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A novel intermediate coronary artery stenosis severity method: Fluoroscopy-Assisted Measurement of Coronary Volume Ratio (The FLAME FFR Trial)

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Abstract. – OBJECTIVE: The fluoroscopy-assisted coronary volume measurement (FLASH) algorithm, based on contrast passage time and vessel size, is a simple and non-invasive method of assessing coronary blood volume. The present study evaluated the diagnostic performance of FLASH flow ratio-derived fractional flow reserve (FFR_{FLAME}) compared to wire-based FFR (FFR_{WB}).

PATIENTS AND METHODS: FFR_{FLAME} was defined as the ratio of FLASH at baseline to maximal hyperemia. Forty-eight patients with one intermediate coronary lesion (30-70% by angiographic visual estimation) were enrolled in this cross-sectional study. FFR_{FLAME} and FFR_{WB} measurements were collected in each patient. Intravenous administration of adenosine was used to achieve maximal hyperemia. The Pearson correlation coefficient and receiver operating characteristic analysis were performed to determine the predictive accuracy of FFR_{FLAME}.

RESULTS: The average age of the patients was 58 years, and 43% (21 of 48) were female. The predominant vessel assessed was the left anterior descending artery system (87.5%). The mean FFR_{WB} was 0.91 ± 0.05 at baseline and 0.83 ± 0.07 at the hyperaemic level, with 27% (13 of 48) of patients having an FFR_{WB} of ≤0.80. For each patient, the mean FFR_{FLAME} was 0.668 ± 0.17. The mean FFR_{FLAME} was 0.85 ± 0.16 for patients having an FFR_{WB} of ≤0.80. A strong relationship existed between FFR_{FLAME} and FFR_{WB} (Pearson's r = - 0.765 *p*<0.001). The optimal cutoff value of the functional significance of coronary artery stenosis for FFR_{FLAME} was determined to be > 0.84 (AUC: 0.899, 84% sensitivity and 97% specificity) when the FFR_{WB} cutoff value for significant lesions was ≤ 0.80.

CONCLUSIONS: FFR_{FLAME}, applied to coronary angiography without the need for an invasive pressure wire, can be a beneficial index for appropriate lesion selection in coronary artery diseases.

Key Words:
Fractional flow reserve, Intermediate coronary lesion, Coronary volume.

Introduction

Fractional flow reserve (FFR), which evaluates invasive coronary physiology, improves patient outcomes and provides more appropriate lesion selection that can benefit from percutaneous coronary interventions (PCIs)[1]. Moreover, the results of the FAME and FAME 2 studies[2,3] emphasizes the importance of FFR in recognizing the functional significance of coronary artery stenosis and its role in decision-making for PCI.

The concept of FFR simply can be defined as the ratio of the maximum achievable blood flow to the myocardial region in the presence of stenosis to the normal maximum achievable blood flow[4]. FFR calculates this ratio of flows by a ratio of pressures by using a pressure-monitoring guide wire at maximal hyperemia. The use of FFRs is still less adopted because of several technical features and economic considerations despite compelling evidence and guideline recommendations.

The fluoroscopy-assisted measure of coronary volume (FLASH) algorithm, based on contrast transition time and vessel size measured by quantitative coronary angiography (QCA), is a simple and non-invasive method to assess coronary blood flow, and it appears to assess coronary blood flow better than TIMI frame count[5].

FLASH flow and hyperaemic stimuli derived FFR (FFR_{FLAME}) is a new candidate, cost-effective technique that avoids the need for a pressure wire and eliminates potential wire-related complications.

The present study mainly aimed at evaluating the diagnostic performance of a novel computational FLASH flow ratio-derived fractional flow reserve (FFR_{FLAME}), applied with coronary angiography, compared to conventional wire-based FFR (FFR_{WB}).

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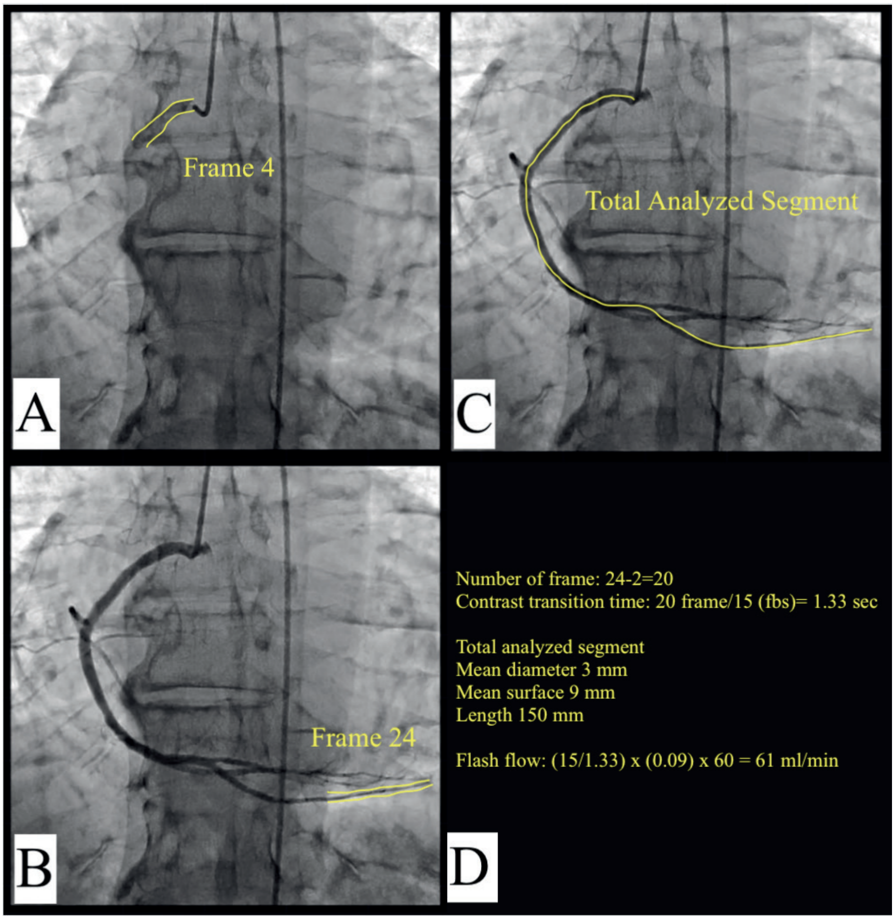

Figure 1. Basic principles of fluoroscopy assisted measure of coronary volume (FLASH) algorithm. **A**, The first frame in which the opaque material fills the coronary ostium. **B**, The frame where the opaque material has reached the distal end point of coronary artery. **C**, Central line along the coronary artery. **D**, Example of FLASH flow calculation based on quantitative coronary angiography software analysis.

Patients and Methods

Study Design and Study Population

This study was a cross-sectional, single-center, single-arm study designed to assess the feasibility and diagnostic performance of FFR_{FLAME}. Assuming an alpha of 0.05, a power of 0.80, an expected correlation coefficient of 0.40, and an expected area under the receiver operating characteristic (ROC) curve of 0.80, the estimated sample sizes were at least 47 and 30, respectively, for the study.

Patients with one intermediate coronary lesion (30-70% by angiographic visual estimation), in which FFR_{WB} measurement was planned, were included in the study. Patients with more than one coronary lesion, bypass graft lesions, an in-stent lesion, acute coronary syndrome, any type of heart failure, hemodynamic instability, a previous history of allergic reaction to iodine contrast agents, adenosine, or adenosine-5-triphosphate and those who were ineligible for FFR_{WB} measurement were excluded.

The study was approved by the Local Ethics Committee (registration number: KAEK-2017-10/32) and conducted according to the Helsinki Declaration. Written informed consent about the study and its publication was obtained from all participants before the study.

FFR_{FLAME} and FFR_{WB} measurements were performed in each patient at baseline and maximal hyperemia. Flame measurements were analyzed after the procedure by the same physician who was blinded to the FFR_{WB} measurement. Technical details are given below.

Hyperaemic Stimuli

Epicardial vasoconstriction was eradicated with a standard bolus of 200 mcg intracoronary isosorbide dinitrate[6]. Maximal hyperemia was achieved by intravenous administration of 140 μg/kg/min adenosine through a large peripheral vein. Measurements were taken at 30-120 seconds after the start of the infusion.

Fluoroscopy-Assisted Coronary Volume Measurement (FLASH) and FLASH Flow Ratio-Derived Fractional Flow Reserve (FFR$_{FLAME}$)

Angiograms were performed and analyzed using Sensis (Siemens Artis zee floor biplane Sensis hemomed vc12 m) with QCA software (Siemens Axiom artis zee). Methodological principles of FLASH flow with an example are demonstrated in Figure 1. In brief, the first frame was considered the frame in which the ostium of the coronary artery was filled with contrast material. The second frame was accepted as the first frame in which the contrast agent reached the distal end of the coronary artery. The distal end of the coronary artery was accepted as the most distal part distal as possible, with the ostium still visible in the same frame. Contrast passage time was calculated based on the time between the two frames. The vessel length and automatic contour of the coronary artery were determined by QCA software. Then, FLASH flow is an estimate of coronary blood volume flow in milliliters per minute by evaluating the mean surface area and length of the coronary artery.

Herein, FLASH flow and FFR$_{FLAME}$ were defined:

$$FLASH\ flow\ (Coronary\ Blood\ Flow)\left(\frac{ml}{min.}\right) = \left[\frac{\text{Distance (cm)}}{\text{Time (sec.)}} \times Cross\ Sectional\ Area\ (cm2)\right] \times 60$$

$$FFR\ FLAME\ = {}^{Flash\ Flow\ at\ baseline}/_{Flash\ Flow\ at\ maximal}\ \text{hyperemia}$$

Wire-Based Fractional Flow Reserve

Measuring intracoronary pressure was provided by using a specific solid-state sensor mounted on a floppy-tipped guide wire and interface system (RadiAnalyzer™ Xpress Measurement System [Abbott., St. Paul, MN, USA]). Before inserting the wire into the target coronary artery, the pressures recorded by the sensor and by the guiding catheter were equalized. FFR$_{WB}$ measurements were taken at the 'lowest' point at baseline and at the hyperaemic level. FFR$_{WB}$ >0.80 has been accepted as the cutoff threshold for excluding inducible ischemia.

Statistical Analysis

All of the statistical analyses were performed using SPSS 23 for Windows (SPSS Inc., Chicago, IL, USA). The distribution of data was evaluated by using the Shapiro-Wilk test. Baseline continuous characteristics are presented as the mean ± standard deviation, and categorical variables are presented as percentages. The correlation of FFR$_{FLAME}$ and FFR$_{WB}$ was investigated with the Pearson correlation coefficient. ROC analysis was also performed to determine the optimal cutoff value of the FFR$_{FLAME}$ with the Youden J index. In all analyses, a two-sided p<0.05 was considered statistically significant.

Table I. Baseline characteristics and laboratory findings of the study patients.

Variables	Study population (n: 48)
Age (years)	57.7±7.4
Sex (n, %) females	10 (20.8%)
Heart rate, bpm	77.8±11.4
Systolic Blood pressure, mm Hg	128±23.5
Diastolic blood pressure, mm Hg	81±11.7
Risk factors, %	
Hypertension, n (%)	27 (56.2%)
Dyslipidemia, n (%)	20 (41.6%)
DM, n (%)	9 (18.7%)
Smoker, n (%)	13 (27%)
Family history, n (%)	7 (14.5%)
BMI (kg/m²)	24.5 ±5.4
Target vessel	
LAD, n (%)	42 (87%)
Non-LAD, n (%)	6 (13%)
Creatinine (mg/dl)	0.88 ± 0.19
LDL (mg/dl)	115.9 ± 54.8
HDL (mg/dl)	45.32 ± 10.24
Na (mmol/L)	138 ± 4.5
K (mmol/L)	4.4 ± 0.7
AST (U/L)	22 ± 9
ALT (U/L)	25 ± 8
Leukocyte (10^9/L)	8172 ± 2291
Hemoglobin (g/dl)	13.05 ± 1.67
Platelet (10^9/L)	266 ±84

DM: Diabetes mellitus, BMI: Body mass index, LAD: Left anterior descending artery, LDL: Light density lipoprotein, HDL: High density lipoprotein, Na: Sodium, K: Potassium, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Results

The analytic study population consisted of forty-eight patients. The average age was 58 years, and 43% (21 of 48) were women. The predominant vessel assessed was the left anterior descending artery system (87.5%). The baseline

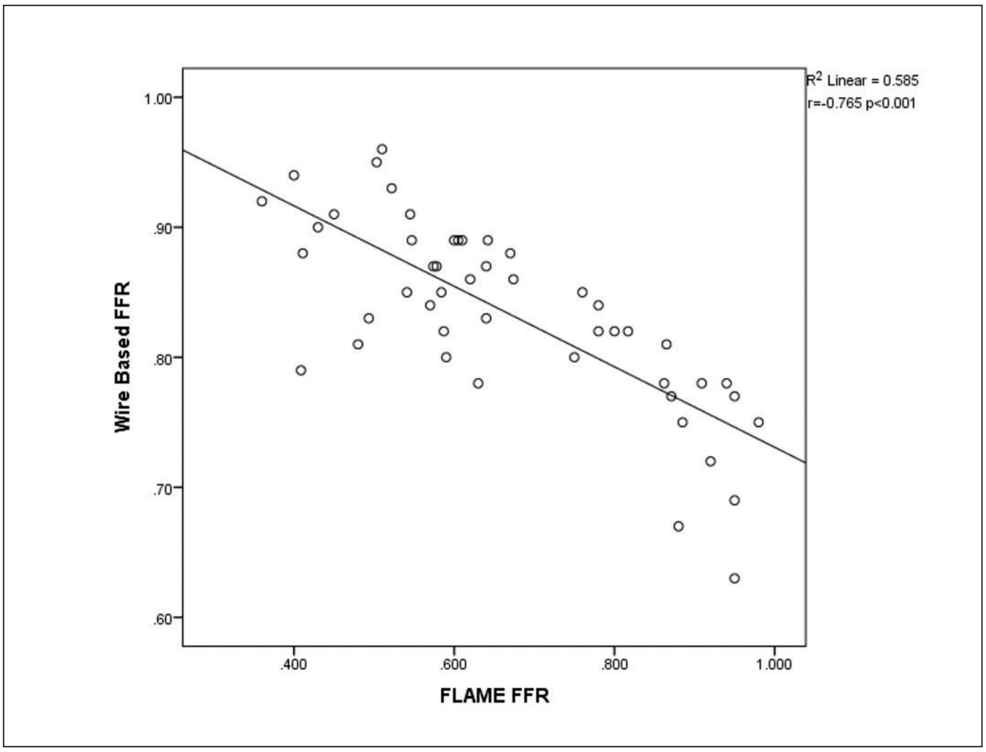

Figure 2. The correlation of fluoroscopy assisted measure of coronary volume and hyperaemic stimuli derived fractional flow reserve (FFR_{FLAME}) and wire based FFR.

characteristics and procedural characteristics of the study patients are presented in Table I. With per-patient FFR_{WB}, the mean FFR_{WB} was 0.91 ± 0.05 at baseline and 0.83 ± 0.07 at the hyperemic level, with 27% (13 of 48) of patients having an FFR_{WB} of ≤0.80. The mean FFR_{WB} was 0.74 ± 0.05 for patients having an FFR_{WB} of ≤0.80 at the hyperemic level.

For each patient, the mean FFR_{FLAME} was 0.668 ± 0.17. The mean FLASH flow was 33.3±16.8 at baseline and 56.9±8.4 at the hyperemic level per patient. Compared with the degree of functional stenosis, the mean coronary flow increased from 34.2±16.7 to 63.9±46.4 for patients having an FFR_{WB} of >0.80. The mean coronary flow increased from 30.9±17.7 to 38.1±20.5 for patients having an FFR_{WB} of ≤0.80. The mean FFR_{FLAME} was 0.85 ± 0.16 for patients having an FFR_{WB} of ≤0.80. The mean FFR_{FLAME} was 0.59 ± 0.12 for patients having an FFR_{WB} of >0.80.

A strong relationship existed between FFR_{FLAME} and FFR_{WB} (Pearson's r = - 0.765 $p<0.001$), as shown in Figure 2. The predictive accuracy of FFR_{FLAME} is shown in Figure 3. The optimal cutoff value for FFR_{FLAME} was determined to be > 0.84, which yielded a sensitivity and specificity of 84% and 97%, respectively (AUC: 0.899), when the FFR_{WB} cutoff value for significant lesions was ≤ 0.80.

Discussion

The findings of the present study suggest that coronary volume-derived FFR (FFR_{FLAME}) can be a beneficial index for appropriate lesion selection in coronary artery diseases. The results also showed high agreement between the FFR_{FLAME} and FFR_{WB} measures. Furthermore, the FFR_{FLAME} value >0.84 was found to be the cutoff for a significant lesion with a sensitivity of 84% and a specificity of 97%.

There are different physiological assessment and intracoronary imaging options, each with its own advantages and disadvantages in the selection of appropriate coronary lesions[7]. To obtain the most accurate results with FFR_{WB}, it is necessary to fully understand the limitations of this technique. It is therefore important to focus on some technical aspects while performing the FFR_{WB} measurement[8]. A method for estimating functional coronary severity without the need for an

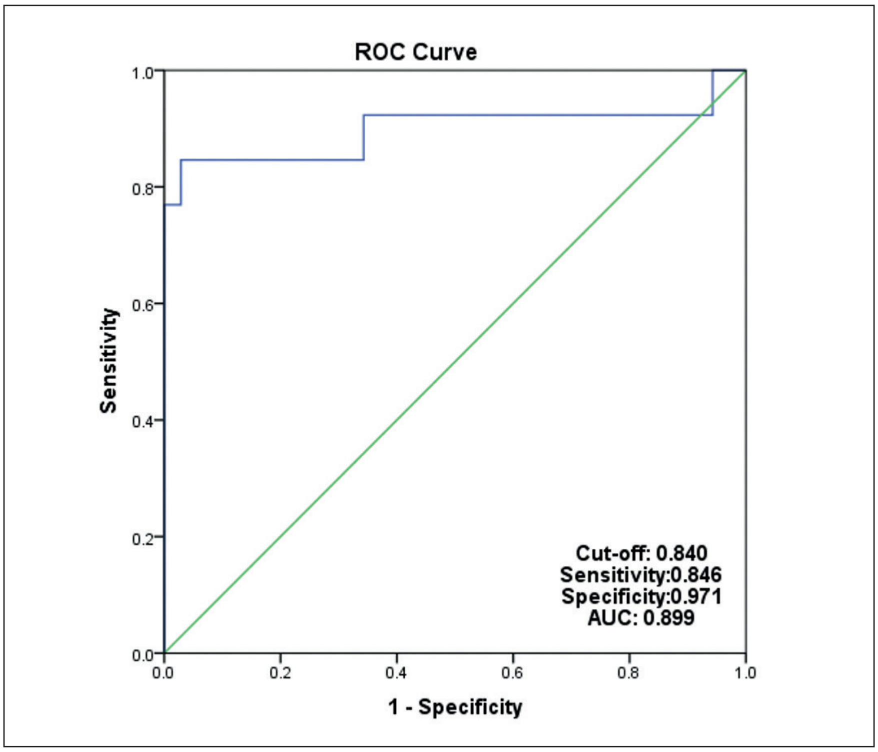

Figure 3. The optimal cut-off value of the functional significance of a coronary artery stenosis for fluoroscopy assisted measure of coronary volume and hyperaemic stimuli derived fractional flow reserve (FFR_{FLAME}) was determined as > 0.84 (AUC: 0.899, 84% sensitivity and 97% specificity).

invasive pressure wire or hyperemia would represent a significant advancement in this field.

Coronary blood flow governs myocardial perfusion and could be an ideal marker of myocardial ischemia compared to coronary artery pressure measurement. In this regard, a large meta-analysis supported the diagnostic accuracy of angiography-derived FFR systems based on computational fluid dynamics for appropriate coronary lesion selection[9]. Recently, the FAST FFR trial demonstrated the validity of using coronary angiography-derived FFR based on a 3-dimensional reconstruction of the coronary arterial system[10]. Despite the reports addressing the concordance between these resting flow concepts and the FFR_{WB}, it remains underutilized due to some requirements.

FFR_{FLAME} measurement is based on the measurement of the coronary volume ratio at baseline and during maximal hyperemia with adenosine based on the FLASH flow algorithm at the target vessel. The FLASH algorithm takes into account the coronary length and diameter of the coronary artery, which are critical determinants of flow resistance[5]. In comparison to other current methods, the functional evaluation of a coronary lesion without the need for a pressure wire is a unique advantage of FFR_{FLAME}[11]. This eliminates the cost of the pressure wire and shortens the procedure time. On the other hand, hyperemia stimuli are still required.

Expressing coronary flow in absolute dimensions (ml/min) has some pitfalls[12]. Mainly, coronary arteries and distribution areas will differ between patients. FFR_{FLAME} overcomes this disadvantage by taking into account the maximum achievable blood flow and expressing the coronary flow result as a ratio. FFR_{FLAME} has the theoretical highest value of 1. An increase of less than 16% in coronary blood flow in maximal hyperemia suggests that the coronary lesion is functionally important.

Recently, a number of new and non-invasive strategies, such as the resting full-cycle ratio, instantaneous wave-free ratio, Pd/Pa at rest, diastolic pressure ratio and diastolic hyperemia-free ratio, have been developed for the functional assessment of coronary artery lesions[13-16]. Most of these are a set of measurements focused on functional assessment without the need for maximum hyperemia. Importantly, unlike FFR_{WB}, these nonhyperemic pressure indices do not have a linear relation with maximum blood flow[17]. Therefore, they cannot measure the maximum blood flow that the myocardium can achieve and cannot provide information about the depth of ischemia. The accuracy of these techniques for detecting myocardial ischemia is approximately 80%[18]. However, in maximal hyperemia, myocardial flow and myocardial pressure are linearly proportional. A change in myocardial pressure will cause a similar change in myocardial flow. One of the striking findings of the current study is that correlation analysis showed a linear relationship between FFR_{FLAME} and FFR_{WB} measurements in all functionally significant and nonfunctional lesion values. This result strongly supports that FFR_{FLAME} can be a parameter to determine the patients' functional capacity.

There are two important steps before FFR_{FLAME} earns recognition in clinical practice. First, it is important to realize that this pioneering study showed the technical feasibility of FFR_{FLAME}. Therefore, randomized controlled prospective studies with a larger cohort, powered by clinical outcomes, for clinical validation are required. Second, the diagnostic performance of FFR_{FLAME} was evaluated in a selected subgroup of coronary artery disease in this study. The utility of FFR_{FLAME} under a number of circumstances, including left main disease, multivessel disease, previous infarction, etc., is still open to evaluation.

Limitations

Before interpreting the results of the study, it is necessary to focus on some limitations. First, this study was conducted in a relatively small number of groups. Second, as mentioned above, the accuracy of FFR_{FLAME} in the presence of special features was not studied in this study. Again, the data about the accuracy of FFR_{FLAME} in the presence of serial stenoses are not available in this study. Absolute blood flow was not measured by the pressure wire as in the Coroventis® software program. However, this method has overcome this limitation by using the measurement as a ratio.

Conclusions

FFR_{FLAME} uses the FLASH algorithm and hyperaemic stimuli to determine the clinical significance of coronary stenosis. FFR_{FLAME} can be a useful complementary index applied with coronary angiography when functional information from non-invasive tests is lacking, especially in catheter laboratories in resource-poor settings.

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Conflict of Interest
The authors have no conflicts of interest to declare.

Authorship Contributions
Concept – HA, AT, AK; Design – HAAT, AK, SS, IZ, Supervision – MD, NB, KS, Funding – ATMK, KS, IZ, Materials – AT, SC, IZ, KS, MK, Data Collection and/or processing – AT, AK, NB, MD, HA, Analysis &/or interpretation – AK, AT, NB, HA, MD, Literature search – HA, AT; Writing – HA, AK, SÇ, AT; Critical review – NB, HA, AT, MD.

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