Review Article

Narrative review of single ventricle: where are we after 40 years?

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Background and Objective: Key medical and surgical advances have been made in the longitudinal management of patients with "functionally" single ventricle physiology, with the principles of Fontan circulation applied to other complex congenital heart defects. The purpose of this article is to review all of the innovations, starting from fetal life, that led to a change of strategy for single ventricle.

Methods: Our literature review included all full articles published in English language on the Cochrane, MedLine, and Embase with references to "single ventricle" and "univentricular hearts", including the initial history of the treatments for this congenital heart defects as well as the innovations reported within the last decades.

Key Content and Findings: All innovations introduced have been analyzed, including: (I) fetal diagnosis and interventions, in particular to prevent or reduce brain damages; (II) neonatal care; (III) post-natal diagnosis; (IV) interventional cardiology procedures; (V) surgical procedures, including neonatal palliations, hybrid procedures, bidirectional Glenn and variations, Fontan completion, biventricular repair; (VI) peri-operative management; (VII) Fontan failure, with Fontan take-down and conversion, and mechanical circulatory support; (VIII) transplantation, including heart, heart and lung, heart and liver; (IX) exercise; (X) pregnancy; (XI) adolescents and adults without Fontan completion; (XII) future studies, including experimental studies on animals, computational studies, genetics, stem cells and bioengineering.

Conclusions: These last 40 years have certainly changed the course of natural history for children born with any form of "functionally" single ventricle, thanks to the improvement in diagnostic and treatment techniques, and particularly to the increased knowledge of the morphology and function of these complex hearts, from fetal to adult life. There is still much left unexplored and room for improvement, and all efforts should be concentrated in collaborations among different institutions and specialties, focused on the same matter.

Keywords: Congenital heart defects; congenital heart surgery; Fontan procedure; single ventricle; univentricular heart

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Introduction

Background

Over the past 40 years, key medical and surgical advances have been made in the longitudinal management of patients with "functionally" single ventricle physiology, from prenatal diagnosis to interventions for failing Fontan in adulthood. Since the introduction of the Fontan procedure for tricuspid atresia (1), principles of the Fontan circulation have been applied to other complex congenital heart defects with "functionally" univentricular heart. Previously considered as inoperable, scant information was available on the natural history of children born with a single ventricle 40 years ago (2), before the advent of electronic record and large databases (3-5). prompting the publication of the article "Univentricular heart: can we alter the natural history?" (6).

Rationale and knowledge gap

The purpose of this article is to review all of the innovations that led to a change in the longitudinal management of patients born with single ventricle from fetal to adulthood care.

Objective

The purpose of our review is to emphasize that there aren't hotspots in this longitudinal management, but the decision-making process have to be always conducted keeping in mind the best treatment for each patient in each specific point of their observation.

Methods

The literature review included all articles found published in English language on the Cochrane, MedLine, and Embase, with our research strategy summarized in *Table 1*. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-573/rc).

Fetal diagnosis

Advancements in prenatal ultrasound technology was among the first substantial achievements for congenital heart defects, permitting accurate and early fetal echocardiographic detection. Currently, virtually almost all heart malformations are recognizable between the 16th and 18th week of pregnancy, with sensitivity greater than 96% and specificity approaching 100% (7,8). In addition to providing information on the presence of associated non-cardiac malformations (9) such as *situs inversus* in heterotaxy syndrome (10), prenatal echocardiography and cardiac MRI better delineates complex congenital heart defects, including "functionally" single ventricle physiology (11-15). Accurate prenatal imaging and diagnosis has been a necessary factor in conducting clinical trials for fetal interventional cardiology procedures (16-18), and have also resulted in planned, coordinated deliveries for babies with complex congenital heart defects at tertiary referral centers with the appropriate level of interventional and surgical care, resulting in improved survival outcomes (11-13,15,19-22).

Fetal brain injury

As survival rates improve for patients with complex congenital heart defects, increased rates of neurodevelopmental impairment has become better recognized in survivors. This has brought about increasing attention and efforts to optimize surgical and perioperative care, as well as improving detection and timing of neurological injury and assessing long-term outcomes (23). Children born with single ventricle physiology have the highest rates of neurodevelopmental impairment due to multiple patient and environmental factors including genetic syndromes and socioeconomic factors (24). Several studies have provided evidence suggestive of brain injury occurring during fetal development, including an alarming rate of brain lesions in the presence of cyanotic congenital heart defects before cardiac surgery (25-27). The mechanism is attributed to reduced oxygen delivery to the brain relative to fetuses with normal cardiac anatomy beginning from the completion of cardiac structural development at approximately 6 weeks of gestational age until the remainder of the gestation period (28,29). Clinical manifestations of neurologic compromise before surgery in infants with single ventricle physiology include smaller head circumference, reduced brain volume, and altered neurobehavior (25,27,30,31). Severe abnormalities in the implantation and morphology of the placenta along with higher rates of maternal pre-eclampsia and in-utero growth restriction has also been observed in the presence of pregnancies affected by congenital heart defects (32,33). Placental insufficiency suggests another cause of hemodynamic compromise to

Table 1 The search strategy summary

Items	Specifications
Date of search	January to September 2022
Database and other sources searched	Cochrane, Embase, MedLine
Search terms used	Single ventricle, Univentricular hearts
	Fetal life, Neonatal care
	Interventional cardiology, Surgery
	Palliations, Cavo-pulmonary connections, Fontan, Fenestration, Ventricular septation
	Peri-operative management, Fontan failure
	Transplantation, Mechanical circulatory support
	Pregnancy, Exercise, Adolescents/Adults
	Experimental studies, Computational studies
	Genetics, Stem Cells, Bioengineering
Timeframe	1971 to 2022
Inclusion criteria	Full articles, English language
Exclusion criteria	Abstracts, non-English language
Selection process	Independently conducted by AFC and TOF
Consensus	Approval of final list of references (AFC, TOF, JDS)

the developing brain, and potential shared developmental pathways between the placenta, heart, and brain are currently under investigation (32,33). Some institutions have introduced maternal hyperoxygenation as a potential therapeutic to improve oxygen delivery to the brain after the fetal diagnosis of cyanotic congenital heart defects (34). However, studied outcomes have included alterations in left-sided cardiac structures, cerebrovascular response, and fetal brain development (35-43). Current investigations are actively recruiting to further study safety and efficacy of the maternal hyperoxygenation.

Neonatal care

The initial neonatal treatment depends on the specific type of single ventricle physiology with main variables including ductal-dependent pulmonary or systemic circulation, reduced or increased pulmonary blood flow, obstructed pulmonary venous connections, restrictive interatrial communication, and obstructed systemic blood flow. Since the 1970s, prostaglandin E_1 infusion has been used to maintain ductal-dependent circulation in newborns (44,45) The availability of prostaglandin E_1 at hospitals have been associated with decreased neonatal morbidity by permitting the stable transfer of newborns with suspected congenital heart defects to a cardiac surgical center (46). Continuous prostaglandin E_1 infusion has also permitted more time after delivery for optimal surgical planning and even delay surgery for growth in preterm or growth-restricted neonates (47).

Post-natal diagnosis

Over the past decade, the field has also seen significant advances in the quality of postnatal diagnosis. The introduction of technological innovations such as three-dimensional echocardiography (48,49) and global longitudinal strain analysis of single ventricle physiology (50) using low radiation-dose computed tomography (51-53) can provide accurate anatomic delineation of congenital heart defects. Functional assessment of myocardial function, in addition to the echocardiographic investigations, with magnetic resonance imaging (54,55) and the introduction of techniques merging different diagnostic imaging modalities (56) facilitate operative decision-making, together with 3-D modeling

and printing of the heart structures (57,58), as well as computational design of the planned surgical procedure with evaluation of the obtainable sizes of ventricular inflows/outflows and ventricular volumes (59).

Interventional cardiology procedures

In single ventricle physiology with ductal-dependent pulmonary blood flow, ductal stenting is an interventional cardiology procedure with beneficial outcomes (60-64). The presence of an intact atrial septum or highly restrictive interatrial communication in neonates with functionally single ventricle, including hypoplastic left heart syndrome, is a very high-risk situation requiring emergency catheter-based intervention and/or surgical procedure (65-68). Fortunately, for many neonates, this situation can be anticipated in the modern era with fetal echocardiography, with the fetal pulmonary venous Doppler detecting a severely restrictive interatrial communication (67). In the presence of obstructed pulmonary venous drainage, the reason for elevated mortality and morbidity has been attributed to severe hypertension in the pulmonary veins, causing either disorder of the fetal lung maturation with fibroelastosis of the alveolar septal parenchyma (68), increased medial thickness (arterialization) of the pulmonary veins and lymphangiectasis of the lung parenchyma (67-70), or underdevelopment of the small pulmonary arteries with or without associated alveolar changes (65). To control the excessive pulmonary blood flow, an interventional cardiology technique using flow restrictors was first studied in animal experimental studies (71) and have now been successfully introduced in the clinical practice (72).

Surgical procedures

As in interventional cardiology, the surgical approach depends upon the specific type of single ventricle, any associated cardiovascular malformations, and the subsequent pathophysiology. In single ventricle with reduced pulmonary blood flow, the most frequently utilized surgical option was, and still remains, a modified Blalock-Taussig shunt (73,74). In neonates with single ventricle and unrestricted pulmonary blood flow, the surgical alternative to catheter-implantable flow restrictors is still pulmonary artery banding and has advantages of reducing distal pulmonary artery pressure and maintaining the possibility for future cavo-pulmonary connections. Pulmonary artery banding can be performed using conventional techniques (75), with an adjustable system (76), and clinical successful outcome have been reported with the telemetrically adjustable FloWatch® (77).

In hypoplastic left heart syndrome, the surgical neonatal approach is the Norwood procedure, either with a modified Blalock-Taussig shunt (78) or with a Sano right ventricle to pulmonary artery conduit (79) with recent improvement in results (80,81). The Sano conduit has utilized either a ring reinforced tubular prosthesis (82), stent-less pulmonary valved conduit (83), or valved femoral venous homograft (84). The type of Sano conduit used is still primarily based upon institutional and surgeon preferences and will require longer follow-up to determine efficacy (85).

The best timing for a Norwood procedure is still a matter of debate and will be discussed later in this review in the section on hybrid procedures.

For newborns with single ventricle physiology, ventriculo-arterial discordance and subaortic stenosis, hypoplasia of ascending aorta and aortic arch, various surgical options were introduced, classically involving early pulmonary banding and aortic arch reconstruction, with or without the enlargement of restricted bulbo-ventricular foramen, or the Damus-Kaye-Stansel procedure, associated with a new source of pulmonary blood flow, either with modified Blalock-Taussig shunt or with Sano right ventricle to pulmonary artery conduit (6,86-92). An alternative approach introduced later was a palliative arterial or ventricular switch, both procedures requiring a longer aortic cross clamp times compared to other options but preserving systolic and diastolic ventricular function and providing a superior anatomic arrangement for the subsequent surgical stages (93-96). Obstructed pulmonary venous connections is a quite rare but extremely severe complication in neonates with single ventricle physiology (97-101), but with proper pre- and post-operative imaging, recurrence can be monitored with reasonable outcomes (102).

Hybrid procedures

The "hybrid" approach, consisting of bilateral pulmonary artery banding, atrio-septostomy and ductal stent, was first introduced by a team in Giessen, Germany. In the beginning, the hybrid approach was utilized only for the high-risk patients, but eventually offered to others with satisfactory outcomes (103-109). Recently, for neonates with hypoplastic left heart structures in critical condition due to pulmonary over-circulation and insufficient systemic perfusion with subsequent multi-organ failure (110), we

adopted this policy, deferring the Norwood procedure and the required cardiopulmonary bypass in neonates with depleted metabolic and functional reserves. All organs, including myocardium, brain, kidneys, liver, and lungs are allowed to recover, thus mitigating the insult of organ injury from diminished oxygen delivery (110).

Generally, the staged surgeries consist of three steps, the first being a palliative procedure in which the systemic and pulmonary circulations are usually placed in parallel; the second stage consisting of a superior cavo-pulmonary anastomosis (or bidirectional Glenn); and the final stage being conversion to a total cavo-pulmonary connection (Fontan physiology). Following the first stage palliation for single ventricle, unstable hemodynamics contributes to morbidity and mortality in the inter-stage period prior to the second stage, particularly for hypoplastic left heart syndrome (111,112). This issue has been best managed with either a lengthy hospitalization while awaiting the second stage, or discharge home through a strict continuous monitoring program (113,114).

Bidirectional Glenn

The *classical Glenn procedure* consisting of an end-to-side anastomosis of the divided superior vena cava to the right pulmonary artery, separated from the pulmonary artery bifurcation (115,116), despite early positive outcomes including relief of cyanosis, was later abandoned because of the high incidence of pulmonary arteriovenous malformations (117-121). The *bidirectional Glenn*, introduced 50 years ago (122) but popularized in more recent years (123,124), consists of the division of the superior vena cava in correspondence of the cavo-atrial junction (preserving the sinus node and its artery) and its end-to-side anastomosis to the upper aspect of the right pulmonary artery, preserving the pulmonary arteries continuity and bilateral lung perfusion. Other advantages of the *bidirectional Glenn* include: (I) increased effective pulmonary blood flow by deviating the most desaturated blood (the superior vena cava return) directly to the lungs; (II) preparation for later Fontan completion without any period of myocardial ischemia; (III) potential for growing, being a direct anastomosis between two native vessels. Furthermore the *bidirectional Glenn* avoids the single stage modified Fontan procedure where the single ventricular chamber must adapt to an abrupt reduction in ventricular filling, with subsequent reduced ventricular compliance and poor functioning of the Fontan circulation (125-128).

In patients with a persistent left superior vena cava, a bilateral bi-directional Glenn procedure is required (129,130).

The bi-directional Glenn procedure can generally be performed at 3–6 months of life, when the pulmonary vascular resistance is usually sufficiently low.

Hemi-Fontan

A surgical alternative to the bidirectional Glenn is the *hemi-Fontan* procedure, consisting of connection of the superior vena cava and the superior portion of the right atrium to both pulmonary arteries, augmentation of the central pulmonary arteries, occlusion of the inflow of the superior vena cava to the right atrium and elimination of the other sources of pulmonary blood flow. The hemodynamics is similar to a bi-directional Glenn procedure except all other sources of pulmonary blood flow are eliminated, avoiding ventricular volume overload. However, for patients with hypoplastic pulmonary arteries this may be a disadvantage since only 40% of the systemic venous return perfuses the pulmonary circulation until the Fontan completion. This potential disadvantage could be compensated by direct enlargement of the central pulmonary arteries, requiring cardiopulmonary bypass with aortic cross clamp, biological or prosthetic materials for central pulmonary arteries augmentation, and suturing lines in proximity to the sinus node or its artery posing a risk for supraventricular arrhythmias. Later conversion is possible to a total cavo-pulmonary connection with lateral tunnel technique, sometimes even without cardiopulmonary bypass (131-133).

Super-Glenn

Insufficient pulmonary blood flow may be increased by the addition of a small systemic-to-pulmonary artery shunt, procedure called super-Glenn (134-136). With the expanding indication for biventricular recruitment, the super-Glenn is a potential approach leaving biventricular recruitment as a future option (137).

Fontan completion

After the initial technique described for tricuspid atresia (1), the Fontan circulation has evolved in technique, beginning from the right atrial to pulmonary connection (6,138-140), to right atrial to right ventricular connection for patients with tricuspid atresia (141-144), to tricuspid valve exclusion for patients with single ventricle (6,145), to now the two

surgical techniques most frequently used: the lateral tunnel (146,147), and the extra-cardiac conduit (148-150). Improvements in intra-operative techniques, as well of the available materials, has allowed accomplishment of Fontan completion while the heart continues to beat, therefore avoiding myocardial ischemia (151), or even without requiring cardiopulmonary bypass (152).

And after a long period without using any valve in the Fontan circulation, the utilization of a biological valve has been reintroduced between inferior vena cava and the pulmonary circulation (153), and bioengineered conduits have also been used for the same purpose (154). Computational simulations studying the distribution of the cavo-pulmonary blood flow has led to the use of an inverted Y-graft to separate the venous return of the inferior vena cava between right and left lung (155). For patients with interruption of the inferior vena cava and systemic venous drainage of the inferior part of the body through the superior vena cava, Kawashima proposed the anastomosis of the superior vena cava end-to-side to the right pulmonary artery, exactly as in the bidirectional Glenn, creating a version of Fontan completion in one stage (156). Improvement in outcomes have resulted in expansion of indication for Fontan completion to patients previously not considered suitable candidates (157-159).

Fenestration

An issue still without generalized agreement in approach is the Fontan fenestration. An "adjustable atrial septal defect" was first introduced by Hillel Laks (160,161) to temporarily reduce excessively elevated systemic venous pressure after a Fontan procedure and reduce the immediate post-operative complications. Since then, it has been renamed "fenestration" by Nancy D. Bridges (162,163), and universally adopted to define a surgically created communication between the diverted systemic venous return and the lower pressure pulmonary atrium using both surgical techniques utilized for Fontan completion, the lateral tunnel and extracardiac conduit.

Early indications for a Fontan fenestration were limited to high-risk candidates to reduce the systemic venous pressure resulting in increased lymphatic drainage with reduction in pleural effusions, and to provide adequate preload to the systemic single ventricle which reduced the post-operative low cardiac output state (164,165). The only prospective randomized study comparing patients undergoing fenestrated versus non-fenestrated Fontan completion demonstrated a reduction in intensive care duration and hospital stay (166). The indication for fenestration was eventually extended to almost all patients, regardless the level of pre-operative risk, and became commonplace for Fontan completion. However, the early benefits of fenestration were at the expense of late complications such as lower systemic oxygenation with prolonged cyanosis and risk of long-term systemic thromboembolism. Additionally, some patients required a later intervention to close the fenestration to improve resting and exercise oxygenation, lower maximal heart rate during exercise, and increase exercise duration (167-171). As a result, fenestration became limited again to select patients facing increased risks of complications in the immediate post-operative period (172).

While two systematic literature reviews and meta-analyses on the early outcomes of a Fontan fenestration demonstrated mixed benefit in the immediate post-operative period (173,174), our meta-analyses on later outcomes showed patients required either late closure or creation/reopening of a fenestration made at the time of Fontan completion (175).

Since then, the pendulum has swung back with indications for Fontan completion now extending to different patient populations including patients with complex congenital heart defects. With the increasing complexity of patients undergoing a Fontan procedure, surgical centers have begun to reconsider the use of fenestration, and in some institutions with high-risk cases, it is used nearly universally (176). The altered hemodynamics in Fontan patients continues to be investigated using mathematical and computational fluid dynamic models comparing those with and without a fenestration (177,178), as well as quantifying the effects of different sizes of fenestration (179).

Ventricular septation

The last available option for the surgical treatment of single ventricle is the staged ventricular septation. This concept of staged surgical approach for bi-ventricular circulation is not novel: in 1984, Paul Ebert proposed "staged partitioning" for the single ventricle (180); in 1986, Roxane McKay reported "staged septation" of a double inlet left ventricle (181); and in 2022, Renee E. Margossian and colleagues reported their revised approach to surgical septation to avoid the Fontan pathway (182).

In our experience, for all newborns with borderline

left heart structures, the pathway towards a bi-ventricular circulation is considered, utilizing appropriate staging of surgical procedures (183,184). For other patients on a uni-ventricular pathway, either a Norwood, bidirectional Glenn, or Fontan completion, extensive imaging and functional investigations are performed before ruling out the possibility for a bi-ventricular conversion (183-193). This decision-making process requires careful consideration of the size of inflow and outflow of the systemic ventricle, morphology and shunt direction through any interatrial and/or ventricular communication, right and left ventricular function and volumes, and morphology and flow of ascending aorta and aortic arch (183,184).

Peri-operative management

In-depth knowledge of the physiology in patients with single ventricle physiology is indispensable to achieving optimal peri-operative management of anesthesia, cardiopulmonary bypass and intensive care. Mortality rates are the highest following the first stage surgical palliation (194). In more recent years, for patients with pulmonary over-circulation and poor systemic perfusion with multi-organ failure, conservative management has been introduced, deferring the first palliative surgery to avoid cardiopulmonary bypass in neonates with already-depleted metabolic and functional reserves (110). The goal of the conservative management prior to the first palliative surgery is to maintain a QP:QS (= pulmonary-to-systemic blood flow ratio) around 1.5–2:1 with adequate utilization of mechanical ventilation with positive pressure and vasoactive medications. This ratio will become 0.5:1 after the bidirectional Glenn, and 1:1 after Fontan completion. In all these processes, a vital role is played in the use of inhaled nitric oxide (195). Better understanding of the unique hemodynamics of single ventricle physiology facilitated by many researchers over the years has resulted in better quality of life for these patients (196-201).

Fontan failure

With the intrinsic properties of the Fontan circulation, its eventual failure is not unexpected and occurs more frequently with increasing age of the patients (197,199-201), despite careful attention to the criteria for indication to this type of surgical procedure (202-204).The causes for failure of the Fontan circulation can be numerous, either anatomical and/or functional, including but not limited to obstruction or narrowing at any level from the cavo-pulmonary connections to the ventricular inlet, atrio-ventricular valve(s) regurgitation, poor systolic and/or diastolic ventricular function, systemic obstructions, elevated pulmonary vascular resistance, supra-ventricular and/or ventricular arrhythmias, etc. (200,201). Recent studies focused on the pharmacological treatment of children with single ventricle and pulmonary hypertension (205). The mechanism for late Fontan failure is multifactorial and depends upon the complex interaction between the ventricle functioning as the systemic ventricle, the ventriculo-vascular coupling, the pulmonary vascular bed, and the venous compartment (206). One of the lesser known issues after a Fontan procedure is the potential exposure of the coronary sinus to the sudden increase in systemic venous pressure with negative consequences on ventricular function (207,208). This, of course, depends entirely upon the type of surgery, lateral tunnel or extracardiac conduit, the arrangement relative to the drainage of the coronary sinus, and the presence and size of fenestration.

Treatment for recurrent protein losing enteropathy and chylothorax, well-known complications of Fontan circulation due to elevated central venous pressure affecting the thoracic duct drainage, has made recent progress by deviating the innominate venous drainage into the lower pressure common atrium. Methods include the direct innominate vein turn-down procedure, interposition of a tubular graft (209,210), or with the selective opacification followed by occlusion of the involved lymphatic vessels (211,212).

Once the reason for Fontan failure is determined, the first approach is to relief the cause of failure with either a catheter interventional or surgical procedure. When there are no identifiable causes, available interventional treatments, or prior interventions failed, alternative options must be considered. The overarching goal to prolong the state of Fontan circulation is to make the patients better candidate for heart transplantation, not at the expense of making them non-transplantable (206). If conservative measures fail, the remaining options are Fontan conversion, if the original surgery was an older arrangement; Fontan take-down, if the hemodynamics of Fontan circulation is not well-tolerated; a form of short or long-term of mechanical circulatory support; and finally, heart transplantation.

Fontan conversion

The atrio-pulmonary connection for Fontan completion has been complicated by failures caused by its non-ergonomic hemodynamics, elevated rates of energy loss

rate and elevated kinetic energy maximum value, as demonstrated in computational simulations (146,213,214). In these instances of failure, the original atrio-pulmonary connection has been converted either to a lateral tunnel (215,216) or to an extracardiac conduit (217-219), with better outcomes. The most frequent reason for Fontan failure is the occurrence and recurrence of supra-ventricular or ventricular arrhythmias (220-224). The treatment has been the conversion of the previous Fontan to either a lateral tunnel or an extracardiac conduit (225,226). Resynchronization therapy was later introduced to tackle the issue of intracardiac conduction delays in these patients (227).

Fontan take-down

The decision for a Fontan take-down has to consider all of the factors related to the pre-operative diagnosis, the decision-making process that led Fontan completion, the surgical procedures performed, and the post-operative findings causing the Fontan failure. Based on all these considerations, the decision for Fontan take-down must be balanced against all the available alternatives, including the possibility of going back to the situation proceeding the Fontan completion, or to create a completely different arrangement based on the anatomical and hemodynamic characteristics of each specific patient (228).

Mechanical circulatory support

The patients with single ventricle physiology have unique anatomical configuration, etiology and mechanisms of failure, indications for *mechanical circulatory support*, and the type of support required, unilateral or bilateral. This makes the interpretation and the generalizability of the limited available data challenging regarding the timing and type of optimal mechanism for support (229-233).

First, the ideal management strategies much be determined by analyzing the three different stages of single ventricle management (234):

- ❖ neonatal palliation, including Norwood Stage I
- ❖ superior cavo-pulmonary shunt (bidirectional Glenn)
- ❖ completion of Fontan circulation (early and late)

Several reports are available on the indication and the type of mechanical circulatory support utilized for each stage (235-241).

Second, the pathophysiologic pattern must be determined for the specific patient. An interesting algorithm has been proposed (242) using patient weight and mechanism of failure to choose the best device for mechanical circulatory support: (I) systolic dysfunction, with elevated end-diastolic ventricular pressure and low cardiac output; (II) diastolic dysfunction, with elevated end-diastolic ventricular pressure and normal cardiac output; (III) increased pulmonary vascular resistance and Fontan failure, with elevated central venous pressure and hepatic congestion; (IV) mixed type, with elevated central venous pressure and end-diastolic ventricular pressure, pulmonary congestion and low cardiac output (242). This algorithm was generated based on these principles: differentiating between the need to improve the antegrade Fontan flow, with a "pushing" device, versus uploading the systemic ventricle with a "pulling" device (242,243).

Third, the availability of three main types of support devices must be considered: (I) veno-arterial extra-corporeal membrane oxygenation, ideal for short-term support; (II) ventricular assist device, for mid and long-term support (244), either as bridge to recovery or to transplantation; (III) total artificial heart (227-232,236-242). When planning to use a ventricular assist device, the differences among pulsatile, axial and centrifugal pumps, having different unloading abilities, must be taken in consideration (242,245). Fontan take-down and use of a temporary support device should also be considered (206,228).

Last, but not least, there are surgical issues to consider: (I) the presence of multiple previous sternotomies, complicating the chest re-entry; (II) the positioning of inflow cannulation, considering the presence of adhesions, masking the coronary arteries, the variable morphology and location of the systemic ventricular cavity, the sub-valvular apparatus of the atrio-ventricular valve; (III) the positioning of outflow cannulation, because of the ascending aorta and aortic arch reconstruction (Norwood, Damus-Kaye-Stansel).

The use of mechanical circulatory support for Fontan failure has been supported by experimental studies on animals, *in vitro* studies, and mathematical and computational fluid dynamic studies.

Experimental studies on animals

Investigating the acute support in a porcine model has provided interesting basic science observations that are translatable to bedside application (246-248).

In vitro studies

Two studies investigated the hemodynamic effects of a totally implantable integrated aortic-turbine venous assist

device (177) with *in vitro* results of ventricular assist devices in right-side failing Fontan (249).

Mathematical and computational fluid dynamic studies

Investigative collaboration with bioengineers and mathematicians has opened a new horizon in the research for mechanical circulatory support even in Fontan circulation, resulting in a large number of publications on the topic (177,238,246-251).

Transplantation

Given the shortage of organ donors, it is clear that cardiac transplantation alone is not a sustainable solution to address the epidemic of heart failure associated with single ventricle pathophysiology. In addition, most patients with Fontan failure present with multi-organ failure making them poor candidates for heart transplantation. Hence, the need for alternative options, particularly mechanical circulatory support, has been increasingly recognized as a means to prolong the state of Fontan circulation and improve their candidacy heart transplantation (206). For transplantation after Fontan procedure, heart transplantation, heart and lung transplantation, and heart and liver transplantation should be discussed.

Heart transplantation

The patients with single ventricle and failing Fontan circulation present challenges, including extremely complex anatomy, multiple previous interventional procedures, unique underlying pathophysiological characteristics, and limited ability to directly assess hemodynamics. These issues complicate the decision-making process for further interventions versus heart transplantation. Consequently, patients with failing Fontan patients constitute one of the highest risk subsets of heart transplant recipients (252). Nevertheless, once only offered after failure of the Fontan circulation (252-256), indications for heart transplantation is now being offered for protein-losing enteropathy (257) and arterio-venous malformations (258). One study described the multicenter experience of heart transplantation in 514 patients with Fontan failure, reporting early mortality ranging from 15% to 23% (177). Another more recent multicenter study reported 177 children with Fontan failure listed for heart transplantation. Among the various phenotypes, abnormal lymphatics, reduced systolic function, preserved systolic function, and "normal" hearts, the group with reduced systolic function had the highest risk of waitlist mortality (21%) and post-transplantation mortality (36%) (259).

An experimental model of heterotopic heart transplantation or failing right heart, with two left ventricles arrangement, has been successful on acute tests on animals, but it has been neve implemented clinically (260).

Heart and lung transplantation

Heart and lung transplantation has historically been used as a definitive treatment for children with end-stage cardiopulmonary failure, although the number performed has steadily decreased over time. Even in patients with failing Fontan, due to the combination of shortage of donors and generally poor outcomes, the indication for heart and lung transplantation in children with single-ventricle physiology has virtually been abandoned as therapeutic option (261).

Heart and liver transplantation

Fontan-associated liver disease can be one of the long-term consequences of the Fontan circulation. By adolescence, virtually 100% of these patients develop clinically silent fibrosis, demonstrated by surveillance biopsies. In the absence of a transplant option, these young patients face a poor quality of life and overall survival because of advanced liver disease, including bridging fibrosis, cirrhosis, and hepatocellular carcinoma (262-265). In the absence of long-term hepatic outcome data after heart transplant alone, there is a progressively increasing incidence of combined heart and liver transplantation (262-265). As experience and knowledge has improved in pre-transplant screenings and peri-operative management, better outcomes have been reported for combined heart and liver transplant in this complex group of patients (266,267).

Pregnancy

With improving rates of post-Fontan survival to adulthood, many now seek advice regarding safe pregnancy. However, little data are available and consists of mainly of anecdotal experience and small series of cases (268,269). A systematic literature review showed that the most reported cardiovascular complications during pregnancy in women with Fontan circulation were arrhythmias, heart failure and thromboembolism. Miscarriages were highly

prevalent as were premature deliveries and intrauterine growth restriction, and post-partum hemorrhage was the most common obstetric complication (269). Fontan circulation may be associated with poor placental health due to the high systemic venous pressure and low cardiac output contributing to stagnation of placental blood flow and resulting in subchorionic fibrin deposition and variable villous hypoplasia. Analysis of placental pathology may help determine both candidacy for future pregnancy and long-term effects of pregnancy for women with Fontan physiology (270). As infertility and first trimester miscarriage are not uncommon in women with Fontan circulation, pregnancy may be high risk and even contraindicated. In vitro fertilization, with or without gestational surrogacy, can be an option with reports of success but poses risks during ovarian stimulation, oocyte retrieval, and the post-procedural period (271).

Exercise

In the past, several studies have shown that adult patients with Fontan circulation have reduced exercise tolerance affecting the quality of life. These patients were discouraged from any form of exercise. Initial attempts at improving the effort tolerance have been reported using intermittent external legs compression (272). More recently, several programs of cardiopulmonary training, including exercise training, fitness intervention trials, home-based long-term physical endurance and inspiratory muscle trainings, have been instituted in Fontan patients. These programs have been shown to be safe and beneficial, improving exercise capacity, cardiorespiratory performance and cardiac biomarker values, and self-reported quality of life (273-277).

Adolescents and adults without Fontan completion

Years ago, there were only case reports of individuals with single ventricle physiology surviving to adulthood. In more recent years, a number of patients have reached adulthood without any type of even palliative surgery (2,278-282), or after some form of palliation but without requiring a Fontan completion (193,283-286). Attempts should be made to identify the morphologic and pathophysiological characteristics of these patients, identify the more favorable patterns, and compare their survival and quality of life with those who underwent all conventional surgical stages.

Future studies

Experimental studies on animals

Traditionally, potential new surgical approaches were first experimented on animals, despite the difficulties of modeling single ventricle circulation and the various surgical stages in animals born with two ventricles and separate pulmonary and systemic circulations (287-291). As a result, many comparative studies focused on animals born with single ventricle physiology, such as amphibians, like axolotl salamanders (*Ambystoma mexicanum*) (292), frogs (*Xenopus laevis*) (293-295), and reptiles, who live unrestricted lifestyle for many years. In frogs and salamanders, the two circulations fuse at the level of single ventricle, splitting at the pulmonary and systemic arterial branches, and the amount of blood flow distributed between pulmonary and systemic circulations is determined by the ratio of the peripheral resistances in the two territories. The anatomic and physiologic features of the amphibian heart does not seem to be even remotely applicable to human cardiac pathophysiology, nor modifiable towards surgical options in patients born with single ventricle. However, the evolutionary origin of normal and abnormal morphogenesis of the human heart (296) has been recently demonstrated (297-299).

Computational studies

In addition animal studies, the current trend is to collaborate with bioengineers and mathematicians by providing them with three-dimensional reconstruction images obtained with computerized tomography or magnetic resonance imaging, together with the clinical information and the hemodynamic data from cardiac catheterization. With the modern computing technology, nowadays every interventional and surgical procedure can be designed and tailored for the specific patient, based on the results of computational simulations. This collaboration is now becoming a routine part of decision-making even for patients with single ventricle physiology at any stage of the surgical plan (177,178,300-302).

Genetics

Genetic studies of animal hearts with single ventricle is become increasingly important in understanding the relationship between morphology and cardiac function (295). Moreover, the underlying molecular

signals responsible for the adaptive tissue responses seen in other species may be useful in our understanding of post-operative complications and the discovery of novel strategies to prevent them. Hypoplastic left heart syndrome is the type of "functionally" single ventricle most frequently requiring surgery in the first weeks of life, prompting extensive genetic investigations in these neonates (303-308).

In hypoplastic left heart syndrome of hemodynamic origin, the first mouse model showed evidence of intrinsic cardiomyocyte proliferation and differentiation defects related to left ventricular hypoplasia (306). The profound genetic heterogeneity and oligogenic etiology in hypoplastic left heart syndrome suggests that the genetic landscape is complex and should be investigated in clinical studies built on a familial study design (306). Furthermore, hypoplastic left heart syndrome can present as either isolated phenotype or as a feature of a larger genetic disorder. Specific genes have been implicated, including rare, predicted damaging *MYH6* variants present in 10% of hypoplastic left heart syndrome patients, which have also been shown to be associated with decreased transplant-free survival (308).

Finally, in the most recent and large genetic study, single-nucleus RNA sequencing has been performed on 157,273 nuclei from control hearts and from patients with congenital heart disease, including hypoplastic left heart syndrome and dilated and hypertrophic cardiomyopathy (309). Specific cell states of congenital heart defects have been found in cardiomyocytes, characteristic of activated cardiac fibroblasts with an immunodeficient state and a profile suggesting deficient monocytic immunity (309). All these comprehensive phenotyping of congenital heart defects provides a roadmap towards future personalized treatments for patients with single ventricle physiology.

Stem cells

The single ventricle of right ventricular type, as in the hypoplastic left heart syndrome, is especially prone to early failure because of its vulnerability to pressure and volume overload, with a mode of failure distinct from ischemic cardiomyopathy. As these patients enter early adulthood, an emerging epidemic of ventricular failure is evident. Regenerative medicine strategies may help preserve or boost the single ventricle function in these patients by promoting angiogenesis and mitigating oxidative stress. Rescuing a single ventricle in decompensated failure may also require the creation of new, functional myocardium (310). Because of these reasons, experimental studies on animals using stem cells have been conducted in various institutions, including a few clinical trials with progenitor stem cells given via direct myocardial injection or administration in the coronary arterial blood (311-317). The preservation of single ventricular function is the key for long-term outcomes, but currently the available methods to preserve or improve the myocardial function are still limited (314). Stem cell therapy and cardiac tissue engineering present revolutionary potential in the treatments of children with single ventricle, although considerable obstacles must be overcome before their clinical translation (310).

Bioengineering

Tremendous progress have characterized the field of bioengineering and related experimental and clinical applications. Over the last years, relatively simple tasks of building biomaterials to use as patch or conduit during surgery for congenital heart defects has now evolved to bioengineering products to use in place of prosthetic materials and repair of damaged or missing myocardium (318-321). Until recently, it was unthinkable to use biomaterials to construct the systemic-to-pulmonary shunt with tunable properties to control and modulate blood flow through the shunt, thus accommodating to physiological changes as the patient grows (322). Thanks to modern technologies, now these bioengineered shunts represent a new methodology to accommodate the need for increasing pulmonary blood flow in this vulnerable patient population (322).

Nowadays tissues with three-dimensional structures can be generated using different approaches such as self-assembled organoids with tissue-engineering methods, such as bioprinting. A promising study compared heart organoids with *in vivo* hearts to understand the anatomical structures still lacking in the organoids, and specifically comparing the development of heart structures based on marker genes and regulatory signaling pathways (323).

Finally, we have already discussed heart transplantation as the ultimate solution for failing Fontan circulation and the limitations of human donor shortages. The waiting list for heart transplantation is higher than for any other solid organ transplantation group. Orthotopic pig heart transplantation, as a bridge to allotransplantation, could offer the prospect of long-term survival to these patients (324). In recent years, several advances in techniques of genetic engineering pigs mitigated the vigorous antibody-mediated rejection of a pig heart transplanted in nonhuman primates

with extended pig cardiac graft survival (324). These experimental studies could help the progress towards clinical trials of bridging cardiac xenotransplantation for neonates and infants (178). In summary, the developing technologies investigating cell therapy, gene therapy, and tissue engineering are potential tools to regenerate hypoplastic cardiac structures and improve outcomes of neonates with single ventricle physiology.

Conclusions

These last 40 years have certainly changed the course of natural history for children born with any form of "functionally" single ventricle, thanks to the improvement in diagnostic and treatment techniques, and particularly to the increased knowledge of the morphology and function of these complex hearts, from fetal to adult life. There is still much left unexplored and room for improvement, and all efforts should be concentrated in collaborations among different institutions and specialties, focused on the same matter.

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