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REVIEW ARTICLE

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Cardiovascular adaptation to the Fontan circulation

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Abstract

Although medium-term survival following Fontan operations in the modern era has improved dramatically, late cardiovascular and extracardiac morbidity are common and are associated with impaired quality of life and premature late mortality. This serves as a reminder of the extraordinary adaptations required of the cardiovascular system when the systemic arterial, systemic venous and pulmonary circulations are placed in series coupled to a single ventricular pump. This article reviews the key features and principles that govern interactions between the ventricle, systemic arterial circulation, the systemic venous and pulmonary circulatory compartments, the microcirculation, and lymphatic circulations. The overarching aim is to provide insight into the integrative pathophysiology that governs the Fontan circulation and stimulate thoughtful approaches to advance research.

KEYWORDS

computational flow, Fontan, single ventricle, pulmonary circulation, ventriculo-vascular coupling, venous physiology

1 | INTRODUCTION

The Fontan operation, in which the total systemic venous return is surgically redirected away from the ventricular mass has been performed for more than four decades in patients with univentricular hearts.[1,2] Survival to the third decade of life is common and the survival rate has improved in the modern era with the advent of total cavo-pulmonary connections and improved perioperative and cardio-protective management.[3] However, late cardiovascular (CV) morbidity, extra-cardiac organ dysfunction, and consequent adverse events are commonplace.[4–6] Joining the systemic arterial and systemic venous circuits in series creates exceptional challenges for CV adaptation.

Univentricular circulations, where the pulmonary, systemic arterial, and venous circulations are connected in series, do occur in nature, for example, in chordates such as the sand shark.[7] Such CV anatomy is accompanied by certain fundamental structural and functional characteristics that address the intrinsic physiologic limits. These adaptations include: (1) vigorous systolic and diastolic ventricular function with ejection fractions of 80–90%, which creates very low common atrial pressures facilitating venous return;[7] (2) a well-developed peripheral muscle pump which augments venous return; (3) horizontal orientation of trunk and limbs which minimizes gravitational venous pooling; and (4) mechanical synchrony between heart contraction and ventilatory movement of the chest wall with coupling ratios of 2:1 or 3:1 favoring venous return. Human Fontan circulations are compromised in each of these domains. this article will therefore review the circulation as follows: (1) the ventricle: anatomy, atrioventricular (AV) synchrony, AV valve function; (2) the

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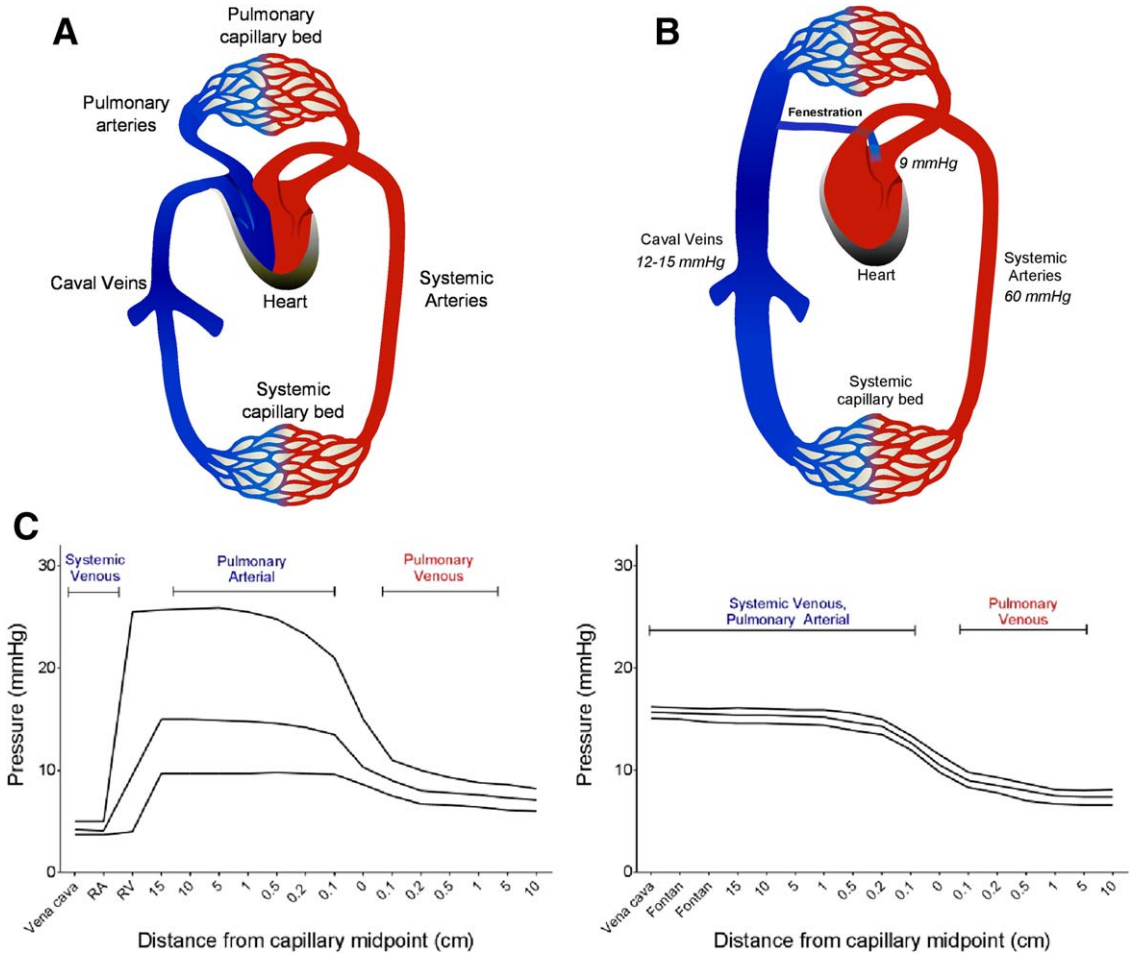

FIGURE 1 (A) Normal biventricular circulation. Line thickness reflects output; color reflects oxygen saturation of hemoglobin. (B) Fontan circulation. The systemic veins are connected to the pulmonary artery without a systemic atrium or subpulmonary ventricle. The lungs are thereby converted into a neoportal system which limits flow to the ventricle. In the absence of a fenestration, there is no admixture of systemic and pulmonary venous blood. A fenestration (shown) allows the systemic venous blood to bypass the Fontan portal system and limits the damming effect. Line thickness reflects output, color reflects oxygen saturation. Typical mean pressures in a well-functioning Fontan circulation are shown next to the respective compartment. (C) Pressure differentials across the normal and Fontan pulmonary circulations. Pressure characteristics are represented as a function of distance from the caval veins in the normal biventricular circulation (left) and Fontan circulation (right). Reprinted with permission from Opotowsky AR. *Circulation*. 2015;131:200–210

systemic arterial circulation and its interaction with the ventricle; (3) the systemic venous, lymphatic, and micro-circulations; (4) the pulmonary arterial circulation; and (5) exercise performance: circulatory adaptations and limitations.

2 | THE VENTRICLE

2.1 | General considerations

In the Fontan circulation, systolic ventricular action drives blood flow through two resistors in series, the systemic arterial and systemic venous circulations (which include the pulmonary circulation) (Figure 1). The pulmonary circulation, because it lacks a subpulmonary pump, is transformed into a classic portal circulation in which the systemic venous capillary bed is drained via another capillary bed prior to returning to the heart. Abnormalities in ventricular mechanics, including those mediated through altered structure, may exert profound upstream (systemic veins and pulmonary arteries) and downstream (systemic arteries) effects.

2.2 | Anatomic and performance characteristics

There are important differences in myocardial architecture between various underlying diagnoses and univentricular morphologies. For example, systemic right ventricular systolic twist differs from that seen in the normal left ventricle, including striking regional variation.[8] The univentricular heart with a systemic left ventricle also differs from that seen in a two-ventricle system. For example, in tricuspid atresia the left ventricle is more spherical in shape[9] and exhibits greater heterogeneity in regional systolic and early diastolic strain and strain rate patterns as compared with the biventricular left ventricle.[10] The presence of noncontractile patch material related to surgery, as well as scar and conduction abnormalities further contributes to variable, less efficient ventricular function.

Fetal cardiac function and geometry, free from extra-uterine physiologic requirements and the injury and abnormal loading conditions associated with surgical palliation, give unique insights into ventricular structure, mechanics and performance relationships. In the normal two-ventricle fetal circulation, the right ventricle performs approximately 60% of systemic perfusion work. In those with hypoplastic left heart syndrome (HLHS), the right ventricle must do all systemic perfusion work. This is successfully achieved through increased ejection force but this is associated with lower work efficiency; the consequence is relatively reduced cardiac output.[11] One barrier to more complete compensation is that the hypoplastic nonfunctional left ventricle, presumably through mechanical constraint mediated by fibroelastosis, negatively influences right ventricular mechanics.[12]

After Fontan surgery, the hypoplastic left ventricle affects diastolic performance of the right ventricle; a larger hypoplastic left ventricle is associated with greater right ventricular end-diastolic stiffness.[13] Those with mitral atresia, aortic atresia and no visible left ventricle appear to have lower right ventricular end-diastolic stiffness.

2.3 | Ventricular volume loading and unloading

After birth, the goal of initial surgical intervention is not only to secure unobstructed flow into and out of the single ventricle but also to prevent development of pulmonary vascular disease by protecting the pulmonary vascular bed from high flow and pressure while at the same time encouraging its growth.

Superior cavo-pulmonary connections are subsequently performed when feasible as the next palliative step once adequate pulmonary arterial growth has been secured. This creates profound volume unloading of the ventricle[9] which together with early conservation of myocardial mass leads to an elevated ventricular mass-to-volume ratio with the potential for diastolic dysfunction.[14] This is most conspicuous in patients transitioning directly from arterial shunt physiology to total cavo-pulmonary connections.[15] In the past, when this surgical strategy was commonplace, some patients exhibited a clinical syndrome of low cardiac output in the context of a very thick walled ventricle with small cavity volume.[16] In contrast, after creation of an isolated superior cavo-pulmonary connection, only superior venous return transits the pulmonary vasculature and inferior venous return continues to fill the ventricle, securing adequate preload.

Placement of a fenestration at the time of total cavo-pulmonary completion can mimic this intermediate physiology, though the effect is more modest. A portion of systemic venous return passes through the fenestration into the atrium, augmenting ventricular filling. Although this causes lower systemic arterial oxygen saturation, oxygen delivery may actually be enhanced depending on the increment in systemic cardiac output.[17] The degree of hypoxemia associated with a standard sized fenestration is usually well tolerated at rest. During exercise however, saturations may fall profoundly with consequent exercise limitation. Fenestration closure eliminates this ventricular preload and raises saturations. Cardiac output however is left vulnerable to perturbations in pulmonary vascular resistance and the consequences of pulmonary vascular coupling to the ventricle.

Histological properties of the ventricular myocardium also contribute to ventricular geometry and performance. An important contributor is myocardial fibrosis. This may be confluent and macroscopic or patchy and microscopic; the former tends to be related to scar or patch material while the latter may be due to chronically elevated myocardial wall stress during early ventricular volume loading, systemic hypoxemia and myocardial oxygen supply-demand mismatch. Fibrosis adversely affects the mechanics of both contraction and relaxation,[18] and is associated with larger end-diastolic volume, increased myocardial mass, and lower ejection fraction after the Fontan operation.[19] Ventricular fibrosis, hypertrophy, and myocardial mass to volume ratio mismatch may persist long after Fontan surgery. Another important, now well recognized contributor to abnormal ventricular mechanics is relative preload deprivation.[20,21] These phenomena manifest as dyssynchronous ventricular relaxation[22,23] and markedly abnormal diastolic properties.[23] At rest and during exercise ventricular filling rates are significantly prolonged in the Fontan circulation as compared with normal biventricular hearts.[24]

2.4 | Atrioventricular valve function

Atrioventricular valve morphology and function are frequently abnormal in univentricular hearts. Regurgitation and stenosis may be mediated through varying combinations of annular, leaflet, subchordal, and ventricular abnormalities. Typical mechanisms vary between diagnoses. Systemic tricuspid valve leaflet tethering and prolapse leading to regurgitation is common with HLHS. Regurgitation in AV septal defects may occur through valve tethering or deficiency in the zone of apposition (so-called cleft),[25–28] and is particularly common in unbalanced AV septal defects. Even minimal regurgitation appears to have a clinically relevant contribution to ventricular volume loading, underscoring the importance of early detection and intervention. Remodeling occurs by means of dilation and increased ventricular sphericity, greater annular dilation, valve tethering, and worsened regurgitation, setting up a vicious cycle.[29] Not surprisingly, the presence of AV valve regurgitation is associated with higher mortality.[28] The need for surgical management of AV valve regurgitation in single ventricle physiology predicts worse outcomes with respect to overall and transplant free survival, thrombotic risk and, incidence of protein losing enteropathy.[30,31] Surgical strategies include replacement or repair of the AV valve.

2.5 | Atrioventricular and ventricular synchrony

Loss of AV synchrony may be precipitated by a number of factors such as sinus node dysfunction, AV conduction disease and the onset of atrial tachyarrhythmia, the most of important of which is atrial fibrillation. Vascular compromise to the sinus node during surgery is not uncommon, especially in those with heterotaxy syndromes.[32] This may occur at the time of Glenn surgery or at Fontan completion. During late follow-up in contemporary series, one-third of Fontan patients suffer loss of sinus rhythm.[32] This is associated with increased risk for atrial tachycardia and fibrillation. Atrial tachyarrhythmias have a prevalence of nearly 30% at fifteen years in those with atrio-pulmonary

connections and 20%–25% in those with extra-cardiac or lateral tunnel connections.[33] Abnormalities in connexin expression, promoted by fibrosis and altered mechanical loading of the single ventricle, are likely to be key contributors to the development of arrhythmia and sinus node dysfunction.[34]

The important contribution of atrial contraction to cardiac output has long been recognized in the normal biventricular circulation.[35] Atrial systole, appropriately coordinated to the cardiac cycle (ie, 0.08–0.20 seconds before the onset of ventricular systole), can contribute to up to 60% of stroke volume.[36] The limited cardiac reserve inherent in the Fontan circulation accentuates the importance of this mechanism. The importance of atrial systole in Fontans has been confirmed by the effect of loss of synchrony during VVI pacing.[37,38] Also atrial fibrillation is associated with lower blood pressure and cardiac output in the Fontan circulation. Asynchronous pacing can cause marked elevation in atrial and Fontan/pulmonary arterial pressures, as well as a decrease in cardiac output early after surgery.[37] Similarly Fontan patients in junctional rhythm demonstrate greater pulmonary venous flow reversal. Preservation of AV synchrony is, therefore, a very reasonable goal in patients with a Fontan circulation. If pacing is necessary, atrial pacing is preferred. When ventricular pacing is necessary, AV synchrony should be established if possible and ventricular synchrony conserved wherever possible.

There is less clarity on the role for proactive intervention to improve ventricular synchrony. As outlined above, there is a high prevalence of ventricular mechanical dyssynchrony in single ventricle Fontan patients.[39] Multisite pacing does improve acute hemodynamics in the postoperative period.[40] Further, there are reports of improvement in select patients who have had clinical deterioration related to ventricular dysfunction.[41] One systematic study found cardiac resynchronization improved mean ejection fraction from 37% to 48% and functional status in a sample of 13 single ventricle patients, most of whom had complete heart block and were already receiving single site ventricular pacing with moderately reduced systolic function.[42] It, therefore, makes sense to consider multisite pacing or thoughtful single lead placement to minimize dyssynchrony in any single ventricle Fontan patient requiring ventricular pacing for other reasons. In stable patients it is unknown if the benefits of multisite pacing outweigh the risks of permanent epicardial lead placement, generator changes and other complications related to chronic pacing. Therefore, it is not standard practice to recommend primary placement of multisite epicardial pacing leads in clinically stable patients in the absence of reduced ejection fraction, ventricular dilation, functional impairment, and intraventricular conduction delay.[43]

2.6 | Ventriculo-vascular coupling in the Fontan circulation

It is essential to consider ventricular-vascular interactions because these ultimately determine the extent to which the "pressure-work" generated by the ventricle is converted into "flow-work" through the vasculature to perfuse end-organs. Abnormalities in ventriculo-vascular coupling are central to CV dysfunction in the biventricular circulation,[44] and a number of pharmacological,[45] and nonpharmacological[46] interventions achieve their effect via improvements in ventriculo-vascular coupling efficiency.

Reasoning from first principles would suggest that efficiency of ventriculo-vascular coupling may not only be important but also especially prone to compromise in the Fontan circulation. For example, the common ventricle faces increased afterload, since it ejects blood into the systemic arterial and pulmonary circulations in series. Also coupling of an adversely remodeled single ventricle to an abnormal systemic arterial load is likely to profoundly challenge the ventricle's contractile reserve. Data from divergent investigative approaches suggest that vascular characteristics in Fontan patients are pathologically altered.[47–49] Computer modeling incorporating the influences of intrathoracic pressure on venous return and the effects of baroreceptor reflexes, suggests that Fontan hemodynamics are best simulated by a state in which baroreceptor activity is increased. Such activation increases splanchnic and extra-splanchnic arteriolar resistance, filling pressures, and ventricular contractility.[50]

Aortic reconstruction, such as in the context of hypoplastic left heart syndrome or coarctation, unquestionably affects large vessel conduit function. Such patients have greater ascending aortic pulse wave velocity consistent with increased stiffness.[49] Impaired endothelial-dependent and endothelial-independent vessel dilation also has been demonstrated in patients after the Fontan operation. The severity of dysfunction appears to be proportional to the duration of hypoxemia prior to Fontan completion among other clinical risk factors.[51,52]

Several studies have examined the interaction between vascular and ventricular function after Fontan operations. At 7 years following Fontan surgery, cardiac output was lower in Fontan patients as compared with biventricular controls; in the Fontan group, cardiac output correlated inversely with arterial elastance (Ea).[53] It was, however, not possible in that study to discern whether reduced cardiac output was the cause or the consequence of elevated Ea.[53] In an acute animal model of the Fontan circulation, ventriculo-vascular coupling appears to be impaired with increased Ea, coupled to a decreased ventricular end-systolic elastance (Ees).[54] Although this model's applicability to common clinical scenarios is unclear, the findings are consistent with reports of a marked increase in Ea, coupled with a persistent reduction in ventricular Ees in Fontan patients up to 15 years following surgery, with Ees particularly reduced in patients with a systemic right ventricle.[55] In contrast, other investigators found that persistent elevation in Ea was matched by an equivalent increase in Ees in HLHS patients up to 12 years after a Fontan surgery.[56] This would suggest preserved ventriculo-vascular coupling in terms of stroke work, at least in childhood. The combination of increased Ea and a compensatory increase in ventricular Ees has been demonstrated, with a biventricular circulation, to be associated with impaired exercise tolerance.[57] Furthermore, matching of Ea and Ees appears to occur, in that context, at the expense of an elevation in right ventricular diastolic stiffness, a condition referred to by Kass as "ventricular vascular stiffening."[58] Elevation in ventricular diastolic stiffness could be particularly detrimental to the Fontan circulation in the absence of a subpulmonary power source.

The presence of systemic arterial dysfunction in patients after the Fontan operation suggests that chronic afterload reduction, for example with an angiotensin converting-enzyme inhibitor, could be beneficial. Few studies have examined the effects of afterload reduction in patients after the Fontan operation. One randomized, placebo-controlled cross-over study demonstrated that 10 weeks of enalapril had no appreciable effect on cardiac index at rest, exercise tolerance, or cardiac index or peak oxygen consumption at maximal exercise.[59] These findings could be due to an unappreciated reduction in venous tone with enalapril, which could counter beneficial effects of reducing ventricular afterload.

2.7 | The venous compartment and cavo-pulmonary connections

2.7.1 | Normal venous physiology

In the normal circulation approximately 80% of blood volume resides in the venous compartment,[60] of which at least half is located in small venules and veins less than 20–50 μm in diameter. These small vessels constitute a very large combined surface area and present low resistance and high compliance (Figure 2). Typical pressure volume relationships observed in veins demonstrate significantly higher unstressed volume (~3 L) as compared with arteries (~0.5 L).[61]

Circulating blood volume, and secondarily ventricular ejection through Starling's mechanism, is controlled through central mobilization of blood from these capacitance venous vessels. This homeostatic mechanism is supported by physiological responses including reflex venoconstriction, passive venous recoil in response to transmural distending pressure, intrinsic viscoelastic properties of the venous wall, constriction of the venous and arterial ends of the capillary bed, and active myogenic alteration in venous tone.[62] Fundamental to the understanding of venous physiology is the concept of mean circulatory filling pressure (Pmcf) defined as the mean vascular pressure that exists after cardiac output is stopped abruptly and redistribution of blood occurs, so that all pressures throughout the vascular system are the same.[63] In the normal biventricular circulation, the pressure in the small peripheral venules is equivalent to the Pmcf, and a gradient exists between these vessels and the right atrium because the latter is maintained at low pressure through the action of the subpulmonary right ventricle.[64] This latter adaptation is absent in the Fontan circulation.

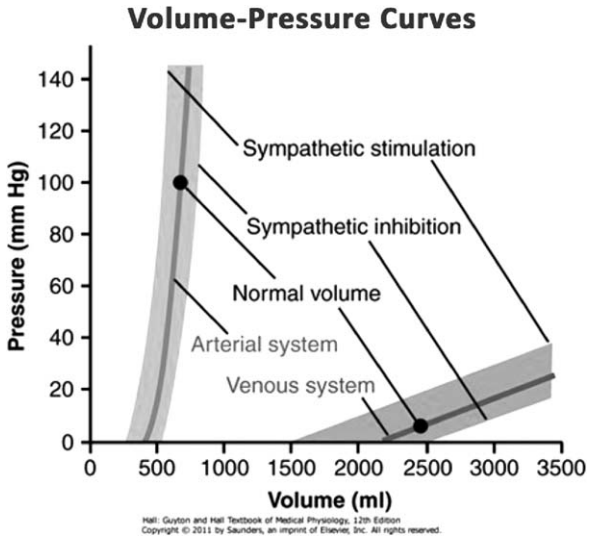

FIGURE 2 Venous versus arterial capacitance. Venous and arterial pressure-volume relationships are displayed across a spectrum of intravascular volume and sympathetic tone states. Reprinted with permission from Guyton and Hall, *Textbook of Medical Physiology*. 12th ed. Chapter 15, Figure 15–1

2.7.2 | Fontan venous pathophysiology

With the Fontan operation the nonpulsatile pulmonary arterial circulation becomes part of an extended venous compartment. The absence of a subpulmonary ventricle creates a state of obligatory systemic venous hypertension. The adaptive mechanisms allowing such extreme pathophysiology to stably sustain the circulation for decades, both at rest and with exercise, are still poorly understood. As in the biventricular circulation, in the Fontan circulation Pmcf is equivalent to the pressure in the small venules and capillaries, but in this case the central venous and pulmonary artery pressures are also the same. In other words, there is no longer an appreciable pressure gradient between the peripheral small venules and the larger central veins. Instead, the driving force for venous return is through maintenance of a single gradient from the small peripheral venules to the left atrium (ie, the transpulmonary gradient). As such, venous return, and ultimately cardiac output, in the Fontan circulation can be approximated by the equation Qvr [total venous return] = (Pcmf − Left atrial pressure) * Gvr [total venous return conductance], where Gvr is greatly affected by blood volume, venous tone, and peripheral resistance.[65]

In experimental models, total resistance to venous return to the left atrium is identical to the pulmonary vascular resistance (PVR), implicating the pulmonary vascular bed as the dominant influence in cardiac output regulation.[65] Factors that may contribute to elevated PVR include impaired dilation and recruitment of pulmonary vessels, asymmetric pulmonary perfusion, and loss of pulsatile flow. Nonpulsatile flow itself may induce an up to fourfold increase in resistance to flow.[66]

The Valsalva maneuver provides insight into mechanisms of venous adaptation. During Valsalva in normal individuals systemic venous return is impeded, cardiac output and pulse pressure decline, and heart rate and systemic vascular resistance increase. Following Valsalva release there is an overshoot in systemic arterial pressure above resting values and a decrease in heart rate as venous return is temporarily accentuated in the context of enhanced sympathetic tone. In patients with a Fontan circulation and depressed cardiac output, the Valsalva response is often grossly abnormal with preservation of blood pressure response during phases 3 and 4, similar to that seen in congestive right heart failure.[67] Regional arteriolar vascular resistance (eg, lower limb) increases with a concomitant decline in flow. However, splanchnic resistance does not change during the maneuver, and splanchnic flow may even be augmented.[68,69] Elevations in systemic ventricular diastolic pressure do not influence this abnormal response,

suggesting that the total pulmonary arteriolar resistance is likely to play an important role.

Venous capacitance and compliance is generally reduced in the Fontan circulation, accompanied by increased regional arteriolar resistance in the lower limb, trunk, and splanchnic circulations. Splanchnic resistance is unable to augment further in response to head up tilting.[69] Intimal medial thickness of the lower limb veins is increased.[70] These changes reflect adaptation to a higher Pmcf, allowing more favorable blood redistribution and better central diversion of venous return, albeit at the expense of greater splanchnic and lower limb resistance to flow. These venous adaptations protect against orthostatic hypotension at rest. Lower limb thresholds for tissue filtration and edema formation also are elevated in concert with the lower venous capacitance. Remarkably similar adaptive changes are observed in mammals subject to high gravitational venous pressures.[71]

It is intuitive that these adaptive venous mechanisms are vulnerable to hemodynamic compromise including pathway obstruction, the presence of noncompliant prosthetic materials (eg, patches, stents, and conduits) and altered PVR. Exertion results in a profound elevation in central venous pressures (often a two- to threefold increase) and an inadequate augmentation of cardiac output.[72] Not surprisingly, the prevalence of chronic venous insufficiency is very high.[73]

2.7.3 | Blood volume

Acutely after creation of the Fontan circulation there is an abrupt increase in venous pressures coincident with a decline in cardiac output.[74] Over the 2–3 weeks following surgery, there is gradual restoration of cardiac output in parallel with an increase in total blood volume. The latter increases by approximately 17% in an experimental model of caval inflow obstruction.[74] The increase in blood volume occurs as a consequence of upregulation of the renin–angiotensin–aldosterone system with elevated angiotensin II and aldosterone and also a drop in cortisol secretion.[75] Blood volume elevation persists long after normalization of angiotensin II and aldosterone levels.

2.7.4 | The lymphatic circulation

Lymphatic drainage is profoundly altered in the presence of elevated central venous pressures.[76] In adult heart failure patients, the lymphatic vessels are dilated; thoracic duct diameter may be increased up to sixfold.[76] Increased drainage via the lymphatic system is a critical adaptation but frequently becomes inadequate as venous pressures rise, thus resulting in tissue edema and congestion.[76] There is evidence that the lymphatics are grossly abnormal in the gut, mesentery and thoracic cavity in Fontan patients.[77] The lymphatic system has been targeted and successfully manipulated with interventional approaches in specific clinical contexts.[78,79] To date there are no pharmacologic approaches to improve lymphatic function in Fontan patients.

2.7.5 | Flow dynamics in the Fontan circulation

The Fontan connection as well as the proximal conduit pulmonary arteries may affect conductance of blood centrally toward the pulmonary venous atrium. Compliance and tensile properties of surgical material differs from native tissue. The proximal pulmonary arteries may also have unfavorable physical properties as their ultrastructure is significantly altered, especially in those with a poorly functioning Fontan circulation.[80] Histological data from our group confirm changes in the central pulmonary arteries toward a more "venous phenotype" while the central systemic veins demonstrate transformation toward a more "arterial phenotype"[81] (Figure 3).

Any vessel distortion or impaired Fontan pathway luminal integrity may precipitate profound energy losses. De Leval et al. seminal work on flow dynamics within Fontan pathways demonstrated superiority of cavo-pulmonary connections (eg, lateral tunnel) over atriopulmonary connections and described extreme energy losses associated with relatively small changes in conduit caliber or inflow–outflow offset.[82]

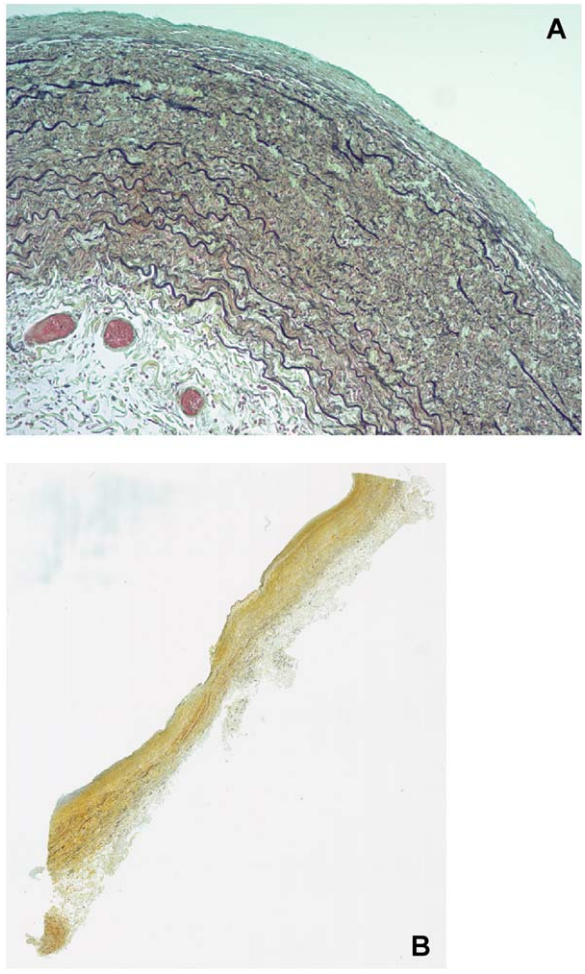

FIGURE 3 (A) High power histologic image of a representative post-mortem Fontan pulmonary artery demonstrating intimal proliferation and fragmentation of the medial elastic fibers consistent with a transition toward a more venous vascular phenotype. Pentachrome stain. (B) Low power image of a representative inferior vena cava demonstrating intimal and medial proliferation consistent with a transition toward an arterial phenotype. Unpublished data from Hays BS, et al. Abstracts from the American Academy of Pediatrics Section on Cardiology and Cardiac Surgery (SOCCS). *Congenit Heart Dis*. 11(5):468–530

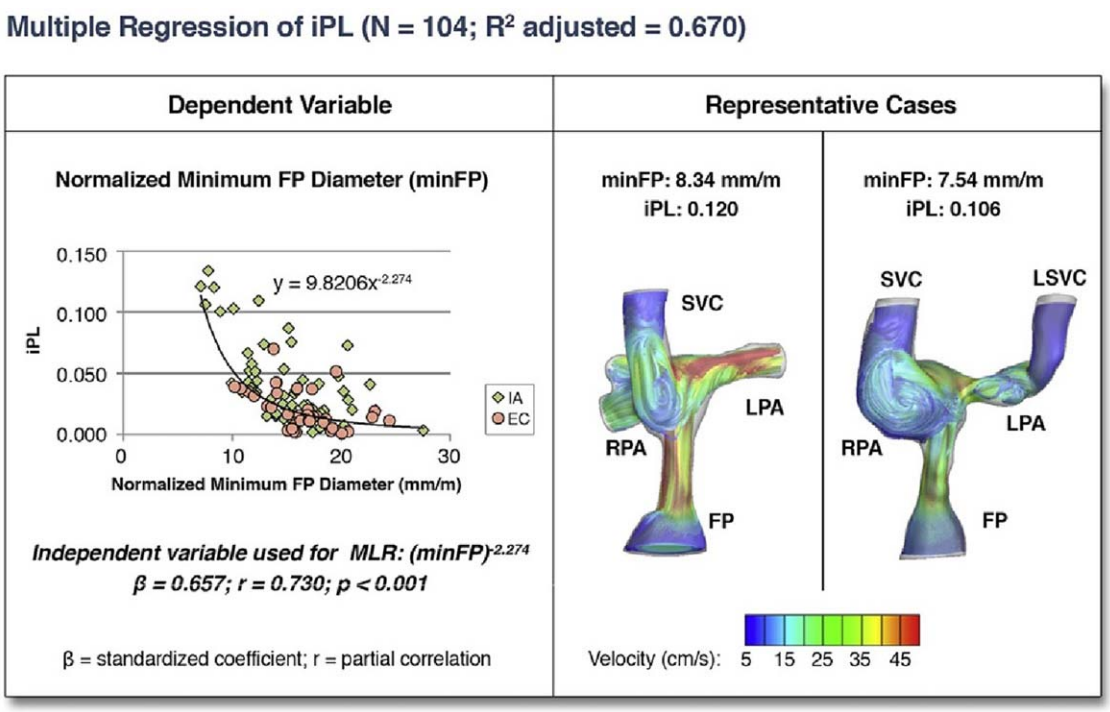

FIGURE 4 Power loss has a negative exponential correlation with minimum Fontan pathway diameter (minFP) on CFD studies. Graph is on the left and representative cases are shown on the middle and right panels. Intraatrial (IA) and extracardiac (EC) Fontan types, indexed power loss (iPL), superior vena cava (SVC), left superior vena cava (LSVC), Fontan pathway (FP), right pulmonary artery (RPA), left pulmonary artery (LPA). Reprinted with permission from Tang E, et al. *JACC: Cardiovasc Imaging*. 2014;7:215–224

Cardiac magnetic resonance (CMR) and reconstructing computational fluid dynamics (CFD) within an anatomico-geometric model, provide powerful tools to understand how streamlines of blood configure and how energy is conserved within individual Fontan pathways. One study performed CMR and CFD on 131 Fontan patients and assessed vessel diameter, angle of connection and caval offset. Power loss was found to have an exponential negative correlation with the minimum vessel diameter of the systemic venous pathway and branch pulmonary arteries when normalized for patient size (Figure 4).[83] Additionally, cardiac index and normalized minimum systemic venous pathway diameter demonstrated a positive correlation.

During exertion, power loss may be exacerbated as increased cardiac output provokes turbulence flow. In a study of 10 Fontan patients using CMR and CFD that simulated an increase in cardiac index to two to three times baseline, power loss increased nonlinearly and dramatically with increasing cardiac index.[84] Flow collisions from unfavorable blood streamlines in many Fontan geometries may also precipitate increased power loss at rest and during exercise.

Another important factor related to pulmonary arterial anatomy and physiology is how hepatic venous blood flow is distributed to each pulmonary artery. It has been hypothesized that the pulmonary bed requires a "hepatic factor," yet to be identified, which prevents pulmonary arteriovenous malformation (PAVM) development. CMR is well suited to visualize and quantify hepatic flow distribution and may help understand why and where PAVMs form in the Fontan circulation (Figure 5).

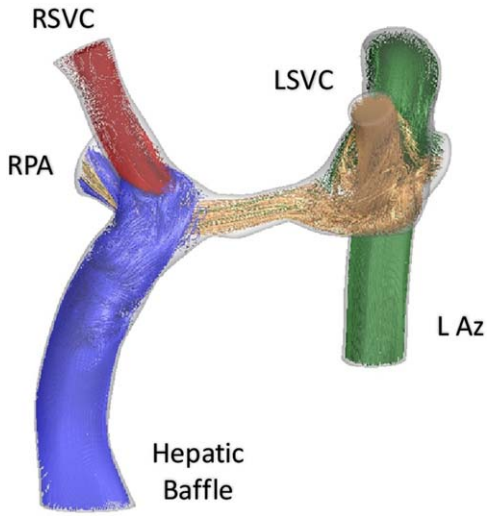

FIGURE 5 CFD modeling study demonstrating differential hepatic venous flow to the lungs in a Fontan patient with left lung PAVMs. Anterior view of systemic venous pathway and pulmonary arteries in a patient with heterotaxy and interrupted inferior vena cava with left azygous (L Az) continuation to a left superior vena cava (LSVC) who underwent a Kawashima operation on the left and a bidirectional Glenn on the right. Hepatic blood flow (in blue) streams to the RPA. Reprinted with permission from Fogel MA, et al. *Circulation: Cardiovasc Imaging*. 2013;6(6):1092

2.8 | The pulmonary arterial circulation

Securing adequate growth and development of the pulmonary arteries is crucial to long-term success of the Fontan circulation. During fetal development, growth of the pulmonary arteries in a single ventricle circulation is frequently suboptimal. This may be due to diminished or absent antegrade flow to some segments, or impaired pulmonary venous runoff such as in HLHS with restrictive atrial septum. Normal and "catch-up" growth needs to occur after birth, and this can be enhanced by a period of mild pulmonary over-circulation. If pulmonary flow is impaired after creation of the partial or complete cavo-pulmonary connection, growth of the pulmonary vasculature will be subnormal.

The first palliative procedure to optimize pulmonary blood flow is therefore critical to the development of the pulmonary vasculature in patients with single ventricle physiology.[85] The initial shunting procedure may cause asymmetric flow, and hypoplasia or mild pulmonary vascular disease of the pulmonary vascular bed. Stenosis resulting from abnormal connections, ductal constriction, surgical scarring, or kinking during growth can further compromise the pulmonary arterial architecture. The volume requirements for optimal growth and development of the pulmonary vasculature often contradict the conditions best suited for ideal ventricular development and ultimate myocardial functioning. While avoidance of ventricular volume overload is important, hypovolemia may cause pulmonary vascular hypoplasia, which may compromise long-term Fontan function.

A number of factors influence transpulmonary flow. These include compliance of the proximal conduit vessels, the dynamic impedance of the pulmonary arterial resistance vessels and ventricular action that is able to overcome the pooling effects and total resistance posed by the pulmonary vascular bed.[86] Ejection fractions of 80%–90% are likely required to maintain normal transpulmonary flow and this is obviously not a feasible therapeutic target. Thus, many believe that the efficiency and capacity of the Fontan circulation is largely fated on pulmonary vascular resistance and its complex interactions with the rest of the circulatory compartments.

The distal pulmonary arteries and micro-circulation in Fontan connections may be strongly influenced by chronically decreased flow, absence of pulsatility,[87] endothelial dysfunction,[88] and absence of episodic high flow and pressure seen during normal exercise. The chronic nonpulsatile, low flow state increases vascular tone, and resistance,[89] resulting in mildly elevated PVR at rest in many patients. Failing Fontan circuits often have high pulmonary vascular resistance. This is usually reversible after transplantation with restoration of pulsatile flow.[90] Treatment effects of several agents have been reported including supplemental oxygen at altitude, prostacyclin analogues, calcium channel blockers, phosphodiesterase inhibitors, and endothelin receptor antagonists.[91–95] Short-term hemodynamic improvements have tended to be modest. Longer-term studies with pulmonary vasodilators are needed to understand whether these agents can impact long-term outcomes after Fontan surgery.

2.8.1 | Exercise responses of the Fontan circulation

Examining the hemodynamic response to exercise gives invaluable insights into CV adaptation of Fontan circulations. In the resting state, cardiac output is normal or modestly reduced. The reduced cardiac output is due not to abnormal ventricular contractility, but rather to adverse "ventricular-vascular" uncoupling.[24] There is an obligatory and significant increase in central venous pressure compared with normal controls. During unloaded cycle exercise, cardiac output increases by approximately a third due to greater venous return facilitated by the lower limb skeletal muscle pump. As exercise progresses there is an initial further increase in cardiac output facilitated by an elevation in heart rate but no additional increase in stroke volume.[21,24] With higher heart rates there is impaired contractile response and limited ventricular filling.[24] The impaired contractile response is not an expected consequence of the preload deprivation, that is, the relative volume insufficiency of the ventricle does not entirely account for the diminished contractile performance. Venous pressures rise, often to greater than 20 mm Hg and pulmonary vascular resistance fails to fall or may even increase. Beta-adrenergic response reserve, as simulated by dobutamine infusion, appears to be normal. It is, however, not accompanied by augmentation in cardiac index, presumably because of the abnormal pulmonary vascular resistance response[96] and limited venous return.[20] Inability to constrict the splanchnic bed, as seen during experiments using head up tilt and the Valsalva maneuver, limits the capacity to augment preload acutely as is required during exercise.[68] Tissue hypoxemia, as evident by abnormal near infrared spectroscopy (NIRS) responses, reflects a significantly greater arterial-venous oxygen difference.[97] Mechanical pulmonary abnormalities, such as diminished lung volumes or paralyzed diaphragm, impose a limitation on peak VO_2.[98] Expiratory load at peak exercise may precipitate a significant reduction in cardiac output.[99] Administration of pulmonary vasodilators such as oral phosphodiesterase 5 inhibitors or inhaled prostanoids generally have a favorable effect on cardiac output augmentation, stroke volume, PVR, and they can improve exercise performance.[21,92] However, these medications may have countervailing adverse effects such as systemic venous dilation.

3 | FUTURE DIRECTIONS AND POTENTIAL RESEARCH

There is a need for novel approaches to interrogate the interaction between the systemic venous compartment, pulmonary vascular bed and the downstream ventricle during the entire cardiac cycle. Study of the flow dynamics of the conduit portion of the Fontan connection will be of great importance to determine conduit diameters and caval offsets that provide optimal flow characteristics both at rest and during exertion. Understanding the interaction between various factors involved in CV homeostasis such as hepatic buffer responses, splanchnic pooling, inflammation, venous insufficiency and conduit function of the large vessels, will benefit from comprehensive computer modeling to integrate their relative contributions. Factors contributing to late development of ventricular diastolic stiffness with advancing age with a Fontan need to be better understood. It is also necessary to define the gross pathologic, histologic, and biochemical mechanisms that

underscore the abnormal contractile responses observed during exercise in the heart as well as the peripheral vasculature.

The development of new pharmacologic agents that aid ventricular contractile function and augment lusitropic properties of the myocardium to maintain low left atrial pressure could also provide clinical benefit. Preventing or reversing myocardial fibrosis may also be a therapeutic target. Pacemakers that depolarize in coordination with respiration merit further evaluation. Technologies to energize and support the venous compartment are currently under development. Instead of complete right heart replacement, a strategy merely to reduce IVC pressure and reciprocally increase pulmonary arterial pressures by as low an increment as 5 mm Hg may potentially be sufficient to reverse many of the adverse long term effects of the Fontan circulation.[100] The pulmonary vascular bed is responsive to existing pharmacologic agents; further study is needed to understand whether combinations of pharmacologic and mechanical manipulation lead to therapeutically useful pulmonary vasodilation.

Other important lessons may be learned from spontaneous models of single ventricle physiology in nature. An exploration of various features including the evolved synchrony between pulmonary mechanical and heart action, exploitation of horizontal posture (eg, swimming vs upright exercise training) and manipulation of the muscle pump to minimize venous pooling and promote central venous return may provide further insights and lead to therapies. Finally, better understanding of the lymphatic circulation may allow its therapeutic manipulation in the failing Fontan circulation.

4 | SUMMARY AND CONCLUSIONS

We have reviewed and discussed the unique hemodynamic challenges posed by a Fontan circulation. The purpose of this review was to stimulate clinical research questions that can lead to new management strategies. Abnormalities of structure, geometry, and function have been described at all levels of the Fontan circulation. Suboptimal interactions between the CV compartments effectively cause systemic venous congestion and diminished cardiac output leading to CV and extracardiac morbidity. Better appreciation and optimization of the physiology of this neo-portal system is needed to improve Fontan outcomes.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

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