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The Fontan circulation: who controls cardiac output?

Marc Gewillig[a,*], Stephen C. Brown[b], Benedicte Eyskens[a], Ruth Heying[a], Javier Ganame[a], Werner Budts[a], Andre La Gerche[a], Matthias Gorenflo[a]

[a]*Paediatric and Congenital Cardiology, University Hospitals Leuven, Belgium*
[b]*Paediatric Cardiology, University of the Free State, South Africa*

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Summary

In a Fontan circuit the mechanisms involved in control of cardiac output at rest and during exercise differ significantly from normal. The classical model presumes an unlimited preload which is not available in the Fontan circuit. This review critically analyses the role of contractility, heart rate, and afterload and highlights the importance of pulmonary vascular resistance (PVR) in determining adequate preload and, therefore, cardiac output in these patients. A conceptual model of the determinants of cardiac output in Fontan patients is presented.

Keywords: Univentricular heart; Fontan circulation; Cavopulmonary connection; Cardiac output

1. Introduction

In a normal subject cardiac output at rest can be predicted by a model including variables such as heart rate, contractility of the ventricle, afterload and preload. A mild increase of heart rate or contractility, or some afterload reduction will result in increase of cardiac output because of intrinsic adequate preload reserve. During exercise, cardiac output can increase up to five-fold and to even more in trained athletes due to augmentation of all the determinants mentioned [1, 2]. It is important to recognise that augmentation of cardiac output is extremely dependent upon preload reserve. Exercise induced increases in cardiac output are partly explained by the Frank Starling mechanism, but left ventricular filling is more important than myocardial contractility in augmenting stroke volume in normal individuals [3]. Clinicians have traditionally used this model to understand the changes of cardiac output in healthy and diseased hearts. This model works extremely well when describing the pathophysiology of primary cardiac problems, such as ischaemic heart disease.

The model becomes less explanatory or predictive in conditions without ventricular preload reserve, such as acute severe blood-loss, dehydration, mitral stenosis, pulmonary hypertension, the Mustard atrial rerouting and the Fontan circulation.

In the Fontan circulation, the systemic vascular bed and the pulmonary vascular bed are connected in series without the presence of a pre-pulmonary pump to add forward energy to flow through the lungs (Fig. 1). Flow return from the pulmonary vascular bed is thereby restricted, resulting in a decreased or absent preload reserve to the ventricle. Typically, cardiac output (and thus preload) in a Fontan circulation at rest is decreased to 70% (range 50–80%) of normal for body surface area. The preload insufficiency is made more apparent by a ventricle which is (at least initially) dilated and/or overgrown from the preoperative volume overloaded state [4].

Clinical experience has shown that in patients after Fontan operation, control of cardiac output differs from normal and becomes quite complex. The regulation of cardiac output in the Fontan circuit is frequently poorly understood, and this has led to frustration for many clinicians who tried to manipulate this circulation making use of conventional strategies.

This overview aims to wrap up current knowledge of the Fontan circuit, and to provide a conceptual model that is more adapted for this physiology. When assessing the nature of this circuit, the ventricle remains a good starting point to describe the different variables: contractility, heart rate, afterload and preload.

2. Contractility

Inotropic drugs can enhance ejection of any ventricle, and will increase output of a ventricle with preload reserve. However, such drugs will fail to achieve a comparable increase of output in a Fontan circulation with limited preload: the ventricle will squeeze harder but not much more! This has been observed numerous times both in the intensive care unit early after the Fontan operation as well as in chronic patients [5, 6]. Only in the Fontan patient with extreme ventricular dysfunction not due to underloading, some increase of output may be observed by inotropics.

*Corresponding author. University Hospital Gasthuisberg, Herestraat 49, B 3000 Leuven, Belgium. Tel.: +32 16 343865; fax: +32 16 343981.
E-mail address: marc.gewillig@uzleuven.be (M. Gewillig).

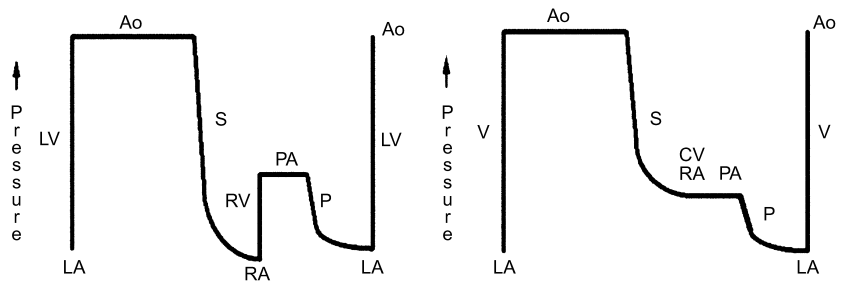

Fig. 1. Schematic representation of the normal cardiovascular circulation (Left) and Fontan circulation (Right). (Left) The pulmonary circulation (P) is connected in series with the systemic circulation (S). The right ventricle maintains a right atrial pressure lower than the left atrial pressure, and provides enough energy for the blood to pass through the pulmonary resistance. (Right) Fontan circuit: the systemic veins are connected to the pulmonary artery (PA), without a subpulmonary ventricle or systemic atrium. In the absence of a fenestration, there is no admixture of systemic and pulmonary venous blood, but the systemic venous pressures are markedly elevated. Ao, aorta; CV, caval veins; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; V, single ventricle.

Systolic function indices are frequently lower in patients after the Fontan operation compared to healthy controls [7]. However, this is not necessarily due to decreased myocardial contractility. Most inferences of depressed contractility have been deduced from measurements with considerable load dependence [8]. The single ventricle typically evolves from volume overloaded, dilated and hypertrophied while shunted or banded, to overgrown, under-filled and 'contracted' after a cavopulmonary connection. Despite the sudden involution of the ventricle after the operation, many studies have shown acceptable ejection indices and that the contractile response to dobutamine in Fontan patients was normal [9, 10], indicating preload dependency. No matter how good the pump, it can only pump out what comes in, both at rest and during exercise.

Early in the Fontan experience during the 1980s, ventricular dysfunction was a risk factor for the operation and the functional outcome in early and medium-term follow-up. Since the 1990s when excessive volume overloading and acute unloading have been avoided, ventricular dysfunction, unless severely impaired, has become a less important risk factor. In recent years, due to expanding indications for Fontan repair, some borderline ventricles have been incorporated in Fontan circuits, making ventricular function once again a more frequent key player. In the long-term with the effects of ageing and declining ventricular function, this may again become more important [11].

- **Conclusion:** ventricular function, when severely impaired, will limit CO. However, in the majority of Fontan patients with reasonable ventricular function, contractility plays no significant role in controlling CO in a Fontan circuit.

3. Heart rate

At rest an increase of the heart rate within physiologic range will increase the output of a ventricle with preload reserve. However, such rate increase has no effect on cardiac output after the Fontan operation. Atrial pacing at different rates at rest showed no change of cardiac output, but a proportional decrease of stroke volume, illustrating that the heart rate is not controlling cardiac output at rest [12]. Only when severely abnormal, such as severe bradyor tachycardia, normalisation of heart rate to physiological rate will improve output and hemodynamics [13, 14].

Fontan patients exhibit what is called 'chronotropic incompetence' during exercise with a heart rate consistently lower than normal controls, and this has typically been attributed to abnormal reflex control of heart rate or adrenergic dysfunction [15–20]. However, adequate preload during exercise is crucial for an increase in heart rate. Every congenital heart surgeon can confirm that, when creating an aorto-pulmonary shunt, heart rate increases significantly upon opening the shunt when removing the vascular clamp. Moreover, the 'chronotropic incompetence' may not be bad at all, or even lifesaving: tachycardia not proportional to output is poorly tolerated in patients with limited preload, such as in patients with a Mustard or a Fontan circuit [14, 21].

Cardiac rhythm is important in this circulation: loss of atrio-ventricular synchronisation will cause an increase of the pulmonary venous atrial pressure and/or a diminished ventricular preload, both of which are known to have negative effects on a Fontan circuit. Maintaining properly timed atrial contractions in patients with a Fontan circuit is more than desirable.

- **Conclusion:** heart rate within physiologic range plays a neglible role in controlling CO in a Fontan circuit.

4. Afterload

When cardiac output decreases, normal homeostatic control of the body will attempt to maintain blood pressure by, amongst others, increasing the systemic vascular resistance. In a failing but normally connected biventricular circulation with a hypocontractile ventricle and preload reserve, a decrease of afterload typically will result in an increase of output. The increase in output will counter the tendency for hypotension, resulting in a good clinical response.

The Fontan patient who is in a chronically low cardiac output state will also generate an increased systemic vascular resistance in order to maintain blood pressure [22–24]. Other reasons for increased vascular resistance may also be involved. In a Fontan circulation, a decrease of afterload without preload reserve will not result in increase of output, but may cause hypotension.

Excessive afterload on the other hand may be detrimental, especially in the systemic right ventricle (RV). Clinicians have frequently observed fast destruction of a systemic RV in the presence of residual or recurrent coarctation.

- **Conclusion:** In patients with a Fontan circuit reduction of afterload most often will not result in a significant increase of CO. Increased afterload is a consequence rather than a cause, and when excessive, may result in rapid deterioration of the ventricle.

5. Preload

It should be no surprise that in a Fontan circulation, where by definition the preload to the ventricle is limited, exactly this preload appears to be the most important determinant for output [25]. Preload to the ventricle is determined by transpulmonary flow and a fenestration if present. Transpulmonary flow is determined by the transpulmonary gradient and transpulmonary resistance.

6. Transpulmonary flow

- **Systemic venous pressure:** at rest there is little variability between 13 mmHg and 20 mmHg. Some degree of congestion is required in order to 'force' transpulmonary flow; pressures above 20 mmHg are rarely seen: the body will rather drop CO, and such pressures will lead to complications, such as oedema, protein losing enteropathy, pleural effusions and ascites [26, 27] requiring administration of diuretics. Systemic venous pressure, therefore, cannot be an important factor of output regulation at rest. At mild to moderate levels of exercise, invasive studies in normal subjects over a wide age range have shown that the mean pulmonary artery (PA) pressure rarely exceeds 25 mmHg [28–30]. Such pressures have been documented during exercise in Fontan circulations [31].
- **Pre-ventricular ('left') atrial pressure:** this pressure shows little variability, and is determined by the atrioventricular valve and ventricular diastolic function: no stenosis, no regurgitation, adequate suction, low filling pressure (not present when severely collapsed or overstretched), adequate coupling of atrial contraction and ventricular filling [32, 33]. When assessing diastolic dysfunction, it is very difficult to discriminate between intrinsic cardiac dysfunction and reduced preload. Many functional diastolic parameters from 'adult' cardiology have been validated in situations with excess preload (e.g. ischaemic heart disease). Senzaki et al. [34] addressed this issue by showing in Fontan patients that measures of diastolic dysfunction were attributable to preload insufficiency rather than intrinsic myocardial properties.
- **Fontan connection resistance:** It has repeatedly been shown that a gradient across the Fontan connection is poorly tolerated with decreasing output. However, current Fontan connections, such as cavopulmonary connections should have no stenosis, and only minimal flow disturbance which might interpose a flow resistance [35, 36]. In well managed patients this factor should, therefore, no longer be a major issue.
- **Pulmonary vascular resistance (PVR):** mild increases of PVR have been shown to significantly decrease output in Fontan circuits [37].

Thus, not only by exclusion but also by reasoning, and supported by a vast amount of circumstantial evidence, PVR appears to be the major determinant of cardiac output in postoperative Fontan patients. Unequivocal proof is tricky and difficult to obtain, but a substantial body of evidence has accumulated over the last years.

- Shachar showed with an early invasive study, that cardiac output both at rest and during exercise is not associated with ventricular ejection indices, but determined by low and decreasing PVR [31].
- A fenestration has been shown to be the single most efficient adjunct in the Fontan circuit to increase cardiac output (in both cross-sectional, serial and cross over studies) [38–42]. Fenestration acts as a restrictive connection between the systemic veins and the preventricular atrium, thereby bypassing the major limitation to flow, namely PVR. If left ventricle (LV) factors were the key limitation, then such a connection would be non- or counter-productive. Any traffic agent or coronary surgeon will confirm that a detour is only efficient when it bypasses the key limiting factor in the circuit; in this case the PVR.
- Positive pressure ventilation is known to increase PVR and will decrease CO in a Fontan patient; negative pressure ventilation has clearly been shown to increase cardiac output in the Fontan patient in the early postoperative period [43, 44].
- Circulating adrenomedullin, a peptide which leads to increased PVR, is elevated in postoperative Fontan patients [45].
- Lévy et al. [46, 47] demonstrated abnormal histology with thickened distal pulmonary vessels in all patients with a Fontan circulation who had pulmonary pressures over 18 mmHg mean and in 51% of those with low pulmonary pressures; endothelin upregulation was identified in those with a failed circuit. Drugs which have an effect on certain endothelial factors (sildenafil, bosentan, nitric oxide) increase cardiac output in selected patients [48–52].
- Several studies have concluded that the most important cause of low cardiac output with impaired diastolic function in the Fontan circuit is due to underfilling i.e. inadequate preload reserve [9, 53–56].
- Using MRI with low dose dobutamine stress testing, Robbers-Visser has demonstrated an abnormal ventricular preload reserve as well as a subnormal response of the pulmonary vasculature in Fontan patients [56, 57].
- Transplant series have shown that the majority of Fontan patients referred for transplant have elevated PVR (>2.8 WU/m^2) and a polymorphism for endothelin-1 receptor [58–60].
- Ventricular contractility has been shown not to be related to increase in cardiac output from rest, unless it is severely impaired; PVR is most likely the cause of impaired CO both at rest and during exercise [17, 34].
- Altitude and Fontan: some patients have a failing Fontan circuit at high altitude, but improve at sea level [61].

Current ethical practises impede finding 'state-of-the-art' evidence that may or may not support these concepts: performing complex invasive studies both at rest and during exercise is currently not acceptable for most Ethics Committees, especially in virtually asymptomatic patients. The reasons why PVR can be elevated either before, or early or late after the Fontan operation is beyond the scope of this article.

7. Conceptual model

Scientists like to work with conceptual models or thought patterns when treating a disease or an abnormal condition. However, it is important to know how limited our insights are regarding Fontan physiology and low flow physiology in general. We are well versed in the myocardial dysfunction resulting from chronic overload but what about 'underload'? Clinicians have frequently observed that in a failing Fontan circulation, even when failure started for a non-cardiac reason with initially a good ventricle, ventricular filling pressures become elevated when reaching the end-stage. At such end-stage failure an elevated left atrial pressure is, therefore, difficult to interpret: is it due to significant primary ventricular diastolic dysfunction or does it reflect chronic deprivation because of preload starvation? Is it possible that ventricular dysfunction in some Fontan patients could result from chronic preload deficiency and lack of 'training' of the stretch/contractile/hypertrophic factors which determine muscular conditioning? This situation is well known in a chronic deprived ventricle due to severe mitral stenosis: impairment of relaxation is unequivocally present with a 'stiff' LV, but balloon angioplasty improves diastolic function within minutes, suggesting that inadequate preload is the major determinant of such 'diastolic dysfunction' [62]. Our current knowledge of the chronic deprived ventricle is very limited, and we must realise that diastolic ventricular function or reserve cannot accurately be assessed in the presence of an 'underloaded' ventricle, especially not with algorithms derived from pathophysiology in 'overloaded' conditions.

The influence of PVR and contractility on cardiac output is reflected in Figs. 2–4. The authors would like to point out that these concepts are based on clinical observations, cross-sectional and serial evaluations of Fontan patients and represent a theoretical model. The graphs reflect that the PVR is the major determinant of circulatory output; ventricular function is important only when severely depressed; systemic venous or atrial pressures also affect cardiac output to lesser degrees; gradients in the baffle should be absent in the well managed patient. One can also understand why fenestration will lead to an acute increase in cardiac output.

Fig. 5 reflects that the degree of PVR where a Fontan patient starts off with, determines future outcome. Many clinicians have observed good Fontan patients with good cardiac output for many years, but borderline Fontan patients tend to have progressively diminishing cardiac output. If one factors in the effects of suboptimal PA growth after Glenn or Fontan [63], absence of pulsatile pulmonary flow, functional loss of lung segments and ageing, it leads to concern.

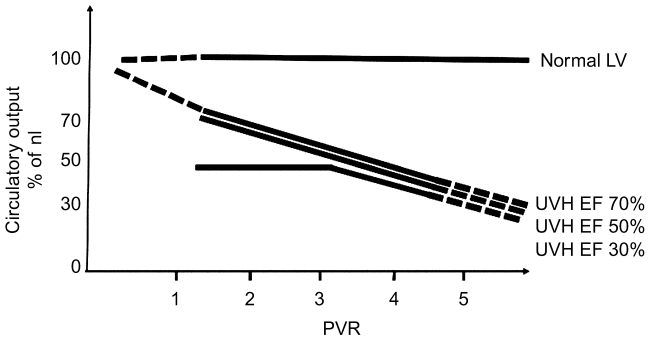

Fig. 3. Relationship of output at rest and pulmonary vascular resistance (PVR) modulated by ventricular function. In a normal subject (solid black line), cardiac output is not influenced by a mild increase of PVR up to 5 Woods Units. An increased PVR is invariably associated with decreased cardiac output at rest in all Fontan patients. If PVR is low, a good output is achieved in patients with normal or moderately depressed ventricular function; however, severely depressed ventricular function invariably results in low output. EF, ejection fraction; F, Fontan; UVH, univentricular heart; LV, left ventricle.

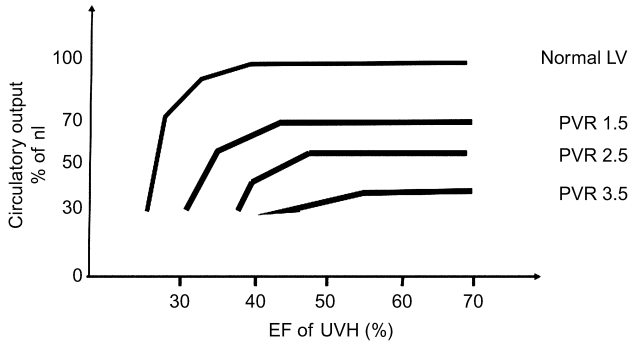

Fig. 2. Relationship of output at rest and ventricular function modulated by PVR. In a normal subject, cardiac output at rest is minimally influenced by ventricular function, except when severely depressed. In Fontan patients, minor changes of PVR result in marked changes of output; only when severely impaired, the ventricle will influence output. EF, ejection fraction; PVR, pulmonary vascular resistance; UVH, univentricular heart; LV, left ventricle.

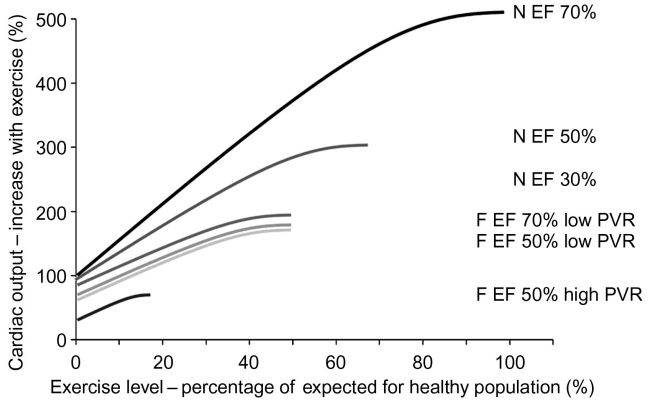

Fig. 4. Relationship of output during exercise, pulmonary vascular resistance (PVR) and ventricular function. A normal (N) subject with a biventricular circuit can increase his output by a factor of 5; if ventricular function is impaired, this will first result in decreased maximal output and subsequently in reduced output at low-level of exercise. In Fontan patients (F) output is more influenced by PVR than by ventricular function; all have significantly impaired exercise capacity. EF, ejection fraction.

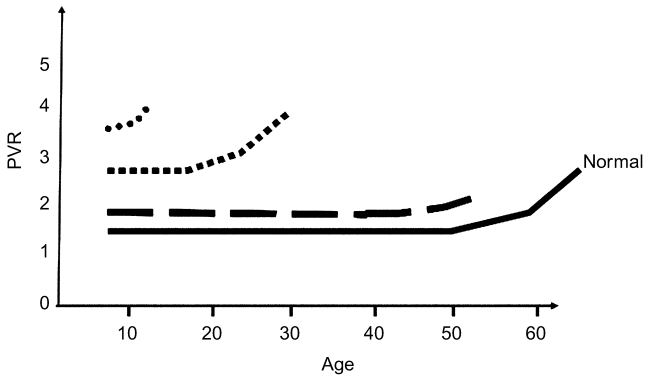

Fig. 5. Evolution of PVR with age. In normal subjects (solid black line), PVR remains low for many decades, and will increase only at old age without significant cardiovascular limitation. In good Fontan patients with low PVR, resistance remains low for many decades, but is expected to increase at older age (semi solid line). In poor Fontan patients with increased PVR (dotted lines), PVR trends to increase faster with poor clinical outcome at resistances beyond 4 units. PVR, pulmonary vascular resistance.

8. Conclusions

- Good circulatory output and thus good long-term outcome in a Fontan patient requires a low PVR;
- Maximal effort must be directed to obtain adequate growth and development of the pulmonary vasculature for the future Fontan circuit; this is especially important at the time of the first palliative procedure;
- Obviously ventricular dysfunction must be avoided, but in a Fontan circuit, good pulmonary vasculature is more important than mild ventricular dysfunction;
- Many conventional cardiac therapeutic measures aiming to alter cardiac function, such as contractility, heart rate and afterload will not significantly influence cardiac output in a Fontan circuit, but will cause frustration for the clinician;
- Abnormal diastolic function may be due to limited preload; algorithms developed in conventional cardiology predominantly dealing with congestive heart failure and unlimited preload should not be extrapolated unchallenged to the Fontan physiology.

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