Computational study on the influence of the location of the distal pressure measurement point in the Fractional Flow Reserve

Rafael Agujetas-Ortiz[1], Conrado Ferrera-Llera[1], Reyes González-Fernández[1], Juan Manuel Nogales-Asensio[1], and Ana Fernández-Tena[2]

[1]University of Extremadura
[2]Instituto Nacional de Silicosis

May 5, 2020

Abstract

Coronary stenosis is largely responsible of severe heart failure as they can stop the blood flow to the myocardial. The Fractional Flow Reserve (FFR) is the most usual functional assessment of the severity of the coronary stenosis. In most cases, its value dictates the clinical decision to set a stent to restore the flow. Therefore, a correct measurement of this variable is crucial. This information can be very important to prevent cardiologists from making the wrong clinical decisions. From the data taken from an anonymous patient who underwent Coronary Computed Tomographic Angiography and cardiac catheterization, a comparison was made with the results of a computational simulation of the model reconstructed from the angiography. The results of the Fractional Flow Reserve obtained by simulation (0.834) agree with those obtained experimentally (0.830), difference less than 0.8%, which indicates that with simulation it is possible to obtain results that would be very difficult to achieve experimentally. The actual invasive procedure to measure the Fractional Flow Reserve is being executed with a protocol that do not consider the influence of the location on the Pd value. The new procedure would avoid false results related to the point where the distal pressure is measured.

1 Introduction

The narrowing (commonly called stenosis) of blood vessels alter the regular flow of blood, being one of the most common places where these situations occur in the coronary arteries. When this situation occurs, not enough oxygen reaches the myocardium, leading to ischemic heart disease (stable or unstable angina pectoris, acute myocardial infarction). This disease is caused by sclerosis of the coronary arteries due to the formation of collagen and accumulation of lipids and inflammatory cells.

In 1996, (Pijls et al., 1996) determined that there is a direct relationship between blood pressure and flow with maximum vasodilation of the artery (conditions of hyperemia). They defined the Fractional Flow Reserve (FFR), currently used as the gold standard to assess the physiological severity of coronary stenosis, as:

$\mathrm{FFR} = \mathrm{Q_{ms}}/\mathrm{Q_{me}}$

being:

- $\mathrm{Q_{ms}}$: maximum achievable blood flow through a stenosis, conditions of hyperemia.
- $\mathrm{Q_{me}}$: maximum expected blood flow, without stenosis in the artery.

The flow rate is the ratio of the pressure difference to the flow resistance:

- $\mathrm{Q_{ms}}$ = (distal diastolic pressure - venous pressure)/maximum resistance vessel stenosis.
- $\mathrm{Q_{me}}$ = (aortic diastolic pressure - venous pressure)/maximum resistance vessel normal.

$$FFR = \frac{(P_d - P_v)/R_s}{(P_a - P_v)/R_n}$$

The venous pressure (P_v) is the same and the resistances (R_s, R_n) in hyperemia are minimal, so it has that Fractional Flow Reserve is the ratio between the pressures (average of the cardiac cycle) distal coronary (P_d) and proximal or aortic (P_a) with respect to the stenosis, in conditions of hyperemia:

$FFR = P_d/P_a$

This is an invasive test, needing to insert a catheter through the coronary stenosis. The standardized medical protocol (Coppel et al., 2019) suggests measuring the distal coronary pressure (P_d) 2-3 cm downstream of the stenosis. They determined that a cut-off value of 0.75 Fractional Flow Reserve could be correctly determined for patients with ischemia, with 93% accuracy. It is currently considered that, under normal flow conditions, the Fractional Flow Reserve value should be in a range between 0.8 and 1 (Toth et al., 2016). Myocardial ischemia is highly possible when this value is below 0.8. The disadvantage of this process is that it limits the region where the pressure is measured without taking into account the evolution of the pressure field downstream of the stenosis.

Since to obtain the distal and aortic pressures it is necessary to perform an invasive test, a possible substitute could be simulating the sanguineous flow in a virtual model using Computational Fluid Dynamics (CFD). This three-dimensional model can obtain from images (Min et al., 2011; Zhang et al., 2018; Owida et al., 2012) of a Coronary Computed Tomography Angiography (CCTA). To obtain clear images of the arteries that supply blood to the heart, an injection of contrast material with iodine is used. This process, known as Fractional Flow Reserve - Computed Tomography (FFR_{CT}), allows visualizing inside the flow all type of variables and, consequently, the distribution of Fractional Flow Reserve in the stenosed artery.

The main objective of this study is to deepen this Fractional Flow Reserve - Computed Tomography (FFR_{CT}) technique examining the influence of the location of the measurement point distal coronary pressure (P_d) in the FFR_{CT}value. For this purpose, a three-dimensional model was obtained from a Coronary Computed Tomography Angiography of an anonymous patient with coronary stenosis (68%) and simulated using Computational Fluid Dynamics. The results were validated with the data of distal and proximal pressures, acquired simultaneously to the same person.

2 Materials and Methods

As mentioned in the introduction, a Coronary Computer Tomography Angiography and a cardiac catheterization were performed in an anonymous patient with a stenosis of 68% in the right branch of the coronary artery.

Experimental tests

These tests were performed at the Cardiology Service, University Hospital of Badajoz (Spain) using an ACIST Navvus Rapid Exchange FFR MicroCatheter (ACIST), which utilizes fiber-optic based sensor technology instead of piezoresistive (electrical) sensor technology. The elliptically-shaped crossing profile of the catheter has a dimension of 0.51 mm × 0.64 mm, comparable to the diameter of a 0.56 mm circular-shaped wire, which has an insignificant effect on vessels of varying diameters. Before each test, the probes are calibrated to ensure that the results obtained are appropriate, with differences below 0.1%. During the tests, first of all, a bolus of isosorbide dinitrate (210 µg) is introduced inside the coronary, and after, maximal hyperemia is induced by intravenous infusion (140 µg/kg min). The catheter, with two pressure probes, is introduced through the brachial artery (arm) to reach the coronary artery, in the aorta. At that point, one of the pressure probes is set to control the aortic pressure (P_a). The catheter is then moved, crossing the stenosis, and the second probe is fixed 2 cm downstream of it to control the distal pressure (P_d). Once it is verified that the probes are giving values in the correct range, the pressures throughout several cardiac cycles are measured, being displayed in a monitor (Figure 1).

The data shown in the Figure are the instantaneous values of the aortic (P_a) and distal (P_d) pressures, together with their mean values and the Fractional Flow Reserve (FFR) value. The red and green fine oscillating lines correspond to instantaneous aortic and distal pressures, while the red and green thick lines correspond to the average values of said pressures. From these average values, the Fractional Flow Reserve is determined, which is the yellow thick line. The upper right of the figure shows the average values of the aortic (P_a, 75 mmHg [?] 99.99 hPa) and distal (P_d, 62 mmHg [?] 82.66 hPa) pressures and the corresponding Fractional Flow Reserve (FFR, 0.830), which coincide with the instantaneous values that are given in the time 0.17 s of a cardiac cycle of 0.96 s.

Numerical model

For the construction of the numerical model, it is necessary to treat the Coronary Computer Tomography Angiography images mentioned above. These images, which cover the coronary tree and the area of the ascending aorta, were exported to the DICOM format (Digital Image and Communication in Medicine) (Figure 2).

The available resolution of the DICOM images is 512 x 512 pixels, being 680 µm the size of each pixel, with a gray intensity value according to the scale of Hounsfield (Hounsfield, 1973). As it is known that there is a direct relationship between the density of each anatomical structure and the gray value assigned to each pixel in the image, the 3D Slicer software (3D Slicer, 2019) was used to group similar gray values, identifying the threshold between the different tissues. In this case, a pixel mask was defined in the region of interest with a threshold range of 190-250 to extract the coronary tree (Fedorov et al., 2012). From the created dynamic region (Figure 3), the 3D model is implemented and a design tool is used to prepare it for the numerical simulation. This tool optimizes the surface of the model by means of adjustment and smoothing processes. The deviation between the original geometry and the resulting model is not expected to significantly affect the results.

The normal boundary condition for performing the simulation is the volumetric flow at the inlet of the aorta, obtained from allometric approximations of the volume pumped by the heart. However, in this case, the aortic pressure (P_a) is known, so this variable can be imposed as an inlet boundary condition. Therefore, the 3D numerical model can be simplified, reducing it to the right coronary artery, where the stenosis is located, as can be seen in Figure 3. This simplification has the advantage that it will considerably reduce the number of cells in the numerical model and, therefore, the computational time.

The geometry was meshed using the code ANSYS version 18.2 (ANSYS, 2017). According to the conclusions shown in a study carried out by the authors themselves (Fernández-Tena et al., 2018), the three-dimensional geometry was made using virtual topology complemented by the patch-independent algorithm. The meshed has two parts, an unstructured portion inside the duct composed of tetrahedral cells (Figure 4), because they adapt better to complex geometries and require less calculation time, and a structured portion composed of eight inflation layers close to the wall, to correctly capture the flow behavior in the boundary layer. The y^+ values are kept below 0.5, which means that the centers of the cells next to the wall are inside the laminar sublayer.

The total number of cells was approximately 1.8×10^6, with a range of sizes between $2.83 \times 10^{-12} m^3$ and $2.39 \times 10^{-16} m^3$. An analysis of the quality of the mesh yielded a very satisfactory result, indicating a magnitude of the equisized skew that was below 0.6 for 99.99% of the cells in the mesh.

Another step was the realization of an analysis of dependence of the results against the size of the mesh, for which 3 additional coarser and finer grids of size 1.2×10^6, $2.4 \times 10^6$and 3.0×10^6 cells were built in order to check the change in predicted flow characteristics as a function of the number of cells. The simulations were carried out by imposing a constant flow rate at the coronary inlet, using as a variable of reference the static pressure drop between the inlet to the coronary artery and the farthest outlet, because this variable is the one that quantifies the resistance to flow on the way. It was observed that the results differed less than 2.2% (compared to the result of the finest mesh), except the coarsest mesh that differed in 5.2%. Therefore, the mesh is chosen with 1.8×10^6 cells, since the required calculation time is significantly shorter than those with the largest number of cells.

Once the 3D model has been constructed, the Fluent solver of the ANSYS code is used to solve the unsteady Reynolds-Averaged Navier-Stokes (URANS) equations, mass and momentum conservation laws, that describe a fluid in movement (Jana, 2015).

The solver was set to pressure-based and implicit with an absolute formulation for the velocity field. The discretization of the spatial and temporal derivatives in the equations was carried out by means of second-order schemes. The discretization of the pressure was a standard centred scheme. The SIMPLEC algorithm was used to solve the coupling between pressure and velocity fields.

Usually, these equations must be solved using turbulence models. The turbulence is defined as a phenomenon of intrinsic instability of the flow that causes its movement to become chaotic, appearing eddies. These eddies appear and disappear without a solution of continuity: the large eddies are divided into smaller ones, and so on. When the eddies become small enough, they dissipate due to their viscosity. Turbulence appears when the Reynolds number exceeds a certain value (between 400 and 2,000). In this case, the Reynolds number at the center of the stenosis is 1,554.

As the flow in the coronary is both laminar and turbulent, with transition zones, the turbulence model that best adapts to these conditions is the SST (Shear Stress Transport) k-omega (Menter et al., 2006; Versteeg & Malalasekera, 2007), which is a combination of the standard models k-epsilon and k-omega. The k-omega model is used for the flow close to the walls while the k-epsilon is used in the far field to the wall. More details of this type of simulation can be found in (Kheyfets et al., 2015).

The working fluid was blood with a constant density of 1,060 kg/m^3 and a dynamic viscosity (18) of:

$$\mu = \mu_\infty \left\{ 1 + 15.2\omega \left[1 + (\lambda\dot{\gamma})^2 \right]^{(n-1)/2} \right\}$$

where μ_∞ (3.5x10^{-3} Pa s) is the Newtonian viscosity, λ (3.31) and n (0.357) are constants obtained from experimental data, ω quantifies the blood non-Newtonian character, corresponding the values 0 and 1 to the Newtonian and Carreau model, respectively.

In any simulation, the choice of boundary conditions is critical. In the case of arterial flow, these conditions are unsteady, having a pulsatile flow. As discussed in the experimental values section, the pressure at the inlet (P_a) is known (Figure 1). As outlet boundary conditions, the results of a vascular resistance model using allometric laws were taken (the output diameters are proportional to the flow resistance). The inlet boundary condition is the pressure during a cardiac cycle (Figure 5). To reproduce this temporal variation of pressure, a user-defined function (UDF) was designed. As it is a transient simulation, it is necessary to choose the appropriate time step, which will depend on the number of Courant-Friedrichs-Levy (CFL), which is the ratio between the time interval and the residence time in a finite volume:

CFL = Δt/(Δx/v) = vΔt/Δx

with a range of 0.1-10, being v the average velocity of the flow in the cell, Δt the time step and Δx the size of the cell.

Since in this case the most relevant variable is aortic pressure instead of time, a uniform step will be used in the dependent variable aortic pressure rather than a uniform step in the independent variable time. This procedure, designed, developed and tested by the authors themselves (Agujetas, 2018; Fernández-Tena, 2014; Fernández-Tena et al., 2017), uses a constant pressure increase, being determined the corresponding time increase. An algorithm, that is incorporated into the program by means of an UDF, determines the appropriate constant aortic pressure variation and calculates the corresponding variable time steps. For example, if with a constant time step of 0.005 s for a cardiac cycle of 0.97 s, 194 steps are necessary, following the described procedure, with a pressure range between 54 and 102 mm in the cardiac cycle, if pressure increments of 1 mm are taken, 96 steps will be required, 50% less. The advantage of this method is that the whole range of the aortic pressure dependent variable will be covered with absolute fidelity, gaining convergence security and computational time.

To verify that the solution converges properly, the pressure difference variable between the inlet and the outlet is controlled, which reaches an almost stationary regime after four cardiac cycles (384 steps), spending a computational time around 22 h on a 1900X RCE 1900X AMD Ryzen Thread 3.80 GHz computer.

3 Results

To compare with the experimental results, it had been said that the mean values of aortic and distal pressures, as well as the Fractional Flow Reserve, coincided with the instantaneous values obtained in time 0.17 s of the cardiac cycle of 0.97 s. Figure 6 shows the pressure distributions along the right coronary artery for the time 0.17 s of the last cardiac cycle. The left part shows the complete coronary artery with the points at which the pressures are measured. The right part shows only the section of the coronary where the pressures are measured, with an enlarged scale to be able to observe more clearly how the pressure decreases as the distance increases downstream the area with stenosis. The average numerical values of the aortic (P_a) and distal (P_d) pressures are 75 mmHg (99.99 hPa) and 62.55 mmHg (83.39 hPa) at the suggested point (P_{d1}) according to the medical protocol (2), 2 cm downstream of the stenosis.

Once it has been verified that the numerical model works right, following the objective of this work, the static pressure is also measured downstream of the previous point. Figure 6 shows how the static pressure is decreasing along the coronary artery, downstream of the stenosis. The measured values at 3 cm (P_{d2}) and 4 cm (P_{d3}) downstream of the stenosis, located at 1 cm and 2 cm from the P_{d1}, are 60.90 mmHg (81.19 hPa) and 58.28 mmHg (77.70 hPa) respectively.

The numerically obtained Fractional Flow Reserve is known as Fractional Flow Reserve - Computed Tomography (FFR_{CT}). If the static pressure decreases downstream of the stenosis, the Fractional Flow Reserve will also decrease. Figure 7 shows the contours of the FFR_{CT} results along the right coronary artery. The FFR_{CT} value at the point P_{d1} is 0.834, with a good agreement with the experimental value FFR 0.830. The FFR_{CT} values in the point P_{d2} and P_{d3} are 0.812 and 0.777 respectively.

4 Discussion

It has been seen how the FFR can be determined in a non-intrusive way through the Computed Fluid Dynamics, simulating the flow in the reconstructed coronary artery from Computed Tomography images. It has also been verified that the current invasive procedure to measure the FFR is being executed with a protocol that do not consider the influence of the location on the P_d value. In the case under discussion, if the protocol is followed, an erroneous clinical decision would be made. As has been shown in Figure 6, the location of the pressure probe must be taken into account. As the types and severities of the stenosis are quite different between different individuals, the pressure field distribution is variable. So, a variation is proposed in the current measurement procedure for the invasive FFR, which consists of moving the pressure probe downstream of the stenosis to take more distal pressure values until it is verified that these pressures values are independent of the position of the probe. Also, this procedure should include a verification process to check that there are no pressure fluctuations downstream of the stenosis. This new procedure would avoid false results related to the point where the distal pressure is measured. In this work, P_{d1} and P_{d2}values could lead to different clinical decisions with respect to the P_{d3} value.

5 Conclusions

Coronary stenosis is largely responsible of severe heart failure as they can stop the blood flow to the myocardial. The Fractional Flow Reserve (FFR), the ratio of the mean distal coronary pressure (P_d) to mean aortic pressure (P_a), is the most usual functional assessment of the severity of the coronary stenosis. The results of the Fractional Flow Reserve obtained by simulation (FFR_{CT}) agree with those obtained experimentally (FFR), difference less than 0.8%. Therefore, the advantage of computer simulation methods is the access to non-invasive testing with results that would be very difficult to achieve by invasive experimental testing. The actual invasive procedure to measure the Fractional Flow Reserve is being executed with a protocol that do not consider the influence of the location on the P_d value. The new procedure would avoid false results related to the point where the distal pressure is measured.

Acknowledgements

Authors acknowledge that this work was partially funded by Junta de Extremadura through Grant IB16119 (partially financed by FEDER) and by the Spanish Ministry of Economy, Industry and Competitiveness—Instituto de Salud Carlos III under Project "Estudio de la influencia de la geometría de las vías respiratorias en las patologías pulmonares obstructivas (PI17/01639)".

References

3D Slicer V4.11.0 (2019). https://www.slicer.org

ACIST, http://acist.com/international/products/acist-rxi-rapid-exchange-ffr-system/acist-navvus-rapid-exchange-ffr-microcatheter/

Agujetas, R., González-Fernández, M. R., Nogales-Asensio, J. M., & Montanero, J. M. (2018). Numerical analysis of the pressure drop across highly eccentric coronary stenoses: application to the calculation of the fractional flow reserve. *Biomedical engineering online* , 17(1), 67. DOI: 10.1186/s12938-018-0503-7.

ANSYS Version 18.2. ©ANSYS Inc; 2017.

Coppel, R., Lagache, M., Finet, G., Rioufol, G., Gómez, A., Dérimay, F., ... & Ohayon, J. (2019). Influence of Collaterals on True FFR Prediction for a Left Main Stenosis with Concomitant Lesions: An In Vitro Study. *Annals of biomedical engineering* , 1-13. DOI: 10.1007/s10439-019-02235-y.

Fedorov, A., Beichel, R., Kalpathy-Cramer, J., Finet, J., Fillion-Robin, J. C., Pujol, S., ... & Buatti, J. (2012). 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magnetic resonance imaging* , 30(9), 1323-1341. DOI: 10.1016/j.mri.2012.05.001.

Fernández-Tena A (2014) Clinical applications of fluid dynamics models in respiratory disease. Ph.D. thesis, University of Oviedo, Spain. http://digibuo.uniovi.es/dspace/handle/10651/29057

Fernández-Tena, A., Marcos, A. C., Martínez, C., & Keith Walters, D. (2017). A new adaptive time step method for unsteady flow simulations in a human lung. *Computer methods in biomechanics and biomedical engineering* , 20(8), 915-917. DOI: 10.1080/10255842.2017.1314469.

Fernández-Tena, A., Marcos, A. C., Agujetas, R., & Ferrera, C. (2018). Simulation of the human airways using virtual topology tools and meshing optimization. *Biomechanics and modeling in mechanobiology* , 17(2), 465-477. DOI: 10.1007/s10237-017-0972-9.

Hounsfield, G. N. (1973). Computerized transverse axial scanning (tomography): Part 1. Description of system. *The British journal of radiology* , 46(552), 1016-1022. DOI: 10.1259/0007-1285-46-552-1016

Janna, W. S. (2015). *Introduction to fluid mechanics* . CRC press.

Kheyfets, V. O., Rios, L., Smith, T., Schroeder, T., Mueller, J., Murali, S., ... & Finol, E. A. (2015). Patient-specific computational modeling of blood flow in the pulmonary arterial circulation. *Computer methods and programs in biomedicine* , 120(2), 88-101. DOI: 10.1016/j.cmpb.2015.04.005.

Menter F, Langtry R, Völker S (2006) Transition modelling for general purpose CFD codes. *Flow, turbulence and combustion* 77:277–303. DOI: 10.1007/s10494-006-9047-1

Min, J. K., Berman, D. S., Budoff, M. J., Jaffer, F. A., Leipsic, J., Leon, M. B., ... & Shaw, L. J. (2011). Rationale and design of the DeFACTO (determination of fractional flow reserve by anatomic computed tomographic AngiOgraphy) study. *Journal of cardiovascular computed tomography* , 5(5), 301-309. DOI: 10.1016/j.jcct.2011.08.003.

Owida, A. A., Do, H., & Morsi, Y. S. (2012). Numerical analysis of coronary artery bypass grafts: An over view. *Computer methods and programs in biomedicine* , 108(2), 689-705. DOI: 10.1016/j.cmpb.2011.12.005.

Pijls, N. H., De Bruyne, B., Peels, K., Van Der Voort, P. H., Bonnier, H. J., Bartunek, J., & Koolen, J. J. (1996). Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *New England Journal of Medicine* , 334(26), 1703-1708. DOI: 10.1056/NEJM199606273342604

Toth, G. G., Johnson, N. P., Jeremias, A., Pellicano, M., Vranckx, P., Fearon, W. F., . . . & De Bruyne, B. (2016). Standardization of fractional flow reserve measurements. *Journal of the American College of Cardiology* , 68(7), 742-753. DOI: 10.1016/j.jacc.2016.05.067.

Versteeg, H. K., & Malalasekera, W. (2007). *An introduction to computational fluid dynamics: the finite volume method* . Pearson education.

Wilcox, D. C. (1998). *Turbulence modeling for CFD* (Vol. 2, pp. 172-180). La Canada, CA: DCW industries.

Zhang, J. M., Shuang, D., Baskaran, L., Wu, W., Teo, S. K., Huang, W., . . . & Ismail, N. B. (2018). Advanced analyses of computed tomography coronary angiography can help discriminate ischemic lesions. *International journal of cardiology* , 267, 208-214. DOI: 10.1016/j.ijcard.2018.04.020.

Figure legends

Figure 1. Aortic and distal pressure throughout several cardiac cycles. Cardiology Service, University Hospital of Badajoz.

Figure 2. DICOM images: axial (left), coronal (center) and sagittal (right).

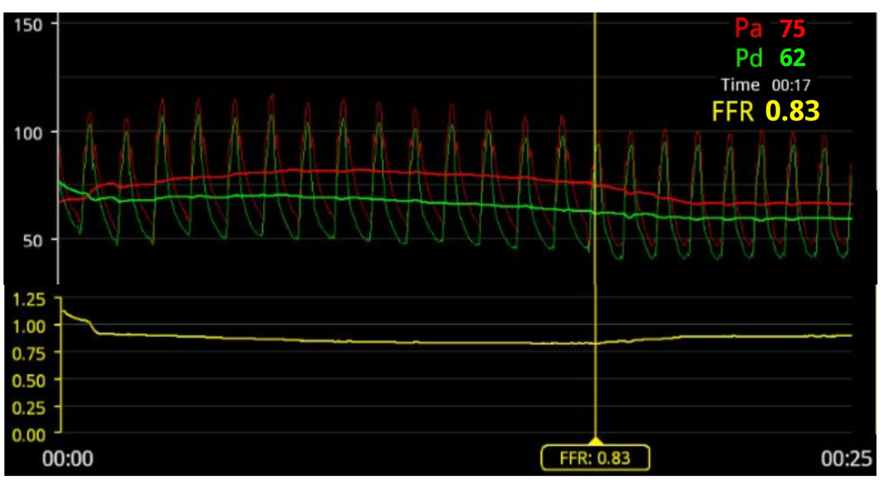
Figure 3. Coronary tree and the ascending aorta area.

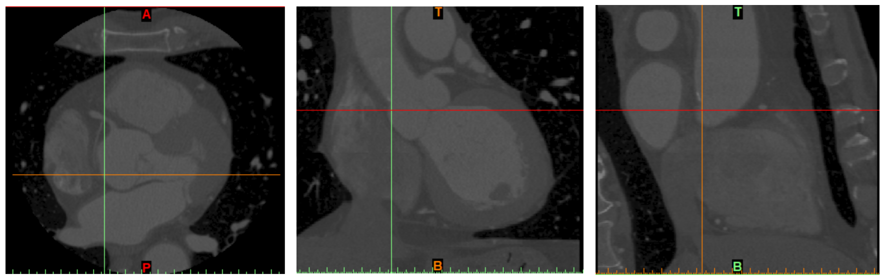
Figure 4. Surface meshes at some zones; it can be observed its tetrahedral shape.

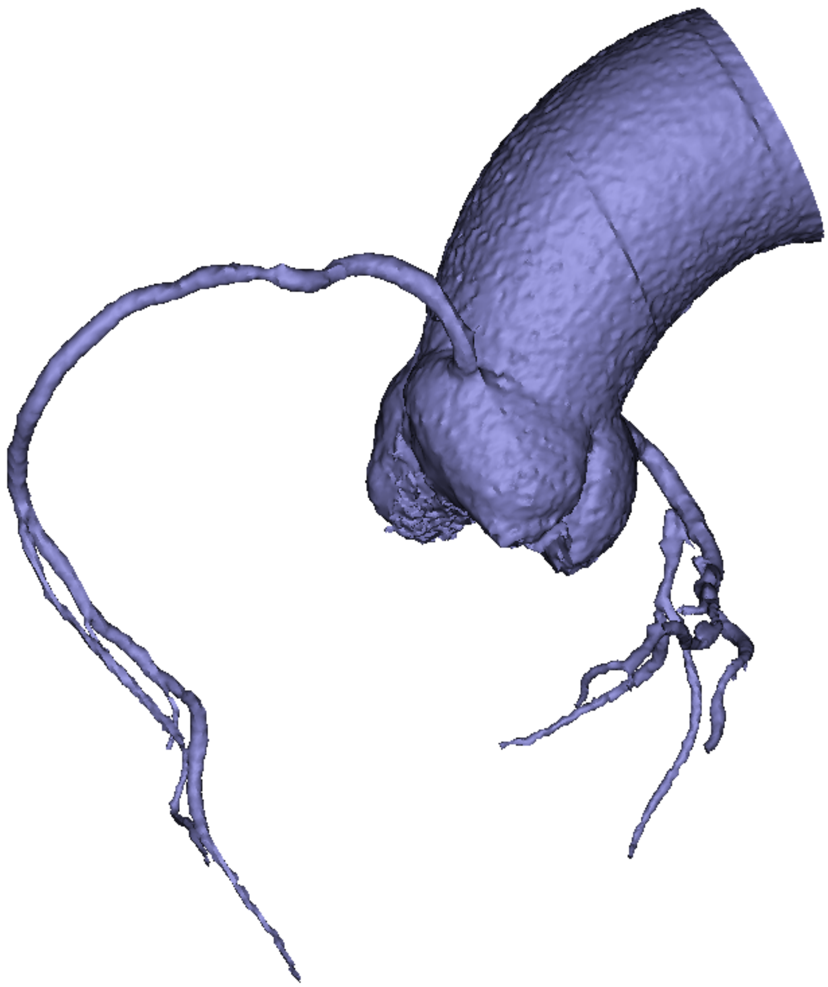
Figure 5. A detailed of the experimental aortic pressure, used as inlet boundary condition.

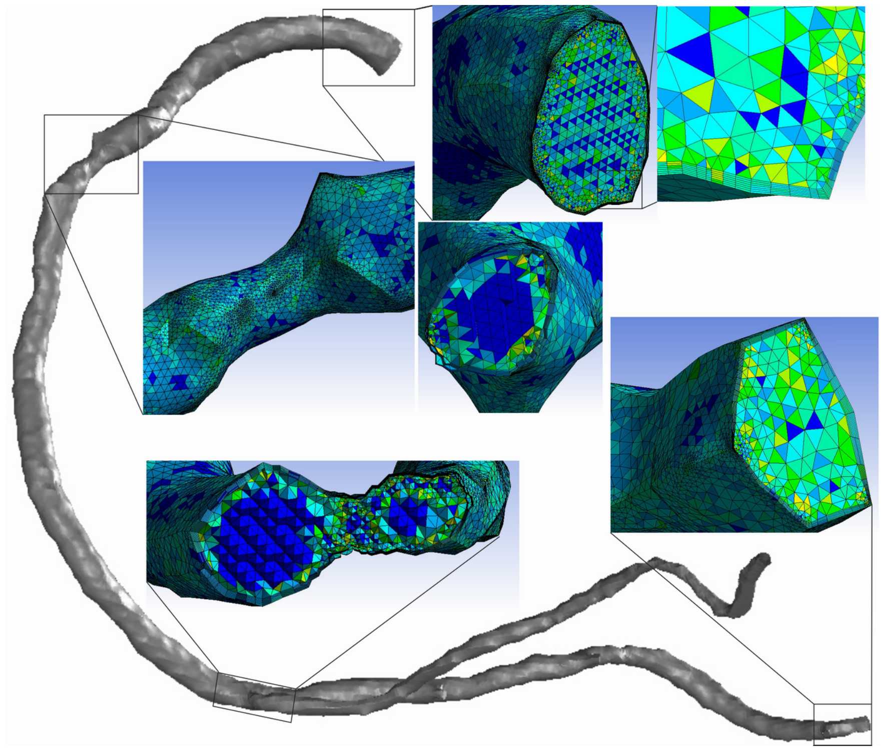
Figure 6. Contours of static pressure, showing the distal acquisition points (P_{d1}, P_{d2} and P_{d3}) at 2, 3 and 4 cm downstream of the stenosis.

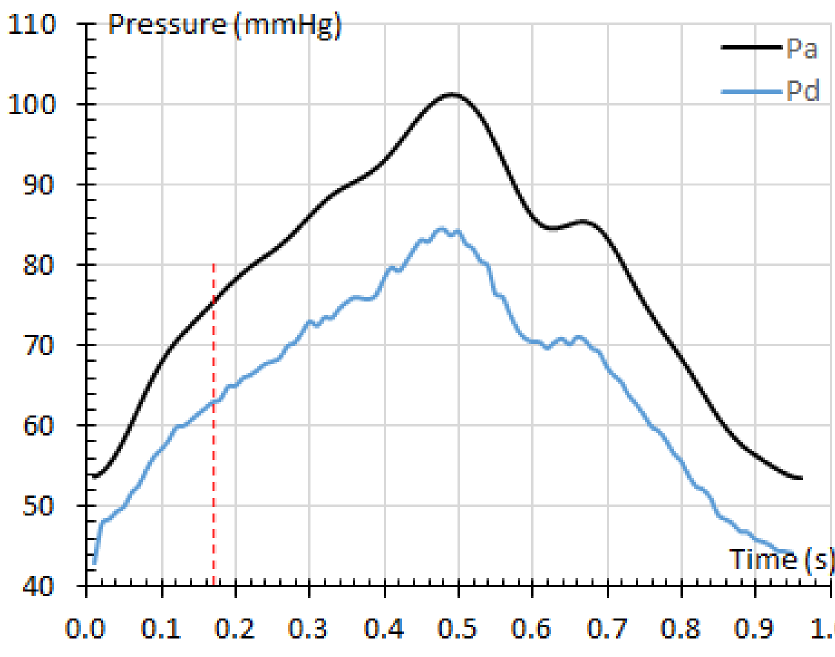
Figure 7. Contours of FFR_{CT}.

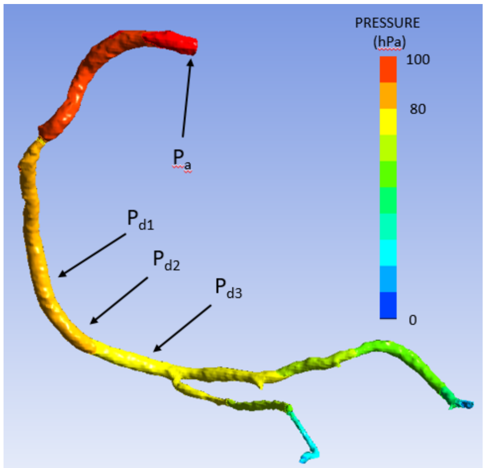


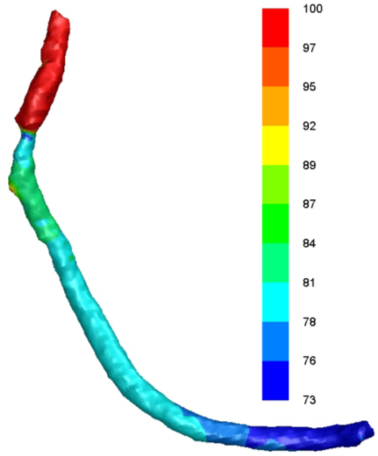

A
P
T
B
T
B

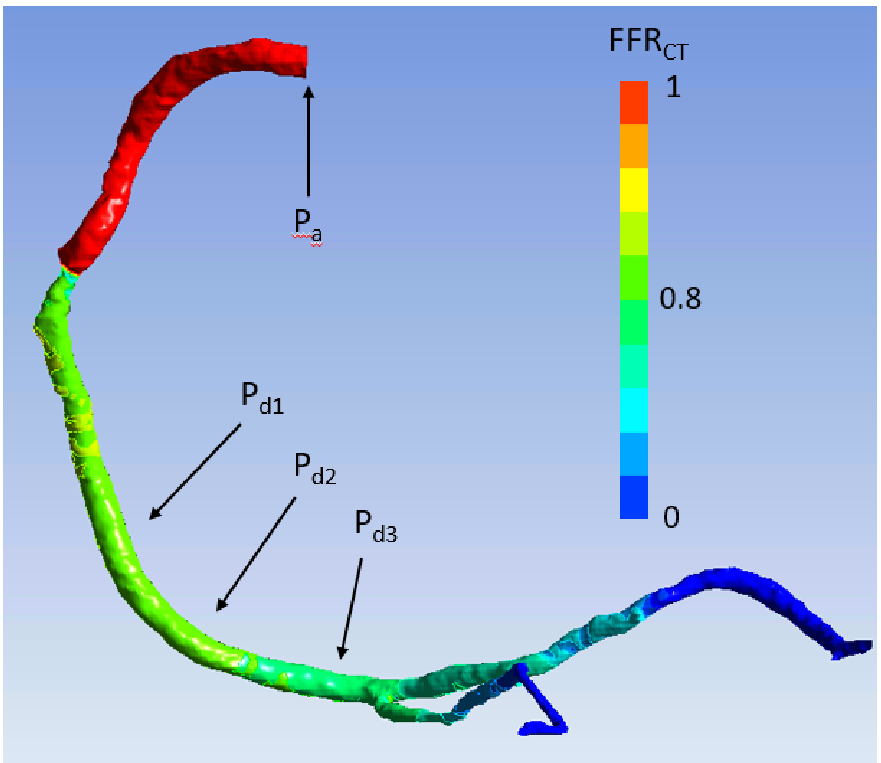





Pressure (mmHg)
110
100
90
80
70
60
50
40
Pa
Pd
Time (s)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0


PRESSURE
(hPa)
100
80
0
P_a
P_d1
P_d2
P_d3


100
97
95
92
89
87
84
81
78
76
73


FFR_CT
1
0.8
0
P_a
P_d1
P_d2
P_d3