Pressure- and 3D-derived coronary Flow Reserve with Hydrostatic Pressure Correction - A Validation by Intracoronary Doppler Measurements

Balázs Tar

Szabolcs-Sztamár-Bereg County Hospital

András Ágoston

Szabolcs-Szatmár-Bereg County Hospital

Áron Üveges

Szabolcs-Szatmár-Bereg County Hospital

Gábor Tamás Szabó

University of Debrecen: Debreceni Egyetem

Tibor Szűk

University of Debrecen: Debreceni Egyetem

András Komócsi

University of Pecs Medical School: Pecs Tudományegyetem Általános Orvostudományi Kar

Dániel Czuriga

University of Debrecen: Debreceni Egyetem

Benjámín Csippa

Budapest University of Technology and Economics: Budapesti Műszaki és Gazdaságtudományi Egyetem

György Paál

Budapest University of Technology and Economics: Budapesti Műszaki és Gazdaságtudományi Egyetem

Zsolt Kőszegi (✉ koszegi@med.unideb.hu)

University of Debrecen: Debreceni Egyetem <https://orcid.org/0000-0002-2817-6900>

Research Article

Keywords: Stable angina, Fractional flow reserve (FFR), Coronary flow reserve (CFR), Quantitative coronary angiography, Coronary microvascular disease, Microvascular resistance reserve (MRR)

Posted Date: December 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1181479/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

**Pressure- and 3D-derived coronary flow reserve with hydrostatic pressure correction:
a validation by intracoronary Doppler measurements**

Balázs Tar MD^{2,3}, András Ágoston MD^{2,3}, Áron Üveges MD^{2,3}, Gábor Tamás Szabó MD^{1,2}, Tibor Szűk MD, PhD^{1,2}, András Komócsi MD, PhD⁴, Dániel Czuriga MD, PhD^{1,2}, Benjámín Csippa MSc⁵, György Paál PhD⁵, Zsolt Kőszegi MD, PhD¹⁻³

¹Institute of Cardiology, University of Debrecen, Debrecen, Hungary

²University of Debrecen, Kálmán Laki Doctoral School of Biomedical and Clinical Sciences, Debrecen, Hungary

³Szabolcs – Szatmár – Bereg County Hospitals and University Teaching Hospital, Nyíregyháza, Hungary

⁴Heart Institute, Medical School, Pécs, Hungary

⁵Department of Hydrodynamic Systems, Budapest University of Technology and Economics, Budapest, Hungary

*These authors equally contributed to this work.

Short title: Pressure and 3D-derived coronary flow reserve

Corresponding author:

Zsolt Kőszegi, M.D., Ph.D.

Institute of Cardiology, University of Debrecen

Móricz Zs. krt. 22, H-4032 Debrecen, Hungary

Tel./Fax: +36 52 255928; E-mail: koszegi@med.unideb.hu

Abstract

Purpose: To develop a method of coronary flow reserve (CFR) calculation derived from three-dimensional (3D) coronary angiographic parameters and intracoronary pressure data during fractional flow reserve (FFR) measurement.

Methods: Altogether 19 coronary arteries of 16 native and 3 stented vessels were reconstructed in 3D. The measured distal intracoronary pressures were corrected to the hydrostatic pressure based on the height differences between the levels of the vessel orifice and the sensor position. Classical fluid dynamic equations were applied to calculate the flow during the resting state and vasodilatation on the basis of morphological data and intracoronary pressure values. 3D-derived coronary flow reserve (CFR_{p-3D}) was defined as the ratio between the calculated hyperemic and the resting flow and was compared to the CFR values simultaneously measured by the Doppler sensor ($CFR_{Doppler}$).

Results

Haemodynamic calculations using the distal coronary pressures corrected for hydrostatic pressures showed a strong correlation between the individual CFR_{p-3D} values and the $CFR_{Doppler}$ measurements ($r=0.89$, $p<0.0001$). Hydrostatic pressure correction increased the specificity of the method from 46.1% to 92.3% for predicting an abnormal $CFR_{Doppler} <2$.

Conclusions: CFR_{p-3D} calculation with hydrostatic pressure correction during FFR measurement facilitates a comprehensive haemodynamic assessment, supporting the complex evaluation of macro- and microvascular coronary artery disease.

Key words

Stable angina; Fractional flow reserve (FFR); Coronary flow reserve (CFR), Quantitative coronary angiography; Coronary microvascular disease, Microvascular resistance reserve (MRR)

Abbreviations

APV average peak velocity at **rest** or during vasodilatation (**vd**) measured by Doppler wire

CFR coronary flow reserve

LCX left circumflex coronary artery

f friction-related pressure loss coefficient

FFR fractional flow reserve

LAD left anterior descending coronary artery

MLA minimum lumen area

MRR microvascular resistance reserve

OM obtuse marginal branch

Pd_{corr}: corrected distal coronary pressure for hydrostatic pressure

Pd/Pa ratio of distal to aortic coronary pressure

Q calculated volumetric flow

RCA right coronary artery

R_μ resistance of the microvasculature

ΔP_{hydrostatic pressure} hydrostatic offset

Introduction

According to the current European guideline on coronary revascularization, pressure wire-derived fractional flow reserve (FFR) measurement is recommended for the functional assessment of lesion severity in patients with 40–90% diameter stenosis and without prior evidence of ischemia [1]. A more recent guideline suggests the consideration of a guidewire-based coronary flow reserve CFR measurement in patients with persistent symptoms but with preserved FFR [2] based on earlier publications [3-5]. The combination of FFR and CFR evaluation may identify the potential components of ischemia originating from the decreased conductance of the epicardial vessels and the increased resistance of the microvasculature [6-9].

As a temperature sensor, the pressure-wire sensor makes it possible to calculate thermodilution, however, this method comes with several limitations, as already detailed in early validation studies [10-12]. On the other hand, the direct measurement of coronary flow velocity by a Doppler sensor is considered technically difficult to perform; consequently, it is not routinely used in clinical practice.

The resistance of the microvasculature (R_{μ}) is defined as the ratio of the distal coronary pressure divided by the distal coronary flow rate. During bolus thermodilution measurements, the resistive reserve ratio was calculated as the index expressing the ratio between hyperemic and basal microcirculation [13]. Lately, the term microvascular resistance reserve (MRR) was suggested for the same index during continuous thermodilution technique [14] and Doppler measurements [15]. MMR is calculated as the ratio of R_{μ} at rest and R_{μ} during hyperemia.

In our study, we aimed at developing a clinically applicable method for calculating specific CFR and MRR values (CFR_{p-3D} and MRR_{p-3D}) during FFR measurement, using simple hemodynamic

calculations that combine intracoronary pressure data and 3D anatomical parameters (**Figure 1**). The results of our calculations were compared to data obtained using invasive Doppler wire measurement, as a gold standard of flow assessment.

It has recently been underlined that pressure differences are systematically detectable between the different segments of the coronary arteries in the supine position [16-18]. We also investigated how the correction of distal pressure for hydrostatic pressure offset affects the pressure-derived flow determination.

Methods

Patient inclusion criteria

Patients, who underwent clinically indicated invasive physiological investigations, were selected for this study, with a single stenosis of intermediate severity (40-80% based on visual assessment) in a main branch of the epicardial coronary artery system. Cases with good quality hyperemic and resting pressure and Doppler traces were included for the evaluations. Only traces without pressure drift (<1 mmHg) confirmed by the pullback of the pressure sensor at the end of the procedure were considered. Patients with an acute coronary syndrome, left main stenosis, ostial stenosis, earlier bypass surgery or diffuse coronary artery disease were excluded. The study has been approved by the local ethics committee of the University of Debrecen and has therefore been performed in concordance with the Declaration of Helsinki.

Invasive coronary angiography and simultaneous pressure and flow measurement by ComboWire

After administering 5000 international units (IU) of intravenous, unfractionated heparin (UFH) and intracoronary glyceryl trinitrate (GTN), diagnostic angiographic cine-recordings were acquired from standard projections, using a digital X-ray equipment (Axiom Artis, Siemens). Diagnostic angiographic images were recorded at 15 frames per second. Low- or iso-osmolar contrast material (CM) (iopamidol [Scanlux] or iodixanol [Visipaque]) was injected in 5 mL fractions with a speed of 3 mL/sec using a dedicated contrast pump (ACIST CVi™, ACIST Medical Systems). If the operator detected a 40-80% diameter stenosis by visual assessment, complete physiological measurements were performed via a 6F guiding catheter, using a ComboWire equipped with both pressure and Doppler sensors (Philips Volcano, San Diego, CA, USA).

After the pressures were equalized with the sensor positioned at the level of the catheter tip, it was advanced through the coronary artery stenosis, and measurements were performed approximately 2 cm distal to the lesion. Following the basal pressure and flow measurements, 150-200 µg intracoronary adenosine was administered, and the pressure and Doppler traces were recorded. One representative measurement is presented in **Figure 2**.

Three-dimensional quantitative coronary artery reconstruction and hemodynamic calculations

Offline 3D angiographic reconstruction was performed from two selected angiograms of good quality, with an at least 25° difference in angle, using dedicated software (QAngio XA Research Edition 1.0, Medis Specials bv, Leiden). The reconstructed vessel segment was marked from the coronary orifice to the location of the wire sensors. Numerous geometric measures describing the lesion (average cross-sectional diameters and vessel segment lengths), as well as the proximally and distally connecting vessel segments were automatically obtained by the software. These values

with intracoronary pressure at the proximal and distal positions during the resting and vasodilation states were combined for hemodynamic calculations. The method and its validation are described in our previous papers in detail [19, 20].

Calculation of the MRR_{p-3D}

The resistance of the microvascular system is the ratio of the distal coronary pressure (P_d) divided by distal coronary flow (Q) during resting condition and hyperemia. The ratio of the resting and hyperemic resistance gives us the microvascular resistance reserve (MRR):

$$MRR = \frac{P_{d_{resting}}/Q_{p-3D \text{ resting}}}{P_{d_{hyperemic}}/Q_{p-3D \text{ hyperemic}}}$$

Correction of the distal coronary pressure for hydrostatic pressure

In supine position, the measured pressure difference between the catheter tip and the pressure sensor distal to the lesion originates from two components, namely the pressure loss caused by the flow through the stenosis, and the difference between the hydrostatic pressure at the catheter tip at the coronary orifice and the level of the distal intracoronary sensor (**Figure 3**).

The latter component can be referred as hydrostatic offset ($\Delta P_{\text{hydrostatic pressure}}$), and can modify the detected pressure ratio values through the “altered” distal pressure value [16-18].

The correction of distal pressure for hydrostatic pressure ($P_{d_{corr}}$) was based on the height differences between the orifice and other coronary artery segments in supine positions. The distal pressure values were corrected, using a correction factor of 0.77 mmHg hydrostatic pressure per 1 cm height difference, where blood density was taken as 1050 kg/m³ (**Figure 3**):

$$Pd_{corr} = Pd - \Delta P_{hydrostatic\ pressure}$$

Statistical analysis

Statistical evaluations were performed in MedCalc Statistical Software, Version 14.8.1 (MedCalc Software bvba, Ostend, Belgium). Following a normality test, Spearman's correlation analysis was carried out. The correlation between CFR_{p-3D} and the CFR_{Doppler} was examined both without and with hydrostatic pressure correction of the distal pressure. Agreement between CFR_{Doppler} and CFR_{p-3D} was assessed using the Bland-Altman analysis. The area under the curve (AUC) calculated by receiver operating characteristic analysis was applied to determine the diagnostic power of CFR_{p-3D} without and with hydrostatic pressure correction. Sensitivity and specificity of CFR_{p-3D} without and with hydrostatic pressure correction were calculated using the standard method.

Results

We performed simultaneous intracoronary pressure and Doppler measurement by ComboWire in 20 patients screened in the study. In 3 cases the Doppler signal quality was insufficient for the calculation, in 1 further case more than 2 mmHg drift was detected at the end of the investigation and the attempt for repeat measurement was also failed. Therefore, sixteen 16 patients (14 males, 2 females) with single, intermediate epicardial coronary stenosis were involved in the study. In 3 cases, measurements were performed both before and after stent implantation.

Patient characteristics are presented in **Table 1**. The results of 3D reconstruction and the measured physiological data are summarized for each interrogated vessel in **Table 2**.

Correlation and agreement between the results of the $CFR_{Doppler}$ measurements and calculated CFR_{p-3D} values without and with the correction for hydrostatic offset

When including morphological data from 3D coronary angiography in the hemodynamic calculation and correcting the values for hydrostatic pressure, a strong correlation was found between the individual CFR_{p-3D} values and the $CFR_{Doppler}$ measurements ($r=0.89$, $p<0.0001$). A weak, but still significant correlation was demonstrated even without the correction of hydrostatic error ($r=0.57$, $p=0.01$) **Figure 4 A-B**. The difference between the two correlations was found to be significant ($p=0.02$).

The Bland-Altman analysis showed the mean differences between the Doppler-measured and the calculated CFR_{p-3D} values with and without hydrostatic offset correction to be -0.02 (± 1.96 SD: 0.47 , -0.50) and -0.05 (± 1.96 SD: 1.38 , -1.48), respectively. After hydrostatic offset correction, the values of CFR_{p-3D} and those of $CFR_{Doppler}$ got closer without any systematic skewing suggesting a higher level of concordance **Figure 4 C-D**).

Correlation and agreement between the results of the ComboWire based MRR measurements ($MRR_{ComboWire}$) and the calculated MRR_{p-3D} values with the correction for hydrostatic offset

The calculated microvascular resistance reserve (MRR_{p-3D}) also demonstrated a good correlation with the measured $MRR_{ComboWire}$ values ($r=0.58$, $p=0.009$) **Figure 5 A**. The Bland-Altman analysis showed the mean differences between the Doppler-measured and the calculated MRR_{p-3D} values with hydrostatic offset correction to be -0.3 (± 1.96 SD: 1.5 , -2.2) with a trend of higher differences

at higher MRR values. It was found that the MRR_{p-3D} values were systematically overestimated compared to the $MRR_{CombWire}$ values **Figure 5 B**.

The results of hydrostatic offset correction on the pressure ratios and on the CFR_{p-3D} in the main coronary branches

Figure 6 shows the clustered multiple variable graphs of resting P_d/P_a (**A**), FFR (**B**), and the CFR_{p-3D} (**C**) without and with hydrostatic pressure correction. In line with the findings of our previous work [18], the correction of the hydrostatic offset resulted in specific concordant differences between the uncorrected and corrected values in the main coronary branches in both resting and hyperemic (FFR) states (**Figure 6 A and B**). The correction definitively increased the values in the LAD, while in the LCx and the RCA, the values decreased. We observed much higher differences in CFRs, especially in the range of higher CFR values (**Figure 6 C**).

Diagnostic powers of CFR_{p-3D} calculated from the distal pressure without and with hydrostatic offset correction for identifying $CFR_{Doppler} < 2$

The diagnostic power of different computations of the CFR_{p-3D} for predicting the abnormal $CFR_{Doppler}$ was assessed using the computed CFR_{p-3D} (cut-off value=2). The AUCs of the values calculated without and with hydrostatic error correction were 0.73 (CI: 0.48-0.90) and 0.96 (CI: 0.78-1.00), respectively. Correcting for hydrostatic pressure offset increased the specificity of the method from 46.1% to 92.3%, while the sensitivity of both calculations was 100%.

Discussion

In a pioneering research, the pressure drop across an arterial stenosis was estimated satisfactorily by simple flow equations [21]. Later the 3D anatomical characteristics of the coronary artery were also incorporated into computational fluid dynamics calculations leading to the virtual, image based FFR assessment [22-24]. Recently, the possibility to determine coronary flow from invasively measured intracoronary pressure has been arisen by “backward” calculations [25, 26]. The so-called pressure-bounded coronary flow reserve (CFR_{pb}) assessment identified the possible range of CFR according to the resting and hyperemic pressures.

Wijntjens and colleagues compared the CFR_{pb} to flow-derived CFR defined by thermodilution and Doppler measurements in 453 intermediate coronary lesions, but they found a poor diagnostic agreement between the two estimations [27]. It is important to emphasize, that in this publications, hydrostatic offset correction of the distal coronary pressure was not applied to CFR calculations.

Similar to the method presented in this article, an absolute flow calculation with fluid dynamic computation (CFD) using the Ansys software (Q_{CFD}) was recently published by Morris et al [28]. In contrast with our method where the distal flow is rendered to the tapered vessel size [19], their *in vitro* and *in vivo* models, did not account for flow to side branches, resulting in underestimation of the volumetric flow [29]. This underestimation could lead to unlikely low resting and hyperemic calculated flow values in major coronary branches, as was pointed out in the editorial responding to their paper [30]. It is very obvious that in their *in vivo* study the hydrostatic pressure error had caused at least partly the very weak correlation to the Doppler results.

The direction of the effect of the hydrostatic offset depends on the orientation of the sensor in the distal position relative to the coronary orifice.

If one interrogates distal LAD with the sensor, the hydrostatic pressure is lower in supine position, which results in higher pressure ratios after hydrostatic offset correction. In contrast, LCx takes a downward course, which leads to higher hydrostatic pressure at the level of the sensor, and consequently the pressure values are lower compared to the measured one following correction. The height correction of RCA measurements can result a slight increase of the distal pressure value, as the distal sensor in the distal RCA is at a lower level compared to the orifice (**Figure 6 A and B**) [18]. Thus, a slight increase in the corrected pressure ratios can be observed (**Figure 6 A and B**).

In our opinion, the correction of distal pressure for hydrostatic pressure is essential when determining pressure-derived CFR. A minor hydrostatic pressure may have a significant influence on the measured pressure gradient, especially in resting state.

This phenomenon is demonstrated in **Figure 6C**, where the correction resulted in significant differences between the calculated CFR_{p-3D} and the uncorrected values, most prominently in the range of higher CFR values.

The $weCFR_{p-3D}$ values calculated after the correction for hydrostatic pressure and those derived from native pressure values were compared with the Doppler flow measurements. A strong correlation was demonstrated between the individual CFR_{p-3D} and the $CFR_{Doppler}$ values when the correction for hydrostatic pressure was made, while only weak correlation was found without hydrostatic pressure correction.

Importantly, the elimination of hydrostatic pressure offset increased the specificity of our method from 46.1% to 92.3%, while the sensitivity of both calculations remained 100% against the “gold standard” Doppler measurement.

Limitations of the study

The main limitation of our pilot study of $\text{CFR}_{\text{p-3D}}$ calculations is represented by the small sample size. However, the archived and statistically highly significant results look promising.

We are aware that our simple model considers only Hagen-Poiseuille-type friction losses and highly simplified Borda-Carnot type separation losses. For this reason, the calculation of the flow rate is also not expected to be always accurate, but because the CFR is by definition a ratio-type parameter, the $\text{CFR}_{\text{p-3D}}$ may be accurate enough for clinical applications [20].

The simplified haemodynamic model used for the calculation of the $\text{CFR}_{\text{p-3D}}$ is able to consider only one stenosis, with a normal proximal and distal segments. Consequently, our flow calculation method in the present form may not be adequate for assessing the hemodynamic relevance of sequential stenoses.

In cases with a very low resting pressure gradient, any small error during the measurement could potentially cause a great deviation in the results, as these values are represented in the denominator during the calculations. However, most of the cases with intermediate coronary lesions showed not less than a 1-2 mmHg resting pressure gradient, which allowed the appropriate calculation of the $\text{CFR}_{\text{p-3D}}$.

Conclusions

In this study, we proposed a method of combined determination of FFR and CFR without the need for Doppler wire or thermodilution procedure. In our opinion, the $\text{CFR}_{\text{p-3D}}$ is applicable for any

coronary angiography with the clinically indicated invasive measurement of the FFR, when the target vessel is suitable for 3D reconstruction. The flow calculation does not require significantly more time this way. We have created an online calculation tool (<http://coronart.unideb.hu/>) available, which enables a more comprehensive assessment of coronary physiology than FFR measurement alone. As a result, the consequences of an epicardial stenosis can be assessed simultaneously with the state of the microvasculature, thereby supporting the clinical decision for selecting the most appropriate therapy. In our opinion, large-scale studies are warranted to investigate the clinical relevance of the pressure-flow relation determined by our technique [31].

Declarations

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Funding

The University of Debrecen supported this work in the framework of a proof-of-concept project (PoC 007).

Á. Ü. was supported by the ÚNKP-20-03 new national excellence program of the Ministry for Innovation and Technology from source of the National Research, Development and Innovation Fund (Hungary).

Conflicts of interest

The authors declare that they have no conflict of interest in the subject matter or materials discussed in this manuscript. The patent of the method detailed in this paper has been issued by the European Patent Office (WO2019175612, applicant: University of Debrecen, inventor: Z.K.).

Availability of data and material

The data that supports the findings of this study are available in the supplementary material of this article.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ *et al*: 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal* 2019, 40(2):87-165.
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T *et al*: 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European Heart Journal* 2020, 41(3):407-477.
3. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A: Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. *JACC Cardiovasc Interv* 2015, 8(11):1445-1453.

4. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC, Tremmel JA: Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation* 2015, 131(12):1054-1060.
5. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K *et al*: Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. *J Am Coll Cardiol* 2018, 72(23 Pt A):2841-2855.
6. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Foin N *et al*: Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv* 2014, 7(4):492-502.
7. Serruys PW, Chichareon P, Modolo R, Leaman DM, Reiber JHC, Emanuelsson H, Di Mario C, Pijls NHJ, Morel MA, Valgimigli M *et al*: The SYNTAX score on its way out or ... towards artificial intelligence: part I. *EuroIntervention* 2020, 16(1):44-59.
8. Warisawa T, Cook CM, Howard JP, Ahmad Y, Doi S, Nakayama M, Goto S, Yakuta Y, Karube K, Shun-Shin MJ *et al*: Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance. *Circ Cardiovasc Interv* 2019, 12(5):e007494.
9. Stegehuis VE, Wijntjens GW, Murai T, Piek JJ, van de Hoef TP: Assessing the Haemodynamic Impact of Coronary Artery Stenoses: Intracoronary Flow Versus Pressure Measurements. *Eur Cardiol* 2018, 13(1):46-53.

10. Barbato E, Aarnoudse W, Aengevaeren WR, Werner G, Klauss V, Bojara W, Herzfeld I, Oldroyd KG, Pijls NH, De Bruyne B: Validation of coronary flow reserve measurements by thermodilution in clinical practice. *European Heart Journal* 2004, 25(3):219-223.
11. Everaars H, de Waard GA, Driessen RS, Danad I, van de Ven PM, Raijmakers PG, Lammertsma AA, van Rossum AC, Knaapen P, van Royen N: Doppler Flow Velocity and Thermodilution to Assess Coronary Flow Reserve: A Head-to-Head Comparison With [(15)O]H(2)O PET. *JACC Cardiovasc Interv* 2018, 11(20):2044-2054.
12. Williams RP, de Waard GA, De Silva K, Lumley M, Asrress K, Arri S, Ellis H, Mir A, Clapp B, Chiribiri A *et al*: Doppler Versus Thermodilution-Derived Coronary Microvascular Resistance to Predict Coronary Microvascular Dysfunction in Patients With Acute Myocardial Infarction or Stable Angina Pectoris. *Am J Cardiol* 2018, 121(1):1-8.
13. Lee SH, Lee JM, Park J, Choi KH, Hwang D, Doh JH, Nam CW, Shin ES, Hoshino M, Murai T *et al*: Prognostic Implications of Resistive Reserve Ratio in Patients With Coronary Artery Disease. *J Am Heart Assoc* 2020, 9(8):e015846.
14. Gallinoro E, Colaioni I, Di Gioia G, Fournier S, Kodeboina M, Candreva A, Sonck J, Pijls NHJ, Collet C, De Bruyne B: Quantifying coronary microvascular disease: assessing absolute microvascular resistance reserve (MRR) by continuous coronary thermodilution. *European Heart Journal* 2020, 41(Supplement_2).
15. van de Hoef TP, de Waard GA, Meuwissen M, Voskuil M, Chamuleau SAJ, van Royen N, Piek JJ: Invasive coronary physiology: a Dutch tradition. *Neth Heart J* 2020, 28(Suppl 1):99-107.

16. Härle T, Luz M, Meyer S, Kronberg K, Nickau B, Escaned J, Davies J, Elsässer A: Effect of Coronary Anatomy and Hydrostatic Pressure on Intracoronary Indices of Stenosis Severity. *JACC Cardiovasc Interv* 2017, 10(8):764-773.
17. Kawaguchi Y, Ito K, Kin H, Shirai Y, Okazaki A, Miyajima K, Watanabe T, Tatsuguchi M, Wakabayashi Y, Maekawa Y: Impact of Hydrostatic Pressure Variations Caused by Height Differences in Supine and Prone Positions on Fractional Flow Reserve Values in the Coronary Circulation. *J Interv Cardiol* 2019, 2019:4532862.
18. Üveges Á, Tar B, Jenei C, Czuriga D, Papp Z, Csanádi Z, Kőszegi Z: The impact of hydrostatic pressure on the result of physiological measurements in various coronary segments. *Int J Cardiovasc Imaging* 2021;37(1):5-14. doi: 10.1007/s10554-020-01971
19. Tar B, Jenei C, Dezső CA, Bakk S, Beres Z, Santa J, Svab M, Szentes V, Polgar P, Bujaky C *et al*: Less invasive fractional flow reserve measurement from 3-dimensional quantitative coronary angiography and classic fluid dynamic equations. *EuroIntervention* 2018, 14(8):942-950.
20. Csippa B, Üveges Á, Gyürki D, Jenei C, Tar B, Bugarin-Horváth B, Szabó GT, Komócsi A, Paál G, Kőszegi Z. Simplified coronary flow reserve calculations based on three-dimensional coronary reconstruction and intracoronary pressure data. *Cardiol J*. 2021 doi: 10.5603/CJ.a2021.0117. Epub ahead of print.
21. Young DF, Cholvin NR, Roth AC: Pressure drop across artificially induced stenoses in the femoral arteries of dogs. *Circ Res* 1975, 36(6):735-743.
22. Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, Gunn JP: Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary

- lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. *JACC Cardiovasc Interv* 2013, 6(2):149-157.
23. Tu S, Barbato E, Köszei Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W *et al*: Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv* 2014, 7(7):768-777.
 24. Kouser CA, Nijjer S, Torii R, Petraco R, Sen S, Foin N, Hughes AD, Francis DP, Xu XY, Davies JE: Patient-specific coronary stenoses can be modeled using a combination of OCT and flow velocities to accurately predict hyperemic pressure gradients. *IEEE Trans Biomed Eng* 2014, 61(6):1902-1913.
 25. Ahn JM, Zimmermann FM, Johnson NP, Shin ES, Koo BK, Lee PH, Park DW, Kang SJ, Lee SW, Kim YH *et al*: Fractional flow reserve and pressure-bounded coronary flow reserve to predict outcomes in coronary artery disease. *European Heart Journal* 2017, 38(25):1980-1989.
 26. Zimmermann FM, Pijls NHJ, De Bruyne B, Bech GJ, van Schaardenburgh P, Kirkeeide RL, Gould KL, Johnson NP: What can intracoronary pressure measurements tell us about flow reserve? Pressure-Bounded coronary flow reserve and example application to the randomized DEFER trial. *Catheter Cardiovasc Interv* 2017, 90(6):917-925.
 27. Wijntjens GWM, van Lavieren MA, van de Hoef TP, Echavarría-Pinto M, Meuwissen M, Stegehuis VE, Murai T, Escaned J, Piek JJ: Pressure-derived estimations of coronary flow reserve are inferior to flow-derived coronary flow reserve as diagnostic and risk stratification tools. *Int J Cardiol* 2019, 279:6-11.

28. Morris PD, Gosling R, Zwierzak I, Evans H, Aubiniere-Robb L, Czechowicz K, Evans PC, Hose DR, Lawford PV, Narracott A *et al*: A Novel Method for Measuring Absolute Coronary Blood Flow & Microvascular Resistance in Patients with Ischaemic Heart Disease. *Cardiovasc Res* 2020.
29. Gosling RC, Sturdy J, Morris PD, Fossan FE, Hellevik LR, Lawford P, Hose DR, Gunn J: Effect of side branch flow upon physiological indices in coronary artery disease. *J Biomech* 2020, 103:109698.
30. Johnson NP, Oldroyd KG: Flow, pressure, anatomy: an eternal golden braid. *Cardiovasc Res* 2021, 117(6):1426-1427.
31. Szabó GT, Üveges Á, Tar B, Ágoston A, Dorj A, Jenei C, Kolozsvári R, Csippa B, Czuriga D, Kőszegi Z. The Holistic Coronary Physiology Display: Calculation of the Flow Separation Index in Vessel-Specific Individual Flow Range during Fractional Flow Reserve Measurement Using 3D Coronary Reconstruction. *J Clin Med*. 2021;10(9):1910. doi: 10.3390/jcm10091910.

Figure legends

Figure 1. *Calculation of CFR and MRR values during FFR measurement*

The method for calculating CFRp-3D and MRRp-3D uses haemodynamic calculations combining intracoronary pressure data (top left panel) and 3D anatomical parameters (bottom left panel). On the basis of the hyperemic and resting pressure data, as well as 3D anatomical parameters, simple haemodynamic equations were used to calculate resting and hyperemic flow, CFR and MRR. The detailed description of the flow calculations is described in the patent of the method: <https://patents.google.com/patent/WO2019175612A2/en> [20].

Figure 2. *Results of simultaneous pressure and flow measurements by the ComboWire*

In this case the average proximal (aortic) and distal pressures were detected to be 95 mmHg and 88 mmHg, respectively. At maximal hyperemia (**P**), the average peak velocity (APV-P) increased to 29 cm/s parallel with the increase in the pressure drop (the proximal and distal pressures were 89 mmHg and 79 mmHg, respectively). The measured FFR was 0.89, while the CFR 2.9 (Case 10).

Figure 3. *The height difference between the LAD orifice and the sensor position*

After 3D reconstruction, the height difference between the orifice and the pressure wire sensor was transformed to mmHg getting hydrostatic pressure (red) (Case 10). This value (5.58 mmHg) influences the gradient between the aortic pressure at the tip of the catheter and the pressure detected by the sensor of the pressure wire, and it has a great impact on the results of the CFR calculation.

Figure 4. Correlations and agreements between calculated CFR_{p-3D} values without and with hydrostatic offset correction, and the measured Doppler CFR values

A and B: Correlations between the calculated CFR_{p-3D} values without and with hydrostatic offset correction and the measured Doppler CFR values: $r=0.57$, $p=0.01$ and $r=0.89$, $p<0.0001$, respectively.

C and D: Bland-Altman analysis of the agreement between the calculated CFR_{p-3D} values without and with hydrostatic offset correction and the measured Doppler CFR values.

The mean differences between the Doppler-measured and the calculated CFR values without and with hydrostatic error correction were found to be -0.05 ($\pm 1.96SD$: $1.38 - 1.48$) and -0.02 ($\pm 1.96SD$: $0.47 - 0.50$), respectively. After hydrostatic error correction the agreement was in a narrower range (without systematic skewing) than before the correction (note the different scales of y axes generated by the statistical software between panel C and D).

Figure 5. Correlation and agreement between the results of the ComboWire based MRR measurements ($MRR_{ComboWire}$) and the calculated MRR_{p-3D} values with the correction for hydrostatic offset

A: The calculated microvascular resistance reserve MRR_{p-3D} demonstrated a good correlation with the measured $MRR_{ComboWire}$ values ($r=0.58$, $p=0.009$).

B: The Bland-Altman analysis showed the mean differences between the Doppler-measured and the calculated MRR_{p-3D} values with hydrostatic offset correction to be -0.3 ($\pm 1.96SD$: $1.5, -2.2$)

with a trend of greater differences at higher MRR values. The MRR_{p-3D} overestimated the $MRR_{ComboWire}$ values in the cases $MRR_{p-3D} > 5$ values.

Figure 6. Clustered multiple variable graphs of resting P_d/P_a , FFR and CFR_{p-3D} without and with hydrostatic pressure correction

In both the resting and the hyperemic (FFR) state (**A** and **B**), the correction of the hydrostatic offset resulted differences in consequent directions between the uncorrected and corrected values in the main coronary branches. The correction significantly increased the values in the LAD, while in the LC and in the RCA the values decreased. Much greater differences with the same direction can be observed for the CFRs, especially in the range of the higher values (**C**).

Table 1: Clinical characteristics

DM: diabetes mellitus; DVT: deep vein thrombosis; CCS: chronic coronary syndrome; PCI: percutaneous coronary intervention; PAD: peripheral artery disease

Table 2: Measured and calculated haemodynamic parameters of the interrogated lesions

* Cases No8, No13 and No19 are the same vessels as No7, No12 and No18 after stent implantation

** Hydrostatic pressure difference is the difference between the hydrostatic pressure between the pressure sensor and the tip of the catheter at the coronary orifice (hydrostatic pressure offset)

*** Corrected values are calculated with the corrected hydrostatic pressures

RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex artery; OM: obtuse marginal branch; prox: proximal vessel segment; med: medial vessel segment; dist: distal vessel segment; P_d/P_a : distal coronary pressure at rest / aortic pressure at rest; FFR: fractional flow reserve; CFR_{p-3D} : coronary flow reserve calculated from intracoronary pressure

data and 3D anatomical parameters; APV: average peak velocity at rest or during vasodilatation (vd) measured by Doppler wire; CFRDoppler: coronary flow reserve measured by Doppler wire; MRRp-3D: microvascular reserve ratio calculated from intracoronary pressure data and 3D anatomical parameters; MRRDoppler: microvascular reserve ratio measured by Doppler wire.

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

Table 1: Clinical characteristics

Patient No.	Age	Gender	Target vessel	Hypertension	DM	Dyslipidaemia	Hyperuricaemia	Chronic renal failure	Aorta stenosis	DVT	CCS (prev)	PCI (prev)	PAD
1	62	f	RCA	✓	✓	×	×	×	×	✓	✓	✓	×
2	51	m	CX	×	×	×	×	×	×	×	✓	✓	×
3	60	m	RCA	✓	×	✓	×	×	✓	×	✓	×	✓
4	66	m	LAD	✓	×	✓	×	×	×	×	✓	✓	×
5	65	m	LAD	×	✓	✓	×	×	×	×	✓	✓	×
6	55	m	LAD	✓	×	✓	×	×	×	×	✓	×	×
7	64	m	RCA	✓	×	×	×	✓	×	×	✓	✓	×
8	55	m	LAD	✓	✓	✓	×	✓	×	×	✓	×	×
9	69	m	LAD	✓	✓	×	×	×	×	×	✓	✓	×
10	43	m	RCA	✓	×	✓	✓	×	×	×	✓	✓	×
11	56	m	LAD	✓	✓	×	×	×	×	×	✓	✓	×
12	52	m	LAD	×	×	✓	×	×	×	×	✓	✓	×
13	66	m	CX-OM	✓	✓	✓	×	×	×	×	✓	✓	✓
14	60	f	CX-OM	✓	✓	×	×	×	×	×	✓	×	×
15	63	m	LAD	✓	×	✓	×	×	×	×	✓	×	×
16	66	m	LAD	✓	✓	×	✓	×	✓	×	✓	×	×

Table 2: Measured and calculated hemodynamic parameters of the interrogated lesions

Case No	Vessel segment	Hydrostatic pressure difference (mmHg)**	Pd/Pa _{rest}	FFR	CFR _{p-3D}	CFR _{p-3D} corrected ***	APV _{rest} (cm/s)	APV _{vd} (cm/s)	CFR Doppler	MRR _{p-3D} corrected ***	MRR _{Doppler} corrected ***
1	RCA med	0,46	0,99	0,94	3,55	2,72	14	42	3	2,83	3,43
2	LCx dist	1,99	0,98	0,92	3,47	2,21	19	45	2,4	2,21	2,86
3	RCA med	0,05	0,96	0,91	1,86	1,85	18	32	1,8	2,02	1,95
4	LAD prox	-2,93	0,92	0,86	1,74	2,30	24	50	2,1	3,05	2,21
5	LAD med	-2,50	0,86	0,63	1,58	1,70	14	29	2,1	2,86	3,26
6	LAD prox	-0,69	0,79	0,64	1,24	1,25	32	42	1,3	1,85	1,91
7*	RCA med	0,76	0,92	0,79	2,21	2,10	15	30	2	2,32	2,27
8	RCA med (post stent)	0,77	0,98	0,94	2,68	2,20	15	33	2,2	2,07	2,30
9	LAD prox	-0,71	0,93	0,79	1,65	1,71	19	36	1,9	2,64	2,86
10	LAD med	-5,58	0,93	0,89	1,33	2,78	10	29	2,9	6,06	3,21
11	RCA med	1,05	0,98	0,90	3,01	2,33	36	86	2,4	2,27	2,50
12*	LAD dist	-4,51	0,89	0,72	1,88	2,34	22	45	2,1	3,16	2,49
13	LAD dist (post stent)	-3,93	0,93	0,85	1,72	2,46	22	55	2,5	3,60	2,93
14	LAD prox	-3,65	0,79	0,53	1,74	1,90	38	46	1,2	2,86	1,70
15	LCx dist (OM)	2,60	0,62	0,54	1,09	1,08	33	36	1,1	1,22	1,27
16	LCx dist (OM)	1,84	0,98	0,91	3,46	2,27	26	62	2,4	2,12	2,81
17	LAD prox	-5,00	0,89	0,79	1,74	2,31	15	31	2,1	3,26	2,37
18*	LAD med	-6,00	0,74	0,62	1,21	1,30	31	43	1,4	1,87	1,70
19	LAD med (post stent)	-6,00	0,87	0,76	1,69	2,74	24	57	2,4	5,30	2,92