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REVIEW

CONGENITAL DISEASE

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How cardiac output is controlled in a Fontan circulation: an update

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How is cardiac output controlled in a Fontan circulation: an update

Summary

By creating a Fontan circuit, control of circulation is transferred from the ventricle to the Fontan portal system consisting of the surgical connection, branch pulmonary arteries, pulmonary microvasculature and the pulmonary veins. We present a formula to assist clinicians in understanding the flow dynamics and where they can intervene post Fontan.

$$CO = \frac{\delta P}{\Sigma R} = \frac{CVP/PA - LAP}{R_{CPC} + PVR} + \frac{CVP - LAP}{R_{fenestration}}$$

CVP: Central Venous Pressure; **ΔP**: Pressure Difference; **LAP**: Left Atrial Pressure; **PAP**: Pulmonary Artery Pressure; **PVR**: Pulmonary Vascular Resistance; $\mathbf{R_{CPC}}$: Resistance Cavo-Pulmonary Connection; **ΣR**: Sum of Resistances; **R**: Resistance.

Abstract

After creating a Fontan circuit, control of the circulation is shifted upstream from the ventricle to the newly created Fontan portal system. The goal of this review was to illustrate that the customary laws of biventricular cardiac output no longer apply and explain why standardized cardiac failure treatment regimens have little or no effect on a failing Fontan patient. A Fontan circulation is, in effect, a circulation in series regulated by the basic rules of any hydrodynamic circuit. We developed a formula that elucidates how flow through the critical bottleneck, and therefore through the whole circuit, is controlled. The critical bottleneck in a hydrodynamic model is the prime determinant of overall flow; other (less critical) bottlenecks may control local upstream congestion, but not overall flow. Once relieved, control of flow shifts to the next most significant bottleneck. The available options for improving flow in a hydrodynamic model are identical to those applicable to any dam: tackle the obstruction (the most impactful approach), push harder upstream (the easiest action) or pull/suck further downstream of the bottleneck (the least efficient strategy). In the early stages, the Fontan neo-portal circulation plays a pivotal role in the pathophysiology. The ventricle has little effect and has an impact only at a late stage. The Fontan formula in the present article stands as a valuable tool, aiding physicians in comprehending the pathophysiological and hydrodynamic intricacies of the Fontan circuit within the context of everyday clinical practice.

Keywords: Fontan • Bidirectional Glenn • Circulation • Flow • Bottleneck

ABBREVIATIONS

CVP	Central venous pressure
HR	Heart rate
LAP	Left atrial pressure
LVAD	Left ventricular assist device
LVEDV	Left ventricular end diastolic volume
PAP	Pulmonary artery pressure
PVR	Pulmonary vascular resistance
R	Resistance
R_{cpc}	Cavo-pulmonary connection resistance
$R_{fenestration}$	Resistance of fenestration
SV	Stroke volume

INTRODUCTION

Basic scientists and clinicians possess a solid grasp of the fundamental physiology governing biventricular circulation and are familiar with the classical determinants of cardiac output (CO) in a normal circulation. When heart failure occurs, the success of treatment regimes strongly relies on targeted manipulation of the critical components. As a result, several guidelines for the treatment of heart failure are readily available, and stepwise treatment based on the underlying pathophysiology and type of heart failure is confidently administered.

In contrast, a failing Fontan circulation presents a vexing problem, often yielding discouraging outcomes. Traditional paradigms, rooted in the customary physical laws of biventricular CO, prove inadequate for these patients, frequently leading to minimal or no discernible benefit and lots of frustration for both the patient and clinician alike. Unexpected and new problems surface during the management of these patients: ascites, exercise intolerance, protein-losing enteropathy, plastic bronchitis, thromboembolic complications, Fontan-associated liver disease, arrhythmias, various arterio-venous fistulae and even nephropathy [1–4]. Moreover, the gradual decline in CO over time adds to the exasperation experienced by physicians. It stands to reason that the cardiovascular pathophysiology of a Fontan circuit is diverse and deviates substantially from our conventional understanding of biventricular physiology.

Control of the circulation or the critical bottleneck in a biventricular circulation with a sick systemic ventricle resides within and immediately around the vicinity of that ventricle (preload, contractility, heart rate and afterload). In contrast, the classic determinants for CO change dramatically following the Fontan operation [2, 5]. With the modern Fontan variant of total cavo-pulmonary connection, the surgeon effectively redirects systemic venous return from the caval system directly into the pulmonary artery, without even touching the ventricle. This surgical manoeuvre positions the pulmonary circulation akin to a dam upstream of the heart, resulting in upstream congestion and diminished downstream inertial flow. Consequently, control over upstream congestion and overall flow through the circulation shifts away from the untouched ventricle and brings a new critical bottleneck with its own hydrodynamic forces into the equation.

From a hydrodynamic point of view, the cardiovascular system can be portrayed as several resistances connected in series or in parallel (Fig. 1). These resistances act as potential bottlenecks to the flow, where the flow through the bottleneck is determined by 3 components: the resistance of the bottleneck, the upstream pushing forces and pulling (sucking) forces downstream. When several bottlenecks are present, each bottleneck may cause some degree of upstream congestion, but in a closed circuit, only 1 single bottleneck takes precedence in determining overall flow—the most severe, which then becomes the critical bottleneck. To enhance flow, interventions at the site of this critical bottleneck are the only effective means to improve flow; adjustments at other bottlenecks will be inefficient to increase overall flow. When modelling a circuit, the formula used to calculate the flow across the critical bottleneck typically includes the components that control the overall flow. Identifying the critical bottleneck is frequently straightforward and intuitive; at times, however, complexities arise, and preconceived notions can impede accurate identification. The task of identifying and subsequently modulating the critical bottleneck is akin to the endeavours of an entrepreneur, hydrodynamic engineer or cardiologist.

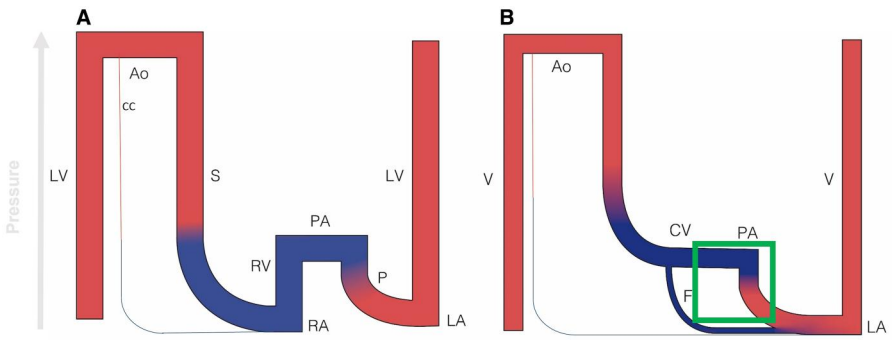

Figure 1: Scheme of the normal cardiovascular circulation and the Fontan circulation. Left: Typical biventricular circulation: the pulmonary circulation is connected in series to the systemic circulation. The right ventricle ensures that the right atrial pressure remains low, typically lower than the left atrial pressure, and delivers the driving force to the blood to overcome pulmonary impedance. Right: Fontan circuit: the caval veins are directly connected to the pulmonary artery; systemic venous pressures are markedly elevated compared to the normal biventricular circulation. The fenestration (F) bypasses the critical bottleneck (green box). Ao: aorta; CC: coronary circulation; CV: caval veins; F: fenestration; LA: left atrial; LV: left ventricle; P: pulmonary circulation; PA: Pulmonary artery; RA: right atrial; RV: right ventricle; S: systemic circulation; V: single ventricle. Line thickness reflects output, colour reflects oxygen saturation.

The goal of this manuscript was to elucidate the physiological determinants and present our conceptual framework regarding the Fontan circulation to enhance our understanding of this complex and unusual circulation. Our objective is to assist clinicians in effectively addressing a failing Fontan circulation by facilitating their understanding of the circuit, ultimately fostering the modulation and enhancement of flow throughout the system.

MODELLING FLOWS IN BIVENTRICULAR AND FONTAN CIRCULATIONS

Output in a biventricular circulation with moderate left ventricular dysfunction

In the context of a biventricular circulation with moderate left ventricular (LV) dysfunction, identifying the critical bottleneck—characterized by its significant resistance—is straightforward: it is essentially the dysfunctional left ventricle (LV) itself (Fig. 1). The conventional formula governing output is expressed as follows [6]:

$$CO = SV \times HR = (LVEDV - LVESV) \times HR = (LVEDV \times EF) \times HR$$

where cardiac output (CO) equals stroke volume (SV) multiplied by heart rate (HR), and SV corresponds to either left ventricular end diastolic volume (LVEDV) minus left ventricular end systolic volume or LVEDV times the ejection fraction.

This formula contains the 3 key components of a critical bottleneck: the 'resistance' linked to the dysfunctional LV (also known as impaired contractility) is captured by the ejection fraction; the upstream pushing force (also known as preload) is reflected by LVEDV; and the force determining downstream flow (also known as afterload) is reflected by LVESV or EF. HR is also incorporated, because the ventricle is a pulsatile system with preload reserve. This formula serves a dual purpose: it enables the computation of flow through the system with variables that are used on a daily basis by the cardiologist; further, because this formula determines flow across the critical bottleneck, it enumerates the variables that act as levers to adjust output in patients with moderate LV dysfunction. Clinicians have experienced that manipulating contractility, preload, afterload and/or HR in a biventricular circulation with LV dysfunction exerts a profound impact on output and congestion.

Output in a Fontan circulation

As previously suggested, the creation of a Fontan circuit effectively positions the pulmonary circulation comparable to a dam upstream of the heart. In this circuit, this newly created critical bottleneck now controls flow to the ventricle and throughout the whole circulation. The contemporary total cavo-pulmonary connection constitutes, in essence, a vascular procedure rather than a traditional cardiac operation. As a matter of fact, the surgeon can create the circuit without even touching the ventricle: cardiopulmonary bypass might be employed for intraoperative comfort, but the ventricle itself remains untouched. This result implies that all ventricular changes observed immediately after the Fontan operation are not primary problems related to the ventricle but are secondary changes caused by altered boundary or loading conditions.

Analogous to any dam, this new bottleneck orchestrates both upstream congestion and diminished downstream inertial flow. Consequently, control over output and congestion shifts away from the ventricle to this newly created critical bottleneck. Whereas the classical biventricular formula can still describe the overall flow, it no longer uses the variables across the new critical bottleneck and therefore no longer encompasses all the modifiable controls of the overall flow. Indeed, clinicians caring for Fontan patients have recognized that, especially early after creation of the Fontan circuit, manipulating contractility, afterload or HR has negligible or no effect on output or congestion.

In a hydrodynamic model, overall flow in a closed circuit with multiple bottlenecks is limited by the flow through the critical bottleneck; that flow is determined by the pressure differences across the critical bottleneck and its overall resistance (Ohm's law). In a Fontan patient, a new critical bottleneck is created: the Fontan portal system, which consists of the surgical connection, the branch pulmonary arteries, the pulmonary microvasculature and the pulmonary veins [2]. Parallel flow is possible through a fenestration (green box in Fig. 1). The formula governing flow across this critical bottleneck (and thus overall output in the Fontan circuit excepted for the minimal coronary flow) can now be expressed as follows:

$$CO = \frac{\delta P}{\Sigma R} = \frac{CVP(PAP) - LAP}{R_{CPC} + PVR} + \frac{CVP - LAP}{R_{fenestration}}$$

CO: cardiac output; CVP: central venous pressure; δP: pressure difference; LAP: left atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; R_{CPC}: resistance of the cavo-pulmonary connection; ΣR: sum of resistances; R: resistance.

This formula contains the 3 key constituents of the critical bottleneck: the total impedance is determined by the collective resistance of the Fontan connection, the pulmonary vascular bed and the fenestration (the 2 former lying in series, and the latter in parallel). The upstream pushing force or preload is reflected by CVP (PAP), whereas LAP reflects the force pulling downstream.

Manipulation of any of these variables results in an immediate change of output. This situation has been demonstrated abundantly in clinical medicine:

- CVP (PAP): Increasing CVP (PAP) leads to an immediate increase in CO. This practice is commonly adopted by intensivists shortly after the Fontan procedure, although keeping in mind that high venous pressures may result in oedema and effusions. Notably, Fontan patients themselves will enhance their output via their skeletal muscular pump—employing their major striated leg muscles to elevate venous pressure up to 30 – 35 mmHg [7–9]. This practice also explains the efficiency of a right ventricular assist device, which increases PAP, resulting in improved output (and decreases CVP, mitigating congestion) [10–12].
- LAP: Theoretically, the ventricle that is downstream of the dam could improve output by creating negative pressure and pulling ('sucking') the blood through the lungs. However, the human ventricle is unable to generate the negative pressures required for such pull. Clinicians have no lusitropic drugs or manoeuvres at their disposal that are of any significant short- or long-term benefit. Diuretics could theoretically be helpful, yet typically they lower CVP more than LAP, creating a negative output balance. In the long run, diuretics further deprive the unloaded ventricle, potentially hastening the progressive stiffening of the Fontan

ventricle. Indeed, the Fontan status with its chronic volume deprivation invariably results in a premature and accelerated increase of LAP, exerting devastating implications on long-term output [13, 14]. Inodilators such as milrinone and levosimendan can improve output in a Fontan circuit but have a mixed effect: they are known to be potent pulmonary vasodilators, but their presumed intrinsic lusitropic effect is controversial and based on indirect echocardiographic measurements of diastolic function (which might be secondary to increased preload and contraction) without lowering the LAP [15, 16]. Secondary mechanisms that can increase LAP may result from intrinsic myocardial systolic or diastolic dysfunction, haemodynamically significant atrioventricular or systemic valve stenosis or regurgitation [17].

- R_{CPC}: The resistance of the surgical connection obviously carries significance. Over the years, surgeons have refined the procedure to eliminate flow restrictors such as a hypoplastic stiff subpulmonary ventricle, venous valves, a bulky atrium or flow vortices. Currently, the Fontan operation has been reduced to its essentials: direct and broad connection of the caval veins to the branch pulmonary arteries with a mild offset limiting flow collision but allowing flow of the hepatic factor to both lungs. The conduit and pulmonary branches should be non-restrictive early and during growth, and not only at rest, but also during exercise.
- PVR: Francis Fontan recognized early on that high PVR was predictive of postoperative mortality and morbidity in the immediate and mid-term follow-up periods. Pre-Fontan management is therefore pivotal for future Fontan patients and should strive for a well-developed, large, low-impedance pulmonary vascular bed. This pre-Fontan care significantly influences late Fontan success or failure. In order to keep the resistance across the lungs low, intensivists have learned to limit positive pressure ventilation and encourage early spontaneous breathing or negative pressure ventilation [18, 19]. Fontan patients can proactively mitigate the gradual rise in PVR by engaging in regular physical activity, which aids in flushing and recruiting lung vessels and practising preventive measures (vaccination, vigorous treatment of bronchitis, weight control) [20]. Pulmonary vasodilators have emerged as a therapeutic tool in Fontan patients, but only in those patients in whom vasoconstrictors, lack of vasodilators or mild pulmonary vascular disease plays a prominent role. Other pulmonary vascular lesions, such as stenosis, distortion, kinking, loss or exclusion, hypoplasia or external compression, are not influenced by pulmonary vasodilators. The role of pulmonary vasodilators in increasing output in a Fontan circuit is therefore modest: in clinical series in non-selected patients, pulmonary vasodilators could augment output on average by 0–8% at most [21–23].
- Fenestration: Introducing a fenestration allows for flow to occur parallel to the Fontan portal system. Similar to any bypass, fenestration-mediated flow reduces upstream congestion and, since it operates across the critical bottleneck, it augments overall output. However, the augmented flow carries desaturated blood, resulting in arterial desaturation as a trade-off.

Equally significant for clinical management, this formula unveils traditional variables that exert minimal or indirect influence, if any, on output:

- Contractility: the formula contains no systolic variable but predicts that the ventricle can augment output only by lowering LAP. Significant systolic dysfunction is nearly always associated with increased LAP. Reduced systolic indices after Fontan are frequently observed to be obligatory due to the primary preload restriction (Frank-Starling), with a disproportional reduction as the ventricle reaches its closing volume, and may additionally be due to myocardial damage secondary to previous management (volume or pressure overload, cyanosis, ischaemia, inflammation and cardiopulmonary bypass). Only the latter components are reactive for inotropes. Inotropes may make the ventricle squeeze harder, but they do not increase volume output due to a limited preload unless it can lower LAP. It therefore comes as no surprise that studies investigating the effect of inotropes on the cardiac index in Fontan patients showed no or minimal effect [24–26]. During exercise, an SV that decreases is therefore not an automatic indication of decreased contractility: if the exercise-induced rise in HR is not preceded by a higher increase in ventricular preload, it will invariably result in a decrease of stroke volume.
- Afterload: among numerous studies conducted, not a single one has managed to reveal a significant positive effect of afterload reducers on output or congestion in Fontan patients. Instead, a multitude of studies either report no impact or indicate a vague non-significant effect on secondary or tertiary end points, or even a detrimental effect [27–29]. Our proposed Fontan formula indicates that systemic vasodilators can only improve a Fontan circulation by lowering the LAP; however, their short-term efficacy in this regard is limited. Over the long term, ACE inhibitors might play a role in preserving ventricular diastolic function, slowing age-related changes or maintaining adequate kidney function, but this role needs to be demonstrated. ACE inhibitors come into play when significant regurgitation of the atrioventricular or semilunar valve(s) occurs, however. Similarly, treating a mild residual coarctation does not result in an immediate improvement of Fontan haemodynamics but can prevent accelerated decline in the long run.
- Heart rate: HR does not appear in the formula, because transpulmonary flow post Fontan is non-pulsatile. Similar to inotropes and afterload manipulation, interventions specifically targeted at augmenting the HR (atrial pacing) have failed to improve CO or congestion [30–32]. However, extreme bradycardia and tachycardia do increase LAP, thus exerting a negative influence on output and congestion. Any increase in HR in a volume-deprived ventricle results in a proportional decrease of SV [31]. The term *chronotropic incompetence*, which is used when describing exercise parameters in Fontan patients, is inappropriate: when comparing HRs at different exercise levels in absolute values, the HRs of Fontan patients are almost invariably faster than those of normal people at comparable exercise levels. Elevating the HR at any exercise level yields no advantage and might indeed be detrimental. Clinicians know that in other preload-deprived ventricles, such as mitral stenosis or patients with a Mustard repair with baffle obstructions, an HR that is inappropriately high for the end-diastolic volume causes a drop in CO and results in hypotension or even cardiovascular collapse [33]. Atrioventricular synchronization is an important factor that can improve CO because it optimizes ventricular filling, thereby also lowering the mean LAP.
- Left ventricular assist device (LVAD): it is well established that an LVAD primarily benefits systolic dysfunction and fares poorly in cases of diastolic dysfunction [10, 12]. In a biventricular circulation compromised by LV dysfunction, an LVAD operates in parallel with the critical bottleneck, yielding significant efficiency. In contrast, within the Fontan circuit, an LVAD is positioned distal to the critical bottleneck, rendering it substantially less efficient because this requires that the LVAD lower the LAP and pull

blood through the Fontan portal system into the ventricle. In cases of Fontan failure with systolic compromise disproportional to the reduced preload, e.g. myocardial dysfunction or ischaemia or when near the closing volume, an LVAD can have a role to play; systolic dysfunction disproportionate to reduced preload typically occurs late in Fontan patients.

ADDITIONAL INSIGHTS INTO THE FONTAN CIRCULATION

Terminology

The term *heart failure* appears inadequate to describe the hydrodynamic problem encountered in the Fontan circulation, especially early after the operation. The heart does not truly fail; it typically pumps all the volume that is provided by the critical bottleneck. The ventricle is not designed to actively pull the blood through the pulmonary vasculature, which in theory would require negative pressures of -20 mmHg or more; even if the ventricle could create such pressures, collapse of the pulmonary veins would make increased return impossible. Immediately after the Fontan procedure, the ventricle is supposed to come out of the operation untouched and should not be regarded as the primary instigator of overall dysfunction. Acute preload reduction triggers the systemic ventricle (which may be enlarged due to previous shunts or regurgitation) to 'collapse', sometimes to near its closing volume, resulting in decreased contractile function (Frank-Starling mechanism) [34]. Moreover, chronic preload deprivation eventually leads to ventricular stiffening, thereby further decreasing transpulmonary flow and thus ventricular preload, with further systolic dysfunction. The term *circulation failure* better captures the scenario than the term *heart failure*, aiding clinicians in recognizing that the ventricle is not inherently—and certainly not primarily—the pivotal factor in Fontan failure. The ventricle initially cannot solve the enigma of the Fontan circulation because it cannot pull blood through the Fontan portal circuit into the LA; however, in the long term, the ventricle may and will aggravate the situation by diastolic stiffening, which reduces transpulmonary gradient and further reduces overall output.

Evolution over time: primary and secondary changes. The cardiovascular system undergoes a continuum of changes from infancy to old age, impacting the efficiency and functionality of the circulation. In the context of Fontan physiology with its specific boundary conditions, certain determinants of the critical bottleneck may experience accelerated changes that further exacerbate circulation failure (Fig. 2).

- **LAP:** aging induces increased LAP in all individuals. Nonetheless, Fontan physiology renders an accelerated and amplified rise more likely, especially in so-called poor Fontan patients [14, 35, 36]. In a failing Fontan circulation, it is not uncommon to witness a rise in LAP up to 20 mmHg and higher, even at a young age. Chronic volume deprivation, a prominent Fontan boundary condition, likely hastens ventricular stiffening. This chronic volume deprivation also prevents intermittent exercise-induced ventricular stretch, which eventually leads to muscle stiffening. The degree of deprivation is determined by many factors such as the flow restriction by the Fontan dam, the degree of ventricular overgrowth, the presence or absence of ventricular remodelling and resting and exercise HRs. During exercise, a normal LV within a biventricular circulation 'stretches' from baseline: the augmented venous return during exercise increases stroke volume in the thin-walled right ventricle, consequently elevating stroke volume in the LV (because both ventricles are synchronized). Endurance training has been shown to decrease LAP in normal athletes and the elderly [37, 38]. In contrast, the Fontan patient experiences limited and blunted exercise-induced flow augmentation due to the absence of a right ventricle and the 'damming' effect of the Fontan portal system on overall output. If, during exercise, the HR -determined by the sinus node- increases faster than the output -determined by the transpulmonary flow- stroke volume will even decrease! The prolonged complete absence of any muscular stretch from baseline detrimentally affects muscular elasticity and, in the case of the systemic ventricle, worsens diastolic compliance. Decreases in physical activity, due either to imposed restrictions or to age-related changes, may thus further compound the problems of the Fontan circulation. Additional ventricular dysfunction may complicate the situation due to several insults over the years, e.g. ventricle-to-pulmonary artery shunts; peri-operative issues with coronary artery perfusion, ischaemia, inflammation, atrioventricular and systemic valve regurgitation or myocardial dysfunction of any cause, may exert additional upstream and downstream changes. These insults should be treated by appropriate and targeted treatment.

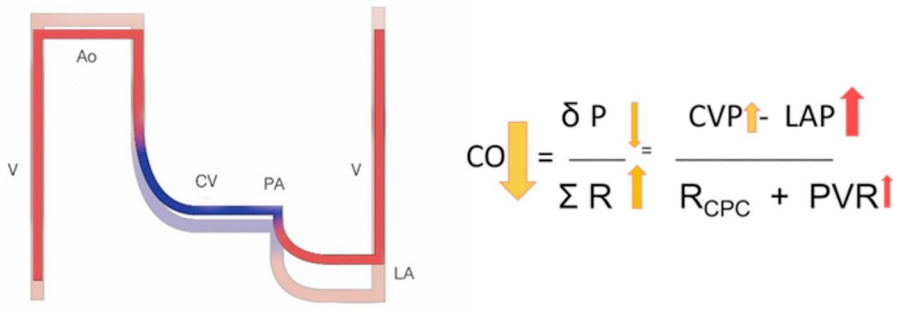

Figure 2: Temporal changes within a Fontan circuit. Primary changes encompass elevated caval vein pressure and reduced flow; secondary changes induce elevated left atrial pressure and rising pulmonary vascular resistance (red arrow); the primary and secondary changes encompass further reductions in cardiac output and the ejection fraction, coupled with further increased central venous pressure and systemic vascular resistance (orange arrow when relevant and present in formula). AO: aorta; CO: cardiac output; CV: caval veins; CVP: central venous pressure; δP: pressure difference; LA: left atrium; LAP: left atrial pressure; PA: pulmonary artery; PVR: pulmonary vascular resistance; R_{cpc}: resistance cavo-pulmonary connection; ΣR: sum of resistances; V: single ventricle.

- **PVR:** in normal subjects, PVR and pressures naturally increase over time [26, 39, 40]. Fontan physiology predisposes one to an accelerated increase in PVR due to the lack of pulsatility, chronic low flow, absence of exercise-induced high-pressure high-flow conditions that normally result in recruitment and flushing of all lung segments, impaired distribution of hepatic factors, circulating vasoconstrictors and vasodilators and potential microthrombi—collectively contributing to altered endothelial function [41]. Pre-Fontan conditions such as fibrosis, scars, mild segmental pulmonary vascular disease and other factors can lead to an additional or accelerated increase in PVR.
- R_{CPC}: age-related growth factors may further impede flow in the Fontan circuit. Even minor gradients of 1 mmHg due to flow disturbances or stenosis, crimping, kinking and outgrowth of or external compression on cardiac conduits further increase resistance to flow—both at rest and especially during exercise [42, 43]. Such flow obstruction may blunt the exercise-induced ventricular stretch that is required to maintain good ventricular compliance.
- CVP: an acute increase in CVP is intrinsic to the early course after the Fontan procedure. Over time, the previously discussed factors contribute to a secondary rise in CVP [44, 45].
- Ventricle: although the ventricle initially acts as an innocent bystander, it may over time contribute due to secondary diastolic and systolic dysfunction [46].

IMPLICATIONS FOR CARE OF THE FONTAN PATIENT

Fundamental hydrodynamic principles dictate that variables present in the formula governing flow across a critical bottleneck in a circuit hold paramount significance as primary, if not exclusive, determinants of that flow. If these variables remain unchanged, flow within the circuit likewise remains unaffected. Formulas serve as concise representations of relationships between different variables, playing a pivotal role in simplifying complex problems into manageable expressions. Through manipulation and observation of variables, scientists discern causal relationships, analyse the consequences of altered circumstances and draw evidence-based conclusions. Additionally, understanding the interplay between variables and their constraints is essential for correct interpretations. Hence, when dealing with the failing Fontan circulation, one should focus on the primary issues and not the secondary or even tertiary (or irrelevant) phenomena.

Clinicians

The key determinants governing flow—R_{CPC}, LAP and PVR—unfortunately offer limited room for manipulation after Fontan creation. This fact emphasizes the vital importance of pre-Fontan management, which should primarily focus on the optimal preparation of the Fontan's building blocks: low R_{CPC}, a high-compliance ventricle and a low-resistance pulmonary vasculature—both in the early and later stages post-Fontan repair.

- Low-resistance pulmonary vasculature: many patients are born with hypoplastic pulmonary arteries, frequently duct-dependent. The initial palliative procedure is crucial: it should provide adequate flow to encourage balanced, symmetrical growth while avoiding residual hypoplasia or pulmonary vascular disease. Post Glenn or Fontan connections, which are low-flow and low-pressure systems, rarely offer further catch-up growth potential or improved symmetrical flow [47, 48]. Consequently, ensuring pulmonary vasculature adequacy before Glenn creation becomes crucial. In cases where residual hypoplasia or asymmetry exists, an intermediate procedure may be a better long-term option, such as more time with the initial shunt, shunt augmentation or even an additional shunt with preferential flow to the smallest (usually left) lung [49, 50].
- Very compliant ventricle: within the Fontan circuit, low diastolic compliance holds paramount importance, surpassing even systolic function. A delicate balance should be found prior to Fontan completion: excessive overload should be avoided because it leads to ventricular globuleus remodelling and to overgrowth that will eventually aggravate post-Fontan volume deprivation; on the other hand, the ventricle should not be overprotected because sufficient flow is required to stimulate adequate growth of the pulmonary vasculature. For the later stages of the Fontan circuit, prioritizing a ventricle with mild dysfunction but impeccable pulmonary vasculature proves wiser than aiming for a perfect ventricle paired with hypoplastic pulmonary arteries.
- Low R_{CPC}: surgeons have effectively addressed the problems of establishing a non-obstructive, low-resistance extra-cardiac conduit. De Leval extensively studied the hydraulic aspects of flow. As a result, modern surgery has become very effective [51, 52]. With time, some connections may become restrictive; we recently reported successful stent expansion of conduits that theoretically should allow increased flow during exercise; time will tell whether this theoretical advantage holds true in practice [42].

Intensivists. Intensivists have intuitively been guided by what is effective treatment postoperatively: adequate filling, prioritizing early extubation or, at a minimum, encouraging spontaneous (negative pressure) breathing, ensuring optimal filling and maintaining low pulmonary artery pressures with vasodilators [18, 19, 53]. Immediately after the Fontan operation, the ventricle essentially experiences preload deprivation. Consequently, administration of inotropes defies logic, as discussed earlier: further increasing contractility and afterload will be detrimental in a volume-deprived ventricle with adequate native contractility. Vasopressors may be needed to guarantee coronary and renal perfusion but will not improve Fontan haemodynamics. Shifting focus from conventional 'cardiac output' to 'perfusion', while using vasodilator-lusitropic drugs such as milrinone, emerges as a more rational postoperative strategy [54]. If significant congestion or low output persists, despite optimizing the previous factors, fenestration or partial take-down should be considered early.

Patients. In addition to adopting healthy lifestyle practices and maintaining an appropriate body weight, which is inherently logical, it has become increasingly evident that exercise assumes a crucial role in the management of these patients [7, 8, 55]. Regular physical activity has been shown to improve recruitment of lung capacity, fortify the skeletal muscle pump and bolster the diaphragm—a critical factor for facilitating transpulmonary flow [56]. These results, in turn, improve preload and consequently boost CO. Moreover, exercise might contribute to delaying ventricular stiffening through the mechanism of exercise-induced ventricular stretch. The potential role of negative chronotropic drugs still needs to be determined.

RESEARCH PERSPECTIVES

According to the formula, accurately evaluating subtle and early alterations around the critical bottleneck necessitates the ability to measure and analyse changes in CVP, PVR and systemic ventricle filling pressure. Without comprehensive measurement and assessment of these primary factors, the effects of targeted treatment on such changes cannot be appropriately investigated [57]. Nonetheless, many of the research efforts targeted at understanding the Fontan circulation have focused on (secondary and tertiary) ventricular factors rather than on the key factors highlighted in this manuscript. Although conventional echocardiography and cardiac magnetic resonance imaging can document numerous secondary changes, they fall short of providing the essential insights into the early and primary changes required by the clinician. Instead of focusing on the mere shadow of the action, clinicians should prioritize understanding the action itself. Exercise-induced changes in pulmonary artery wedge pressures have been demonstrated to unmask underlying diastolic dysfunction in Fontan patients with adequate systolic function [58, 59]. This approach could emerge as another vitally important invasive option to detect early dysfunction and to direct treatment efforts.

CONCLUSION

In navigating complex scenarios, reliance on established guidelines derived from commonly encountered clinical occurrences should take a back seat to a foundation of basic physiology. To ensure effectiveness, treatment should primarily be directed to the critical bottleneck and its primary determinants. The available options are well-defined: tackle the obstruction (the most impactful approach), push upstream (the most straightforward action) or pull/suck downstream of the bottleneck (the least efficient strategy). Physicians managing such patients must carefully differentiate between primary and secondary effects, tailoring interventions correspondingly. The Fontan formula in the present article stands as a valuable tool, aiding physicians in comprehending the pathophysiological and hydrodynamic intricacies of the Fontan circuit within the context of everyday clinical practice. The key determinants governing flow offer limited room for manipulation after Fontan creation. This observation emphasizes the vital importance of pre-Fontan management, which should focus primarily on the optimal preparation of the Fontan's building blocks: low R_{CPC}, a high-compliance ventricle and a low-resistance pulmonary vasculature.

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ETHICS

All authors have contributed significantly and were involved in all stages of preparation of this manuscript. This is an original manuscript and has not been submitted elsewhere.

DATA AVAILABILITY

No new data are presented; data are adequately represented in the reference section.

Author contributions

Marc Gewillig: Conceptualization; Data curation; Formal analysis; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing. **Thomas Salaets:** Formal analysis; Resources; Writing—review & editing. **Alexander Van de Bruaene:** Formal analysis; Validation; Visualization; Writing—review & editing. **Jeff Van den Eynde:** Supervision; Writing—review & editing. **Stephen C. Brown:** Conceptualization; Formal analysis; Project administration; Writing—original draft; Writing—review & editing.

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Review