Veselova T.N.[1], Ternovoy S.K.[1,2], Chepovskiy A.M.[3], Borisenko V.V.[4], Gavrilov A.V.[4], Blagosklonova E.R.[5], Dolotova D.D.[5], Mironov V.M.[1], Arutunyan G.K.[1]

[1] National medical research Center of cardiology of the Ministry of Healthcare of Russia, Moscow
[2] I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia
[3] Peoples Friendship University of Russia (RUDN University), Moscow, Russia
[4] Lomonosov Moscow State University, Moscow, Russia
[5] Gammamed-Soft, Ltd, Moscow, Russia

Evaluation of the Fractional Flow Reserve by Computer Tomography Data: Comparison of the Calculated Parameters with the Results of Invasive Measurements

Aim To create a three-dimensional mathematical model of coronary flow in patients with ischemic heart disease based on findings of computed tomography angiography (CTA) with subsequent calculation of the fractional flow reserve (FFR_{CTA}) and comparison of estimated FFR_{CTA} with FFR reference values measured by coronary angiography (CAG).

Material and methods The study included 10 patients with borderline stenosis (50–75%) as determined by CTA performed with a 640-slice CT-scanner. Based on CTA findings, three-dimensional mathematical models were constructed for further calculation of FFR_{CTA}. Later, an invasive measurement of FFR (FFR_{INV}) was performed for all patients. FFR values <0.8 indicated the hemodynamic significance of stenosis.

Results FFR_{CTA} and FFR_{INV} values differed insignificantly in most cases (n=9) and exceeded 5% in only one case. The regression analysis showed a close correlation between estimated and invasively measured FFR values.

Conclusion Preliminary results showed a good consistency of calculated and measured FFR values. Therefore, further development of the method for mathematical modeling of three-dimensional blood flow by CTA findings is promising. Noninvasive evaluation of FFR is particularly relevant for analysis of hemodynamic significance of borderline (50–75%) coronary stenoses.

Keywords Fractional flow reserve; computed tomography angiography; ischemic heart disease; mathematical model

For citation Veselova T.N., Ternovoy S.K., Chepovskiy A.M., Borisenko V.V., Gavrilov A.V., Blagosklonova E.R. et al. Evaluation of the Fractional Flow Reserve by Computer Tomography Data: Comparison of the Calculated Parameters with the Results of Invasive Measurements. Kardiologiia. 2021;61(7):28–35. [Russian: Веселова Т.Н., Терновой С.К., Чеповский А.М., Борисенко В.В., Гаврилов А.В., Благосклонова Е.Р. и др. Оценка фракционного резерва кровотока по данным компьютерной томографии: сравнение расчетных показателей с результатами инвазивных измерений. Кардиология. 2021;61(7):28–35].

Corresponding author Veselova T.N. E-mail: tnikveselova@gmail.com

Introduction

Fractional flow reserve (FFR) refers to the gradient between the mean coronary pressure proximal to the stenosis site and the mean aortic pressure. The invasive measurement of FFR is recognized by international experts as the gold standard for determining the functional significance of stenosis [1]. Many studies have shown that myocardial revascularization is associated, depending on FFR values, with a decrease in the risk of developing severe adverse cardiovascular events, including acute myocardial infarction and death [2].

In 2011, Koo et al. [3] published the first FFR assessment trial obtained by mathematical modeling of the coronary bed according to computed tomographic angiography (CTA, FFR_{CTA}) of coronary arteries. Since then, many data have been published on this technique, along with various non-invasive methods for assessing the functional significance of stenosis [3–5]. However, the meta-analysis showed that the calculation of FFR has the greatest diagnostic significance and comparability with the indicators of invasive measurement of FFR_{CTA} using the HeartFlow FFRCT mathematical modeling (HeartFlow, Redwood City, CA) [6]. This is the only available method approved by both the US Food and Drug Administration (FDA) [7] and the UK National Institutes of Health (NIH) [8]. The PLATFORM and FORECAST trials have demonstrated that providing a definition of FFR_{CTA} at the first stage of examination of patients with chronic coronary artery disease (CAD) significantly lessens the number of invasive diagnostic

 ISSN 0022-9040. Kardiologiia. 2021;61(7). DOI: 10.18087/cardio.2021.7.n1540

procedures and repeated non-invasive tests, as well as reducing financial costs [9, 10].

Due to the high diagnostic potential of the non-invasive determination of FFR_{CTA}, developing a hydrodynamic model of coronary blood flow is an essential task for radiation diagnostics. The authors are developing a technique for constructing a 3D computational blood flow model based on the finite volume method of approximation to fluid motion equations described earlier [11–14].

Aim

Develop a 3D mathematical model of coronary blood flow in patients with coronary artery disease based on the CTA data with the subsequent calculation of FFR_{CTA} and comparison of the calculated FFR_{CTA} with the results of invasive measurements of FFR (FFR_{INV}).

Material and methods

We examined 12 patients admitted to the intensive care unit from March 2019 to February 2020 with the suspected acute coronary syndrome (ACS) and detected borderline (50–75%) coronary stenosis shown by CT on a 320-row detector scanner. The study group included patients with negative troponin tests and no ischemic changes in electrocardiography (ECG).

The exclusion criteria comprised: the presence of more than one >50% stenotic lesions per artery; new focal lesion or post-MI scar in the artery bed of interest, renal failure (glomerular filtration rate less than 50 mL/min/1.73 m^3); history of allergy to iodine-containing drugs, pregnancy or breastfeeding; severe concomitant diseases affecting the prognosis independently; claustrophobia.

The study received ethical approval. All patients signed the informed consent for CTA and CAG with the invasive measurement of FFR.

Clinical characteristics of patients included in the study are given in Table 1.

Computed tomography coronary angiography

Coronary CTA was carried out using a 320-row detector scanner. During one X-ray tube rotation lasting for 0.275 seconds, a total of 640 tomographic slices 0.5 mm thick were simultaneously made without bed motion, with intravenous administration of 50–70 mg (depending on patient weight) of a contrast agent (350–370 mg iodine/mL). The X-ray tube voltage was 100 kV with body mass index (BMI) <25 kg/m^2 (120 kV with BMI ≥25 kg/m^2) When the thoracic topography was performed, the area of interest was 1 cm above the aortic root up to the diaphragm level.

The contrast agent was administered intravenously at a rate of 5 mL/s using an automatic syringe. The arterial phase of the examination began automatically when the peak concentration of the contrast agent was reached in the lumen of the aortic root, which was equal to 250 Hounsfield units. Prospective ECG gating was used in the R – R range from 75% to 95%. An oral or intravenous beta-blocker was used with heart rate (HR) >65 bpm. Coronary scans were analyzed on a Vitrea workstation; the degree of stenosis was assessed for each coronary segment. All images were of good quality.

Construction of a 3D computational model of coronary arteries based on computed tomography angiograms

The calculation method of FFR includes two stages [11]. At the first stage, a 3D geometric model of a vessel is created on the basis of the CTA findings in order to construct a hydrodynamic blood flow model. At the second stage, the blood flow characteristics are calculated using hydrodynamic modeling for the vessel's geometric model obtained at the first stage.

The 3D vessel geometry is built based on the CTA data. The construction technique of the 3D vessel model has been described in our previous works [12, 13]. The procedure uses the voxel-based seeded region growing algorithm to combine automatic detection with partially manual processes, which are often inevitable in the cases of complex and non-standard vessel geometry, insufficient contrast-enhancement of tomographic slices, uneven distribution of contrast agent in the blood, etc.

The 3D geometric model of the aorta and coronary arteries is constructed based on CTA findings using a 3D algorithm of seeded region growth. The triangulation is built as the surface of multiple voxels isolated from the general circulatory model resulting from an interactive semi-automatic procedure. The surface is smoothed using the Taubin algorithm and the uniform Laplace operator [15]. A computational prismatic grid is automatically constructed on the basis of the mathematical hydrodynamic 3D vessel model, which significantly reduces the number of computational cells in hydrodynamic modeling.

Subject to an additional mathematical morphology procedure, the voxel model of the aorta and coronary arteries allows calcifications to be isolated. Dilation is carried out following detection in order to clarify the margins. Using different threshold values for the density function allows a determination of the margin between the vessels and areas outside the voxel model and separating voxels inside the vessel, which represent blood with a contrast agent, on the one hand, and calcifications, on the other. As a result, the interior of the calcifications is removed from the triangulation, and the inner margins of the calcifications are included in the outer margin of the model. The implemented technique makes it possible to calculate the triangulation of the inner surface of the aorta and coronary arteries considering the calcifications [12, 13]. Special software is used to analyze the patient's CT scans in DICOM format and create a file with triangulation of the 3D model in any of three formats: Wavefront OBJ (preferred), STL, VRML. This then comprises the input file for the ANSYS simulation software suite.

The computational hydrodynamic blood flow model was based on the calculations described earlier [14]. The blood flow calculation is based on the finite element method implemented in the ANSYS CFX hydrodynamics module, which is a part of the ANSYS Workbench 19 (ANSYS, Inc) computational complex. The ANSYS CFX suite is used to calculate the hydrodynamic parameters of blood flow in the 3D blood vessel model. Our task was to describe stationary fluid flow in the vascular system, as captured by the Navier-Stokes equations in conjunction with the mass and fluid flow conservation conditions. The calculation did not consider the elasticity of the vessel walls but provided for the no-slip condition, which means that the velocity of the marginal fluid is zero. The measured pressure values were used as the borderline conditions for the region of computation.

Coronary angiography and fractional flow reserve

Coronary angiography (CAG) was performed using an Allura Xper FD-10 device with a 6F catheter, which was placed at the mouth of the coronary artery via a radial approach. Non-ion iodine-containing contrast agents were used. Angiograms were analyzed visually and automatically in the Xcelera system.

Nitroglycerin 250 mcg was injected intracoronarily to dilate epicardial arteries for the measurement of FFR. The intracoronal pressure sensor was then brought to the tip of the guiding catheter to measure pressure in the proximal coronary bed. When the pressure curves normalized, the intracoronary probe was moved distally from the coronary stenosis. Maximum hyperemia was achieved by injecting papaverine into the artery (20 mg for the left coronary artery, 12 mg for the right coronary artery). FFR was then measured, followed by a manual retraction of the probe to the artery mouth to determine the hemodynamic significance of an atherosclerotic plaque at different coronary artery levels. The threshold FFR value was 0.80. The coronary lesion was hemodynamically insignificant with FFR ≥0.80 and hemodynamically significant with FFR <0.80.

Table 1. Clinical characteristics of patients with acute coronary syndrome

Parameter	Value
Total number of patients	12
Mean age, years	63±7.8
Sex, M/F	8/4
Postinfarction cardiosclerosis	3
Arterial hypertension	9
Hypercholesterolemia	8
Diabetes mellitus	3

Results

The effective removal of calcifications from the mathematical model was impossible in 2 cases due to severe calcification, which deliberately distorted the calculated FFR. Therefore, these patients were excluded from the study. The final analysis included ten patients. The invasive (FFR_{INV}) and calculated FFR (FFR_{CTA}) were evaluated in one coronary artery of each patient. The measurement results are presented in Table 2.

According to the data presented, the calculated and invasively measured FFR values differ insignificantly in most cases: only in one case, the difference exceeded 5%.

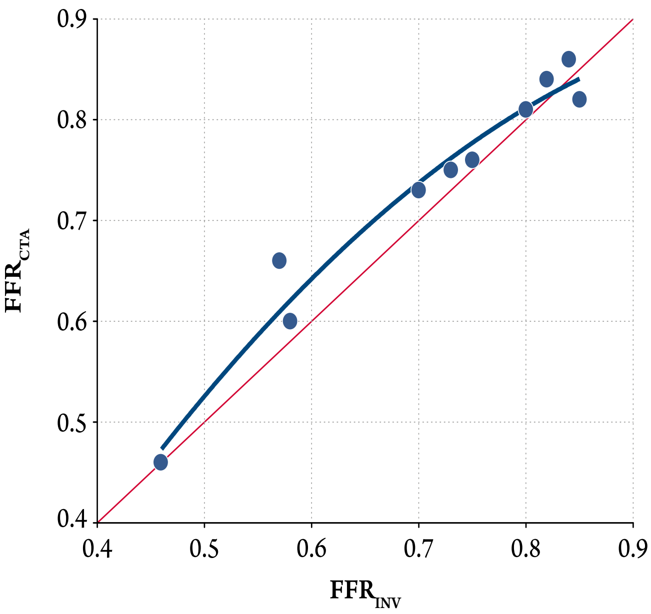
Table 2. Comparison of calculated and invasively measured values of fractional flow reserve

Patient	Vessel type	Stenosis degree, %	FFR_{INV}	FFR_{CTA}	Deviation of FFR_{CTA} from FFR_{INV}, %
#1	RCA	75	0.85	0.82	3.5
#2	LAD	70	0.7	0.73	4.3
#3	LAD	75	0.73	0.75	2.7
#4	LAD	70	0.56	0.6	3.4
#5	RCA	75	0.75	0.76	1.3
#6	RCA	75	0.57	0.66	16
#7	LAD	75	0.46	0.46	0
#8	RCA	55	0.84	0.86	2.4
#9	RCA	60	0.8	0.81	1.3
#10	LAD	65	0.82	0.84	2.4

RCA – right coronary artery; LAD – left anterior descending artery; FFR – fractional flow reserve; CTA – computed tomographic angiography; FFRINV – invasively measured fractional flow reserve.

ISSN 0022-9040. Kardiologiia. 2021;61(7). DOI: 10.18087/cardio.2021.7.n1540

Figure 1. Regression plot of calculated and invasively measured values of fractional flow reserve



FFR – fractional flow reserve; CTA – computed tomographic angiography. FFRINV – invasively measured fractional flow reserve.

Figure 1 shows the results of the comparison of the calculated and invasively measured FFR values. The dot indicates the calculated value of FFR (FFR_{CTA} on the vertical axis) corresponding to the invasively measured FFR value (FFR_{INV} on the horizontal axis). The dashed line corresponds to the quadrant bisector, on which the points should lie if the invasively measured FFR values (FFR_{INV}) match the values resulting from the hydrodynamic calculation (FFR_{CTA}).

The solid line in Figure 1 depicts a polynomial quadratic approximation of the corresponding FFR values. The approximation curve indicates a close correlation between the measured and calculated values. The Pearson correlation coefficient between the sets of calculated FFR values and the corresponding invasively measured FFR values is 0.974637812, i.e., two values are strongly correlated (see the regression graph in Figure 1). Based on the data in Table 2 and the regression plot in Figure 1, it is evident in the case of invasively measured significant physiological damage (FFR about 0.80) that the deviation of the calculated value from the measured value decreases, while the accuracy of the computed FFR exceeds 90%.

In general, this comparison of the measured and calculated values showed a good correlation of the data and, thus, the efficacy of the new method.

Two examples of hydrodynamic calculation based on CTA data can be given here for clarity: patient #4 (Figure 2) and patient #5 (Figure 3). For both patients, 3D images of the coronary artery geometry were reconstructed based on the CTA data. Then hydrodynamic calculations of blood flow were carried out, as described above. In patient #4, the left anterior descending artery (LAD) was analyzed: the calculated and invasively measured FFR values were 0.6 and 0.58, respectively. In patient #5, the right coronary artery (RCA) was analyzed: the calculated and invasively measured FFR values were 0.76 and 0.75, respectively.

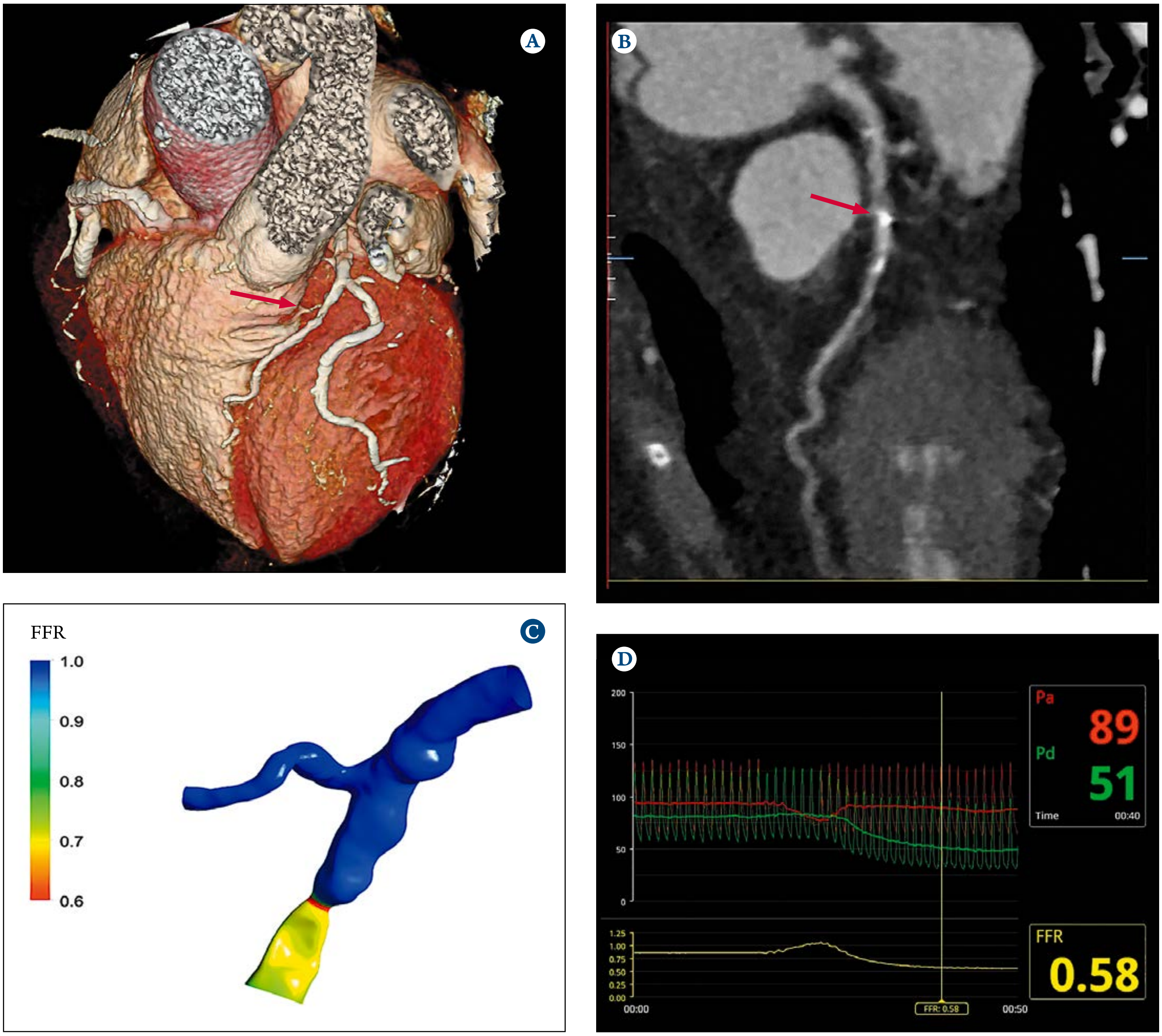
Discussion

The results of our comparative analysis of FFR_{CTA} and FFR_{INV} are intermediate since mathematical modeling of ten coronary arteries was performed at this stage of the study, which is not sufficient for appropriate statistical data processing. Moreover, our study was significantly limited by the inclusion of patients with borderline stenosis. This approach was driven by the clinical feasibility of invasive measurement of FFR in this category of patients in order to decide on revascularization. In moderate or marginal stenosis, the pressure gradient in the artery is low before and after stenosis. Therefore, the FFR values are in the so-called gray zone, i.e., close to 0.8, when a small deviation may be significant for assessing hemodynamic significance stenosis. Nevertheless, despite these limitations, the regression analysis showed a good correlation between the calculated and invasively measured FFR values.

Recent studies have shown good comparability between FFR_{CTA} and FFR_{INV} and demonstrated the relationship of FFR_{CTA} to unfavorable outcomes of CAD in ambulatory patients [16–19]. Large multicenter studies reported that the quality of 71–89% of CTA data was sufficient to calculate FFR [17]. The purposeful optimization of CTA protocols made it possible to increase the number of high-quality images for the FFR calculation to 97–99% [20, 21]. The PROMISE study found a strong correlation between FFR_{CTA} and the severity of stenosis, while discrepancies between CTA data and FFR_{CTA} values were observed in 31% of patients [18]. These data are consistent with the results of the FAME study, which showed 25% of discrepancies in the FFR_{INV} values compared with the findings of invasive CAG [22].

After analyzing the ROMICAT II data, Ferencik et al. [23] found a strong relationship between FFR_{CTA} <0.8 and the final diagnosis of ACS in patients hospitalized with acute chest pain without ST-segment elevation on ECG. Among 27 patients with ACS, 23 (85%) had FFR_{CTA} ≤0.8. This study showed once again that the hemodynamic significance of stenosis is an essential predictor of ACS in acute chest pain. The data obtained by Ferencik et al. [23] are consistent

Figure 2. Case study (patient #4) 52-year-old male with acute coronary syndrome shown by computed tomography



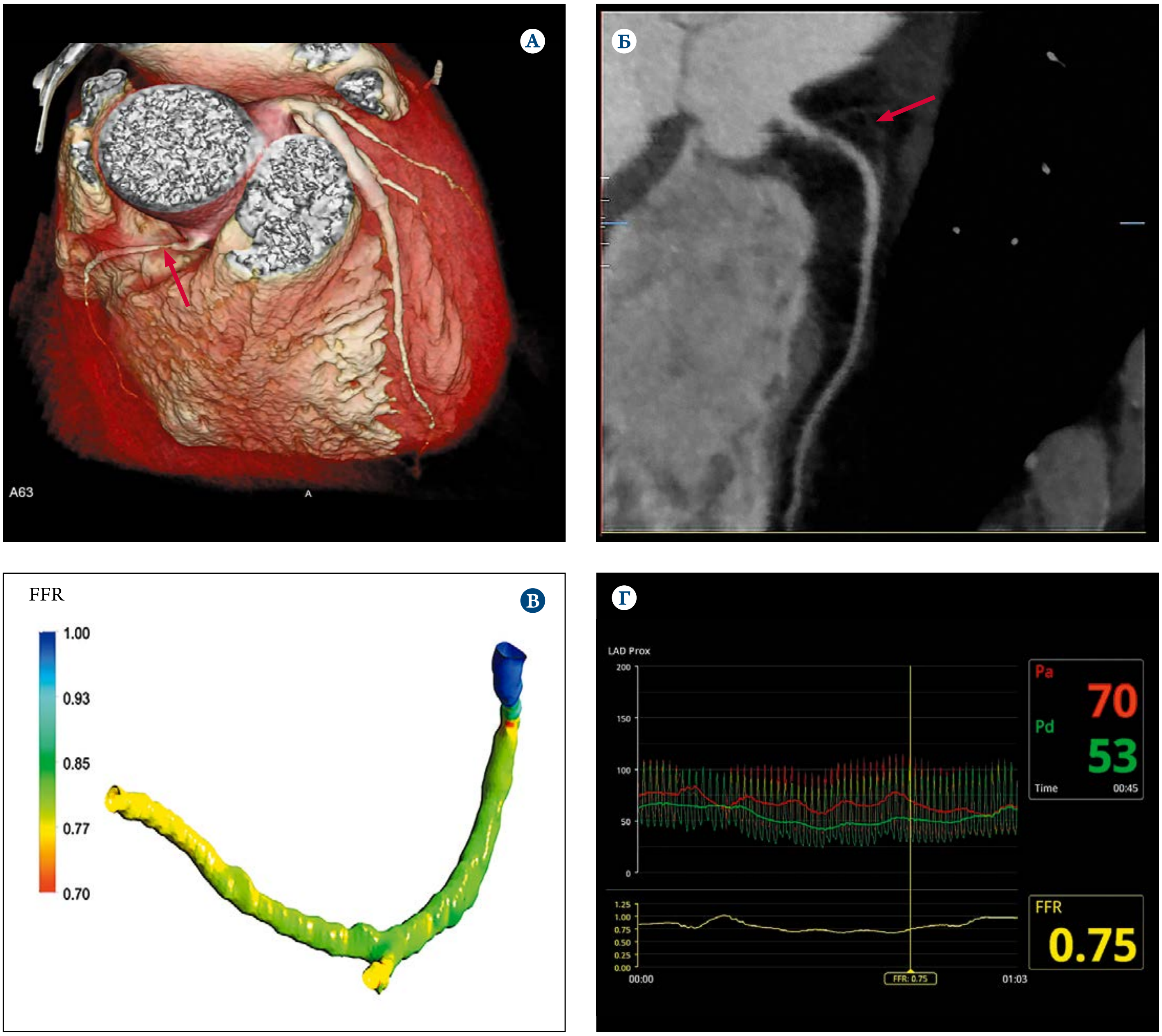
A – 3D reconstructions; B – multiplanar reconstructions:
70% stenosis of the left anterior descending artery (arrows); C – FFR_{CTA} = 0.6;
D – FFR_{INV} = 0.58, which confirms the hemodynamic significance of the stenosis.
FFR – fractional flow reserve; CTA – computed tomographic angiography. FFR_{INV} – invasively measured fractional flow reserve.

with the results of the PROMISE study, in which the hemodynamic significance of stenosis based on FFR_{CTA} was more frequently associated with the number of revascularization procedures and cardiovascular complications than with the severity of stenosis based on CTA (odds ratio 4.31 vs. 2.90; p=0.033). These findings show the need for further study of the relationship between the anatomical and functional parameters of the coronary system, which is important for predicting coronary complications and making revascularization decisions, especially in borderline stenosis.

We have demonstrated the possibility of assessing FFR_{CTA} in patients with acute chest pain without ischemic changes on ECG and with a negative troponin test. Preliminary research data showed that, in the case of FFR_{CTA} assessment in patients without pronounced calcification, the construction of a 3D vascular model produces data consistent with the invasive measurement of FFR. However, in the presence of severe calcification and minimal vessel lumen, the computational results are unstable and depend on the algorithm parameters used to detect and remove calcifications (threshold

ISSN 0022-9040. Kardiologiia. 2021;61(7). DOI: 10.18087/cardio.2021.7.n1540

Figure 3. Case study (patient #5) 68-year-old male with clinical signs of acute coronary syndrome based on computed tomography



A – 3D reconstructions; B – multiplanar reconstructions: 75% stenosis of the right coronary artery (arrows);
C – FFR_{CTA} = 0.76; D – FFR_{INV} = 0.75, which confirms the hemodynamic significance of the stenosis.
FFR – fractional flow reserve; CTA – computed tomographic angiography.
FFR_{INV} – invasively measured fractional flow reserve.

values, parameters of the methods of mathematical morphology applied, etc.). For such cases, the proposed method requires further experiments and clarification of the algorithms used.

Conclusion

Based on the results of computational experiments, we can conclude that the calculated values of the fractional flow reserve based on the developed mathematical model are comparable with the invasively measured fractional flow reserve. Further development of the mathematical modeling of volumetric blood flow based on computed tomographic angiography data is a promising area of cardiology in Russia. However, in order to consider all possible types of calcifications and a hydrodynamic model of blood flow with an appropriate correct accounting of the margin conditions and viscous flow models, it is necessary to further clarify the 3D geometric model of coronary arteries. In order to solve this problem and validate the calculated values of fractional flow reserve, more patients will need to be included in the study.

Funding

The study was supported by the Russian Foundation for Basic Research as a part of projects #18-29-26012 and #18-29-26007.

No conflict of interest is reported.

The article was received on 25/01/2021

REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019;40(2):87–165. DOI: 10.1093/eurheartj/ehy394
2. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P et al. Prognostic Value of Fractional Flow Reserve: Linking physiologic severity to clinical outcomes. Journal of the American College of Cardiology. 2014;64(16):1641–54. DOI: 10.1016/j.jacc.2014.07.973
3. Koo B-K, Erglis A, Doh J-H, Daniels DV, Jegere S, Kim H-S et al. Diagnosis of Ischemia-Causing Coronary Stenoses by Noninvasive Fractional Flow Reserve Computed From Coronary Computed Tomographic Angiograms. Journal of the American College of Cardiology. 2011;58(19):1989–97. DOI: 10.1016/j.jacc.2011.06.066
4. Coenen A, Lubbers MM, Kurata A, Kono A, Dedic A, Chelu RG et al. Fractional Flow Reserve Computed from Noninvasive CT Angiography Data: Diagnostic Performance of an On-Site Clinician-operated Computational Fluid Dynamics Algorithm. Radiology. 2015;274(3):674–83. DOI: 10.1148/radiol.14140992
5. Nørgaard BL, Fairbairn TA, Safian RD, Rabbat MG, Ko B, Jensen JM et al. Coronary CT Angiography-derived Fractional Flow Reserve Testing in Patients with Stable Coronary Artery Disease: Recommendations on Interpretation and Reporting. Radiology: Cardiothoracic Imaging. 2019;1(5):e190050. DOI: 10.1148/ryct.2019190050
6. Agasthi P, Kanmanthareddy A, Khalil C, Egbuche O, Yarlagadda V, Sachdeva R et al. Comparison of Computed Tomography derived Fractional Flow Reserve to invasive Fractional Flow Reserve in Diagnosis of Functional Coronary Stenosis: A Meta-Analysis. Scientific Reports. 2018;8(1):11535. DOI: 10.1038/s41598-018-29910-9
7. FDA. 510(k) Premarket Notification. [Internet] Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
8. NICE. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical technologies guidance [MTG32]. [Internet] Available at: https://www.nice.org.uk/guidance/mtg32
9. Colleran R, Douglas PS, Hadamitzky M, Gutberlet M, Lehmkuhl L, Foldyna B et al. An FFR CT diagnostic strategy versus usual care in patients with suspected coronary artery disease planned for invasive coronary angiography at German sites: one-year results of a subgroup analysis of the PLATFORM (Prospective Longitudinal Trial of FFR CT: Outcome and Resource Impacts) study. Open Heart. 2017;4(1):e000526. DOI: 10.1136/openhrt-2016-000526
10. Mahmoudi M, Nicholas Z, Nuttall J, Bresser M, Maishman T, Berry C et al. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain: Rationale and Design of the FORECAST Trial. Cardiovascular Revascularization Medicine. 2020;21(7):890–6. DOI: 10.1016/j.carrev.2019.12.009
11. Ternovoy S.K., Chepovskiy A.M., Veselova T.N., Borisenko V.V., Serova N.S. Mathematical modeling of coronary blood flow to assess the functional significance of stenotic lesion according to computed tomography. Russian Electronic Journal of Radiology. 2019;9(2):205–12. [Russian: Терновой С.К., Чеповский А.М., Веселова Т.Н., Борисенко В.В., Серова Н.С. Математическое моделирование коронарного кровотока для оценки функциональной значимости стенотического поражения по данным компьютерной томографии. Российский Электронный Журнал Лучевой Диагностики. 2019;9(2):205-12]. DOI: 10.21569/2222-7415-2019-9-2-205-212
12. Borisenko V.V., Veselova T.N., Ternovoy S.K., Chepovskiy A.M. Building a 3D model of heart vessels with the removal of calcifications. Systems of high availability. 2020;16(3):58–65. [Russian: Борисенко В.В., Веселова Т.Н., Терновой С.К., Чеповский А.М. Построение 3D-модели сосудов сердца с удалением кальцинатов. Системы высокой доступности. 2020;16(3):58-65]. DOI: 10.18127/J20729472-202003-06
13. Borisenko V.V., Serova N.S., Chepovskiy A.M. Reconstruction of Three-Dimensional Geometry of the Vessels by Computed Tomography Data. Vestnik NSU. Series: Information Technologies. 2019;17(3):5–17. [Russian: Борисенко В.В., Серова Н.С., Чеповский А.М. Восстановление трехмерной геометрии сосудов по данным компьютерной томографии. Вестник Новосибирского государственного университета. Серия: Информационные технологии. 2019;17(3):5-17]. DOI: 10.25205/1818-7900-2019-17-3-5-17
14. Ternovoy S.K., Veselova T.N., Borisenko V.V., Blagosklonova E.R., Gavrilov A.V., Dolotova D.D. et al. Noninvasive assessment of fractional flow reserve according to coronary computed tomography angiography using hydrodynamic calculations. Russian Electronic Journal of Radiology. 2020;10(2):71–7. [Russian: Терновой С.К., Веселова Т.Н., Борисенко В.В., Благосклонова Е.Р., Гаврилов А.В., Долотова Д.Д. и др. Неинвазивная оценка фракционного резерва коронарного кровотока по данным компьютерной томографии коронарных артерий с использованием гидродинамических расчетов. Российский Электронный Журнал Лучевой Диагностики. 2020;10(2):71-7]. DOI: 10.21569/2222-7415-2020-10-2-71-77
15. Taubin G. A signal processing approach to fair surface design. SIGGRAPH '95: Proceedings of the 22nd annual conference on Computer graphics and interactive techniques. 1995. P. 351-358. DOI:10.1145/218380.218473.
16. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA et al. 1-Year Outcomes of FFR CT-Guided Care in Patients With Suspected Coronary Disease. Journal of the American College of Cardiology. 2016;68(5):435–45. DOI: 10.1016/j.jacc.2016.05.057
17. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR CT: outcome and resource impacts study. European Heart Journal. 2015;36(47):3359–67. DOI: 10.1093/eurheartj/ehv444
18. Lu MT, Ferencik M, Roberts RS, Lee KL, Ivanov A, Adami E et al. Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. JACC: Cardiovascular Imaging. 2017;10(11):1350–8. DOI: 10.1016/j.jcmg.2016.11.024
19. Ko BS, Cameron JD, Munnur RK, Wong DTL, Fujisawa Y, Sakaguchi T et al. Noninvasive CT-Derived FFR Based on Structural and Fluid Analysis: A Comparison With Invasive FFR for Detection of Functionally Significant Stenosis. JACC: Cardiovascular Imaging. 2017;10(6):663–73. DOI: 10.1016/j.jcmg.2016.07.005
20. Duguay TM, Tesche C, Vliegenthart R, De Cecco CN, Lin H, Albrecht MH et al. Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve Based on Machine Learning for Risk Stratification of Non-Culprit Coronary Narrowings in Patients with Acute Coronary Syndrome. The American Jour-

nal of Cardiology. 2017;120(8):1260–6. DOI: 10.1016/j.amjcard.2017.07.008
21. Lu MT, Meyersohn NM, Mayrhofer T, Bittner DO, Emami H, Puchner SB et al. Central Core Laboratory versus Site Interpretation of Coronary CT Angiography: Agreement and Association with Cardiovascular Events in the PROMISE Trial. Radiology. 2018;287(1):87–95. DOI: 10.1148/radiol.2017172181
22. Tonino PAL, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN et al. Angiographic Versus Functional Severity of Coronary Artery Stenoses in the FAME Study. Journal of the American College of Cardiology. 2010;55(25):2816–21. DOI: 10.1016/j.jacc.2009.11.096
23. Ferencik M, Lu MT, Mayrhofer T, Puchner SB, Liu T, Maurovich-Horvat P et al. Non-invasive fractional flow reserve derived from coronary computed tomography angiography in patients with acute chest pain: Subgroup analysis of the ROMICAT II trial. Journal of Cardiovascular Computed Tomography. 2019;13(4):196–202. DOI: 10.1016/j.jcct.2019.05.009