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Can time-averaged flow boundary conditions be used to meet the clinical timeline for Fontan surgical planning?

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ABSTRACT

Cardiovascular simulations have great potential as a clinical tool for planning and evaluating patient-specific treatment strategies for those suffering from congenital heart diseases, specifically Fontan patients. However, several bottlenecks have delayed wider deployment of the simulations for clinical use; the main obstacle is simulation cost. Currently, time-averaged clinical flow measurements are utilized as numerical boundary conditions (BCs) in order to reduce the computational power and time needed to offer surgical planning within a clinical time frame. Nevertheless, pulsatile blood flow is observed *in vivo*, and its significant impact on numerical simulations has been demonstrated. Therefore, it is imperative to carry out a comprehensive study analyzing the sensitivity of using time-averaged BCs. In this study, sensitivity is evaluated based on the discrepancies between hemodynamic metrics calculated using time-averaged and pulsatile BCs; smaller discrepancies indicate less sensitivity.

The current study incorporates a comparison between 3D patient-specific CFD simulations using both the time-averaged and pulsatile BCs for 101 Fontan patients. The sensitivity analysis involves two clinically important hemodynamic metrics: hepatic flow distribution (HFD) and indexed power loss (iPL). Paired demographic group comparisons revealed that HFD sensitivity is significantly different between single and bilateral superior vena cava cohorts but no other demographic discrepancies were observed for HFD or iPL. Multivariate regression analyses show that the best predictors for sensitivity involve flow pulsatilities, time-averaged flow rates, and geometric characteristics of the Fontan connection. These predictors provide patient-specific guidelines to determine the effectiveness of analyzing patient-specific surgical options with time-averaged BCs within a clinical time frame.

1. Introduction

Cardiovascular flow simulation is a non-invasive high-resolution technique to augment the knowledge gained from current medical imaging and clinical measurements (Marsden and Esmaily-Moghadam, 2015). In single ventricle lesions, especially at the Fontan stage, numerical simulations have been used to understand patient hemodynamics (Khiabani et al., 2015; Marsden et al., 2007; Tang et al., 2014), test novel treatment concepts (Esmaily-Moghadam et al., 2015; Trusty et al., 2016; Yang et al., 2013), and predict surgical outcomes (de Zélicourt et al., 2011; de Zélicourt and Kurtcuoglu, 2015; Haggerty et al., 2012; Kung et al., 2013; Sundareswaran et al., 2009a). Cardiovascular simulation has become a fruitful area of translational research and has potential to impact clinical decisions, especially by assisting surgical planning (de Zélicourt and Kurtcuoglu, 2015; Fogel et al., 2013; Marsden and Esmaily-Moghadam, 2015; Marsden, 2014; Restrepo et al., 2015b). Fig. 1 illustrates a standard procedure of the surgical planning for congenital single ventricle heart diseases. It consists of four steps: 1) Image Acquisition, which obtains medical images; 2) Image Processing, which reconstructs anatomy and

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Abbreviations: BSA, body surface area; IA, intra-atrial; EC, extra-cardiac; HLHS, hypoplastic left heart syndrome; IVC, inferior vena cava; SVC, superior vena cava; LSVC, left superior vena cava; AZ, semi-azygos vein; LPA, left pulmonary artery; RPA, right pulmonary artery; RUPA, right upper pulmonary artery; Qs, total venous flow; SD, standard deviation

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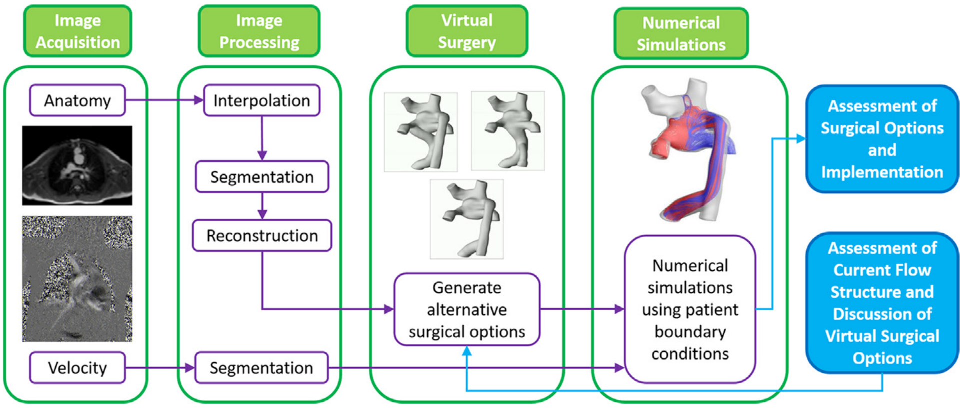

Fig. 1. A schematic drawing of standard surgical planning procedure; reproduced from Fogel et al. (2013).

segments blood flow velocity; 3) Virtual Surgery, which generates alternative surgical options; 4) Numerical Simulation, which conducts computational analysis for hemodynamics of the surgical options. Extensive discussions usually happen at step 3 for potential surgical options, as well as after step 5 for assessment of surgical options and implementations. In general, the timeline for surgical planning cases is around one or two weeks.

Recently, with the assistance of cardiovascular simulations, optimization techniques were introduced to seek optimal patient-specific surgical treatments (de Zélicourt et al., 2010; Marsden, 2014, 2013). A geometric robustness analysis was also developed to assess the discrepancy in surgical planning outcomes between the proposed and implemented anatomies (Restrepo et al., 2015b). However, numerous challenges limit the effectiveness and applicability of surgical planning. Major limitations include high computational cost, lack of verification, and limited validation of the current surgical planning process. In terms of the computational cost, it often takes days to finish a simulation even with modern high-performance computing power (de Zélicourt et al., 2009; Wei et al., 2014), but fast turnover time is key for surgical planning (Fogel et al., 2013). Moreover, high computational cost may prevent the clinical adoption of the previously mentioned leading-edge surgical planning techniques, (i.e. optimization of surgical treatments and geometric robustness analysis) which require many simulations.

The utilization of time-averaged flow BCs instead of pulsatile flow BCs in cardiovascular simulations is currently a viable option from a cost-standpoint for surgical planning in Fontan patients. On average, it reduces the total simulation time by 50% (Khiabani et al., 2012). Moreover, time-averaged BCs have been widely used and validated in cardiovascular simulations (de Zélicourt et al., 2009; DeGroff, 2008; Wang et al., 2007). Nevertheless, *in vivo* blood flow is undoubtedly pulsatile (Fogel et al., 1997). Marsden et al. (2007) first demonstrated that pulsatility could impact the numerically predicted Fontan hemodynamics. Dur et al. (2012) further emphasized the importance of taking into account flow pulsatility for Fontan hemodynamic prediction by systematically analyzing the effect of pulsatile BCs using an idealized Fontan model. Therefore, it is critical to quantitatively understand the sensitivity of using time-averaged BCs in place of physiologically accurate BCs regarding key Fontan hemodynamic metrics. The findings can be used to assess the effectiveness of using time-averaged BCs for reducing computational cost, hence, enhancing the applicability and generalization of Fontan surgical planning. Previous simulations statistically ($n=35$) showed good agreement between using time-averaged and pulsatile BCs in simulating Fontan hemodynamics (Haggerty et al., 2014). Additionally, a 10% discrepancy in flow energy loss through the Fontan connection between using time-averaged and pulsatile BCs was found when the weighted pulsatility of venous return flow is less than 30%. (Khiabani et al., 2012). However, these previous studies rely on small sample sizes limiting their ability to comprehensively understand the sensitivity of using time-averaged BCs on Fontan simulations at a population level. In addition, most of the previously mentioned studies focus on Fontan energetics and only marginally discussed hepatic flow distribution, which some argue is a more important Fontan hemodynamic metric for current clinical practice (de Zélicourt and Kurtcuoglu, 2015; Pike et al., 2004; Srivastava et al., 1995; Sundareswaran et al., 2009a; Yang et al., 2013).

To address these limitations, the current study carried out a systematic investigation evaluating the sensitivity of both Fontan connection power loss and hepatic flow distribution to using time-averaged BCs rather than the more physiological pulsatile BCs for a large cohort of patients. Benefiting from the large patient cohort, statistical analyses are conducted to explore potential demographic differences, as well as investigate the best predictors of sensitivity to the time-averaged BCs. These predictors can be used to estimate the patient-specific sensitivity of using time-averaged BCs. Together with the clinical time constraint, the effectiveness of employing time-averaged BCs for surgical planning can be identified.

2. Materials and methods

2.1. Patient cohort

This study was a retrospective investigation using consecutive patient data from the Georgia Tech-Children's Hospital of Philadelphia Fontan database. Exclusion criteria include severe CMR artifacts, insufficient phase contrast data, and diagnosis of Ebstein's anomaly. These exclusions resulted in a 101 patient study. All patients had a completed Fontan connection. Informed consent was obtained and the protocol was approved by the Georgia Institute of Technology and Children's Hospital of Philadelphia institutional review boards. Patient demographic details are provided in Table 1. The demographic sub-divisions listed in Table 1 have been found clinically important in previous literature (d'Udekem et al., 2007; Haggerty et al., 2014; Khiabani et al., 2015, 2012; Tang et al., 2014).

2.2. Anatomy and velocity reconstruction

Magnetic resonance imaging (MRI) data were acquired at the Children's Hospital of Philadelphia. The MRI scans were taken under breath-held conditions and electrocardiogram gated. The transverse bright blood contiguous MRI slices were used to build isotropic voxels by using an adaptive control grid interpolation technique (Frakes et al., 2008, 2003) implemented in MATLAB (The MathWorks, Inc., Natick, MA). The regions of interest were then selected by utilizing a bouncing ball algorithm (Frakes et al., 2003). Finally, surfaces of the *in vivo* 3D anatomies were reconstructed with Geomagic Studio (Geomagic Inc., NC, USA). Phase contrast magnetic resonance imaging (pcMRI) was also acquired and an in-house methodology using parametric active contours with gradient vector flow was used to segment through-plane velocities to obtain vessel specific blood flow waveforms (Frakes et al., 2004; Sundareswaran et al., 2009b).

2.3. Computational fluid dynamics

All simulations in this study were carried out using an in-house immersed boundary (IB) method (de Zélicourt et al., 2009). The method is based on a sharp interface scheme and tailored to an unstructured Cartesian grid in order to improve