SHORT THESES OF THE DOCTORAL (PHD) DISSERTATION

Image-based Fractional Flow Reserve (FFR) Calculation Based on 3-dimensional (3D) Coronary Angiographic Reconstruction Data and Fluid Dynamic Equations

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Debrecen, 2022

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The Examination will be held online on April 29, 2022, at 09:00

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The PhD Defense will be held online on April 29, 2022, at 10:30

For online access please send your registration email to tarbalazsdr@gmail.com until 12:00, April 28,2022

1. INTRODUCTION, LITERATURE REVIEW

1.1. The significance of cardiovascular diseases

Cardiovascular diseases are deemed as the leading causes of death worldwide; and in the past few decades, global healthcare systems have made significant efforts for the prevention, more accurate diagnosis, as well as more efficient treatment of these conditions in order to reduce mortality and the number of life-years lost to them. Even though in comparison with the European Union average, Hungary is considerably falling behind in terms of the above mentioned indicators; a favourable tendency has been recently identified in our country. This improvement in mortality data has been facilitated by the following factors: an increase in the number of catheterization laboratories and invasive cardiologists, making primary percutaneous intervention possible in acute myocardial infarction cases; the emergence of newer-generation drug-eluting stents, increasingly more efficient intensive therapy procedures, novel methods helping the prevention and efficient treatment of short- and long-term complications (extracorporeal circulatory support devices, pacemaker implantation with primary and secondary prevention indications, the application of more efficient platelet aggregation inhibition drugs, novel medications for the treatment of heart failure, such as aldosterone antagonists, sacubitril-valsartan, and SGLT-2 receptor inhibitors); as well as state-of-the-art rehabilitation approaches. While in the vast majority of acute coronary syndromes the confirmation and localization of myocardial ischaemia with an underlying coronary disease is evident, cardiologists are still faced with a significant challenge when it comes to identifying and choosing the optimal treatment strategy for different patients with chronic coronary syndrome and tissue hypoxia, leading to declining quality of life, chest pain, and ultimately, an unfavourable prognosis.

1.2. Confirming myocardial ischaemia as an underlying cause of adverse clinical outcomes

1.2.1. A brief overview of the physiology of coronary circulation

The heart is our organ with the highest oxygen demand (50–100 μl O_2/min/g), with the extent of oxygen extraction from arterial blood being also extremely high (70–80%). An extremely complex process control system makes it possible that, between relatively broad boundaries, the coronary artery blood flow (Q) is almost independent from the aortic pressure maintaining the pressure gradient (Δp), which is necessary for sustaining the flow. The body achieves this aim by adequate adaptations of resistance (R):

$$\boldsymbol{Q = \frac{\Delta p}{R}}$$

The major levels of control determining resistance can be summarized as follows:
- myogenic control
- metabolic influence (local control: adenosine, pO_2, pCO_2, H^+, K^+)
- endothelial control (vasodilator and vasoconstrictor molecules partially influenced by shearing stress: endothelin, nitrogen-monoxide, prostacyclin, endothelial hyperpolarising factor)
- neural effect (transmitted by sympathetic-parasympathetic fibres: adrenaline, noradrenaline, acetylcholine, P-substance)
- hormonal control (angiotensin-II, vasopressin, histamine, bradykinin, thromboxane A2, serotonin)
- extravascular compression.

With an increase in oxygen demand, the amount of blood flowing in the coronary arteries also increases with the help of the above listed controlling mechanisms. However, if the extent of the increase is not sufficient and the oxygen supply cannot satisfy the increased demand anymore, ischaemia appears. From the perspective of the detection and optimal treatment of the disease, the confirmation of myocardial ischaemia is thus of key importance.

1.2.2. Confirming myocardial ischaemia by non-invasive testing

Different diagnostic modalities can detect the following ischaemia-caused signs:
- EKG changes (EKG, stress EKG),
- wall movement disorder (echocardiography, MRI),
- perfusion defect (myocardial scintigraphy, perfusion MRI, PET, contrast echocardiography).

These phenomena can present in a resting state or can be induced in the following ways:
- increasing the oxygen demand of the cardiac muscle, which can be achieved by:
- physical stress,
- drugs (dobutamine) or,
- administering pharmacological agents inducing localized changes in myocardial perfusion:
- dipyridamole,
- adenosine,
- regadenoson.

Furthermore, various imaging modalities can also be used to detect ischaemia-causing coronary stenoses (CTA, MRA).

1.2.3. Confirming myocardial ischaemia with invasive tests

1.2.3.1. Determining the velocity and volumetric flow of the blood flowing in the epicardial vessels

Already in the early stages of performing the coronary angiographies it became obvious for the investigators that one cannot draw precise conclusions concerning the actual haemodynamic significance of stenoses based exclusively on visual estimates of percent diameter coronary stenosis. When the concept of Coronary Flow Reserve (CFR), which is expressed as the ratio of the maximal flow induced by vasodilation and the resting flow, was introduced; this parameter was hoped to be able to provide a better characterization of the haemodynamic effects of stenoses, as it points beyond the morphological features of coronary stenoses. It seemed that by detecting a pathological CFR value (<2) and then supplementing the angiographic data with this functional parameter, coronary lesions could be characterized in an even more accurate manner.

Animal experiments showed a strong correlation between directly measured absolute coronary artery blood flow (ml/min) and the velocity data of Doppler measurements, as well as the values calculated from angiographic morphological data. Yet, for a long time, direct flow measurements are not a part of everyday clinical practice.

Having studied the technical difficulties of Doppler velocity ($CFR_{doppler}$) and flow determination (CFR_{flow}), a further option for the examination of coronary circulation was developed with the help of animal experiments: thermodilution-based measurements and CFR_{thermo} determination. In the case of this procedure, a coronary wire fitted with temperature sensors is applied, and the CFR ($CFR_{thermo}=Tmn_{resting}/Tmn_{vasodilatation}$) is determined from the changes in the mean transit time (Tmn) of the room temperature physiological saline solution travelling between the sensors, forming as a result of maximal vasodilatation. Following human validation, the comparison of $CFR_{doppler}$, $CFR_{thermo,}$ and CFR_{flow} (based on absolute flow measurement) was performed as well, where a close correlation was identified between the values measured with both CFR measurement methods as well as $CFR_{flow,}$ the latter serving as the basis of comparison.

A novel technique based on the thermodilution principle is the intracoronary measurement of the absolute flow. Absolute flow in the vessel is measured based on the effect the physiological saline solution has on the temperature of the blood, where the temperature of the saline solution is taken by a micro-catheter, and it is being circulated with a pre-determined speed. This method, however, is still being investigated by several clinical studies, and it is thus not currently routinely applied yet.

CFR simultaneously characterizes the effects of the stenosis in the epicardial vessel and those of the microvascular resistance pertaining to the myocardial areas of the interrogated vessel. For the purpose of characterizing myocardial microcirculation, hyperaemic microvascular resistance (HMR) is applied during Doppler measurements; while in the case of thermodilution measurement, the index of microcirculatory resistance (IMR) is used.

1.2.3.2. Investigating pressure changes measurable in epicardial vessels

Due to the above described difficulties of determining volumetric flow and blood flow velocity in epicardial coronaries, the measuring of the pressures maintaining the flow has become the focus of various studies; presuming that due to their easier applicability, these measurements can be more suitable for the characterizing of stenoses in everyday practice. As a result of such efforts, the concept of fractional flow reserve (FFR) was developed and validated. By definition, FFR is expressed as the ratio of the blood flow in a stenosed coronary artery, which is perfusing a given myocardial area during maximal vasodilation (Q_s) and the theoretically available maximal blood flow in the same area without stenosis (Q_n). Following a few simplifications, this result can be calculated in the following way from the ratio of the pressures measured distally from the interrogated stenosis under maximal vasodilation and the pressures registered simultaneously in the aorta:

$$\boldsymbol{FFR = \frac{Q_s}{Q_n}}$$

Based on Ohm's law, the flow can be expressed as the ratio of the pressure maintaining it (the difference of the arterial and venous systems: $P_a - P_v$) and the resistance hindering it (R).

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

If one succeeds in reducing the resistance to the minimal level (by inducing maximal vasodilatation), and if the venous pressure is presumed to be negligible, then the equation can be further simplified:

$$\boldsymbol{FFR = \frac{P_d}{P_a}}$$

In possession of the data derived from clinical studies, currently FFR $\leq$ 0.8 is the cut-off value characterising haemodynamically significant stenoses. The studies DEFER, FAME I and II have provided definitive proof that:

- the revascularisation of non-significant stenoses does not bear any clinical benefits,
- in the case of multi-vessel disease, an FFR-driven intervention is more advantageous than angiographic assessment-based decision-making,
- FFR-based decision-making leads to significantly fewer major cardiovascular events (MACE) only in comparison with drug therapy.

Based on the above results, the latest guideline recommends FFR measurement on the highest evidence level (class I, level A) in cases where there is no non-invasively confirmed ischaemia present in the vessel segment with intermediate stenosis.

The vasodilators administered during FFR determination might cause a slight discomfort in a small group of patients. Also, the induction of vasodilatation and the waning of the drug effect might increase the examination time with a few minutes; moreover, the application of these drugs causes extra costs. These potential problems have promoted the studying of the clinical applicability of non-hyperaemic pressure parameters. It was observed during the detailed investigation of resting state pressure measurements that myocardial resistance is minimal in a certain part of diastole. The ratio of the mean distal pressure and the mean aortic pressure measured in this wave-free period was named iFR (instantaneous wave-free ratio). Intensive investigations were initiated to assess the diagnostic accuracy of iFR and the strength of the correlation between this parameter and simultaneously measured FFR. Based on the results of two major studies, an IA-level guideline currently recommends iFR measurement to assess the haemodynamic significance of intermediate stenoses.

Besides iFR, classical resting state distal and aortic pressure ratios (Pd/Pa), as well as several other non-hyperaemic parameters were described.

In terms of diagnostic accuracy, these non-hyperaemic pressure ratios are equivalent to each other. Pressure gradients determined without the application of vasodilation, with the help of different technical devices and different methods, are also suitable for the resting state haemodynamic characterization of coronary stenoses. However, they do not accurately anticipate pressure drops forming during a hyperaemic state. Thus, without inducing vasodilatation, one cannot get a comprehensive picture of the given patient's coronary pathophysiology. Consequently, in our opinion, FFR measurements cannot be omitted from daily clinical practice at present.

1.2.4. Previous attempts at the substitution of FFR measurement

1.2.4.1. Previous attempts at calculating measurable invasive haemodynamic parameters

After improving the general formula of pressure drop forming on coronary stenoses by validating it under experimental conditions and providing a more accurate description of the constants featured in it, the first calculated parameter for the description of stenoses became stenosis/stenotic flow reserve. However, the general application of this method has not gained ground in everyday clinical practice. As CFR-based stenosis specification was replaced by FFR-based decision-making on the basis of evidence from several clinical studies, FFR modelling became a significant field of research.

1.2.4.2. The methodology of FFR modelling

Despite the fact that the necessity of FFR measurement is underlined by strong evidence-based guidelines, its application still varies between wide margins and shows a very low frequency (10–20%). With regard to the above facts, for several years the development of methods which could fully or in certain cases completely obviate FFR measurement has been the subject of several studies. These procedures are collectively referred to as image-based FFR determination.

The above methods can be further classified based on:

- what kind of diagnostic imaging modality is used,
- what kind of flow model is applied,
- is vasodilatation applied (hyperaemic vs. non-hyperaemic methods) during FFR calculation.

Imaging modalities used during pressure gradient calculation:

In the framework of image-based FFR calculation, various clinical studies have applied several different imaging modalities, including:

- 3D angiography following coronary angiography,
- intravascular ultrasound (IVUS),
- optical coherence tomography (OCT),
- coronary computed tomography (CCTA-FFR_{CTA}).

The mathematical models applied in pressure gradient calculation can be divided into two major groups:

- the formula described by Young et al., supplemented by further studies by Gould.
- computational fluid dynamics (CFD) models, which attempt to perform flow-related calculations in highly complex and time-consuming ways.

In the literature, two main directions of FFR calculation-related approaches can be identified. One of them is the simplification of CFD models, which requires supercomputers and several days for modelling. The other approach is the route we have taken: the refining of earlier, simpler imaging and mathematical procedures in order to ***create a feasible, yet sufficiently accurate model.***

Vasodilation applied in pressure gradient calculation:

In the majority of models developed for FFR calculation, vasodilatation is deemed unnecessary for the sake of further simplification, despite the fact that it is an inevitable, theoretically grounded condition of the invasive measuring of the pressure gradient.

In our opinion, the minimisation of vascular resistance is definitely justified during FFR measurement, because only in this way, and by ignoring venous pressure, is it possible to convert the flow ratio in its original definition into pressure ratio.

2. OBJECTIVES

1. The development of a simple, and thus widely applicable model and its integration into clinical decision-making, through which the pressure ratio (**FFR calculated by a simple method: FFR_{sim}**) and the pressure drop forming in the interrogated coronary stenosis during maximal vasodilatation can be calculated.

2. The validation of the method by FFR measurements.

3. The comparison of the diagnostic accuracy of FFR_{sim} calculated by applying the above model with the non-hyperaemic FFR value calculated without applying vasodilatation.

3. PATIENTS AND METHODS

3.1. Calculating FFR_{sim}

3.1.1. The investigated patient population

We retrospectively analysed the data of 64 patients with coronary stenoses of intermediate severity by using the database from the FARAO study, which was initiated earlier in cooperation with 4 Hungarian centres.

The cardiac catheter indication of the patients involved in the study was that they all presented with stable angina pectoris, and the performed coronarography confirmed intermediate level (40–70%) stenoses on one or several epicardial coronaries with a diameter over 2 mm. Patients with a history of bypass grafts, chronic total occlusion (CTO), bifurcation lesions, stenoses affecting orifices, as well as main stem disease were excluded from the study. The average age of the patients was 62 years, the ratio of men was 65.6%, the frequency of hypertension, diabetes mellitus, and hyperlipidemia was 79.7%, 26.6%, and 89.1%, respectively.

3.1.2. Coronary angiography and FFR measurement

Diagnostic coronary angiography images were recorded with the help of standard fluoroscopic views. If the visual assessment of the coronary stenosis deemed it intermediate (40–70% diameter stenosis), then FFR measurement was performed. 150–200 μg adenosine was administered intracoronary, followed by an angiography – still under maximal vasodilation – in order to identify the optimal position of the pressure-measuring sensor under maximal hyperaemia. These frames were later used for the calculation of coronary blood flow velocity. If the FFR value was ≤ 0.80, the coronary stenosis was regarded as haemodynamically significant and in line with professional guidelines, a percutaneous coronary intervention (PCI) was performed.

3.1.3. 3-dimensional (QCA) reconstruction

As our model required highly specific anatomical data, 3-dimensional (3D) imaging was necessary, which was performed by a dedicated software (QAngio XA Research Edition 1.0, Medis Specials bv, Leiden) following the invasive measurements. The interrogated vessel segment was reconstructed in 3D from the origin of the given coronary to the level of the pressure-measuring sensor. The highly precise data derived this way were used for the calculation of FFR_{sim} values.

3.1.4. Determining the volumetric flow required for FFR_{sim} calculation

3.1.4.1. Applied flow dynamics equations

FFR can be calculated after determining the pressure drop forming on the stenosis, in the knowledge of the arterial pressure.
In the model developed by us, the flow equations were applied in the following way.

- $\Delta p = f*Q + s*Q^2$
- $\Delta p_{laminarflow} = [(8*\pi*\eta*L)/A^2]*Q$
- $\Delta p_{flowseparation} = k*\rho/0{,}266*(1/MLA - 1/A_{distal})^2*Q^2$

$$k = 1{,}21*0{,}08*[L_{lesion}/(2*D_{lesionref.})]$$

ρ – blood density (1055 g/l)

η- blood viscosity (3.5 cPoise)

L – lesion length (mm)

3.1.4.2. The anatomical model

In our calculations, the data required by the above equations were derived from an anatomical model created with 3D reconstruction in order to solve the flow equations.

3.1.4.3. Determining the volumetric flow

To calculate the flow (Q), we took mean flow velocity as a basis. For the sake of defining the „distance" ($s_{contrast}$) necessary for the precise calculation of velocity, we used the position of the pressure sensor as a distal endpoint of reference, while the proximal point of reference was the level of the vessel's originating. The exact length of the vessel segment was determined by 3D reconstruction. The time necessary for the given distance ($t_{contrast}$) was calculated based on the image recording speed (15 or 30 frames/sec) and the frame count ($TIMI_{frame\ count}$).

$$t_{contrast} = TIMI_{frame\ count} * 1/15\ (sec)$$

or

$$t_{contrast} = TIMI_{frame\ count} * 1/30\ (sec)$$

(depending on image-recording speed)

The mean velocity of the blood mixed with contrast material, that is, the mean velocity of the blood flow in the interrogated coronary segment, was determined in the following way:

$$v_{contrast} = s_{contrast} / t_{contrast}$$

The calculation of the volume flows was performed with the help of the following equations:

$$Q_{prox} = v_{contrast} \times A_{prox\text{-}average}$$

$$Q_{dist} = v_{contrast} \times A_{dist\text{-}average}$$

This concept also takes into consideration the reduction of the side branches, the distal volume flow (Q_{dsit}) decreases proportionally with the reduction of the mean area of the distal vessel segment ($A_{dist\text{-}average}$).

3.1.5. Determining calculated FFR (FFR_{sim})

By substituting the results of the above described measurements and calculations into the equation system describing the pressure changes, the pressure drop forming on the entire interrogated vessel segment can be calculated. By extracting this from the mean arterial pressure measured during the examination (p_a), the mean distal pressure becomes determinable (p_d). Based on the known formula, FFR_{sim} can be calculated as the ratio of the two pressures:

$$p_d = p_a - \Delta p_{all}$$

$$\Delta p_{all} = \Delta p_{prox.laminar} + (\Delta p_{lesion\ laminar} + \Delta p_{flow\text{-}separation}) + \Delta p_{dist.laminar}$$

$$FFR_{sim} = p_d / p_a$$

3.1.6. Statistical methods

In the case of normal distribution, constant variables were expressed as mean ± distribution, in the case of categorical variables, frequency was expressed as percentages. The strength of the relationship between FFR_{sim} and $FFR_{measured}$ was examined with the help of the Spearman's rank-order correlation. The comparative analysis of FFR_{sim} and $FFR_{measured}$ was performed with the help of the Bland−Altman plot and ROC analysis. To calculate $FFR_{sim,}$ a Microsoft Excel for Windows program was used, for the statistical analysis, a MedCalc Statistics software (14.8.1 version, MedCalc Software BVBA, Ostend, Belgium).

3.2. Comparison of the diagnostic accuracy of FFR_{sim} and calculations without the application of vasodilatation

3.2.1. Patient population

In the first phase of the study, 50 out of 64 patients had all the necessary image documentation for the performance of the calculation protocol to be detailed below.

3.2.2. Coronary angiography and FFR measurement

The methodologies of coronarography and FFR measurement are identical with the descriptions in chapter 3.1.2.

3.2.3. 3-dimensional (QCA) reconstruction

Following a cardiac catheter examination, a 3D reconstruction was prepared. The method and use of this reconstruction, as well as the description of the anatomical model used as the basis of further calculations can be found in chapters 3.1.3. and 3.1.4.

3.2.4. Calculation of fixed FFR_{sim} , rest.FFR_{sim} and *hyp.FFR_{sim}*

3.2.4.1. FFR calculation took place as described in chapter 3.1.5. The mean flow velocity data necessary to determine the volumetric flow were derived from three different methods. Taking the methodology of the FAVOR 1 study into consideration, we performed our calculations with the use of the three velocity data below.

3.2.4.2. **FixedFFR_{sim}** calculation: **$vcontrast_{vasodilatation}$** = 35cm/s, which was expressed as the empirical vasodilatation velocity determined by earlier studies.

3.2.4.3. **RestFFR_{sim}** calculation: the basis of the method is that the pressure gradient is calculated from the vasodilatation flow velocity (**HVF**: hyperaemic-flow velocity), which is extrapolated with the help of the equation describing the interrelation between resting and vasodilatation velocities derived from a database, calculated in a resting state (without using a vasodilator) from contrast-flow velocity (CFV).

$$\mathbf{CFV = v_{contrast\ resting} = s_{contrast}/t_{contrast}}$$

(as described in chapter 3.1.4.3.)

$$\mathbf{HFV = 0{,}1+1{,}55*CFV+0{,}93*CFV^2}$$

3.2.4.4. **$HypFFR_{sim}$** calculation: The determination of hyp FFR_{sim} by reaching maximal hyperaemia was performed according to the methodology developed by us and described in detail in chapters 3.1.2–3.1.5.

3.2.5. Statistical methods

We used ROC analysis, Sperman rank-correlation and the Bland–Altman plot in order to determine the diagnostic accuracy of the various methods and to compare the non-hyperaemic fixedFFR_{sim} and the restFFR_{sim} hypFFR_{sim} calculated with vasodilation, as well as the measured FFR value, which qualifies as a standard diagnostic tool.

4. RESULTS

4.1. Calculation and validation of FFR_{sim}

4.1.1. Characteristics of the investigated stenoses

In the framework of the study, we examined 64 patients' 68 coronary segments and their haemodynamic significance with the help of the method developed by us. The distribution of the 68 vessels was the following: 44 LAD, 18 CX/OM, and 6 RCA. The mean maximal diameter stenosis (DS%), the area stenosis (AS%), and the minimal lumen area (MLA) were 46%, 71%, and 1.98 cm^2, respectively, on the basis of data reconstructed by 3D–QCA.

4.1.2. Studying the correlations and correspondences between FFR_{sim} and measured FFR

Following normality tests, we performed a Sperman rank-correlation analysis. We found a close correlation between FFR_{sim} and FFR_{meas}: r (rho)=0.86 ($p<0.0001$).
The Bland–Altman plot also showed a strong correlation between the calculated and measured values: mean difference: –0.01±0.08 (p=0.579).

4.1.3. The diagnostic value of FFR_{sim} in the identification of haemodynamically significant stenoses

We evaluated the diagnostic potential of the simplified FFR_{sim} calculation by comparing the results with those of standard invasive FFR measurements. Sensitivity and specificity were 90% and 100%, respectively, in the case of pathological, haemodynamically significant ≤0.80 FFR. The positive and negate predictive value of the FFR_{sim} were 100% and 92.7%, respectively. During ROC analysis, the area under curve (AUC) was 0.96 (95% CI: [0.91–1]).
In the ranges > 0.88 and ≤0.8, FFR_{sim} showed a 100% negative, as well as a positive predictive value. In our study, 69% of the results fell into one of the above ranges, providing a solid system of classification.

4.1.4. Comparison of the diagnostic accuracy of morphological data derived from FFR_{sim} and 3D-QCA

Earlier study data have repeatedly confirmed the greater accuracy of morphological measurements derived from 3D-QCA reconstruction in comparison with 2D QCA calculations. In several other studies, authors identified greater diagnostic accuracy during FFR calculation if the method also included flow data derived from a CFD model, in comparison with the prognostic value of merely 3D morphological

data. In our study, a closer correlation was found between FFR_{sim} with a measured FFR than with 3D-MLA and 3D AS% data (AUC FFR_{sim} vs. MLA: 0.96 vs. 0.8 ($p = 0.0065$); AUC FFR_{sim} and AS%: 0.96 vs. 0.76 ($p = 0.0005$).

4.2. Comparison of the diagnostic accuracy of FFR calculation methods using hyperaemic and non-hyperaemic data

4.2.1.

During FFR_{sim} calculation, 50 patients from the examined group (27 males / 23 females) had image representations that were suitable for retrospectively performing the FFR calculation according to the three previously described methods.

4.2.2.

The correlation between hyperaemic and non-hyperaemic FFR values with measured FFR:

In our study, out of the three calculated FFR_{sim} values, $hypFFR_{sim}$ using hyperaemic velocity data showed the closest correlation with measured FFR

AUC $hypFFR_{sim}$ vs. $restFFR_{sim}$: 0.96 vs. 0.8 ($p = 0.0065$)

AUC $hypFFR_{sim}$ vs. $fixedFFR_{sim}$: 0.96 vs. 0.76 ($p = 0.0005$)

Beside the statistically significant differences between AUCs, the strongest correlation was found between FFR_{sim} and measured FFR both in terms of correlation and in the case of the Bland–Altman plot:

$fixedFFR_{sim}$	r (rho)= 0.60, p<0.0001 [0.39-0.76],
$restFFR_{sim}$	r (rho)= 0.76, p<0.0001, [0.61-0.86],
$hypFFR_{sim}$	r (rho)= 0.83, p<0.0001, [0.72-0.90].

5. DISCUSSION

5.1. Historical overview

FFR measurement is an indispensable testing method today in determining the haemodynamic effects of stenoses already mentioned in connection with coronarography. Despite IA-level guides and several clinical studies and expert opinions, it is still a rarely applied method, regardless of geographical location or the level of healthcare services, even though it is often indicated by cardiac catheter examination numbers. The under-representation of this method can be caused by several factors: the time-consuming nature of the examination, maybe a fear connected to the potential mechanical complications caused by the pressure wires, which are stiffer than standard coronary wires; the temporary and not common difficulties caused by vasodilator drugs, or even the pricing of vasodilators. Whatever the cause might be, several working groups have started research projects with the aim of identifying a method that can replace FFR measurement, and thus the determination of the haemodynamic significance of a stenosis can become possible by non-invasive method.

Already in the early stages of cardiac catheter examinations it was recognized that the visual assessment of stenoses in itself is not sufficient for the accurate evaluation of their haemodynamic effects. The pressure and flow changes presenting in stenoses were first investigated in animal experiments, and then got validated by human clinical trials. By using the Hagen–Poiseuille and the Borda–Carnot equations, a basic formula was created, describing the pressure drop in the stenosis as the sum of two components: pressure drop forming as a result of laminar flow (viscous friction) and pressure drop resulting from exit flow separation caused by turbulent flow after the blood leaves the stenotic segment:

$$\Delta p = fQ + sQ^2$$

The widespread use of measuring intracoronary velocity and flow was halted, and for several years it was almost exclusively limited to research projects, despite the fact that the early studies have already made it clear that the simultaneous measuring of flow and pressure are necessary for the accurate description of stenotic effects.

FFR indicates the haemodynamic features and consequences of the interrogated coronary stenosis, and in order to be able to calculate FFR instead of measuring it (the latter being currently recommended with an IA indication), one needs to know the aortic pressure as well as the extent of the pressure drop forming on the stenosis:

$$\boldsymbol{FFR = \frac{P_a - \Delta P}{P_a}.}$$

To calculate this value, we need to be familiar with the major anatomical features of the interrogated vessel segment, as well as the volume of the flow forming under vasodilatation.

5.2. Development of invasive and non-invasive imaging modalities

5.2.1. Yet another milestone in the morphological characterization of stenoses was quantitative angiography, the introduction and spreading of the QCA method. With this method, more accurate measurements could be performed as compared to previous ones. However, the limited assessment of asymmetry and foreshortening continued to be major error factors in a significant number of examinations.

5.2.2. The next step in the development of imaging methods was the appearance of 3D-QCA, with the help of which it became possible to describe the major morphological features of stenoses in an even more accurate way, such as: the diameter of the vessel segment preceding the stenosis, its area, the length of the stenosis, its average diameter, the minimal lumen diameter and area, as well as diameter changes following the stenosis and cross-sectional areas.

5.2.3. Novel intravascular imaging modalities also appeared, creating further possibilities for the increasingly more detailed morphological description of coronaries and stenoses. IVUS and then OCT made the morphological representation of the coronary lumen and walls more specific. Currently, both modalities are available as integrated into one system, combining the benefits of the two imaging modalities.

5.2.4. Besides the evolution of invasive imaging modalities, the development of coronary CTA also created an opportunity for the detailed characterization of coronary morphology and the haemodynamic effects of the detected stenoses, without the use of invasive examinations.

5.2.5. *Selecting a morphological data source for our model*

When planning our research, we selected the **3D angiographic reconstruction** method out of all the options available to us, as it is suitable for providing sufficiently accurate results in order to determine anatomical parameters. We initially used a 3D software, integrated into a Siemens Axiom Artis x-ray device used in cath labs, and later, as this imaging modality developed, we switched to a special program which offers better and more detailed reconstruction opportunities (QAngio XA Research Edition 1.0, Medis Specials bv, Leiden).

5.3. A review of the mathematical methods applied for FFR calculation

Basically, two main methods were developed side by side:

5.3.1. Simple mathematical models took the classic Lance–Gould formula as their basis, and different working groups tried to achieve a more accurate approach by modifying frictional (f) as well as separation (s) constants.

5.3.2. Another methodology is the CFD model, originating in the engineering sciences, gradually gaining ground in the medical sciences as well, with the help of which pressure changes can be simulated to model flow relations in any area of the human vascular system, including the coronaries, to be examined in a very specific, but also highly time-consuming manner.

5.3.3. *Selecting a calculation method used in our model*

Already at the beginning of the research we set the goal that we would like to develop a method that can actually be useful in everyday clinical practice. Thus, we selected an imaging and calculation method that we believed to be sufficiently accurate but still available in an average cath lab.

We followed the modifications of classical fluid dynamic equations, and selected a formula which is sufficiently accurate and widely cited in the literature. This formula used to be considered inaccurate due to the use of morphological data obtained from 2D QCA.

In the course of the tests, it emerged as a novel idea that by applying the combination of the improved version of the classical equation and 3D-QCA we could calculate the pressure drops in the interrogated stenoses, and throughout this, as well as in the knowledge of the aortic pressure, also the FFR value characterizing the lesion could be computed.

With the application of the CFD model in the investigations, it became obvious that the method requires special, high-performance IT background. Initially, more than 24 hours were necessary for the calculations, and as a result, the method could not immediately support the interventional cardiologist's clinical decision-making process in the cath lab. Thus, a necessary condition of the continued use of the CFD method became the reducing of examination time. Also, recent examination data suggested that the simplification of the CFD method also entails a greater potential for error and that the difference from measured FFR values is especially expressed in the case of severe stenoses. Still, our idea on the basis of the initial results still was that we had to create a sufficiently accurate, yet simple, quick, and cost-effective method. Our concept was also supported by the fact that we identified a working group who, instead of using the earlier CFD-based approach, later applied a calculation method based on classical fluid dynamics equations in order to estimate the FFR. Eventually, this model has come to be the foundation of the QFR method, which is widely applied today.

5.4. Key steps of the proposed model, potential sources of error

5.4.1. Performing 3D (QCA) reconstruction

High-quality angiography-derived images are necessary for an optimal 3D reconstruction. We select two frames, recorded with at least a 25° difference in angle, with an unchanged iso-center, which clearly show, without overlapping, the vessel segment including the interrogated stenosis. The two frames identified this way are then imported into a 3D reconstruction program. If the contours recommended by the computer algorithm in the stenosis are unsatisfactory, they can be modified. We aim at performing as few manual corrections as possible, so as to achieve the most objective reconstruction result. We provide the length of the interrogated vessel segment, from the origin of the vessel to the level of the pressure-measuring sensor, in order to make the reconstruction free of foreshortening and to obtain a detailed morphological description. The entire length of the reconstructed vessel segment is used for the calculation of flow velocity, while the anatomical parameters of the stenosis and the segments before and after the stenosis are substituted into the appropriate parts of the equation characterizing the pressure drop.

5.4.2. Determining flow data

When calculating the data necessary to solve the equation describing the extent of the pressure change, we introduced a new methodology, which has not been applied in the literature before. Since the introduction of TIMI frame count (TFC), there has been a generally applied method of characterizing the blood flow in the coronaries by counting the frames necessary for the reaching of dedicated anatomical targets with the help of contrast material flow fronts identified during the angiography. To our knowledge, we are the first to propose that the coronary blood flow velocity and the size of the flow can be calculated – whether in a resting state or under maximal vasodilation – as the ratio of the time parameter received from the calculation of TFC and the distance data derived from the 3D (QCA) reconstruction of the coronary segment of a freely chosen location and length.

Determining the time taken to travel the full length of the reconstructed vascular segment by following the front of the contrast agent is a key step in the model, which has several potentials for error.

The forward-moving contrast quantity is significantly reduced by the large amount of contrast material flowing back into the aorta in the case of a flow accelerated under vasodilation and a non-coaxial catheter position, resulting in the hindering of visual assessment. Our tests did not confirm the significant effect of the actual moment of the cardiac cycle and the starting of the contrast material.

This phenomenon could be explained by the fact that in most cases the assessment included both systolic and diastolic frames, on the other hand, if stenoses were present, in the changed distal flow profile, significant differences were neutralized between the stenosis-free vessels and the systolic and diastolic velocity integrals. In the course of our examinations, we injected 5 ml contrast dye with a 3 ml/sec speed under standard circumstances, as generally applied in catheter laboratories, by using an ACIST^{TM} device.

Based on these circumstances, the contrast material enters the main stem with a 118 cm/sec speed, when using a 6F size guiding catheter with an inner diameter of 1.8 mm and taking into consideration the contrast dye injection speed of 3 ml/sec. This is somewhat greater than the hyperaemic velocity value measured under normal circumstances in the epicardial coronaries. As a result, in the proximal segment of the interrogated vessels, the contrast flow can be even faster than the blood flow velocity; however, at the beginning of the medial and distal vessel segments, these velocity differences are already balanced. Following the injection of the dye, it is diluted while moving forward in the vessel, and thus, especially in the case of the long, interrogated vessel segment it might become difficult to recognize the front of the contrast material. With the increasing number of examinations and in possession of a due amount of experience, the frame count calculation can be performed increasingly safely even under vasodilation.

In everyday clinical practice, the image-recording speed while performing a coronary angiography is 15 images/sec. If this speed is increased to 30 images/sec (only for the purpose of reducing exposure to radiation during the velocity measurement), then the time unit necessary for the calculations is reduced from 0.067 seconds (1/15 s) to 0.033 seconds (1/30 s), consequently making the velocity determination even more precise.

In general, in the case of image-based FFR calculation the opinion is becoming increasingly dominant that in the course of the calculation, the induction of maximal vasodilation may be obviated. This approach is especially supported by reasons connected to financial and patient protection reasons, as well as the reduction of examination time. In a meta-analysis including 13 studies, apart from our publication, vasodilatation was only induced in two other studies, in 10 other studies no vasodilator drugs were used. Even though this meta-analysis did not identify a statistically significant difference between the two study methods, we still find it advantageous to apply maximal vasodilation. The reason for this is that this way in the given examination unforeseeable microvascular resistance can be fully switched off, and also, higher flow velocity can be achieved. Ignoring these factors might explain the inadequate accuracy of calculations without vasodilatation.

Even if the extent of the resting flow is known exactly, we do not have information concerning the extent of the vasodilatation compensatory processes used by the given patient’s body to maintain this flow. Thus, it cannot be estimated either how much potential is available for further compensations, that is, how much higher the extent of the flow can rise if the increased oxygen demand of the myocardial muscles requires it.

The state and reactivity of the microvasculature is influenced by several factors:

- risk factors (sex, age, obesity, hyperlipidemia, smoking, early menopause, insulin resistance)
- co-morbidities causing a significant cardiovascular risk (hypertension, diabetes mellitus, chronic kidney disease)
- chronic auto-immune and rheumatoid diseases

- coronary atherosclerosis (prior myocardial infarction, its extent, the extent of a potential collateral network)
- non-atherosclerotic heart diseases (aortic stenosis, hypertrophic cardiomyopathy, myocarditis, post-COVID 19 condition, dilated cardiomyopathy)
- the above risk factors as well as the dose of the drugs used for the treatment of these diseases, compliance with drug therapy, reaching target blood pressure, blood fat and blood sugar values.

On the basis of all this, it is fully understandable that the uncertain interplay of so many factors makes the estimation of microvascular reaction highly difficult.

Crucial data have been recently published in a clinical study concerning the relationship between microvasculature and the QFR determination method, as well as the effect of microvascular dysfunction on the diagnostic accuracy of QFR, which is the most intensively studied one currently and does not require vasodilatation. In the framework of a multi-centre study, the diagnostic accuracy was significantly worse in patients with a high IMR: in the case of 46% of patients, a wrong decision would have been made on the basis of QFR data, leading to revascularisation (PPV:67), or they would have wrongly recommended drug therapy only (NPV: 87).

Moreover, patients suffering from microvascular damage made up 28% of the examined population. In the course of the meta-analysis of the clinical studies performed with QFR, the data concerning the diagnostic accuracy of QFR were the following: (819 patients, 969 interrogated vessels) sensitivity 84% (95%CI: 77–90, $I^2 = 70.1$), specificity 88% (95%CI: 84–91, $I^2 = 60.1$); positive predictive value 80% (95%CI: 76–85, $I^2 = 33.4$), negative predictive value 95% (95%CI: 93–96, $I^2 = 75.9$). On the basis of the above data, in a general population, the performing of interventions guided by QFR measurements leads to inadequate decisions in 25% of the cases!

The complete replacement of FFR measurements will probably not be possible later on either. The methods targeting calculations fit the examination processes in a way that the measurement is not recommended below and over a cut-off value (for example in the case of $FFFR_{sim}$ values below 0.8 and over 0.88), which is characteristic of the given method and indicates with great accuracy negative or positive results. However, in the case of the grey zone in between the two, it has to be performed by all means. This way, in comparison with the present situation, proportionally fewer invasive pressure measurements would be needed, and as a result, in the really relevant cases the examination would be more probable to be actually performed. With the application of $FFR_{sim,}$ for instance, in 69% of the clinically indicated cases FFR measurement was possible to be obviated.

Image-based FFR models, based on the application of a similar algorithm, may prove the most useful in the decision-making process concerning the revascularization of patients in everyday practice, thus contributing to better clinical outcomes, the improvement of the quality of life of patients living with chronic coronary syndrome, as well as the reduction of mortality.

6. SUMMARY

FFR determination has become the golden standard for assessing the haemodynamic significance of intermediate coronary stenoses and predicting the need for intervention as well as the prognosis of the disease. Despite a considerable amount of evidence and high-level (IA) recommendations, this method is still under-represented in cardiac catheterisation laboratories. Methods attempting to determine the FFR value of a given lesion without intravascular pressure measurements are currently the subjects of intensive research.

In our research, we have developed a method that can predict the measured FFR with high accuracy by relying on morphological data obtained from 3D coronary angiography and the Lance–Gould formula, which was previously used and later modified to calculate pressure drops forming at coronary stenoses. This way, the method is capable of the prediction of invasively measured FFR values with high accuracy.

The method was validated with pressure wire FFR measurements retrospectively collected from multiple centres. We proposed a diagnostic algorithm that uses FFR_{sim} to select those from the patient population under study who definitely need intervention and those who can only receive conservative treatment. This approach can obviate invasive FFR measurement in certain cases, thus contributing to the successful performance of this procedure in the case of patients who are really in need of it.

7. KEY OBSERVATIONS

Based on the results of our research, the following new findings can be summarized:

1. Using our proposed model, pressure drops in coronary stenoses can be calculated from 3D (QCA) reconstruction and TIMI frame count data with an accuracy level acceptable from the perspective of daily clinical practice.

2. FFR_{sim} calculated from the model shows a close correlation with invasively measured FFR values.

3. The method can be applied to haemodynamically characterize coronary stenoses of intermediate severity, thus reducing the number of pressure wire-based FFR measurements.

4. Diagnostic accuracy can be improved by using vasodilatation during image-based FFR determination.

8. ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor and current head of department, Dr. Zsolt Kőszegi, for the continued support he provided during the entire research process and the writing of the dissertation, including several Hungarian and international presentations and publications on which it is based.

I thank Prof. Dr. Péter Polgár, my former head of department, as well as Prof. Dr. István Édes and Prof. Dr. Zoltán Csanádi, former and current chairs of the Institute of Cardiology, University of Debrecen Clinical Center, for making it possible to pursue my research at their institute.

Also, I am grateful to all of my colleagues for their help and support during the research process.

Finally, I am especially grateful to my family, who supported my work all the way through and bore with me even in the most intense periods of preparing the individual publications, when I was not the attentive husband, the caring child, and good father I meant to be.

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Nyilvántartási szám: DEENK/486/2021.PL
Tárgy: PhD Publikációs Lista

Jelölt: Tar Balázs
Doktori Iskola: Laki Kálmán Doktori Iskola

A PhD értekezés alapjául szolgáló közlemények

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A közlő folyóiratok összesített impakt faktora: 35,904
A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre): 6,755

A DEENK a Jelölt által az iDEa Tudóstérbe feltöltött adatok bibliográfiai és tudománymetriai ellenőrzését a tudományos adatbázisok és a Journal Citation Reports Impact Factor lista alapján elvégezte.

Debrecen, 2021.11.08.

DEBRECENI EGYETEM Egyetemi és Nemzeti Könyvtár