CME

Fontan Physiology Revisited

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The Fontan operation places the systemic and pulmonary circulations in series, driven by a single ventricular chamber. It has become the treatment strategy of choice for palliating single-ventricle congenital heart disease. This anatomy engenders profound changes in physiology, affecting the cardiovascular and respiratory systems with direct implications for anesthetic and intensive care. The physical basis of these changes and their sequelae are reviewed. (Anesth Analg 2015;121:172–82)

The Fontan operation places the systemic and pulmonary circulations in series, driven by a single ventricular chamber. It was first described by Francois Marie Fontan for repair of triscupid atresia.[1] It has become the treatment strategy of choice for palliating single- ventricle congenital heart disease (Fig. 1). The development of this operation was the result of bench and clinical research that began in the early 1940s. The realization that the pressures in the pulmonary vasculature were relatively low led to speculation that venous pressure alone might be sufficient to propel blood flow through the lungs. In the 1940s, ingenious animal models demonstrated that the right ventricle (RV) could be incapacitated without changing pulmonary artery (PA) pressure or systemic venous pressure.[2–4] Subsequent work by pioneering physiologists and surgeons demonstrated that a single ventricle could, in fact, support both circulations under appropriate circumstances.[5] Understanding of the complex physiology associated with the Fontan circulation has evolved considerably over the years since its conception; it is the intent of this review to summarize our current understanding.

AFTERLOAD, CONTRACTILITY, AND PRELOAD

The physiology of venous return, filling pressures, and cardiac output for 2-ventricle circulations has been debated extensively in the physiology literature beginning with Guyton's experiments in the 1950s.[6–8] Guyton and coworkers analyzed compliant-circuit models and found an almost linear relationship between systemic venous return (cardiac output) and right atrial pressure. Guyton interpreted his model to imply that right atrial pressure exerts a backward force that impedes return to the right atrium.[6] Levy's interpretation of the Guyton model was that as cardiac output increases venous pressure decreases because the venous reservoir is depleted.[9] Both Guyton's original interpretation and subsequent interpretations remain hotly contested[6,10] but hold conceptual relevance to introducing the hemodynamic limitations of the Fontan circulation. The ventricular preload is limited in the setting of a nonpulsatile, low-pressure pulmonary driving force and a pulmonary vascular system that has both cellular and mechanical factors prohibiting adequate recruitment of the pulmonary vascular bed. Consequently, cardiac output is limited.[11] Attempts to raise the ventricular filling pressure result in decreased potential energy across the pulmonary vascular bed, essentially increasing afterload and further inhibiting pulmonary flow, as suggested in Guyton's original model. Practically, attempts to access preload recruitable stroke work have the consequence of potentially impeding return across the pulmonary vasculature and further increasing afterload on the single ventricle. This is in addition to the intrinsically increased afterload as a result of the arrangement, in series, of 3 resistance beds: the systemic vascular bed, the cavopulmonary connection pathway, and the pulmonary vascular bed. The Fontan circulation is thus not only a single-ventricle circulation but one of inherently and simultaneously decreased ventricular preload and increased afterload (Fig. 2).

The physiology can be further clarified by reviewing the individual hemodynamic components. Systemic and pulmonary ventricular afterloads are composed of both pulsatile and nonpulsatile components. The nonpulsatile component is systemic or pulmonary vascular resistance (SVR or PVR) or [mean pressure]/[mean flow]. The pulsatile component is defined by the compliance characteristics of the great vessel, reflected wave phenomena, and inertia. The most comprehensive description of afterload is the aortic or PA input impedance (Z), the ratio of oscillatory pressure to flow.

Effective arterial elastance (E_a), derived from ventricular pressure volume loops, is also a measure of afterload. E_a combines the nonpulsatile and pulsatile components of arterial load into a single number but, unlike input impedance analysis, does not provide information on their relative contributions.[12] Ventricular end-systolic elastance (E_{es}), also derived from ventricular pressure volume loops, is a relatively preload-independent measure of contractility that incorporates afterload. Simultaneous analysis of E_a and E_{es} and determination of E_a/E_{es} provide assessment of ventriculoarterial coupling.[13] This coupling ratio is inversely related to ejection fraction (EF); $EF = 1/[1 + E_a/E_{es}]$.[14] Ventricular stroke work and mechanical efficiency are optimal at or near an E_a/E_{es} of 1 and decrease exponentially at greater values consistent with afterload-contractility mismatch.[15]

Animal models of the Fontan circulation and mathematical simulations of the Fontan circulation using sophisticated Windkessel modeling allow characterization of multiple

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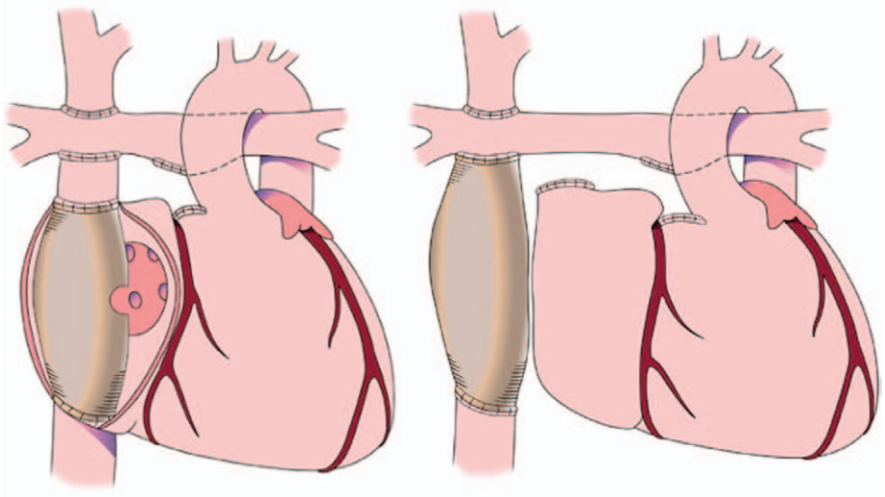

Figure 1. Illustrations of a fenestrated lateral tunnel (intra-atrial baffle) Fontan (left), and an unfenestrated extracardiac Fontan (right). Both place the inferior vena cava and superior vena cava in continuity with the pulmonary arteries, a complete cavopulmonary connection, with no interposed ventricle. The fenestration allows a "pop off" of blood from the systemic venous circulation to the pulmonary venous (common) atrium when baffle pressures are elevated. This allows cardiac output to be maintained in the presence of elevated resistance across the cavopulmonary connection and the pulmonary vascular bed in exchange for lower systemic arterial saturation (Adapted from https://apps.childrenshospital.org/clinical/mml/).

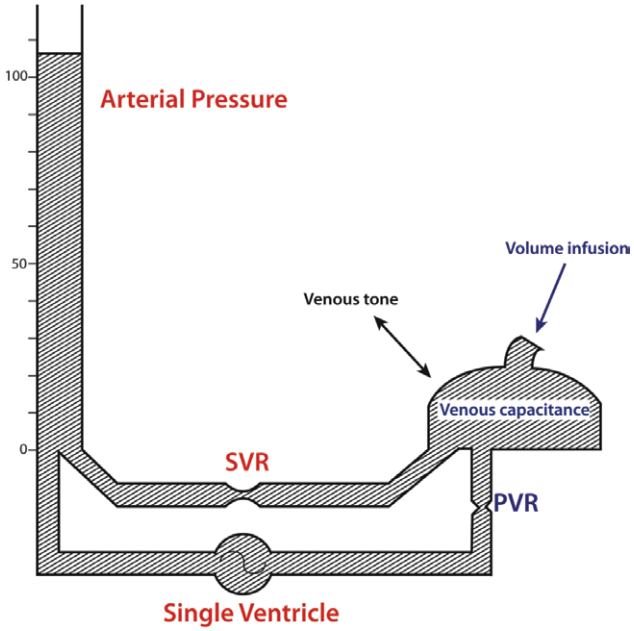

Figure 2. A hydraulic schematic of the Fontan circulation in which the systemic and pulmonary resistance beds are arranged in series. The single ventricle is represented as a pump that moves blood from a high-compliance, low-pressure venous reservoir into a low compliance, high pressure arterial reservoir. Blood return to the venous reservoir is gradient driven across a single resistance, the systemic vascular resistance (SVR). Unlike a 2-ventricle circulation, blood return to pump (ventricular preload) is gradient driven from the venous reservoir across 2 interposed resistances: the pulmonary vascular resistance (PVR) and the resistance across the cavopulmonary connection (not shown separately here but incorporated in PVR). Two means exist whereby the driving pressure in the venous reservoir can be increased to increase ventricular preload: increase the volume of the venous reservoir by expanding the blood volume or reduce venous capacitance. Unique to the Fontan circulation is the fact that increases in venous reservoir pressure simultaneously increase preload and afterload to the single ventricle because all resistances and pressures are in series. All the energy necessary to provide sufficient gradients for flow in the presence of elevated venous pressure is supplied by the single ventricle (Adapted from Tyberg[7] by Katherine Black).

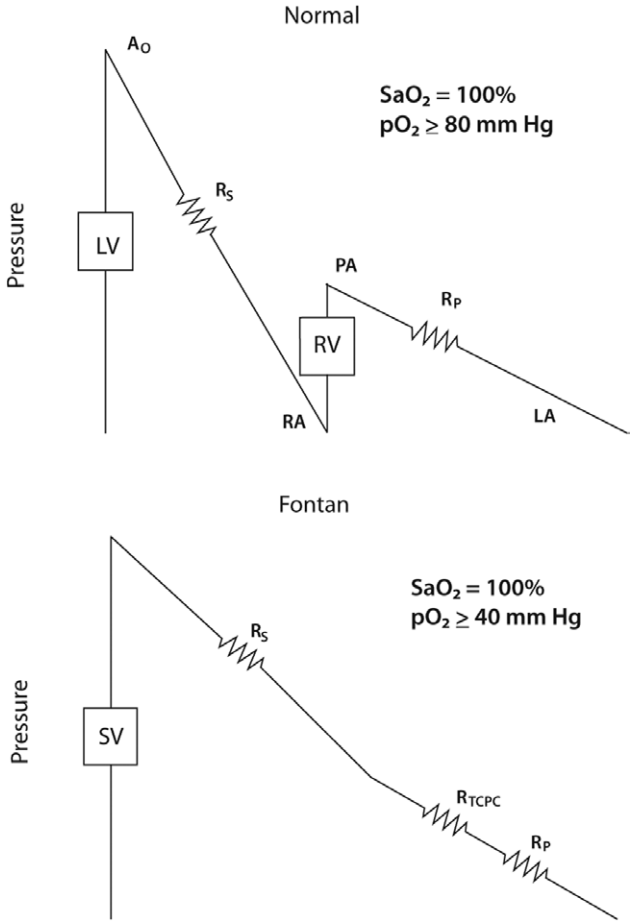

Figure 3. Schematic of the normal and Fontan circulation demonstrating a single-ventricle driving flow across 3 resistances in series; systemic (R_S), total cavopulmonary connection (R_{TCPC}), and pulmonary (R_P). In a normal, 2 ventricle circulation, each ventricle drives flow across 1 resistance (Adapted from Rodefeld et al.[22] by Katherine Black).

physiologic variables.[16] These models confirm the presence of elevated E_a and E_a/E_{es}, impaired ventricular energetics and efficiency, and reduced preload and contractile reserve in the Fontan circulation.[17–21] Increased afterload seen in patients with Fontan physiology, as suggested above, is the result of the arrangement, in series, of 3 resistance beds: the systemic vascular bed, the cavopulmonary connection, and the pulmonary vascular bed (Fig. 3).[17,18,20,22]

Clinical studies have substantiated these physical models.[23,24] The relationship between ventricular afterload and ventricular work in patients with Fontan physiology, at rest and during dobutamine stress, was evaluated in a study in which investigators compared 17 patients with Fontan physiology with 15 patients with single-ventricle physiology with a modified Blalock-Taussig shunt and with 13 patients with a normal 2-ventricle circulation.[25] The patients with Fontan physiology had a greater nonpulsatile load (vascular resistance) and a greater pulsatile load (low frequency impedance) both at rest and during dobutamine stress than the other 2 groups. Total hydraulic power, W_t, is the product of flow and pressure. Both W_t and cardiac index (CI) were diminished in the patients with Fontan physiology compared with the other groups at both baseline and with dobutamine. The hydraulic power cost per unit forward flow (W_t/CI) is a measure of ventricular efficiency. Ventricular efficiency was reduced in the Fontan circulation as compared to normal circulation. The Fontan circulation required 75% more power per unit forward flow at a time when forward flow (CI) was 37% lower. Afterload as measured by E_a increases after both superior cavopulmonary anastomosis and Fontan repair. E_a/E_{es} also increases, indicating an afterload mismatch resulting in a reduction in mechanical efficiency and poorer ventricular energetics.[26–28] Staging to a Fontan via a superior cavopulmonary anastomosis is of benefit in that patients having undergone superior cavopulmonary anastomosis before a Fontan repair have a lower E_a and E_a/E_{es} than patients having undergone a primary Fontan repair.[26]

Ventricular contractility, strictly defined, refers to intrinsic force-generating properties of the ventricle not attributable to changes in loading conditions (preload and afterload). Systolic ventricular function, generally assessed by fractional shortening (FS) or EF, is a ventricular performance parameter dependent on loading conditions. Patients having undergone the Fontan procedure in the last decade have a lower average EF than age-adjusted healthy controls, despite staging via a superior cavopulmonary anastomosis with completion of the Fontan before the age of 5 years. Nonetheless, 73% of these patients have an EF within 2 SD of normal control patients.[29] In a comparison of 17 patients with Fontan physiology with good functional status with 20 patients with a normal 2-ventricle circulation, E_{es} was found to be similar at rest and during dobutamine stress (consistent with normal contractility), whereas E_a and E_a/E_{es} were greater in the Fontan group (consistent with greater arterial afterload).[28] At rest, CI and FS were lower in patients with Fontan physiology than in controls, despite similar E_{es} because of an elevation in E_a. During beta-adrenergic stimulation with dobutamine, patients with Fontan physiology exhibited a smaller increase in CI and FS than controls because of a limitation in ventricular preload reserve. Other investigations support the concept that reduced ventricular function in patients with Fontan physiology is the result of increased afterload and reduced preload rather than of decreased contractility and inherent myocardial dysfunction, as will be discussed further below.[25–27,30,31] However, in a cohort of patients who underwent Fontan procedures at older than 10 years of age, impaired contractility clearly influenced the genesis of diminished ventricular function.[30]

The systemic venous circulation is interposed between the systemic vascular bed and the cavopulmonary connection and pulmonary vascular bed. Increased systemic venous pressure is a necessity in Fontan physiology because the interposition of the cavopulmonary connection and pulmonary vascular bed between the systemic venous system and the pulmonary venous atrium results in an increase in the resistance to venous return.[19–21] The resistance characteristics of the Fontan circuit are dynamic, with cavopulmonary connection pathway resistance increasing nonlinearly as flow increases with exercise.[20] As resistance to venous return increases as the result of increases in cavopulmonary connection resistance, PVR, or both, ventricular preload (pulmonary venous atrial pressure or ventricular end-diastolic pressure) will decrease unless systemic venous pressure (and concomitantly, systemic ventricular afterload) increases sufficiently. Incremental increases in systemic venous pressure, although necessary to provide adequate preload to the systemic ventricle, have the unfortunate consequence of simultaneously increasing systemic ventricular afterload.[20] This situation does not exist in a normal 2-ventricle circulation because in addition to providing a pulsatile source of pulmonary blood flow, the RV serves as a compliant reservoir system for the systemic venous circulation.[32]

In the normal 2-ventricle circulation, the compliance (change in volume relative to change in pressure) of the venous system is 20 to 30 times greater than that of the arterial system, with 70% of the total blood volume contained in the venous system.[7,33,34] Venous capacitance is the volume of blood in the venous system at a given pressure and is the sum of stressed and unstressed volume. Stressed volume is the volume of blood in the venous system that generates a pressure greater than the pressure in the surrounding tissue. The remainder of volume is defined as unstressed volume. Normally, approximately 30% of total blood volume is stressed volume.[34,35] Thus, for a given venous volume, a decrease in venous capacitance caused by an increase in venous vascular tone will convert a large volume of blood from unstressed to stressed volume, thereby increasing venous pressure. Intravascular volume infusion increases venous pressure for a given venous capacitance because stressed volume increases as a result of an increase in venous volume. Alternatively, high venous pressure can be maintained with a low venous volume when venous capacitance is low because stressed volume is larger relative to unstressed volume.

Patients with Fontan physiology have diminished venous capacitance and thus a smaller unstressed volume at baseline compared to normal subjects.[36] Venous capacitance vessels are much more sensitive to sympathetic input than are arterial resistance vessels.[34] Compared with normal subjects, patients with Fontan physiology exhibit diminished venous compliance, particularly in the lower extremities, commence microvascular filtration at a greater venous pressure (thereby limiting edema formation), and have greater lower-extremity and splanchnic resistance. Perhaps most importantly, patients with Fontan physiology have reduced splanchnic capacitance.[37] Five percent of the cardiac output is derived from the splanchnic bed. This system drains the intestines and the spleen into the portal veins, through hepatic sinusoids into the hepatic veins, and

then into the inferior vena cava (IVC). In adults, 65% of total venous return is from the IVC; 40% of IVC drainage is from hepatic veins and 60% is from the infrahepatic IVC.[38,39] The splanchnic venous bed is highly compliant compared with nonsplanchnic venous beds. The hepatic veins or the liver itself are the main source of resistance to splanchnic venous return.[34] As a consequence, a large volume of blood can be sequestered in the splanchnic bed.

As a result of these compensatory mechanisms, patients with Fontan physiology exhibit superior tolerance to orthostasis (head-up tilt) and the Valsalva maneuver compared with normal individuals[37]; however, patients with Fontan physiology are exceedingly vulnerable to acute decreases in intravascular volume and to acute increases in venous capacitance, such as those caused by the direct effects of vasodilator agents or by diminished central sympathetic output. Acute increases in venous capacitance and or compliance can result in lower pulmonary perfusion pressures and subsequently lower ventricular filling pressures, resulting in low cardiac output.

The increased caval and splanchnic pressures in patients with Fontan physiology are transmitted to the liver, resulting in chronic hepatic venous congestion which, in combination with relatively low cardiac output, results in inflammation, fibrosis, and eventually cirrhosis.[40] This has been demonstrated to result in marked changes in the hepatic architecture, diffuse sinusoidal fibrosis, and a type of cirrhosis labeled "Fontan-associated liver disease."[40,41] Generally, increase in liver enzymes is minimal because of the lack of significant inflammation and a low rate of damage to the hepatocytes. Typically, hepatic function is well preserved in Fontan-associated liver disease until late in the course of the disease. Clinical findings such as caput medusae or splenomegaly typically are absent. Appreciation of this compromise is important because of the striking effect of liver disease on outcome from cardiac surgery; even mild disease is associated with a mortality of 17%.[42] The ubiquitous presence and insidious onset of hepatic dysfunction in the Fontan population make it particularly problematic, and some have advocated for screening liver biopsy.[43] Liver dysfunction is just one consequence of the increased caval pressures described previously and detailed in other reviews of failing Fontan physiology.[44]

Clinically, the need for sustained high systemic venous pressure renders these patients vulnerable to acute decreases in intravascular volume and to acute increases in venous capacitance, such as those caused by the direct vasodilators or diminished central sympathetic output. The sequestration of blood into the venous system, e.g., in the setting of low output, inflammation, or recent Fontan conversion, can be addressed in 2 ways: by expanding blood volume or by administering a pharmacologic agent capable of reducing venous capacitance. An ideal agent is elusive, however, because the available venoconstrictors are relatively ineffective and also induce some degree of unwelcome arterial constriction.[45]

EFFECTS OF VENTILATION

Although large instantaneous increases in pulmonary blood flow are seen in patients with Fontan physiology with normal inspiration the magnitude of the incremental augmentation of flow associated with normal inspiration is quite modest when considered over the entire ventilatory cycle. Doppler flow assessment of pulmonary flow in adult patients with atriopulmonary connections demonstrated that pulmonary blood flow was 35% greater during the inspiratory phase of the respiratory cycle than during the expiratory phase.[46,47] This represents, however, an increase in total flow of only 24% due to the ratio of inspiratory time to expiratory time.

Nonetheless, in adult cavopulmonary connection patients, approximately 30% of systemic venous flow to the pulmonary arteries is respiratory dependent as compared with 15% in normal 2-ventricle patients.[39,48] Furthermore, although inspiration augments pulmonary flow in cavopulmonary connection patients, aortic blood flow is greater during expiration,[49] identical to the response seen in normal 2-ventricle patients. In patients with 2 ventricles, inspiration results in a more negative transmural pressure in the RV with resultant improved right ventricular filling. In contrast, left ventricular filling in healthy patients decreases during spontaneous inspiration as the result of interventricular interactions and compression of pulmonary vasculature impeding return to the left atrium. This interventricular dependence results in an inspiratory increase in RV end-diastolic volume and stroke volume, with a simultaneous reduction in LV end-diastolic volume and stroke volume.[50] In contrast, in single-ventricle patients with a cavopulmonary connection, there are no interventricular interactions; the primary mechanism of expiratory increase in stroke volume during spontaneous ventilation is caused by "release" of the large reservoir of blood stored in the pulmonary vascular system with subsequent augmentation of preload to the single-ventricular chamber.[49]

The absence of interventricular dependence in cavopulmonary connection has other consequences as well. Despite the presence of enhanced cardiorespiratory coupling, these patients do not manifest pulsus paradoxus in association with cardiac tamponade or obstructive airway disease because of the absence of interventricular interdependence in single ventricle hearts. As a result, pulsus paradoxus is absent in these patients, regardless of the severity of tamponade. In healthy patients, superior vena cava (SVC) flow increases by 13% during inspiration whereas IVC flow increases by 53%,[51] suggesting that inspiratory increase in venous flow is attributable primarily to an increase in IVC flow.[49] This increase in IVC flow with inspiration is in turn largely caused by an increase in hepatic venous return.[39,52–54] In contrast, during lower-extremity exercise using supine bicycle ergometry in patients with Fontan physiology, increases in venous return are caused primarily by increases in IVC flow, similar to healthy individuals. As exercise intensity increases, inspiratory augmentation of flow is increasingly less important, because the reduction in venous capacitance that accompanies the peripheral pumping action of muscles increases.[49,55,56]

The distribution of venous return from the SVC and IVC is age dependent. In infants, SVC flow accounts for 49% of cardiac output, increasing to a maximum of 55% at age 2.5 years, followed by a gradual decrease to adult values of 35% by age 6.6 years.[57] Given this distribution of blood flow and the predominant effects of respiration on augmentation of

hepatic venous flow, it can be anticipated that the effects of respiration on augmentation of pulmonary blood flow and cardiac output would be more prominent in older patients with Fontan physiology.

Diaphragmatic motion is important in augmenting hepatic venous flow in inspiration, particularly with patients in the upright position.[39,52–54] The liver has been described as a reservoir of blood that can be drawn on during inspiration as a consequence of changes in venous pressure and direct pressure by diaphragmatic descent.[58] Diaphragm plication (right, left, or bilateral) after paralysis does not restore normal inspiratory augmentation of hepatic venous flow in either 2-ventricle or cavopulmonary connection patients.[53]

Given the effects of negative intrathoracic pressure on pulmonary blood flow, the effects of positive pressure ventilation on Fontan hemodynamics are of concern. Unfortunately, these effects have not been evaluated systematically. Early experience with patients with atriopulmonary connections demonstrated that increasing levels of positive end-expiratory pressure (PEEP) while progressively increasing Pao_2, progressively reduced cardiac output.[59] It is important to emphasize that this oft-cited study examined the effects of PEEP, not the effects of positive pressure ventilation per se. In observational studies, early initiation of spontaneous ventilation after Fontan surgery has been identified as a factor in improved outcome, and reduced hospital stay and costs.[60,61] Negative pressure ventilation via use of a cuirass has been shown to improve pulmonary blood flow and cardiac output compared with positive pressure ventilation in patients with Fontan physiology, after tetralogy of Fallot repair, and in healthy children.[62–64] Negative pressure ventilation has been shown to promote a greater peak systolic pressure after an increase in diastolic pressure, which is the expected response to a greater stroke volume. Although an increased afterload was observed, it would appear that the benefits of the preload augmentation outweigh any negative impacts on increased afterload.[65] Negative pressure ventilation, however, is not a readily available clinical tool.

When positive pressure ventilation is used, it has been suggested that a near-linear inverse relationship exists between mean airway pressure and cardiac output.[58] Thus, when positive pressure ventilation is initiated in a patient with Fontan physiology, it is important that tidal volume, PEEP, inspiratory:expiratory ratio, respiratory rate, and gas-flow pattern be manipulated to provide the lowest possible mean airway pressure compatible with the desired lung volume, minute ventilation, and gas exchange parameters. The deleterious effects of positive pressure ventilation, however, may be more than offset by the effects of hypercarbia, hypoxemia, and reduced lung volumes on PVR and pulmonary blood flow that accompany inadequate spontaneous ventilation.

PULMONARY CIRCULATION

In the Fontan circulation, pulmonary vascular impedance is the single most important factor limiting cardiac output.[66] The components of impedance to flow in the pulmonary vascular and systemic systems are identical, but the arrangements of these components are very different.[67–70] The ventricle ejecting blood into the systemic circulation must overcome both resistive load, primarily determined by small peripheral vessels, and a pulsatile load determined primarily by the capacitance of the thoracic aorta.[70] Thus, the primary resistive and capacitive components of the system are in physically different locations.

In the pulmonary arterial system, the components of resistance and compliance are more equally distributed throughout the pulmonary vascular bed; only 15% to 20% of total pulmonary compliance is determined by the proximal pulmonary arteries.[70] The number of arterioles in the pulmonary circulation is 10 times greater than the systemic circulation; resistance is 10 times lower and compliance is 10 times greater than in the systemic circulation. The effect of compliance on pulmonary vascular impedance is greater than that in the systemic vasculature due to the larger ratio of the pulse pressure to the mean pressure.[70] Given the importance of capacitance in the pulmonary vascular bed, it becomes obvious that resistance (as opposed to impedance) is an incomplete index of right ventricular load in a normally pulsatile right heart/lung system.[70] In the normal pulmonary circulation, the pulsatile components of pressure and flow constitute as much as one-third to one-half of the W_t output of the RV.[71] This pulsatile flow in the pulmonary circulation is responsible for recruitment of pulmonary capillaries. The total number and cross-sectional area of capillaries increases by 100% with initiation of pulsatile flow under steady flow conditions in experimental animals.[72] This recruitment leads to a 30% reduction in measured PVR,[73] an efficiency not present in minimally pulsatile pulmonary vasculature of the Fontan circulation. Of further concern in patients with Fontan physiology is accumulating evidence that chronic pulsatile flow deprivation in the pulmonary bed leads to impaired endothelial function and nitric oxide (NO) release, reduced vascular recruitment, and impaired lung growth, all of which serve to elevate PVR.[74–77]

Patients a median of 9 years after a Fontan procedure have been demonstrated to have increased basal PVR and exhibit a mean 0.5 Wood unit decrease in the PVR upon exposure to 20 ppm exogenous inhaled NO.[78] Response to nonendothelial, exogenous NO donor-mediated vasorelaxation via agents such as nitroprusside appears to be preserved as well.[73] These findings are consistent with flow pulsatility enhancing endothelial NO release, a PVR-lowering mechanism lost in the Fontan circulation.[79]

Heart rate also has important effects on pulmonary vascular impedance in the normal pulsatile right heart as the result of the resistor-capacitor characteristics of the vascular system. In dogs, because of a steep decrease in impedance between zero and 3 cycles/s, and the rate-dependent change in the harmonic structure of flow pulsations, there is inverse relationship between heart rate and the amount of power needed for a given mean flow. Thus, tachycardia in a normal circulation can increase pulmonary blood flow by as much as 35% with an increase in pulmonary arterial input power of less than 5%, without changing the diameter or impedance of the pulmonary bed.[71] This efficiency is entirely attributable to the capacitive features not available to the Fontan circulation.

It follows that nonpulsatile perfusion of the PA and failure to recruit additional pulmonary vascular cross-sectional area are associated with increased PVR compared with pulsatile flow at the same throughput.[80]

Not only does the Fontan circulation lack a dedicated ventricle for the pulmonary circulation, it has a significantly less efficient pulmonary vascular system as the result of mechanical and cellular changes. This situation is further complicated by energy losses inherent in the low energy, nonpulsatile Fontan circuit leading into the lungs. Flow-related energy losses within the Fontan circulation have been modeled extensively by the use of computational fluid dynamics modeling. Several mechanisms are responsible for energy loss in the Fontan circuit, including the size of the pulmonary arteries, wall shear stress, the collision of blood coming from the SVC and IVC into the pulmonary arteries, and the effect of aortopulmonary collaterals. Some of these analyses suggest that wall shear stress (the friction created by a fluid flowing past a fixed vessel wall) is the major contributor to energy losses, with the collision of blood at the cavopulmonary connection being less influential.[81] Others have looked at optimizing flow through the cavopulmonary connection by maximizing the pulmonary arterial cross-sectional area or novel anastomoses such as the Y-graft.[82–84]

Further complicating the hemodynamic picture, an estimated 80% of patients undergoing Fontan-type operations have, or subsequently develop, aortopulmonary collaterals as a consequence of ongoing hypoxia. Flow from the arterial circulation into the Fontan circuit results in wasted cardiac output, energy losses due to turbulence, and increased pressure in the Fontan pathway and pulmonary arteries together resulting in an association with poor postoperative outcome.[85]

It has been recognized recently that strategies for staging to the Fontan procedure in patients with a univentricular heart are associated with a "volume load paradox." That is, the strategies for preservation of ventricular function by preventing prolonged volume loading are at odds with the goal of promoting development and growth of the pulmonary vascular bed through increased pulmonary blood flow.[86] Early performance of bidirectional superior cavopulmonary anastomosis in a child with a Sano or modified Blalock-Taussig shunt reduces the volume load on the single ventricle from 2.5 to 3.5 times normal (for a biventricular circulation) to normal. Simultaneously, this procedure reduces pulmonary blood flow from 1.5 to 2.0 times normal to 0.5 to 0.7 of normal. It is now recognized that this pulmonary blood flow restriction limits PA growth and results in further impediment to pulmonary flow beyond that induced by the physiologic and molecular mechanisms previously discussed.[87] To promote PA growth and forestall the development of the pulmonary arteriovenous malformations that result from lack of direct perfusion of the pulmonary capillary bed with blood from the gut that passes through a functioning liver, maintenance of residual antegrade pulmonary blood flow at the time of superior cavopulmonary anastomosis has been suggested.[88,89] Such flow could be provided by maintaining a Sano shunt (RV to PA conduit), a banded main PA, or a stenotic right ventricular outflow tract; each of these results in pulsatile flow. Given the observation that pulsatile flow is more effective in promoting vascular growth, each of these is, at least theoretically, superior to an aortopulmonary shunt, which would be less pulsatile and more continuous in its delivery of flow.

EXERCISE CAPACITY AND LIMITATIONS IN THE FONTAN CIRCULATION

Exercise studies provide insight into the adaptation of the cardiovascular and respiratory systems to stress. Limitations to cardiac output in the Fontan circulation have been described as "cavopulmonary failure," consistent with concept that the patient's poor cardiopulmonary status is not associated with "pump failure" but rather is secondary to inability to drive blood through the lungs at physiologic systemic venous pressures.[90] Failing Fontan physiology is characterized by low cardiac output in the setting of high systemic venous pressure, despite the absence of significant ventricular systolic and diastolic dysfunction or atrioventricular valve dysfunction.

In healthy patients with biventricular circulation, the pulmonary vascular bed accommodates increased cardiac output by distending and recruiting vasculature, such that PVR decreases by more than 50% and compliance increases by 30% with no change in characteristic impedance.[91] Thus, there is not a linear relation between cardiac output and pulmonary arterial pressure.[92–95] In addition, the 2-ventricle circulation is capable of increasing systolic PA pressure to the levels necessary (50–70 mm Hg systolic) to provide sufficient cardiac output at extremely high workloads. This hemodynamic adaptation is not possible in the Fontan circuit.[91]

Patients with Fontan physiology lack these adaptations. As a result, their ability to increase cardiac output in response to exercise is limited. In a large cross-sectional study of patients with a Fontan circulation in the first 2 decades of life, maximal aerobic exercise capacity was reduced compared to healthy subjects. Even among patients who expended near maximal effort (respiratory exchange ratio ≥1.1), peak oxygen consumption averaged only 67% of predicted. Oxygen pulse (a surrogate for the effective stroke volume at peak exercise) was the most important factor accounting for the variance in aerobic performance. When the 3 factors responsible for oxygen delivery during exertion (heart rate, arterial oxygen content, and stroke volume) were evaluated, calculated stroke volume reserve was almost exclusively responsible for the variation in aerobic performance in patients with Fontan physiology.[11] In a low ventricular preload state, in which the ability to augment preload is limited by a relatively fixed but exogenous vasodilator-reactive PVR, it follows that maximal cardiac output is limited by venous return through the cavopulmonary connection.

Exogenously administered pulmonary vasodilators have been shown to improve exercise capacity and myocardial performance in patients with Fontan physiology. Improvement in echocardiographically derived myocardial performance index and the product of dominant outflow tract velocity time integral and heart rate (as a surrogate measure of cardiac output) were seen after administration of oral sildenafil in a cohort of patients with Fontan physiology.[96] Although formal exercise testing in a cohort of primarily teenaged patients with Fontan physiology, enrolled in a randomized, cross-over trial of oral sildenafil, did not detect a sildenafil-related improvement in peak oxygen consumption, improvements in ventilatory efficiency during peak and submaximal exercise were observed.[97] In another study, administration of iloprost (an inhaled form of prostacyclin)

resulted in improvements in peak oxygen pulse and peak oxygen consumption, and it was particularly beneficial among patients with impaired function.[98] Given that oxygen saturation was not affected, the increase in oxygen pulse was almost exclusively related to an increase in the forward stroke volume after iloprost, suggesting that lowered PVR resulted in augmentation of ventricular preload, and increased cardiac output.

A study in which investigators used cardiac magnetic resonance imaging demonstrated that a single oral dose of sildenafil improved exercise hemodynamics in young adult patients with Fontan physiology, although the mechanism of cardiac output improvement appeared to be more complex than augmentation of preload alone.[99] These authors found that, among patients with Fontan physiology, increasing levels of exercise induced a progressive decrease in indexed SVR, a progressive increase in transpulmonary resistance, a progressive increase in heart rate, and a decrease in stroke volume, due to a progressive decrease in indexed end diastolic volume. The result is that cardiac output does not increase between moderate and high levels of exercise. After sildenafil, there was a progressive increase in cardiac output due primarily to an increase in heart rate with a stable transpulmonary resistance, stroke volume, and end-diastolic volume in the setting of a reduced SVR and end-systolic volume. Thus, although the absolute value of stroke volume did not increase, sildenafil enhanced ventricular filling by inducing a greater increase in end-systolic volume relative to end-diastolic volume, despite the shorter diastolic interval that is invariably associated with tachycardia.[99] Sildenafil is not a selective pulmonary vasodilator and the concomitant decrease in SVR complicates these experiments. Unfortunately, a comparison with nitric oxide or more selective pulmonary vasodilators was not undertaken in this study. Long-term outcome studies of pulmonary vasodilator therapy in the Fontan circulation are not yet available, but early studies are encouraging and suggest that the decrease in PVR achieved with pulmonary vasodilators can be beneficial in Fontan physiology as well as in situations of increased metabolic demand.[98]

CARDIOPULMONARY RESUSCITATION IN PATIENTS WITH FONTAN PHYSIOLOGY

The unique physiology of patients with cavopulmonary connections is typically the antithesis of that needed to perform ideal cardiopulmonary resuscitation (CPR) and may explain the limited efficacy of CPR in this population. There is increasing evidence supporting the importance of coronary perfusion pressure and cerebral perfusion pressure in all patient outcomes after CPR. During chest compressions, coronary and cerebral perfusion pressures may be limited by increased common atrial and SVC/IVC pressures, respectively.[100] It is not uncommon, especially in patients with a single RV, for significant atrioventricular valve regurgitation to be present. A regurgitant atrioventricular valve will compromise forward blood flow and increase common atrial and central venous pressures. There is no compressible chamber/valve combination between the systemic venous return (SVC and IVC) and the pulmonary vasculature, rendering the compression/release mechanism of CPR less effective. In other words, venous blood in the pulmonary vascular bed and pulmonary arteries can go backward from the chest into abdomen, head, and upper extremities, depending on the relative impedance and capacitance of those respective areas. During decompression, when the chest wall is allowed to recoil and there is a transient relative decrease in intrathoracic pressure, systemic venous return must similarly cross the pulmonary vascular bed before returning to the common atrium. Acidosis and hypercarbia typically present in CPR situations increase the baseline elevated PVR (as the result of mechanical and cellular changes as described previously). Overall, the combination of these factors limits the return of oxygenated blood to the heart, while simultaneously increasing caval pressure and hence intracranial pressure, subsequently limiting cerebral perfusion pressure. This combination is thought to contribute to high mortality and significant neurologic injury in patients with cavopulmonary connections requiring CPR.[100,101] If these phenomena persist for too long, irreversible myocardial and neurological injury are likely to occur. There are case reports of abdominal and chest compressions resulting in an increase in arterial pressure during resuscitation.[102] This is interesting, given the physiology of the Fontan, but may have risks in the setting of gut and hepatic congestion.

EXTRACORPOREAL SUPPORT OF THE FONTAN CIRCULATION

Support of the failing single ventricle circulation with extracorporeal membrane oxygenation (ECMO) is difficult.[100,101] Adequate venous drainage is complicated by the anatomy of the cavopulmonary connection. Given the difficulty of transthoracic cannulation in this population, peripheral cannulation may be used, resulting in inadequate decompression of either the superior or inferior vena cava unless cannulation of both the femoral and internal jugular veins is undertaken. The trade-off is that with adequate cavopulmonary decompression, preload to the single ventricle is decreased due to reduced blood flow through the lungs. The single ventricle is often failing, and imposing high afterload from external arterial flow can inhibit ventricular ejection of any blood traversing the pulmonary bed. Together, these factors can create a situation where most of the cardiac output and systemic oxygen delivery must be provided by ECMO flow, with little or no contribution from ventricular ejection; however, fully supportive flows often cannot be achieved with peripheral cannulation alone. Veno-atrial ECMO avoids imposition of additional afterload. It has been used in a circumstance where ventricular function was preserved and a reversible cause of elevated PVR was present.[103] It is conceivable that this approach would be effective in other circumstances where a reversible pulmonary process existed in conjunction with adequate ventricular function.

Given that CPR is generally ineffective, and despite the challenges associated with ECMO support, elective cannulation and initiation of ECMO before cardiopulmonary arrest in patients with potentially reversible causes of a failing Fontan circulation has been used.[100,101] In the largest series of 230 patients, 35% of all patients with Fontan physiology on ECMO survived to discharge. As would be expected, CPR prior to ECMO initiation was associated with nonsurvival. The presence of greater central venous

pressure in patients with failing Fontan physiology may increase the risk of central nervous system and end organ injury during CPR, thus limiting survival, even after ECMO deployment. Mortality also was associated with the duration of ECMO support and the development of renal failure or neurological complications.[101]

Use of ventricular assist devices (VAD) as a bridge to cardiac transplantation or for support of the "Failing Fontan" circulation has been attempted with mixed results.[104,105] The heterogeneous cause of Fontan "failure" requires that an individualized approach to circulatory support be taken for each patient.[104,105] Single-pump pulsatile and nonpulsatile VAD to support the systemic ventricle have been used when ventricular dysfunction is the primary cause for failing Fontan circulation. However, in circumstances in which there is increased pulmonary vascular and/or cavopulmonary resistance, it may be necessary to insert an additional pump from the systemic venous to the pulmonary circulation to address systemic venous hypertension and to provide adequate preload to the systemic VAD. This approach requires revision of the Fontan pathway to separate the systemic venous and pulmonary circulations. Total artificial heart implantation also has been reported as a definitive bridge to transplantation.[106] Survival after heart transplantation is similarly complicated by the complex etiology of heart failure in patients with Fontan physiology. As reviewed elsewhere, cardiac transplant patients with Fontan physiology have inferior long-term outcomes as compared to 2-ventricle patients with isolated ventricular dysfunction.[107,108]

CONCLUSIONS

It has been more than 40 years since the first Fontan operation was performed and 60 years since the formative work was performed to enable its fruition.[5] It is now the treatment of choice for patients with single ventricle physiology. Patients who underwent these procedures as children are now appearing as adults, including parturients. Their presence in the intensive care unit and operating room for both cardiac and noncardiac surgery is increasingly common. A detailed understanding of the unique resultant physiology is essential to the anesthetic and intensive care management of these unique patients. ■

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