

# Usefulness of the Fractional Flow Reserve Derived by Intracoronary Pressure Wire for Evaluating Angiographically Intermediate Lesions in Acute Coronary Syndrome

Ramón López-Palop, Pilar Carrillo, Araceli Frutos, Jesús Castillo, Alberto Cordero, Marlon Toro, and Vicente Bertomeu-Martínez

Servicio de Cardiología, Hospital Universitario de San Juan de Alicante, San Juan de Alicante, Alicante, Spain

**Introduction and objectives.** In contrast to findings in stable ischemic heart disease, in acute coronary syndrome (ACS), measurement of the fractional flow reserve (FFR) using an intracoronary pressure wire has not been shown to be useful for evaluating angiographically equivocal coronary lesions. The aim of this study was to analyze outcomes at 1 year in ACS patients with lesions that were classed as intermediate on coronary angiography and which were not nonrevascularized because of the FFR value determined by intracoronary pressure wire.

**Methods.** The observational study involved a cohort of patients admitted for ACS who had intermediate lesions on coronary angiography that were not revascularized because the FFR was  $>0.75$ . Functional studies were not carried out if there was angiographic evidence of instability. All-cause mortality, non-fatal myocardial infarction, revascularization of the target lesion and readmission for cardiac causes in the first year of the study were recorded.

**Results.** The study included 106 patients with 127 lesions that were not revascularized because the FFR was  $>0.75$ . Their mean age was  $69.9 \pm 10$  years, 92 (86.8%) had non-ST-elevation ACS, the mean angiographic stenosis was  $40.5 \pm 7.8\%$ , and the mean FFR was  $0.88 \pm 0.06$ . There were no complications during the procedure. The follow-up rate at 1 year was 95.1%. Events observed at 1 year were: 2 deaths (total mortality 1.9%), 0 fatal acute myocardial infarctions, 1 (0.9%) target lesion revascularization and 5 (4.7%) readmissions for cardiac causes.

**Conclusions.** Once lesions with clear angiographic signs of instability are excluded, intracoronary pressure wire measurement could be useful in ACS patients for avoiding unnecessary revascularization of angiographically intermediate coronary lesions.

**Key words:** Coronary disease. Coronary angiography. Coronary angioplasty. Unstable angina.

**Utilidad de la reserva fraccional de flujo obtenida mediante guía intracoronaria de presión en la valoración de lesiones angiográficamente moderadas en el síndrome coronario agudo**

**Introducción y objetivos.** A diferencia de lo que ocurre con la cardiopatía isquémica estable, en el síndrome coronario agudo (SCA), la reserva fraccional de flujo (RFF) medida con guía intracoronaria de presión no ha demostrado utilidad para evaluar lesiones coronarias angiográficamente dudosas. El objetivo de este estudio es analizar el pronóstico a 1 año de los pacientes con SCA y lesiones intermedias en la coronariografía no revascularizados con base en las cifras de RFF obtenida con guía intracoronaria de presión.

**Métodos.** Estudio observacional de una cohorte de pacientes ingresados por SCA con lesiones coronarias de gravedad angiográfica intermedia no revascularizadas por presentar una RFF  $> 0.75$ . El estudio funcional no se realizó en presencia de evidencia angiográfica de inestabilidad. Se evaluaron los eventos muerte, infarto no fatal, revascularización de la lesión estudiada y el reingreso por causa cardíaca durante el primer año tras el estudio.

**Resultados.** Se incluyó a 106 pacientes con 127 lesiones no revascularizadas por obtenerse una RFF  $> 0.75$ . Edad,  $69,9 \pm 10$  años; SCA sin elevación del segmento ST, 92 (86,8%); estenosis angiográfica media,  $40,5\% \pm 7,81\%$ ; RFF media,  $0,88 \pm 0,06$ . No se observaron complicaciones durante los procedimientos. Se obtuvo un seguimiento al año del 95,1%. Los eventos observados al año fueron: mortalidad total, 2 (1,9%); infarto no fatal, 0; revascularización de la lesión estudiada, 1 (0,9%); reingreso por causa cardíaca, 5 (4,7%).

**Conclusiones.** Excluyendo las lesiones con evidentes signos angiográficos de inestabilidad, la guía intracoronaria de presión puede ser una herramienta útil en el SCA para evitar revascularizaciones innecesarias de lesiones coronarias angiográficamente moderadas.

**Palabras clave:** Enfermedad coronaria. Angiografía coronaria. Angioplastia coronaria. Angina inestable.

Correspondence: Dr. R. López Palop.  
Vía Láctea, 38. Urbanización la Glorieta. 30110 Churra. Murcia. España.  
E-mail: mlopezs@meditex.es

Received August 25, 2009.

Accepted for publication January 20, 2010.

## ABBREVIATIONS

ACS: acute coronary syndrome

FFR: fractional flow reserve .

## INTRODUCTION

Fractional flow reserve (FFR) has been shown to be useful in determining the functional repercussion of angiographically moderate or dubious lesions<sup>1-5</sup> and in deciding whether to proceed with revascularization or not in patients with stable ischemic heart disease.<sup>6-10</sup> An FFR measuring  $>0.75$  or  $0.8$  in a specific lesion means revascularization can safely be postponed in the knowledge that long-term adverse events are unlikely to occur, while symptoms can be monitored as they would be in patients who do undergo treatment.<sup>6,8</sup> Currently, most routine cardiac catheterizations are indicated for acute coronary syndrome (ACS). In these patients, the percentage of coronary angiographies that find no significant lesions, or show stenosis that is angiographically moderate or difficult to quantify, varies. In these cases, the prognostic value of pressure-wire measured FFR has either been little studied or proven controversial.<sup>3,11</sup> The dynamic nature of lesions in ACS—presence of disturbed vasomotor tone, thrombus, areas of stunned myocardium or distal embolizations—can make decisions based on FFR questionable.<sup>3,11</sup>

In the present study, we analyze prognosis at 1 year in a series of patients with ACS and non-revascularized angiographically moderate lesions based on FFR measured via intracoronary pressure wire.

## METHODS

This is a descriptive observational study of a consecutive cohort of patients. We analyzed all procedures in our center between January 1, 2006 and June 30, 2008, that involved pressure-wire study of an angiographically moderate lesion (50%-70% visual stenosis). From these procedures, we selected patients hospitalized for ACS. We only included those whose medical record included a diagnosis of ACS made by a cardiologist (according to the definition current at the time)<sup>12</sup> and then, only if the coronary angiography had been requested because of

the indication of ACS. We conducted a follow-up of those patients who did not undergo revascularization of a lesion because of the FFR measurement.

We excluded coronary angiography studies indicated for chest pain of uncertain origin or in patients with valvular heart disease or cardiomyopathy which might have caused their clinical condition. We also excluded patients who underwent catheterization of a causal lesion and in whom the pressure wire was used to study lesions other than those being treated. A pressure-wire functional study of the lesion was performed at the criteria of the interventional cardiologist. Standard practice in our center is to not perform a pressure-wire study if—despite the fact we are dealing with an angiographically moderate lesion—the presence of thrombus is clear, the lesion causes  $<3$  TIMI distal flow, or an image compatible with spontaneous dissection or ulcerated plaque can be seen.

## Coronary Angiography, Invasive Study, and Treatment

Following our standard protocol, before the procedure all patients received aspirin (100 mg/day or 300 mg loading dose if not previously administered) and clopidogrel (75 mg/day or 600 mg loading dose if not previously administered). Unless contraindicated, patients admitted for ACS received dual oral antiplatelet therapy for 1 year after discharge. On deciding to perform a pressure-wire study, we administered 5000 U intravenous sodium heparin if this had not been administered previously. Once the decision to perform a functional study of an angiographically moderate lesion had been taken, the diagnostic catheter was replaced by a 6 Fr guide catheter. With this, we repeated the projections, obtaining the best possible view of the lesion, with greater visual stenosis, and without superimposed branches or loss of length due to curvature. Functional measurement was with a 0.014" intracoronary pressure wire (Pressure Wire, Radi Medical Systems, Uppsala, Sweden). The guidewire was calibrated externally and then advanced to the distal end of the guide catheter. We verified the balance between the pressure curves in the catheter and the pressure wire. After administering 200-300  $\mu$ g intracoronary nitroglycerin, the guide was advanced until the sensor was  $\geq 10$  mm distal from the lesion being studied. We measured FFR by administering 300-500  $\mu$ g intracoronary adenosine. We took special care to avoid wedging the catheter in the coronary ostium after bolus injection of the drug. We measured FFR through the coefficient, beat by beat, between mean aortic pressure (aP) (at the tip of the guide catheter) and mean distal pressure (dP) on the lesion (recorded with the pressure wire),

in maximum hyperemia. We measured FFR at least 3 times. Decision-making was based on the lowest FFR measurement. We only attempted a maximum 500 µg dose of intracoronary adenosine if a lower amount failed to produce a period of  $\geq 6$  s asystole. Patients with lesions of  $\text{FFR} \geq 0.75$  did not undergo coronary revascularization.

Medical treatment regimens before and after the procedure were always at the criteria of the physician responsible.

## Variables

Patient baseline characteristics and procedure results were gathered from hospital medical records and catheterization laboratory registries of procedures in the hospital where the study took place or the center where the angiographic recording of the procedure was viewed. We considered enzyme elevation compatible with myocardial necrosis had occurred when, prior to coronary angiography, troponin I or T, or MB fraction creatine kinase (CK-MB) data were greater than figures considered normal in the laboratory where extraction took place.

## Quantitative Analysis

Quantitative analysis was performed offline by an experienced interventional cardiologist blinded to the functional study results. Measurements were with MEDIS QAngio XA v 7.1 software (Medis Medical Imaging Systems, Leiden, The Netherlands).

## Follow-up

Follow-up was conducted 1 year after the functional study by telephone and by consulting the medical records of patients who had required readmission. In patients undergoing repeat coronary angiography, we viewed the recording again to determine the state of the lesion previously studied. During follow-up, our primary outcome variables were cardiac- or unknown-cause death, non-fatal acute myocardial infarction, need for revascularization of the lesion studied, and the combination of all 3 events. We also recorded non-cardiac mortality, need for readmission due to ischemic heart disease, and need for revascularization of a lesion other than the one studied.

We considered myocardial infarction during follow-up to be hospitalization with a medical record giving that diagnosis upon discharge.

## Statistical Analysis

Quantitative variables are expressed as mean (SD) and categorical variables as absolute values

and percentage. For comparisons, we used Student *t* test for quantitative variables if the Kolmogorov-Smirnov test proved the distribution was normal. For non-normal distributions, we used the non-parametric Mann-Whitney *U* test. We performed linear regression analysis of the percentage of stenosis by diameter figures generated by offline digital quantification for each lesion studied and the FFR measurement determined by intracoronary pressure wire. We constructed the corresponding Kaplan-Meier survival analysis curves for each event analyzed in the 1-year follow-up. Statistical analysis was done with SPSS 15.0 for Windows.

## RESULT S

Between January 1, 2006 and June 30, 2008, 111 patients fulfilled our inclusion criteria. A priori, we excluded 5 patients who were visitors to Spain and would not, therefore, be available for 1-year follow-up. The final sample consisted of 106 patients. During the study period, another 37 moderate lesions were treated because they presented an  $\text{FFR} < 0.75$  and were suspected of causing the ACS episode in 33 patients. The 144 patients undergoing pressure-wire studies in moderate lesions that possibly caused the clinical signs and symptoms of ACS were 7.8% of the total 1843 patients undergoing cardiac catheterization in our center and diagnosed with ACS in this period.

Baseline patient characteristics are in Table 1. Twenty-one percent of patients presented myocardial necrosis marker elevation and 28% presented dynamic ST-segment changes during episodes of pain (13% ST-segment elevation; 15% ST-segment depression) when these were observed. Some 12% of patients with non-ST segment elevation acute coronary syndrome (NSTEMI) were discharged with a diagnosis of non-ST segment elevation acute myocardial infarction (NSTEMI). Of these, 80.4% were diagnosed with unstable angina and the rest with chest pain without significant lesions. Over 95% of patients received antiplatelet drugs before coronary angiography and 73% received dual oral antiplatelet therapy with aspirin and clopidogrel. Other treatment regimens are in Table 2.

We studied 127 lesions in the 106 patients enrolled. In 14 patients, we studied 2 lesions (13%); in 2 patients, 3 lesions (1.9%); and in 1 patient, 4 lesions (0.9%). In most patients, 89 (86%), we studied a single lesion. Of the 127 lesions studied, 8 were restenosis in the stent (6%) and the rest, de novo lesions.

During procedures, we observed no complications other than frequent episodes of atrioventricular block and one case of paroxysmic atrial fibrillation after the adenosine-induced pause, which reverted

**TABLE 1. Patient Baseline Characteristics**

Patients	106
Personal case history	
Age (years), mean (SD)	69.9 (10.3)
Women	35 (33)
Diabetes mellitus	38 (35.8)
HBP	73 (68.9)
Dyslipidemia	48 (45.3)
Smoking	46 (43.4)
Prior myocardial infarction	29 (27.4)
Prior coronary revascularization	18 (17)
Prior PCI	15 (14.2)
Prior heart surgery	1 (0.9)
Indication for coronary angiography	
NSTEMACS	92 (86.8)
STEMACS	14 (13.2)
Time from admission to coronary angiography, (days) mean (SD)	2.7 (1.4)
Dynamic electrocardiographic alterations	30 (28.3)
Myocardial necrosis marker elevation	22 (20.8)
Ventricular function, mean (SD)	55.2 (14.9)
Angiographic characteristics	
Artery studied	
Left anterior descending artery	58 (54.7)
Circumflex artery	24 (21.6)
Right descending coronary artery	34 (32.1)
Angiographically significant coronary disease <sup>a</sup>	22 (20.7)
Number of vessels studied, mean (SD)	1.1 (0.3)
Number of lesions studied, mean (SD)	1.2 (0.5)

HHBP indicates high blood pressure; NSTEMACS, non-ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEACS, ST-segment elevation acute coronary syndrome.

<sup>a</sup>Defined as >50% angiographic stenosis in a vessel other than the one studied. Figures express n (%) or mean (SD).

spontaneously at 3 hours. All episodes of bradycardia ended spontaneously.

The results of computerized quantification of the lesions are in Table 3. We found statistically significant differences in reference diameter and minimum lumen diameter of lesions with FFR greater and less than 0.75, although their size was not relevant. We found a clear superimposition of the percentage of stenosis between lesions that were functionally significant and those that were not (Figure 1). Ten lesions (7.9%) had an FFR between 0.75 and 0.8. Linear regression

**TABLE 2. Drug Treatment Prior to Procedure**

	No. (%)
Patients	106
Aspirin	93 (87.7)
Clopidogrel	85 (80.2)
Aspirin or clopidogrel	101 (95.3)
Aspirin and clopidogrel	77 (72.6)
Anti-GPIIb/IIIa	6 (5.7)
LMWH	46 (43.4)
Beta-blockers	60 (56.6)
ACE inhibitors/ARA-II	74 (69.8)
Statins	74 (69.8)
Nitrates	57 (53.8)
Calcium antagonists	25 (23.6)
Diuretics	33 (31.1)

ACE inhibitors indicates angiotensin converting enzyme inhibitors; Anti-GPIIb/IIIa glycoprotein IIb/IIIa receptor inhibitors; ARA-II, angiotensin II receptor antagonists; LMWH, low molecular weight heparin.

analysis found no correlation ( $r=0.06$ ) between FFR measurements and computerized quantification of lesions (Figure 1).

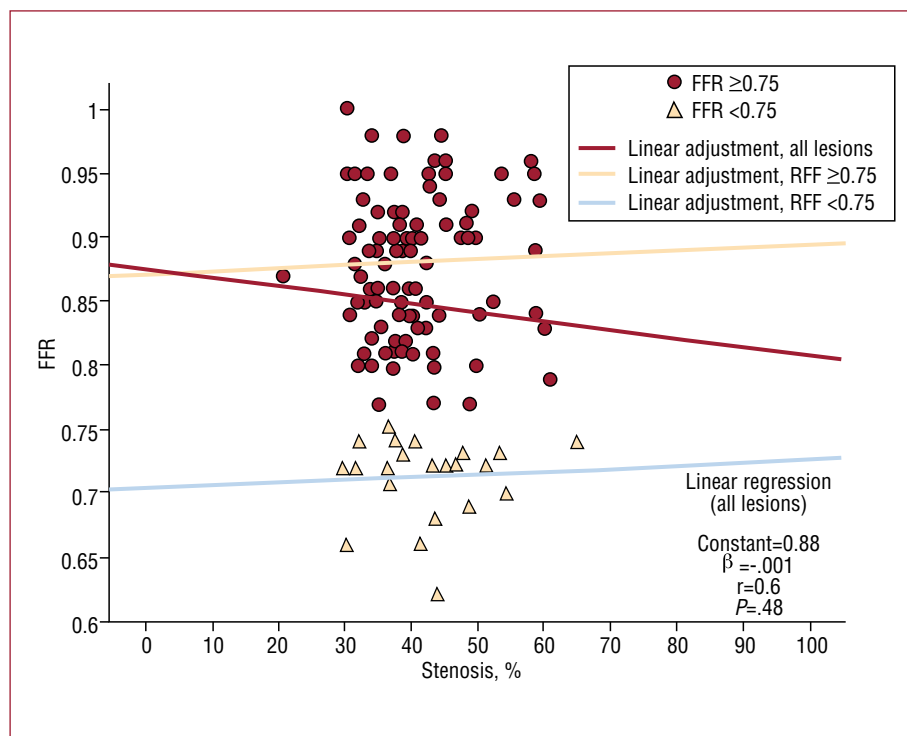
In the follow-up, we found no in-hospital complications. We achieved complete follow-up at 1 year in 103 patients (97.2%). Two men, aged 78 and 73 years, died during follow-up (FFR 0.85 and 0.96, respectively). Both had severe ventricular dysfunction at the time of the functional study. The first died in-hospital following admission for heart failure at 78 days after coronary angiography (without presenting new associated symptoms of angina or cardiac marker elevation); the second died in his sleep, at home, 325 days after coronary angiography. One patient (FFR=0.92) was readmitted at 70 days following coronary angiography for a new episode of angina at rest and underwent percutaneous coronary intervention (PCI) of the lesion previously studied on finding clear angiographic progression of the stenosis. We recorded no episode of acute myocardial infarction during 1-year follow-up. Similarly, 97.2% of

**TABLE 3. Quantitative Analysis and Fractional Flow Reserve in the Lesions Studied**

	FFR >0.75 (Non-Treated, n=127)	FFR <0.75 (Treated, n=37)	P
Reference diameter	2.87 (0.69)	2.49 (0.39)	<.0005
Minimum lumen diameter	1.69 (0.4)	1.41 (0.26)	<.0005
Percentage of stenosis	40.5 (7.81)	42.7 (8.26)	.21
Length	19.75 (9.85)	21.94 (14.14)	.36
FFR <sup>a</sup>	0.89 [0.84-0.92]	0.72 [0.7-0.73]	<.0005

FFR indicates fractional flow reserve.

<sup>a</sup>In this variable we used the Mann-Whitney non-parametric U test as the criteria of normality were not fulfilled. Figures express mean (SD) or median [interquartile range].



**Figure 1.** Correlation between angiographic stenosis (by diameter) obtained using offline digital quantification and fractional flow reserve measurement. FFR indicates fractional flow reserve.

patients remained free of the combined outcome. Survival curves are in Figure 2.

Twelve patients (11.3%) were readmitted during the first year of follow-up. Only 5 readmissions were for cardiac causes (4.7%). Repeat coronary angiography revealed no significant lesions in 2 patients: one underwent the PCI described above; in the other, we found angiographic improvement of the lesion studied.

## DISCUSSION

The present study shows the good prognosis of a consecutive series of >100 patients admitted for ACS with angiographically moderate lesions that were the only possible cause of their clinical signs and symptoms but who did not undergo revascularization because of their FFR measurement obtained by pressure-wire study. To date, this is the largest reported consecutive series in which FFR has been used to decide on the revascularization of the only lesions that could possibly have caused ACS. An earlier study<sup>13</sup> of 124 patients with ACS also used FFR to decide on the revascularization of angiographically moderate lesions. However, in contrast to the present study, 28% of patients received treatment for other significant lesions, which were probably the cause of their clinical condition, in the same procedure.

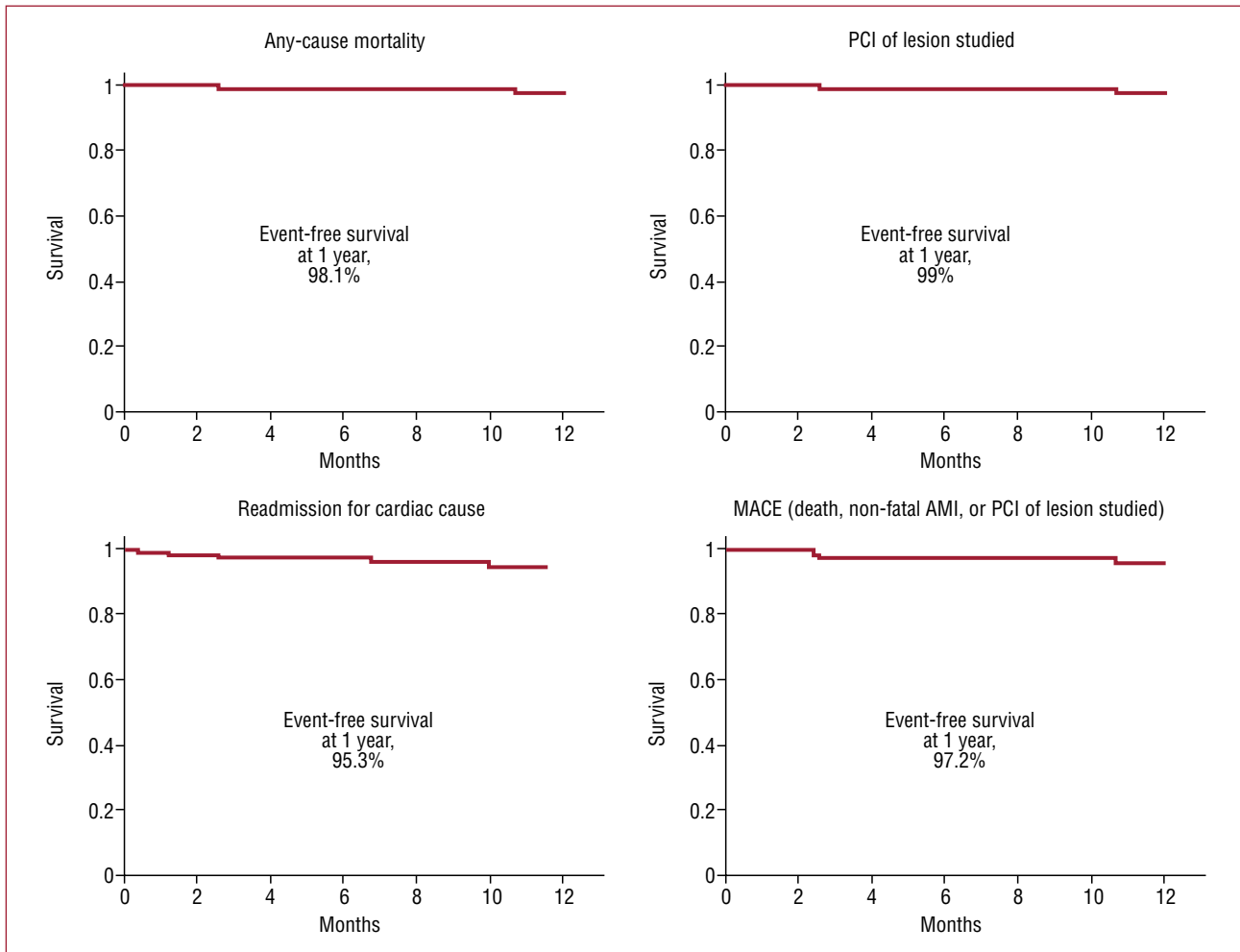
Fractional flow reserve determined with intracoronary pressure wire has proved useful in

measuring angiographically moderate lesions<sup>1-10</sup> and, recently, in deciding on the revascularization of angiographically significant lesions.<sup>14</sup> Most studies were conducted in patients with stable ischemic heart disease but the value of pressure-wire studies in the evaluation of lesions in ACS has been questioned.<sup>3,11,15,16</sup>

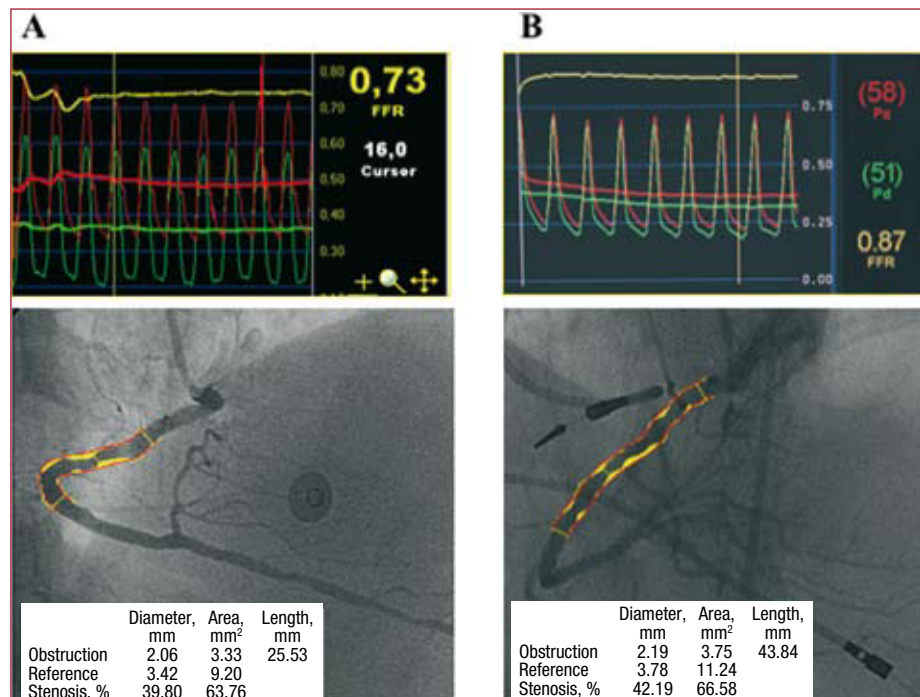
In daily clinical practice, ACS is the most frequent indication for coronary angiography. Early invasive management of ACS and the availability of coronary angiography mean many such interventions are conducted without a prior test for ischemia. Up to 6%-10% of coronary angiographies indicated for ACS reveal moderate lesions or the absence of significant lesions.<sup>17</sup> To this, we should add the indeterminate number of patients in whom we find chronic lesions or diffuse disease unrelated to ACS and lesions of dubious functional significance elsewhere in the coronary tree. In our experience, angiography was insufficient to determine the functional repercussion of lesions analyzed (Figure 3).

The decision to revascularize moderately significant lesions can be taken in the catheterization laboratory itself on the basis of the clinical and angiographic data available. Alternatively, this decision can be taken on the basis of an invasive functional test during the procedure, or of non-invasive tests. Decision-making, together with a possible revascularization, can then be postponed until a second intervention. In this context, in a small study<sup>18</sup> FFR measured with pressure wire at





**Figure 2.** Kaplan-Meier survival curves for the different events analyzed. PCI indicates percutaneous coronary intervention; MACE, major adverse cardiovascular event.



**Figure 3.** Example of 2 patients with acute coronary syndrome. Both present lesions in right descending coronary artery. A: long stenosis in right descending coronary artery quantified in 39.8% and significant FFR (0.73). B: stenosis in right descending coronary artery quantified in 42.2% and non-significant FFR (0.87).

the time of the coronary angiography showed cost-reduction benefits with the same incidence of long-term clinical events as did isotopic gammagraphy in patients with dubious lesions and ACS.

Although there is insufficient scientific evidence to support it, the intracoronary pressure wire is used on a daily basis to determine the functional significance of lesions in ACS.<sup>7,10,13,14,19</sup> Doubts about the validity of the pressure wire in ACS are justified, on the one hand, by the transitory changes in microcirculation in the first hours of ACS (presence of thrombus, microvascular ischemic dysfunction, myocardial contusion)<sup>20</sup> that can temporarily limit the vasodilatory response to the drug administered and give rise to an overestimation of FFR because maximum hyperemia is not achieved. On the other hand, the dynamic nature of the lesions means the pressure wire cannot predict the progress of the stenosis studied.

In our series, we found no adverse events directly attributable to the lesions studied and not revascularized, except in one patient who needed revascularization during follow-up. In line with current guidelines on ACS, the standard practice of anticoagulation and antiplatelet therapy at admission and dual antiplatelet therapy after discharge, together with statin treatment,<sup>12</sup> doubtless favors the stabilization of lesions in which, due to our selection criteria, stenosis is not important, flow is normal, and angiographic evidence of instability does not exist.

In our study, only 1 (0.8%) of 127 lesions studied required revascularization during follow-up because stenosis had progressed since functional evaluation. A similar case was reported earlier.<sup>11</sup> The patient evolved as would be expected for a new readmission for angina at rest without infarction or any other major event. In 99.2% of the remaining lesions, although coronary angiography was not performed during follow-up, the patients' favorable clinical evolution suggests the stability of the lesions studied.

Diagnosis of ACS is fundamentally clinical. In our series, following the inclusion criteria, all patients had been diagnosed with ACS by a cardiologist and coronary angiography was requested for this indication. Given the coronary angiography findings, we cannot ignore the fact that the clinical condition of some patients included may have been of noncoronary origin. Far from diminishing the value of pressure-wire studies in these patients, we believe this enhances it because we avoid revascularizations that might be considered even less necessary.

Based on these results, we are unable—nor is it our intention—to consider FFR measured with an intracoronary pressure wire as the parameter that, on its own, would enable us to decide about the revascularization of angiographically moderate

lesions in ACS. In our study, we excluded lesions presenting clear angiographic signs of instability. The value of the intracoronary pressure wire in the presence of visible thrombus, ulcerations, dissections or coronary flow deterioration has not been studied, and should not be used as a decision-making tool in these clinical situations. The results of this study lead us to believe that FFR measured with the intracoronary pressure wire is a useful tool that, added to angiography and clinical data, safely enables us safely to not revascularize patients admitted with a diagnosis of ACS and moderate coronary lesions, even when doubt exists about a possible relationship with the clinical signs and symptoms motivating hospitalization.

## Limitations

Over 80% of patients had normal troponin levels, indicating we are dealing with an ACS population at low risk and/or with chest pain of uncertain origin. However, this does not undermine the validity of the study, which aims to evaluate FFR as a means of responding to clinical doubt arising in a real context, in patients hospitalized for chest pain, arriving at the catheterization laboratory and presenting the interventional cardiologist with a dubious lesion.

As we have discussed, the conclusions of this study are only applicable to lesions with the characteristics specified. We cannot possibly confirm the validity of FFR in decision-making in cases of visible thrombus, dissection or ulceration, or <3 TIMI flow.

In all cases, FFR measurement was with intracoronary adenosine. Several studies have shown this approach achieves a lower level of hyperemia than intravenous adenosine.<sup>21-24</sup> To date, all published studies have used <250 µg intracoronary adenosine.<sup>21-25</sup> In fact, one comparative study found no significant differences between intravenous and intracoronary administration of 150 µg adenosine.<sup>26</sup> One recent study has found that intracoronary administration of high doses of adenosine in perfusion can be better than intravenous administration to ensure maximum hyperemia.<sup>27</sup> Our research group routinely uses >300 µg intracoronary adenosine, carefully administered and with equally careful FFR calculation, with no evidence of adverse effects. We believe that significant overestimation of FFR figures is unlikely. However, given the objective of our study (to test the safety of non-revascularization of specific lesions on the basis of FFR measurements), small overestimations of FFR would not modify the conclusions.

We cannot disregard the fact that in some patients included in the study, the causal lesion might differ from that studied and might not cause even moderate stenosis. Nor can we discount the possibility, as

mentioned in the discussion, of a noncardiac cause for the signs and symptoms of some patients. However, these issues do not detract from the validity of the study. Even in this minority of patients, the study would answer the question as to whether or not it is valid to use FFR in moderate lesions considered the potential cause (whether correct or not) in patients diagnosed (correctly or not) with ASC to avoid unnecessary revascularization procedures.

## CONCLUSIONS

In ACS, as in stable ischemic heart disease, FFR measured by intracoronary pressure wire can be a useful tool to avoid the unnecessary revascularization of angiographically moderate coronary lesions when and if they have been carefully selected to exclude those cases with angiographic signs of instability.

## REFERENCES

- Pijls NH, Van Gelder B, van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183-93.
- Pijls NH, De Bruyne B, Peels K, van der Voort PH, Bonnier HJ, Bartunek J, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-8.
- Kern MJ, Lerman A, Bech JW, de Bruyne B, Eeckhout E, Fearon WF, et al. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation*. 2006;114:1321-41.
- Uren NG, Melin JA, de Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med*. 1994;330:1782-8.
- de Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation*. 1994;89:1013-22.
- 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.
- Dominguez-Franco AJ, Jiménez-Navarro MF, Muñoz-García AJ, Alonso-Briales JH, Hernández-García JM, de Teresa Galván E. Pronóstico a largo plazo de diferir la intervención coronaria en diabéticos sobre la base de la reserva fraccional de flujo. *Rev Esp Cardiol*. 2008;61:352-9.
- Pijls NH, Van SP, Manoharan G, Boersma E, Bech JW, van't VM, 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.
- Kern MJ, Donohue TJ, Aguirre FV, Bach RG, Caracciolo EA, Wolford T, et al. Clinical outcome of deferring angioplasty in patients with normal translesional pressure-flow velocity measurements. *J Am Coll Cardiol*. 1995;25:178-87.
- Chamuleau SA, Meuwissen M, Koch KT, 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.
- Ruiz-Salmerón RJ, Sanmartín M, Mantilla R, Bravo M, Castellanos R, Goicolea J. ¿Puede la reserva fraccional de flujo guiar la estrategia terapéutica en el síndrome coronario agudo? *Rev Esp Cardiol*. 2003;56:315-7.
- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2007;50: e1-157.
- 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.
- Tonino PA, de Bruyne B, Pijls NH, Siebert U, Ikeno F, Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-24.
- Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol*. 2007;49:839-48.
- Magni V, Chieffo A, Colombo A. Evaluation of intermediate coronary stenosis with intravascular ultrasound and fractional flow reserve: Its use and abuse. *Catheter Cardiovasc Interv*. 2009;73:441-8.
- Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20-6.
- Leesar MA, Abdul-Baki T, Akkus NI, Sharma A, Kannan T, Bolli R. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. *J Am Coll Cardiol*. 2003;41:1115-21.
- López-Palop R, Pinar E, Lozano I, Carrillo P, Cortes R, Pico F, et al. Utilización habitual de la guía de presión intracoronaria. Experiencia de un centro. *Rev Esp Cardiol*. 2002;55:251-7.
- de Bruyne B, Sarma J. Fractional flow reserve: a review: invasive imaging. *Heart*. 2008;94:949-59.
- de Bruyne B, Pijls NH, Barbato E, Bartunek J, Bech JW, Wijns W, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation*. 2003;107:1877-83.
- Jeremias A, Whitbourn RJ, Filardo SD, Fitzgerald PJ, Cohen DJ, Tuzcu EM, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J*. 2000;140:651-7.
- Jeremias A, Filardo SD, Whitbourn RJ, Kernoff RS, Yeung AC, Fitzgerald PJ, et al. Effects of intravenous and intracoronary adenosine 5'-triphosphate as compared with adenosine on coronary flow and pressure dynamics. *Circulation*. 2000;101:318-23.
- Di Segni E, Higano ST, Rihal CS, Holmes DR Jr, Lennon R, Lerman A. Incremental doses of intracoronary adenosine for the assessment of coronary velocity reserve for clinical decision making. *Catheter Cardiovasc Interv*. 2001;54:34-40.



25. López-Palop R, Saura D, Pinar E, Lozano I, Pérez-Lorente F, et al. Adequate intracoronary adenosine doses to achieve maximum hyperaemia in coronary functional studies by pressure derived fractional flow reserve: a dose response study. *Heart*. 2004;90:95-6.
26. Casella G, Leibig M, Schiele TM, Schrepf R, Seelig V, Stempfle HU, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for the assessment of fractional flow reserve? *Am Heart J*. 2004;148:590-5.
27. Yoon MH, Tahk SJ, Yang HM, Park JS, Zheng M, Lim HS, et al. Comparison of the intracoronary continuous infusion method using a microcatheter and the intravenous continuous adenosine infusion method for inducing maximal hyperemia for fractional flow reserve measurement. *Am Heart J*. 2009; 157:1050-6.