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Original article

Results of Fractional Flow Reserve Measurement to Evaluate Nonculprit Coronary Artery Stenoses in Patients With Acute Coronary Syndrome

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ABSTRACT

Introduction and objectives: Multivessel disease is usually present in almost half of patients with acute coronary syndromes. Angiography is insufficiently accurate to decide on coronary revascularization in moderate nonculprit lesions. There is some debate about the usefulness of fractional flow reserve assessed by intracoronary pressure wire in acute coronary syndromes. We studied the results of using fractional flow reserve values to decide whether to perform coronary revascularization of nonculprit angiographically moderate lesions in patients with acute coronary syndrome and multivesel disease.
Methods: The fractional flow reserve was used to decide whether to revascularize angiographically moderate nonculprit lesions in a cohort of consecutive patients with acute coronary syndromes recruited in 2 centers.
Results: One hundred and seven patients were included. Based on fractional flow reserve values, 81 patients (75.7%) were not revascularized. All lesions studied were revascularized in 26 patients (24.3%). Patient characteristics of the nontreated group and treated group were, respectively, diseased vessels, 1.3 (0.7) vs 1.4 (0.6) ($P<.4$); fractional flow reserve-studied lesions, 1.2 (0.5) vs 1.1 (0.4) ($P=.3$); stenosis, 46.1 (8.3)% vs 47.9 (10.3)% ($P=.4$); fractional flow reserve, 0.86 (0.1) vs 0.70 (0.1) ($P<.005$). After 1 year of follow-up, no significant differences in major cardiovascular events were observed between groups. There no deaths or nonfatal myocardial infarctions attributable to fractional flow reserve - deferred lesions. Coronary revascularization of the studied lesions was performed in 3 nontreated group patients (3.7%) due to disease progression.
Conclusions: Fractional flow reserve assessed by intracoronary pressure wire is useful in deciding whether to revascularize angiographically moderate nonculprit lesions in patients with acute coronary syndrome and multivessel disease.

Resultados del empleo de la reserva fraccional de flujo en la valoración de lesiones no causales en el síndrome coronario agudo

Palabras clave:
Enfermedad coronaria
Angiografía coronaria
Angioplastia coronaria
Angina inestable
Reserva fraccional de flujo

RESUMEN

Introducción y objetivos: Casi la mitad de los pacientes con síndrome coronario agudo presentan enfermedad multivaso. En ocasiones la angiografía no es suficiente para decidir la revascularización de lesiones distintas de la que causa el síndrome coronario agudo. La validez de la reserva fraccional de flujo medida con guía intracoronaria de presión es controvertida en el síndrome coronario agudo. Analizamos los resultados de basar la decisión de revascularización de lesiones angiográficamente dudosas en la reserva fraccional de flujo obtenida mediante guía de presión en pacientes con síndrome coronario agudo y enfermedad multivaso.
Métodos: Estudio observacional de una serie consecutiva de pacientes cateterizados en dos centros por síndrome coronario agudo, en los se utilizó la reserva fraccional de flujo para decidir el tratamiento de lesiones angiográficamente moderadas distintas de la causal.
Resultados: Se incluyó a 107 pacientes. Tras tratar la lesión causal, en 81 pacientes (75,7%) alguna de las lesiones no fue tratada según la reserva fraccional de flujo obtenida (grupo no tratado); en 26 (24,3%) se revascularizaron todas las lesiones estudiadas (grupo tratado). Características (grupo no tratado/grupo tratado): vasos enfermos, 1,3 ± 0,7/1,4 ± 0,6 (p = 0,4); lesiones estudiadas, 1,2 ± 0,5/1,1 ± 0,4 (p = 0,3); porcentaje de estenosis, 46,1 ± 8,3%/47,9 ± 10,3% (p = 0,4); reserva fraccional de flujo, 0,86 ± 0,1/0,70 ± 0,1 (p < 0,005). No se observaron diferencias significativas entre los grupos en la tasa de eventos cardiovasculares al año. No se produjeron fallecimientos ni infartos no fatales atribuibles a las lesiones no tratadas según la reserva fraccional de flujo. En el grupo no tratado 3 pacientes (3,7%) recibieron revascularización de la arteria estudiada por progresión de la enfermedad.

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Conclusiones: La reserva fraccional de flujo obtenida con guía intracoronaria de presión permite decidir la revascularización de lesiones angiográficamente dudosas en el paciente con síndrome coronario agudo y enfermedad multivaso.

Abbreviations

ACS: acute coronary syndrome
FFR: fractional flow reserve
MACE: major adverse cardiovascular events

INTRODUCTION

Up to 50% of patients with acute coronary syndrome (ACS) may have multivessel disease and angiographic evidence of further lesions in addition to those causing the acute symptoms.[1,2] Multivessel disease has been associated with poor prognosis in ACS,[3–5] although studies have shown a reduction in events when other lesions are revascularized during treatment of the culprit lesion.[6–9] Most studies have based the decision to revascularize on angiographic parameters. The presence of angiographic stenosis, which is used to guide decisions on whether to revascularize in most procedures in clinical practice, has recently been shown to have some limitations in multivessel disease.[10,11] Fractional flow reserve (FFR) measured by intracoronary pressure wire is considered the gold standard when deciding whether to revascularize in angiographically intermediate or doubtful coronary stenosis.[12] However, doubts remain about the reliability of using this FFR measurement to guide revascularization decisions in acute ACS. It has been suggested that transitory microvascular damage in myocardial territories other than the culprit lesion and the dynamic nature of the injuries may limit the reliability of FFR values obtained during ACS. To date, no studies have analyzed the clinical outcomes associated with use of FFR values obtained during the acute phase of ACS to guide revascularization of nonculprit coronary lesions.

The aim of this study was to investigate the safety of using FFR measured with an intracoronary pressure wire to guide decisions on whether to revascularize intermediate or doubtful nonculprit coronary lesions in patients with ACS. Safety was assessed in terms of clinical events at 1 year.

METHODS

Observational, descriptive cohort study of consecutively recruited patients.

Patients

All procedures meeting the following criteria in 2 centers were included: coronary angiography requested because of ACS with or without ST elevation, successful stenting of the culprit artery, and at least one angiographically moderate, nonculprit lesion studied using a pressure wire (visual stenosis between 50% and 70%). The culprit lesion was determined based on angiographic characteristics and electrocardiographic changes.

Coronary Angiography and Interventional Procedures

Prior to the procedure, all patients received aspirin (100 mg/day, or a loading dose of 300 mg if not previously taking aspirin) and clopidogrel (75 mg/day, or a loading dose of 600 mg if not previously taking clopidogrel). As this was an observational study, the indication for treating angiographically significant nonculprit lesions, the interventional technique, the type of stent used, and use of platelet glycoprotein IIb/IIIa (anti-GPIIb/IIIa) were at the interventionist's discretion. Six experienced interventional cardiologists (over 1000 coronary interventions) chose and performed the procedures. All patients received 100 IU/kg sodium heparin before the procedure or 70 IU/kg if anti-GPIIb/IIIa was used. Oral antiplatelet therapy was maintained for 1 year after hospital discharge in patients hospitalized for ACS, unless contraindicated. Treatment before and after the procedure was decided by the treating physician.

Determination of Fractional Flow Reserve

The methodology for determining the FFR has been described previously.[13] After deciding to perform a functional study of the nonculprit lesion, 200 to 300 μg of nitroglycerin were administered through the catheter guidewire. Projections providing the best visualization of the lesion were repeated with this catheter, ie, those which maximized visual stenosis without superimposed branches or loss of length because of curvature. The functional evaluation was performed with a 0.014-inch intracoronary pressure wire (Pressure-Wire™, St. Jude Medical Systems AB, Uppsala, Sweden or Volcano Primewire™, Volcano Inc., Rancho Cordova, California, United States). The guidewire was calibrated externally and then advanced to the distal end of the guiding catheter while verifying the equality of the pressure curves in the catheter and the pressure wire. The guide was advanced until the sensor was located at least 10 mm distal to the lesion being studied. The FFR was obtained by administering 300 to 500 μg of intracoronary adenosine, while taking special care to avoid wedging the catheter in the coronary ostium after bolus injection of the drug. The beat-to-beat ratio of the mean aortic pressure at the end of the guide catheter and the pressure distal to the lesion, obtained via the pressure wire in a situation of maximum hyperemia were used to calculate the FFR. At least 3 FFR determinations were made, and the lowest FFR was used for decision-making. A maximum dose of 500 μg of intracoronary adenosine was used as long as a lower dose did not produce a period of asystole $\geq$6 s. Lesions with an FFR $\geq$0.75 were not revascularized.

Variables

Patient baseline characteristics and procedure outcomes were collected from hospital medical records and the registry of procedures in each cardiac catheterization laboratory in the hospitals where the study was performed, or through visualization of the angiographic recording of the procedure. Complete revascularization was defined as the absence of significant lesions in a $>$2 mm diameter vessel.

Quantitative Analysis

Quantitative analysis was performed offline by an experienced interventionist in one of the two participating centers. The analyst was not aware of the results of the functional study. Measurements

were made using MEDIS QAngio XA v 7.1 software (Medis Medical Imaging Systems, Leiden, the Netherlands).

Follow-Up

Follow-up was performed 1 year after the functional study by telephone and by consulting the clinical records of patients rehospitalized over that period. If a further coronary angiography was performed, the recording was reviewed to assess the status of the previously studied lesion. Primary endpoints in the follow-up period were a combined event (major adverse cardiovascular events [MACE]), death through cardiac or unknown causes, nonfatal myocardial infarction, and revascularization of the lesion studied. We also analyzed each of the isolated events making up MACE and noncardiac death, rehospitalization for ischemic heart disease, and revascularization in a lesion other than that initially studied. Myocardial infarction during follow-up was considered as a new hospital admission, with that specific diagnosis.

Statistical Analysis

Continuous variables are shown as means (standard deviation) and categorical variables as absolute values and percentages. We analyzed the correlation between the degree of angiographic stenosis, obtained by digital analysis and measured as percent diameter, and the observed FFR value. Kaplan-Meier survival analysis was performed for each of the events analyzed during follow-up. Analyses were performed using the SPSS (version 15.0) statistical package for Windows.

RESULTS

We studied 128 lesions in 107 patients. All patients received angioplasty with stenting of the ACS culprit lesion. In all cases, the functional study of the nonculprit lesion was performed during hospitalization motivated by the ACS. In a nontreated group (NTG) of 81 (75.7%) patients, some of the lesions studied were not revascularized based on FFR values; some nonculprit lesions were revascularized in 26 (24.3%) patients (treated group [TG]). Patient baseline characteristics and procedures are described in Table 1. There were no significant differences in clinical profile between the 2 patient groups, except for a higher proportion of women in the NTG. The indication for coronary angiography was ACS with ST-segment elevation in 11 patients (10%), 2 of whom had received primary angioplasty 2 and 3 days, respectively, before the study to assess acute myocardial infarction-related nonculprit lesions.

Table 1
Patient Baseline Characteristics by Treatment Group

	NTG (n=81)	TG (n=26)	*P*
Personal history			
Age, years	63.3±10	65.2±13.1	.510
Women	23 (28.4)	2 (7.7)	.030
Diabetes mellitus	27 (33.3)	9 (34.6)	.900
High blood pressure	59 (72.8)	17 (70.8)	.850
Dyslipidemia	42 (51.9)	15 (57.7)	.600
Smoking	38 (46.9)	16 (61.5)	.190
Previous myocardial infarction	24 (29.6)	6 (23.1)	.520
Previous coronary revascularization	15 (18.5)	5 (19.2)	.930
Previous stroke	6 (7.4)	1 (3.8)	.520
Type of ACS			.330
No ST elevation	74 (91.4)	22 (84.6)	
ST elevation	7 (8.6)	4 (15.4)	
Ventricular function, %	63.3±7.5	60±7.1	.410
Angiographic characteristics			
Artery studied			
Descending anterior	54 (66.7)	20 (76.9)	.330
Circumflex	25 (30.9)	4 (15.4)	.120
Right coronary	15 (18.5)	3 (11.5)	.410
ACS culprit artery			
Descending anterior	18 (22.2)	5 (19.2)	.750
Circumflex	28 (34.6)	10 (38.5)	.720
Right coronary	34 (42)	11 (42.3)	.980
Saphenous vein graft	1 (1.2)	0	.570
Number of diseased vessels	1.3±0.7	1.4±0.6	.400
Number of vessels studied	1.2±0.4	1.1±0.3	.190
Number of lesions studied	1.2±0.5	1.1±0.4	.260
*Number of vessels treated**	1.1±0.3	1.9±0.6	<.005
Number of stents implanted /procedure	1.4±0.7	2.5±1.3	<.005
Number of drug-eluting stents/procedure	0.8±0.8	1.9±1.5	.003
Complete revascularization	64 (79)	21 (80.8)	.850

ACS, acute coronary syndrome; NTG, nontreated group; TG, treated group.
Data are expressed as mean ± standard deviation, or no. (%).
* Includes ACS culprit vessels and vessels studied with fractional flow reserve in the treatment group.

Table 2
Quantitative Analysis and Fractional Flow Reserve in the Lesions Studied

	FFR≥0.75 (not treated)	FFR<0.75 (treated)	*P*
Patients	92	35	
Reference diameter	2.74±0.63	2.78±0.85	.850
Minimum luminal diameter	1.48±0.40	1.45±0.50	.810
Stenosis, %	46.06±8.33	47.91±10.28	.440
Length	20.75±10.33	21.73±11.13	.720
FFR	0.86±0.06	0.70±0.13	<.005

FFR, fractional flow reserve.
Data are expressed as mean ± standard deviation.

In the TG (positive FFR), treatment based on FFR values was performed in a nonculprit vessel in 17 patients (65.4%), in the same vessel as the culprit lesion but in a different segment in 6 patients (23%), and in an angiographically severe nonculprit lesion other than the one studied in 3 patients (11.5%). In the NTG (negative FFR), revascularization was performed on a vessel other than the culprit vessel, and in a lesion other than the one studied in 11 patients (13.5%). In all other patients in this group, only the culprit artery was treated.

In TG patients, the number of vessels treated and the number of bare metal and drug-eluting stents implanted was significantly higher (Table 1). There were no significant differences between groups in terms of the baseline angiographic characteristics of the lesions studied (Table 2). The correlation between FFR values and angiographic stenosis (diameter) measured without knowledge of the outcomes of the functional studies was low (r=0.25 [0.09], *P*=.02) (Fig. 1).

All procedures were performed during hospitalization for ACS. The only complications associated with use of the intracoronary pressure wire were transient episodes of atrioventricular block.

Events during follow-up are shown in Table 3. There were 5 deaths during the first year after the procedure: 3 from stroke (2 ischemic and 1 hemorrhagic), 1 in the context of sepsis after abdominal surgery for malignancy, and 1 sudden cardiac death 45 days after the procedure in a 71-year-old NTG patient. The patient had moderate left ventricular dysfunction and diffuse disease of the left coronary artery and was treated with 3 drug-eluting stents in the proximal and middle sections of the left anterior descending artery and in the proximal section of the left circumflex artery. The patient also had a functionally insignificant lesion in the middle right coronary artery. No new nonfatal infarctions were observed during follow-up.

Coronary angiography was repeated due to clinical recurrence of angina in 10 patients, 8 of whom required revascularization. No significant lesions were observed in the other 2 cases.

In 4 patients (4.9%), the lesion originally studied had to be revascularized when no intervention had initially been performed because of FFR >0.75. Worsening of angiographic stenosis was observed in 3 cases (3.7%). In one of those, repetition of the functional study revealed an FFR of <0.75 when the value in the index procedure had been >0.80; in another case (also in the NTG), bypass surgery was performed and no further worsening of the lesion under study (in the anterior descending coronary artery) was observed. However, this patient was readmitted for unstable angina, and restenosis was observed in the treated right coronary artery together with significant disease in the common left trunk which did not exist in the index study.

In the first year of follow-up, 10 patients (9.3%) were readmitted due to cardiac causes. Of these, 9 (8.4%) were admitted with chest pain and 1 because of worsening heart failure.

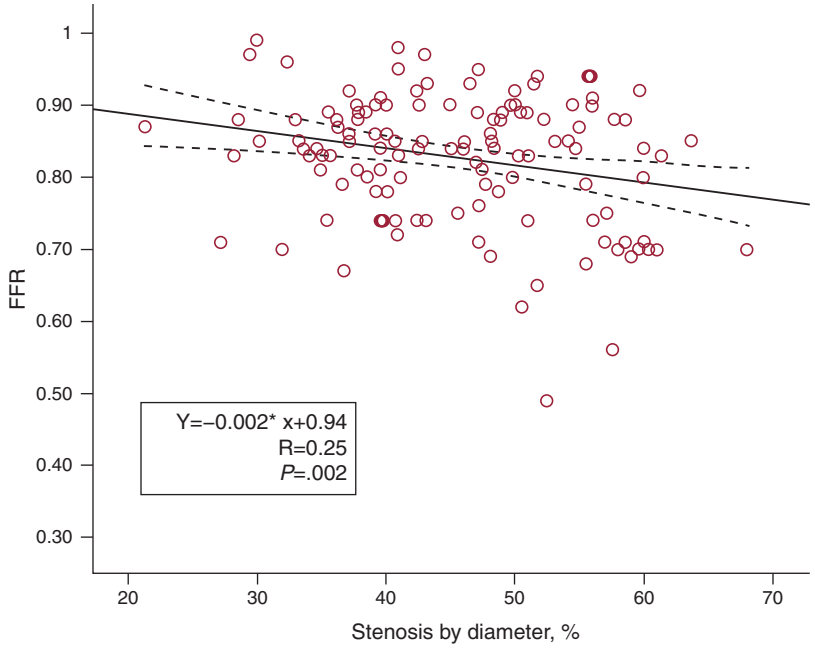

Figure 1. Correlation between fractional flow reserve and angiographic stenosis (diameter) obtained by offline digital measurement. Linear fit with 95% confidence interval. FFR, fractional flow reserve.

Table 3
Events Occurring During One Year of Follow-Up

	Total (n=107)	NTG (n=81)	TG (n=26)	*P*
Any cause mortality	5 (4.7)	4 (4.9)	1 (3.8)	.82
Cardiac-related mortality	1 (0.9)	1 (1.2)	0	.57
Nonfatal infarction	0	0	0	—
New coronary revascularization	8 (7.5)	6 (7.4)	2 (7.7)	.96
Revascularization of studied lesion (not treated)	4 (3.7)	4 (4.9)	—	—
Revascularization of treated artery	3 (2.8)	1 (1.2)	2 (7.7)	.08
Surgical revascularization	1 (0.9)	1 (1.2)	0	.57
New unscheduled coronary angiography	10 (9.3)	8 (9.9)	2 (7.7)	.74
Any-cause readmission	13 (12.1)	11 (13.6)	2 (7.7)	.42
Cardiac-related readmission	10 (9.3)	8 (9.9)	2 (7.7)	.74
Stent thrombosis (confirmed or probable)	0	0	0	—
MACE	8 (7.5)	6 (7.4)	2 (7.7)	.52

MACE, major adverse cardiovascular events (cardiac-related mortality, nonfatal infarction or need to revascularize any lesion studied using pressure guidewire or treated in the index procedure); NTG, nontreated group; TG, treated group.
Data are expressed as no. (%).

After 1 year of follow-up, no significant differences were observed between NTG and TG in terms of cardiac death (*P*=.971), revascularization of the lesion under study (*P*=.8), nonfatal myocardial infarction or fixed combined event (*P*=.97). There were also no differences between groups in terms of the need for coronary angiography (*P*=.73), coronary revascularization (*P*=.98) or rehospitalization due to cardiac causes (*P*=.72). Significance was studied using Mantel-Cox log rank survival analysis (Fig. 2 and Table 3).

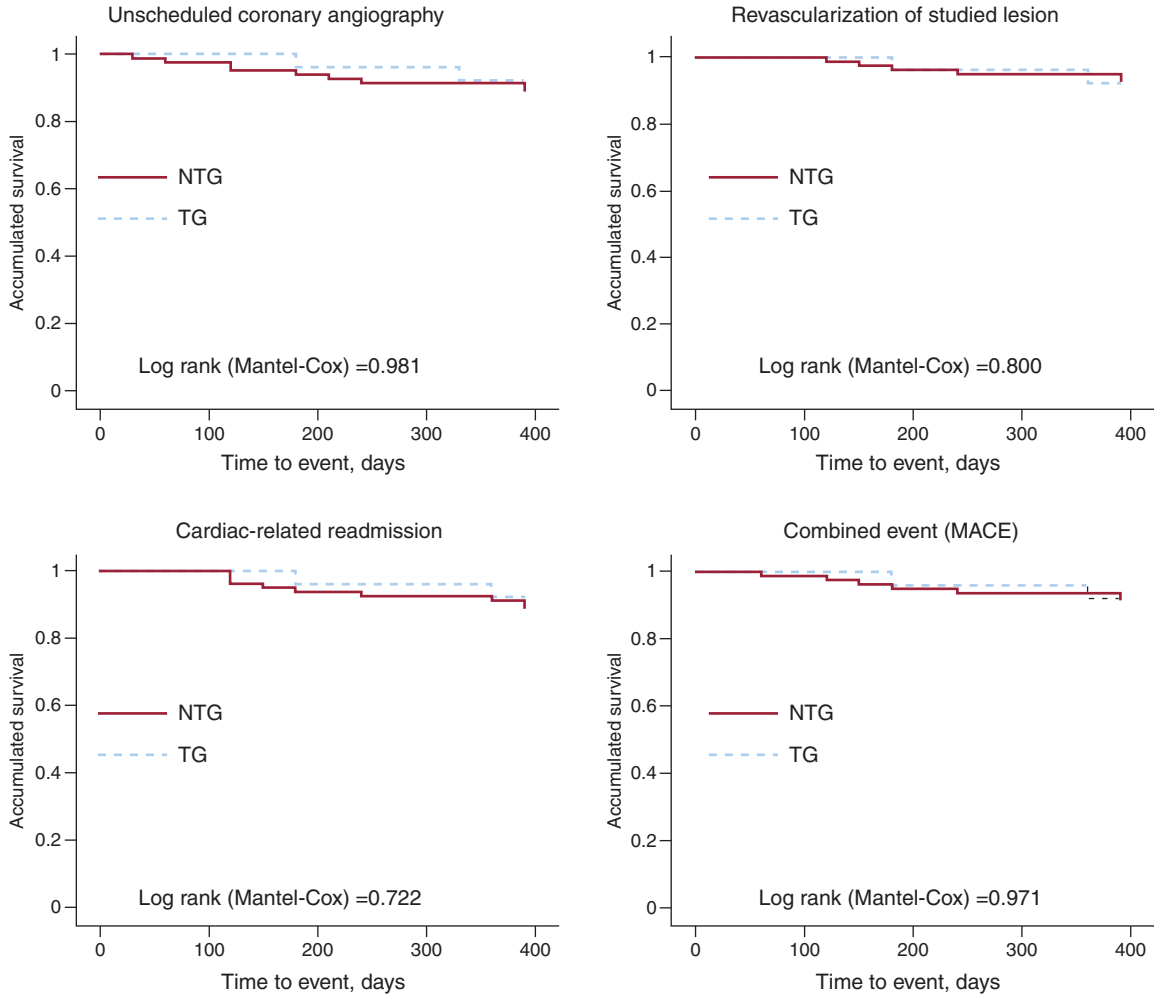

Figure 2. Kaplan-Meier survival curves for unscheduled repeat revascularization, revascularization of the lesion studied, readmission for cardiac causes, and combined events (major adverse cardiovascular events). MACE, major adverse cardiovascular events; NTG, nontreated group; TG, treated group.

DISCUSSION

The results of this study demonstrate that it is safe to use FFR obtained by intracoronary pressure wire to defer revascularization of angiographically inconclusive nonculprit lesions in patients with ACS and multivessel disease.

In line with the most current practice guidelines, a large number of ACS patients are catheterized early.[1,12,14] In both ST-segment elevation ACS, for which primary angioplasty is the reperfusion therapy of choice, and in cases where primary angioplasty cannot be performed or in ACS without ST-segment elevation, coronary angiography is performed so early that in many cases the patient is catheterized without prior performance of a noninvasive test to localize ischemia. In ACS, up to 50% of patients can have multivessel disease, depending on the series.[1,2] Several studies have indicated that revascularization of significant nonculprit lesions of ACS may be associated with better prognosis. Angiography alone may have limitations when deciding if a lesion is functionally significant or not.[15] Based on the results of the FAME study,[10,11] recent coronary revascularization guidelines[12] have proposed the "liberal" use of pressure wires in such situations. The strength of the findings from a high-quality clinical trial such as FAME has led to recommendations to use FFR in a wide range of clinical scenarios. However, in the FAME study only 35% of patients had a clinical diagnosis of ACS. In patients with a diagnosis of stroke, the assessment would have been made at least 5 days later. Our study, which was performed exclusively in patients with acute phase ACS, demonstrates that FFRs obtained with pressure wires can be used to assess the functional impact of angiographically inconclusive lesions in the same procedure in which the culprit lesion is revascularized. This strategy means that the patient's coronary artery disease can be fully assessed and can prevent further catheterizations. As noted in previous studies, this in turn can reduce hospital stay and costs.[16] The invasive nature of coronary angiography means that both the physician requesting the procedure and, above all, the patient who has to undergo the procedure will expect a definitive diagnosis of the problem and, if possible, a recommendation for definitive treatment. Using FFR helps reduce uncertainty about the significance of coronary lesions and consequent delays in diagnosis and treatment due to the need for further diagnostic tests. It may also reduce the need for second procedures. The results of this study show that it is safe to base decision-making on FFR in nonculprit lesions of ACS patients, but comparison with other decision strategies was not possible.

Although it has been suggested that FFR should be used during angioplasty to evaluate nonculprit lesions in the context of acute myocardial infarction,[17] in our opinion such an assessment, if carried out at all, should be done in a separate procedure. Multivessel treatment is not currently recommended during primary angioplasty except in highly selected cases. Verification of the functional significance of an angiographically dubious lesion would lead to removal of the guidewire and revascularization in a second procedure or multivessel revascularization at the time of reperfusion.

Recent European guidelines on myocardial revascularization have consolidated the role of FFR in evaluating angiographically dubious lesions, although the recommendations were based on studies[12] that primarily included patients with stable coronary artery disease.[10,18] The two most important potential limitations for FFR values obtained with intracoronary pressure wires in ACS are: *a)* that existing microvascular dysfunction may make it difficult to achieve the level of hyperemia required to calculate FFR even, according to some studies, in territories other than those causing the ACS, and *b)* the dynamic nature of coronary lesions in ACS.[19]

With regard to the first potential limitation, transient microvascular dysfunction in ACS has been observed in experimental and clinical studies, both in territories supplied by the culprit artery as well as in distal myocardial regions.[20–22] However, it has not been shown to hinder calculation of the FFR in studies specifically designed to explore this aspect.[17,23,24] The most recent of those studies included 101 patients with ACS and multivessel disease,[17] and intracoronary pressure wires were used to study nonculprit lesions of ACS in the acute phase and 1 month later. No differences were observed in FFR values between these time points, a fact which led the authors to argue for the validity of FFR values obtained in ACS. They also noted, however, that clinical studies were required to analyze the safety of FFR to guide revascularization in this subgroup of patients and lesions. The current study was performed with that aim in mind and found a low rate of adverse events in patients with FFR-deferred lesions. Fewer than 5% of these patients required revascularization of the untreated lesion during follow-up, and there were no major adverse events attributable to the untreated lesion.

As regards the second potential limitation, in 3 patients who required follow-up coronary angiography we observed an increase in stenosis in the lesion under study. This phenomenon has been described previously,[13,25] and may be due to the progression of atherosclerotic disease, independently of ACS, or to changes caused by plaque triggered by the inflammatory process in ACS.[19,26,27] The FFR is a hemodynamic measurement, obtained at one time point, which integrates flow restrictions stemming from stenosis, the state of microcirculation, and the amount of myocardium distal to the lesion studied.[28] To date, no studies have indicated a role for FFR in predicting the evolution of atherosclerotic plaques, and conceptually it would not seem to be the right tool for that task. It would also not appear to be appropriate to use FFR to decide on treatment for lesions in which there are evident signs of instability.

Limitations

The observational nature of this study means the FFR-guided strategy cannot be compared with strategies in which only angiography or noninvasive ischemia tests are used, or in which questionable nonculprit angiographic lesions are simply not revascularized. In 24% of patients in our series, the lesions studied could have produced myocardial ischemia and would have been candidates for later revascularization. On the other hand, the low correlation between the degree of angiographic stenosis and FFR values would have made any decision to revascularize these lesions almost random.

The study sample was also small, although the low event rate observed in FFR-deferred patients suggests that use of a larger sample would not significantly affect the study conclusions.

CONCLUSIONS

In patients with ACS, it is safe to use FFR values obtained by pressure wire to guide decisions on the revascularization of angiographically moderate nonculprit lesions. After 1 year of follow-up, patients with FFR-deferred lesions showed very low event rates in connection with the untreated lesion.

CONFLICTS OF INTEREST

None declared.

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