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Review Article

Considerations for Fontan Individualization in Patients with Isomerism (Heterotaxy)

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Abstract

"Fontan palliation has been used as the final stage in functionally univentricular palpation for several years. The Fontan has undergone several iterations, having begun as an atriopulmonary connection and then evolving into the extracardiac conduit. Innovations in computer modeling and flow simulation has now allowed for studies to be conducted to characterize flow within the Fontan conduit and compare the efficiency of various different Fontan geometries. We review data pertaining to various Fontan geometries in this manuscript".

Keywords: *Fontan Palliation; Isomerism; Heterotaxy; Cavopulmonary*

Introduction

Isomerism, less ideally referred to as heterotaxy, is a unique clinical finding characterized by mirror-imaged findings of the thoracic organs and seemingly random arrangement of the abdominal organs [1]. Likely the consequence of disruption in the earliest phase of left-right patterning, isomerism leads to anatomic and functional perturbations [2,3]. Abnormalities of every organ system have been documented in the setting of isomerism, although the number of organs systems affected and the extent of this involvement, is highly variable from patient to patient [4-15].

Congenital malformations of the heart are frequently complex in the setting of isomerism and patients often will require a functionally univentricular palliation. Morbidity and mortality at each surgical stage is influenced by a number of factors [16,17]. Of particular challenge in children with isomerism is the issue of Fontan completion. While Fontan geometry is of importance in those with functionally univentricular hearts without isomerism, Fontan geometry is arguably of even greater importance in those with isomerism. This is particularly true due to the high prevalence of bilateral superior caval veins and interruption of the inferior caval vein in the setting of isomerism. Both of these findings, in isolation or in combination, can greatly alter flow patterns within the superior and inferior cavopulmonary anastomoses. Pulmonary arteriovenous malformations are frequently found in children with isomerism and interruption of the inferior caval vein after the Kawashima procedure and Fontan geometry can be vital to halting and reversing the progression of these, subsequently leading to an improvement in arterial oxygen saturation [18].

It is imperative that Fontan circuits become increasingly individualized, particularly for those with isomerism. Careful preoperative planning and selection of most ideal Fontan geometry will likely lead to improved outcomes. This manuscript discusses timing of Fontan completion as well as modifications which may be considered in children in the setting of isomerism. While these can be considered in

children without isomerism as well, this manuscript will discuss the data surrounding these modifications in the particular setting of isomerism.

Fontan completion at the time of the Kawashima

Timing of Fontan completion is highly variable and is often physician dependent. Data has now emerged that has identified factors that may be taken into consideration when timing Fontan completion. These risk factors are generally those that predict longer duration of mechanical ventilation, chest tube drainage, intensive care unit stay, and hospital stay. Our group did a similar study in Fontan patients with isomerism and found that the age at time of surgery and arterial oxygen saturation were important to take into consideration for Fontan timing in those with isomerism. An arterial oxygen saturation of less than 84% and age less than 3 years tended to be associated with increased duration of mechanical ventilation, chest tube drainage, and hospital stay with arterial oxygen saturation have a more profound effect on these outcomes. Additionally, while younger age was statistically significantly associated with slight worsening of these outcomes the true clinical significance is questionable as severe morbidity and mortality was not noted to be increased.

With this data being placed in the context of increased risk of pulmonary arteriovenous malformations in those with isomerism, it becomes apparent that the challenge in those with isomerism is deciding how aggressive to be with early Fontan completion.

In children with interruption of the inferior caval vein, the Kawashima acts much like a Fontan completion in that a majority of the systemic venous return is directed to the pulmonary artery, having bypassed the right heart. Thus, the staging effect of the separate superior and inferior cavopulmonary anastomoses is lost. The hepatic veins which remain for Fontan completion handle up to 20% of cardiac output and thus this additional volume should not significantly impact immediate postoperative outcomes or lead to a significant increase in pulmonary artery pressure above that of the Kawashima. Arterial oxygen saturations should be above 90% after Fontan completion in the patients in the absence of pulmonary disease or significant pulmonary arteriovenous malformations. Benefits of a simultaneous Kawashima and Fontan completion are prevention of pulmonary arteriovenous malformations, elimination of an additional planned sternotomy, and elimination of an additional planned cardiopulmonary bypass run for centers that do not routinely do Fontans off-pump. The elimination of another hospitalization and the additional expense and emotional trauma associated with this hospitalization are also important considerations.

Anecdotally, some have performed Fontan completion at the time of the Kawashima although many centers still perform the Fontan completion separately [19]. For those who elect to perform the Fontan completion apart from the Kawashima it may be done within a year to several years after Kawashima. The significance of pulmonary arteriovenous malformations does increase with time and thus once they have developed they will continue to cause progressive arterial desaturation [18].

In those without interruption of the inferior caval vein, the situation is different. In this instance, there is still at least 50% of cardiac output that remains returning via the inferior caval vein. This inferior caval venous return continues to drain to the heart and leads to desaturation. In this situation, however, it becomes more difficult to advocate for Fontan completion at the time of the stage II Glenn palliation as this going to add a significant amount of nonpulsatile flow returning directly to the pulmonary circulation in addition to the Glenn palliation [20]. This is likely to result in altered postoperative course with prolonged mechanical ventilation, prolonged chest tube duration, greater frequency of chylous draining, and longer intensive care and total hospital stay. Case reports of total cavopulmonary anastomoses being performed do exist, even specifically for isomerism patients [21].

Ligation or division of a single superior caval vein in the presence of bilateral superior caval veins

A large proportion of those with isomerism will have bilateral superior caval veins. In most situations when a right superior caval vein is present it will drain directly into the roof of the right sided atrium while a left sided superior caval vein may drain directly into the roof of the left sided atrium or into the coronary sinus when it is present. It should be noted that the coronary sinus is only present in the set-

ting of left isomerism and that the coronary sinus in this situation lies in the left sided atrioventricular groove. The presence of bilateral superior caval veins can impact arterial oxygen saturations to some extent depending on the route and subsequent course venous blood from the left superior caval vein takes, has implications for institution of cardiopulmonary bypass, and ultimately can alter blood flow patterns in the cavopulmonary system.

It is the last point that is of most importance in those with isomerism. Both superior caval veins should be incorporated into the superior cavopulmonary anastomosis such that there are two separate anastomoses. What can be considered, however, is the ligation or division of one of the superior caval veins. In the setting of an interrupted inferior caval vein the superior caval vein accepting the azygos or hemiazygos vein may be ligated proximally to the insertion of the azygos or hemiazygos vein while in the setting of an inferior caval vein returning directly to the right sided atrium, the more diminutive of the two may be ligated [22].

Ligation of one of the two superior caval veins may be of assistance after Fontan completion. Flow from the superior caval vein has been demonstrated to impact flow from the Fontan. In a standard arrangement of the Fontan, such that the superior and inferior cavopulmonary anastomoses are directly superior-inferior to one another, the collision of blood from the superior and inferior anastomoses leads to turbulence and power loss. This collision of blood also impacts the distribution of venous return to the right and left pulmonary arteries. This becomes increasingly important in the setting of isomerism since many children will develop pulmonary arteriovenous malformations after the Kawashima. Fontan completion in these children can halt, and even reverse, the progression of these pulmonary arteriovenous malformations. This effect is believed to be mediated by a yet-to-be-identified "hepatic factor" [23].

Thus, ligation of one of the superior caval veins may help create a situation in which there is decrease in turbulence, decrease in power loss, and increase in the equality of hepatic venous return. While this has anecdotally been discussed it has not been published. Some have also discussed rerouting of one superior caval vein to the other at the time of the superior cavopulmonary anastomosis such that both superior caval veins provide venous return but via a single cavopulmonary anastomosis. Ligation and or rerouting can be done at the time of a stage I Norwood style operation or can be done at the time of the superior cavopulmonary anastomosis.

As discussed earlier, hepatic venous flow distribution needs to be optimized in the setting of isomerism. While a 50-50 split of hepatic venous flow to the right and left pulmonary artery would be ideal, this is not necessary for addressing the issue of pulmonary arteriovenous malformations. While the minimal percentage of hepatic flow a lung must see to avoid development of pulmonary arteriovenous malformations is not known at this time, it is certainly below 50% of total hepatic venous flow.

An offset has long been used by many at the time of the Fontan. Since in most instances there is a right sided superior caval vein, which tends to provide more flow to the right pulmonary artery, an offset of the inferior cavopulmonary anastomosis such that it is more leftward than that of the superior cavopulmonary anastomosis is often used. This has been demonstrated to decrease turbulence, decrease power loss, optimize total venous flow distribution, and optimize hepatic venous flow distribution. Hepatic venous flow to the left pulmonary artery increases with the offset in those with a single right sided superior caval vein [24,25].

This situation changes when there are bilateral superior caval veins present, however. Now the presence of flow from the left sided superior caval vein must also be taken into account. Depending on the flow from the left sided superior caval vein, less hepatic venous return will direct itself to the left pulmonary artery. If flow is greater in the left sided superior caval vein the hepatic venous return may nearly uniformly be directed to the right pulmonary artery. Interruption of the inferior caval vein will further impact this as well since the superior caval vein accepting the azygos or hemiazygos will now see more overall flow than the other superior caval vein. For instance, in a child with bilateral superior caval veins and interruption of the inferior caval vein with hemiazygos continuation to the left sided superior caval vein, flow in the left sided superior cavopulmonary anastomosis will be greater and hepatic venous return after Fontan completion will likely tend to direct itself rightward. This would then leave the left lung susceptible to the development or progression

of pulmonary arteriovenous malformations. A similar situation can arise from such an arrangement in which there is interruption of the inferior caval vein with azygos continuation to the left sided superior caval vein except that now hepatic venous return will likely direct more leftward and thus leave the right lung susceptible [25].

Thus, the position of the superior cavopulmonary anastomosis is crucial to the success of the Fontan. Restrepo and colleagues demonstrated this via computed fluid dynamics. This study identified 10 patients who had undergone Fontan completion with a Y-graft and had undergone postoperative magnetic resonance imaging. They then modeled flow through the superior and inferior cavopulmonary anastomosis after changing the location of the superior cavopulmonary anastomosis. The study concluded that direction of hepatic venous return is sensitive to the position of the superior cavopulmonary anastomosis, particularly in the setting of lower flow in the inferior cavopulmonary anastomosis [26]. Other computational modeling studies have demonstrated potential benefit of Y-grafts as well [27-34]. Clinical findings are not always entirely in harmony with findings from computational modeling, however [27,35-37].

Fontan completion with hepatic vein to azygos or hemiazygos anastomosis

Another modification for Fontan completion in the setting of isomerism can be made when there is interruption of the inferior caval vein with hepatic veins that return directly to the heart. In these patients, the hepatic veins can actually be anastomoses directly to the azygos or hemiazygos vein such that hepatic venous return then mixes with azygos or hemiazygos venous return which is then naturally distributed through the pulmonary artery system.

The issue with such an arrangement lies in the fact that the distribution of hepatic venous return is once again dependent on natural flow patterns as discussed previously. This becomes a particular issue in the setting of bilateral superior caval veins. Hepatic venous return will likely direct itself to the ipsilateral pulmonary artery, leaving the other pulmonary artery at risk for developing pulmonary arteriovenous malformations.

Yet another option in a situation where there is interruption of the inferior caval vein is to incorporate both the azygos or hemiazygos vein and the hepatic veins into the Fontan conduit. The Fontan conduit can then be routed anywhere as deemed ideal. This would be particularly helpful in the setting of bilateral superior caval veins when there is nearly equal flow from both superior caval veins. A flared inferior cavopulmonary conduit could be used to route mixed hepatic and azygos or hemiazygos venous blood per natural flow conditions. In the situation of bilateral superior caval veins with equal flow this should result in a fairly even distribution of hepatic venous return as long as pulmonary vascular resistance isn't discrepant between the two lungs.

Much remains unknown about these particular modifications in terms of power loss and wall shear stress although in certain patients and situations it is understandable how this could offer advantages over a standard Fontan approach.

Y-graft

Another modification on the Fontan that may be particularly helpful in the setting of isomerism is the Y-graft. In the Y-graft, an initial conduit gives rise to two separate limbs that then are anastomosed to the pulmonary arteries such that one goes to the left and the other to the right pulmonary artery. Y-grafts can be done using commercially available aortoiliac grafts or by preparing a Y-graft to one's own specifications. The goals of the Y-graft have become to reduce power loss in the inferior cavopulmonary anastomosis, evenly distribute hepatic venous return, and to bypass any discrete areas of pulmonary artery stenosis or distortion.

It is necessary to understand the methodology of the studies that have been conducted. There are studies that have simply reported clinical follow-up in patients who have undergone a Y-graft (initial Fontan or Fontan revision), studies that have used patient magnetic resonance data from before the Fontan to model various Fontan geometries, studies that have used patient magnetic resonance data from before the Fontan to model various Fontan geometries and the have compared these to postoperative Fontan magnetic resonance imaging

studies to determine the accuracy of preoperative modeling, and then studies which have simply created hypothetical models to perform computational fluid dynamics with simulated Y-grafts.

A total of 11 studies were identify that fit into one of the categories of studies described above. Of these, 5 studies fell into the first category describing clinical outcomes in 33 patients who had undergone Fontan palliation with a Y-graft. Two studies described the same cohort which results in 27 unique patients across these studies.

The patients in these studies underwent magnetic resonance imaging studies before the Fontan to help delineate their postoperative flow dynamics to help plan the specific Fontan geometry that would suit them best. A majority of these 5 studies conducted virtual surgery and then used computational fluid dynamics to determine which Fontan geometry of the several virtually applied were the most ideal. In all these situations the patients were felt to be best served by a Y-graft.

The Y-grafts were done mostly with use of cardiopulmonary bypass although Goksel and colleagues did report a patient in whom a Y-graft was placed without the use of cardiopulmonary bypass. Only one study compared cardiopulmonary bypass and cross-clamp times between those having undergone a Y-graft to those who underwent a more conventional inferior cavopulmonary anastomosis and found that there was no statistically significant difference. There were no major perioperative complications mentioned. From a technical standpoint the sizing of the Y-grafts used varied. Conduits had an initial segment diameter of 18mm most commonly. The two Y-limbs were generally both 12 mm in diameter. It is important to note that a Y-graft size of 18 x 9 x 9 does not represent a situation in where the limbs have the same cross-sectional area as the initial segment of the Y-graft. In fact, if an 18mm initial segment is used, 12 mm limbs are what are needed to provide equal cross-sectional area. Other reported sizes were 14 x 7 x 7, 20 x 10 x10, 18 x 9 x 9 and 22 x 11 x 11 [26-39].

Duration of clinical follow-up is limited in these studies and ranged from 6 to 3.2 years. Adverse events in follow-up, specific to the Y-graft itself, was left limb occlusion in 1 out of the 27 patients (4%). The occlusion occurred 3 months postoperatively while the patient was receiving antiplatelet therapy. Magnetic resonance imaging flow studies led to the conclusion that an area of low shear wall stress led to the limb becoming susceptible to occlusion. None of the other Y-graft patients had any adverse events reported related to the graft itself [27,28,36].

Multiple computed flow dynamics studies have compared various Fontan geometries. In most studies an iteration of the Y-graft emerges as the ideal Fontan geometry. It is important to note that many of these studies include multiple Y-grafts in their modeling, with each Y-graft having various graft sizes and points of anastomoses. The overall decision what is the ideal Fontan geometry is subjective but is made on the aggregate of all the objective data available. This usually includes consideration of power loss within the inferior cavopulmonary anastomosis, distribution of hepatic venous return to each pulmonary artery, and feasibility of accomplishing modeled surgery. Thus it becomes apparent that individual studies have demonstrated that the Y-graft is often the Fontan geometry associated with least power loss and is associated with the most equal distribution of hepatic venous return while remaining technically feasible [26,27,29-31,33,38,39].

With decisions on Fontan geometry being based on computation fluid dynamics it then becomes necessary to assess the accuracy of preoperative modeling compared to postoperative outcomes. Haggerty and colleagues demonstrated this in a study of patients who had magnetic resonance imaging studies preoperatively as well as postoperatively after Y-graft [25,33].

The Y-graft's appeal in the setting of isomerism becomes quite evident. The high frequency of pulmonary arteriovenous malformations in these patients underscores the need to ensure adequate distribution of hepatic venous return to both lungs. As clinical and computational fluid dynamics study have demonstrated that this is in fact the case, this becomes a potentially valuable tool in this setting. Additionally, the complication rate that is documented to date is quite low. With 1 in 27 patients (4%) having a thrombus in a single limb of the Y-graft, the risk of such events seems low.

While not necessarily a Y-graft , Soerensen and colleagues described what they have called the OptiFlo system. This was reported only after some *in vitro* and computer based modeling and there is no clinical experience with this particular Fontan geometry, it is worth noting here. The OptiFlo system is unique in that it is based on a design in which the inferior cavopulmonary anastomosis is in a Y-shape but so is the superior cavopulmonary anastomoses. This results in a diamond configuration. But as there have been no clinical reports of this it will not be discussed further [40].

Fontan images

Figures 1 and 2 demonstrate the Fontan conduit in necroscopy specimens with hypoplastic left heart syndrome. Both specimens have been sectioned along the long-axis to produce a view similar to that of the echocardiographic four-chamber view. The panel on the left demonstrates the anterior portion of the heart while the right sided panel demonstrates the posterior portion of the heart. A lateral tunnel Fontan is seen coursing posterior to the heart and then coursing superiorly to the atrium to where the anastomosis to the pulmonary artery was prior to removal of the heart. A transcatheter device can be seen in figure 2 occluding what was once a fenestration in the Fontan conduit.

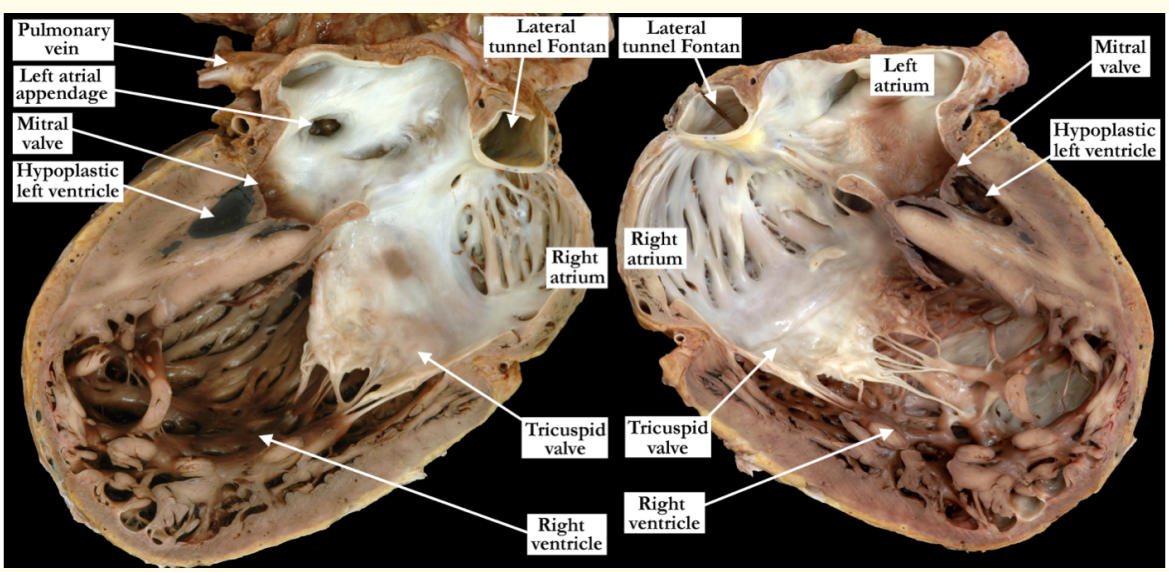

Figure 1: *A necroscopy specimen demonstrating a heart with hypoplastic left heart syndrome sectioned along its long-axis. The left sided panel demonstrates the anterior portion of the heart while the right sided panel demonstrates the posterior portion. There is a severely hypoplastic left ventricle with mitral stenosis. The right ventricle is of good size and has a tricuspid valve which appears normal in structure. There is a good-sized atrial communication. A lateral tunnel Fontan conduit is seen coursing posteriorly to the heart and then superiorly to the atrium. The anastomosis of the Fontan conduit to the pulmonary arteries is not demonstrated as the heart was removed from the pulmonary arteries.*

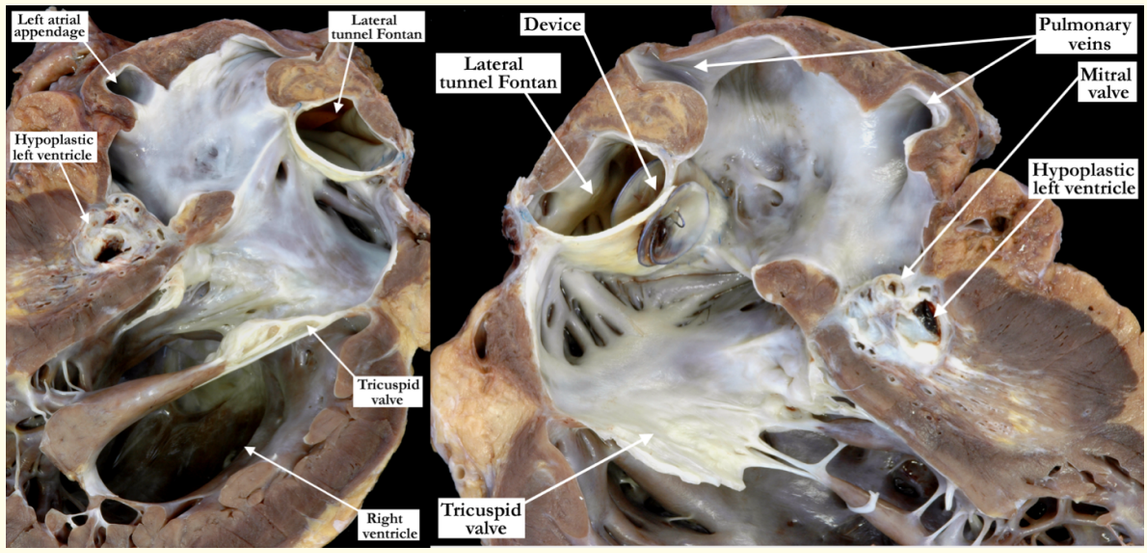

Figure 2: *A necroscopy specimen demonstrating a heart with hypoplastic heart syndrome sectioned along its long-axis. The left sided panel demonstrates the anterior portion of the heart while the right sided panel demonstrates the posterior portion. There is a severely hypoplastic left ventricle with mitral atresia. The right ventricle is of good size and there is a normal appearing tricuspid valve. There is a large atrial communication. A lateral tunnel Fontan conduit is seen coursing posteriorly to the heart and then superiorly to the atrium. The anastomosis of the Fontan conduit to the pulmonary arteries is not demonstrated as the heart was removed from the pulmonary arteries. A transcatheter device is also seen in the Fontan conduit occluding a Fontan fenestration between the Fontan and right atrium.*

Figure 3 demonstrates potential different Fontan geometries. A Y-graft Fontan, T-junction Fontan, and offset Fontan are demonstrated.

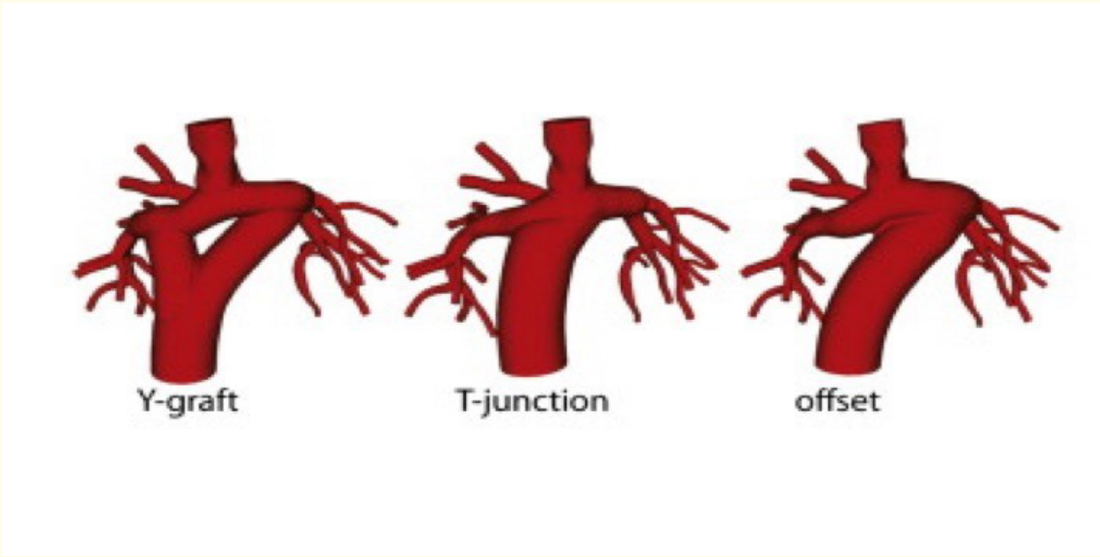

Figure 3: *A cartoon depicting three different Fontan geometries. The left-most demonstrates a Y-graft Fontan, the middle demonstrates a T-junction Fontan, while the right-most demonstrates an offset Fontan.*

Figure 4 demonstrates magnetic resonance imaging of a patient with left isomerism who underwent a Kawashima and extracardiac Fontan. This series of images demonstrates the various imaging capabilities of magnetic resonance imaging in the setting of a Fontan.

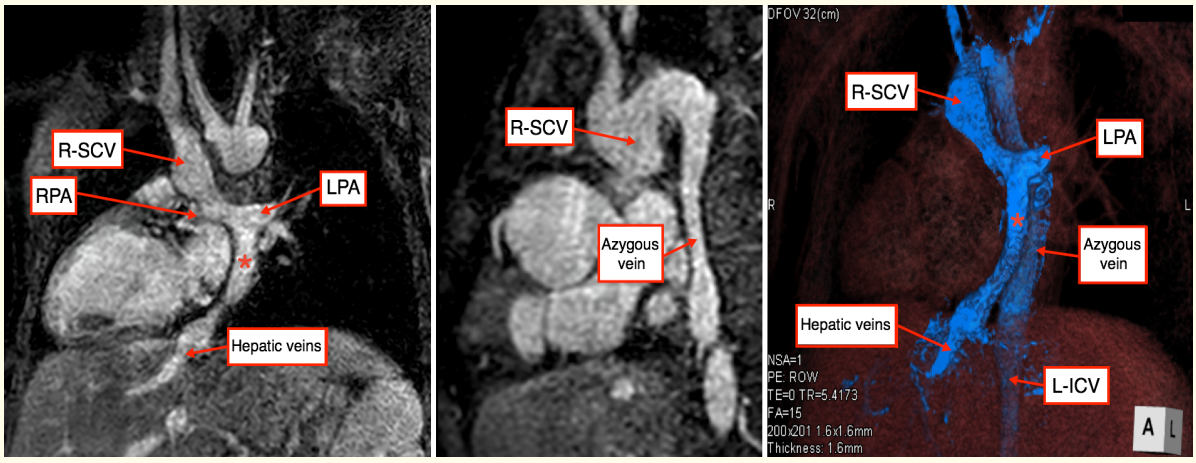

Figure 4: *Magnetic resonance images of a patient with left isomerism status post Kawashima and extracardiac Fontan. (Left hand panel) 3D mDixon MR sequence in an oblique coronal plane demonstrating the hepatic veins incorporated through a left-sided extracardiac Fontan (red asterisk) anastomosed to the left pulmonary artery. The right superior caval vein is anastomosed to the right pulmonary artery. (Middle panel) The same sequence reformatted in an oblique sagittal plane demonstrates a dilated azygous vein draining into the right superior caval vein. (Right hand panel) A 3D reconstruction of this sequence demonstrates the azygous continuation of the interrupted left inferior caval vein to the right superior caval vein.*

Discussion

The Fontan palliation has undergone several iterations since its conception. Historically the atriopulmonary Fontan has now been replaced by the lateral tunnel and extracardiac Fontan. Additional variations within these also exist. Advances in magnetic resonance imaging now allow for advanced preoperative modeling to perform virtual surgery on patient specific data to predict postoperative outcomes using various Fontan geometries with good accuracy.

While such techniques would be reasonable to apply in all children undergoing Fontan palliation, practical considerations may not allow for this currently. Higher risk patients, however, such as those with isomerism are certainly patients who would truly benefit from such evaluation and planning. The variations in both superior and inferior caval vein anatomy can lead to marked changes in flow distribution within the superior and inferior cavopulmonary anastomoses, particularly in respect to the hepatic venous return. This is of utmost importance in patients with isomerism as they are at increased risk for pulmonary arteriovenous malformations.

While morbidity and mortality for those with isomerism has decreased over the years there are still certain complications that occur with more frequency. Additionally, there are still "sicker" patients with isomerism that die in the neonatal period and do not make it to the point of consideration of Fontan completion. Once we are able to get this subset of patients to Fontan completion, such strategies will be even more helpful.

Cardiologists, cardiac intensivists, cardiac anesthesiologists, and cardiac surgeons must consider a variety of Fontan geometries for all patients, but particularly higher risk patients. Efforts should be made to make objective decisions on ideal Fontan geometry. Inexperience with a certain Fontan geometry should not preclude it from being a possibility and being considered as this could impact patient outcomes.

Conclusion

Understanding of various Fontan geometries is important and various Fontan geometries should be considered during preoperative planning. Use of magnetic resonance imaging techniques and computed fluid dynamics now enable accurate preoperative modeling to determine the ideal Fontan geometry. Heart centers should not be hesitant to alter timing and approach to the Fontan when objective data indicates that such deviations may be clinically beneficial. While this is important in all patients undergoing functionally univentricular patient this is particularly important with more complex patients such as those with isomerism.

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