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APPLICATION OF PAK SOFTWARE FOR THE CALCULATION OF vFFR IN CORONARY ARTERIES

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Abstract

X-ray angiography is one of the diagnostic procedures applied in clinical practice to analyze the state of patient-specific coronary arteries. During this examination a parameter called fractional flow reserve (FFR) is invasively measured to quantitatively assess the existence of potential stenosis and its significance. The software proposed in this paper presents an alternative method to calculate a virtual FFR equivalent and this approach can reduce the cost and invasiveness of the diagnostic approach. The angiography images are used to perform a 3D reconstruction of the coronary artery, the finite element mesh is automatically generated and an adapted PAK software is used to perform blood flow simulations and calculate the FFR equivalent. The calculated values and the clinically measured values of FFR are compared in order to validate the proposed methodology and a good agreement of results is obtained. Within the developed software the user is also provided with options to analyze the distribution of relevant hemodynamic parameters in the arterial tree, which makes it a useful tool that provides assistance in patient-specific treatment planning.

Keywords: X-ray angiography, coronary arteries, virtual fractional flow reserve, finite element method, computational fluid dynamics

1. Introduction

X-Ray angiography (XRA) is one of the diagnostic procedures applied in clinical practice to analyze the state of patient-specific coronary arteries. During this examination a parameter called fractional flow reserve (FFR) is used to quantitatively assess the existence of potential stenosis and its significance. The FFR parameter is calculated as the ratio of two pressure values – the aortic blood pressure and blood pressure after the considered segment with possible stenosis. These two pressure values are invasively measured by placing a pressure wire within the examined artery. Clinical standards and published studies (Morris et al. 2015, Morris et al. 2017) state that the value of FFR of ≤ 0.80 corresponds to the so-called ischemic threshold and it demonstrates a presence of clinically relevant stenosis. Measuring the FFR helps easier, faster and more accurate diagnostics of stenotic arteries and also reduces the number of unnecessary

stenting treatments. However, this diagnostic tool has also some disadvantages - it is time-consuming, invasive, uncomfortable for the patient and increases the clinical costs, as it requires the pharmacological induction of hyperemia (Zhang et al. 2015). A non-invasive alternative is to use computer-aided tools to reconstruct the arterial tree and use numerical models on these reconstructed geometries to simulate blood flow and obtain the virtual fractional flow reserve parameter (vFFR), FFR equivalent. Several studies in literature performed 3D reconstruction of coronary arteries from computed tomographic (CT) coronary angiography or X-ray coronary angiography and afterwards used methods of computational fluid dynamics (CFD) to calculate vFFR (Morris et al. 2017, Nørgaard et al. 2014, Yan et al. 2024).

The software proposed in this paper uses diverse segmentation techniques that are applied on the DICOM images obtained during XRA examination to perform the automated reconstruction of the arterial tree and generation of the finite element (FE) mesh. PAK software is adapted such that it performs blood flow simulations and calculates the FFR equivalent, so-called virtual functional assessment index (vFAI), proposed by Papafaklis et al. (2014). The results of the PAK software are imported into the developed software and the user is also provided with the options to visualize the hemodynamic parameters of interest - velocity, pressure and wall shear stress (WSS). This way not only FFR equivalent is provided to the user (clinician), but also other relevant data that could be of interest for a more precise diagnosis.

The paper is organized as follows. Section 2 briefly presents the segmentation approach, and the details of the calculation of vFAI parameter that were implemented in PAK software. Section 3 presents the developed software, together with the results of validation of obtained results, and Section 4 concludes the paper.

2. Materials and Methods

This Section presents the segmentation approach used within the developed software, describes the equations used to simulate blood flow and the procedure applied to calculate the vFAI parameter.

1.1 3D reconstruction from angiography images

The developed software requires two DICOM images of XRA examination, from two angiography projections. The first version of the developed software used manual annotation of the regions of interest of the arterial tree to perform the 3D reconstruction (Vukicevic et al. 2018, Djukic et al. 2024b). This process required from the user to define the starting and ending point of the vessel segment on both projections and to choose several bifurcation points on both projections for the purpose of calibration of parameters. In practical use of the software this proved to be tedious and time-consuming, so additional efforts were applied to automate this part of the software and AI-enhanced segmentation was implemented (Djukic et al. 2024a).

The segmentation of patient-specific DICOM images obtained during X-Ray coronary angiography is performed in order to gain information about 2D shapes of main blood vessels within the observed region of interest. Coronary artery segmentation is performed using a seven-step image processing pipeline. The main challenges of artery segmentation stem from background interference of other objects contained within the images, like ribs, spinal cords, pigment fluid leaks, as well as the inherent noise produced by X-Ray devices.

Image segmentation is conducted using different image filters and transformations. The first step in the pipeline includes the passing of the image through a contrast limited adaptive histogram equalization (CLAHE) filter for noise reduction. Noise reduction provided by

CLAHE pertains to the elimination of aforementioned inherent X-Ray noise. Filtered images are then color inverted and passed through a top-hat transformation in order to create a new base in which coronary arteries are more distinguished from the background tissue. The application of top-hat transformation eliminates large areas of background objects that interfere with the segmentation of the arteries with the exception of edges of those objects.

A hessian matrix filter is applied to the image resulting from top-hat transform. The hessian matrix is tasked with uncovering ridges, the biggest of which are standout blood vessel bodies. Hessian matrix also discovers ridges contained in the heart tissue that are not important for segmentation. These ridges are small in terms of surface area, but they require the application of blur filtering in order to be removed from the image. Blur filtering is conducted using a Gaussian blur filter. In addition to the removal of background noise, blur filtering reduces the size of discontinuations along the main blood vessels to create a singular coronary artery tree. Finally, image filtering is completed using a combination of 32 Gabor filters with different parameters in terms of amplitudes and orientations. The main goal of Gabor filters is to detect edges of coronary arteries. A large number of filters is required to discover as many important edges as possible. Different orientations of the filter search for edges in all ordinal and cardinal directions, while different wavelength amplitudes allow for the discovery of edges of objects with different thicknesses.

The final step in coronary artery segmentation is the extraction of a single object that possesses the largest surface area in terms of pixels. Pixels belonging to each continuous group of foreground pixels are counted and any pixels belonging to smaller objects are relegated to the background. Smaller objects that are merged with the image background are in all cases remnants of background noise that was not eliminated throughout the filtering pipeline or very small blood vessels that have very little to no contribution to final calculations of vFAI during simulations. The resulting image is a black and white grayscale image within which the black pixels represent the background and the white pixels represent the main coronary artery tree which is further used for 3D reconstruction.

After the extraction of the coronary artery tree body is complete, a binary skeletonization algorithm is applied to extract the centerline of the artery in 2D. In addition to skeletonization, distance is measured from the extracted centerline to the nearest orthogonal pair of arterial walls in order to gain information on the thickness of the artery along the length of the centerline. Centerline information, in tandem with artery thickness from both XRA projections are used for reconstructing the tree in 3-dimensional space. Branch length equalization based on multipoint matching and duplicate removal was conducted in order to avoid manual point annotation in multiple XRA projections. Epipolar geometry based on XRA C-ARM position, distance from the patient, screening angles and matching point pair positions in different views was used to create the centerline and surface point cloud reconstructions in 3D space.

The centerline data obtained from the above mentioned segmentation pipeline is used to define the non-uniform B-spline representations (Piegl and Tiller, 1995) of each segmented vessel branch. Within the reconstruction procedure it is assumed that each segment of the arterial tree can be modeled as tube-like curved surface. Since only two angiography projections are used for the reconstruction, it is possible to obtain only 4 points defining the lumen area of each segment (2 points per each projection). These 4 points are used to define the circular cross-sections (patches) of the vessel lumen. The Frenet–Serret formulas (Han and Kwon, 2011) are used to position these patches along the B-spline representations of the centerlines of the vessel segments and thus positioned they are further used to define the parametric NURBS surface (Non-Uniform Rational Basis Splines) (Piegl and Tiller, 1995). The 3D FE mesh of each coronary tree branch is generated using the NURBS surface and the branches are afterwards connected to each other following the procedure described by Vukicevic et al. (2018).

1.2 Blood flow simulations

For the simulations of blood flow within the reconstructed arterial tree, the version of PAK software specialized for fluids – PakF is used (Filipovic et al. 2006). This software was successfully applied for many diverse applications within EU financed projects and it was extensively validated in literature (Filipovic et al. 2006, Kojic et al. 2008, Parodi et al. 2012, Rakocevic et al. 2013).

Within this study, the blood is considered an incompressible, viscous Newtonian fluid, whose density is equal to ρ=1.05 g/cm^3 and kinematic viscosity is equal to ν=0.035 cm^2/s. Within PakF the traditional CFD equations are solved – the Navier-Stokes equation and the continuity equation, that are given by:

$$\rho\left(\frac{\partial v_i}{\partial t}+v_j\frac{\partial v_i}{\partial x_j}\right)=-\frac{\partial p}{\partial x_i}+\mu\left(\frac{\partial^2 v_i}{\partial x_j\partial x_j}+\frac{\partial^2 v_j}{\partial x_j\partial x_i}\right) \tag{1}$$

$$\frac{\partial v_i}{\partial x_i}=0 \tag{2}$$

where v_i denotes the blood velocity in direction x_i, p represents blood pressure and μ represents the dynamic viscosity. In Eqs. (1) and (2) it is assumed that the summation over the repeated indices (i and j) is performed.
These equations are transformed in an incremental-iterative form that is given by:

$$\left(\frac{1}{\Delta t}\mathbf{M}_{\mathbf{v}}+{}^{t+\Delta t}\mathbf{K}_{\mathbf{vv}}^{(i-1)}+{}^{t+\Delta t}\mathbf{K}_{\mu\mathbf{v}}^{(i-1)}+{}^{t+\Delta t}\hat{\mathbf{K}}_{\mu\mathbf{v}}^{(i-1)}+{}^{t+\Delta t}\mathbf{J}_{\mathbf{vv}}^{(i-1)}+\mathbf{K}_{\lambda\mathbf{v}}\right)\Delta\mathbf{v}^{(i)}={}^{t+\Delta t}\hat{\mathbf{F}}_{\mathbf{v}}^{(i-1)} \tag{3}$$

where $\mathbf{M_v}$ denotes the mass matrix, $\mathbf{K_{vv}}$ and $\mathbf{J_{vv}}$ represent convective matrices, $\mathbf{K_{\mu v}}$ and $\mathbf{K_{vp}}$ represent the viscous matrix and pressure matrix, respectively, and $\mathbf{F_v}$ and $\mathbf{F_p}$ denote forcing vectors. The time step is denoted by Δt, and the left upper index "t+Δt" represents the values of the quantities in question, evaluated at the end of time step.

Eq. (3) is solved using the finite element method and penalty formulation (Filipovic et al. 2006) within PakF software. For the purposes of this study a mesh with 8-node hexahedral finite elements is considered.

Apart from velocity and pressure, the values of WSS in the nodes on the walls are also calculated in the numerical simulations, using the tangential velocity in each node u_t and the normal to the arterial wall in these nodes **n**, using the following relation:

$$\tau=-\mu\frac{\partial\mathbf{u}_t}{\partial\mathbf{n}} \tag{4}$$

1.3 Calculation of FFR equivalent

As it was already mentioned in the Introduction section, within this study a numerical approach is applied to calculate a FFR equivalent, the vFAI parameter. This approach was proposed by Papafaklis et al. (2014). The goal of the approach is to calculate the pressure gradient for two cases and then determine the dependence of the pressure ratio from blood flow. The two considered cases represent the blood flow during rest and under stress. For these cases the flow rates are defined to be 1 and 3 ml/s, respectively. The blood flow simulations are performed within PakF software as steady state simulations, with the following boundary and initial conditions: the pressure of 100 mmHg is applied at the inlet and the mentioned flow rates are

applied at the outlet. In case of simulations within the arterial tree with several outlet branches, the flow rate is proportionally divided among the outlet branches.

For the purpose of easier explanation, in the sequel of this Section a single vessel will be considered, although the same logic is also applied for the calculation of vFAI in the arterial tree. The value of inlet pressure is denoted as P_a, and the value of outlet pressure is denoted as P_d. The pressure gradient ΔP is calculated as the difference between these two values. It is possible to define the relation between pressure gradient and blood flow Q:

$$\Delta P = 0 + f_v Q + f_s Q^2 \tag{5}$$

where f_v represents the coefficient of pressure loss due to viscous friction and f_s represents the coefficient of pressure loss due to flow separation (Gould 1978). These coefficients can be calculated from the two equations obtained for the two considered cases of blood flow.

Equation (5) can now be transformed as follows:

$$\frac{P_d}{P_a} = 1 - f_v \frac{Q}{P_a} - f_s \frac{Q^2}{P_a} \tag{6}$$

By drawing a graph of change of the pressure ratio for different blood flow rates and calculating integral of this function for a flow range between 0 and 4 ml/s it is possible to calculate the vFAI value. Mentioned flow range from 0 to 4 ml/s is chosen since 2 ml/s represents the mean value of hyperaemic blood flow rate for a normal human coronary artery and the ±2SD difference of this mean value is considered. Finally, the patient-specific vFAI value for the considered arterial segment is determined by comparing the obtained value of the integral (area under the curve for that particular arterial segment) with the reference value.

In order to calculate vFAI the PAK software is modified accordingly. Within the input DAT file the prescribed values of inlet pressure and outlet velocities are defined. It should be noted that the velocities are calculated by using the 2 considered blood flow rates and the patient-specific outlet area. Two steady-state simulations are performed in PAK, afterwards the coefficients f_v and f_s are calculated and the procedure described in the previous paragraph is implemented within PAK to obtain vFAI value. The outputs of the simulation in PAK are the traditional UNV file and the TXT file containing the calculated vFAI value.

3. Results

The software presented in this paper is implemented in programming language C++. The GLUT library is applied for the user interface, and OpenGL library is applied for the visualization. Also, the CUDA architecture is used within the visualization implementation, to ensure the most optimal usage of the resources of the graphics card and faster visualization of complex geometries. Programming language Python is used for the implementation of the AI-enhanced segmentation. The SkImage and OpenCV libraries are applied for image processing and NumPy library is applied for the numerical operations. The PAK software is implemented in programming language FORTRAN.

The segmentation part of the software and PAK software are called externally from the main software that controls the entire execution. Fig. 1. shows the flowchart of execution of the software. First the DICOM images containing patient-specific XRA projections are loaded by the user. Then, the procedure for the segmentation is initialized by choosing the appropriate

option. The main program starts the segmentation executable and waits for its execution to finish.

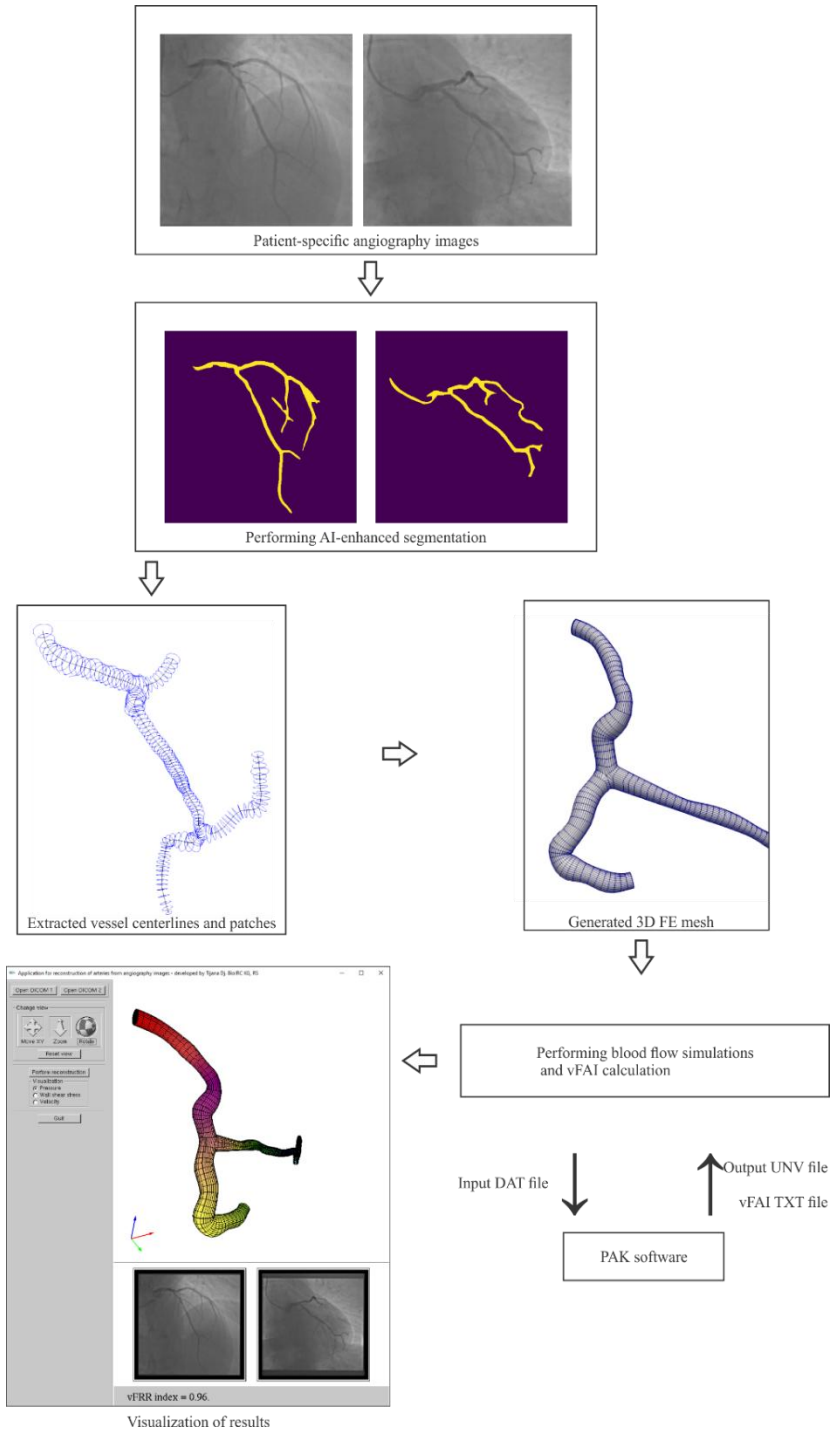

Fig. 1. The flowchart of the execution of the developed software.

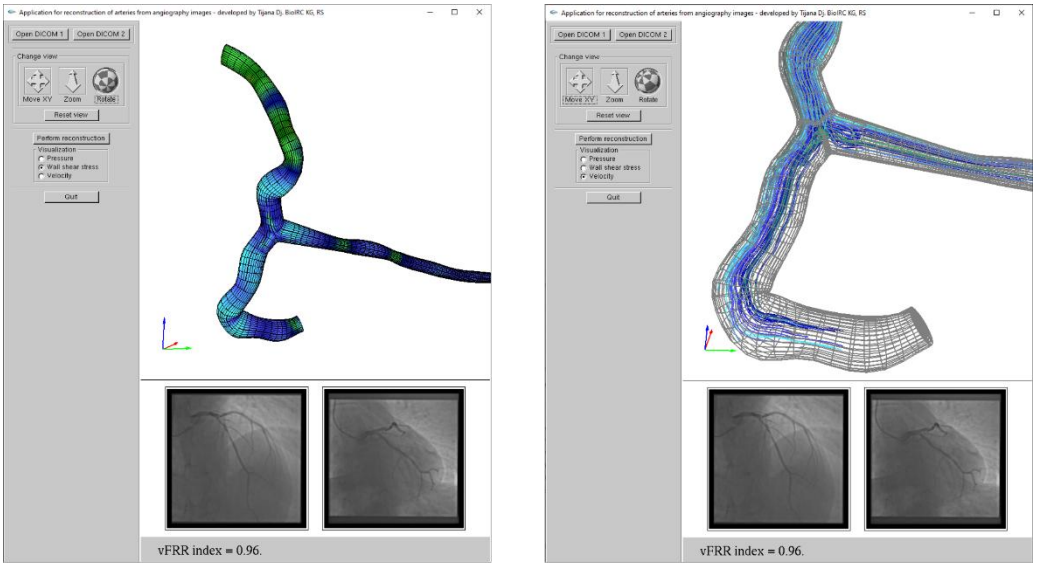

Fig. 2. Screenshots of the developed software. (a) Visualization of the calculated distribution of WSS. (b) Visualization of the calculated velocity streamlines.

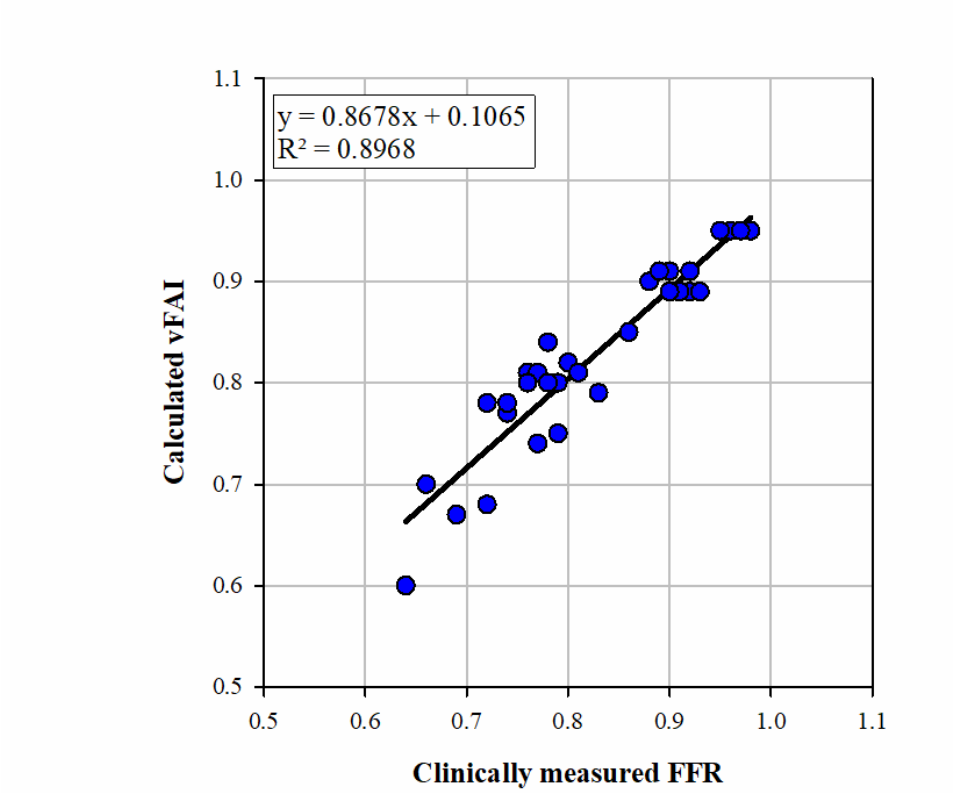

Fig. 3. Comparison of calculated values of vFAI with the clinically measured FFR values.

After this phase is finished, the main program uses the extracted data for centerlines and patches (stored in a TXT file) to create first the NURBS surface and then the 3D FE mesh. Now the main program creates the PAK DAT file and starts the execution of PAK software. While the PAK software is performing in the background, the user is allowed to manipulate and analyze the created 3D FE mesh. The manipulation options allow the user to move, rotate or zoom the model of the arterial tree. After the execution of the PAK software is finished, the main software loads the output files from PAK software. It loads first the TXT file containing the vFAI value and displays this value on the status bar and then it loads the UNV file containing the results of blood flow simulations and stores these values in appropriate buffers, for further visualization. It also post-processes the data for velocity and calculates the velocity streamlines and stores this data for further visualization too. The user is provided with choices which hemodynamic parameter should be visualized (pressure, WSS or velocity streamlines) and the program adapts to this choice and shows the chosen distribution. At the bottom right corner of Fig. 1. a screenshot of the software is shown while the distribution of pressure is visualized, and Fig. 2. shows the screenshots of the software when the distribution of WSS and velocity streamlines is shown (in Fig. 2(a) and Fig. 2(b), respectively).

The overall execution time of the software for one set of XRA images is between 3 to 5 minutes, depending of the complexity of the reconstructed arterial tree. The execution time for the case presented in this study, in Fig. 2., was 3 minutes and 2 seconds, for a mesh with overall 35900 finite elements and 40000 nodes. The visualization of results and manipulation with the geometry is always performed in real time, thanks to the implemented visualization techniques that use CUDA architecture and the capabilities of the graphics card.

In this study the validation of the results of vFAI calculation is performed by using angiography data for a cohort of 34 patients. The patient-specific XRA DICOM images and the corresponding clinically measured FFR values were obtained through the project MobVirFFR, financed through the Proof-of-Concept Program, of the Innovation Fund of the Republic of Serbia. The clinical examination of patients was performed using a routine protocol in the University Clinical Centre of Serbia. The validation of the vFAI calculation was also performed in literature (Djukic et al. 2024b), where data collected through the same project was used and a more extensive comparison was performed. But in cited literature the previous version of the software was used, that required manual annotations from the user in order to perform the reconstruction. In this study, one part of this data was used to validate the new version of the software with automated segmentation. Fig. 3. shows the linear regression plot that is used as a comparison tool between measured and calculated values. The correlation coefficient is equal to 0.89, which demonstrates the accuracy of the proposed approach.

4. Conclusions

Within this study the PAK software is applied to simulate blood flow through patient-specific coronary arteries and a calculation of virtual FFR equivalent. The developed software performs an automated segmentation, 3D reconstruction, FE mesh generation and preparation of input files for PAK software. The PAK software is adapted to perform simulations and afterwards calculate the mention FFR equivalent. The validation of the proposed approach is performed using clinically measured values of FFR for a cohort of patients from clinical examination. The proposed software is fully automated, easy and intuitive to use and represents a good alternative to the invasive FFR measurements as it reduces the cost of the examination and simplifies the procedure for the patients, while it provides the clinicians with desired results within a few minutes. Besides, this approach provides not only a single value of vFAI, but also the possibility to analyze the state of the patient-specific coronary arterial tree, in terms of

hemodynamical quantities like velocity and pressure, but above all WSS, which is very significant for the processes of atherosclerosis, but difficult to measure clinically. The developed software can be a useful tool for the clinicians during the diagnostics and subsequent patient-specific treatment planning.

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