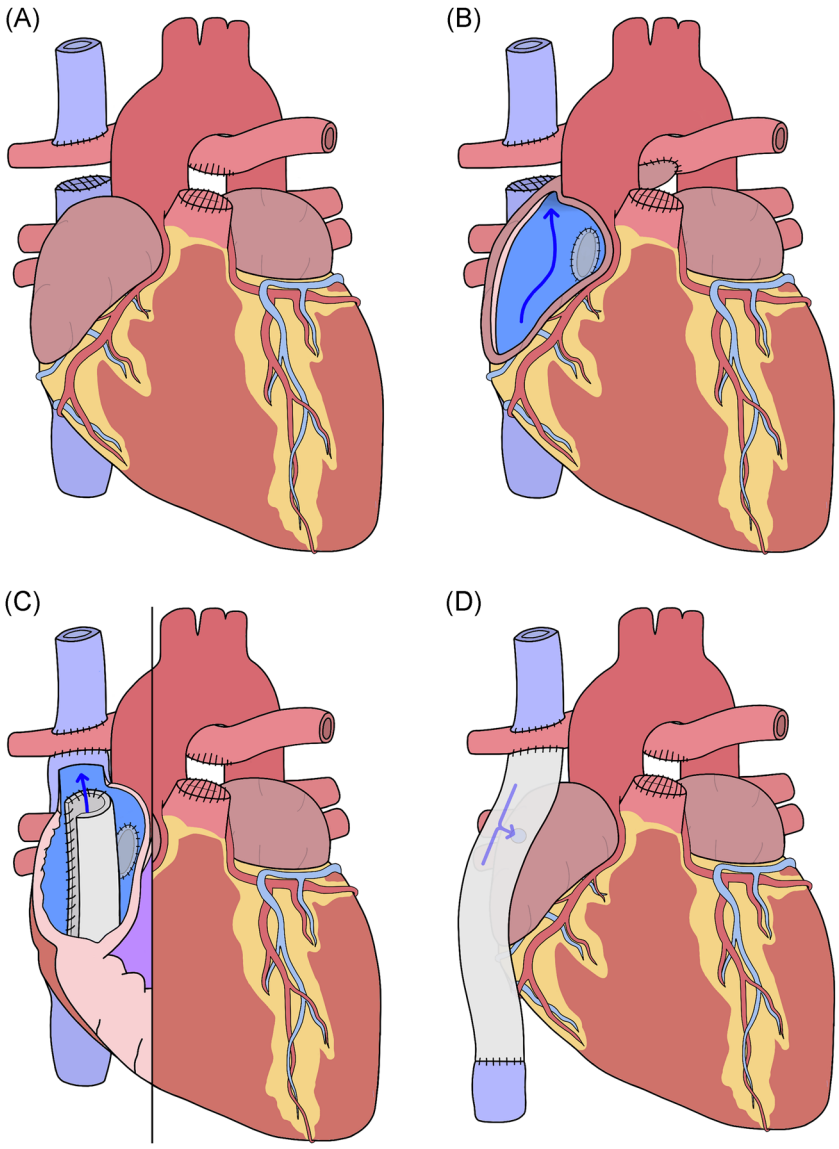

FIGURE 3 Surgical repair of tricuspid atresia. A, Bidirectional Glenn procedure. B, Original Fontan procedure. C, Intra-atrial lateral tunnel Fontan technique. D, Extracardiac conduit Fontan technique with fenestration

long-term complications associated with a Fontan circulation, some parents prefer end-of-life care at a younger age.[59] In their view, this prevents the prolongation of their child's suffering, however, this remains a highly controversial issue.[59]

6.3 | Postoperative management

Angiotensin-converting enzyme inhibitors (ACEi) may also help in managing TA by inhibiting the production of angiotensin II and its vasoconstrictive effects, thereby decreasing systemic vascular resistance (SVR). This may be especially useful in those with Fontan circulations, as it is believed that the hemodynamic changes that occur in these patients result in activation of the sympathetic nervous system, an increased SVR, and a decreased cardiac output.[60] In line with this, ACEi improves cardiac function and reduce the degree of ventricular hypertrophy in children with volume overload.[61] However, there are no current guidelines for their use in functionally univentricular neonates.[62] Only one large-scale double-blinded RCT has been performed to date focusing on the use of ACEi in univentricular CHD.[63] In this study, the authors administered enalapril to 230 infants with single ventricle defects in the first year of life and found no significant differences in ventricular function or heart failure severity at 14 months.[63] The use of ACEi also extends to reducing AV valve regurgitation and pleural effusions in post-Fontan patients.[62,64]

Where post-Fontan arrhythmias occur, clinicians may be tempted to use antidysrhythmic medications. However, patients are often resistant to these, and catheter ablation is associated with a lower recurrence of atrial tachyarrhythmia.[65] Early referral to a specialty center should therefore be considered.[65] Postoperative protein-losing enteropathy can be treated using the dietary limitation of long-chain triglycerides, medications including diuretics and corticosteroids, as well as surgical management, such as a Fontan fenestration.[57]

More recently, it has been shown that selective glue embolization of leaking intestinal lymphatic trunks led to a prompt reversal of PLE.[66] Third, post-Fontan patients are at a high risk of thrombus formation. As such, they should receive individualized thromboprophylaxis. According to a recent multicenter study, antiplatelet agents result in a lower incidence of combined thromboembolic events than anticoagulation for this purpose.[67] Other post-Fontan complications are reviewed elsewhere.[57]

6.4 | Other anatomical variants

As described above, TA can occur alongside various other cardiac defects. Many of these are seen in day-to-day practice, such as VSDs or less commonly, TGA.[21] However, other rarer anatomical variants can also occur. These are worth discussing as they often demand nonroutine surgical management. One such variant is the presence of an interrupted IVC in patients with TA (or other functionally univentricular CHDs). This may occur below the level of the hepatic veins, such that they are still able to drain into the RA. These cases are treated via the Kawashima operation, which involves anastomosing the SVC and azygos veins with the pulmonary arteries.[68] Interestingly, this same procedure has been used to treat two children with TA and bilateral SVCs.[69] In this study, the authors conclude that the Kawashima operation is a safe and effective method of treating bilateral SVCs and enables preparation for future total cavopulmonary shunting.[69]

Milovanovic et al[70] report the rare occurrence of TA with an aortopulmonary window or connection between the aorta and pulmonary trunk. They subsequently suggest that the initial stage of palliation should involve full separation of the aorta and pulmonary artery using patch angioplasty.[70] Following this, a systemic-to-pulmonary shunt (such as the MBTS) is placed, with the aim of establishing a full Fontan circulation in the future.

7 | CONCLUSION

TA is a complex CHD that is associated with significant morbidity and mortality. It is important that clinicians are aware of its variable presentations, the investigations that are required in these patients, and the multiple steps involved in surgical palliation. There is a need for future studies focusing on the pathophysiology, interstage outcomes, and postoperative or long-term management of patients with TA. This is likely to become increasingly more important as patient longevity improves.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

AMHAMM researched the preoperative sections. HK researched the classification section. ASS researched the management sections. Both ASS and HK contributed equally to the writing of the manuscript. All co-authors contributed to editing. HK created all figures.

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