JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3, NO. 12, 2010

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.08.025

CLINICAL RESEARCH

Fractional Flow Reserve for the Assessment of Nonculprit Coronary Artery Stenoses in Patients With Acute Myocardial Infarction

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Objectives We investigated the reliability of fractional flow reserve (FFR) of nonculprit coronary stenoses during percutaneous coronary intervention (PCI) in acute myocardial infarction.

Background Assessing the hemodynamic severity of the nonculprit coronary artery stenoses at the acute phase of a myocardial infarction could improve risk stratification and shorten the diagnostic work-up.

Methods One hundred one patients undergoing PCI for an acute myocardial infarction (n = 75 with ST-segment elevation myocardial infarction [STEMI], and n = 26 with non–ST-segment elevation myocardial infarction) were prospectively recruited. The FFR measurements in 112 nonculprit stenoses were obtained immediately after PCI of the culprit stenosis and were repeated 35 ± 4 days later. In addition, left ventricular ejection fraction, quantitative coronary angiographic measurements of the nonculprit stenoses, Thrombolysis In Myocardial Infarction (TIMI) flow, corrected TIMI frame count (cTFC), and the index of microcirculatory resistance (n = 14) of the nonculprit vessels were assessed in the acute phase and at control angiogram.

Results The FFR value of the nonculprit stenoses did not change between the acute and follow-up (0.77 ± 0.13 vs. 0.77 ± 0.13, respectively, p = NS). In only 2 patients, the FFR value was higher than 0.8 at the acute phase and lower than 0.75 at follow-up. The TIMI flow, cTFC, percentage diameter stenosis, minimum lumen diameter, and index of microcirculatory resistance did not change. Left ventricular ejection fraction increased significantly in patients with STEMI (from 54 ± 13% to 57 ± 13%, p = 0.03).

Conclusions During the acute phase of acute coronary syndromes, the severity of nonculprit coronary artery stenoses can reliably be assessed by FFR. This allows a decision about the need for additional revascularization and might contribute to a better risk stratification. (J Am Coll Cardiol Intv 2010;3:1274–81) © 2010 by the American College of Cardiology Foundation

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Manuscript received March 8, 2010; revised manuscript received August 2, 2010, accepted August 5, 2010.

Whether microvascular function during an acute myocardial infarction (MI) is abnormal in remote myocardial areas remains unclear. Therefore, the assessment of stenoses in the "nonculprit" arteries is generally postponed to a later stage. Yet, multivessel coronary artery disease is present in approximately one-half of patients with an acute MI (1–4). This finding is associated with a worse clinical outcome (2). Some data suggest that revascularization of nonculprit coronary artery stenoses during the first month after primary percutaneous coronary intervention (PCI) might result in a significant survival benefit (2).

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In these studies, however, the presence of multivessel coronary artery disease was defined by visual estimation of the stenoses. Precise assessment of the hemodynamic severity of nonculprit coronary artery stenoses with fractional flow reserve (FFR) during the acute phase of an MI could improve risk stratification and shorten the duration of hospital stay by decreasing the need for additional noninvasive stress testing to detect residual myocardial ischemia.

The goal of the present study was to assess the reliability of FFR in nonculprit coronary artery stenoses during the acute phase of acute coronary syndromes (ACS). Therefore we measured FFR in nonculprit coronary artery stenoses during the acute phase of an MI and repeated these measurements within 3 months.

Methods

Study patients. The study was prospectively conducted at 4 institutions. Patients were included in the study if they fulfilled the following criteria: 1) the presence of an acute ST-segment elevation myocardial infarction (STEMI) treated by primary PCI or a non–ST-segment elevation myocardial infarction (NSTEMI) scheduled for PCI of the culprit stenosis within 72 h after the onset of chest pain; 2) the presence of at least 1 nonculprit coronary artery stenosis in which PCI was contemplated on the basis of the angiogram (more than 50% diameter stenosis [%DS] by visual estimate); and 3) stable hemodynamic condition.

Study protocol. ACUTE PHASE. A biplane coronary angiography was obtained after administration of nitrates. The culprit stenosis was identified on the basis of electrocardiographic and angiographic data. A PCI of the culprit lesion was performed according to local routine. Thrombus aspiration, antiplatelet treatment, as well as stent implantation and the type of the stent were left to the discretion of the operator. Thereafter, a high-quality angiogram focusing on the nonculprit coronary artery stenoses was repeated to measure reference diameter, minimum lumen diameter, and %DS by quantitative coronary angiography (ACOM PC 5.01, Siemens Medical Systems, Inc., Malvern, Pennsylvania) as previously described (5). Thrombolysis In Myocardial Infarction (TIMI) flow and corrected TIMI frame count of the nonculprit coronary artery stenoses were assessed as well, after nitrate administration before positioning the pressure wire for the FFR measurements. All angiographic parameters were quantified offline by 2 independent operators. Either at the beginning (54%) or at the end (46%) of the catheterization a biplane left ventricular angiogram was acquired. Left ventricular volumes and left ventricular ejection fraction (LVEF) were calculated according to the Simpson's method. Left ventricular end diastolic pressure (LVEDP) was also recorded before and after left ventricular angiography.

FFR. The FFR was assessed in nonculprit coronary artery stenoses as follows: after another administration of 200 μg of isosorbide dinitrate, a pressure-monitoring guidewire (PressureWire Certus, St. Jude Medical Systems AB, Uppsala, Sweden) was advanced distal to the stenosis. Hyperemia was obtained after administration of intravenous (140 μg/kg/min, n = 14) or intracoronary adenosine (Bolus of 50 μg, n = 87). By protocol, the route of adenosine administration was left at the discretion of each operator, because both intravenous and intracoronary adenosine induce a similar degree of hyperemia in humans, provided sufficient doses are used (6). When the intracoronary route was used, the measurements were done in duplicate, and the average value was recorded. The exact position of the sensor was filmed to enable the operator to position the sensor in the exact same place at control angiography. The FFR was automatically calculated by dividing the mean distal coronary artery pressure by the mean aortic pressure during maximal hyperemia.

Abbreviations and Acronyms

%DS = percentage diameter of stenosis
ACS = acute coronary syndromes
FFR = fractional flow reserve
IMR = index of microcirculatory resistance
LVEDP = left ventricular end diastolic pressure
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Microvascular function. In a subgroup of 14 patients studied at 1 site (Aalst), the microvascular function of the territory supplied by the nonculprit coronary artery measured by FFR was assessed with the thermodilution-derived index of microcirculatory resistance (IMR), as described by Fearon et al. (7). Briefly, the pressure/temperature sensor of the Certus PressureWire (St. Jude Medical Systems AB) was positioned in the distal third of the artery. During steady state hyperemia obtained by intravenous administration of

adenosine, a coronary thermodilution curve was obtained by bolus injection of 3 to 4 ml of saline at room temperature. In stenoses with an FFR value larger than 0.75, the IMR was calculated as the product of mean distal coronary pressure and mean hyperemic transit time. In stenoses with an FFR value of <0.75, IMR was calculated as the product of mean aortic pressure, mean hyperemic transit time, and the FFR value (8).

BIOCHEMICAL PARAMETERS. Peak total creatinine phosphokinase was measured at the acute phase as an estimate of the extent of myocardial damage.

Follow-up. Four days to 3 months later, the patients underwent a second catheterization. The LVEDP was recorded, and a biplane left ventricular angiogram was also performed. Coronary angiography of both culprit and nonculprit vessels after intracoronary isosorbide dinitrate was obtained in the same projections as during the acute phase. The FFR measurements were repeated after reviewing the angiogram obtained at the acute phase to ensure the exact same position of the pressure-monitoring guidewire. In patients in whom IMR had been obtained, these measurements were repeated as well.

The treatment of the nonculprit stenosis was left to the discretion of the operator and guided by FFR. Quantitative coronary angiography was performed offline and blinded to the FFR results. All angiographic measurements reported in this study are derived from quantitative coronary angiography. All analyses of FFR and IMR were done on a per-stenosis basis.

Statistical analysis. Statistical analysis was performed with the GraphPad Prism 5 Software (La Jolla, California). Continuous variables are summarized as mean ± SD. Paired and unpaired samples *t* tests were used to analyze differences in continuous variables with normal distribution, and Mann-Whitney *U* test was used for continuous variables with non-Gaussian distribution. Categorical variables are expressed as frequencies and percentages. Chi-square and Fisher exact test were used for the comparison of categorical variables. Bland-Altman analysis was used for the estimation of the reproducibility of the FFR and %DS. Pearson and Spearman tests were used for the correlation of Gaussian and non-Gaussian distributed variables, respectively. Clinical data as well as hemodynamic and angiographic parameters were compared between STEMI and NSTEMI subgroups and between acute phase and follow-up in both subgroups. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics. One hundred twelve patients (85 STEMI, and 27 NSTEMI) were prospectively included. In 13 patients, 2 lesions were studied. From them, 3 patients died, and 8 other patients withdrew consent before the follow-up measurements. Finally, 112 nonculprit stenoses with a %DS between 30% and 91% were evaluated in 101 patients. An intermediate stenosis (40% to 70%) was present in most of the cases (71%, n = 79 nonculprit stenoses).

The clinical, procedural, biological, and angiographic characteristics of patients with STEMI and NSTEMI during the acute phase are listed in Table 1. The mean duration of symptoms to PCI was 230 ± 201 min for STEMI and 52 ± 45 h for NSTEMI. Door to balloon time for the STEMI group was 35 ± 33 min. Thrombus aspiration was used more often in STEMI patients. History of arterial hypertension and hyperlipidemia was more frequent among the NSTEMI group. Higher creatinine phosphokinase values were observed in the STEMI group. The %DS and minimum lumen diameter of the nonculprit stenoses assessed by FFR were similar in STEMI and NSTEMI patients. After PCI of the culprit, TIMI flow grade 3 in the revascularized vessel was present in 96% and 89% of the STEMI and NSTEMI patients, respectively.

Follow-up data. Follow-up catheterization was performed 35 ± 4 days (median 27 days, range 4 to 128 days) after the acute phase. Table 2 shows the hemodynamic, angiographic, and physiological parameters at the acute and follow-up phases.

The LVEDP and LVEF did not change significantly between acute and follow-up phase. However, when only patients with STEMI were considered, a modest but significant decrease in LVEDP (19 ± 8 vs. 18 ± 6 mm Hg, $p < 0.05$) and an increase in global LVEF (54 ± 13% vs. 57 ± 13%, $p < 0.05$) were observed.

As shown in Figure 1, FFR remained unchanged between acute and follow-up phases in patients with STEMI (0.78 ± 0.10 vs. 0.76 ± 0.10, respectively, p = NS) and NSTEMI (0.77 ± 0.10 vs. 0.77 ± 0.20, respectively, p = NS), although in 2 patients, the FFR value was higher than 0.8 during the acute phase and lower than 0.75 at follow-up.

Similarly, in "angiographically intermediate stenoses" (40% to 70%), FFR did not change significantly between the acute and follow-up phases (0.79 ± 0.10 vs. 0.78 ± 0.10, p = NS, median change of: −0.02, range: −0.04 to +0.02).

When only patients in the lowest quartile of LVEF at the acute phase were considered, the significant increase in LVEF at follow-up (from 42 ± 8% to 51 ± 12%, p = 0.005) was not paralleled by a change in FFR of the nonculprit stenoses (0.82 ± 0.10 vs. 0.81 ± 0.10, p = NS) (Fig. 2).

In most of the patients (83%, n = 85) FFR was reassessed more than 7 days after the acute phase. Nevertheless, FFR did not change significantly whether the follow-up measurements were performed <7 days (0.79 ± 0.10 vs. 0.79 ± 0.09, p = NS) or more than 7 days after the acute phase (0.77 ± 0.10 vs. 0.77 ± 0.10, p = NS). The median FFR change between acute phase and follow-up was −0.02

Table 1. Clinical, Procedural, Biological, and Angiographic Characteristics of All Study Population, STEMI, and NSTEMI Subgroups During the Acute Phase

Characteristics	All Patients (n = 101)	STEMI (n = 75)	NSTEMI (n = 26)	p Value
Age (yrs)*	63 ± 12	64 ± 12	61 ± 12	NS
Men/women	79/21	81/19	74/26	NS
BMI (kg/m^2)*	28 ± 4	28 ± 4	28 ± 4	NS
Arterial hypertension	57	49	78	<0.0001
Current smoker	41	43	33	NS
Hyperlipidemia	50	41	78	<0.0001
Diabetes mellitus	11	11	12.5	NS
Family history of CAD	20	21	15	NS
Anterior infarction	25	24	26	NS
BMS/DES (culprit)	80/20	79/21	81/19	NS
Thrombus aspiration	36	46	11	<0.0001
GP IIb/IIIa inhibitors	23	23	22	NS
CPKmax (IU/ml)†	464 (193–1,018)	818 (455–2,097)	235 (136–4,437)	<0.0001
Culprit: LAD/LCX/RCA/other	23/27/45/6	24/24/49/3	22/38/33/7	0.001
Nonculprit: LAD/LCX/RCA/other	56/18/21/5	58/20/17/5	52/14/31/7	0.044
DS nonculprit*	56 ± 14	56 ± 14	56 ± 15	NS
MLD nonculprit (mm)*	1.32 ± 0.46	1.29 ± 0.48	1.44 ± 0.38	NS

Values are percentages, unless otherwise indicated. *Mean ± SD; †median (interquartile range). The p values indicate the statistical difference between the ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial infarction (NSTEMI) groups.

BMI = body mass index; BMS = bare-metal stent(s); CAD = coronary artery disease; CPK = creatinine phosphokinase; DES = drug-eluting stent(s); DS = diameter of stenosis; GP = glycoprotein; LAD = left anterior descending coronary artery; LCX = left circumflex artery; MLD = minimum lumen diameter; RCA = right coronary artery.

(range: −0.06 to +0.02) in patients with FFR reassessment in a time period of <7 days and −0.014 (range: −0.03 to +0.20) in patients with FFR reassessment in more than 7 days (p = NS).

The reproducibility of the FFR values measured in acute phase and at follow-up, was superior ($r = 0.91$, $p < 0.0001$) compared with the reproducibility of the angiographic %DS ($r = 0.78$, $p < 0.0001$) (Fig. 3).

The IMR of the territory depending on the nonculprit stenoses was obtained in a subgroup of patients (n = 14). The IMR values were found in the normal range (<30 IU) in 11 of 14 patients (79%). In addition, these values did not change significantly between the acute and the follow-up phase (Table 2).

Table 2. Angiographic, Hemodynamic, and Functional Measurements of Nonculprit Stenoses in Acute Phase and at Follow-Up in All Study Patients

	Acute Phase (n = 101)	Follow-Up (n = 101)	p Value
LVEF (%)	59 ± 15	61 ± 14	NS
LVEDP (mm Hg)	18 ± 7	17 ± 7	NS
FFR nonculprit	0.77 ± 0.13	0.77 ± 0.13	NS
IMR nonculprit (IU)	20 ± 3	24 ± 6	NS
DS nonculprit (%)	56 ± 14	55 ± 14	NS
MLD nonculprit (mm)	1.32 ± 0.46	1.31 ± 0.50	NS
RD nonculprit (mm)	2.9 ± 0.70	2.7 ± 0.70	NS
TIMI flow nonculprit	2.93 ± 0.30	2.97 ± 0.20	NS
cTFC nonculprit	15 ± 6	15 ± 6	NS

Values are mean ± SD.

cTFC = corrected TIMI frame count; DS = diameter of stenosis; FFR = fractional flow reserve; IMR = index of microcirculatory resistance; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; MLD = minimum lumen diameter; RD = reference diameter.

Discussion

The present data indicate that FFR measurements in nonculprit coronary artery stenoses do not change significantly when measured during the acute phase of a MI and some days or weeks later. These findings suggest that the severity of nonculprit stenoses can reliably be assessed by FFR during the setting of primary PCI. In only 2% of patients, the change in FFR value between the acute phase and the control angiogram might have induced a change in revascularization strategy. The microvascular dysfunction that had been described in the contralateral territories during the early weeks after an acute MI was not found in the present study. Furthermore, in comparison with quantitative coronary angiography, FFR showed less variability in assessing the nonculprit stenoses.

Clinical significance of the nonculprit stenoses in ACS. In patients with acute MI and 1 or more angiographically significant nonculprit coronary artery stenoses, the incidence of heart failure (9), recurrent ACS (10), and need for further revascularization (10,11) has been reported to be significantly higher, and survival has been reported to be significantly lower (2,12). In addition, recent data indicate that revascularization of these nonculprit stenoses within the first month after the acute phase of the index MI improves survival (2). In contrast, in patients with a recent

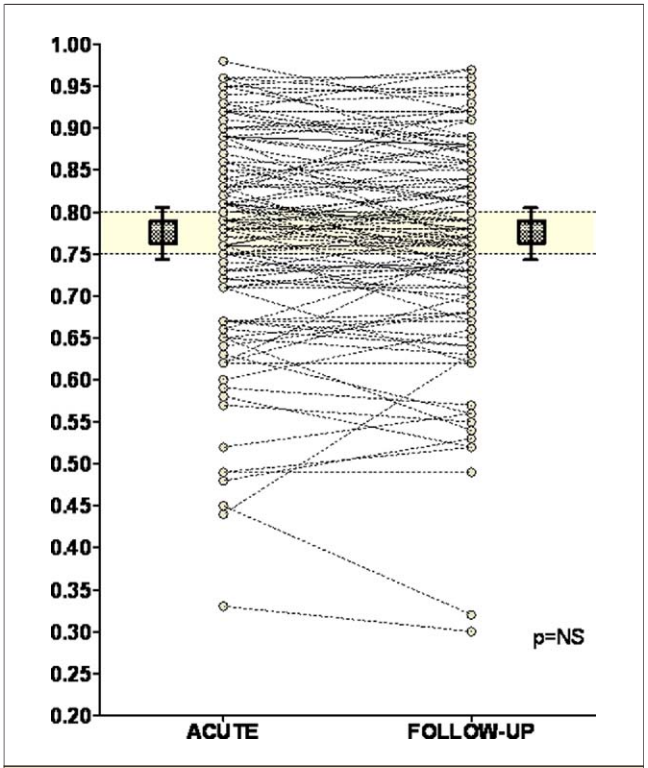

Figure 1. Plot of FFR Values of Nonculprit Coronary Artery Stenoses During the Acute Phase and at Follow-Up

FFR = fractional flow reserve; NS = not statistically significant.

MI, nonsignificant nonculprit stenoses have been shown to rarely progress, even in the "pre-statin" era (13). Work by Rioufol et al. (14) demonstrated that, in patients with an ACS, more than 1 ruptured plaque in the nonculprit vessel could be identified but that only the lesions with a hemodynamically significant narrowing were responsible for clinical events.

In stable patients, the long-term clinical outcome of hemodynamically nonsignificant stenoses has been shown to be excellent and is not improved by PCI (15). The recent FAME (Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease) trial confirms this approach in patients with multivessel disease (16). Therefore, the assessment of the actual severity of the nonculprit coronary artery stenoses is clinically important soon after primary PCI. Because the angiographic assessment of lesion severity is notoriously inaccurate (17,18), the functional assessment of these lesions is traditionally performed by noninvasive testing in the first days or weeks after primary PCI. These tests, however, often prolong hospital stay (19), are expensive, and are often difficult to perform or interpret soon after the acute event, and eventually a second catheterization is required. Therefore, measuring FFR of the nonculprit stenoses in the setting of primary PCI might be an interesting alternative.

FFR as an alternative to noninvasive testing in ACS. Like myocardial perfusion imaging, FFR assesses the impact of an epicardial stenosis on myocardial perfusion. The major advantages of FFR are its reproducibility, higher specificity, and unsurpassed spatial resolution. In addition, it can be obtained in a few minutes in the catheterization laboratory (i.e., at the very place where the revascularization can be applied) (20). Yet, to be valid, FFR should be obtained during maximal microvascular dilation. Animal experiments showed focal myocardial necrosis and regional derangements in lactate metabolism in the nonculprit areas (21,22). Earlier human studies using positron emission tomography (23), angiography (corrected TIMI frame count) (24), and the Doppler wire (25) have suggested significant microvascular dysfunction of both culprit and nonculprit areas during the acute phase of a STEMI. Extensive ischemia in adjacent territories, vasoconstriction mediated by local neurohumoral reflexes (26), and elevated LVEDP (25) were considered as possible underlying pathophysiologic mechanisms for the interpretation of these findings. Other experimental (27–29) and clinical investigations (23,30) concluded that even the presence of subendocardial ischemia was sufficient to induce significant microvascular dysfunction remote to the ischemic territory. In contrast, in chronic MI, recent data suggest that microvascular function in the nonculprit territories is normal (31).

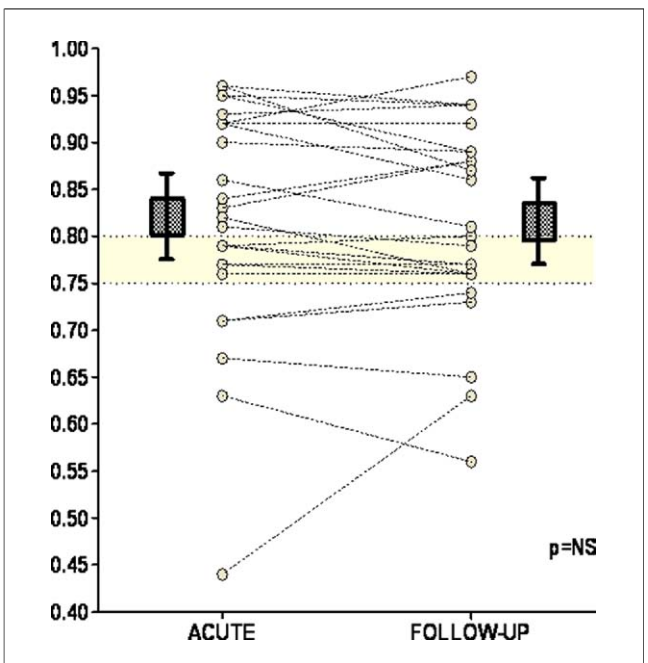

Figure 2. Plot of FFR Values of Nonculprit Coronary Artery Stenoses During the Acute Phase and at Follow-Up in Patients on the Lowest LVEF Quartile

Mean left ventricular ejection fraction (LVEF) of 42 ± 8% at the acute phase increasing to 51 ± 12% at control angiography. Abbreviations as in Figure 1.

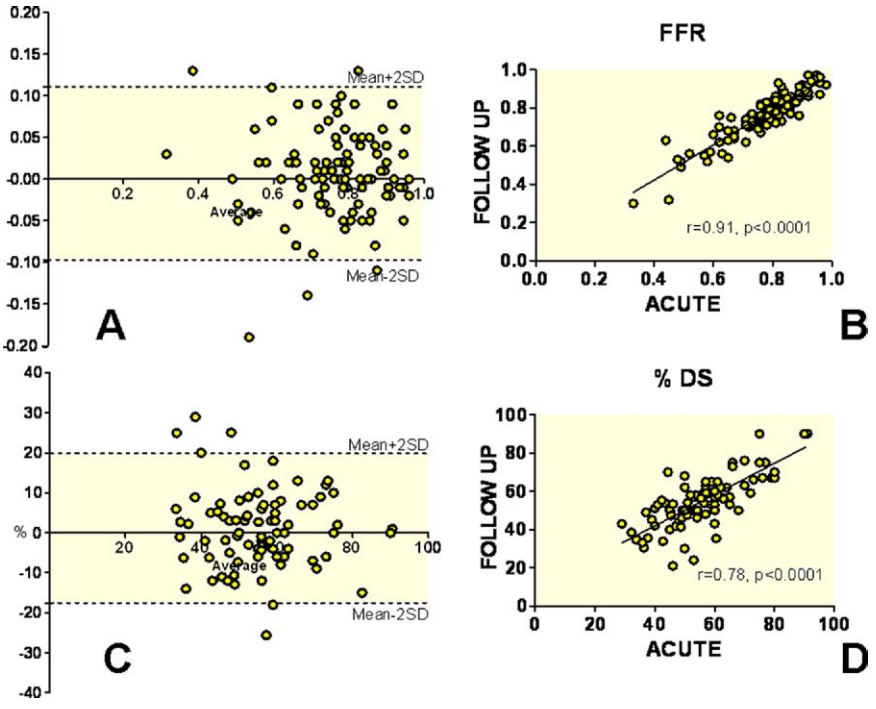

Figure 3. Bland-Altman Analysis and Correlation for FFR and %DS

(A) Bland-Altman plot displaying the changes in fractional flow reserve (FFR) between the acute and follow-up phases versus the average FFR value. **(B)** Plot of correlation of the FFR values between the acute and follow-up phases. **(C)** Bland-Altman plot displaying the changes in percentage diameter stenosis (%DS) between the acute and follow-up phases versus the average value of diameter stenosis. The **dotted lines** correspond to ± 2 SDs of the average values of FFR **(A)** and %DS **(C)**, respectively. **(D)** Plot of correlation of the %DS values between the acute and follow-up phases.

In the present study, microvascular function was directly assessed in a subgroup of patients with IMR, an index specific for the microvasculature (7). This index was normal in the nonculprit territories even during the acute phase of large MIs. The value of IMR did not change significantly after a few days or weeks, suggesting that if some degree of microvascular dysfunction was present it was not related to the adjacent MI but rather to the atherosclerotic process. The absence of significant reversible microvascular dysfunction constitutes the basis of the reliability of FFR in assessing nonculprit coronary artery stenoses in patients with ACS.

Study limitations. The absence of changes in microvascular function reported in the present study might be related to the relatively short (median 27 days) delay between the 2 measurements. Several studies have indicated that microvascular dysfunction might persist up to 3 months in remote, noninfarcted territories after an acute MI (23,32). Therefore, it cannot be excluded that the absence of changes observed in the present study actually corresponds to a constant derangement of the microvasculature in the 2 time points assessed.

In most cases (STEMI and NSTEMI), the infarction was located in the inferior and lateral wall. Also, patients considered "hemodynamically unstable" were excluded. Therefore these results should be applied with caution to patients with extensive necrosis and cardiogenic shock. However, in these patients, the need for measuring the significance of a nonculprit stenosis is exceptional. It is also good clinical practice not to induce hyperemia in hemodynamically unstable patients.

Nonculprit stenoses with an FFR of <0.80 underwent PCI at follow-up catheterization, whereas the other stenoses were treated medically. The present study was not powered to investigate differences in clinical outcome. Larger trials should be performed to address this question.

The results of this study do not suggest that the nonculprit stenoses should be revascularized during the acute phase of an MI. At present, multivessel revascularization in the acute phase of an MI should be contemplated only in patients with cardiogenic shock and critical nonculprit stenoses (33).

Advantages and disadvantages of measuring FFR at the acute phase of an acute MI. Measuring FFR will prolong the procedure. This time depends mainly on the experience of the laboratory with this kind of measurement. Also the amounts of contrast medium and of radiation will be higher. However, this should be largely offset by the reduced need

for noninvasive imaging and repeat catheterization in many patients. In addition, the feasibility and accuracy of noninvasive measurement soon after an MI, especially in patients with multivessel disease, is low (34). Therefore, FFR measurements performed in the setting of primary PCI of the culprit lesion should minimize the need for additional diagnostic work-up.

Conclusions and Clinical Implications

Even though FFR measurements should be discouraged in ACS to evaluate culprit stenoses, the present data support that FFR measurements are safe and reliable for evaluating the actual severity of nonculprit stenoses during primary PCI. In addition to coronary anatomy and left ventricular function, FFR can thus provide accurate functional information on nonculprit stenoses even during the acute phase of an acute MI. It is hypothesized that early assessment of residual myocardial ischemia in the setting of primary PCI might improve risk stratification and hasten clinical decision-making about the need for additional revascularization. This might indeed decrease the need for further noninvasive testing or repeated catheterization and therefore shorten diagnostic work-up after an MI.

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Key Words: acute myocardial infarction ■ fractional flow reserve ■ nonculprit coronary artery stenosis.