Simulation of aortopulmonary collateral flow in Fontan patients for use in prediction of interventional outcomes

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Summary

Purpose Patients with complex congenital heart disease may need to be converted to a Fontan circulation with systemic venous return surgically connected to the pulmonary circulation. These patients frequently form aortopulmonary collaterals (APC), that is arterial inflows to the pulmonary artery vascular tree. The aim of this study was to develop a method to calculate the effect of APC on the pulmonary flow distribution based on magnetic resonance imaging (MRI) measurements and computational fluid dynamics simulations in order to enable prediction of interventional outcomes in Fontan patients.

Methods Patient-specific models of 11 patients were constructed in a 3D-design software based on MRI segmentations. APC flow was quantified as the difference between pulmonary venous flow and pulmonary artery flow, measured by MRI. A method was developed to include the modulating effect of the APC flow by calculating the patient-specific relative pulmonary vascular resistance. Simulations, including interventions with a Y-graft replacement and a stent dilatation, were validated against MRI results.

Results The bias between simulated and MRI-measured fraction of blood to the left lung was 2.9 ± 5.3%. Including the effects of the APC flow in the simulation (n = 6) reduced simulation error from 9.8 ± 7.0% to 5.2 ± 6.3%. Preliminary findings in two patients show that the effect of surgical and catheter interventions could be predicted using the demonstrated methods.

Conclusions The work demonstrates a novel method to include APC flow in predictive simulations of Fontan hemodynamics. APC flow was found to have a significant contribution to the pulmonary flow distribution in Fontan patients.

Introduction

Children with complex heart malformations not suited for biventricular repair can be converted to a Fontan circulation in a stepwise approach. The final step in this process, the total cavopulmonary connection (TCPC), is implemented around the age of 2–4 years. The aim of the intervention is to improve oxygenation by routing the systemic venous blood from the caval veins directly to the pulmonary arteries, thereby bypassing the heart and creating a serially connected systemic- and pulmonary circulation (Fontan & Baudet, 1971).

The TCPC must be carefully planned before implementation, and patients are meticulously followed throughout life (Gewillig, 2005). The postsurgical flow distribution to the lungs is difficult to predict, and various surgical or endovascular interventions may be required to address specific circulatory issues. For example, endovascular angioplasty may be required to dilate hypoplastic pulmonary arteries in an effort to remove even discrete stenosis and optimize pulmonary flow distribution (Noonan et al., 2016; Schwartz et al., 2016). Furthermore, assuring equal distribution of hepatic blood flow to both lungs is important to avoid pulmonary arteriovenous malformations that decrease systemic oxygenation (Duncan & Desai, 2003).

Aorto-pulmonary collaterals (APC) are arterial inflows to the pulmonary artery vascular tree and are frequently found in TCPC patients (Triedman et al., 1993) and can be quantified using MRI measurements (Grosse-Wortmann et al., 2009; Whitehead et al., 2015). In these patients, APC’s have been suggested to adversely influence the circulation, for example...
with competition of venous inflow to the lungs, pressure elevation, energy losses, volume loading of the heart and longer hospital stay following TCPC surgery (Kanter et al., 1999; Powell, 2009). In such situations, endovascular methods are used to identify and close APCs (Stern, 2010). It is, however, not known how APC’s influence the flow distribution and hemodynamics inside the TCPC.

Patient-specific computational fluid dynamics (CFD) simulations can evaluate the flow distribution and hemodynamic characteristics of TCPC junctions (Haggerty et al., 2012, 2013; Bossers et al., 2014) and have in selected cases been shown to predict the outcome of surgical interventions (Haggerty et al., 2012; Corsini et al., 2014a). However, the described CFD simulations do not include the effects of APC’s in the analyses as a means to simulate bias of flow between the lungs to predict outcome of interventions.

Magnetic resonance imaging (MRI) is a non-invasive, non-ionizing imaging modality that in the same session can provide both pre-interventional anatomy and flow measurements. Simulations of a TCPC anastomosis generally require vessel anatomy, flow information at the inlets and pressure and pulmonary vascular resistance (PVR) at the outlets. MRI cannot measure absolute pressures and therefore not absolute values of PVR. We propose using measurements of flow from MRI to calculate patient-specific relative PVR for each lung, and that this is sufficient to perform clinically relevant predictions of interventions.

The aim of this study was, therefore, to develop a method to include the effect of APC on the TCPC flow distribution based on MRI measurements and CFD simulations to predict interventional outcomes on TCPC patients. Furthermore, in order to increase clinical accessibility and shorten the lead time of the simulations, it was also a desired aim to reduce the complexity of the process as much as possible.

Methods

Patient population

Patients with Fontan circulation after TCPC referred to the Department of Medical Imaging and Physiology at Skane University Hospital for a MRI examination were prospectively included in the study. Eleven patients (median age 11, range 3–29 years, three females) with Fontan circulation were included from November 2013 to January 2015 and underwent MRI scanning. A 4D PC-MRI flow acquisition was added to the routine clinical examination. Six patients were found to have quantifiable APC flows defined as pulmonary vein flow that exceeded the pulmonary artery flow. Two patients who underwent interventions (a dilation of LPA stent from 6 to 8 mm, and a Y-graft surgical implantation between the hepatic vein confluence and the pulmonary arteries, respectively) had repeated postintervention MRI scanning. These interventions were modelled and compared to postinterventional MRI results. The study was approved by the Regional Ethical Review Board, Lund, Sweden. Written informed consent was obtained from all subjects or their parents if below 18 years of age.

MRI

MRI flow measurements and cine images of the heart and intrathoracic vessels were acquired using a 1.5T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands). Cine images were acquired using a steady state free precession (SSFp) sequence (TR/TE/flip angle: 2.9 ms/1.5 ms/60°, slice thickness 5 mm, in-plane resolution 1.2 mm×1.2 mm). Two dimensional phase contrast MRI (2D PC-MRI) flow measurements were acquired using a phase velocity encoded fast field echo sequence (TR/TE/flip angle: 10 ms/6.5 ms/15° in-plane resolution 1.2 mm×1.2 mm). Flow measurements of the superior and inferior vena cava, the TCPC tunnel and the pulmonary veins were typically velocity encoded at 80 cm s⁻¹ and the aorta at 200 cm s⁻¹. Additionally, the region of the heart and neighbouring great vessels was imaged using 4D PC-MRI velocity mapping turbo field echo sequence (typical TR/TE/flip angle: 6.2 ms/3.6 ms/8°, velocity encoding 100 cm s⁻¹) as previously described (Töger et al., 2012) and validated in vivo (Carlsson et al., 2011) and in vitro (Töger et al., 2016).

Fluoroscopy angiography and catheterization

All patients underwent cardiac catheterization in a dedicated paediatric catheterization laboratory equipped with a biplane X-ray system. All procedures were performed under general anaesthesia by paediatric cardiologists. After obtaining femoral or jugular access, pressures were obtained in different vascular segments with a 5 French multipurpose catheter (Cordis Endovascular, Warren, NJ, USA), followed by angiographic assessment of the Fontan circulation with a 5 French pigtail catheter (Cordis Endovascular). In patient 4, the proximal part of the LPA, which was previously stented with a 6 mm×17 mm Visi-Pro stent (Covidien, Plymouth, MN, USA), was further dilated with 8 mm×2 cm Powerflex balloon (Cordis Endovascular). Angiography was thereafter repeated to rule out vascular damage, and pressures were re-measured. There were no intra-procedural complications.

Image analysis

All MRI segmentation and analysis were performed using the freely available software Segment v2.0 (http://segment.heiberg.se; Heilberg et al., 2010). Eddy currents and other background effects were compensated for and velocity aliasing was corrected using phase unwrapping. Flow measurements of the inferior and superior vena cava were obtained for use as boundary conditions at the inlets of the CFD simulation model. Flow measurements at the left and right pulmonary artery were acquired as reference to the corresponding CFD flow predictions. Aortopulmonary collateral flow was calculated by subtracting the pulmonary arterial flow (Q_{LPA} in Fig. 1) from the
pulmonary venous flow \((Q_{LPV} \text{ in Fig. 1})\) on each side, respectively (Grosse-Wortmann et al., 2009). Segmentation curves were placed on the boundaries of the TCPC vessels in transversal, sagittal and coronal SSFP images. 4D MRI flow visualization was performed using the in-house developed FourFlow software (http://fourflow.heiberg.se/).

3D model construction

Segmentation curves were imported into the 3D CAD software Creo Parametric 3.0 (PTC, Needham, MA, USA), where a continuous 3D model was formed on the anatomical boundaries (Fig. 2). In three patients, fluoroscopy angiography images were superimposed on the 3D model to aid reconstruction in areas where segmentation curves were unavailable due to stenting-induced MRI artefacts. From the combined MRI and angiographic information, a 3D-reconstruction of the complete TCPC could be created (Fig. 3). If branches of the pulmonary arteries could be clearly segmented in the MRI data, they were included in the 3D model, otherwise the pulmonary artery was truncated just prior to where the first bifurcation was expected to be. The pulmonary arteries were then extended with a straight 12 mm segment to accommodate an internal 10 mm long segment to be used as porous media to simulate pulmonary resistance in the CFD solver (Sun et al., 2013). Interventions were simulated by modifying the corresponding vessels using geometry modelling tools available in Creo Parametric.

CFD analysis

The CFD analysis was performed with Mentor Graphics FloEFD 14 (Mentor Graphics Corp, Wilsonville, OR, USA), integrated in the PTC Creo Parametric user interface. The software is an immersed boundary solver with adaptive mesh density algorithms. The solver repeatedly adapts the local Cartesian mesh density by splitting mesh cells in flow regions with significant flow activity. Local truncation errors in calculations of conservation of mass and energy are used as indicators of whether further mesh refinement is required. Additionally, user-specified measurements of the flows in the left and right pulmonary artery were tracked to ensure that they converged to a steady state during the solution process.

Inlet flows in the caval veins were measured from phase contrast MRI acquisitions and applied to the CFD model approximated as time-averaged constant flow with a flat velocity profile. The solver used a rigid wall assumption with no slip boundary conditions.

Patient-specific relative PVR was simulated by applying porous media properties to a 10 mm long internal segment of the extended pulmonary arteries. In the used CFD tool, porous media provide a means to add resistance to flow through a vessel segment such that the pressure drop over the segment is proportional to the flow through the segment. A common atrial pressure of 10 mm Hg was bilaterally applied as boundary condition at the distal outlets.

In pulmonary artery branches that could be identified, corresponding resistances were distributed inversely to the cross section area of the branch.

Simulations were performed, and the fraction of pulmonary arterial blood routed to the left pulmonary artery was compared with in vivo measurements from 2D PC-MRI.

If interventions were performed on the patients in the study group such that the interventions affected the geometry of the TCPC vessels, the interventions were modelled and compared to postinterventional MRI results.

Accounting for APC flow

Our simulation of the effects of APC on the TCPC flow distribution is based on the relationship between the pulmonary artery pressure, total pulmonary artery flow and pulmonary resistance. Using measurements exemplified on the left pulmonary artery in the principal schematic shown in Fig. 1, this relationship can for the left lung be expressed by Eq. (1).
Equation (1) shows that elevated pulmonary flow and increased pulmonary resistance increases the pulmonary artery pressure. When APC flow is present, the total pulmonary artery flow increases and is the sum of the proximal venous inflow to the pulmonary artery and the APC flow. It follows from Eq. (1) that as APC flow increases, the pressure in the TCPC will increase.

By only considering the proximal pulmonary artery flow (Q_LPA in Fig. 1), the same pulmonary artery pressure can result from an increased net pulmonary resistance R'. For the left lung, this can be expressed by Eq. (2).

\[ p_1 - p_0 = (Q_{LPA} + Q_{APC}) R' \]  

(1)

This can be interpreted as an apparent increase in pulmonary resistance due to the presence of APC flow in the distal pulmonary artery. From the above equations, the net pulmonary resistance R' can be calculated by multiplying the pulmonary resistance R with a correction factor based on flows. For the left lung, R' can be expressed as shown in Eq. (3).

\[ R' = R \frac{Q_{LPA} + Q_{APC}}{Q_{LPA}} \]  

(2)

This can be implemented in CFD by calculating the value of R' and using this value as the pulmonary resistance in the simulation. MRI measurements are used to calculate patient APC flow (Q_{APC}) as the difference between pulmonary vein and pulmonary artery flow. Pulmonary artery flow (Q_{LPA}) is included in the equation for R', but of note it is not the measured value from MRI that is used here, as it is the intent of the simulation to provide this value. An initial guess of Q_{LPA} (e.g. 50% of TCPC inflow) is provided, and the result of the simulation is returned to Eq. (3). After 3–4 iterations, the value of Q_{LPA} will stabilize and converge within 1% of the previous value, at which point further iterations are deemed unnecessary. This approach is meaningful because prior to interventions on the TCPC, APC flow is often known from previous MRI scans. Postinterventional pulmonary artery flow is obviously not known and is desired to be predicted. The simulations in the study are performed as if they were predictions, even when no interventional change was imposed on the model.

R' is a patient-specific relative PVR that is calculated for each lung. For purposes of the CFD simulation an absolute value of PVR must be provided. For all calculations in this study, we chose an intrinsic PVR of 1.5 Wood Units (WU), which is in the low range of physiological PVR (Gewillig & Brown, 2016). As relative PVR is used, it is not meaningful to calculate patient-specific Fontan pressures with this method. When APC flow was present, the simulation was performed with and without taking the APC flow into account.

**Hardware**

All software used was running on a MacBook Air with 8 GB RAM and dual core i7 processor, in a virtualized Parallels Desktop Windows 7 environment with 4 GB RAM dedicated. A standard desktop PC with an external HD screen was used for capturing screenshots of 4D MRI visualizations using the FourFlow software.

**Statistical analysis**

Statistical analysis was performed using GraphPad (v7.0, La Jolla, CA, USA). Values are shown as mean ± standard deviation. Bias was calculated as mean ± standard deviation of the difference against the reference method.

**Results**

**CFD modelling results**

The difference between the simulated and the MRI-measured fraction of pulmonary arterial blood routed to the left pulmonary artery (LPA%) according to Bland–Altman analysis (Fig. 4) was 2.9 ± 5.3%. In patients where significant APC flow was found (n = 6), including the effect of APC flow in the simulation reduced simulation error from 9.8 ± 7.0% to 5.2 ± 6.3%. Table 1 shows the effect of APC flow on the TCPC flow distribution in the patients where such collaterals were found.

**Modelling predicting results from interventions**

Simulation of the patient with stent dilatation showed an LPA flow of 32.6% before and 34.9% after stent dilatation. MRI 2D flow showed similar results, an LPA flow of 30.2% before and 32.1% after dilatation (Fig. 5). CFD modelling of the surgical y-
In this study, invasive measurements of pressure were not required in the process to calculate or predict the TCPC flow distribution. Instead, non-invasive MRI measurements of APC flows were used to estimate patient-specific relative values of the net pulmonary resistance $R'$ for each lung. If given bilaterally equal values in the physiological range, the numeric value of the intrinsic pulmonary resistance $R$ does not affect the bias of the RPA/LPA flow. This means that using non-invasive, non-ionizing MRI measurements may be sufficient as basis for clinically relevant, patient-specific predictive CFD simulations of TCPC flow distribution.

Discussion

This study shows that APC flow significantly affects the TCPC hemodynamics and demonstrates that it is possible to include the effect of such APC flow on the TCPC flow distribution during patient-specific CFD simulations. A recent review of the field of patient-specific simulation of the Fontan circulation concluded by highlighting the need for validation of predictive capabilities (de Zélicourt & Kurtcuoglu, 2016). Our contribution to this endeavour is preliminary findings in two patients, showing that the effect of surgical and catheter interventions can be predicted using the proposed CFD analysis. Using a freely available segmentation tool and a commercial off-the-shelf software with integrated geometric and CFD modelling tools, including porous properties to simulate PVR, resulted in a process that allowed performing the start-to-end segmentation and simulation process on a standard laptop.

With this method there is no tuning involved, in other words there was no arbitrary adjustment of internal model parameters to minimize differences between simulation results and patient measurements. Differences between model and patient measurements are due to the limitations of the physiological model and the accuracy of the measured patient data. This is central for patient-specific, pre-interventional predictive simulations. The simulations in the study are performed as if they were predictions, even when no interventional change was imposed on the model.

The use of non-invasive imaging methods

In this study, non-invasive imaging methods of pressure were not required in the process to calculate or predict the TCPC flow distribution. Instead, non-invasive MRI measurements of APC flows were used to estimate patient-specific relative values of the net pulmonary resistance $R'$ for each lung. If given bilaterally equal values in the physiological range, the numeric value of the intrinsic pulmonary resistance $R$ does not affect the bias of the RPA/LPA flow. This means that using non-invasive, non-ionizing MRI measurements may be sufficient as basis for clinically relevant, patient-specific predictive CFD simulations of TCPC flow distribution.
The effect of APC flow

In five of the six patients with quantifiable APC flows, including the effect of APC flow in the simulation improved the CFD results relative to measured MRI results. In patients with APC flow, the simulated results have a higher bias with the results measured in MRI compared with the non-APC patients. This suggests that there may be more hemodynamic effects of APC flow on TCPC flow that the present study is not accounting for. For example, proximal APC inflow as inferred by a catheterized oxygen saturation step up may affect hemodynamics differently than distal APC inflow (Stern, 2010). Considering this, the results show that APC flows have a measurable impact on the TCPC flow distribution. These effects of APC may require treatment using embolization to close the APC (Stern, 2010; Dori et al., 2013). The proposed CFD simulations may be useful to show the effects of APC before intervention and predict the effects of APC closure on TCPC hemodynamics.

Simulation of pulmonary resistance

To be able to predict the effect of geometric TCPC interventions on the flow distribution to the lungs, the simulation needs to be designed such that the pulmonary artery flows are a result of the numerical solution. In previous studies on the effect of changing the TCPC geometry, various strategies for setting outlet boundary conditions have been reported, such as using fixed pre-interventional static flows (Restrepo et al., 2016), using multi-element Windkessel models for time-varying flows (Mirabella et al., 2013) and more sophisticated one-dimensional physiological circulatory models (Corsini et al., 2014b). We used porous media in the CFD model to simulate pulmonary resistance in TCPC vessels (Sun et al., 2013). In the used CFD tool, porous media provide a means to add resistance to flow through a vessel segment such that the pressure drop over the segment is proportional to the flow through the segment. At present, we have only utilized a linear relationship between flow and pressure drop. The benefit of this approach is that it is available in other commercially available CFD tools and it is quick to implement. On the negative side, it does not allow simulation of capacitance (pulmonary blood buffering) or impedance (PVR depending on flow velocity) for time-dependent flows. Recent work has, however, shown that time-averaged flow is a reasonable assumption for simulation of pulmonary flow bias (Wei et al., 2016).

Methodological considerations for MRI

We used 2D PC-MRI (Töger et al., 2012) to validate CFD modeling and 4D PC-MRI to visualize in vivo patient flow. Of note, 4D PC-MRI is not needed to generate CFD results as the input data are generated from clinical 2D PC-MRI methods commonly used due to its high precision and accuracy (Razavi et al., 2003; Carlsson et al., 2012). The 4D PC-MRI data were acquired during free breathing, and we have shown that the results generated without navigator have preserved quality (Kanski et al., 2015). The two reasons to obtain the data during free breathing in the patients with TCPC were (i) reducing acquisition time of the MRI and (ii) to obtain results throughout the breathing cycle as the flows in TCPC patients are dependent on breathing (Marsden et al., 2007). Both the CFD
Simulation and the reference method were thus carried out during free breathing meaning that the results represent the mean during a respiration cycle.

The use of fluoroscopic angiography to supplement MRI data

When transcatheter interventions such as stenting are performed, the metal properties of the stents will cause artefacts in the MRI data that limit the segmentation of the vessel near the stent. The method used in this study shows that fluoroscopic angiography obtained during the stenting procedure can be taken advantage of to complement the MRI images during the patient-specific reconstruction of the TCPC vessels. While a fluoroscopic image is projected onto a plane, the 3D orientation of the vessel can be inferred from multiple projections. The reconstructed vessel segment can sometimes also be merged with vessel ends that are reconstructed from MRI data distal to the artefacts. This means that no additional ionizing radiation is required for the reconstruction, as the fluoroscopy images already obtained during the stenting procedure can be used.

Limitations

The approach of using constant resistance properties to simulate the throttling effects of APC flow could be expanded to include time-dependent properties, such as impedance and capacitance of the pulmonary circulation, and even aortic pulsatility of the APC inflow. Resistive properties alone can, however, not account for situations where flow reversal may occur such as may happen with pulmonary vein stenosis and high APC inflows. Time-averaged flows were used as inlet boundary conditions in this study to reduce simulation complexity and have been used in previous predictive simulations of TCPC implementations (Haggerty et al., 2012). While this study does not measure power losses, it has been shown that the use of time-dependent flow at the inlets due to cardiac pulsatility increase the predictive accuracy of power losses in the TCPC (Khiabani et al., 2012). Time-dependent patient-specific inflows have been shown to increase simulation accuracy of hepatic flow distribution, albeit at the cost of longer computation times (Wei et al., 2016).

Conclusion

Aortopulmonary collaterals were found to have a significant contribution to the flow distribution to the pulmonary circulation in Fontan patients, and a method was developed to incorporate such contributions in the predictive CFD analysis process. The new method makes it possible to non-invasively quantify the effects of APC flow on the net pulmonary resistance. Furthermore, initial results demonstrate the possibility to predict the outcome of interventions such as a γ-graft implementation and a stent dilatation on TCPC vessels.

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Conflict of interest

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Ethical approval

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