ORIGINAL ARTICLE

Predictive value of corrected thrombolysis in myocardial infarction frame count for fractional flow reserve: an easy tool for patient selection

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KEY WORDS
coronary artery disease, corrected TIMI frame count, fractional flow reserve

ABSTRACT

BACKGROUND Treatment of moderate stenosis of all coronary arteries remains a challenge for interventional cardiologists. Usually, the hemodynamic significance of moderate stenosis has to be assessed in the catheter laboratory. Fractional flow reserve (FFR) is the preferable method, but it is an invasive technique associated with additional costs. Corrected thrombolysis in myocardial infarction frame count (cTFC) is a simple, repeatable, objective, noninvasive, and quantitative method that allows an indirect assessment of microvascular dysfunction and epicardial coronary stenosis. Only 40% of moderate stenosis cases are found to be hemodynamically severe after FFR measurement; therefore, an additional test would help avoid the use of this invasive tool in the remaining 60% of patients.

AIMS We aimed to assess the value of cTFC for predicting FFR.

METHODS A total of 238 consecutive patients who underwent FFR for the assessment of moderate stenosis were enrolled. Coronary angiography records were used to calculate cTFC. Patients were divided into 2 groups: with an FFR value of less than 0.8 (FFR+) and an FFR value of 0.8 or higher (FFR–).

RESULTS We noted a significant correlation between cTFC and FFR when used both as a categorical and continuous variable. The cTFC of the FFR+ group was higher as compared with that of the FFR– group (27.68 [11.79] vs 20.39 [8.39]; P <0.001). In the receiver operating characteristic curve analysis, the sensitivity and specificity of the test for predicting FFR below 0.8 were 82% and 52%, respectively, at the cutoff cTFC value of 19.

CONCLUSIONS Our study showed that cTFC can predict FFR. Moreover, it can be used for patient selection for FFR measurement and as a basic physiological assessment tool for moderate coronary stenosis.

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Received: December 21, 2019.
Revision accepted: March 14, 2020.
Published online: March 17, 2020.
Kardiol Pol. 2020; 78 (4): 311-317
doi:10.33963/KP.15237

INTRODUCTION Treatment of moderate stenosis of all coronary arteries remains a challenge for interventional cardiologists, and the importance of assessing the ischemic potential of such stenosis is often underestimated.[1] There is a high degree of variability among observers in the visual assessment of the severity of moderate lesions during coronary angiography.[2-5] Percutaneous coronary intervention (PCI) performed on the basis of the operator's visual assessment may be associated wit 2 potential problems: a lesion that does not cause ischemia can be treated unnecessarily and a lesion causing ischemia can also be left untreated. If the noninvasive assessment was not performed before coronary angiography, it is particularly important to evaluate the hemodynamic significance of moderate lesions in the catheter laboratory. Fractional flow reserve (FFR) is the preferred method in clinical practice. It can be defined as the ratio of the mean

WHAT'S NEW?

To the best of our knowledge, this is the first study that demonstrated the value of corrected thrombolysis in myocardial infarction frame count (cTFC) for predicting fractional flow reserve (FFR). While cTFC can be acquired from basal angiographic records, FFR is measured by an extra guidewire with pressure detection sensors on it. The FFR guidewire should pass the stenosis to detect a difference in pressure; therefore, it is associated with the risk of complications and adds an extra cost to the procedure. Our study demonstrated that cTFC, which can be obtained without additional cost and intervention, can predict FFR with a sensitivity and specificity similar to those of an exercise stress test. Moreover, our results show that cTFC has the potential to guide patient selection for FFR and facilitate cost-effective diagnostic procedures.

distal coronary pressure (Pd) to mean aortic pressure (Pa) during maximal hyperemia.[6]

An important advantage of FFR is that it provides prognostic information. Generally, it is believed that patients with moderate coronary stenosis with an FFR exceeding 0.75 can be spared interventional treatment.[3,7-15] Although FFR measurements are useful in clinical practice, the technique is limited by its invasiveness and additional cost. The FFR measurement is not only related to the degree of coronary stenosis, but also coronary microvascular disease affects FFR. Although there is currently no technique that can directly assess the microvascular bed in humans, the corrected thrombolysis in myocardial infarction frame count (cTFC) is a simple repeatable, objective, noninvasive, and quantitative tool that allows an indirect assessment of microvascular dysfunction and epicardial coronary stenosis.[7] The prognostic value of a combination of FFR and cTFC measurements has been reported.[16] However, there have been no studies investigating the value of cTFC for predicting FFR. The measurement of FFR is an invasive method associated with an extra cost and the risk of complications such as coronary dissection.[17] If cTFC can predict FFR, its calculation could facilitate patient selection for FFR assessment, thus reducing the unnecessary use of FFR in moderate coronary lesions. Therefore, the aim of our study was to evaluate the role of cTFC in predicting FFR.

METHODS

The study included 238 consecutive patients who underwent FFR measurement for one coronary artery in our hospital. The FFR values were obtained from catheter laboratory records, while cTFC was calculated retrospectively on the basis of coronary angiography records. Other variables were obtained from patient medical records.

Coronary angiographies of patients who underwent FFR were evaluated. For cTFC calculation, the best angiographic view of the proximal and distal part of the artery included in the FFR measurement was chosen. cTFC measurements were calculated by operators who were blinded to the FFR from angiographic images, which were obtained before giving vasodilators used for FFR. In accordance with the literature, the first frame was accepted as the frame that was reached by contrast agent to both walls of the target artery. The last frame was determined as the moment the contrast agent entered the distal region, in line with literature data. These standardized regions were the first branch of the posterolateral artery for the right coronary artery; the distal obtuse marginal branch that includes the culprit lesion for the left circumflex artery; and distal bifurcation (also known as the "moustache," "pitchfork," or "whale's tail") of the left anterior descending artery (LAD). Since the LAD is longer than the other 2 arteries, the values for the LAD were divided by 1.7.

As the rate of coronary angiography imaging in our hospital was 15 frames per second, the values obtained were multiplied by 2. Contrast agent was injected manually in all evaluated images. Images taken after nitrate injection were not evaluated. 7F guiding catheters without side holes and 0.014 pressure wires were used. Before the procedure, an intravenous bolus of heparin was administered according to the weight of each patient. After calibration and basal measurements, to ensure maximal hyperemia, 200 mg of isosorbide mononitrate and adenosine were administered by the intracoronary route using a guiding catheter. Adenosine at a dose of 100 mg for the right coronary artery and 100 mg for the left coronary artery system was administered. If FFR was higher than 0.8 for the left coronary artery system, the test was repeated with 200 mg of adenosine. Baseline FFR was measured as the ratio of baseline Pd to baseline Pa before hyperemia was achieved. Following maximal hyperemia, FFR was calculated as the ratio of mean Pd to mean Pa. FFR lower than 0.8 was accepted as hemodynamically relevant, in line with literature data.[3,18-20]

There were no tandem lesions, chronic total occlusions, or severe valvular diseases that could affect FFR measurements. In all patients, one vessel was assessed with FFR (238 vessels). There were 228 lesions in the LAD; 2, in the left main coronary artery; 5, in the left circumflex artery; and 2, in the right coronary artery.

To evaluate the predictive value of cTFC for FFR measurement, patients were divided into 2 groups based on FFR: FFR+ group (hemodynamically significant; FFR <0.8) and FFR– group (hemodynamically insignificant; FFR ≥0.8). Demographic and clinical characteristics of patients were compared, and correlations between cTFC and FFR measurements were evaluated.

The study was approved by the ethics committee of the local hospital and was carried out in accordance with the Declaration of Helsinki.

TABLE 1 Comparison of baseline demographic and laboratory parameters between patients with fractional flow reserve value of less than 0.08 (FFR+) and of 0.8 or higher (FFR–)

Parameter		FFR+ (n = 106)	FFR– (n = 132)	*P* value
Age, y	Mean (SD)	61.59 (9.89)	63.53 (9.23)	0.12
	Median (IQR)	61 (54–70)	63 (57–70)	
Male sex, n (%)		82 (77)	93 (70)	0.24
Glucose, mg/dl	Mean (SD)	128.69 (56.68)	122.11 (48.92)	0.48
	Median (IQR)	110.5 (93–135.5)	104.50 (93.5–136.5)	
Urea, mg/dl	Mean (SD)	40.67 (18.71)	38.42 (15.35)	0.49
	Median (IQR)	35 (30–45)	35.5 (30–43)	
Creatinine, mg/dl	Mean (SD)	0.99 (0.55)	0.98 (0.59)	0.99
	Median (IQR)	0.91 (0.77–1.07)	0.92 (0.77–1.06)	
AST, IU/l	Mean (SD)	28.41 (46.42)	22.77 (17.53)	0.15
	Median (IQR)	20 (17–25)	20 (16–24.5)	
ALT, IU/l	Mean (SD)	23.92 (16.88)	23.12 (14.08)	0.98
	Median (IQR)	20 (14–27)	20 (14–27)	
Total cholesterol, mg/dl	Mean (SD)	181.39 (45.52)	188.49 (39.42)	0.21
	Median (IQR)	174 (147–205)	191.5 (157.5–220)	
HDL-C, mg/dl	Mean (SD)	41.54 (11.33)	44.79 (16.19)	0.09
	Median (IQR)	40 (34–46)	42 (36–49.5)	
LDL-C, mg/dl	Mean (SD)	105.45 (37.17)	115.50 (38.57)	0.048
	Median (IQR)	97 (83–127)	115 (85.5–138.5)	
Triglycerides, mg/dl	Mean (SD)	172.88 (121.77)	159.17 (76.10)	0.94
	Median (IQR)	143 (100–206)	140 (106–200.5)	
TSH, µU/ml	Mean (SD)	1.43 (1.28)	1.58 (1.46)	0.16
	Median (IQR)	1.08 (0.67–1.79)	1.24 (0.82–1.86)	
Hemoglobin, g/dl	Mean (SD)	13.71 (1.83)	14.55 (3.83)	0.15
	Median (IQR)	14 (12.8–14.9)	14.1 (13.3–15.2)	
Platelets, 1000/ml	Mean (SD)	259.50 (63.42)	252.17 (62.52)	0.47
	Median (IQR)	252 (220–280)	243.5 (214.5–292.5)	
WBC, 1000/ml	Mean (SD)	8.73 (2.51)	7.94 (2.24)	0.01
	Median (IQR)	8.24 (6.8–10)	7.61 (6.51–9.29)	
NLR	Mean (SD)	3.7 [2.39]	2.43 [1.18]	<0.001
PDW, %	Mean (SD)	43.62 [9.78]	43.62 [9.78]	0.02
Smoking, n (%)		62 (58)	58 (44)	0.03
Diabetes mellitus, n (%)		62 (58)	44 (33)	<0.001
Hypertension, n (%)		69 (65)	81 (61)	0.59

SI conversion factors: to convert LDL-C and HDL-C to mmol/l, multiply by 0.0259; triglycerides to mmol/l, by 0.0113; glucose to mmol/l, by 0.0555.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFR, fractional flow reserve; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; TSH, thyroid-stimulating hormone, IQR, interquartile range; WBC, white blood cells

Statistical analysis All statistical analyses were performed using the SPSS statistical package for Windows version 22.0 (SPSS Inc., Chicago, Illinois, United States). Descriptive statistics for numerical variables and number tables for categorical variables were created. All variables were presented as mean (SD) and median with interquartile range. Categorical

variables were given as percentages. The χ^2 test was used to analyze differences between categorical variables. The 1-way analysis of variance was used to test for homogeneity, and the Kolmogorov–Smirnov test was applied to test for normality. The independent-sample *t* test was used for normally distributed variables, and the Mann–Whitney test, for variables without normal distribution. The receiver operating characteristic (ROC) curve analysis was used to assess the predictive value of cTFC for FFR. A *P* value of less than 0.05 was considered significant.

RESULTS The baseline characteristics of the study groups are presented in TABLE 1. Of the 238 patients enrolled in the study, 175 were male. In 132 patients, the FFR values were lower than 0.8. The FFR+ and FFR– groups did not differ in terms of age, levels of biochemical and hematologic parameters (except low-density lipoprotein cholesterol levels, white blood cell count, neutrophil-to-lymphocyte ratio, and platelet distribution width), or the presence of hypertension (TABLE 1).

There were more active smokers and more patients with diabetes in the FFR+ group than in the FFR– group. Low-density lipoprotein cholesterol levels were lower in the FFR– group than in the FFR+ group. White blood cell count, neutrophil-to-lymphocyte ratio, and platelet distribution width were higher in the FFR+ group (TABLE 1).

The Gensini score was higher in the FFR+ group than in the FFR– group. The adenosine amount used for FFR measurement was higher in the FFR– group than in the FFR+ group. In the FFR+ group, basal FFR measurement values were significantly lower than in the FFR– group. Data are presented in TABLE 2.

According to the visual stenosis evaluation, the stenosis degree in the FFR+ group was significantly higher than in the FFR– group. There was no difference in stenosis degree between groups according to the quantitative coronary

TABLE 2 Comparison of angiographic parameters between patients with fractional flow reserve value of less than 0.08 (FFR+) and of 0.8 or higher (FFR–)

Parameter		FFR+ (n = 10)	FFR– (n = 132)	*P* value
Gensini score	Mean (SD)	35.66 (22.38)	19.97 (24.03)	<0.001
	Median (IQR)	32 (19–47)	12.0 (6–23.5)	
Adenosine amount	Mean (SD)	144.86 (41.86)	165.61 (43.21)	<0.001
	Median (IQR)	150 (120–150)	150 (150–180)	
Basal FFR value	Mean (SD)	0.87 (0.06)	0.93 (0.03)	<0.001
	Median (IQR)	0.88 (0.83–0.91)	0.94 (0.91–0.95)	
cTFC	Mean (SD)	27.68 (11.79)	20.39 (8.39)	<0.001
	Median (IQR)	27 (20–32)	18 (14–25)	
Stenosis degree (visual evaluation before FFR)	Mean (SD)	57.26 (9.41)	54.70 (9.44)	0.046
	Median (IQR)	60 (50–60)	50 (50–60)	
QCA stenosis degree	Mean (SD)	55.60 (6.79)	55.06 (8.17)	0.59
	Median (IQR)	57 (51–58)	55.5 (49–59)	
cTFC value[a], n (%)		87 (82)	63 (48)	<0.001

a Used as a categorical variable (cTFC ≥19 accepted as significant)

Abbreviations: cTFC, corrected thrombolysis in myocardial infarction frame count; QCA, quantitative coronary analysis; others, see TABLE 1

TABLE 3 Cross table for categorical analysis of the relationship between corrected thrombolysis in myocardial infarction frame count and fractional flow reserve

FFR	cTFC		Total	*P* value
	<19	≥19		
≥0.8	69	63	132	<0.001
<0.8	19	87	106	
Total	88	150	238	–

Abbreviations: see TABLES 1 and 2

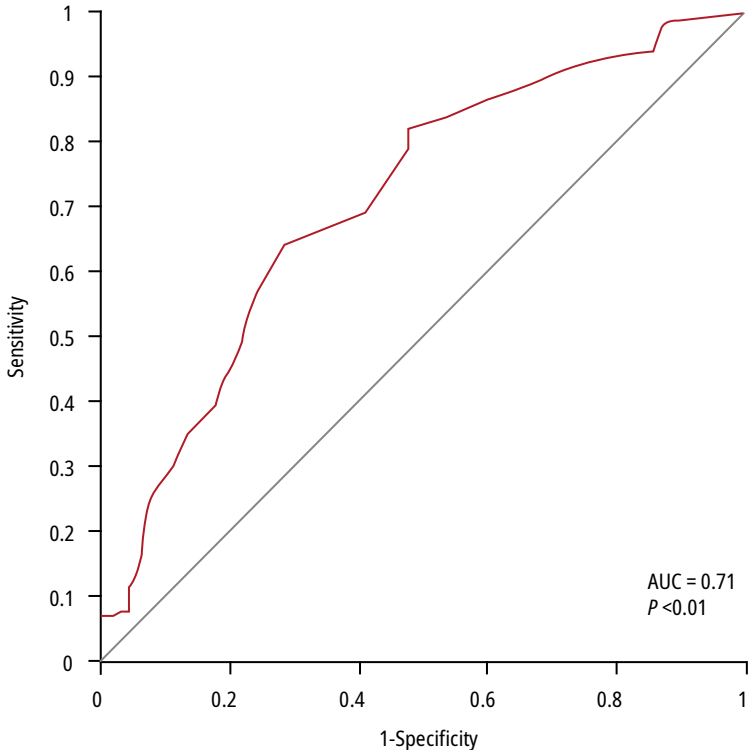

FIGURE 1 Receiver operating characteristic curve analysis of correlation between corrected thrombolysis in myocardial infarction frame count and fractional flow reserve. Diagonal segments are produced by ties.
Abbreviations: AUC, area under the curve

angiographic (QCA) analyses (TABLE 2). The cTFC values were higher in the FFR+ group than in the FFR– group. For cTFC as a categoric variable (when the cutoff value of 19 was used), more patients had a cTFC value of 19 or higher in the FFR+ group than in the FFR– group (TABLE 2).

The area under the curve in the ROC curve analysis of the correlation between FFR and cTFC was 71% (FIGURE 1).

In tables of categorical variables, the cTFC value of 19 or higher was found to have a sensitivity of 82%, specificity of 52%, negative predictive value of 78%, and positive predictive value of 58% for detecting hemodynamically significant stenosis (FFR <0.8) (TABLE 3).

DISCUSSION In this study, we investigated the relationship between selected variables and FFR. The presence of diabetes mellitus and smoking, which are the traditional risk factors for coronary artery disease, was higher in the FFR+ group than in the FFR– group. Low levels of low-density lipoprotein cholesterol in the group with significant stenosis was a surprising finding. Since medical treatment (use of statins, lipid-lowering drugs) was not evaluated in our study, we assumed that these patients might be more symptomatic and exposed to more aggressive medical treatment and lifestyle changes.

Basal FFR was lower and stenosis degree was higher on visual assessment in the FFR+ group. There was no difference in QCA results between groups. Thus, we can speculate that basal FFR measurements and visual assessment of stenosis can also help predict FFR. However, these findings should be confirmed by well-designed prospective studies.

The amount of adenosine used for the FFR measurement was lower in the FFR+ group. This finding may be due to the fact that operators stopped using adenosine when they reached a significant value in the FFR+ group and used a higher amount of adenosine in the FFR– group to reach a significant value.

Despite strong evidence supporting FFR-guided intervention and guideline recommendations, FFR is still an underused test.[21,22] This may be due to an extra cost of pressure wires, extra time needed for the test, risk of complications, vessel tortuosity, and need for pharmacological induction of hyperemia.[23] The rate of using physiological assessment of stenosis is lower than 10% in most parts of the world.[24]

Another limitation of FFR is that it requires considerable expertise and a careful interpretation of results. Both the procedure itself and subsequent interpretation are prone to numerous flaws. Procedural flaws include those made during setting zero pressure, flushing the pressure lines, as well as pressure mistakes caused by inappropriate engagement of catheters.[25] While analyzing pressure waveforms, minor flaws can seriously affect test results. It is important to check the accuracy of Pd and Pa waveforms during pressure wire pullback to reduce the risk of such errors.[26]

Because of the above limitations, some novel techniques have been developed. The quantitative flow ratio is a new method that enables computation of FFR by using 3-dimensional reconstructed QCA rendered from 2-dimensional views as well as estimation of contrast flow velocity during angiography obtained from cTFC.[27] This technique was found to be well correlated with conventional hyperemia-induced pressure wire–dependent FFR.[23,28] The quantitative flow ratio has a potential to reduce the need for pressure wires and medical-induced hyperemia by two-thirds. This novel technique can also increase the rate of using physiological assessment of moderate coronary stenosis. However, in contrast to cTFC, the method has some limitations that prevent its wider application in clinical practice. As mentioned above, cTFC can be easily obtained from angiographic records without any additional cost.

Our study showed that cTFC measurement can be used as an auxiliary method for patient selection for FFR. Although FFR measurement is useful for assessing the physiological significance of the lesion and planning

revascularization in patients with moderate stenosis, only 44% of cases had an FFR value of less than 0.8. An unnecessary invasive intervention is associated with additional cost and risk of serious complications, such as coronary artery dissection.[17] Therefore, there is a need for a cost-effective, noninvasive, and highly feasible test that could be used to evaluate coronary blood flow in such patients and to identify patients requiring FFR. In our opinion, *c*TFC, which can be easily applied after coronary angiography, is a suitable method.

Our results suggest that apart from facilitating patient selection for FFR, *c*TFC can also be easily used as a basic tool for physiological assessment of stenosis, which is widely underused in clinical practice. We showed a significant association between FFR and *c*TFC when used both as a categorical and continuous variable. Although the specificity of *c*TFC measurement for predicting an FFR of less than 0.8 was quite low, the sensitivity was similar to that observed for noninvasive stress tests used to evaluate ischemia. Therefore, the use of FFR measurement in patients with moderate coronary artery disease with increased *c*TFC seems to be a reasonable approach.

In our study, the negative predictive value of *c*TFC as a categorical variable (*c*TFC <19) was 78%. According to this result, the probability of a significant stenosis on FFR measurement is reduced in patients with a *c*TFC of 18 frames or lower. Therefore, it may be reasonable not to perform FFR measurement in these patients. However, prospective studies are needed to provide data on short- and long-term major cardiovascular events and mortality after FFR assessment is abandoned on the basis of *c*TFC measurement in this population.

As there were no tandem lesions, chronic total occlusions, or severe valvular diseases in our study population and the number of non-LAD lesions was limited, the results should be interpreted with caution and cannot be extrapolated to a wider population.

In light of our results, *c*TFC seems to be a safe, practical, and helpful method for patient selection for FFR measurement. Moreover, it is a cost-effective tool for predicting FFR and has a potential to be used as a basic method for physiological assessment of coronary stenosis. Further prospective, multicenter, randomized controlled trials with larger populations and long-term follow-up are needed to confirm the predictive role of *c*TFC.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

HOW TO CITE Cebeci M, Karanfil M, Topaloğlu S. Predictive value of corrected thrombolysis in myocardial infarction frame count for fractional flow reserve: an easy tool for patient selection. Kardiol Pol. 2020; 78: 311-317. doi:10.33963/KP.15237

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