

# Approaching the 50<sup>th</sup> anniversary of the first Fontan procedure. What is the current state of treatment provided to patients with functional single ventricles?



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Kardiochirurgia i Torakochirurgia Polska 2017; 14 (3): 186-191

## Abstract

Nearly 50 years after the pioneering procedure performed by Francis Fontan and Eugene Baudet, which has saved the lives of thousands of children, there are still more questions than answers regarding therapeutic management. The complex pathophysiology of Fontan circulation, the lack of clear guidelines, and the shift in the care of such patients from pediatric cardiological and cardiac surgical centers to ones dealing with adult patients, cause new threats. This paper outlines the fundamental issues related to the pathophysiology of Fontan circulation and reviews the literature on the methods of treating complications characteristic of this group of patients.

**Key words:** Fontan procedure, congenital heart defects.

## Introduction

Congenital heart defects which cannot be surgically corrected to reconstruct normal anatomic conditions of “biventricular circulation” are often described as defects with a “functional single ventricle”. Despite their significant morphological variety, the surgical treatment for these defects is the same and consists in performing a Fontan procedure. The most commonly diagnosed defect from this group is hypoplastic left heart syndrome, followed by: tricuspid valve atresia, unbalanced atrioventricular canal, double-inlet left ventricle, some forms of double-outlet left ventricle defects, Ebstein’s syndrome, and others.

“Functional single ventricles” represent approx. 7.7% of all congenital heart defects [1, 2].

Before the introduction of the Fontan procedure, most children with single ventricles would die within the first year of their life. At present, according to a recently published Australian register, the rate of 25-year survival amounts to 83%. The optimism inspired by this data must be confronted with the fact that only 29% of the patients from this group will not develop severe, and often life-threatening,

## Streszczenie

Minęło niemal 50 lat od pionierskiej operacji Francisca Fontana i Eugene’a Baudeta, która uratowała życie tysiącom dzieci, a wciąż jest więcej pytań niż odpowiedzi dotyczących postępowania terapeutycznego. Złożona patofizjologia krążenia fontanowskiego, brak jasnych wytycznych i wynikające z większej przeżywalności przesunięcie ciężaru opieki nad tymi pacjentami z pediatrycznych ośrodków kardiologiczno-kardiochirurgicznych na te, które zwyczajowo zajmują się pacjentami dorosłymi, stwarzają nowe zagrożenia. W niniejszym opracowaniu przedstawiono podstawowe zagadnienia związane z patofizjologią krążenia fontanowskiego, a także dokonano przeglądu piśmiennictwa dotyczącego metod leczenia powikłań charakterystycznych dla tej grupy pacjentów.

**Słowa kluczowe:** operacja Fontana, wrodzone wady serca.

complications [3]. Therefore, one should keep in mind that Fontan circulation is only an imperfect substitute of normal circulation, and the patients are burdened with numerous complications that are often difficult to treat. Due to the distinctness of Fontan circulation and the lack of detailed guidelines, the cases of these patients are often most challenging. Concurrently, as the survival period increases, the burden of caring for these patients increasingly shifts from pediatric cardiology wards to adult wards.

The present article discusses the fundamental issues related to the pathophysiology of Fontan circulation and sums up the current studies concerning the treatment of Fontan patients.

## The Fontan procedure in the past and today

The primary goal of multistage treatment is to decrease the volume overload of the single ventricle and to separate pulmonary circulation from systemic circulation, while balancing the ratio between pulmonary and systemic flow ( $Q_p/Q_s$ ), which should result in arterial blood

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**Received:** 13.02.2017, **accepted:** 18.03.2017.

saturation values that are close to normal. The benefit of the procedure consists in prolonging life and improving its quality in patients with the most complex congenital heart defects.

The classic Fontan procedure was first performed in 1968 and consisted in the creation of anastomoses between the superior vena cava and the right pulmonary artery and between the inferior vena cava and the left pulmonary artery by means of valvular homografts [1]. Since then, many modifications have been made to the procedure; the most important ones include:

- the introduction of “multistage” Fontan procedures in the 1980s with an intermediate stage consisting in a Glenn or hemiFontan anastomosis (Fig. 1),
- substituting the direct atriopulmonary connection (APC), which was widely used until the early 1990s, with the creation of a lateral tunnel (LT), and later with the newest generation of Fontan circulation procedures using an extracardiac conduit (ECC),
- the introduction of fenestration in the lateral tunnel,
- the lowering of the age at which the individual stages of creating Fontan circulation are performed (at present, the Glenn/hemiFontan anastomosis is performed at the age of approximately 4–6 months, and the Fontan procedure is performed when the patient is approximately 2–3 years old).

The above mentioned modifications along with improvements in the process of qualifying patients for the procedure resulted in decidedly better treatment outcomes, both short- and long-term.

In the 1970s, Choussat and Fontan formulated the so-called “ten commandments” for selecting appropriate candidates for single ventricle correction. Although some of these rules have been modified, the basic principles are still used in everyday practice as valuable guidelines not only for qualifying patients for the procedure, but also for their later evaluation.

Of the original Choussat’s “commandments”, the following are still in use:

- maintaining sinus rhythm,
- normal venous return,
- low mean pulmonary artery pressure (below 15 mm Hg),
- low pulmonary vascular resistance (lower than 2–3 WU/m<sup>2</sup>),
- normally developed pulmonary arteries,
- good systolic function of the single ventricle.
- no significant insufficiency of the atrioventricular valve.

Fontan circulation can be expected to function well in patients who meet these criteria. However, any disturbances in this delicate system, such as even a slight increase in pulmonary resistance, may lead to dramatic consequences.

### Pathophysiology of Fontan circulation

The mechanism by which circulatory failure develops in patients after Fontan procedures differs from that observed in patients with anatomically normal circulatory systems. As underscored by Gewillig, the lack of a “pumping” subpulmonary chamber is the creation of a specific portal

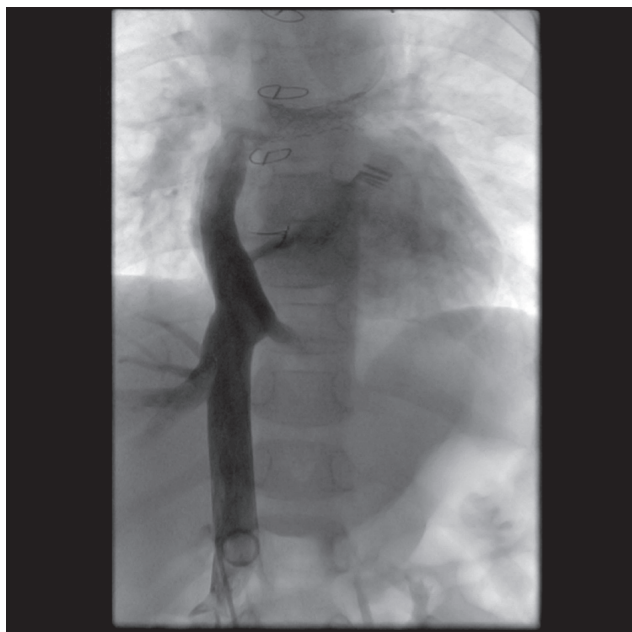
system in which the postcapillary energy of systemic circulation drives the flow through pulmonary capillaries [4]. The only mechanism of maintaining blood flow through the lungs is to increase the systemic venous pressure significantly (above the values typical for pulmonary capillary wedge pressure). This dramatic change in pressure ratio, although indispensable for maintaining pulmonary flow, causes venous stasis and contributes to the development of complications such as edemas, effusion, chylothorax, liver fibrosis, kidney failure, susceptibility to thrombosis, protein-losing enteropathy (PLE), or plastic bronchitis.

Increasing exercise cardiac output after Fontan procedures is difficult due to the lack of a pumping subpulmonary ventricle and the passive flow of blood through the lungs, which does not rise adequately to the level of physical activity. This leads to insufficient preload of the single ventricle and the development of circulatory insufficiency. The patients do not experience excessive fatigue during regular, everyday activities, but their exercise tolerance is much lower not only in comparison to the healthy population, but also in comparison to patients undergoing other types of congenital heart defect correction. It has also been proven that their fitness is not improved by regular physical exercise [5].

One solution for chronic insufficient preload of the single ventricle is the creation of a so-called fenestration (Fig. 2), i.e., a small connection between the systemic venous system and the atrium of the systemic ventricle, performed during the last stage of the surgical treatment. This serves a double purpose. On the one hand, the fenestration becomes a “safety valve” in case of an excessive pressure rise in the systemic venous system; on the other, the additional shunt increases the preload of the single ventricle as well as cardiac output. Although the addition of blood from systemic veins to blood flowing from pulmonary veins causes a slight desaturation in the aorta (optimally to ap-



Fig. 1. A 6-year-old patient after a Glenn procedure. The additional left superior vena cava is closed by Amplatzer Vascular Plug 4



**Fig. 2.** A 9-year-old patient after a Fontan procedure. A fenestration and a stent in the left pulmonary artery are clearly visible

prox. 90%), this is offset by the advantage of increased cardiac output.

Fenestration is useful in the early postoperative period, when the heart goes through shock associated with the rapidly reduced preload, as well as in older patients, in whom aging results in increased pulmonary vascular resistance and elevated pressure in the systemic venous system. On the other hand, its benefits are less obvious several months or years after the procedure in patients with optimal hemodynamic conditions.

### Complications of Fontan circulation

Most patients with Fontan circulation develop a number of associated complications. The most serious occur when the patients are in their 20s–30s, but they may also occur shortly after the procedure. The most important ones include: systolic and/or diastolic dysfunction of the single ventricle, cardiac dysrhythmias and conduction disturbances, thromboembolic complications, edemas and effusions into body cavities, chylothorax, liver fibrosis and cirrhosis, kidney failure, protein-losing enteropathy, plastic bronchitis, and the development of abnormal vascular connections in the pulmonary and systemic circulation.

The subject literature often features the term “failing Fontan”, which denotes advanced circulatory insufficiency with concurrent development of several of the abovementioned complications, especially if they include protein-losing enteropathy or plastic bronchitis.

### Postoperative treatment after Fontan procedures

As mentioned above, the exercise tolerance of patients undergoing Fontan procedures is limited from the outset,

which stems from the fact that, in optimal conditions, the cardiac output of their single ventricles amounts to only approx. 70% of normal values [4].

Notwithstanding, most patients remain in low NYHA functional classes for years: they attend schools, achieving results similar to their peers, their lifestyle is almost normal, and the quality of life is acceptable [6].

According to various studies, the level of development and IQ of children with functional single ventricles is only slightly lower than that among the general population, falling within the norm. However, a much more frequent problem, affecting as many as 65% of patients undergoing Fontan procedures, is constituted by mental disorders, especially increased anxiety, depressive tendencies, or hyperactivity (ADHD) [7]. For this reason, it is important to provide such patients with multispecialist care, including psychological and psychiatric support.

One should also remember that heart defects as such are a risk factor for the development of malnutrition. Patients undergoing Fontan procedures are shorter and have lower muscle mass than the general population [8]. They are more likely to experience iron deficits (despite the increased hematocrit levels) and vitamin D deficits, which should be controlled and balanced through supplementation [9].

An important issue that requires consideration after puberty is the question of having children and the consequences related to pregnancy. The population risk of giving birth to a child with a serious heart defect is approx. 6 : 1000; the defect's occurrence is influenced by both genetic (abnormal karyotype or microdeletions) and environmental factors [10]. In most cases, a heart defect in a parent is associated with a slight increase in the risk of a heart defect in the offspring. Therefore, before making decisions about having children, the future parents should seek genetic advice. The risk of pregnancy failure in patients with Fontan circulation is estimated by the European Society of Cardiology (ESC) as moderate or high (WHO class III/IV) [11, 12]. Decisions concerning pregnancy should be preceded by detailed analysis of the circulatory system performed in a specialist center, and the patient should be informed of the risks involved, including preterm birth, low birth weight of the neonate, and NYHA class deterioration of the mother. Only patients with optimally functioning Fontan systems can be expected to successfully complete pregnancy. In other cases, pregnancy should be discouraged, and effective methods of contraception should be recommended.

Furthermore, all patients after Fontan procedures should undergo infective endocarditis prophylaxis [13].

There are no universally accepted guidelines for preventing and treating circulatory insufficiency in a patient with a “functional single ventricle”. The type and dosage of cardiac agents as well as indications for their introduction largely depend on the experience of individual centers. Significant differences are observed in the use of specific groups of agents. According to an analysis by Anderson *et al.*, subjects' medication usage ranged from 32% to 76%

for angiotensin-converting-enzyme inhibitors (ACEis), 33–97% for antithrombotics, 22–55% for digitalis glycosides, and 7–45% for diuretics [14].

What is more, the effectiveness of most of these agents has not been sufficiently verified by studies of appropriate design, and their use is based either on empirical experiences or guidelines regarding patients with normal anatomy of the circulatory system.

A good example of this is the widespread use of angiotensin-converting-enzyme inhibitors. According to a register from New Zealand and Australia, 36% of patients after Fontan procedures receive ACEis, and the most common reason for their introduction into the treatment is systolic or diastolic dysfunction [15]. While this group of agents is well-established in the ESC guidelines on the treatment of heart failure in patients with normal cardiac anatomy, their efficacy in patients after Fontan procedures has not been confirmed so far [16, 17]. Moreover, some researchers point to their possibly adverse effects [4]. By assumption, ACEis reduce systemic resistance by decreasing afterload and systemic pressure, which results in increased cardiac output. In the case of Fontan circulation, cardiac output is mainly limited by chronic, insufficient ventricular preload; as a result, reducing systemic resistance does not increase cardiac output, but may cause arterial hypotension instead [4].

Similarly, no favorable effects of spironolactone on endothelial function or the reduction of inflammatory cytokine concentration have been proven. Other potential benefits from its use, such as its influence on myocardial remodeling, require further studies [18].

Digitalis glycosides and diuretics are also widely used in Fontan patients despite the fact that their benefits have not been proven [14]. The use of the latter agents should be restricted to patients with fluid retention as they may have an impact on the already reduced preload.

Certain hopes are associated with the use of carvedilol. Japanese researchers proved that the use of this agent with the target dose of 0.4 mg/kg/day was associated with improvements of the NYHA functional class and ejection fraction assessed by echocardiography, especially in patients with a morphologically single left ventricle [19].

Currently, the most convincing evidence for physical capacity improvement after Fontan procedures has been gathered with regard to agents influencing the pulmonary bed. The prospective, randomized, double-blinded TEMPO study proved the favorable impact of bosentan on both physical capacity and NYHA class [20]. Similar results were achieved in several studies using sildenafil; its positive effect on hemodynamic conditions was documented [21, 22].

On the other hand, it should be pointed out that all studies so far had short follow-up periods (up to 14–16 weeks) and that physical capacity improvement does not necessarily have to translate into improvements of more crucial parameters such as survival length or time until clinical deterioration.

One third of patients experience cardiac dysrhythmias requiring treatment within 15 years after the Fontan pro-

cedure. This condition is associated with poor prognosis [6, 23]. The prevalence of dysrhythmias is significantly influenced by the employed procedural technique. They are most common in elderly patients in whom atriopulmonary connections are created. Newer procedural techniques, such as the lateral tunnel or the extracardiac conduit, significantly reduce this risk [3].

The conservative treatment options for supraventricular dysrhythmias (most commonly atrial: atrial fibrillation/flutter) are limited. Despite challenges, the treatment should always aim to maintain sinus rhythm. In order to achieve this, Vaughan-Williams class III agents (amiodarone, sotalol) are administered, or cardioversion is performed. If this proves ineffective, or in the case of pharmacotherapeutic complications, percutaneous ablation should be performed. Although the procedure is technically challenging, especially in patients with extracardiac conduits, its effectiveness is high, and the number of associated complications low. According to the data published by Correa *et al.*, ablation was fully or partially successful in 85% of patients after Fontan procedures with lateral tunnels or complete extracardiac conduits. Notwithstanding, dysrhythmias recurred in long-term follow-up in 50% of the patients [24].

The most common treatment for symptomatic bradyarrhythmias is double-chamber stimulation (Fig. 3), preferably with the use of steroid-eluting electrodes [25, 26]. Despite the lack of connections between the superior vena cava and the single ventricle, it is possible to use endocavitary electrodes even in patients with extracardiac conduits [27, 28].

Due to the slowed flow of blood in the systemic venous system, chronic inflammation, and increased platelet activity (despite the often reduced platelet count), patients after

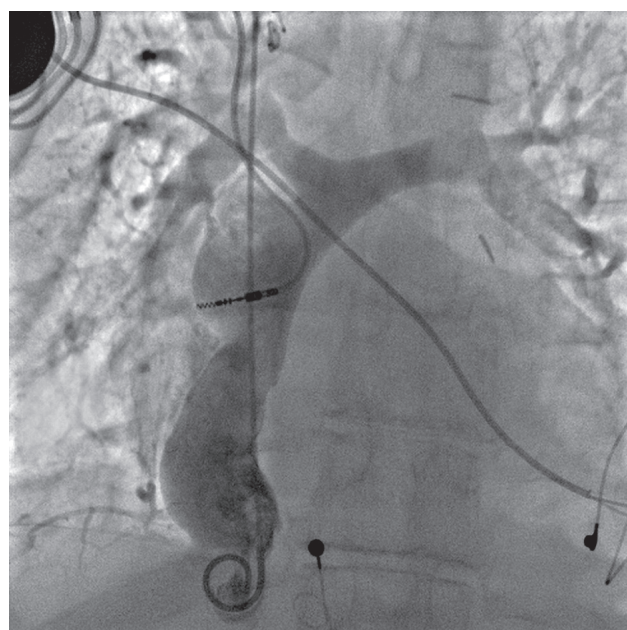


Fig. 3. A 16-year old patient after a Fontan procedure, who was implanted with a DDDR pacemaker due to a 3<sup>rd</sup> degree atrioventricular block (an endocavitary atrial electrode and an epicardial ventricular electrode)

Fontan procedures are especially vulnerable to thromboembolic complications and thus require anticoagulation or antiplatelet treatment. There is currently no decisive evidence on which of these antithrombotic prevention methods is better [29, 30]. Regardless, the use of anticoagulation is universally accepted in the following cases: during the first year after the creation of a complete extracardiac conduit, in elderly patients with atrioventricular anastomosis, in patients with atrial dysrhythmias, and, obviously, in patients with previous thromboembolic incidents.

Protein-losing enteropathy, plastic bronchitis, and chylothorax result from chronic pressure elevation in the systemic veins. It should be stressed that the occurrence of these complications is associated with unequivocally poor prognosis; their presence accompanied by progressive circulatory insufficiency is described as a “failing Fontan” [31].

In the treatment of chylothorax, good results may be achieved by introducing proper diet, i.e., limiting the consumption of fat while supplementing medium-chain triglycerides (MCTs) [32]. Furthermore, adequate consumption of calories and protein should be ensured.

Providing successful treatment for protein-losing enteropathy is challenging. This condition involves not only hypoalbuminemia, but also immune disorders and coagulopathy. Increased stool concentrations of  $\alpha$ 1-antitrypsin are an important biomarker for the diagnosis of this condition.

In the case of PLE, the first diagnostic priority should be to exclude its inflammatory background as well as factors promoting increased pressure in the systemic venous system (e.g., stenosis of the Fontan tunnel or the pulmonary arteries).

The first stage of treatment involves conservative therapy with steroids (oral budesonide) and heparin [33, 34]. Benefits of sildenafil administration have also been noted [35]. It has been demonstrated that inflammatory changes and mesenteric perfusion disorders coexist in PLE patients, causing damage to the intestinal mucosal barrier. Administering sildenafil to these patients, apart from influencing the pulmonary bed, also contributes directly to reducing resistance and improving perfusion in the mesenteric vessels, thus reducing protein loss [36]. There are also reports demonstrating the efficacy of somatostatin analogues [31].

When pharmacological methods do not yield expected improvement, interventional treatment or cardiac surgery should be considered, including heart transplantation.

Cardiac catheterization with a concurrent interventional procedure should be considered in all cases when the patient's condition deteriorates. The introduction of modern interventional methods, such as angioplasty and stenting for stenoses in the Fontan system or closure of *de novo* occurring vascular connections using various plugs, has strongly improved the patients' comfort and has contributed to prolonging their lives.

According to recommendations by the American Heart Association (AHA), creating a fenestration (or enlarging an already existing one) should be considered in patients with “failing Fontan” physiology [37]. The creation or enlarge-

ment of the fenestration offers hemodynamic improvement by decompressing the venous system and improving the filling of the single ventricle by increasing preload and cardiac output. On the other hand, these benefits may be offset by hypoxemia and the risk of crossed emboli.

Both cardiac surgery (e.g., converting an atriopulmonary connection to an extracardiac conduit) and heart transplantation are burdened with a high risk of complications due to the often complicated anatomy, the high risk of another sternotomy, and the severe general condition of patients. In many cases, a heart transplant is the only effective method of treating PLE. Approximately 40% of patients qualified for heart transplantation had been previously diagnosed with PLE. Previous reports had underscored that this is one of the most important factors increasing perioperative mortality (approx. 40% of PLE patients died), but newer studies do not appear to confirm this [38]. The effects of heart transplantation in Fontan patients are increasingly better; at present, the survival of such patients is similar to that of patients receiving heart transplants for other reasons. One-year and 5-year survival vary, respectively, from 76% to 84.8% and from 68% to 70.8% [39, 40].

## Conclusions

In 1968, Francis Fontan and Eugene Baudet performed a pioneering procedure, which has since saved the lives of thousands of children [1]. The method creates a new type of circulation with distinct hemodynamic properties. However, it is associated with new complications that are not encountered in other types of patients, thus requiring a different therapeutic approach. Good understanding of the pathophysiology of this system is key for making accurate treatment decisions. Optimism can be found in the strong development of large registers of Fontan patients and the increasing number of prospective studies concerning their treatment. This contributes to improved care for this group of patients, resulting not only in prolonging their lives, but also in improving their comfort. Notwithstanding, more studies are needed to create universally accepted guidelines for the treatment of patients undergoing Fontan procedures.

## Disclosure

Authors report no conflict of interest.

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