Long-Term Prognosis in Diabetic Patients in Whom Revascularization Is Deferred Following Fractional Flow Reserve Assessment

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Introduction and objectives. The fractional flow reserve (FFR) has been shown to be a valid and useful measure in the functional assessment of coronary stenoses of intermediate severity. Our aim was to determine the usefulness of FFR assessment in diabetic patients, in whom determination of the FFR can be influenced by microvascular dysfunction.

Methods. Between 1997-2004, FFR assessment was used to evaluate 222 consecutive coronary lesions judged by an interventional cardiologist to be of intermediate severity (ie, 40%-70%). Intravenous adenosine (140 μg/kg per min) was used to achieve maximum hyperemia. The occurrence of cardiac events (ie, death, non-fatal acute myocardial infarction, and target lesion revascularization) was compared in diabetics and nondiabetics in whom FFR assessment gave a negative result and intervention was deferred. The mean follow-up period was 30 (21) months.

Results. Revascularization was deferred for 144 lesions (in 136 patients) in which the FFR was ≥0.75. Of these, 42 lesions (29.2%) were in diabetics (40 patients). The proportion of patients who were female or who had hypertension, dyslipidemia, or multivessel disease was greater in the diabetic group. There was no difference in indications for coronary angiography. In both groups, the most frequently investigated vessel was the left anterior descending coronary artery. The mean FFR was 0.87 (0.06), and there was no difference between the groups. On long-term follow-up, there was no difference in the rate of death or acute myocardial infarction. Overall, 8.8% of nondiabetics and 14.3% of diabetics with a negative FFR test result required target lesion revascularization (*P*=.32).

Conclusions. Our results indicate that deferring percutaneous coronary intervention in diabetics with a moderately severe coronary artery stenosis and an FFR ≥0.75 is safe.

Key words: *Fractional flow reserve. Diabetes mellitus. Coronary intervention.*

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Pronóstico a largo plazo de diferir la intervención coronaria en diabéticos sobre la base de la reserva fraccional de flujo

Introducción y objetivos. El cálculo de la reserva fraccional de flujo (RFF) es una herramienta útil y validada en la aproximación funcional de estenosis coronarias de severidad intermedia. Nuestro objetivo fue conocer su utilidad en diabéticos, cuya disfunción microvascular puede afectar a dicho cálculo.

Métodos. Entre 1997 y 2004, se evaluaron mediante RFF 222 lesiones coronarias consecutivas de severidad intermedia (40-70%) a criterio del hemodinamista. Se utilizó adenosina intravenosa para alcanzar hiperemia máxima (140 μg/kg/min). Comparamos los eventos clínicos cardiacos (muerte, infarto de miocardio no fatal, revascularización de la lesión evaluada) en diabéticos y no diabéticos en los que la RFF fue negativa y no se intervino. El seguimiento medio fue de 30 ± 21 meses.

Resultados. La revascularización no se indicó en 144 lesiones (136 pacientes) con RFF ≥ 0,75. Había 42 lesiones de 40 pacientes diabéticos (29,2%). Hubo más mujeres e hipertensos, dislipémicos y con enfermedad multivaso en el grupo de diabéticos. No hubo diferencias en la indicación de la coronariografía. En ambos grupos, la arteria descendente anterior fue el vaso más estudiado. El valor medio de la RFF fue 0,87 ± 0,06 y no hubo diferencias entre grupos. En el seguimiento a largo plazo, no encontramos diferencias en muerte o infarto de miocardio. El 8,8% de los no diabéticos frente al 14,3% de los diabéticos con RFF negativa precisaron revascularización de la lesión inicialmente evaluada (p = 0,32).

Conclusiones. Nuestros resultados indican que diferir la intervención coronaria en diabéticos con estenosis coronarias intermedias y RFF ≥ 0,75 parece una estrategia segura.

Palabras clave: *Reserva fraccional de flujo. Diabetes mellitus. Intervención coronaria.*

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ABBREVIATIONS

AMI: acute myocardial infarction
DM: diabetes mellitus
FFR: fractional flow reserve

INTRODUCTION

Angiography provides excellent anatomical data on the epicardial coronary arteries, but its contribution regarding the functional significance of a given level of coronary stenosis is quite limited. However, this information is essential when the stenosis is of intermediate severity. The fractional flow reserve (FFR), as measured with a pressure-monitoring guidewire, is defined as the ratio of the peak coronary flow to the myocardium in the presence of stenosis divided by the peak coronary flow in the hypothetical absence of such stenosis.[1,2] This parameter is easy-to-obtain and replicate, and some studies have shown a good correlation between this and non-invasive ischemia detection tests,[3-6] establishing a 0.75 cutoff value for FFR. However, there is a gray area for FFR ranging from 0.75 to 0.80 where the results should be interpreted with caution.

The induction of maximum hyperemia is the key requirement for this technique, as in such conditions the pressure-flow relationship becomes linear.[7] Microcirculatory dysfunction modifies the slope of this relationship, reducing the pressure gradient across the stenosis[8] and overestimating FFR. On the other hand, if maximum hyperemia is not obtained, the gradient is also underestimated and FFR overestimated. Theoretically, diabetes mellitus entails microvascular dysfunction,[9-11] which could interfere in the measurement of FFR and lead to false normal results.

This paper assesses the long-term prognosis of diabetic patients with intermediate severity coronary lesions, in whom revascularization was deferred based on an FFR ≥0.75.

METHODS

Patients

This was an observational retrospective cohort study that included every consecutive patient with intermediate severity coronary stenosis (40%-70% of stenosis by visual estimation under angiography) undergoing a pressure-monitoring guidewire study to calculate the FFR in a cardiac catheterization laboratory between 1997 and 2004. Patients with a recent coronary syndrome in a stable clinical condition (>4 days from onset) were included. Criteria for diabetes were diagnosed prior to cardiac catheterization. Multivessel coronary artery disease was defined as stenosis ≥50% in 2 or more epicardial coronary arteries. The final population in our study was 136 patients (144 lesions), as 2 coronary lesions were studied in different arteries in 6 non-diabetic patients and in 2 diabetic patients. The study met the Declaration of Helsinki criteria and was approved by the local Ethics Committee. Informed consent was obtained from all patients.

Fractional Flow Reserve Calculation

A 0.014 intracoronary pressure-monitoring guidewire was used (Radi Medical, Uppsala, Sweden, or Cardiometrics EndoSonics, Hut Cordova, California, USA). A 6 Fr guide catheter was advanced up to the ostium of target coronary artery. Fifty U/kg of intravenous heparin and 200-300 µg of intracoronary nitroglycerin were administered. The guidewire was calibrated before introducing it into the guide catheter and the guide catheter pressure matched to that of the guidewire. The distal pressure-monitoring guidewire was advanced toward to the lesion site. The FFR (ratio between average pressure obtained at the guidewire and the average pressure obtained at the catheter) was calculated after intravenous infusion of 140 µg/kg/min of adenosine over 2 min to induce maximal coronary flow. The cutoff point was set at 0.75 (negative, ≥0.75), based on the literature.

Quantitative Coronary Angiography

A second angiography was performed by an independent observer blind to clinical data and FFR values. This was done using validated edge-detection software (CAAS II 4.1 for Windows, Pie Medical Imaging, Maastricht, Netherlands). A calibrated guide catheter was used to calculate the reference diameter and the minimum luminal diameter, as well as the percentage of stenosis (ratio of both values). The final values were taken from the mean of 2 orthogonal projections.

Follow-up and Clinical Events

Follow-up was performed in all patients by a check-up visit in the cardiology department or, if this was not possible, by telephone. Indications for a new coronary angiography was left to the discretion of the physician in charge of the patient based on myocardial ischemia symptoms or signs. The following were considered major events at follow-up: death (considered as cardiac unless another cause could be demonstrated), myocardial infarction (thoracic pain plus increased creatine kinase levels double the laboratory's reference values), and the need for percutaneous or surgical

TABLE 1. **Baseline Clinical Characteristics of Patients**

	Non-Diabetic	Diabetic	*P*
Patients, n	96	40	
Age, mean (SD), y	61 (10)	64 (7)	.04
Men, %	84.3	71.4	.07
Hypertension, %	33.7	59.5	.004
Dyslipidemia, %	32.4	59.5	.003
Smokers, %	52	38.1	.13
Multivessel disease, %	63.7	81	.043
LVEF, mean (SD), %	63 (12)	58 (14)	.079
Revascularization of another vessel, %	31.4	28.6	NS
Acute coronary syndrome, %	56.9	54.8	NS
NSTEACS, %	84	77.8	NS
Admission ACS-FFR, mean (SD), d	6.4 (3.4)	7 (2.4)	NS
Target vessel cause of ACS, %	19	12	NS
Target vessel with underlying AMI, %	9.5	12.7	NS
Target vessel with FFR			NS
Lesions, n	102	42	
Left main coronary artery, n (%)	16 (15.6)	9 (21.4)	
Left anterior descending artery, n (%)	57 (55.8)	23 (54.7)	
Right anterior descending artery, n (%)	25 (24.5)	6 (14.2)	
Circumflex, n (%)	4 (3.9)	4 (9.5)	

AMI, acute myocardial infarction; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; NS, nonsignificant; NSTEACS, non-ST segment elevation acute coronary syndrome; SD indicates standard deviation.

revascularization in the lesion initially assessed using the FFR.

Statistical Analysis

The quantitative variables are expressed as mean (standard deviation). Qualitative variables are expressed as percentages. The Student *t* test was used to compare the means of quantitative variables with a normal distribution, and the χ^2 test or Fisher's exact test for qualitative variables. Combined event-free survival or death/heart attack-free survival were assessed in the 2 groups by Kaplan-Meier analysis (log-rank test). A *P* value less than .05 was considered statistically significant. The statistical analysis was done using SPSS for Windows software, version 12.0. (SPSS, Chicago, Ill., USA)

RESULTS

A total of 222 lesions of intermediate severity were studied in the period (206 patients); of these, the FFR was <0.75 in 72 lesions (70 patients), where revascularization was indicated. The FFR was ≥0.75 in 150 lesions. In 6 of these cases, the specialist recommended revascularization despite the result not being indicative of ischemia. In line with the results obtained by the pressure-monitoring guidewire, revascularization was not indicated for the remaining 144 lesions in 136 patients, which became our study population.

Comparison Between Diabetic and Non-Diabetic Patients

Table 1 summarizes the baseline characteristics of both groups of patients.

Of the diabetic patients, 17/40 (42.5%) were insulin-dependent and 23/40 (57.5%) were non-insulin-dependent (only 10% were undergoing dietary treatment). The diabetic population was older and presented a higher prevalence of cardiovascular risk factors (hypertension and dyslipidemia), as well as a higher frequency of multivessel disease. No differences were found regarding the target vessel nor in indications for coronary angiography. The lesions assessed in the cases evaluated after an acute coronary syndrome (most of which involved non-ST segment elevation) were, in general, non-causal; there was an average of 6.5 days (Table 1) between admission and the FFR study.

Quantitative angiographic data are shown in Table 2. No differences were found between diabetic and non-diabetic patients in the parameters under analysis (stenosis percentage, reference luminal diameter, minimum luminal diameter, lesion length). The average FFR values were similar in both groups.

Long-Term Follow-up

All patients underwent clinical follow-up (average, 30 [21] months). The patients who underwent major events did not initially present more severe lesions as indicated by angiography or FFR values (0.87 in both groups). There

TABLE 2. **Quantitative Angiographic Data of Lesions Assessed by Fractional Flow Reserve**

	Non-Diabetic	Diabetic	*P*
Lesions, n	102	42	
Stenosis, mean (SD), %	52 (11)	50.7 (12)	NS
Reference diameter, mean (SD), mm	3.08 (0.67)	3.02 (0.85)	NS
MLD, mean (SD), mm	1.69 (0.77)	1.53 (0.70)	NS
Length, mean (SD), mm	9.4 (3.5)	10.5 (4.5)	NS
FFR, mean (SD)	0.87 (0.06)	0.87 (0.06)	NS
Associated IVUS, %	10.7	16.2	NS

FFR, fractional flow reserve; IVUS, intravascular ultrasound imaging; MLD, minimum luminal diameter; NS, nonsignificant; SD indicates standard deviation.

were 10 deaths and 3 acute myocardial infarctions (AMI) (Table 3). In 4 cases, death was due to non-cardiac causes (lung cancer, lung thromboembolism, digestive hemorrhage, and acute kidney failure). In the 6 remaining cases, the cause of the death was cardiac with sudden death occurring in 3 patients; no association could be established with the target artery by the FFR. Of the 3 AMI cases, 2 cases (1 in each group) were related to the target lesions. Major events (cardiac death/AMI) probably associated with the lesions initially evaluated as moderate was estimated at 3/96 (3.1%) in non-diabetic patients and 2/40 (5%) in diabetic patients (without statistical significance).

Revascularization was performed in 15 (10.4%) lesions during follow-up. Table 4 shows the main characteristics of these patients. Revascularization was indicated by clinical evidence, recurrence of angina, or positive ischemia induction tests. Disease progression was observed in two-thirds of these patients, with no differences between diabetic and non-diabetic patients. Revascularization was performed in 6/42 diabetic patients (14.3% of lesions), and in 9/102 non-diabetic patients (8.8%; *P*=.32) (Figure 1). Within the diabetic group, revascularization was performed in 4/18 (22.2%) of insulin-dependent patients and in 2/24 (8.3%) non-insulin-dependent patients(*P*=.20).

No differences were found in cardiovascular mortality (3.5% vs 5.4%; *P*=.23), infarction (2.3% vs 0%; *P*=.37), or need for revascularization (12.5% vs 7.1%; *P*=.30) between patients assessed after acute coronary syndromes and stable patients.

Figure 2 shows the event-free Kaplan-Meier survival curve (mortality and AMI) and Figure 3 shows the combined event-free Kaplan-Meier survival curve (death, infarction, and need for revascularization). No significant differences were found.

Safety of the Procedure

As reported by other groups,[12] no major complications occurred when using this technique. There was 1 case of coronary vasospasm. Intravenous adenosine infusion had to be suspended in 2 patients due to bronchial hyperreactivity, and so this agent was administered via the intracoronary route.

TABLE 3. **Major Coronary Events During Follow-up**

Patient	Vessel	Initial Diagnosis of ACS	Vessel Cause of ACS	Cause of Death (Time)	Diabetes Mellitus
Death (n=10)					
1	LMCA	NSTEACS	Yes	Lung cancer (8 months)	No
2	Cx	No		Lung thromboembolism (24 months)	No
3	RCA	NSTEACS	Yes	Sudden death (12 months)	No
4	LMCA	NSTEACS	No	Digestive hemorrhage (30 months)	No
5	RCA	No		AMI (12 months)	No
6	LAD	No		Sudden death (24 months)	No
7	LAD	No		Sudden death (24 months)	Yes
8	LAD	No		Heart failure (36 months)	Yes
9	LAD	NSTEACS	No	Heart failure (30 months)	Yes
10	LMCA	NSTEACS	No	Acute kidney failure (3 days)	Yes
Non-fatal AMI (n=3)					
1	RCA	NSTEACS	No	Not found (5 months)	No
2	LAD	NSTEACS	No	Anterior infarction (24 months)	No
3	LAD	NSTEACS	No	Anterior infarction (9 months)	Yes

ACS, acute coronary syndrome; AMI, acute myocardial infarction; Cx, circumflex artery; LAD, left anterior descending artery; LMCA, left main coronary artery; NSTEACS, non-ST segment elevation acute coronary syndrome; RCA indicates right coronary artery.

TABLE 4. **Revascularization During Follow-up of the Lesion Assessed by Fractional Flow Reserve**

Patient	Vessel	Initial Diagnosis of ACS	Vessel Cause of ACS	Cause of Revascularization (Time)	Diabetes Mellitus
1	LAD	NSTEACS	Yes	Disease progression (2 months)	No
2	LAD	NSTEACS	No	Disease progression (1 month)	No
3	LAD			Persistent symptoms (5 months)	No
4	LAD			Disease progression (30 months)	No
5	RCA	NSTEACS	No	Disease progression (12 months)	No
6	RCA	NSTEACS	No	Persistent symptoms/non-invasive ischemia test (11 months)	No
7	RCA	NSTEACS	No	Persistent symptoms (1 month)	No
8	LMCA			Disease progression (24 months)	No
9	LMCA			Disease progression (4 months)	No
10	LAD			Disease progression (9 months)	Yes
11	Cx	NSTEACS	No	Disease progression (9 months)	Yes
12	LAD	STEACS	No	Disease progression (24 months)	Yes
13	LAD			Persistent symptoms/noninvasive ischemia test (3 months)	Yes
14	LAD	STEACS	Yes	Disease progression (1 month)	Yes
15	RCA			Persistent symptoms/noninvasive ischemia test (26 months)	Yes

AMI, acute myocardial infarction; Cx, circumflex artery; LAD, left anterior descending artery; LMCA, left main coronary artery; NSTEACS, non-ST segment elevation acute coronary syndrome; RCA indicates right coronary artery; STEACS, ST-segment elevation acute coronary syndrome.

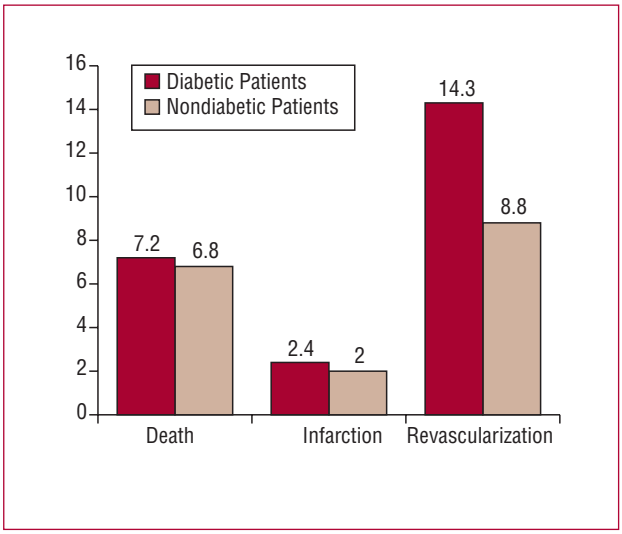

Figure 1. Major coronary events in diabetic and non-diabetic patients.

DISCUSSION

One of the most frequent and difficult issues to resolve in a cardiac catheterization laboratory is to establish whether a lesion is important or not, whether it is causing ischemia, and whether it should be treated.[13] In the last decade, the calculation of the FFR using an intracoronary pressure-monitoring guidewire has become a useful tool to study coronary circulation physiology in order to assess intermediate lesions.

Both retrospective[14-17] and randomized[18] studies have shown that deferring coronary intervention based on an FFR ≥0.75 is safe and does not lead to a worse prognosis for patients with stable angina. Recently, several works have found that this approach is safe in patients with acute coronary syndrome.[19,20] In our study, lesions in patients undergoing an acute coronary syndrome were assessed after suitable clinical stabilization; most of these lesions were not the cause of the acute situation.

Criticism of the use of FFR focuses on the fact that it has been validated in patients with preserved ventricular function and vessel disease. In addition, the FFR value is modulated by the status of the microcirculation.[7,8] Diabetes mellitus is a good example of a condition where functional and structural microcirculation abnormalities might lead to apparently normal FFR values. Furthermore, multivessel disease (with moderate lesions) after acute coronary syndrome is a frequent finding in diabetic patients.

Our work is the first to assess the strategy of deferring coronary intervention based on FFR in the diabetic population. The results indicate that this strategy appears to be safe: there was a slight but non-significant tendency for more target lesion revascularization procedures in the diabetic group (14.3% vs 8.8%) and the incidence of major events (death/AMI) associated with the target lesion during long-term follow-up was low (5% in diabetic patients vs 3.1% in non-diabetic patients; non-significant).

The direct treatment of intermediate lesions offers an alternative to this strategy. In an ad hoc analysis of 4 clinical trials. Moses et al[21] reported that the treatment of stenotic lesions <50% with drug-eluting stents seemed safe: an event rate of 5.6% versus 25.4% with bare-metal stents. However, only a quarter of this population was diabetic and follow-up was just 1 year; besides this, the

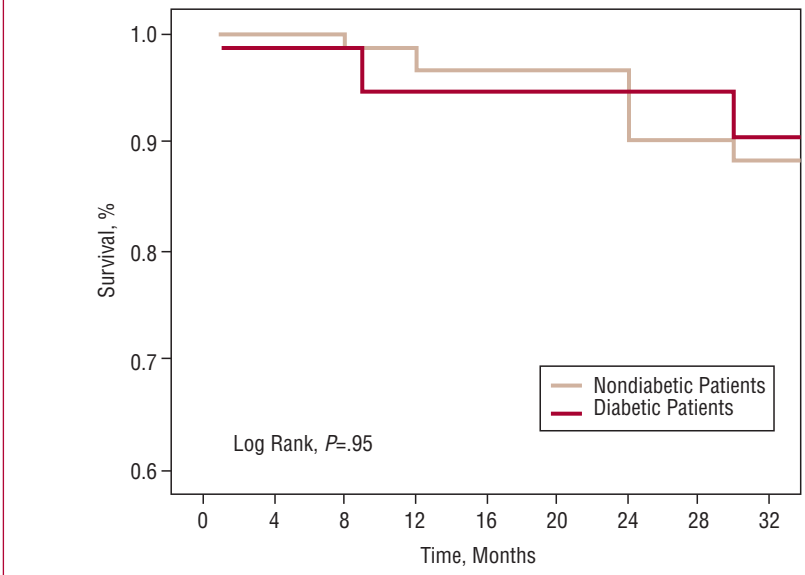

Figure 2. Death/infarction-free Kaplan-Meier survival curve.

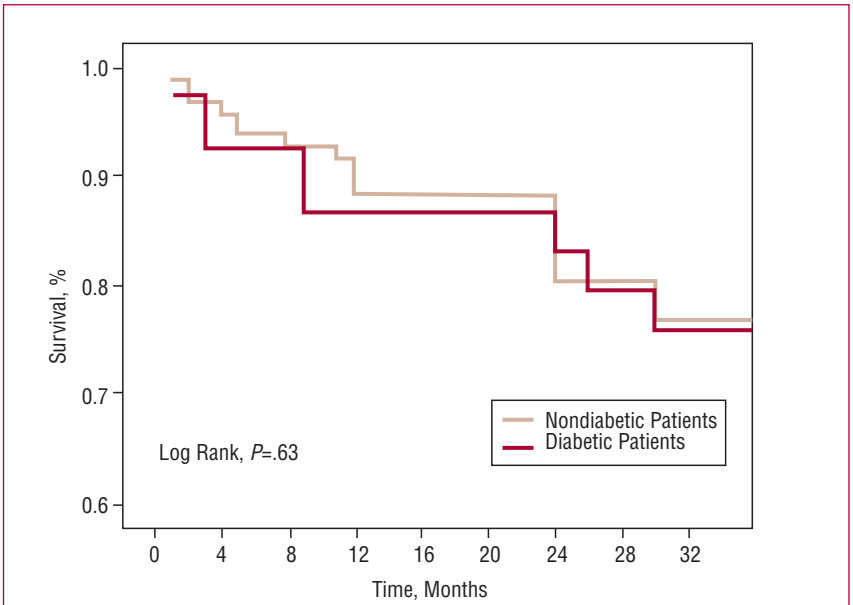

Figure. 3. Death/infarction/revascularization-free Kaplan-Meier survival curve.

cost of these strategies would be far higher and the incidence of late thrombosis, although minimal, would not be well-tolerated in this population.

In the diabetic group, 2 new revascularization procedures were performed in non-insulin-dependent patients (8.3%), whereas 4 were performed in insulin-dependent patients (22.2%)—who might have greater microvascular impairment—without reaching statistical significance probably due to sample size.

In a previous study, Yanagisawa et al[22] studied 304 stable coronary lesions in 96 diabetic patients and 149 non-diabetic patients assessed by FFR and pyrophosphate myocardial scintigraphy (SPECT), to determine the value of FFR in diabetics, demonstrating that a cut-off value of 0.75 was valid for detecting ischemia in this population. Glycemic control had an effect on FFR, since in those patients with poor control (glycohemoglobin >7%) the specificity of FFR was

lower, probably related to inadequate arteriolar vasodilatation. This suggests that chronic hyperglycemia may have an important influence on vascular dysfunction.[10]

Another aspect to take into account is the presence of target-vessel infarcted territory. Previous studies[23] have reported that for a similar degree of stenosis, the FFR value depends on viable myocardium. In our study, few lesions with these characteristics were included (11.7%), and only 1 patient needed revascularization during follow-up.

The agent used and the form of administration to obtain maximum vasodilatation are key factors, especially in the diabetic population where the capacity to obtain vasodilatation may be reduced. Suboptimal levels of coronary hyperemia lead to underestimating the pressure gradient. We use intravenous adenosine (140 µg/kg/min) as the standard protocol in our laboratory, which has been validated in initial studies. A recent study[24] that compared 50 lesions with different hyperemic stimuli (increasing doses of intracoronary adenosine and intravenous adenosine) concluded that stimulation with intravenous adenosine at 140 µg/kg/min produces the most pronounced hyperemia and should be the method of choice for the calculation of FFR.

In 12.5% of the lesions, the use of a pressure-monitoring guidewire was compatible with intravascular sonography (mainly in lesions in the left main coronary artery and in the proximal segment of the anterior descending artery). Both techniques are complementary, and the anatomical data on the vascular wall provided by intracoronary ultrasound is highly relevant. Nevertheless, the calculation of the FFR offers the advantage of determining the level at which the stenosis restricts maximum myocardial flow and therefore the improvement rate derived from the intervention.

Limitations of the Study

Our work has important limitations. The main one is that it was a retrospective observational study, which can affect the quality of data collection. The number of cases involving diabetic patients was low, which means that this should be considered a hypothesis-generating study. There was a selection bias, since the decision to use FFR to assess lesions of intermediate severity was made at the specialist's discretion, and not all such lesions were assessed in the given period. This means that the conclusions should not be extrapolated to all intermediate severity lesions in diabetic patients, but rather only to those assessed (basically, focal lesions, and proximal segments). Data on glycemic control are not available which may have affected the results of FFR. Coronary flow reserve as assessed by Doppler guidewire for the detection of microvascular disease was not studied.

CONCLUSIONS

Our results indicate that deferring coronary intervention in diabetic patients with intermediate coronary stenosis and FFR ≥0.75 seems to be a safe strategy.

REFERENCES

1. de Bruyne B, Bartunek J, Sys SU, Heyndrickx GR. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. Circulation. 1995;92:39-46.
2. Pijls NHJ, de Bruyne B, Peels K, van der Voort P, Bonnier H, Bartunek J, et al. Measurement of fractional flow reserve to assess the functional severity of coronary stenoses. N Engl J Med. 1996;334:1703-8.
3. de Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Boj A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation. 1994;89:1013-22.
4. Bartunek J, van Schuerbeeck E, de Bruyne B. Comparison of excercise test electrocardiography and dobutamine echocardiography with invasively assessed myocardial fractional flow reserve in evaluation of severity of coronary arterial narrowing. Am J Cardiol. 1997;79:478-81.
5. Candell-Riera J, Martín-Comin J, Escaned J, Peteiro J. Valoración fisiológica de la circulación coronaria. Papel de las técnicas invasivas y no invasivas. Rev Esp Cardiol. 2002;55:271-91.
6. Jiménez Navarro M, Alonso Briales JH, Hernández García JM, Rodríguez Bailón I, Gómez Doblas JJ, de Teresa Galván E. Measurement of fraccional flow reserve to assess moderately severe coronary lesions: correlation with dobutamine stress echocardiography. J Interven Cardiol. 2001;14:499-504.
7. Escaned J, Conde C, Ferrer MC, Gonzalo N. Fundamentos fisiológicos para el uso de la guía de presión intracoronaria. En: Hernández JM, editor. Manual de cardiología intervencionista. Madrid: SCM; 2005. p. 293-316.
8. Meuwissen M, Chamuleau SAJ, Siebes M, Schotborgh CE, Koch KT, de Winter RJ, et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate lesions. Circulation. 2001;103:184-7.
9. Nahser PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patient with diabetes mellitus. Circulation. 1995;91:635-40.
10. di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the patogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol. 2003;41:1397-3.
11. Akasaka T, Yoshida K, Hozumi T, Takagi T, Kagi S, Kawamoto T, et al. Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. J Am Coll Cardiol. 1997;30:935-41.
12. López Palop R, Pinar E, Lozano I, Carrillo P, Cortes R, Picó F, et al. Utilización habitual de la guía de presión intracoronaria. Experiencia de un centro. Rev Esp Cardiol. 2002;55:251-7.
13. Botas J. Evaluación y guía terapéutica de las lesiones coronarias intermedias en el laboratorio de hemodinámica. Rev Esp Cardiol. 2003;56:1218-30.
14. Bech GJ, de Bruyne B, Bonnier HJ, Bartunek J, Wijns W, Peels K, et al. Long-term follow-up after deferral of percutaneous transluminal coronary angioplasty of intermediate stenosis on the basis of coronary pressure measurement. J Am Coll Cardiol. 1998;31:841-7.
15. Chamuleau SAJ, Meuwissen M, Kock KT, van Eck-Smit BL, Tio RA, Tijssen JG, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. Am J Cardiol. 2002;89:377-80.
16. Rieber J, Schiele TM, Koenig A, Erhad I, Segmiller T, Stempfle HU, et al. Long-term safety of therapy stratification in patients with

intermediate coronary lesions based on intracoronary pressure measurements. Am J Cardiol. 2002;90:1160-4.
17. Jiménez Navarro MF, Hernández Garcia JM, Alonso Briales JH, Kuhlmorgen B, Gómez Doblas JJ, García Pinilla JM, et al. Should we treat patients with moderately severe stenosis of the left main coronary artery and negative FFR results? J Invas Cardiol. 2004;16:398-400.
18. Pijls NH, van Schaardenburgh P, Manoharan P, Boersma E, Bech JW, vant Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol. 2007;49:2105-11.
19. Fisher JJ, Wang XQ, Samady H, Sarembock IJ, Powers ER, Gimple LW, et al. Outcome of patients with acute coronary syndromes and moderate coronary lesions undergoing deferral of revascularization based on fractional flow reserve assessment. Catheter Cardiovasc Interv. 2006;68:544-8.
20. Potvin JM, Rodes-Cabau J, Bertrand OF, Gleeton O, Nguyen CN, Barbeau G, et al. Usefulness of fractional flow reserve measurements to defer revascularization in patients with stable or unstable angina pectoris, non-ST-elevation and ST-elevation acute myocardial infarction, or atypical chest pain. Am J Cardiol. 2006;98:289-97.
21. Moses JW, Stone GW, Nikolsky E, Mintz G, Dangas G, Grube E, et al. Drug-eluting stents in the treatment of intermediate lesions. J Am Coll Cardiol. 2006;47:2164-71.
22. Yanagisawa H, Chikamori T, Tanaka N, Usui Y, Takazawa K, Yamashina A. Application of pressure-derived myocardial fractional flow reserve in assessing the functional severity of coronary artery stenosis in patients with diabetes mellitus. Cir J. 2004;68:993-8.
23. de Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, de Winter W, et al. Fraccional flow reserve in patients with prior myocardial infraction. Circulation. 2001;104:157-62.
24. Casella G, Leibig M, Schiele T, Schrepf R, Seelig V, Stempfle HU, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for assessment of fractional flow reserve? Am Heart J. 2004;148:590-605.