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Imaging and patient-specific simulations for the Fontan surgery: current methodologies and clinical applications

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1. Introduction

Clinical observations together with recent modeling, imaging, and *in vitro* experiments have shown that the geometry of the Fontan connection plays a key role in energy losses, hepatic flow distribution, associated strain on the cardiovascular system, and Fontan outcomes (Ryu, Healy et al. 2001; Khunatorn, Mahalingam et al. 2002; Migliavacca, Dubini et al. 2003). Initial pioneering simulation work of DeLeval and colleagues compared energy loss in the standard “T” junction Fontan with a newly proposed “offset” model, and led to the adoption of the offset model as the currently preferred surgical method (deLeval, Dubini et al. 1996; Dubini, deLeval et al. 1996; Migliavacca, Dubini et al. 2003).

Since that time a decade ago, there has been ongoing and increasing interest in modeling the Fontan circulation. This interest, coupled with increases in computational power, has led to the development of more sophisticated computational tools and increasingly physiologically realistic simulations (Migliavacca, Dubini et al. 2003; Marsden, Vignon-Clementel et al. 2007; Whitehead, Pekkan et al. 2007; Sundareswaran, de Zelicourt et al. 2009). In this paper, we outline recent advances in simulation and imaging methods that have increased the physiologic realism and clinical applicability of Fontan simulations. We begin with an overview of the clinical problem and challenges. We then present the state of the art in clinical imaging, experimental methods and numerical simulations and discuss newly proposed surgical solutions and emerging methods for individualized surgical planning. Finally, we outline important challenges that remain before simulations can be used in day-to-day clinical practice for the management of single ventricle patients.

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2. Single-Ventricle Heart Defects: Review of the Clinical Problem

Single Ventricle Heart Defect (SVHD)

The incidence of children born with a SVHD, in which there is one effective cardiac pumping chamber, is about 2 per 1000 births. In patients with such an anatomy, oxygenated and deoxygenated blood mix in the single ventricle (Figure 1, central panel). Without surgical intervention this set of lesions is generally lethal, resulting in 95% mortality within the first month of life. The concept of a total right ventricular bypass, first introduced by Fontan and Baudet in 1971 (Fontan and Baudet 1971), is a palliative surgical procedure aimed at separating the systemic and pulmonary circulations thus eliminating venous blood mixing (Figure 1, right panel). The currently accepted palliation strategy culminates in the total cavopulmonary connection (TCPC), which is generally performed in three stages, progressively separating the systemic and pulmonary circulations. In the 1st stage, performed when pulmonary vascular resistance is relatively high, the systemic and pulmonary circulations are connected in parallel, often utilizing a shunt between the systemic and pulmonary arteries in a Norwood or Sano procedure. This shunt is removed in the 2nd stage, and the superior vena cava (SVC) is connected to pulmonary arteries (PAs) in a Glenn procedure, resulting in a superior cavopulmonary connection and partial right ventricular bypass. The TCPC (also described as the Fontan connection) is completed in the 3rd stage with the connection of the inferior vena cava (IVC) to the superior cavopulmonary connection.

Long-term outcomes & problems

The modifications to the original Fontan procedure, as well as improved management and care, have steadily improved surgical outcomes, reducing post-operative mortality to the level of many biventricular congenital heart disease repairs (Mair, Puga et al. 2001; Gaynor, Bridges et al. 2002; Petrossian, Reddy et al. 2006). However, Fontan patients are still susceptible to numerous, long-term complications (Driscoll, Feldt et al. 1987; Durongpisitkul, Driscoll et al. 1997). While most institutions now report 95% post-operative survival rates, the 10-year survival rate drops to 60–80% (Marino 2002; Lee, Choi et al. 2003; Jayakumar, Addonizio et al. 2004; Sittiwangkul, Azakie et al. 2004). Progressive ventricular dysfunction, atrial arrhythmias, atrioventricular valve regurgitation, pulmonary arteriovenous malformations (PAVMs), diminished exercise capacity, protein losing enteropathy (PLE), somatic growth retardation, thrombotic complications, and poor neurodevelopmental outcomes (Jayakumar, Addonizio et al. 2004) are some of the most commonly reported complications. The fact remains that the Fontan procedure results in a non-physiologic cardiovascular configuration where the single ventricle has to pump blood through both the systemic and pulmonary vascular beds in series. As a result, the single ventricle experiences an increased afterload (including both systemic and pulmonary vascular resistances) and decreased preload (ventricular filling). In addition, there is a significant increase in central venous pressure due to the lack of pressure step-up typically provided by the right ventricle (Rychik and Cohen 2002).

Failure Mechanisms

There are two key components to the Fontan circulation, the single pumping ventricle on the one hand and the vascular resistances and compliances on the other. Focusing on the ventricular side, Altmann and colleagues (Altmann, Printz et al. 2000) found the native right ventricle function to be the best predictor for operative survival for SVHD patients born with HLHS. Sundareswaran et al. demonstrated that native single right ventricles has a significantly lower power output capacity than native single left ventricles (Sundareswaran, Kanter et al. 2006). Accordingly, while the chronic pressure overloaded condition of the single ventricle in a Fontan circulation makes it susceptible for ventricular dysfunction and heart failure, the failure rate is further conditioned by the native configuration and function of the ventricle.

The vascular resistance imposed by the systemic, TCPC and pulmonary circuits in series is another key component of the abnormal Fontan circulation. PLE and liver dysfunction have been correlated with the high central venous pressures observed in Fontan patients (Kiesewetter, Sheron et al. 2007; Procelewska, Kolcz et al. 2007). In absence of a right pumping chamber, the pressure difference between the IVC and the left atrium is the only force left to drive blood through the TCPC and lungs. Therefore, the higher the vascular resistance downstream of the liver, the higher the pressure difference required to achieve a given cardiac output. This observation falls back to Guyton's isolated venous theory (Guyton, Abernathy et al. 1959; Guyton 1961), which states that the cardiac output in single ventricle patients is highly sensitive to the vascular resistance downstream of the venous compliance. Even though Guyton's theory focused on the effect of pulmonary vascular resistance (PVR), the vascular segment of interest in practice includes both the TCPC and lungs, both of which lie in series downstream of the venous compliance. Vasodilating agents (Torres Pharm and Nieves 2009) have been utilized successfully to lower PVR. However, in Fontan patients all blood flow has to first travel through the TCPC, such that if the effective resistance of the connection is high, improvements in PVR alone may be insufficient to improve preload and cardiac output, especially under the increased demands of exercise or other high output states (e.g., illness, pregnancy). Even when cardiac output is not measurably affected, lowering TCPC resistance might allow for reduced medication and small but important decreases in central venous pressure such that long-term outcome and quality of life are improved.

Clinical and simulation-based evidence suggests that exercise conditions place an even greater strain on the single ventricle circulation, accentuating the effects of increased resistance discussed above. Unlike healthy individuals, Fontan patients only respond to exercise by increasing their heart rate, while the stroke volume, which is typically limited by the pre-load, remains approximately constant (Senzaki, Masutani et al. 2002; Senzaki, Masutani et al. 2006). In addition, an early clinical study of Shachar et al. (Shachar, Fuhrman et al. 1982) observed a dramatic pressure rise during exercise. It is not currently understood why some patients exhibit significantly lower exercise capacity than others, or how to predict which patients will fall into each category. However, these studies indicate that exercise conditions should play an important role in determining an optimal treatment course.

Another major complication that results in Fontan failure and depends on the TCPC design is progressive hypoxia due to the development of unilateral PAVMs (Moore, Kirby et al. 1989; Pandurangi, Shah et al. 1999; Shinohara and Yokoyama 2001; Duncan and Desai 2003; Brown, Ruzmetov et al. 2005). PAVMs are intrapulmonary shunts, connecting the pulmonary arteries directly to the pulmonary veins, thus allowing the de-oxygenated blood from the systemic circulation to return to the left atrium without flowing through the gas exchange units. The primary consequence of PAVMs is decreased oxygen saturation. Furthermore, the intrapulmonary shunts lead to a drop in pulmonary vascular resistance, which tends to direct more flow to the diseased lung creating a positive feedback loop of increasing hypoxia. Although the underlying mechanism leading to PAVMs is unknown, studies have shown that liver derived factors present in the hepatic venous blood prevent their formation (Pandurangi, Shah et al. 1999; Justino, Benson et al. 2001; Shinohara and Yokoyama 2001; Duncan and Desai 2003; Pike, Vricella et al. 2004). While it is not known what concentration of this hepatic factor is required for normal lung development, it is clear that an unbalanced hepatic flow distribution to the left and right lungs due to an inadequate design of the IVC-to-PA conduit during the 3rd stage of the TCPC surgery puts patients at risk for PAVMs. Clinically, once the extent of PAVMs is such that oxygen saturation is critically low, the only palliative option is to re-operate and re-orient the IVC conduit to achieve a better hepatic flow distribution (Uemura, Yagihara et al. 1999; Steinberg, Alfieri et al. 2003; Pike, Vricella et al. 2004; Wu and Nguyen 2006; AboulHosn, Danon et al. 2007).

Summary

From the above clinical follow-up studies, which demonstrate the morbidity and decreased functional status of Fontan patients, it is clear that improvements are needed. Several palliative options have been discussed in the literature (Stamm, Friehs et al. 2002; Pike, Vricella et al. 2004; AboulHosn, Danon et al. 2007), but clearly the wide variety of patient anatomies makes it difficult to design a general “one-size-fits-all” procedure for Fontan patients. In parallel, the complexity and variability of *in vivo* anatomies pose significant clinical challenges to identify the surgical option for a given patient, i.e. the one that will optimally distribute hepatic flow to the lungs and offer the lowest vascular resistance. This setting is the typical example of a clinical scenario that could benefit from the recent advances in virtual surgery simulations and optimization of individual treatment plans. This area has been explored by a number of research groups and will serve as the basis for our discussion in the following sections.

3. In vivo Investigations of TCPC Hemodynamics

The above clinical follow-up studies not only demonstrate the morbidity and decreased functional status of Fontan patients, but clearly emphasize the need for improvements in surgical and interventional procedures. A number of studies have sought to assess the geometrical characteristics of different options used to perform the TCPC surgery and characterize their impact on TCPC hemodynamics, the single ventricle performance, and overall patient outcome. Magnetic resonance imaging (MRI) has emerged as an attractive non-invasive and low-risk imaging technology to assess TCPC hemodynamics *in vivo* as it

allows for the acquisition of both anatomy and flow. With the advent of image segmentation, interpolation, surface fitting and visualization methods, raw magnitude and phase contrast MRI (PC MRI) techniques can be used to reconstruct the 3D *in vivo* anatomies and velocity fields, respectively.

MRI has been used by several groups to reconstruct Fontan anatomies and obtain time-varying flow information. In particular, Dr Yoganathan's laboratory at the Georgia Institute of Technology has collected a large database of Fontan anatomies and flows, which now includes data for over 250 patients recruited at the Children's Healthcare of Atlanta (CHOA), the Children's Hospital of Philadelphia (CHOP), and the Children's Hospital Boston (CHB). This wealth of *in vivo* data has provided a unique opportunity to look at the geometrical characteristics of a wide range of TCPC implementations (Figure 2). Variations in the geometry of the completed TCPCs depend on the surgical options retained at each one of the TCPC stages (e.g. intra-atrial vs. extra-cardiac) as well as on the native patient anatomy (e.g. presence of a single or bilateral SVC, normal or interrupted IVC, or heterotaxy syndrome). As can readily be anticipated from the diversity of the anatomies displayed in Figure 2, it is highly unlikely that there would be one single surgical implementation that will be optimal for all patients.

An early study that benchmarked anatomic variability and quantitatively compared TCPC geometries was conducted by Krishnankutty et al. (KrishnankuttyRema, Dasi et al. 2008). The analysis process involved the reconstruction of 26 TCPC geometries (13 intra-atrials and 13 extra-cardiacs), the extraction of the TCPC skeleton (or vessel axes), and finally the systematic quantification of the vessel cross-sectional area, vessel curvature, and IVC-SVC offsets. Intra-atrial options were found to have significantly higher area variations than extra-cardiacs, due to the more irregular geometry of intra-atrial baffles when compared to the smooth extra-cardiac grafts. In addition, this study demonstrated that irrespective of the TCPC option, patients born with HLHS were at higher risk of LPA narrowing than those without HLHS. This was attributed to the aortic arch reconstruction done in stage 1 for HLHS patients, during which surgeons tend to oversize the aortic arch, compressing the LPA and preventing its growth. Such a quantitative geometric characterization was a critical step to correlate hemodynamic performances with geometric features.

Fontan flow characteristics were quantified by Fogel et al. (Fogel, Weinberg et al. 1999) using PC MRI to measure the IVC and SVC flow rates in ten SVHD patients with an intra-atrial TCPC (1.8 ± 0.3 years old). By superimposing a pre-saturation pulse on the IVC and the SVC selectively, the authors assessed the portions of inferior and superior venous returns that were directed to the LPA and RPA. Distributions of blood to each lung were almost equal for all patients ($RPA/LPA \text{ blood} = 0.94 \pm 0.11$), but on average the LPA received a significantly larger amount of IVC blood ($67 \pm 12\%$) than the RPA (Fogel, Weinberg et al. 1999).

Hjortdal et al. used real-time PC MRI to quantify the impact of respiration on TCPC flow rates (Hjortdal, Emmertsen et al. 2003) during rest and supine exercise. They demonstrated that inspiration facilitated IVC flow under resting conditions, increasing it to 2.99 ± 1.25 L/min/m² during inspiration versus 0.83 ± 0.44 L/min/m² during expiration. SVC flow was

not significantly affected by the respiratory cycle. Under exercise conditions, the peripheral muscular pump seemed to have more influence than respiration on the Fontan circulation, and the respiratory component was increased further. Results confirmed previous clinical observations in both echocardiography and catheterization data that respiration contributes to larger variations in IVC flow than cardiac pulsatility.

Be'eri et al. used ECG-gated 3D PC MRI to compare the flow dynamics of five atrio-pulmonary connections and five TCPC connections at multiple time points across the cardiac cycle (Be'eri, Maier et al. 1998). The authors selected the orientation of their PC MRI acquisition plane slice so as to include the caval, atrial, and pulmonary components of the Fontan pathway. This is one of the few studies quantifying the velocity fields within the Fontan construct and not only at its inlets and outlets (in cross-sections of the IVC, SVC, LPA and RPA), but still remains limited to a single plane acquisition.

The fact that *in vivo* investigations of Fontan patients remain scarce and limited in their domain of investigation may in part be attributed to the prohibitively long PC MRI acquisition time, which have been a limiting factor for adult applications and pose an even greater challenge in pediatrics, where it is difficult to keep infants and young children still for extended periods of time. Interpolation methods (Frakes, Smith et al. 2004; Sundareswaran 2008) offer new means to reduce the acquisition time by limiting the number of acquisition plane required, while still providing an appropriate representation of the blood flow field. Sundareswaran et al. (Sundareswaran 2008; Sundareswaran, de Zelicourt et al. 2009) apply a divergence-free interpolation methodology to provide a continuous representation of the TCPC velocity based on only 5 or 6 PC MRI slices acquired in the coronal direction. The continuous representation of the 3D time-dependent blood flow fields allows the authors to visualize the *in vivo* blood flow pathways, as is illustrated in Figure 3 for three different TCPC templates, and quantify *in vivo* surrogate markers for TCPC performance such as the distribution of hepatic flow to the lungs (Sundareswaran, de Zelicourt et al. 2009). Metrics such as energy dissipation and wall shear stress should still be handled with caution as PC MRI cannot adequately resolve all length scales due to high noise levels in the vicinity of the vessel walls, and is often associated with signal loss in regions of high flow disturbances. *In vitro* experiments and numerical modeling have arisen as attractive means to complement these *in vivo* measurements for in depth hemodynamic analyses.

4. State of the art in Experimental and Computational Modeling of TCPC Hemodynamics

Most of the complications mentioned in section 2 are more or less directly related to pressure build up in the venous return, distribution of blood flow, or increased workload on the heart. As the TCPC connection is the parameter over which surgeons have some degree of control, it is critical that its design be optimized for a minimal contribution to the overall pressure drops and power losses across the circulatory system. Previous *in vivo*, *in vitro* and numerical studies have all demonstrated a direct relationship between TCPC design and efficiency. Early *in vitro* or numerical studies have investigated the impact of different geometric parameters such as caval offset (Sharma, Goudy et al. 1996), baffle size (DeGroff,

Carlton et al. 2002) or vessel flaring (Ensley, Lynch et al. 1999) to the overall efficiency in highly simplified geometries with steady flows and rigid walls. While these studies illustrated simple clinically applicable design concepts, their clinical relevance and validity remained unknown due to the use of significant underlying assumptions. For example, Ryu et al. (Ryu, Healy et al. 2001) observed a dependence of the power losses on the radius of curvature of the PAs but also reported that this effect was negligible when compared to that of vessel diameter. Optimizing the TCPC geometry therefore requires a thorough understanding of the complete *in vivo* picture, including anatomically-accurate TCPC geometries, inflow conditions, wall material properties or wall motion, respiration and lung resistance, as well as an exhaustive characterization of the end-points of interest, such as minimizing the TCPC resistance and optimizing the global and hepatic flow distribution to the two lungs.

The need for more realistic modeling is illustrated by one of the most debated clinical questions regarding TCPC implementation: whether to use 1) an intra-atrial tunnel or 2) an extra-cardiac conduit to perform the 3rd and final stage of the TCPC procedure. In the first option, the IVC is routed through the right atrium, using part of the atrial wall to construct the baffle. The second option bypasses the heart, extending the IVC with an artificial graft. Differences between the two procedures include the baffle geometry, wall properties and wall motion, pulsatility levels, growth potential, and impact on cardiac electrophysiology. Bioengineering studies may identify critical differences in the flow fields, efficiency, and other biomechanical quantities in these two configurations. However, without physiologically realistic simulations including the aforementioned features, results will likely not lead to conclusive clinical findings.

4.1. Patient-Specific modeling

To increase anatomic and physiologic realism, recent experimental and computational work has included patient-specific anatomies (Migliavacca, Dubini et al. 2003; Hsia, Migliavacca et al. 2004; de Zélicourt, Pekkan et al. 2005; Pekkan, de Zélicourt et al. 2005; Pekkan, Kitajima et al. 2005; de Zélicourt, Pekkan et al. 2006; Marsden, Vignon-Clementel et al. 2007; Wang, Pekkan et al. 2007; Whitehead, Pekkan et al. 2007; Kitajima, Sundareswaran et al. 2008; Marsden, Reddy et al. 2010). Not surprisingly, these studies revealed greater flow disturbances and energy dissipation than in the earlier idealized geometries, as well as a large inter-patient variability. For example, the *in vitro* power losses reported by de Zélicourt et al. for one extra-cardiac (de Zélicourt, Pekkan et al.) and one intra-atrial (de Zélicourt, Pekkan et al. 2005) patient specific TCPC were, respectively, 5 and 70 times higher than those previously reported by Sharma et al. (Sharma, Goudy et al. 1996) using an idealized offset model. This increase was likely due to smaller vessel diameters as well as the irregular shape of the patient specific anatomy. This was further supported by a set of parametric studies in idealized geometries, which progressively incorporated the features of the *in vivo* intra-atrial TCPC (de Zélicourt 2004). Dissipation was further increased when the central connection area was enlarged to mimic the bulging IVC intra-atrial tunnel. The sudden expansion of the IVC and SVC into the central connection area accentuated the presence of flow recirculation and instabilities, increasing chaotic mixing in the patient-specific case.

Seeking to identify the main sources of energy dissipation in patient-specific geometries, Dasi et al. (Dasi, Krishnankuttyrema et al.) compiled the experimental and numerical power losses obtained across 22 patient-specific anatomies, and correlated them with geometrical metrics, including vessel diameters, curvature, offset and irregularity. Results showed that, irrespective of the connection type, the minimum PA cross-sectional area was the strongest correlate for normalized energy dissipation rate (R^2 -value of 0.898 and $P < 0.0002$). The same authors (Dasi, Pekkan et al.) went on to derive a simple analytical form of normalized energy dissipation rate which includes cardiac output, flow split, body surface area, Reynolds number, and pulmonary artery size, leaving two free parameters. The excellent fit provided by this expression re-iterates that the vessel dimensions at the time of TCPC completion play a key role in the magnitude of the TCPC power losses in the immediate post-operative period, emphasizing the need to i) avoid LPA constriction in stage 1 and ii) dilate any stenosed vessel in later stages. These findings support the use of PA catheterization measurements in these patients, which is the standard in current clinical practice to determine the need for vessel dilation and stenting.

While many previous studies have focused on energy loss as the sole determinant of Fontan performance, it is clear that a energy loss alone is not sufficient for comprehensive evaluation on a patient specific basis. To illustrate this, a recent study of Marsden et al. (Marsden, Reddy et al. 2010) used a multiparameter approach in six patient specific models to evaluate multiple clinically relevant quantities derived from simulations, including energy loss, pressure levels, wall shear stress, and hepatic flow distribution. Results were used to rank patients from best to worst performing, and demonstrated that rankings were different for each parameter. For example, although it is clinically well accepted that Fontan pressures should be kept low whenever possible, and that outcomes are generally more favorable for patients with lower pressures, this study demonstrated low Fontan pressures may have high energy loss and inefficiencies. Likewise, patients with high energy efficiency were found to have highly unequal hepatic flow distribution, and some designs that had high energy efficiency at rest were found to be suboptimal at exercise.

Further investigating the differences between intra-atrial and extra-cardiac TCPC, Dasi et al. compared the hepatic flow distributions predicted by CFD for 5 patient-specific geometries of each template (Dasi, Whitehead et al. 2010). This study highlights that intra-atrial TCPCs, which were perceived as detrimental from an energy point of view, may be beneficial in terms of hepatic flow distribution due to a better mixing of all systemic venous returns in the intra-atrial baffle. Furthermore, inclusion of a caval offset in extra-cardiac TCPCs biased the hepatic flow towards the closest lung. Optimizing hepatic flow distribution and minimizing energy losses thus leads to conflicting recommendations, the optimal design resulting from a tradeoff between the two. All of these findings emphasize the need to consider multiple hemodynamic factors and physiologic states in making a clinical decision, and to link these findings with patient outcome data.

4.2. Physiologic outflow boundary conditions and multi-scale modeling

Recent advances in boundary condition methods for cardiovascular simulations have enabled simulations to achieve physiologic levels of pressure that can reproduce pressure

levels and time-varying pressure fluctuations obtained via cardiac catheterization (Vignon-Clementel, Figueroa et al. 2006; Marsden, Vignon-Clementel et al. 2007; Balossino, Pennati et al. 2009; Marsden, Reddy et al. 2010). This is essential for accurate prediction of flow splits with multiple pulmonary branches, wave propagation, and vessel wall deformability. Clinical pressure measurements from catheterization continue to be a gold standard in clinical decision-making for single ventricle patients, and both pressure levels and pressure drops factor into treatment planning. Direct incorporation of catheterization measurements in simulations can only be done via proper handling of the outflow boundary conditions. This increases accuracy of simulation results with multiple pulmonary branches and enables prediction of pressure changes resulting from alternative surgical geometries, and exercise conditions.

The use of resistance, impedance and lumped parameter Windkessel-type boundary conditions have become an essential component of modeling TCPC hemodynamics. Development of these boundary conditions and their use in 3D simulations is outlined in recent work of Vignon, Olufsen, and Spilker (Olufsen 1999; Olufsen, Peskin et al. 2000; Vignon-Clementel and Taylor 2004; Vignon-Clementel, Figueroa et al. 2006; Spilker, Feinstein et al. 2007). The application of resistance and RCR (resistor-capacitor-resistor) boundary conditions to TCPC simulations has been demonstrated in recent work of Marsden and others (Marsden, Vignon-Clementel et al. 2007; Marsden, Bernstein et al. 2009; Marsden, Reddy et al. 2010). These simulations used patient specific catheterization data to determine boundary condition values, and can reliably reproduce resting pressure levels pressure drops to the pulmonary arteries measured in catheterization. In addition, the choice of RCR parameter values incorporated human pulmonary morphometry data to match the impedance of downstream vascular trees.

Lumped parameter boundary conditions have been increasing in sophistication to the point where we can now construct circuit analogies to the entire circulation in a closed-loop network (Bove, Migliavacca et al. 2008; Balossino, Pennati et al. 2009). Lucas et al. (Lucas, Cole et al. 2008) implemented a thorough representation of the Fontan circulation, allowing to probe the sensitivity of circuit to different graft material properties and demonstrate the potential of left ventricular assist devices to relieve the single ventricle (Pekkan, Frakes et al. 2005). Recent work of Corsini, Migliavacca and colleagues report coupled 3D CFD and lumped parameter simulations, assessing the detailed TCPC hemodynamics within the global single ventricle circulation (Figure 4). This work built upon previous work in modeling the stage one (Norwood) single ventricle repair using a lumped parameter approach (Migliavacca, Dubini et al. 2003; Bove, Migliavacca et al. 2008). In this work the response of, for example, cardiac output to changes in shunt size could be determined. This enables modeling of the global systemic and cardiac response to changes in local geometry and hemodynamics, which is not possible using isolated 3D simulations. The future combination of patient specific modeling with clinically validated lumped parameter values is a promising approach for the prediction of global responses to local changes in geometry and flow conditions.

4.3. Pulsatile flow and respiratory effects

Beyond the efforts made on the geometrical accuracy, numerical studies have also sought to incorporate more physiologic inflow conditions (Orlando, Hertzberg et al. 2002; Marsden, Vignon-Clementel et al. 2007). State of the art simulations now incorporate PC MRI data in the IVC, SVC, LPA and RPA to determine patient specific pulsatile inflow conditions. DeGroff et al. (DeGroff and Shandas 2002) demonstrate up to 100% increase in power losses with pulsatile inflow conditions compared to steady flow. It has been demonstrated that the use of anatomically realistic geometries, even with steady inflow conditions, is enough to produce complex and unsteady flow structures (de Zélicourt, Pekkan et al. 2005).

A recent study by Marsden et al. (Marsden, Vignon-Clementel et al. 2007) investigated the impact of pulsatile inflow conditions in anatomically-accurate geometries with rigid walls. In that study, the authors made use of two patient specific geometries, catheterization data, and patient specific flow curves from PC MRI when available. The impact of lower limb exercise was modeled by increasing the heart rate and mean IVC flow rate and decreasing outflow resistances. Results demonstrated significant differences in energy losses compared to steady inflow conditions at rest and exercise. This study was the first to include effects of respiration by incorporating real-time MRI data of Hjortdal et al. (Hjortdal, Emmertsen et al. 2003) to construct respiratory inflow boundary conditions. Results demonstrated reasonable reproduction of catheter pressure tracings in simulations for the same patient (Figure 5).

In an effort to characterize the error introduced by the non-pulsatile assumption, de Zélicourt et al. (De Zélicourt 2010) compared the hemodynamic efficiency under pulsatile and non-pulsatile conditions for three patient-specific TCPCs (one intra-atrial, one extra-cardiac, and one with interrupted IVC). Patient-specific pulsatile flow curves were obtained from PC MRI measurements, while the non-pulsatile simulations were conducted using the mean vessel flow rates averaged over the cardiac cycle. For the intra-atrial and extra-cardiac patient with a normal systemic venous return, flow pulsatility led to a less than 5% increase in power losses compared to the predicted non-pulsatile value. In the patient with an interrupted IVC, on the other hand, the distribution of hepatic flow was reversed for approximately half of the cardiac cycle. The non-pulsatile assumption failed to capture the global flow characteristics and efficiency metrics. The impact of respiration on predictions of hepatic flow distribution should be investigated in future work.

Although limited to very small sample sizes, the results of Marsden et al. (Marsden, Vignon-Clementel et al. 2007) and de Zélicourt et al. (De Zélicourt 2010) collectively suggest that pulsatile flow is essential to reproducing physiologic flow conditions in TCPC simulations. While there may be a threshold below which non-pulsatile simulations might provide satisfactory predictions of energy loss, pulsatility ought to be included in the numerical model for accurate clinical recommendations.

4.4. Vessel wall deformation

The majority of TCPC simulations to date have employed a rigid wall approximation. Orlando et al. (Orlando, Hertzberg et al. 2002; Orlando, Shandas et al. 2006), were the first to look into the impact of wall compliance on the TCPC hemodynamics, reporting a 10%

increase in power losses when compared to the same simulations conducted using rigid walls. However, this study used an idealized TCPC geometry and a uniform approximation of TCPC vessel wall elasticity.

Recent advances in fluid structure interaction (FSI) capabilities have enabled simulation in complex patient-specific geometries with realistic vessel wall deformation. Efficient algorithms for FSI have been developed and tailored for cardiovascular applications (Figuerola, Vignon-Clementel et al. 2006; Zhang, Bazilevs et al. 2007; Bazilevs, Calo et al. 2008). Bazilevs and Marsden demonstrated significant overprediction of wall shear stress using rigid vs. deformable walls in a patient specific TCPC simulation, particularly under exercise flow conditions (Figure 6) (Bazilevs, Hsu et al. 2009). Fluid structure interaction should be incorporated into future work, particularly for situations with large known vessel wall deformation such as the lateral tunnel TCPC surgery.

4.5. Prediction of hepatic flow distribution

Simulations offer the capability to quantify distribution of hepatic flow to the pulmonary arteries, which is known to have direct clinical implications in the formation of PAVM's. While it is not known what concentration of hepatic flow is required for normal lung development, it is a reasonable assumption that hepatic flow should be distributed as equally as possible, taking into account the potential for postoperative pulmonary artery remodeling.

Flow visualization under steady flow conditions has typically been done looking at vector fields or 3D streamtraces. Under dynamic conditions, streamtraces are not a valid means to quantify flow distribution, and Lagrangian particle tracking, representing the pathways of massless particles advected by the blood stream should be used (Shadden and Taylor 2008). Such approach is illustrated in Figure 7. Reversal of the hepatic flow during part of the cardiac cycle leads to a deep penetration of the SVC particles (in dark blue) into the hepatic baffle, followed by a thorough mixing of hepatic and SVC particles in the acceleration phase. Beyond dynamic flow visualization, Lagrangian particle tracking also allows for the quantification the distribution of hepatic nutrients (Marsden, Reddy et al. 2010) (Figure 8) or the characterization of the shear stress history and residence times of platelets and red blood cells to assess the risk of thrombus formation.

4.6. In vitro validation of simulation predictions

The notion that CFD is a mature technology that can be indiscriminately applied to model any flow physics is becoming *de facto* in the biomedical field. In reality, the continuous evolution of CFD algorithms and capabilities and their application to new fields necessitates careful ongoing validation with in vitro experiments. This is of particular importance in biomedical engineering since due to the presence of complex geometries, compliant walls, pulsatile effects, three-dimensional separation and vortex formation, flow reversal and intermittent transition to turbulence. In spite of these complexities, which pose a formidable challenge to even the most advanced CFD tools, there have been relatively few studies that have performed adequate validation of TCPC simulations. The study by Khunatorn et al. (Khunatorn, Mahalingam et al. 2002) found caval offset to be detrimental from a power loss point of view, contrary to the experimental findings by Sharma et al. in the same geometry

(Sharma, Goudy et al. 1996). Khunatorn et al. (Khunatorn, Shandas et al. 2003) later demonstrated that their numerical approach failed to capture the flow instabilities at the center of the connection and secondary flow structures in the PAs, which could explain discrepancies even in global efficiency measures such as energy dissipation rates. Pekkan et al. pointed out that overall 2nd order accuracy was required to capture patient-specific TCPC flow structures, even when considering time-averaged flow fields (Pekkan, de Zélicourt et al. 2005). The limitations of CFD tools for TCPC simulations have been documented on many occasions (Freitas 1993; Freitas 1995; Laccarino 2001; Khunatorn, Shandas et al. 2003; Pekkan, de Zélicourt et al. 2005), and all of these studies reinforce the need for high-order numerical schemes, adequate mesh resolution, and comprehensive experimental validation (Freitas 1993). In addition, the complexity of the experiments used for validation should appropriately represent the complexity of the numerical simulations, including not only the anatomical complexity, but also flow pulsatility (Haggerty, Dasi et al. 2009), and wall compliance if these are to be modeled as well. An exciting new development is the use of *in vitro* mock circuits to simulate the part of or the entire circulatory system. In, for example, the three stages of Fontan repair, which are currently being developed by Figliola and colleagues (see related article in this issue) (Gohean, Figliola et al. 2006; Camp, Stewart et al. 2007; Chiulli, Conover et al. 2010). Alternatively, Steele and colleagues used an *in-vivo* sheep model of the Fontan circulation to quantify the effect of respiration on the pulmonary circulation and validate their coupled 1D/structured-tree representation of the pulmonary vasculature (Lucas, Ketner et al. 2006; Clipp 2007). All of these systems have the potential to validate lumped parameter networks of the global circulatory response, while also including detailed 3D geometries of the Fontan connection.

5. Recent progress towards clinical application

Although, most CFD studies to date have been limited to retrospective theoretical investigations, the potential benefit of CFD techniques for improved diagnostics and surgical planning for single ventricle patients is gaining interest in the clinical community. Well resolved, image-based CFD simulations offer the opportunity to complement clinical *in vivo* data, allowing clinicians to access wall shear stress, flow distribution, energy dissipation or pressure data that would otherwise not be available. More importantly, numerical tools offer a unique opportunity to consider multiple “What if?” scenarios, at no risk to the patient. Of particular interest is the ability to predict the patient’s response under exercise conditions and to virtually plan and optimize the surgery for a specific patient prior to entering the operating room. In this section we outline the major areas of potential clinical application of simulations and discuss issues of clinical validation.

5.1. Virtual Exercise Testing

Simulations of exercise flow conditions have the potential to be valuable as a clinical tool, particularly since measurements of exercise pressures and flow are challenging to perform *in vivo*. Exercise is a complex physiologic state, and comprehensive modeling of exercise conditions is challenging. However, recent simulation work has emphasized the need to consider exercise conditions in the evaluation of TCPC designs. In particular, results have demonstrated that designs optimal at rest may not be optimal at exercise and vice versa.

Simulating exercise conditions across multiple Fontan patients, both Marsden et al. (Marsden, Reddy et al. 2010) and Whitedhead et al. (Whitehead, Pekkan et al.) demonstrated that hemodynamic quantities, including pressure and energy efficiency, vary dramatically with exercise. Marsden et al. (Marsden, Reddy et al. 2010) emphasized that pressures can rise to alarming levels during exercise for some patients, with pressures in the range of 25–35 mmHg at maximum exercise, yet remain at more moderate levels for other patients. A clinical study of Shachar et al. (1982)(Shachar, Fuhrman et al. 1982) confirms the dramatic pressure rise during exercise on the order of values predicted by this work, but surgical techniques have evolved significantly since then, and further clinical study focusing on exercise pressures in the current patient population with ECC- and LT-type Fontans is needed. The lumped-parameter study of Sundareswaran et al. (Sundareswaran, Pekkan et al.) also points out that above a certain TCPC resistance patients may simply be unable to achieve the desired cardiac output, thereby limiting their exercise capacity. Exercise flow conditions may thus prove to be an essential component to clinical decision-making and surgical planning for particular patients.

5.2. Patient-Specific Surgical Planning

Examining the range of anatomical configurations observed *in vivo*, it is apparent that there cannot be a “one-size-fits-all” procedure that would be optimally suited for all Fontan patients. Furthermore, optimizing the TCPC geometry for both minimum energy dissipation and balanced hepatic flow distribution, for example, can lead to seemingly contradictory surgical guidelines because of trade-offs between competing performance parameters. However, with the advances in clinical imaging, image processing, human-computer interaction and numerical simulations, patient-specific surgical planning has reached the point where it should be incorporated into clinical practice. These new tools would allow surgeons to investigate the pre-operative hemodynamics of their patient, envision and virtually perform different possible operations, and finally decide on the best option based on CFD performance assessments.

Pioneering attempts towards patient-specific TCPC surgical planning using 3D CFD were performed by Yoganathan et al. for two commonly encountered scenarios: (i) severe LPA stenosis due to aortic arch reconstruction(Pekkan, Kitajima et al. 2005) and (ii) large IVC-to-LSVC offset in dual SVC cases(de Zelicourt, Pekkan et al. 2006). For the first case, a virtual LPA angioplasty was performed, while, in the second case, the IVC was shifted towards the center of the connection, with the aim of better perfusing the segment bounded by the two SVCs. For both cases, the virtual modifications brought in significant improvements in lung perfusion, cardiac output and cardiac energy loss in simulation results.

A novel Y-graft design for the Fontan connection has been tested using CFD simulations in two recent studies. These serve as an example of the use of simulations to test and optimize new surgical methods prior to clinical implementation. Soerensen and colleagues suggested the use of a bifurcated graft, or Optiflo connection, to avoid blood mixing at the center of the connection, reduce secondary flow structures in the PAs, and ultimately minimize energy dissipation (Soerensen, Pekkan et al. 2007). Proof of concept was provided both

experimentally and numerically in highly idealized geometries, revealing energy dissipation levels 50% lower than in other idealized configurations. The potential benefits of a bifurcated Y-graft over traditional offset and T-junction designs was then demonstrated in a patient-specific scenario by Marsden et al. (Figure 9) (Marsden, Bernstein et al. 2009) that incorporated respiration, morphometry-based boundary conditions, exercise conditions, and Lagrangian particle tracking. Evaluating multiple clinically relevant parameters, results of the Y-graft simulations demonstrated decreased energy dissipation and lower SVC pressures at rest and exercise, while confirming that shear stress remained in the normal range. Both groups also confirmed that the bifurcated graft significantly improved hepatic distribution to the lungs in simulations, which may be of critical interest to prevent the formation of PAVMs in the clinic.

The first clinical implementation of an integrated surgical-planning framework is reported by Sundareswaran and de Zélicourt (Sundareswaran, de Zelicourt et al. 2009) who evaluated competing re-operative strategies for the case of a failing Fontan patient with severe PAVMs. This patient had a heterotaxy syndrome with an interrupted IVC and azygous continuation, resulting in an unusually complex cardiovascular anatomy and TCPC geometry. The patient underwent an MRI evaluation for 3D anatomy and flow reconstruction. Multiple re-operation strategies were designed using an interactive virtual-surgery platform, wherein the user reproduces the surgical procedure using 3D magnetic trackers in place of a scalpel (Pekkan, Whited et al.). Considered options included an Optiflo bifurcated graft, an azygous-to-hepatic shunt and a hepatic-to-azygous shunt. Based on the CFD performance predictions, the latter option was retained as the best candidate to restore an equal distribution of hepatic nutrients to the lungs for that patient. The surgery was performed using this approach, and the oxygen saturation increased from 68% at the time of PAVM diagnosis up to 94% five months after surgery, demonstrating the closure of PAVMs. de Zélicourt et al. (De Zélicourt 2010) report five additional pre-operative surgical planning studies, following the same protocol.

A major challenge that arises in predicting the post-operative hemodynamic state is that the surgical alterations of the TCPC geometry will not only impact the local TCPC hemodynamics but also the global cardiovascular response, thereby altering the inflow/outflow boundary conditions. For example, if the chosen surgical plan successfully increases hepatic flow to the diseased lung, PAVMs will regress, increasing the lung resistance on that side and subsequently decreasing flow to that lung. For lack of models that can predict remodeling and changes in pulmonary resistance, current approaches should evaluate a range of potential surgical outcomes and post-operative flow conditions (De Zélicourt 2010), and use uncertainty quantification tools to determine error estimates and confidence interval for the predicted performances, as discussed in Section 5.3.

5.2.1. Automated Optimization

To date, the majority of surgical planning studies have examined a small number of geometry variations using a “trial-and-error” approach to surgical design (Marsden, Bernstein et al. 2009; Sundareswaran, de Zelicourt et al. 2009). In contrast, many engineering fields such as aeronautics and automotive design commonly rely on automated

optimal shape design in their design process. The potential benefits of optimization for patient specific surgical planning compared to trial and error methods include 1) systematic and efficient exploration of the design space, 2) potential identification of non-intuitive designs, and 3) a guarantee that the best design has been identified. However, the application of automated optimization tools to surgical planning presents several significant challenges. First, appropriate measures of performance (cost functions and constraints) for cardiovascular designs must be defined based on physiologic information and hemodynamics. Second, the choice of optimization method must be appropriate for expensive, pulsatile, 3D fluid mechanics problems. Third, efficient parameterization of patient-specific geometries poses a formidable challenge and expense. And finally, the cost of evaluating the cost function and, if needed, the cost function gradient, may become extremely expensive as the problem complexity increases and the number of design parameters becomes large.

There have been a few studies reporting the use of automated shape optimization for blood flow applications, however most have required gradient information, and have been limited to steady flow conditions and idealized geometries (Quarteroni and Rozza 2003; Abraham, Behr et al. 2005; Abraham, Behr et al. 2005; Agoshkov, Quarteroni et al. 2006). A new approach has been proposed by Marsden and colleagues using an integrated framework (Marsden, Feinstein et al.) that includes (1) 3D anatomical reconstruction, (2) pulsatile 3D CFD simulations with physiologic boundary conditions and (3) a derivative-free approach for the efficient optimization of expensive functions. Their derivative-free optimization uses the surrogate management framework (SMF) together with mesh adaptive direct search methods. The algorithm relies on pattern search theory for mathematical convergence and a surrogate function in the design space for increased efficiency, and handling of non-linear constraints via a filter method (Booker, Dennis et al. 1999; Audet, Custodio et al. 2007; Marsden, Vignon-Clementel et al. 2007). Recent work of Sankaran and Marsden has extended the SMF algorithm to the stochastic case to perform optimization in the presence of uncertainty with the goal of performing robust design for surgical applications (Sankaran, Audet et al. 2010).

The SMF framework was applied to several cardiovascular problems using pulsatile flow and idealized models by Marsden et al. (Marsden, Feinstein et al. 2008), including a stenosis, end-to-side anastomosis and vessel bifurcation. The process is illustrated in Figure 10, and requires linking of the optimization algorithm, model construction, meshing, flow solver, and cost function computation software components in an automated loop. The framework has since then been applied to perform the first automated optimization of the Fontan surgery (Yang, Feinstein et al. 2010). This work used the energy dissipation as a cost function, with a constraint on areas of low wall shear stress that may be linked to thrombosis formation. Six design variables were defined to optimize the shape of an idealized Y-graft bifurcated design for the Fontan junction (Figure 10). The algorithm identified optimal shapes under a range of rest and exercise conditions and illustrated that shapes optimal for rest are not optimal for exercise. Findings also uncovered trade-offs in the design between dissipation and low shear, and confirmed previous findings that larger Y-graft branches in the range of 12–14 mm in diameter were a more favorable design choice.

5.3. Clinical Validation and Uncertainty Quantification

Despite the advances in patient specific surgical planning, there are still relatively few studies to date that demonstrate a direct benefit of simulations and making quantitative comparisons between simulation predictions and clinical outcomes data. CFD codes have been and continue to be validated against *in vitro* experimental data, but this is insufficient to prove that simulations can successfully reproduce *in vivo* conditions and predict clinical outcomes. As a result, there have been relatively few advances in surgical technique for single ventricle patients that are the direct result of CFD simulations. This is due to several factors, including a lack of validation with clinical data, a lack of clinical studies incorporating simulation-based parameters, and a lack of systematic uncertainty analysis on simulation results. In a recent review DeGroff et al. (DeGroff, Birnbaum et al. 2005) issued a ‘call to arms’ to increase the sophistication and clinical impact of Fontan simulations.

Uncertainties commonly arise in cardiovascular simulations stemming from noise in anatomic and flow data, uncertainty in outflow resistances, material properties, and physiologic variability. The effect of uncertainty in simulation results should be systematically quantified, and proper confidence intervals should be defined on quantities derived from the CFD results. This will serve to increase confidence on the part of clinicians, and help to identify areas for future validation studies.

While uncertainty has been explored in previous studies, it has been limited to a small number of parameters due to high computational expense. In an attempt to increase efficiency and rigor of uncertainty quantification for cardiovascular simulation, stochastic collocation methods have recently been applied to idealized and patient specific Fontan simulations by Sankaran and Marsden (Sankaran and Marsden 2010). Using these methods, input uncertainties are identified, and statistics and confidence intervals are determined. These findings can be used to rank output quantities such as pressure drop or energy dissipation in order of sensitivity to simulation inputs.

6. Future directions and clinical application

The examples provided in this manuscript serve as a basis to review the current state of the art in *in vivo* imaging and cardiovascular modeling, and their application to refine diagnosis and treatment options for patients born with single ventricle heart defects. By providing means to reproduce a surgical procedure and predict the associated hemodynamics for an individual patient, simulation-based virtual-surgery frameworks have the potential to aid in the establishment of optimal surgical procedures and clinical care on a patient-specific basis, ultimately resulting in improved patient-outcome and reduced clinical costs. Automated optimization frameworks are currently in development that will determine the optimal surgical design for an individual patient with minimal surgeon/user interaction.

However, while predictive simulations and virtual environment are gaining interest and popularity, they should still be considered with care. Past and ongoing efforts have established robust fluid dynamic solvers and fluid-structure interaction algorithms, inflow/outflow boundary conditions, and vessel wall mechanics. But each of these models carries an inherent set of simplifications and assumptions, and their coupling into a single unified

framework remains limited. Critical points to consider include the assessment of the spatial and temporal accuracy of clinical imaging and interventional modalities used to the capture *in vivo* anatomies, flows, and pressures, and their suitability to serve as CFD boundary conditions. Simulations then require the critical evaluation of each modeling assumption, weighing their computational cost against the accuracy gain.

The creation of virtual post-operative configurations is even more challenging in that models should not only reproduce the local changes in the TCPC geometry, but also the impact of the procedure on the entire physiology. While optimization may be performed to predict an optimal post-operative design, it may not account for subsequent growth and adaptation in the patient. Growth and remodeling methods are thus needed for the prediction of long-term outcomes based on hemodynamic changes, which will also require multi-scale numerical methods since remodeling processes typically occur over several months or years. A first step in that direction was taken by Figueroa et al. (Figueroa, Baek et al. 2009) who implemented a global model for the response and remodeling of an arterial wall to mechanical stimuli and applied it to the formation of a fusiform aneurysm in the basilar artery. Similar models are needed for the pediatric population and other regions of the cardiovascular system, which will require a tight interaction with the biological and clinical community for their establishment and validation.

Beyond modeling challenges, the time required to conduct a given optimization is a major issue for the deployment of numerical platforms in the clinical community. Clearly, for such platforms to represent an appealing and economically viable option, simulations should run in short time frames compromising between the competing demands for accuracy and efficiency. Improvement in hardware speed, such as the advent of GPU computing, as well as the optimization and parallelization of the numerical flow solvers are available options to reduce computational times. Cloud computing using multiple interconnected computers on internal or external networks (Steele, Draney et al. 2003) could allow for massively parallel simulations even in clinical settings where large computer clusters may not be available.

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Figure 1.
Cartoon depicting the normal, single ventricle and Fontan physiology

Figure 2.

Representative sample of *in vivo* TCPC anatomies from the GeorgiaTech MRI database. (a) and (b) show the geometries that may result from different surgical procedures (intra-atrial and extra-cardiac TCPC), while (c) and (d) highlight the different native anatomical configurations.

Figure 3.

Example of continuous in vivo velocity fields reconstructed from a stack of coronal PC MRI images and subsequent visualization of the 3D instantaneous particle streamtraces. Hepatic flow distribution to the two lungs may then be computed by quantifying the flux of IVC or hepatic particles exiting through the left or right pulmonary artery. Courtesy of Kartik Sundareswaran, Georgia Institute of Technology (Sundareswaran 2008)

Figure 4.
A closed-loop multiscale model of the TCPC junction with heart, systemic and pulmonary circulations. Image courtesy of Chiara Corsini, Politecnico di Milano.

Figure 5.
Comparison of simulated LPA pressure with respiratory variation with patient-specific pressure tracings from cardiac catheterization.

Figure 6.

Fluid structure simulations in a patient specific Fontan simulation demonstrate an over-prediction of wall shear stress by as much as 30% under exercise flow conditions.

Figure 7.

Lagrangian particle tracking in a TCPC with interrupted IVC. The particles are color coded by their vessel of origin to better elucidate the inflow interactions.

Figure 8. Simulation predictions of hepatic flow distribution in six patient specific models using Lagrangian particle tracking.

Figure 9.

Comparison of simulated velocity magnitude in competing T-junction (MRI-derived), offset, and Y-graft designs for the Fontan surgery in a patient specific model.

Figure 10. Automated optimization of a Fontan Y-graft. Left: Paramterized design with 6 geometric variables, Right: Steps required for automated optimization.