Influence of the position of the distal pressure measurement point on the Fractional Flow Reserve using in-silico simulations

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Abstract

Coronary stenosis is largely responsible of severe heart failure as they can stop the blood flow to the myocardial. The Fractional Flow Reserve, the ratio of the mean distal coronary pressure to mean aortic pressure, 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. The objective of this work is to evaluate how the Fractional Flow Reserve value is altered depending on the point where the distal pressure is measured. This information can be very important to prevent cardiologists from making the wrong clinical decisions.

From the data taken from anonymous patients 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 more results can be obtained than experimentally would be impossible to achieve.

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 distal pressure value. The new procedure would avoid false results related to the point where the distal pressure is measured.

1 Introduction

The first cause of death in the world is the coronary disease. A recent report shows an alarming number of more than 16 million Americans over 20 years old are affected by this illness [1]. An elevated level of cholesterol and apolipoprotein B increase the risk of developing atherosclerosis and cardiovascular events [2]. The accumulation lipoproteins inside the artery wall leads to a series of events that conclude in an atheromatous plaque formation. The plaque presence reduces the vessel lumen. This particular case of lumen narrowing is called stenosis. A coronary stenosis modifies not only the type of blood flow but also its amount. This is important because coronary flow irrigates the myocardium and an important reduction could lead to an ischemic heart disease.

Of the two existing procedures to evaluate coronary stenosis, the traditional anatomical one is becoming obsolete compared to the functional one [3]. The anatomic lies on a visual inspection of the lumen narrowing in images from an angiography. Nevertheless, its assessment may lead to false positives of ischemia [4, 5]. The alternative is a hemodynamic or functional assessment. Among the different techniques, the FFR measurement is the most widely accepted [6]. FFR was defined as the ratio between the maximum blood flow through a stenosis in hyperemia conditions and the same value in the ideal case of a healthy artery [7]. As it is impossible to know the flow rate in the original geometry of a vessel when it already has a stenosis, a different procedure is followed. This procedure is a catheterization to measure the pressure in two points distal and proximal to the stenosis. Then, FFR is defined as the
minimum value of the ratio $P_d/P_a$ in several cardiac cycles, being $P_d$ and $P_a$ the mean values over a cardiac cycle as defined in [8]. The FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) [9] and FAME II [10] trials have proved that, in critical lesions (FFR < 0.80), a substantial reduction in urgent revascularizations is achieved performing FFR-guided PCI plus the best medical therapy in contrast to applying only the best medical therapy. Although these studies have proved the validity of this technique, it is applied in a very reduced percentage of patients [11]. A recent study over 60,000 ICA cases has reported a tiny 6.1% of cases where the invasive FFR was employed [6]. Several reasons such as the use of adenosine, the need of an experienced interventionist, the economic costs and the risk of an invasive intervention have encouraged the shift to a non-invasive alternative [11].

The use of in-silico simulations combining medical imaging (e.g. CCTA), digital image processing and computational fluid dynamics (CFD) has been proposed as a non-invasive alternative to calculate hemodynamical parameters in coronaries [12]. The early years of the 2010 decade brought the calculation of non-invasive FFR values [13–15]. Since then, several techniques have been introduced to perform this task: rotational angiography plus zero order Windkessel boundary conditions [16], 3D-QCA [17], 3D-QCA plus the TIMI frame [18], allometric laws combined with estimates of coronary microvascular resistance [19], lumped parameter models [20, 21], and machine learning algorithms [22, 23]. The result is a non-invasive FFR named in different ways (FFR$_{angio}$, FFR$_{CFD}$, FFR$_{ML}$, FFR$_{CT}$, etc.). As these techniques continue developing, several trials have been employed to compare the non-invasive FFR$_{CT}$ against CTA taking invasive FFR as the standard [24–26]. The performance of the FFR$_{CT}$ is superior to that of the CTA [6], and according to the PLATFORM trial, has resulted in a drastic reduction of the scheduled ICA procedures and their associated costs [6, 27]. The future seems bright for these technologies. The computation time is reducing continuously from days to several hours, using the complete transient simulation, and to a few minutes if the CFD analysis is reduced [27]. A company has commercially offered these calculations and several institutions declare safe this technology [6]. There are new techniques emerging such as MPI to calculate the MBF and its authors claim to obtain better results in flow limiting stenoses [29]. Nevertheless, all these models estimate the FFR value with an accuracy that ranges from ± 0.15 to ± 0.10 in the best scenario and several authors point that a calculation will never match invasive FFR [28].

So, there is a fundamental question: what does it happen if a FFR$_{CT}$ value of 0.75–0.85 is obtained? In those cases, invasive FFR remains as the gold standard as the pressure wires limit the error to a ± 0.03 (PressureWire® Aeris manual [30]). There are several references which argue about the location where the distal pressure should be measured. Toth et al. [31] suggested the measurement 2–3 cm downstream the stenosis, Ihdayhid et al. [32] and Matsumura et al. [33] proposed to measure as distal as possible and, just a short time ago, Renard et al. [34] found that the distance suggested by [31] reduce measurement errors.

As there is a growing debate about the distance at which the sensor should be placed, this paper uses the FFR$_{CT}$ to examine the issue of the location. As FFR$_{CT}$ provides computed values along the affected
coronary, the variation of this parameter in space from the lesion will be checked. The 3D coronary tree of an anonymous patient will be reconstructed from CCTA images. The CFD will be used to simulate the coronary stenosis performing a transient simulation with a constant increase of pressure at the inlet of the model. Rather than using a constant time, a constant increase of pressure makes it possible to run the boundary condition function with absolute fidelity. The results will be validated with invasive data acquired to this patient. Then the analysis will be extended to three more cases.

2 Methods

As mentioned in the introduction, a CCTA and a cardiac catheterization were performed in four anonymous patients, having the first patient a stenosis grade of 68% in the right branch of the coronary artery.

In vivo measurements

These tests were performed at the Cardiology Service of University Hospital using an ACIST Navvus Rapid Exchange FFR MicroCatheter [35]. This catheter 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. These dimensions are comparable to the circular-shaped wire diameter (0.56 mm). The wire effect on vessels whose diameter changes is negligible. Before each test, the probes were calibrated to ensure that the results obtained were reproducible with differences below 0.1%. During the tests, first of all, intracoronary nitroglycerin (200 µg) was introduced inside the coronary. Then maximal hyperemia was induced by introducing a bolus of adenosine (240 µg/kg min). The guide catheter was introduced through the radial artery to reach the right coronary artery and to measure the $P_a$. The microcatheter was then moved, crossing the stenosis, and its position was fixed 2 cm downstream of it to control the $P_d$. Once it was verified that both pressures were in the correct range, their values were recorded throughout several cardiac cycles, being displayed in a monitor (Fig. 1). These values correspond to the first patient.

This figure shows the instantaneous values of the $P_a$ and $P_d$, together with their mean values and the 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. The yellow thick line corresponds to the FFR. The upper right of the figure shows the average values of the $P_a$ (75 mmHg $\equiv$ 99.99 hPa) and $P_d$ (62 mmHg $\equiv$ 82.66 hPa) and the 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.

In silico simulation

The construction of the numerical model begins with the 3D geometry reconstruction. A set of images taken from the CCTA were exported to the DICOM format. The region exported covers the coronary tree and the area of the ascending aorta (Fig. 2).
The available resolution of the DICOM images is 512 x 512 pixels, being 640 µm the pixel size. Each pixel has a gray intensity value according to the scale of Hounsfield [36]. As it is known, 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 [37], 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 HU to extract the coronary tree [38]. A 3D model was implemented from the created dynamic region (Fig. 3) and a design tool was employed to adapt it for the numerical simulation. Slight adjustments and a smooth process were performed using this tool. We expected a negligible effect in the calculations as a result of the tiny deviation between the original geometry and the resulting model.

Before the geometry was set, we did an additional simplification. In these problems it is usual to take the volumetric flow at the inlet of the aorta. This flow is obtained from allometric approximations of the volume pumped by the heart [39]. However, in our first patient, the P\textsubscript{a} is known, so this variable can be imposed as an inlet boundary condition. Therefore, the 3D numerical model can be simplified, reducing the analysis to the right coronary artery, where the stenosis is located (Fig. 3). This simplification will considerably reduce the number of cells in the numerical model and, therefore, the computational time. The same simplification will be applied to the remaining patients but in those cases, we will take into account the brachial pressure.

The imported geometry was meshed using the code ANSYS version 18.2 [40]. According to the conclusions shown in [41], the combination of virtual topology and the patch-independent algorithm was employed. The mesh has two parts, an inner unstructured portion and an outer one. Tetrahedral cells (Fig. 4) covered the inner part of the duct because they adapt better to complex geometries and require less calculation time. The structured portion, composed of eight inflation layers close to the wall, is necessary to correctly capture the flow behavior in the boundary layer. The $y^+$ values were 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 $1.8 \times 10^6$, with a size range 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. A 99.99% of the cells in the mesh had an equisized skew value under 0.6.

The dependence of the results against the size of the mesh was also analyzed. Three additional grids (one coarser, $1.2 \times 10^6$ cells and two finer grids, $2.4 \times 10^6$ and $3.0 \times 10^6$ cells) were built to check the change in the predicted flow characteristics with the cell number. The simulations were carried out by imposing a constant flow rate at the coronary inlet. The static pressure drop between the inlet to the coronary artery and the farthest outlet was employed as a reference variable. This variable quantifies the resistance to flow on the way. The obtained results differed less than 2.2% against the finest mesh. A 5.2% difference was found if the coarsest mesh is taken into account. Therefore, the chosen mesh was the one with $1.8 \times 10^6$ cells, since the required calculation time is significantly shorter than those with a larger number of cells. The URANS equations, mass and momentum conservation laws, that describe a fluid in
movement [42] were solved with the Fluent solver of the ANSYS code. 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 SIMPLE algorithm was used to solve the coupling between pressure and velocity fields.

On the other hand, 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). We conducted simulations in four patients. The patient, whose in-vivo measurements were used to validate the simulation, has a Reynolds number value of 1,554. The remaining patients have 5,300, 1,200 and 1,820 respectively. The flow is both laminar and turbulent with transition zones in the coronary arteries we are studying. The turbulence model that best adapts to these conditions is the SST k-omega [43, 44], 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 [45]. The working fluid was blood with a constant density of 1,060 kg/m³ and a dynamic viscosity of:

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

where $\mu_\infty$ ($3.5 \times 10^{-3}$ Pa s) is the Newtonian viscosity, $\lambda$ (3.31) and $n$ (0.357) are constants obtained from experimental data and $\omega$ quantifies the blood non-Newtonian character (0 and 1 to the Newtonian and Carreau models, respectively). Finally, one of the most critical parts in any simulation is the choice of boundary conditions. Concerning the inlet, the pressure value is known (Fig. 1) as stated in Sect. 2. Moreover, a vascular resistance model using allometric laws was employed (the output diameters are proportional to the flow resistance) to calculate the outlet boundary conditions. Additionally, we have to take into account that the flow is a pulsatile one, so our inlet boundary condition is the pressure value during a cardiac cycle (Fig. 5). To reproduce this temporal variation of pressure, a UDF was designed. We needed to choose an appropriate time step. It depends on the number of CFL, which is the ratio between the time interval and the residence time in a finite volume:

$$\text{CFL} = \Delta t / (\Delta x / v) = v \Delta t / \Delta x$$

with a range of 0.1–10, being $v$ the average velocity of the flow in the cell, $\Delta t$ the time step and $\Delta x$ 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 [8,46,47] 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 0.5 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. This time can be reduced to 2h in a more powerful computing machine.

3 Results

According to the in-vivo measurements, the mean values of the aortic and distal pressures, as well as the Fractional Flow Reserve, matched the instantaneous values at the instant 0.17 s of the cardiac cycle of 0.97s.

Figure 6 shows the pressure distributions along the right coronary artery for the time 0.17 s of the last cardiac cycle computed. The left part shows the full coronary artery with the points at which the pressures are calculated. The right part shows a detail of the section where those pressures are calculated. An enlarged scale shows clearly how the pressure decreases as the distance increases downstream the stenosis. The average numerical values of the $P_a$ and $P_d$ 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 cm, downstream of the stenosis [31]. These values match with the experimental measurements. Once it has been verified that the numerical model works right, following the objective of this work, the static pressure is also analyzed in different locations downstream of the previous point. We remember that several references debate about the location of the invasive pressure sensor. While Toth et al. [31] and Renard et al. [34] suggest 2–3 cm downstream the stenosis, Ihdayhid et al. [32] and Matsumura et al. [33] propose to measure as distal as possible. Figure 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. As the static pressure is decreasing downstream, so is the computed $\text{FFR}_{\text{CT}}$.

Figure 7.a-b shows the flow streamlines and the values of the $\text{FFR}_{\text{CT}}$ along the right coronary artery. The $\text{FFR}_{\text{CT}}$ value at the point $P_{d1}$ is 0.834, with a good agreement with the experimental value FFR 0.830. The $\text{FFR}_{\text{CT}}$ values in the point $P_{d2}$ and $P_{d3}$ are 0.812 and 0.777 respectively. The flow is clearly turbulent.
downstream of the stenosis. It increases its velocity, which causes its pressure drop suddenly, and consequently the FFR\textsubscript{CT} value. The Fig. 7.c shows how the vortexes disappear downstream with slight crossings between streamlines. In that section, the flow is reorganizing itself and the pressure is increasing, and consequently the FFR\textsubscript{CT}. Starting from this region, the flow is relaminarized and the value of the pressure, and the FFR, decreases linearly. This situation will remain until a new geometrical alteration is reached (e.g. a new stenosis or a bifurcation).

Additional calculations were done for three more patients. Figures of the patients 2, 3 and 4 are shown in 8, 9 and 10 respectively. Concerning the dependence of the FFR value with the distance downstream of the stenosis, Figs. 7 and 10 present a similar behavior. The FFR value drops drastically, then recovers (a second drop can appear while the flow is stabilizing) and finally decrease linearly. Contrarily, Figs. 8 and 9 do not show this drastic drop. The reason can be found in the figures representing the streamlines. Patients 1 and 4 streamlines show a clear turbulent flow appearing as a consequence of the stenoses. In the remaining patients, the flow is not so altered. Patient 2 shows more disturbances before the stenosis than patient 3 but these disturbances are not reinforced after the stenosis. In patient 2 case, the streamlines are not relaminarized quickly after the stenosis due to the presence of a ramification. The flow is laminar in case 3 for several reasons, the stenosis is not as severe as in case 2, the artery geometry does not favor turbulence arising and the branch appearing downstream of the stenosis is slightly further.

4 Discussion

Previous sections have shown how the FFR can be determined in a non-intrusive way employing CFD in the reconstructed coronary artery from CT images. Patient 1 and 3 in vivo measurements coincide with the simulation results. 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\textsubscript{d} value. Concerning the patient 1, if Toth et al. \cite{31} and Renard et al. \cite{34} criterion is followed, a catheterization could be avoided as the FFR is 0.83. However, this catheterization would be suggested according Ihdayhid et al. \cite{32} and Matsumura et al. \cite{33} indications. If the sensor is placed 4 cm downstream, the FFR value would be under 0.8.

In this paper, we present relevant information that could be helpful to assist in the invasive procedure. It is necessary to study the graphs of both the evolution of the FFR\textsubscript{CT} value from the stenosis and the streamlines behavior.

In the first case, streamlines are reorganized 2.8 cm after the stenosis (see arrow in Fig. 7). This should be the point where the sensor should be located and that would mean an FFR value of 0.81. That location is close to the suggested in the medical protocols (2 cm) but as seen in the remaining patients, the types and severities of the stenosis are quite different between different individuals and the pressure field distribution is variable. For example, patient 2 streamlines are not reorganized (Fig. 8). We could measure right after the stenosis but the presence of a branch does not help the stabilization of the flow. It is not
recommendable to place a pressure sensor just in the vicinities of a ramification. For this reason, if one pays attention to the FFR_{CT} value evolution, after a slight increase in 2.5 cm, the slope of the FFR_{CT} is constant and stable and this place should be chosen to place the sensor. The location chosen (arrow placed in both figures), would differ significantly from Toth et al. [31] and Renard et al. [34] suggestions and would approximate better to Ihdayhid et al. [32] and Matsumura et al. [33] criterion. The behavior of patient 3 (Fig. 9) seems similar to that of patient 2, although there are differences concerning the geometry. The flow is much more stable before the stenosis and the severity of the stenosis is not as acute as in patient 2. For this reason, as the flow is very stable, we recommend to place the pressure sensor before the branch is reached. In this case this ramification would not mean an important influence in the flow because of its position and origin from the principal artery. Finally, patient 4 (Fig. 10) resembles to patient 1. The figure shows clearly the place where the streamlines are reorganized. This point is located 3 cm downstream of the stenosis and as it is clearly seen, the slope is almost constant since this location is reached.

All these cases, show that new non-invasive technologies are quite helpful when performing an invasive FFR. The previous studies about the location of the probe, are quite useful but its validity depends on the coronary geometry. One possibility would be to move 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. This procedure should include a verification process to check that there are no pressure fluctuations downstream of the stenosis and would avoid false results related to the point where the distal pressure is measured. The result would be taking different clinical decisions because P_{d1} and P_{d2} values differ significantly from the P_{d3} value. However, this procedure would imply to add more adenosine to the patient to perform all these pressure measurements. Here we propose a method based on the information provided by the CFD simulation. This method would indicate the cardiologist the best angle to visualize the intervention and a limited region where the sensor should be set.

5 Conclusion

Coronary stenosis is largely responsible of severe heart failure as they can stop the blood flow to the myocardial. The FFR, ratio of the P_{d} to P_{a}, is the most usual functional assessment of the severity of the coronary stenosis. The numerical results of the FFR_{CT} are in good agreement with those obtained experimentally (FFR) in multiple references in the bibliography. Nevertheless, the invasive protocol would be recommended in limiting cases (0.75 < FFR_{CT} < 0.85).

In this paper we have performed simulations that match the invasive measurements taken in two different patients. Once our method is validated, we have taken advantage of the simulation technology and obtained useful information that it is quite helpful to the invasive procedure. The present paper, assess with Fluid Dynamics principles, the best region to place the sensor in an invasive pressure measurement. This region is not fixed and it depends on the patient. This procedure would avoid false results related to the pressure variations concerning the point where the distal pressure is measured.
Additionally, would help the cardiologist with the intervention planning. As the measurement area is constrained and the location is known, the interventionist could indicate the best position for the visualization of the coronary and could limit duration of the procedure.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| 3D           | Three-Dimensional |
| QCA          | Quantitative Coronary Angiography |
| CFD          | Computational Fluid Dynamics |
| CCTA         | Coronary Computed Tomography Angiography |
| CFL          | Courant-Friedrichs-Levy |
| DICOM        | Digital Image and Communication in Medicine |
| FFR          | Fractional Flow Reserve |
| FFR\(_{CT}\) | Fractional Flow Reserve-Computed Tomography |
| HU           | Hounsfield Units |
| ICA          | Invasive Coronary Angiography |
| MPI          | Myocardial Perfusion Imaging |
| MBF          | Myocardial Blood Flow |
| PCI          | Percutaneous Coronary Intervention |
| Pa, Pd       | Aortic and Distal Pressures |
| SST          | Shear Stress Transport |
| TIMI         | Thrombolysis in Myocardial Infarction |
| UDF          | User-Defined Function |
| URANS        | Unsteady Reynolds-Averaged Navier-Stokes |

**Declarations**

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**Author contributions**: R.A. has developed and designed the paper, being the general responsible. R.A. and C.F. have written the paper. R.G. and J.N. have carried out the analysis and interpretation of the results.
A.F. has carried out the critical review. R.A, C.F. and A.F. have given the final approval and have obtained the funding.

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