Fontan circulation has improved life expectancy for infants born with complex heart disease over the last 50 years but has also resulted in significant morbidity

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Abstract
The prognosis for infants born with complex heart disease improved dramatically with the introduction of the Fontan circulation 50 years ago. With today’s carefully designed and staged operations to a Fontan circulation, life expectancy has increased and most children will survive into adult life. The Fontan circulation entails an unphysiological circulation with high risk for multiple organ system dysfunction. Neurodevelopmental disabilities with adverse psychosocial effects are prevalent. The Fontan circulation may eventually fail and necessitate heart transplantation.

Conclusion: Fifty years development of the Fontan circulation to today’s staged surgical procedures has improved survival but also revealed the burden of a high morbidity for a growing number of patients.

Keywords
Fontan circulation, life expectancy, morbidity, surgery, univentricular heart malformation

1 | INTRODUCTION

The first patient, who survived a cavopulmonary and atriopulmonary connection as a treatment for tricuspid atresia, was described 50 years ago by Fontan et al. Before that, most infants and children with univentricular heart malformations died young from cyanosis and heart failure. Few were palliated with pulmonary artery banding or aortopulmonary shunts. Severe complications were common from shunt obstruction, cyanosis, thromboembolism, bleeding, heart failure and often associated with a very poor quality of life. Only a few reached adult age. With the introduction of the Fontan operation and the resulting Fontan circulation, the prognosis improved dramatically. It is estimated that almost 25,000 patients are alive today in Europe with a univentricular heart malformation palliated with some type of Fontan operation. The large and increasing number of young and adult subjects with a Fontan circulation is all under regular follow-up by specialised cardiologists. However, they may also occasionally be seen by paediatricians and family doctors who should have a brief understanding of the Fontan circulation and the most frequent complications.

The Fontan operation was initially used in subjects with tricuspid atresia. With modifications of the operation, most types of univentricular heart malformations could be successfully converted to a Fontan circulation. The original incorporation of the right atrium
in the cavopulmonary connection often resulted in dilatation of the right atrium with risk for arrhythmias, thromboembolism and disturbed flow to the pulmonary arteries. One modification introduced by Björk et al was to incorporate the hypoplastic right ventricle in order to augment pulsatile blood flow into the pulmonary arteries. However, the most important improvement and modification came with the introduction of total cavopulmonary connection via an intra-atrial lateral tunnel by de Laval et al. This modification excluded the cardiac cavities from systemic venous return to the pulmonary arteries. Most centres are now making the connection with an extracardiac synthetic conduit from the inferior caval vein and hepatic veins and placed outside the heart up to the confluent pulmonary arteries. Connection of the descending superior caval vein to the pulmonary arteries, a Glenn shunt, was usually already performed at an earlier operation. The venous connections have been improved by meticulous attention to the different anastomoses, in order to allow for undisturbed laminar venous blood flow to both pulmonary arteries.

Univentricular heart malformations are diagnosed in 0.1–0.4 per 1000 live births. A decreased incidence among live-born infants has been reported in some countries due to the termination of pregnancy after prenatal detection. Foetal ultrasound screening early in pregnancy can detect most cases of univentricular heart defects. This has permitted delivery and initial care to be planned in advance and has been reported to improve survival. The most common univentricular heart malformations are hypoplastic left heart syndrome, tricuspid atresia and double-inlet left ventricle. There is a large variation in expression and associated malformations are common, for example, heterotaxia syndromes. Three staged operations are usually necessary to achieve a functioning Fontan circulation but with individual variations depending on the type of malformation and the haemodynamic effects of previous palliative procedures.

2 | NEONATAL OPERATION

Most newborn infants with a univentricular heart malformation have a ductus dependent pulmonary or systemic blood flow. Prostaglandin infusion is started at birth, in order to keep the ductus open, until the first palliative operation can be performed. The patent ductus is usually replaced by another type of aortopulmonary shunt, for example, a modified Blalock-Taussig shunt. Some centres have used a less-invasive initial palliation with stent implantation in the ductus by catheter technique and bilateral pulmonary artery banding. A synthetic conduit can also be positioned between the ventricle and the pulmonary arteries, as a Sano shunt. This ventriculo-pulmonary shunt is frequently used in infants with hypoplastic left heart syndrome where the hypoplastic ascending aorta and aortic arch are reconstructed in a Norwood operation. The ventriculo-pulmonary shunt has the advantage of not compromising diastolic coronary blood flow, but can be difficult to size and has a significant risk for obstruction. The common goal with the first palliative operation is to guarantee adequate systemic blood flow and oxygen delivery and control of pulmonary blood flow with acceptable volume load on the ventricle. A certain degree of systemic oxygen desaturation must be accepted together with some initial pulmonary hyperperfusion and volume load on the ventricle. As the infant grows, both the oxygen saturation and volume load decrease as they outgrow the shunt, and they need a new operation.

3 | THE BI-DIRECTIONAL GLENN OPERATION

The second operation is performed when oxygen saturation falls as a result of impaired pulmonary blood flow and the pulmonary vascular resistance has decreased to normal levels. This is usually between 4–10 months of age. The superior caval vein is detached from the right atrium and the cranial part anastomosed to the pulmonary arteries, as a bidirectional Glenn shunt (Figure 1A). Thus, the returning venous blood from the head and arms in the superior caval vein is perfusing the pulmonary circulation. The inferior vena cava blood still enters the right atrium and mixes with fully saturated blood from the pulmonary veins and into the left atrium and single ventricle. The aim of the bidirectional Glenn operation is to control pulmonary blood flow and moderate the volume load on the heart but guarantee adequate oxygen uptake and systemic delivery. Venous return from the head and arms is now providing a non-pulsatile low-pressure pulmonary circulation.

4 | THE TOTAL CAVOPULMONARY CONNECTION

The Glenn-palliated univentricular heart can be seen as a partial, or semi-Fontan circulation. The child is still somewhat cyanotic, but the moderate volume load on the heart and circulation usually allows for a near-normal growth and development. The third operation is usually performed as an elective procedure between 1–4 years of age. The haemodynamic effects of the earlier operations are closely followed in order to find the optimal age for the final total cavopulmonary connection and Fontan circulation. For a smooth postoperative
course and a successful long-term Fontan circulation, a number of preoperative requisites must be met. The most important are a low pulmonary vascular resistance, a good ventricular function, no obstruction in the venous pathways, the pulmonary arteries or in the aorta and absence from tachyarrhythmias. In addition, there should be no major atrioventricular valve incompetence. The operation is tailored to the individual patient and further corrections are sometimes necessary before the full Fontan circulation can be offered.

The total cavopulmonary connection is created by connecting the inferior caval vein and liver veins to the confluent pulmonary arteries (Figure 1B). This is usually accomplished by a wide synthetic tubular conduit outside the heart and a broad anastomosis to the pulmonary arteries. The total cavopulmonary connection and Fontan circulation result in normal systemic oxygen saturation for the first time since birth.

The systemic and pulmonary vascular beds are connected in series in the Fontan circulation but without a pre-pulmonary ventricle. This creates an unphysiological circulation with many potential problems.29-32 The single pumping ventricle has to provide enough blood flow energy to perfuse the systemic as well as pulmonary vascular beds. This entails increased afterload for the ventricle and significantly increased systemic venous pressure and venous congestion in most organs. The elevated venous pressure increases fluid filtration and is a challenge for the lymphatic circulation in most organs.23 The lymphatic elimination of excessive tissue fluid is also hampered by the high venous pressure in the central veins, where the lymphatic duct empties. The pathophysiology is complex but the elevated venous and lymphatic pressures may give rise to inflammation and fluid accumulation in many organs and cavities.

The non-pulsatile pulmonary blood flow depends on high systemic venous pressure, low pulmonary vascular resistance and a low-pressure gradient across the pulmonary vascular bed. The elevated systemic venous pressure and venous congestion in most organs poses an increased long-term risk for metabolic consequences and multiple organ dysfunction, morbidity and mortality. Unfortunately, pulmonary vascular resistance also tends to increase over time and this limits filling of the systemic ventricle and cardiac output.

Many Fontan patients have a reduced health-related quality of life and also a low-physical capacity.24-29 Psychiatric dysfunction and cognitive disability are more common in Fontan patients.30-32 Adolescents have been reported to have increased anxiety problems and attention deficit hyperactivity disorder.33 Nevertheless, some young Fontan patients have adapted to these limitations and may report a good general quality of life.

The normal increase of cardiac output during exercise is also reduced, without a pumping pre-pulmonary ventricle. Reduced physical capacity may deter young Fontan patients from participating in sports and physical exercise in school. This is unfortunate since skeletal and respiratory muscle work augments the Fontan circulation.34 Regular endurance and muscular training have been suggested to improve the Fontan circulation, oxygen uptake and exercise tolerance.35 Deterioration of heart function, oxygen uptake, physical capacity and quality of life have all been shown to be predictive of hospital admissions and death in adult Fontan patients.2,24,36-38 We believe it is important to follow physical capacity, activity in daily life and sports, self-perceived health and quality of life as well as measures of heart and other organ functions, in all patients with Fontan circulation. Since most patients will experience a gradual deterioration of these health parameters, it may be important for the growing young Fontan patient to be encouraged to develop a generally healthy lifestyle early in life.
Apart from the frequent and sometimes severe postoperative complications, morbidity remains high among patients with Fontan circulation and is increasing with age. Before the final Fontan operation, the single ventricle is exposed to volume overload and often also to periods of hypoxia. After the Fontan operation, the ventricle is volume deprived with limited ability to increase stroke volume. The abnormal shape and function of the ventricle can lead to myocardial inflammation and fibrosis, further reducing output. Heart failure with low output and venous congestion becomes symptomatic, but the common underlying mechanism may be a slowly progressing pulmonary vascular resistance. Chronic vasculopathy in the lungs with increased resistance will limit pulmonary blood flow, increase venous and lymphatic congestion and reduce the filling of the ventricle. This may be detrimental for the Fontan circulation and result in overt heart failure. Increased pulmonary vascular resistance further raises central venous pressure, lowers cardiac output and a vicious circle may arise. When pulmonary blood flow decreases, the pulmonary venous return to the atrium, and preload for the ventricle, are reduced. Reduced ability to increase cardiac output during exercise is an early consequence.

Cyanosis and low arterial oxygen saturation may develop over time, usually at first only during exercise, but later also at rest. This may be explained by venovenous shunting through collaterals developing between the high-pressure systemic veins and the low-pressure pulmonary venous system. If a significant symptomatic desaturation progresses, catheter-based occlusion of collaterals may be considered. Cyanosis may also develop from intra-pulmonary shunts and ventilation-perfusion mismatch.

Arrhythmias are more prevalent after the earlier Fontan operation techniques. Extensive surgery in the atrial walls and dilatation of the right atrium was a common substrate for atrial tachyarrhythmia. Bradyarrhythmia, usually sinus node dysfunction, is frequently reported and can be treated if symptomatic, with pacemaker and epicardial leads. Pacemakers have been implanted in 10–20% of adult Fontan patients, but still is a risk factor associated with increased mortality. Venous congestion and elevated organ and central venous pressures impair organ lymphatic drainage and may cause intestinal inflammation and symptomatic protein-losing enteropathy. With low serum albumin, ascites and pleural effusions may occur. Pleural and pericardial effusions are common in the immediate postoperative period in response to the abrupt increase in central venous pressure and surgical trauma but usually resolves. However, retention and accumulation of fluid can also occur any time later in life. Protein-losing enteropathy is reported in 5–20% of Fontan patients. Plastic bronchitis is another severe and life-threatening condition. It is the result of extravasation of protein into the bronchi and forming casts. This has been reported in 1–4% of young Fontan patients. Abnormal lymphatic vessels or lymph flow directions can be visualised and occluded with catheter-based techniques. All forms of late lymph and fluid accumulation, in Fontan patients, are severe complications without a universally successful treatment and with a poor long-term prognosis.

Structural liver changes are common and may lead to function abnormalities. These increase with age and may lead to fibrosis, cirrhosis and in rare cases hepatocellular carcinoma. The combination of venous and lymphatic congestion together with reduced cardiac output is believed to cause hepatocellular inflammation and cell death. Hypoxic events at surgery may further aggravate the liver damage. Unfortunately, clinical signs and symptoms of advanced liver disease are late features and often non-specific. Jaundice, ascites, palmar erythema, lethargy and thrombocytopenia may indicate liver cirrhosis. Portal hypertension and oesophageal varices may become life-threatening consequences.

Renal function may also deteriorate over time due to the chronic venous congestion. Thromboembolic complications are often seen as silent thrombi in the systemic veins and conduit and are the results of low-velocity venous flow and coagulation factor abnormalities. Larger thrombi may develop in the pulmonary arteries or in the heart secondary to arrhythmias and become life-threatening. Fontan patients should be given prophylactic treatment with anticoagulants, but the type of anticoagulant remains controversial.

Thus, many organs are at risk for malfunction in the Fontan circulation. Follow-up programmes include examinations and tests in order to find early signs of disease. Pharmacological treatment and surgical or catheter re-interventions are common. Heart transplantation may be the final solution to most severe complications, and it has been reported in 1–5% of Fontan patients.

The risk of death is highest in infants at the first palliative operations and with complex malformations including hypoplastic left heart syndrome. Mortality at the final Fontan operation mortality was initially high but has decreased over time to less than 1%, as the surgical techniques have improved and postoperative care has become much more advanced. Since most subjects will undergo at least three different operations, within the first couple of years, it is reasonable to consider the total risk for death until the Fontan circulation is completed. Mortality differs depending on the complexity of heart defect, prenatal diagnosis, associated malformations, neonatal care, surgical techniques and centres, postoperative care, interoperative follow-up and care, selection criteria for Fontan operation, age at Fontan and much more. Right ventricular dominance is also a risk factor. The accumulated risk for death in the early days of staged operations for univentricular heart defects half a century ago was well over 50%. Infants and children with complex defects, such as hypoplastic left heart syndrome, were not palliated or unsuitable for the full Fontan circulation. Today, most forms of univentricular heart defects are palliated according to the staged Fontan protocol. The cumulative mortality during childhood and adolescence in subjects with univentricular heart defects has decreased to less than 20%.
Late mortality after completion of the Fontan circulation has also decreased over time but is still significant especially among adult patients (Figure 2). The cumulative mortality, 15 years after the Fontan operation, has decreased from 18–48% in the early days to less than 10% in later reports. Cumulative mortality was 17% in one study 25 years after the Fontan operation (Figure 2). The predominant final cause of late death in the adult population with Fontan circulation seems to be ventricular failure but protein-losing enteropathy, thromboembolic events, arrhythmias and sudden death are also frequently reported as the cause of death. The common underlying causes for most lethal complications are the inevitable haemodynamic consequences of the Fontan circulation, especially the gradual increase in pulmonary vascular resistance. Implantation of mechanical ventricular assist devices has been attempted, both short term and long term. Most centres still regard heart transplantation as the final solution, but timing is crucial for a successful long-term result. It is important to remember that today’s patients are very different from the early days of Fontan. Infants palliated as neonates are now in a much better preoperative condition than before. Timing of the following operations are more optimal and the children are both younger and in much better haemodynamic condition than before, when converted to the full Fontan circulation. This will likely result in significantly lower short-term and long-term mortality and, hopefully, reduced morbidity.

8 CONCLUSION

The Fontan operation has been used for 50 years. A large and increasing number of newborn infants with univentricular heart disease survive through childhood and into adult age. Unfortunately, the Fontan circulation has significant negative haemodynamic effects and carries a high risk for multi-organ disease. Most complications increase in severity over time. Life expectancy has increased but also revealed a significant burden of failing organ functions and psychosocial and neurodevelopmental deficits. Fontan patients are cared for by specialised cardiologists but may also be seen by paediatricians and family doctors. These healthcare providers should have a basic knowledge about the Fontan circulation and the most common complications.

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