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Executive Summary of the Thesis

Computational study of the hemodynamics in healthy and diseased pulmonary arteries

Laurea Magistrale in Mathematical Engineering - Ingegneria Matematica

Author: Eleonora Sharon Dacatra

Advisor: Prof. Christian Vergara

Co-advisors: Ivan Fumagalli, Stefano Maria Marianeschi

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1. Introduction

The purpose of this work was to provide a computational study of the hemodynamics in the pulmonary artery of two patients with a repaired congenital heart disease (Tetralogy of Fallot). The two patients, after living for years without a pulmonary valve, underwent a pulmonary valve replacement (PVR) operation. We adopted a 3D-0D geometric multiscale coupled fluid dynamics model of the heart circulation based on the Navier-Stokes equations for the 3D domain of the pulmonary artery, reconstructed thanks to the computed tomographies of the patients provided by the Niguarda Hospital of Milan, and on electrical circuit analogies for the rest of the circulation. We propose a novel comparison among a healthy, a pre-operative and a post-operative scenario in order to assess the efficacy of the valve replacement operation in an image-based patient-specific context. Moreover, we perform a study on the flow repartition at the main pulmonary bifurcation based on three different approaches for the imposition of boundary conditions. The method has been implemented in the Finite Element C++ library $Life^x$.

2. Medical context

The pulmonary valve is placed at the outflow of the right ventricle of the heart, in the pulmonary artery. The valve opens when the pulmonary artery pressure is higher than the ventricle one and closes when the blood flow rate starts to change direction. We refer to ventricle *systole* as the heartbeat phase when the ventricles contract and pump the blood out, while the ventricle *diastole* is the phase of relaxation after the systole. Regarding the terms left and *right* referred to the heart, in medicine a common practice is to adopt the patient's perspective. In this work we will use the medical notation which is inverted with respect to the figures.

The two patients under study were both affected by *Tetralogy of Fallot* (TOF). TOF is one of the most common cyanotic Congenital Heart Diseases (CHD) occurring every one out of 3000 live births. It consists of four features: a non restrictive ventricular septal defect, an overriding aorta, hypertrophy of the right ventricle and a right ventricle outflow tract obstruction. The most dangerous consequence of this disease is a low level of oxygen in the blood and, while an initial palliation can be done at a neonatal age (before the first month of age), a complete re-

pair is often needed and usually takes place in the first couple of years of life.
Regarding the complete repair, a possible procedure used to treat some of the patients with CHDs is the *Ross procedure*. This method consists in the replacement of a diseased aortic valve with the patient's own pulmonary valve. The main follow-up of this procedure consists in the replacement of the removed pulmonary valve with a prosthetic one or a natural one from a donor.
Both the patients under study (from here on, *Patient 1* and *Patient 2*) were treated with a Ross procedure as infants, and later, as adults, underwent a pulmonary valve replacement (PVR) operation with the implantation of the $No-React^{®}$ Injectable $BioPulmonic^{TM}$ Prosthesis (Bio Integral Surgical, Inc., Mississauga, ON, Canada) valve at the Niguarda Hospital of Milan [1]. The successful outcome of the PVR operation greatly depends on the hemodynamics in the pulmonary artery, therefore, a quantitative study which compares the preoperative condition of the patients with the post-operative one and with a simulated healthy scenario, is very important.

3. Imaging and preprocessing

In this work we have performed some computational fluid dynamics (CFD) simulations employing patient-specific medical images of the two patients. The images were volume Computed Tomographies (CTs) provided by MD Stefano Marianeschi, the head of the pediatric cardiac surgery division at the Niguarda Hospital of Milan. For each patient, the CT scans were taken after the PVR operation, therefore, at the moment of the scans, both patients had the prosthetic valve implanted. The valve is composed: by a prosthetic stent, which is attached to the artery wall and visible through the medical exams, and by porcine valve leaflets.

3.1. Image acquisition and segmentation

Our first goal was to reconstruct the geometry of the pulmonary arteries of the two patients in order to numerically simulate the blood flowing inside of them. An image segmentation procedure named *front propagation technique* was adopted. Image segmentation consists in the reconstruction of an image by identifying its borders, in particular the artery walls. The user also has to set the artificial boundaries at the inflow and outflows in order to define the domain of interest. The images were initially in the standard medical *DICOM* format and were segmented thanks to the softwares *VMTK* and *Paraview*.

3.2. Overview on the 3D case-scenarios

Our aim was to simulate three different scenarios for each patient:

- A *Healthy* scenario with a functioning and natural pulmonary valve;
- A Pre-operative (in what follows *Pre*) scenario corresponding to the situation before the PVR operation, therefore in absence of the pulmonary valve;
- A Post-operative (in what follows *Post*) scenario corresponding to the situation after the PVR operation, with the prosthetic valve implanted.

The main difference between the *Healthy* and the *Pre* scenarios consisted in the presence or absence of the pulmonary valve, which was taken into account through the addition or removal of a diode in the 0D model. A diode, indeed, has a similar function to that of a cardiac valve, though in the context of electrical circuits. We therefore hypothesised no differences between the *Healthy* and *Pre* scenarios from a 3D point of view. Indeed, the simulations for the *Healthy* scenario did not aim at simulating the blood circulation for an average healthy person but our goal was to obtain the best possible results for a patient having a functioning valve but that specific and possibly pathological shape of the artery.
Regarding the *Post* scenario, from a 3D point of view, we had to take into account of the presence of the prosthetic stent at the inflow of the pulmonary artery, which channeled the flow into a narrower and more regularly-shaped inflow. We therefore constructed two 3D geometries for the pulmonary artery of each patient: a *Healthy/Pre* one, considering the artery wall at the inflow, and a *Post* one considering instead the prosthetic stent.

3.3. Reconstruction of the arteries

Our zone of interest for the 3D geometries of the arteries consisted in: the main pulmonary trunk where the valve was placed, the first bifurcation and the two main branches (right and left). We proceeded by identifying from the medical images the valve stent in order for the domain's inflow to coincide with this zone. For the construction of the post-operative mesh, since the domain where the blood flowed when the valve leaflets were open was quite rounded, we decided to model the prosthetic stent as a cylinder using Paraview. We suitably set its size and position by employing the patients' medical images. During this operation we noticed that the stent of the valve of Patient 2 did not seem to be aligned to the arterial wall, contrary to that of Patient 1, but was slightly tilted toward the right branch. We finally constructed the two meshes (*Healthy/Pre* and *Post*) for both patients adopting anisotropic elements whose sizes varied according to the level of interest of the zone.

4. Mathematical and Numerical models

Numerical modeling of the cardiovascular system is a very challenging field. Indeed, the cardiovascular system is composed by an intricate network of blood vessels that makes its geometry very complex. Moreover, it is characterized by both a multiphysics and a multiscale nature [2]. In spite of these challenges, there are many cardiovascular models in literature, especially on the left side of the heart. In [2] the authors analyse the geometric multiscale approach for blood flow problems focusing both on the stand-alone problems (3D and 0D) and on their coupling (3D-0D). This work also describes the "defective problems" that arise because of the interface coupling of heterogeneous models and proposes different mathematical techniques to overcome them. In our model we considered blood as an incompressible, homogeneous and Newtonian fluid and adopted two separated models to simulate the blood flowing in the pulmonary artery and the one flowing in the rest of the cardiovascular system:

- For the 3D part of our model, which coincided with the pulmonary artery, we adopted a computational fluid dynamics (CFD) model based on the incompressible Navier-Stokes equations.
- Concerning the 0D part of the model, corresponding to the rest of the circulation, we considered an electrical analogy of the cardiovascular system [2] divided in multiple compartments. We referred to the blood flow rate as a current and to its pressure as a voltage and adopted circuit elements such as resistors (R), inductors (L), capacitors (C) and diodes to simulate the different behaviours of the circulatory system. In particular, an RLC circuit was placed both at the inlet and at the outlets of the 3D domain.

4.1. The 3D-0D geometric multiscale approach

The two adopted models (3D and 0D) needed to exchange information and appropriate boundary conditions had to be applied to both of them. We adopted a 3D-0D geometric multiscale model composed by the Navier-Stokes equations (1), the ODE system of the 0D model (6) and the corresponding set of interface coupling conditions (2)-(5). The unknowns of the problem were the blood velocity $\mathbf{u}$ and pressure p for the 3D model and the vectors $\mathbf{y}$ and $\mathbf{z}$ of the 0D flow rates, pressures and volumes of the different compartments of the 0D model.
The complete model takes the following form:
For each $t \in T$ find $\mathbf{u}$, p, $\mathbf{y}$ and $\mathbf{z}$ such that:

3D model

$$\begin{cases} \rho \dfrac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u} \cdot \boldsymbol{\nabla})\mathbf{u} + \boldsymbol{\nabla} p \\ \quad -\mu \boldsymbol{\nabla} \cdot (\boldsymbol{\nabla}\mathbf{u} + \boldsymbol{\nabla}\mathbf{u}^T) = \mathbf{0} \text{ in } \Omega, \\ \boldsymbol{\nabla} \cdot \mathbf{u} = \mathbf{0} \text{ in } \Omega, \\ \mathbf{u}(\mathbf{x}, t) = \mathbf{0} \text{ on } \Gamma_{WALL}, \\ \mathbf{u}(\mathbf{x}, 0) = \mathbf{0} \text{ in } \Omega; \end{cases} \tag{1}$$

Interface conditions

$$Q_{IN} = \int_{\Gamma_{IN}} \mathbf{u} \cdot \mathbf{n} \, d\gamma, \tag{2}$$

$$P_{IN} = -\frac{1}{|\Gamma_{IN}|} \int_{\Gamma_{IN}} T_F \mathbf{n} \cdot \mathbf{n} \, d\gamma, \tag{3}$$

$$Q_{OUT} = \sum_{j=1}^{2} \int_{\Gamma_{OUT,j}} \mathbf{u} \cdot \mathbf{n} \, d\gamma \tag{4}$$

$$P_{OUT} = -\frac{1}{|\Gamma_{OUT,j}|} \int_{\Gamma_{OUT,j}} T_F \mathbf{n} \cdot \mathbf{n} \, d\gamma, \tag{5}$$

with $j = 1, 2$;

0D model

$$\begin{cases} \frac{d}{dt}\mathbf{y}(t) = f_1(t, \mathbf{y}, \mathbf{z}, P_{IN}, Q_{OUT}), \\ \mathbf{y}(0) = y_0, \\ \mathbf{z} = f_2(t, \mathbf{y}). \end{cases} \tag{6}$$

The domain Ω represents the 3D geometry of the artery while the variable $\Gamma_W ALL$ is the artery wall. Q_{IN}, Q_{OUT}, P_{IN} and P_{OUT} are the scalar interface quantities of the two models at the 3D inlet boundaries Γ_{IN} and Γ_{OUT}.

4.2. The partitioned algorithm

In order to solve problem (1)-(6) in time we adopted a partitioned procedure based on the exchange of the interface conditions between the two models. In particular, we imposed at the inlet of the 3D model a Dirichlet boundary condition for the velocity by using the information on the 0D flow rate at the previous time step, while at the outlets, in an analogous way, a Neumann condition was considered. The two remaining conditions were instead prescribed as input for the 0D model.

Regarding the 3D model, in order to overcome the problem of the *defective boundary conditions* prescribed by the 0D model, we hypothesized: the absence of tangential strains on the artificial borders, a flat velocity profile at the inlet and a normal constant traction on each outlet.

At each iteration the 3D model is solved first, the interface conditions (3) and (4) are computed and passed to the 0D model, which is then solved too. The interface conditions computed from the 0D model (2) and (5) are then assigned to the 3D model at the following iteration. We underline the imposition of the same Neumann condition at the two outlets from the 0D quantity P_{OUT}.

4.3. Differentiating the 0D outlets

In order to analyse more closely the flow repartition at the pulmonary bifurcation and evaluate a possible limitation of our model, we introduced a new variant of the model described in section 4.2, in which the two 0D outlets, corresponding to the two pulmonary branches, were modeled by means of not one but two different RLC circuits. The purpose of this differentiation was to be able to assign different Neumann boundary conditions at the two outlets of the 3D domain by modifying the resistance values R of the outlet RLC circuits of the 0D model.

We performed, for each of the three scenarios of both patients, three different simulations:

- A simulation based on the model described in section 4.2, therefore applying the same Neumann boundary conditions at the two outlets: *Healthy*, *Pre* and *Post* simulations;
- A simulation based on the variant of the model in which the 0D outlets were differentiated in order to obtain the flow repartition predicted by Murray's law: *Healthy-Murray*, *Pre-Murray* and *Post-Murray* simulations. Murray's law estimates the repartition of the flow as a function of the diameters of the two branches that generate from the bifurcation;
- A simulation based on the variant of the model in which the 0D outlets have been differentiated in order to obtain the flow repartition predicted by the *Chnafa* law: *Healthy-Splitting*, *Pre-Splitting* and *Post-Splitting* simulations. This law was applied by [3] in a 2D study of the pulmonary artery flow of rTOF patients and it estimates a more equal repartition of the flow between the two outlets compared to the one obtained with the *Murray* approach.

4.4. Calibration procedure

To perform the simulations of both patients, we had to appropriately tune the 0D parameters of the model. We focused on the *Healthy* simulation of Patient 1, since we had at our disposal some specific clinical measures of this patient taken during a follow-up exam of the PVR operation. In particular, this exam contained the measures for the right ventricle end diastolic and end systolic volumes (respectively RVEDV, RVESV) and of the right ventricle ejection fraction (RVEF). Our goal was to obtain realistic results for all the compartments, according to both the specific clinical measures of Patient 1 and physiological values taken from medical literature regarding the right ventricle and the velocity and pressure of the flow in the pulmonary artery.

Concerning the 0D parameters, we mainly focused on the inlet and outlet RLC circuits, varying the values of R,L and C in order to obtain suitable flow rates and pressures ranges, and on the 0D the right ventricle parameters that regulated the ventricle volume variation during the heartbeat simulations. In Table 1 we present the results of the calibration procedure on the right ventricle measures. We tried to reproduce the values reported in the column Measures of the table and obtained, for all quantities, an error below 10 %. Comparing the clinical values with average values in healthy conditions, we noticed that Patient 1 had a low RVEDV and therefore a low RVEF.

Patient 1	Measures	Computations	Errors
RVEDV	110ml	112ml	1.8%
RVESV	58ml	54.58ml	5.9%
RVEF	47%	51.26%	9.1%

Table 1: Comparison between the RV clinical measures and the values obtained for Patient 1.

5. Numerical Results

To analyse the results of the simulations, we adopted the software *Paraview* for 3D visualizations in time and simulated multiple heartbeats. From our results, the pulmonary valve replacement operation seemed to restore the trend of the hemodynamics quantities making them closer to a healthier condition, in particular concerning the velocity. On the other hand, we have highlighted the importance of the valve position and artery geometry and this factor could be interesting to investigate from a medical point of view. These considerations can be deduced from Figure 1, which shows the trend of the velocity during the diastolic phase in the *Healthy* (left), *Pre* (center) and *Post* (right) simulations. At the top we can see a zoom of Patient 1's right branch, where a recirculation region is formed in all three cases. However, we can notice that the ricirculation is more predominant in the Pre simulation with respect to the other two. The bottom figures, instead, show a zoom of Patient 2's left branch. Once again, a recirculation region is present and more predominant in the *Pre* simulation with respect to the Healthy one, however, in this case, the swirl of the flow seems to be more and more evident if we look at the figures from left to right. A possible explanation for the presence of a greater recirculation region in the *Post* simulation is that it depends on the valve's position. Indeed, we had noticed from the CT scans of this patient that the prosthetic valve was not aligned to the artery wall and it is possible for the flow to be channeled into the right branch creating a swirl behind it and toward the left branch. Another important result of our simulations regards the fact that, for both patients, the velocity magnitude in the *Post* simulation was greater than in the other two simulations. This is noticeable in Figure 1 and can be considered as a positive result, since, according to the medical values of Patient 1, his flow rate was below the norm, due to the low RVEDV and RVEF. Regarding the *Pre* simulation, we would have expected a more significant backflow (or pulmonary regurgitation) due to the absence of the pulmonary valve. This phenomenon was significantly noticed only in the 0D quantities, where a clear indication for surgery was highlighted both by the entity of the backflow across the zone of the diode and by the pressure overload on the right ventricle.

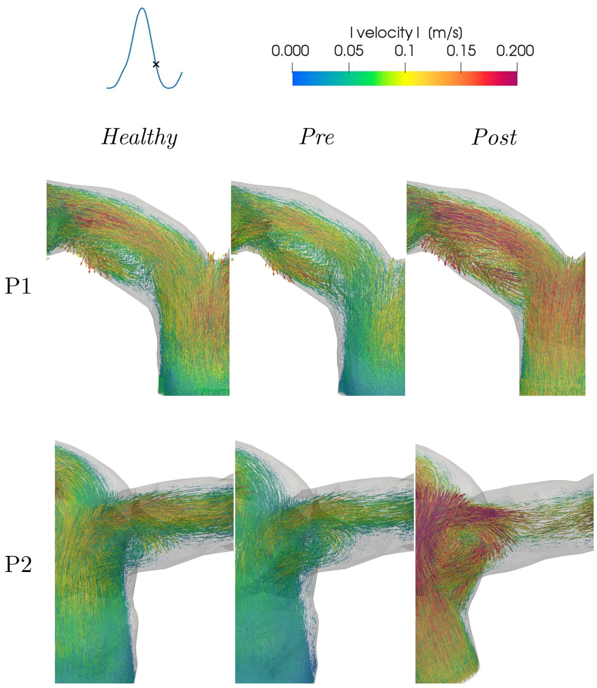

Figure 1: Velocity field during the diastolic phase in the *Healthy* (left), *Pre* (center) and *Post* (right) simulations. Top: Patient 1's right branch. Bottom: Patient 2's left branch.

Concerning the three -*Murray* and the three -*Splitting* simulations, we have found that, when analysing the whole heartbeat, it is important to impose the correct boundary conditions at the outlets. In Figure 2 we can see the three *Post* simulations of Patient 1. When the two outlet

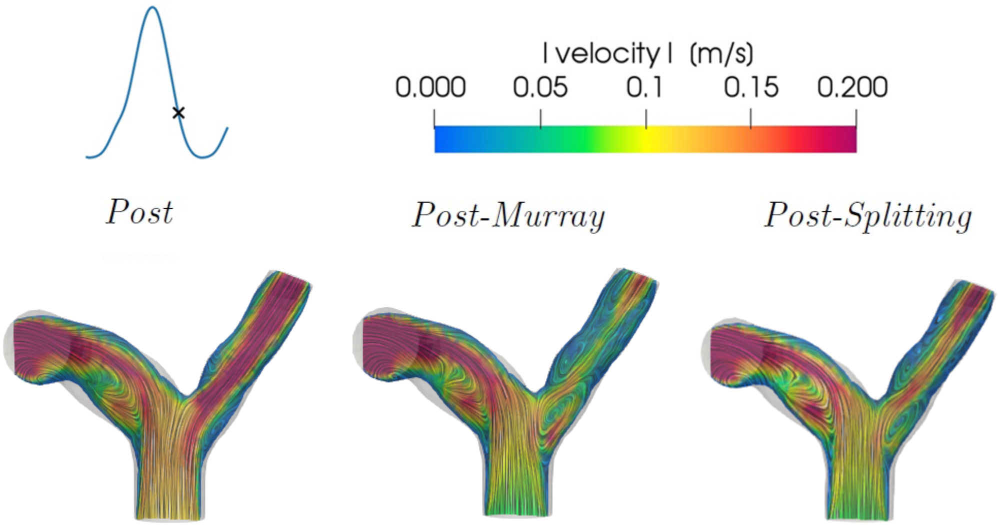

Figure 2: Velocity field during the diastolic phase in the three *Post* simulations of Patient 1.

boundary conditions are not differentiated (on the left), no significant recirculation is formed in the left branch. On the other hand, both the *Post-Murray* and the *Post-Splitting* simulations (on the right) present some recirculation regions, particularly in the *Post-Murray* case. This result was in agreement with the fact that the boundary conditions were more differentiated in the *Murray* simulation with respect to the *Splitting* one. From a medical point of view, the results on the formation of recirculation regions are interesting since an eventual transition to a turbolent regime may cause the onset of atherosclerotic lesions due to local stasis and jet-stream impingement upon the arterial wall.

We underline that the results obtained for Patient 2, though meaningful thanks to the geometry reconstruction from the patient's CT scans, are not as accurate as the ones for Patient 1 because of the missing medical information. On the other hand, we noticed a more unbalanced flow repartition for Patient 2 with respect to Patient 1 in all the corresponding simulations and this result demonstrated the importance of the geometric patient-specificity of the model.

Moreover, some medical indications for the correct flow repartition of the two patients would be useful to establish which one among the *Murray* and *Splitting* simulations is the best. Indeed, it is likely for the pressures inside the two branches to differ because of their different shapes and sizes.

In conclusion, since Tetralogy of Fallot is one of the most common cyanotic Congenital Heart Diseases and not many works have been performed on this subject to this day, we hope that our work will be seen as a starting point for future studies on patients with similar medical conditions.

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