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The pathophysiology and complications of Fontan circulation

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Abstract. The Fontan operation has been the final palliation for patients born with congenital heart defects with a functional single ventricle for more than 4 decades. The "normal" Fontan physiology is characterized by the loss of the sub-pulmonary ventricle with consequent elevated pressure in the caval system, non-pulsatile blood flow in the pulmonary circulation and at least mild reduction of the systemic output. When successful, this procedure is associated with a range of benefits including improved arterial saturation and abolishment of chronic volume overload, allowing a fairly normal life to the majority of patients through early adulthood. As we enter the 5th decade of caring for patients palliated with the Fontan procedure, it is evident that adult survivors face significant morbidity due to multiorgan dysfunction, early mortality and need for heart transplantation. Several late complications may occur: ventricular dysfunction, arrhythmia, cyanosis, exercise intolerance, elevated pulmonary vascular resistance, protein-losing enteropathy, plastic bronchitis, hepatic and renal complications. The mechanism of late Fontan failure is multifactorial and not completely understood, it depends on interactions between the ventricle, the pulmonary vascular bed, the venous and lymphatic compartments. *Conclusions:* the aim of this review is to describe the pathophysiology of Fontan circulation and the clinical and hemodynamic characteristics of early and late failing Fontan survivors, their association with morbidity and mortality, and the strategies for their management. (www.actabiomedica.it).

Key words: Fontan Circulation, Univentricular Heart, Pathophysiology, Complications

Introduction

The Fontan operation has been the final palliation for patients born with congenital heart defects with a functional single ventricle for more than fifty years. This procedure allows a near normalization of arterial saturation and the removal of chronic volume overload.

The original Fontan operation was first performed in 1968 by Fontan and colleagues (1) in order to completely separate the pulmonary and systemic circulations in patients with tricuspid atresia. This operation consisted in the classical Glenn shunt (2) and atrio-pulmonary connection: the superior vena cava (SVC) was connected to the right pulmonary artery (PA) and the right atrium (RA) to the left pulmonary artery, with the interposition of a homograft.

Since the first description, several modifications have been introduced. In 1980 Kreutzer et al. (3) described their modified atrio-pulmonary connection techniques. These techniques no longer included the interposition of a homograft, that would not have worked properly when subjected to a continuous passive flow.

In 1979 Björk and colleagues (4) devised an operation in which the RA appendage (RAA) was anastomosed to the right ventricle (RV) in order to use it as a pumping chamber.

Finally, total cavo-pulmonary connection (TCPC) was described by the group of De Leval (5) in 1988. This procedure consisted in an end-to-side anas-

tomosis of the SVC to the undivided right pulmonary artery and the channeling of the inferior vena cava (IVC) blood flow towards the pulmonary artery, using an intra-atrial tunnel. The advantages of this technique were essentially a reduced arrhythmic risk and a diminished energy loss in the system.

At the end of the 1980s, Puga (6) and Marceletti (7) introduced the extracardiac TCPC that, via the interposition of an IVC-to pulmonary artery extracardiac tunnel, led to the complete redirection of the systemic venous flow. This procedure allowed a further reduction of the arrhythmic risk due to the absence of sutures and the lower pressure at the sinus node and crista terminalis area.

Notwithstanding the recent modifications, which have improved the life expectancy of these patients, the Fontan procedure remains a palliative surgery prone to a number of late complications.

The Fontan circulation is achieved throughout three stages: stage 1 most commonly consists in a systemic-to-pulmonary arterial shunt, but it can vary depending on the underlying cardiac malformation. Stage 2 consists in replacing the systemic-to-pulmonary shunt with a superior cavo-pulmonary connection that unloads the systemic ventricle. Finally, stage 3 consists in the completion of the TCPC, by interposing an extracardiac IVC to PA conduit with or without fenestration. Although in most centers stage 2 is performed at the age of 6-12 months and stage 3 at the age of 18 months-4 years, the ideal age for Fontan procedure remains a matter of debate (8).

Good candidates for this procedure must have a good ventricular function, a normally functioning atrioventricular valve, good size of the pulmonary vessels and low pulmonary vascular resistance (PVR).

Pathophysiology of Fontan circulation

Differently from the normal cardiovascular system, where the pulmonary and systemic circuits are connected in series and driven by two synchronized pumps, in the Fontan circulation, the loss of the subpulmonary pump is associated with an elevated pressure in the caval system, a non-pulsatile blood flow in the pulmonary circuit and at least a mild reduction of the systemic output (8).

In this non phisiologic circulation the venous flow through the cavo-pulmonary circuit is maintained via a combination of passive and weakly active forces.

The central venous pressure should be equal or higher than the pulmonary pressure in order to recruit the whole pulmonary vascular bed. It should typically be in the range of 12 to 14 mmHg. At the same time, it should be low enough to prevent lymphatic stasis and edema. This concept is well known as the "Fontan paradox".

The ventricular pump compels the blood flow into the pulmonary vascular bed, mainly during systole. At the same time, the ventricle, pulling downwards the atrioventricular valve/s and expanding the atrial volume, exerts a suction force drawing blood forward (9). Similarly, passive ventricular filling is guaranteed by both normal diastolic compliance and low end–diastolic pressure (8,10) (Fig. 1).

Cardiac output

The presence of a passive cavo-pulmonary flow and the absence of a subpulmonary ventricle influence the cardiac output state. This system is not able to deliver a normal quantity of blood volume across the pulmonary vascular bed; the consequence is a reduced ventricular filling and a low stroke volume. This chronic volume depletion state is worsened by the ventricular inability to increase stroke volume during exercise or whenever the demand increases (11,12).

It is evident that the ventricle does not control the cardiac output, pumping only the amount of blood volume supplied by the cavo-pulmonary system, and that the real determinant of cardiac output is the impedance of the system.

Over time, volume depletion causes a progressive decline of ventricular function, leading to a vicious cycle characterized by increased end-diastolic pressure, systemic venous congestion and low cardiac output.

Pulmonary vascular resistance

It is well known that the quality of pulmonary vascular bed is the cornerstone of the Fontan circulation and the major determinant of patients' outcome (13).

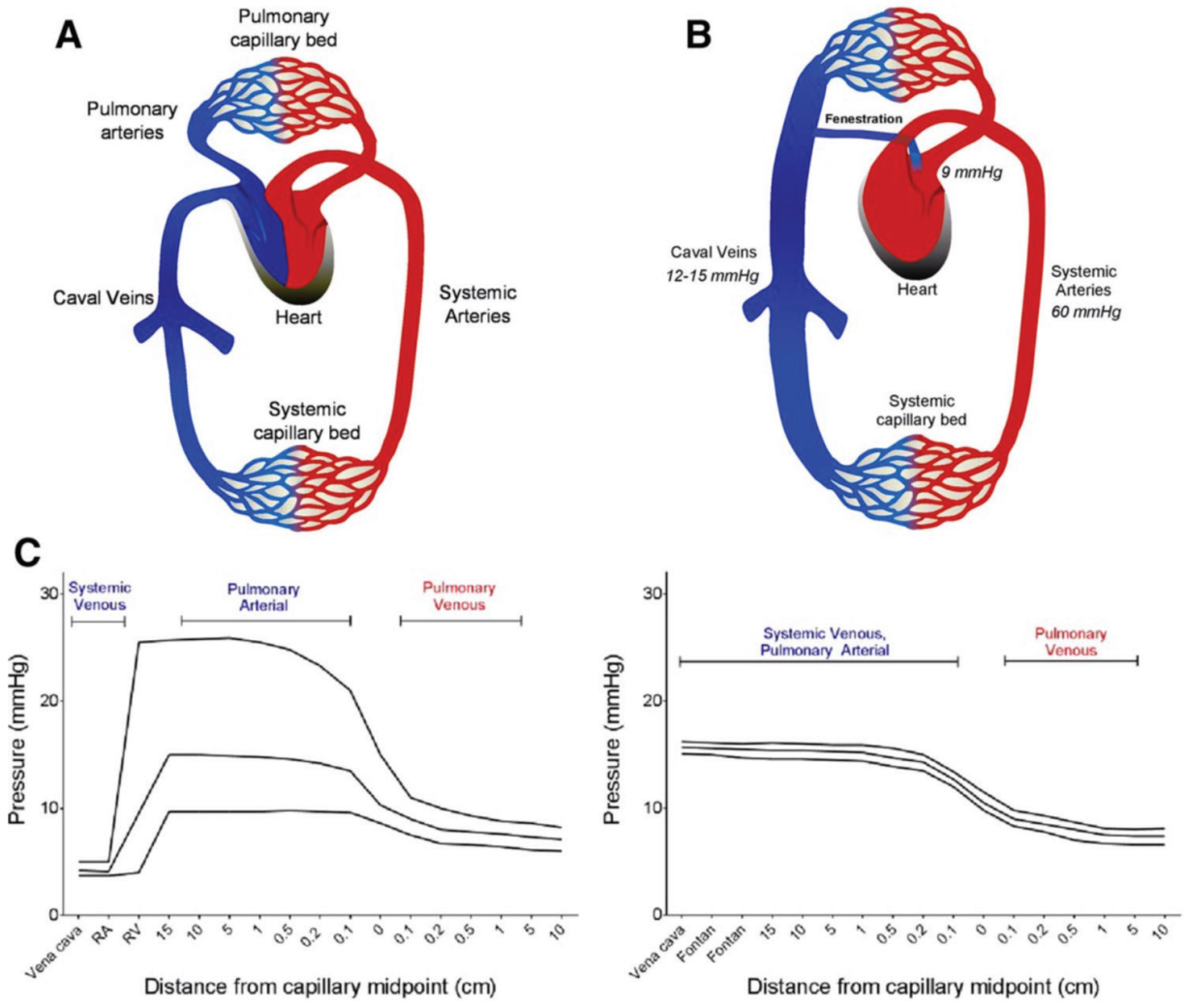

Figure 1. Fontan Physiology. [From G. R. Veldtman et al Congenital Heart Disease. 2017; 12:699–710 (10)]

Gewillig (8) compares the cavo-pulmonary system to an hourglass with different bottlenecks, PVR represents the critical bottleneck of the entire system since it controls the cardiac output.

Pulmonary vasculature is generally abnormal in patients with functional single ventricle. Indeed, during fetal life, pulmonary flow is often reduced, leading to an inadequate development of pulmonary arteries (14).

Pulmonary vascular bed can still grow after birth, but only if sufficient flow is driven at an adequate pressure (15). This can be obtained only immediately after birth, at first palliation, when a systemic-to-pulmonary arterial shunt is placed to increase pulmonary blood flow. Thus, the first step is the most important one, as it may improve the quality of pulmonary vascular bed.

Failing Fontan and long-term complications

Although the hospital survival after Fontan procedure is now greater than 80%, the likelihood of being free from any morbidity over time remains quite low (16).

In fact, the presence of non-pulsatile pulmonary blood flow through the cavo-pulmonary system prompts an endothelial dysfunction characterized by a decreased production of nitric oxide (17,18) and an increased

level of endothelin (19). Moreover, surgical scarring and potential mechanical obstructions in the cavo-pulmonary system may contribute to deteriorate the pulmonary vascular bed, increase PVR (20) and reduce exercise capacity (21).

There is great variability in the clinical outcome of Fontan patients: some of them exhibit minimal clinical symptoms, while others show significant complications.

A recent study collecting data from 683 adult Fontan survivors from the Australian and New Zealand Fontan Registry, reported a variety of common morbid complications, and a substantial incidence of premature death, particularly in patients with atrio-pulmonary connections.

Higher rates of death or heart transplantation due to heart failure were reported among patient with functional univentricular heart and systemic right ventricle (22).

The natural history of Fontan patients is characterized by a progressive increase in PVR and a subsequent reduction of cardiac output. This, together with other poorly known mechanisms, leads to Fontan circulation failure.

The rising in PVR causes a chronic venous hypertension prompting peripheral stasis and congestion in the lymphatic system. The major complications of Fontan circulation are: cyanosis, hepatic dysfunction, protein-losing enteropathy (PLE), plastic bronchitis (PB), arrhythmia and coagulation abnormalities. A pro-inflammatory state, increasing the risk of complications after Fontan repair, has also been described (23).

Cyanosis

Even though Fontan circulation should ideally allow a near normalization of the systemic arterial saturation, these patients are often mildly hypoxemic (23).

The major causes of desaturation are: the presence of a surgically created fenestration or baffle leaks, the drainage of the coronary sinus into the left atrium and the presence of pulmonary arteriovenous malformations and veno-venous collaterals draining into the pulmonary veins or into the left atrium (9).

The diagnosis of these shunts can be challenging and echocardiography, even when performed with agitated saline contrast administration, could not be accurate enough to detect small collateral vessels.

The gold standard for the diagnosis remains angiography: it allows the detection of both pulmonary arterio-venous malformations and veno-venous collaterals as well as baffle leaks.

Furthermore, transcatheter therapy is an effective and safe treatment for most causes of cyanosis: it consents the embolization of veno-venous pulmonary collaterals as well as the occlusion of fenestration and baffle leaks with percutaneous devices (24,25).

Hepatic dysfunction

During the long-term follow-up after Fontan palliation, both high central venous pressure and systemic hypoperfusion lead to congestive hepatopathy. Minor fibrosis, to liver cirrhosis (LC), and even hepatocellular carcinoma (26) can be found in nearly all patients with Fontan circulation (Fig. 2).

Mild hepatomegaly, thrombocytopenia and mild to moderate elevations in serum liver enzymes are common but rarely have a clinical manifestation. Ascites, reduced drug clearance, decreased synthetic function, and hepatic encephalopathy can also be found in failing Fontan circulation at its end-stage (27).

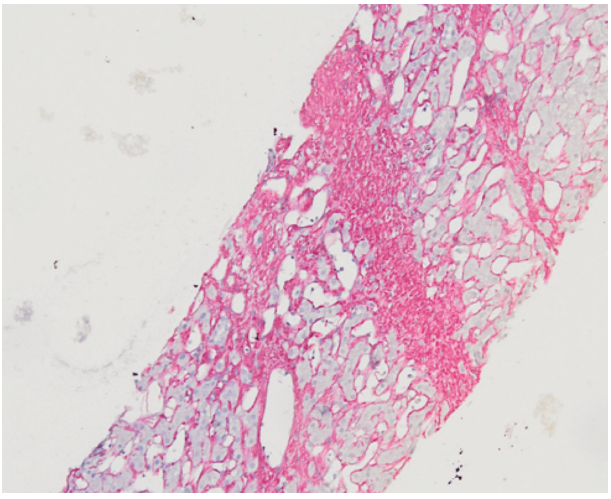

Figure 2. Fontan associated liver disease (FALD) histology. Trichome stains from a patient 7 years post-Fontan showing expanded fibrosis band resulting in nodule and fibrosis which extend from portal tracts with pericellular fibrosis in the areas of dilated sinusoids. (Images courtesy of P. Calvo, MD).

In order to early detect direct or indirect signs of liver fibrosis, several authors have measured serum biomarkers and/or used various techniques such as ultrasound, CT, MR and biopsy (28,29).

Recently, the decline in percent-predicted peak VO2 and oxygen pulse at the cardiopulmonary exercise testing (CPET), has been associated with increased odds of liver disease in adults (30).

However, biopsy remains the gold standard to detect liver damage, even if it is not frequently used as a screening technique in asymptomatic Fontan patients, due to its limited sensitivity and some risk.

Among noninvasive assessments of fibrotic histological changes, hepatic elastography, initially reported as a reliable and easily available technique for liver stiffness (LS) evaluation (31), has been recently questioned for its poor correlation with the biopsy (32).

However, it has been demonstrated that LS rapidly increases after TCPC, and it strongly correlates with the PVR.

Finally, the MELD-XI score (Model for End-stage Liver Disease excluding INR), previously described as a risk factor for death from congestive heart failure, sudden cardiac death, and cardiac transplantation, increases linearly with the time interval since Fontan and correlates with LS. Thus, both methods, initially designed to evaluate chronic hepatitis, might be a useful tool to follow patients with Fontan circulation (33). However, their use in Fontan patients has not been validated so far.

It is now clear that Fontan circulation causes early, progressive and irreversible liver damage. In order to prevent or delay this condition, a strict multi-disciplinary follow-up, focusing on the liver status is mandatory. Early medical treatment targeted at lowering PVR and managing portal hypertension might be an option.

Protein-losing enteropathy

Protein-losing enteropathy (PLE) occurs in 5-15% of Fontan patients and is associated with significant morbidity and mortality (34).

PLE refers to the loss of serum proteins into the gut lumen, leading to chronic diarrhea, general abdominal discomfort and peripheral edema.

The diagnosis should be made only if clinical manifestations (peripheral edema, abdominal distension or discomfort, diarrhea, ascites, pleural or pericardial effusion) coexist with laboratory criteria (35) (Tab 1).

In addition to classical clinical and laboratory manifestations, patients with PLE often show immune abnormalities, such as CD4 lymphopenia and hypogammaglobulinemia. In most cases this condition is not associated with an increased infectious risk, apart from a delayed clearance of cutaneous viral infections (36,37).

Even though PLE etiology is not yet fully understood, it has been speculated that the increased systemic venous pressure leads to an increased lymph production and reduced chyle drainage from the thoracic duct to the great veins (34). Moreover, the chronic low cardiac output could lead to increased mesenteric vascular resistance and, eventually, to intestinal inflammation, with reduced integrity of the enterocytes barrier. This hypothesis has been recently confirmed by detection of high levels of fecal calprotectin in these patients (38).

Risk factors for PLE include AV valve regurgitation previous to Fontan, longer cross-clamp time dur-

Table 1. Criteria for the diagnosis of PLE.

Clinical manifestations	+	**Hypoproteinemia**	+	**Augmented enteric protein loss**	
Peripheral edema Abdominal distension Diarrhea Ascites Pericardial effusion Pleural effusion	**AND**	Decreased serum albumin <3.5 g/dL And Total proteins level <6.0-6.3 g/dL	**AND**	Fecal aplpha-1-antitrypsin clearance	
				>56 mL/24h *With Diarrhea*	>27 mL/24h *Without Diarrhea*
				OR	
				Spot Fecal alpha-1-antitrypsin concentration >54 mg/dL	
				OR	
				Nuclear scintigraphy	

ing operation, prolonged pleural effusions after surgery, early Glenn procedure and HLHS (39,40).

This condition, despite the improvement in medical, surgical and interventional management, has a high mortality risk, close to 30%. In survivors, symptoms do rarely regress (41).

Strategies to control PLE should include attempts to reduce mechanical obstruction, enhance cardiac output, reduce enteric protein loss and improve nutritional status.

Therefore, a high-protein, low-fat diet with medium-chain triglyceride supplementation is recommended.

Subcutaneous unfractionated heparin has proven to decrease basal membrane permeability and reduce enteric inflammation. Similarly, budesonide an enteric-specific steroid, can be effective in reducing inflammation in these patients (42).

Pulmonary vasodilators, like sildenafil and inhaled prostacyclins, seem to be useful in PLE treatment, by reducing PVR and improving cardiac output. Spironolactone improves cardiac and endothelial cell function and reduces inflammation. Finally, octreotide has been used with some success, but evidence remains limited (43).

Surgical and interventional strategies include the relief of possible Fontan obstruction, the creation of a fenestration, the decompression of the thoracic duct by diverting the innominate vein into the right or left atrial appendage (44) and the percutaneous embolization of hepato-duodenal lymphatic channels, identified by hepatic lymphangiography and contrast-guided duodenoscopy (45).

Cardiac transplantation remains a potential treatment when other strategies have failed, with a good survival rate (91% at 2 years) (43,46). PLE severity, duration, and treatment do not influence post-transplantation outcome and it seems to resolve in nearly all survivors (47).

In some patients a mechanical support device can be necessary as a bridge to transplant (48).

Plastic bronchitis and lymphatic congestion

Plastic bronchitis (PB), reported in 1-4% of children after Fontan palliation, is a severe respiratory disorder, characterized by the development of gelatinous plugs within the airways having typical bronchial "casts" shape (34) (Fig. 3).

Risk factors include prolonged chest tube drainage, postsurgical chylothorax or ascites, previous aortopulmonary collateral coiling and aortic arch reconstruction (49).

The pathophysiology of PB is still largely unknown. Like PLE, PB probably has a multifactorial origin where genetic factors, inflammation, elevated systemic venous pressure and lymphatic stasis, play a role (50).

It is well known that increased systemic venous pressure leads to a higher lymphatic pressure and promotes lymph accumulation in the pulmonary interstitium (51). An abnormal dilation of lymphatic channels with retrograde lymph flow towards the pulmonary carina has been shown (52,53).

Current evidence suggests that the inflammation is superposed on a dysregulated mucus secretion due to endobronchial lymph leakage (45). Therefore, in accordance with the prevailing mechanism PB might have a prevalent inflammatory or non-inflammatory etiology (type I and II PB) (34).

If an obstruction in the Fontan circuit has been ruled out, initial management of PB includes bronchodilators, steroids, inhaled hypertonic saline, mucolytics, antibiotics, bronchoscopic toilet and chest physiotherapy. Pulmonary vasodilators, and macrolides with their mucoregulatory and anti-inflammatory effect, could also be effective (49).

Figure 3. Expectorated bronchial casts from a 9-year-old patient with plastic bronchitis 3 years after Fontan operation. These casts are composed of proteinaceous material and they are typically acellular.

Inhaled topical treatments, such as heparin, urokinase, tissue plasminogen activator, recombinant DNAse and N-acetyl cysteine, target the cast components and may have some positive effects in these patients (52,53).

Finally, surgical interventions such as fenestration of the Fontan circuit or innominate vein shunting into the atrium, and percutaneous strategies such as lymphatic channels embolization or thoracic duct branches isolation with covered stents, may also be helpful (34).

Thoracic duct ligation is not considered the treatment of choice, due to the risk of worsening ascites and/or PLE (34,39).

Arrhythmia

Although the onset of arrhythmia has been decreased in patients with TCPC, it remains one of the most common complications in patients with atriopulmonary anastomosis, affecting more than 50% of them (54).

It is well known that arrhythmia has a detrimental effect on the Fontan hemodynamics.

The most common tachy-arrhythmia is intra-atrial re-entrant tachycardia, which may occur for multiple macro-re-entry circuits as a result of postoperative atrial scarring and atrial enlargement (54).

Re-entrant arrhythmia poorly responds to antiarrhythmic drugs. Moreover, only few drugs can be safely used in patients with a univentricular heart. Although radiofrequency catheter ablation has proven to be effective, it is burdened by the risk of relapse over a period of 6-12 month in over 80% of patients (55). Moreover, in this population, ventricular arrhythmias are responsible for the majority of sudden deaths (9,2%) (56).

Brady-arrhythmias due to sinus node dysfunction (SND) and/or the presence of suture lines and scars often require permanent pacing. Heart rate variability analysis could have a role in identifying Fontan patients at risk of developing SND (57).

Anticoagulation therapy remains the cornerstone in Fontan patients, regardless the occurrence of arrhythmia (58).

Thromboembolic complications

Fontan patients have a higher risk of thromboembolism, occurring in up to 20% of patients (59).

The loss of pulsatile flow in the pulmonary circulation and the subsequent venous stasis lead to a hypercoagulative state, that is worsened by the deficiency of protein C, protein S, antithrombin III and increased platelet reactivity (59).

Pulmonary thromboembolism is a serious and potentially lethal complication of Fontan circulation since it increases PVR and suddenly impairs cardiac output, leading to hemodynamic instability. Systemic embolization can also occur causing myocardial ischemia or stroke.

Even though there is no general consensus on the optimal medical treatment to reduce thromboembolic risk, these patients should be treated with either aspirin or vitamin K antagonists (60). Recently some authors reported a successful use of novel oral anticoagulants (NOACs) in a small group of adult Fontan patients (61).

Hormonal dysfunction

A portal system exists in the pituitary gland as well as in the liver, and it becomes a superportal system after the completion of Fontan operation. As a consequence of central venous congestion, pituitary volumes tend to enlarge in Fontan patients. This condition might be responsible for the impaired synthesis and secretion of the anterior pituitary hormones, including somatotrophins, thyrotrophins, corticotrophins, lactotrophins, and gonadotropins (62). In fact, in Fontan survivors a higher prevalence of short stature, abnormal BMI and delayed puberty has been observed (63). The dysregulation of calcium metabolism has also been described. This might be due to parathyroid glands dysfunction, and it leads to vitamin D deficiency despite age, time after Fontan procedure, and presence of PLE (64). Therefore, vitamin D measurement and its supplementation are recommended.

Conclusions

The Fontan operation is the treatment of choice for patients born with a functional single ventricle. Nevertheless, this procedure remains a palliative sur-

gery which has a high incidence of long-term complications. In order to improve the outcome, a perfect completion of the TCPC should ideally be obtained in every patient. This population should undergo a strict and multidisciplinary follow-up aimed at preventing multiorgan failure.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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