Efficacy of fractional flow reserve measurement in the assessment of stenotic lesions of coronary artery

[Eficacia de la medición de la reserva fraccional de flujo en la evaluación de lesiones estenóticas de la arteria coronaria]

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Abstract

Context: The decision to perform an intervention on a narrowed coronary artery depends on the ischemia caused by the stenosis. The indication for intervention usually applies to cases with ≥70% stenosis of vascular diameter because of the risk of myocardial ischemia.

Aims: To define the efficacy of fractional flow reserve (FFR) measurement in the evaluation of coronary artery stenosis.

Methods: This prospective study was conducted on patients with intermediate coronary artery stenosis who underwent quantitative coronary angiography after coronary computed tomography angiography.

Results: The study population consisted of 46 men and 26 women with a mean age of 66.0 ± 12.9 years. FFR was significantly correlated with the grade of angina pectoris ($r = -0.387$; $p<0.01$) and showed a negative correlation with percentage diameter stenosis ($r = -0.241$, $p<0.05$) and a positive correlation with the minimal lumen diameter (MLD; $r = 0.377$, $p<0.05$). The cut-off value to predict positive FFR was >55.62% diameter stenosis and MLD ≤ 1.08 mm. FFR ≤ 0.80 indicating intervention and FFR > 0.80 indicating medical therapy were observed in 56.9% and 43.1% of the cases, respectively. No major cardiac complications occurred during 12 months of follow-up in both groups.

Conclusions: FFR measurements for intermediate stenosis of the coronary artery should be used to evaluate the possibility of myocardial ischaemia. If FFR is not available, a cut-off point of >55.62% diameter stenosis or MLD ≤ 1.08 mm can be used to predict the FFR results.

Keywords: coronary artery; fractional flow reserve; stenosis.

Resumen

Contexto: La decisión de realizar una intervención en una arteria coronaria estrechada depende de la isquemia provocada por la estenosis. La indicación de intervención suele aplicarse a casos con estenosis del diámetro vascular ≥70% debido al riesgo de isquemia miocárdica.

Objetivos: Definir la eficacia de la medición de la reserva fraccional de flujo (RFF) en la evaluación de la estenosis de la arteria coronaria.

Métodos: Este estudio prospectivo se realizó en pacientes con estenosis coronaria intermedia a quienes se les realizó una coronariografía cuantitativa después de una angiografía por tomografía computarizada coronaria.

Resultados: La población de estudio estuvo formada por 46 hombres y 26 mujeres con una edad media de $66,0 \pm 12,9$ años. La RFF se correlacionó significativamente con el grado de angina de pecho ($r = -0,387$; $p<0,01$) y mostró una correlación negativa con la estenosis del diámetro porcentual ($r = -0,241$, $p<0,05$) y una correlación positiva con el diámetro mínimo de la luz (MLD; $r = 0,377$, $p<0,05$). El valor de corte para predecir la RFF positiva fue >55,62% de estenosis de diámetro y DLM ≤ 1,08 mm. FFR ≤ 0,80 que indica intervención y FFR> 0,80 que indica terapia médica se observaron en 56,9% y 43,1% de los casos, respectivamente. No se produjeron complicaciones cardíacas importantes durante los 12 meses de seguimiento en ambos grupos.

Conclusiones: Las mediciones de FFR para estenosis intermedia de la arteria coronaria deben usarse para evaluar la posibilidad de isquemia miocárdica. Si no se dispone de FFR, se puede utilizar un punto de corte de estenosis de diámetro >55,62% o DLM ≤ 1,08 mm para predecir los resultados de FFR.

Palabras Clave: arteria coronaria; estenosis; reserva fraccional de flujo.

INTRODUCTION

The decision to perform an intervention on a narrowed coronary artery depends on the ischemia caused by the stenosis (Ostojic et al., 2019). Interventions are usually performed in cases with ≥70% stenosis of the vascular diameter because of the risk of myocardial ischemia (Rezende et al., 2019). However, many studies have shown that myocardial perfusion can be affected by coronary stenosis of 50% of the diameter or more (Gould, 2009; Knott et al., 2019). Therefore, to ensure an optimal treatment strategy, functional measurement of a narrow segment should be coordinated with coronary computed tomography angiography, especially in cases with intermediate stenosis (Curzen et al., 2014; Balanescu, 2016).

In 1990, Pijls and his colleagues developed a technique for measuring the fractional flow reserve (FFR) of coronary arteries, which facilitated the evaluation of coronary artery function on the basis of the pressure gradient at the site of narrow segments (Pijls et al., 1993). On the basis of the results of large-scale clinical trials such as DEFER (Pijls et al., 2007), FAME I (Tonino et al., 2009), and FAME II (De Bruyne et al., 2012) have been recommended by many associations, especially for intermediate coronary artery stenosis (50-70%) (Levine et al., 2011; Montalescot et al., 2013; Windecker et al., 2014).

In Vietnam, various cardiac centres have recently begun to study the application of this technique in cases requiring interventions. Our cardiovascular centre, which is located in the central zone of Vietnam, conducts more than 2000 cases of angiography and interventions every year and uses FFR measurement techniques to assess the severity of coronary stenosis. The application of the FFR technique can help accurately determine the functional severity of coronary stenosis, thereby indicating the appropriate treatment. In the immediate future, this approach will reduce treatment costs by precluding the need for interventions or surgeries when the lesions do not affect haemodynamics. In the long term, this approach may help avoid the potential complications after intervention or bypass surgery or post-treatment complications. For these reasons, we conducted this study to define the efficacy of fractional flow reserve (FFR) measurement in the evaluation of coronary artery stenosis.

MATERIAL AND METHODS

Study population

This prospective study was conducted at the Cardiovascular Center of Hue Central Hospital from May 2016 to June 2018, on patients with intermediate (50%-69%) coronary artery stenoses evaluated by quantitative coronary angiography (QCA) after coronary computed tomography angiography (CCTA).

We collected data regarding the patients' medical history, clinical symptoms/signs, and laboratory tests as well as other necessary information, and performed CCTA with QCA and FFR measurement in accordance with the procedures of the Ministry of Health. After measuring the coronary FFR, the subjects were divided into two groups: 1) medical therapy group, which included patients with FFR > 0.80 and intermediate coronary lesions and 2) percutaneous coronary intervention (PCI) group, which included patients with FFR ≤ 0.80.

Both groups continued to receive treatment according to the current recommendations. The patients were closely monitored throughout the hospital stay and follow-up every three months and underwent evaluations at the end of the treatment process. At each follow-up, the patient underwent clinical and laboratory examinations, and the following complications were noted: stroke, gastrointestinal bleeding, angina pectoris, myocardial infarction, sudden death to cardiac arrest, and the requirement for target revascularization.

Ethics

The research proposal was approved by the Scientific Council, Department of Science and Technology of Thua Thien Hue Province and the Medical Ethics Council of Hue Central Hospital under the reference number 1769/QD-UBND (dated on April 11, 2016). Written informed consent was obtained from all patients before the study. The patients and/or their families received detailed explanations regarding the study, consented to participate in the study, and could withdraw from the study freely under any circumstances. The personal and medical information of the patients was kept completely confidential. The research methods, diagnostic criteria, and treatment methods all complied with the recommendations of the Vietnam National Heart Association, the Ministry of Health, and other worldwide Cardiovascular associations. Moreover, the study was conducted in accordance with the Declaration of Helsinki.

FFR assessments

FFR is suitable for the assessment of intermediate lesions (50%–70%) and could be used for guiding coronary artery intervention in patients with myocardial ischaemia. Revascularization for narrow-segment FFR ≤ 0.80 and application of medical treatment for

FFR > 0.8 is a safe and recommended approach for patients who show angina pectoris and positive results on stress tests. When FFR is in the grey zone, between 0.75 and 0.85, especially between 0.77 and 0.83, it is necessary to collect clinical information to determine the possibility of ischaemia due to myocardial lesions. FFR measurements can help guide PCI for patients with multiple microvascular lesions (Achenbach et al., 2017; Thakur et al., 2020).

The contraindications for FFR measurements were followed Guidance on Cardiology Procedures of Vietnamese Ministry of Health (2015), including: (1) a narrow segment that was too distal with inappropriate anatomical features for FFR measurement; (2) acute myocardial infarction with ST elevation; (3) unstable coronary disease: dissection and embolism; and (4) contraindications to adenosine administration (asthma or chronic obstructive pulmonary disease).

The FFR was evaluated in the following steps:

Step 1: Determining the site of FFR measurement.

Step 2: Connecting the FFR equipment with a pressure wire, entering the patient's name and ID, and preparing the adenosine mixture (10 µg/mL).

Step 3: FFR measurement. *Stage 1*: Standardising systemic arterial pressure: Air bubbles were removed from the intervention catheter, and it was filled with NaCl 9‰, and the coronary artery was flushed with heparin to record the arterial pressure waveform. *Stage 2*: A pressure wire was introduced into a guiding catheter for equalisation of the two pressures. *Stage 3*: The pressure wire was advanced into the coronary artery beyond the stenosis, and the sensor was placed at least 10-20 mm beyond the stenosis. Next, 100-200 µg of nitro-glycerine was flushed into the coronary artery as the pressure wire passed the stenosis to prevent vasospasm of the coronary artery. *Stage 4*: Maximum hyperaemia was achieved with adenosine: 40 µg for the right coronary artery (RCA), 60 µg for the left coronary artery (LCA). The FFR measurements were obtained after each administration of adenosine. When vasodilation was not maximal, the dose was increased to 60–80–100 µg for the RCA and 90–120–150 µg for the LCA. *Stage 5*: The accuracy of the FFR measurement procedure was evaluated. The pressure of the pressure-sensing guide wires and catheter was checked after the procedure to determine whether there were any significant differences. When the difference in pressure was <5 mmHg, the FFR results were considered reliable. However, if the pressure difference was >5 mmHg, the FFR was measured again. *Stage 6*: The obtained FFR measurements were evaluated; an FFR > 0.8 indicates that the stenosis has minimal haemodynamic significance. Revasculariza-

tion was indicated when FFR was ≤0.8 (Adjedj et al., 2016; Levine et al., 2011).

Statistical analysis

All data analyses were conducted using SPSS 16 (SPSS, Inc, Chicago, IL). The data were expressed as frequency and percentage for qualitative variables, as the mean and standard deviation for quantitative variables. *Chi* square test was used to compare proportions among independent groups. Results were considered significant at p<0.05.

RESULTS

A total of 82 patients met all the inclusion criteria. However, during the study, 10 patients were excluded because of loss of contact due to changes in address and contact numbers or refusal to continue because of personal issues. Thus, the final research sample consisted of 72 patients with 72 intermediate coronary stenotic lesions.

Baseline characteristics

The study population included 46 men and 26 women with a mean age of 66.0 ± 12.9 years (range: 36-94 years). Among the risk factors for coronary artery disease (CAD), hypertension accounted for the highest percentage (62.5%), followed by dyslipidaemia (41.7%) and obesity (37.5%). Table 1 shows the clinical features and laboratory test results on admission. Among these patients, 73.6% were admitted to the hospital with stable angina pectoris, with Canadian Cardiovascular Society (CCS) I and CCS II accounting for a majority (90.6%) of these cases. Most patients with intermediate coronary stenosis showed no changes in ST-T or QS appearance on admission (62.5%), and 93.1% of these patients showed left ventricle ejection fraction ≥ 50 %.

Table 1. Characteristics of angina pectoris.

Characteristics of angina pectoris	N (%)
Unstable	19 (26.4)
Stable	53 (73.6)
CCS I	*23 (43.4)*
CCS II	*25 (47.2)*
CCS III	*5 (9.4)*

CCS: Canadian Cardiovascular Society.

Results of CCTA with QCA and the FFR procedure

A total of 51.4% of the lesion sites were located on the anterior interventricular branch of the left coronary artery (LAD). Type A lesions accounted for 73.6% of cases. The % diameter stenosis was 58.30% ±

7.77%, and the mean length was 10.30 ± 4.62 mm (as shown in Table 2). Forty-one lesions had an FFR ≤ 0.80, with a mean FFR of 0.71 ± 0.08; this patient group received interventional treatment. The remaining 31 subjects had FFR > 0.80, with a mean FFR of 0.89 ± 0.05. This group received medical therapy (Table 3). The interventional treatment was performed using the right radial artery as the entrance to the FFR measurement. The mean procedure time was 13 ± 5 minutes, and the mean adenosine dose was 120 ± 33 µg (Table 4).

The correlation between FFR and clinical characteristics

The CCS grade for angina pectoris was negatively and significantly correlated with FFR results (Fig. 1). The % diameter stenosis and MLD showed a signifi-cant and low negative correlation with the FFR results (Fig. 2). The possibility of predicting FFR results based on MLD and % diameter stenosis was moderate (Fig. 3). In cases with >55.62% stenosis, the possibility of FFR ≤ 0.8 was 3.78 times higher than that in cases with ≤55.62% stenosis. For cases with an MLD ≤ 1.08 mm, the possibility of FFR ≤ 0.8 was 4.95 times higher than that in cases with MLD > 1.08 mm (Table 5).

Complications

While 94.4% of the cases showed no complications, 4.2% showed sinus bradycardia and transient AV blockage, while 1.4% showed hypotension (Table 6). The proportion of complications in both groups was insignificant, and the intergroup difference was not statistically significant ($p > 0.05$) (Table 7).

Table 2. Results of CCTA with QCA at the site of FFR measurement.

Index	X ± SD	Median
% Diameter stenosis	58.30 ± 7.77	57.19 (53.77 - 63.30)
Minimum lumen diameter (mm)	1.19 ± 0.36	1.22 (0.92 - 1.34)
Reference diameter (mm)	2.85 ± 0.62	2.80 (2.42 - 3.15)
Length of narrow segment (mm)	10.30 ± 4.62	9.04 (7.30 - 12.73)
Concentric	0.58 ± 0.28	0.65 (0.34 -0 .81)

CCTA: coronary computed tomography angiography; QCA: quantitative coronary angiography; FFR: fractional flow reserve. X ± SD: mean ± standard deviation.

Table 3. Results of FFR measurements.

| Parameter	General FFR	FFR ≤ 0.80	FFR> 0.80
Number of sites	72	41 (56.9%)	31 (43.1%)
Results	0.79 ± 0.12	0.70 ± 0.08	0.89 ± 0.05

FFR: fractional flow reserve.

Table 4. Characteristics of the FFR procedure.

| Features of FFR measurement		Results
Entrance	Right radial artery	72 (100%)
Time of procedure (min)	Mean ± standard deviation	13 ± 5
	Range	10-40
Adenosine dose (µg) for RCA`	Mean ± standard deviation	87 ± 24
	Range	30-120
Adenosine dose (µg) for LCA	Mean ± standard deviation	120 ± 33
	Range	30-150

FFR: fractional flow reserve; RCA: right coronary artery; LCA: left coronary artery.
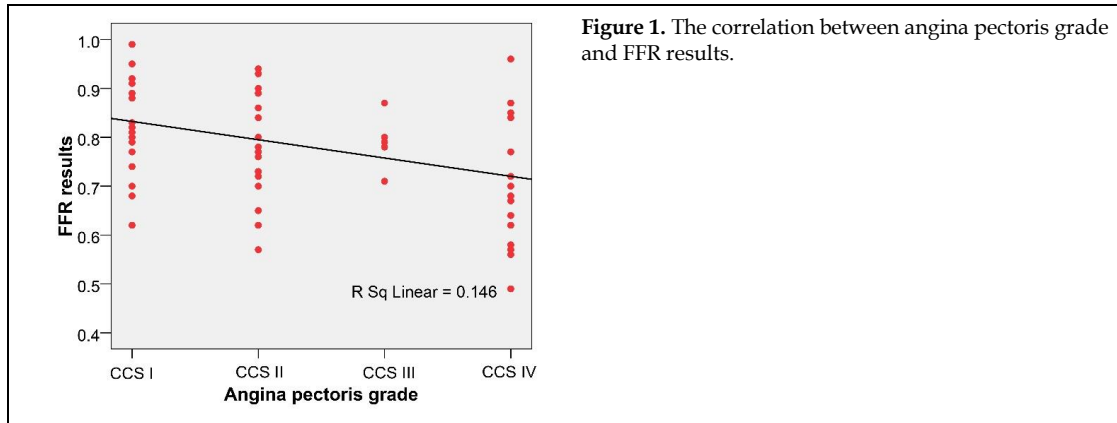
Figure 1. The correlation between angina pectoris grade and FFR results.
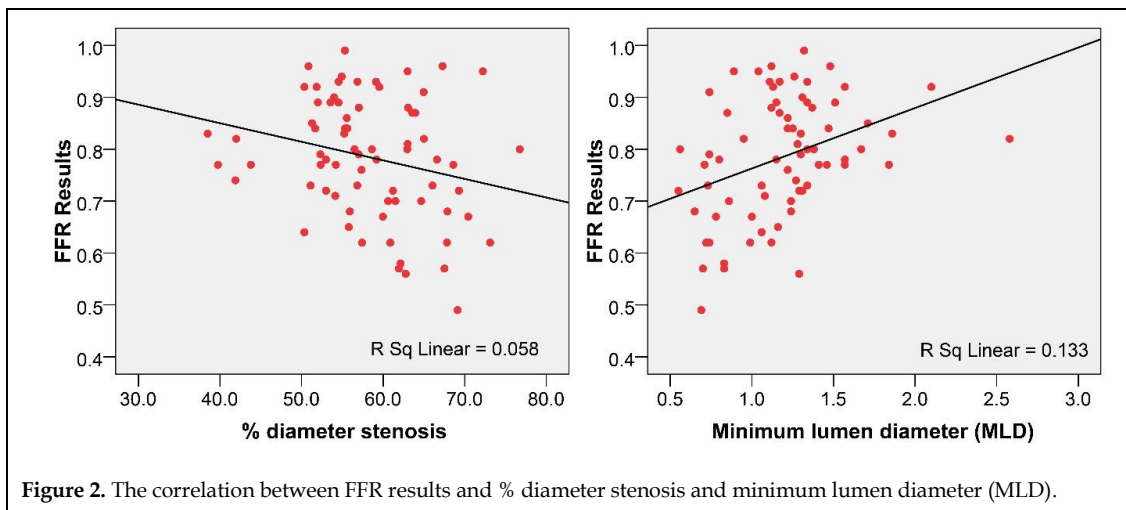
Figure 2. The correlation between FFR results and % diameter stenosis and minimum lumen diameter (MLD).
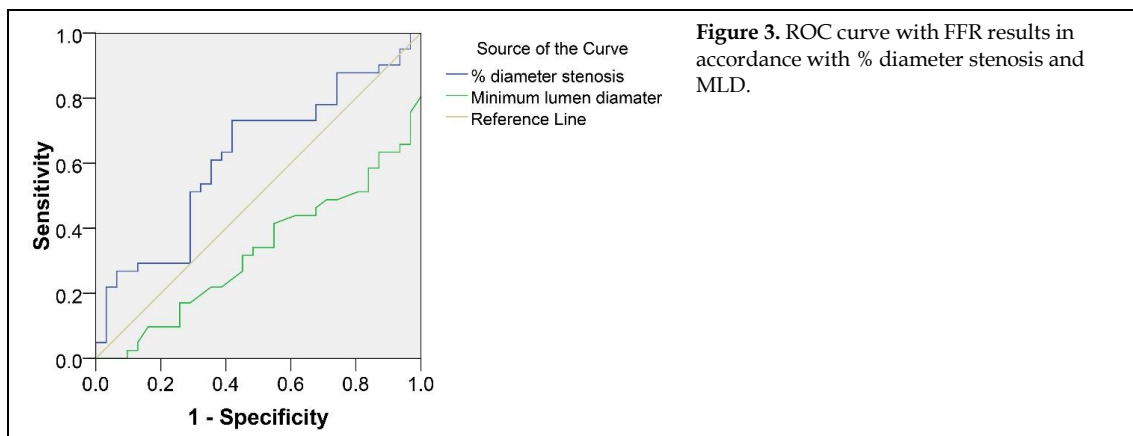
Figure 3. ROC curve with FFR results in accordance with % diameter stenosis and MLD.

Table 5. Prediction of FFR based on % diameter stenosis and minimum lumen diameter.

Index	Odds ratio (CI 95%)	p-value
% Diameter stenosis ≤ 55.62%	1	<0.01
% Diameter stenosis > 55.62%	3.78 (1.40– 10.19)	
MLD > 1.08	1	<0.01
MLD ≤ 1.08	4.95 (1.59– 15.43)	

FFR: fractional flow reserve; MLD: minimum lumen diameter.

Table 6. Complications during FFR measurement.

Complications	Frequency	Percent (%)
Sinus bradycardia	1	1.4
Transient AV block	2	2.8
Hypotension	1	1.4
Myocardial rupture	0	0
Coronary artery dissection	0	0

FFR: fractional flow reserve; AV: atrioventricular.

Table 7. Complications over 12 months of monitoring.

Complications	Medical therapy (N = 31, FFR > 0.8)	Intervention (N = 41, FFR ≤ 0.8)	p-value
Stroke	0 (0%)	0 (0)	>0.05
Gastrointestinal bleeding	0 (0%)	1 (2.4%)	>0.05
Angina pectoris	1 (3.2%)	1 (2.4%)	>0.05
Dysrhythmia	1 (3.2%)	0 (0%)	>0.05
Recurrent myocardial infarction	0 (0%)	0 (0%)	>0.05
Re-intervention or bypass surgery	0 (0%)	0 (0%)	>0.05
Cardiac death	0 (0%)	0 (0%)	>0.05

FFR: fractional flow reserve.

DISCUSSION

In our study, the proportion of male patients was significantly higher than that of female patients, consistent with the incidence of CAD in the community (Manfrini et al., 2020; Kuneman and Bax, 2021). The average age of the patients was 66.0 ± 12.9 years, and the presence of a CAD patient aged 36 years indicated the risk of CAD at younger ages and the importance of early screening for risk factors. The risk factors showed differing prevalences in the study population: hypertension, dyslipidaemia, and obesity were the most prevalent risk factors (62.5%, 41.7%, and 37.5%, respectively). These findings are consistent with those reported in studies on CAD by Kellenset et al. (2016) and Smits et al. (2017).

All cases in our study showed angina pectoris on admission, with 73.6% of the patients showing stable angina pectoris; 90.6% of the stable angina pectoris cases could be categorized under CCS grades I and II (Table 1). In addition, 62.5% of the patients showed no specific ECG changes, and most of them had a normal systolic left ventricular contractile function.

The quantitative results of CCTA revealed various sites of lesions. Narrow sites were mostly located on the LAD (51.4%). The three types of coronary lesions showed different rates, with type A constituting the majority (73.6%). The mean % diameter stenosis was 58.30% ± 7.77%, with a mean length of 10.30 ± 4.62

mm (Table 2). These findings are consistent with features of an intermediate stenosis, showing similarity and variation with the results reported by Yong et al. (2011), Sun et al. (2015), Takashima et al. (2015), and Nishi et al. (2017). This diversity in lesions improved our evaluation of the efficacy of FFR in clinical application. Our measurements showed 41 lesions with FFR ≤ 0.80 (56.9%) and 31 with FFR > 0.80 (43.1%) (Table 3). Thus, FFR prevented the need for stenting in 43.1% of the patients in our study, reducing the cost of treatment by approximately USD 1000/patient. The incremental cost-effectiveness ratio (ICER) for one angina-free year is USD 2531, but follow-up data over many years are required to calculate the disability-adjusted life years (DALY) and quality-adjusted life years (QALYs).

Myocardial ischaemia caused by the narrow segment is an important consideration in the decision-making process. When clinical symptoms are not specific and subjective evaluation and ECG changes show no significance, FFR can be used to arrive at a diagnosis. Thus, this procedure plays an important role in the evaluation of these patients. When assessing the influence of ischaemia on the angina pectoris grade, a change from CCS grade I to unstable angina pectoris is likely to be accompanied by a reduction in the FFR: the FFR result for CCS grade 1 was 0.84 ± 009 while that for unstable angina pectoris was 0.72 ± 0.14, and the difference was statistically

significant (p<0.05). However, the inverse correlation between FFR and angina pectoris was not considerable (r = - 0.387) (Fig. 1). With regard to coronary artery stenosis, the % diameter stenosis (r = - 0.241) and MLD (r = 0.360) were correlated with FFR measurements (p<0.05) (Fig. 2).

The low correlation between form and function has been proven in other studies, such as those by Ben-Doret et al. (2012) and Sun et al. (2015). We used the ROC curve to predict FFR results in accordance with these two stenosis parameters, and the results showed that their accuracy was moderate. The cut-off points for these predictions were >55.62% and ≤1.08 mm, respectively (Fig. 3). Moreover, while assessing the ability to predict FFR results on the basis of odds ratios, we found that in cases with >55.62% diameter stenosis, the possibility of FFR ≤ 0.8 was 3.78 times higher than that in cases with ≤55.62% diameter stenosis. For cases with an MLD ≤ 1.08, the possibility of an FFR ≤ 0.8 was 4.95 times higher than that in those with an MLD > 1.08. Therefore, the FFR had a higher value than clinical features and stenosis in haemodynamic assessment of narrow segments. Based on our findings, we suggested a new cut-off value of >55.62% diameter stenosis or minimal lumen diameter (MLD) ≤ 1.08 mm to predict the fractional flow reserve (FFR) results.

Safety is an important consideration related to the use of FFR for choosing between intervention and medical therapy. This is especially pertinent for patients with diameter stenosis values that correspond to approximately the upper limit (70%) of intermediate stenosis. After 12 months of clinical treatment and follow-up, we assessed various conditions, including recurrent angina pectoris, ventricular dysrhythmia, and major cardiac events (MI, death, need for coronary artery catheterization), and we recorded 2 cases of recurrent angina pectoris, which were equally distributed in the medical therapy and intervention groups (3.2% and 2.4%, respectively). Among these two patients, the patient in the medical therapy group had a premature ventricular contraction. In this study, no patient died (0%) and none of the patients showed recurrent MI (0%) or required coronary artery intervention after receiving medical therapy. The difference in cardiac complications was not statistically significant between the groups. One case of GI bleeding was recorded in the coronary artery intervention group (24%). Thus, the proportion of complications throughout the post-treatment period was insignificant. Furthermore, this proportion was lower than that reported in other studies. In comparison with the results reported by Kelly et al. (2010), our findings clearly proved that FFR measurement was safe and cost-effective.

Technically, all patients underwent FFR measurements from the right radial artery (100%). For assessment of coronary circulation, approaches exist through the brachial arteries, radial arteries, and femoral arteries. However, the approach through brachial arteries is not commonly used, and approaches through the radial and femoral arteries are widely applied. The radial artery is a favourable site for the interventionist. In four large clinical trials, including 17 133 patients, the proportion of the radial artery approach was 6.3% in comparison with 1.7% for the femoral artery approach (Ando and Capodanno, 2015). In fact, the choice of approach sites (radial or femoral artery) depends on various factors, including experience levels, approaching techniques, anatomical features, the purpose of the procedure, and the expected benefits. In comparison with the femoral artery, the use of the radial artery is considered more effective. The radial artery approach reduces the dose of contrast dye and the duration of the procedure (Brasselet et al., 2007; Jolly et al., 2011). In our study, the mean duration of the procedure was 13 ± 5 min; the shortest and longest procedures lasted 10 and 40 min, respectively. The radial artery approach also ensured patient comfort, thereby shortening hospital time. In the study by Romagnoli et al. (2012), the median hospital time was 5 days (interquartile range: 4-7 days) with the radial artery approach in comparison with 6 days for the femoral artery approach (interquartile range: 5-8 days). Notably, various studies showed fewer complications with the radial artery approach in comparison with the femoral artery approach, including a lower risk of bleeding (1.4% *vs.* 2.9%), lower risk of death (2.7% *vs.* 4.7%), and lower probability of bleeding at the site of penetration (2.1% *vs.* 5.6%) (Karrowni et al., 2013). According to recommendations of the European Society of Cardiology (ESC), the radial artery should be preferred over other arteries (evidence level of IIa) (Kolh et al., 2014). However, the femoral approach would be applied if the radial pulse is weak or hard to palpate, if there was vasospasm, or if catheterisation had been performed previously, for example, in an arteriovenous fistula in patients undergoing haemodialysis.

During the procedure, we directly injected adenosine into the coronary artery after administering nitroglycerine. The mean adenosine dose for the LCA was 120 ± 33 µg, with the lowest and highest doses being 30 µg and 150 µg, respectively. For the RCA, the mean adenosine dose was 87 ± 24 µg, with the lowest and highest doses being 30 µg and 120 µg, respectively. Because the area of perfusion of the LCA is more significant than that of the RCA, the adenosine dose on the left side was higher.

With regard to intraprocedural complications, we recorded 1 case of sinus bradycardia (1.4%), 2 cases of transient AV block (2.8%), and 1 case of hypotension (1.4%). None of the cases showed myocardial rupture or coronary artery dissection. The patients showing transient AV block and hypotension quickly recovered without significant complications. To date, no severe complications related to FFR measurement, and the use of adenosine have been noted. Thus, FFR measurement can have been considered safe for clinical application, and the use of adenosine at the maximum dose can also be considered to be safe.

Limitations of the study

In this study, we did not investigate in detail the cases of multivessel lesion of the coronary artery, the cases of the abnormal dominant coronary artery, as well as the location of narrowing near the coronary artery ostium or not. As such details may affect the results of the FFR measurement.

CONCLUSION

FFR measurement is a safe technique that can be used to evaluate the possibility of myocardial ischaemia in patients showing intermediate stenosis of the coronary artery. The use of intervention only for cases showing haemodynamic effects can reduce the treatment costs for intervention and medical therapy after the intervention.

In cases where FFR is not available for assessment, doctors can use cut-off points of >55.62% diameter stenosis or MLD ≤ 1.08 mm to forecast FFR results. Thus, a suitable treatment strategy should be developed based on the stenosis lesions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Ho AB	Nguyen NS	Ngo LX	Cao-Thi TP	Phan AK	Hoang AT	Nguyen CL
Concepts or ideas	x	x	x	x	x	x	x
Design	x	x	x	x	x	x	x
Definition of intellectual content	x	x	x	x	x	x	x
Literature search	x	x	x	x	x	x	x
Clinical trial	x					x	
Experimental studies	x					x	
Data acquisition	x	x	x	x	x	x	x
Data analysis	x					x	
Statistical analysis	x					x	
Manuscript preparation	x	x	x	x	x	x	x
Manuscript editing	x					x	
Manuscript review	x	x	x	x	x	x	x