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JACC: CARDIOVASCULAR INTERVENTIONS VOL. 4, NO. 10, 2011

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ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

DOI: 10.1016/j.jcin.2011.08.004

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Effects of Increasing Doses of Intracoronary Adenosine on the Assessment of Fractional Flow Reserve

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Objectives The purpose of this study was to investigate the effects of increasing dose of intracoronary adenosine on fractional flow reserve (FFR) measurement.

Backgrounds FFR is a validated method for the assessment of the severity of coronary artery stenosis. It is based on the change in the pressure gradient across the stenosis after the achievement of maximal hyperemia of the coronary microcirculation that may be obtained by either intracoronary bolus or intravenous infusion of adenosine. No study has explored so far the effects of very high doses of intracoronary adenosine on FFR.

Methods FFR was assessed in 46 patients with 50 intermediate lesions during cardiac catheterization by pressure-recording guidewire (PrimeWire, Volcano, San Diego, California). FFR was calculated as the ratio of the distal coronary pressure to the aortic pressure at hyperemia. Increasing doses of adenosine were administrated (60, 120, 180, 360, and 720 μg) as intracoronary boluses. Exclusion criteria were: 1) allergy to adenosine; 2) baseline bradycardia (heart rate $<$50 beats/min); 3) hypotension (blood pressure $<$90 mm Hg); and 4) refusal to provide signed informed consent.

Results High doses of intracoronary adenosine were well tolerated, with no major side effects. Increasing doses up to 720 μg progressively decreased FFR values and increased the percentage of patients showing an FFR $<$0.75. Among angiographic parameters, both percent stenosis and lesion length were independently associated with lower FFR values.

Conclusions This study shows that high doses of intracoronary adenosine (up to 720 μg) increased the sensitivity of FFR in the detection of hemodynamically relevant coronary stenoses. Furthermore, lesion length and stenosis severity were independent angiographic determinants of FFR.
(J Am Coll Cardiol Intv 2011;4:1079–84) © 2011 by the American College of Cardiology Foundation

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Manuscript received February 14, 2011; revised manuscript received July 25, 2011, accepted August 4, 2011.

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Even though coronary angiography still represents the gold standard in the diagnosis of coronary artery disease (CAD), it has the major limitation that it cannot provide certainty on the hemodynamic relevance of the observed stenosis. The measurement of fractional flow reserve (FFR) is a standardized and well-established method frequently used in clinical practice to evaluate the hemodynamic significance of epicardial coronary stenoses identified by coronary angiography (1). Achievement of maximal hyperemia is a key requisite for an accurate calculation of FFR (2). Although intravenous infusion of adenosine is considered

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the gold standard (3), its use in the catheterization laboratory may have some drawbacks compared with intracoronary adenosine, such as the need of a large amount of adenosine and therefore higher costs (4), and a higher occurrence of systemic adverse effects, in addition to being more time-consuming. For these reasons, intracoronary currently remains a preferred route of administration of adenosine in many cardiac catheterization laboratories. Some studies have suggested a larger reduction in FFR by higher doses of adenosine (up to 150 μg) (5,6). However, no study has explored so far the effects of very high dose of intracoronary adenosine. Therefore, the aim of the current study was to evaluate the effects of increasing doses of intracoronary adenosine on FFR.

Abbreviations and Acronyms

CAD = coronary artery disease
CVR = coronary flow velocity reserve
FFR = fractional flow reserve
QCA = quantitative coronary angiography

Methods

Study population. A total of 46 patients with a total of 50 intermediate coronary stenoses were prospectively enrolled. Exclusion criteria were: 1) allergy to adenosine; 2) baseline bradycardia (heart rate <50 beats/min); 3) hypotension (blood pressure <90 mm Hg); and 4) refusal to provide signed informed consent. All patients signed the informed consent to participate in the study.

Study protocol. Coronary angiography was performed with the femoral approach. Heart rate and arterial pressure were continuously monitored throughout the procedure. Heparin was administered at the beginning of the procedure (60 U/kg), and nonionic contrast material was used for all patients. After coronary angiography, a 0.014-inch high-fidelity pressure-recording guidewire (PrimeWire, Volcano, San Diego, California) was introduced through a 6-F guiding catheter into the coronary artery. The guidewire was externally calibrated and then advanced to the distal tip of the catheter, as previously described (7), with the pressure sensor positioned in the coronary artery just out of the catheter to verify equalization between the pressure recorded through the catheter and the pressure wire. The pressure wire was subsequently advanced into the coronary artery with the pressure sensor placed beyond the lesion site. Distal coronary and aortic pressures were measured at baseline and at maximal hyperemia. Pressure signals were continuously recorded at a paper speed of 25 mm/s, and a beat-to-beat analysis of mean pressure was performed automatically. Once a stable pressure signal was obtained, baseline measurements were recorded. In all patients, intracoronary nitroglycerin (0.2 mg) was administered before coronary angiography and before each FFR measurement except in the case of blood pressure <100 mm Hg.

Pharmacological protocol. All patients received multiple intracoronary adenosine boluses (60, 120, 180, 360, and 720 μg) (Fig. 1). Each bolus was followed by a flush with saline. Measurement of FFR was started 3 s after bolus administration. Each bolus was administrated at least 1 min after the previous one (in all cases until pressure curves returned to baseline values). To minimize and standardize fluid volume infusion, we prepared the drug with a special dilution of 60 μg/ml and 360 μg/ml (the last one used for 360 μg and 720 μg doses).

Calculations of pressure-derived FFR. FFR is defined as the ratio of the hyperemic flow in a stenotic artery to the hyperemic flow in the same artery in the hypothetical case in which there is no stenosis present (8). FFR expresses maximum hyperemic blood flow in a stenotic vessel as a fraction of normal maximal blood flow in that vessel. FFR is calculated from intracoronary and aortic pressure measurements obtained during maximal hyperemia with this equation: $FFR = P_d - P_v/P_a - P_v$, or $FFR = P_d/P_a$ (when P_v is negligible), in which P_a is the mean proximal coronary pressure (mean arterial pressure), P_d is the mean distal coronary pressure, and P_v is the mean central venous pressure. In this study, the simplified formula (in which P_v is considered negligible) was applied.

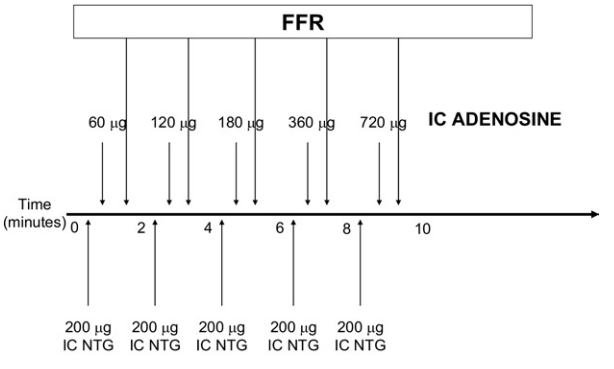

Figure 1. Study Protocol

FFR = fractional flow reserve; IC = intracoronary; NTG = nitroglycerin.

Table 1. Baseline Demographic and Clinical Characteristics in 46 Patients Enrolled in the Study

Demographic characteristics	
Male	78.3
Weight, kg	77 (70–85)
Height, cm	170 (165–175)
Body mass index, kg/m^2	26 (22–29)
Abdominal waist, cm	95 (90–103)
SBP, mm Hg	131 (110–152)
DBP, mm Hg	69 (59–75)
HR, beats/min	69 (60–78)
Age, yrs	67 (59–73)
Clinical characteristics	
Hypertension	82.6
Smoking	28.3
Dyslipidemia	63
Diabetes	26.1
Previous AMI	28.3
Previous PCI	37
Previous CVA	2.2
Creatinine clearance <60 ml/min	15.2
Indication for angiography	
Stable angina	15.2
Silent ischemia	6.5
Unstable angina	21.7
NSTEMI	28.3
Recent STEMI	8.7
DCM	13

Values are % or median (25th to 75th percentile).

AMI = acute myocardial infarction; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DCM = dilated cardiomyopathy; HR = heart rate; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

Coronary angiography and quantitative coronary angiography analysis. Coronary angiography (carried our by Siemens Axiom ARTIS *d*TC, Erlangen, Germany) was routinely performed by the Judkins technique using 6-F right and left heart catheters. Quantitative coronary angiography was performed by 2 experienced interventional cardiologists who had no knowledge of the patients' clinical information, by an automatic edge-detection systems (Siemens Acom Quantcor quantitative coronary angiography [QCA]). After the visual inspection of the coronary artery, the frame of optimal clarity was selected, showing the lesion at maximal narrowing and the arterial silhouette in sharpest focus. After the calibration of the guiding catheter, the analyzed arterial segment with the coronary lesion was defined by moving the cursor from the proximal to the distal part of the coronary artery to ensure adequate determination of reference diameter. We have measured minimal luminal diameter, reference diameter, percent diameter stenosis, and length of the lesion. A stenosis was considered significant if the diameter was more than 70%, and borderline if between 30% and 70%.

Statistical analysis. Continuous data are presented as the median (25th to 75th percentile), whereas categorical variables as shown as percentages. The change in the percentage of patients with significant FFR (<0.75) and the absolute FFR values after each incremental intracoronary adenosine bolus were analyzed by the Cochran Q test for repeated categorical measures and analysis of variance for repeated measures (Bonferroni *t* test was used for paired multiple comparisons), respectively. Multiple linear regression analysis with a stepwise forward model was used to identify QCA parameters independently associated with FFR. Results were considered statistically significant when the p value was <0.05.

Results

Patient characteristics. Baseline patients' characteristics and medical therapy at admission are reported in Tables 1 and 2. All patients were in sinus rhythm. In 4 cases (8%), FFR was performed in vessels that were in the vascular territory of a

Table 2. Angiographic Characteristics

Number of lesions	50
TIMI flow grade 3	100
Number of diseased vessels	
1	44
2	26
3	30
Target vessel FFR	
LAD	68
Circumflex	14
RCA	12
AL	2
LM	4
QCA target lesion	
RD, mm	2.97 (2.57–3.45)
MLD, mm	1.23 (0.9–1.5)
Percent stenosis, %	57 (49–70)
Length, mm	11 (8–19)
Lesion characteristics	
Type A	2
Type B1	4
Type B2	86
Type C	8
Lesion location	
Proximal	34
Mid	58
Distal	6
Calcifications	16
In-stent restenosis	10
Bifurcation	12.5

Values are % or median (25th to 75th percentile).

AL = anterolateral branch; LAD = left anterior descending artery; LM = left main; MLD = minimum lumen diameter; QCA = quantitative coronary angiography; RCA = right coronary artery; RD = reference diameter; TIMI = Thrombolysis In Myocardial Infarction.

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Table 3. Prevalence and Timing of Side Effect Determining Premature Study Termination

	60 μg	120 μg	180 μg	360 μg	720 μg
RCA	0	0	1	2	0
LAD	0	0	0	0	0
Circumflex	0	0	0	1	0

The side effect that terminated the study is defined as complete atrioventricular block with pause longer than 4 s.
LAD = left anterior descending artery; RCA = right coronary artery.

previous infarction. Procedural success was 100% for advancing the pressure wire distally to the stenosis. There were no procedure-related complications. Adenosine elicited an asymptomatic transient atrioventricular block of more than 4 s in 8.7% of patients (3 patients with right coronary artery stenosis and 1 patient with left circumflex stenosis) (Table 3). In these cases, the protocol was stopped because of the inability to correctly measure FFR.

FFR measurements. The mean aortic and distal coronary pressure and the heart rate were not significantly different after each step (Fig. 2). The dose–effect relationship of adenosine in the measurement of FFR is shown in Figure 3. The mean FFR progressively decreased up to 720 μg of adenosine, with a progressive significant increase in the proportion of patients reaching significant FFR values (≤0.75) ($p < 0.001$). The cumulative percentage of patients reaching 0.75 is depicted in Figure 4, showing the highest percentage at 720 μg (51.2%).

All analyzed QCA parameters, such as lesion length ($r = -0.28$, $p = 0.079$), percent stenosis ($r = -0.45$, $p = 0.003$), and minimum lumen diameter (MLD) ($r = -0.44$, $p = 0.004$) were related with FFR values at 720 μg. However, by multivariate analysis, only percent stenosis ($r = -0.53$, $p < 0.001$) and lesion length ($r = -0.38$, $p = 0.007$) were independently related to FFR values at 720 μg.

Discussion

This study showed for the first time, to our knowledge, a dose–effect relationship of intracoronary adenosine (administrated up to 720 μg) in the measurement of FFR. Furthermore, lesion length, in addition to the severity of the stenosis, resulted an independent angiographic determinants of FFR.

High-dose intracoronary adenosine: implications for FFR measurements. CAD is a leading cause of mortality in developed countries. Even though coronary angiography still represents the gold standard in the diagnosis of CAD, it has the major limitation of being unable to assess the hemodynamic importance of the observed disease. FFR is a standardized and well-established method to detect the hemodynamic importance of intermediate coronary artery lesions and therefore may represent an important complement to coronary angiography. Several advantages have contributed to widespread use of FFR, currently the preferred test used in the catheterization laboratory. In fact, this measure is independent of hemodynamic variation (7,9), and has an ischemic threshold value of 0.75 closely related to noninvasive indexes of inducible ischemia (1,10). Even though intravenous adenosine may achieve a more complete and stable vasodilatation and is more convenient for the assessment of tandem lesions or diffuse CAD, an intracoronary bolus is cheaper and more easily administrated, in addition to having a rapid onset of action and a

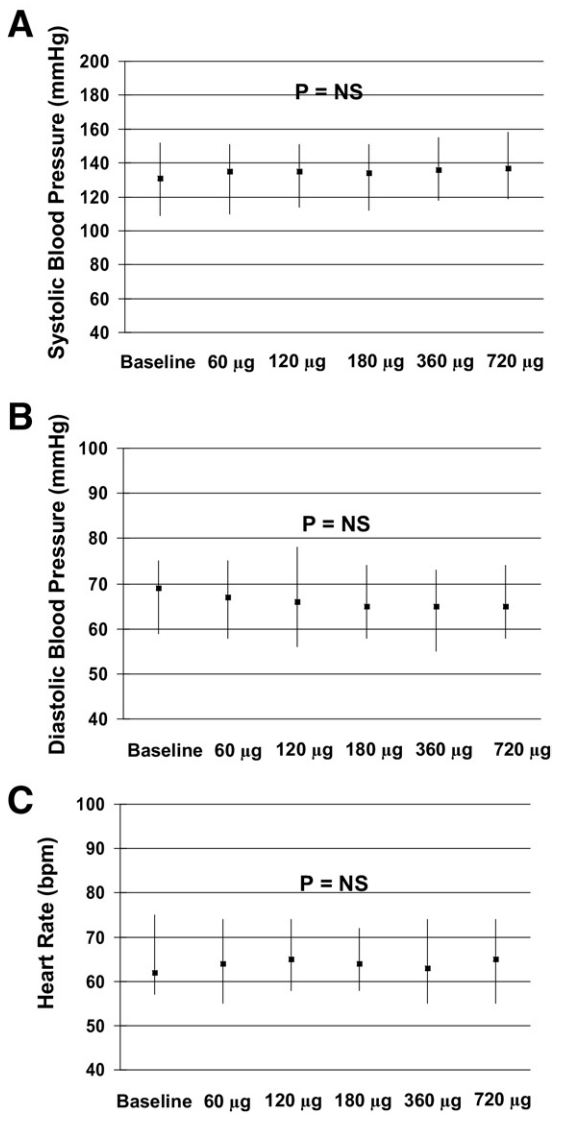

Figure 2. Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate at All Steps

This figure shows systolic blood pressure **(A)**, diastolic blood pressure **(B)**, and heart rate **(C)** at all steps from baseline up to 720 μg. Values are median (25th to 75th percentile). NS = not significant.

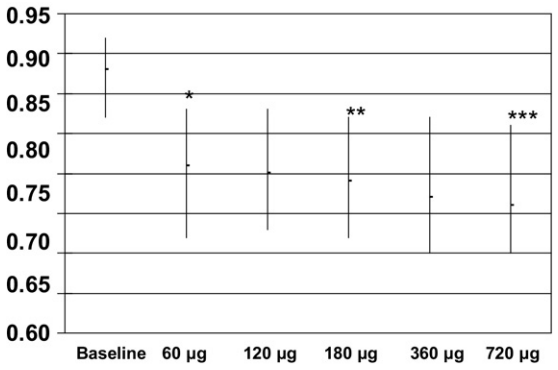

Figure 3. FFR at All Steps

This figure shows the fractional flow reserve (FFR) at all steps from baseline up to 720 μg. Data are reported as median (25th to 75th percentile). *p < 0.001 versus baseline; **p = 0.007 versus 120 μg; ***p = 0.085 versus 360 μg.

short half-life, which makes it ideal for repetitive measurements. Furthermore, intracoronary administration is associated with fewer systemic adverse effects. No major adverse events related to the intracoronary drug administration have been reported from multiple large trials measuring FFR (11). However, submaximal hyperemia may contribute to underestimatation of the functional severity of the lesion. According to initial studies, intracoronary adenosine was administered in a single bolus of 8 to 12 μg in the right coronary artery and 15 to 18 μg in the left coronary artery. However, a failure to produce maximal hyperemia with intracoronary adenosine was reported in approximately 10% to 15% of cases (12). A clear dose–response relationship for intracoronary adenosine doses as high as 100 μg has been demonstrated in animals and humans (5,6,13). Di Segni et al. (13) observed that incremental doses (54 μg for the left coronary artery and 42 μg for the right coronary artery) of intracoronary adenosine attained further vasodilatation and more accurate coronary flow velocity reserve (CVR) measurements. Similar findings were observed by Murtagh et al. (6) when assessing FFR of intermediate lesions with doses as high as 48 μg. Therefore, at present, larger dosages (30 to 40 μg for the right coronary artery and 40 to 80 μg for the left coronary artery) are recommended (14,15). However, even with these higher doses, Jeremias et al. (12) demonstrated that intracoronary FFR overestimates intravenous FFR in 8.3% of patients. Casella et al. (5) compared in 50 patients increasing doses of intracoronary adenosine (up to 150 μg) versus intravenous infusion. Despite the high baseline dose (60 μg), 10% of vessels with an initial FFR value >0.75 had a subsequent value less than the cutoff point when additional higher doses of intracoronary adenosine or intravenous adenosine were administered. Despite all previous studies, no investigation has been performed so far to evaluate a dose–effect relationship with very high doses of adenosine.

In our study, we found a dose–effect relationship of intracoronary adenosine (up to 720 μg) in the measurement FFR. In fact, FFR significantly decreased from baseline to 60 μg, from 120 to 180 μg, with an additional increase (p = 0.087) from 360 to 720 μg of adenosine. We observed a progressive increase in the number of patients with FFR <0.75 up to 720 μg. In agreement with data found by De Bruyne et al. (16), when we analyzed the impact of QCA parameters on FFR, we found that both percent stenosis and lesion length were independently associated with FFR. This is an important issue that can explain the presence of ischemia in case of long diseased segments with angiographically judged mild to moderate stenoses.

Study limitations. To remain close to a real clinical scenario, we enrolled more unselected patients as compared with previous studies, such as those patients with arterial hypertension, diabetes mellitus, and myocardial infarction, which are known to be associated with more microvascular dysfunction. Furthermore, intracoronary adenosine produces a plateau hyperemic phase of approximately 4 s, which corresponds to 3 to 6 beats, but not to a true steady state. The absence of a prolonged hyperemic state is a strong limitation to FFR measured after intracoronary adenosine administration, especially in the case of mild to moderate tandem stenoses or in cases of diffuse disease when a pullback maneuver of the pressure wire is necessary to detect the exact location of the critical lesion. In fact, we recognize as a major limitation of our study the fact that we did not compare intracoronary adenosine to intravenous adenosine infusion (regarded as the gold standard). It would have been interesting to escalate the doses of adenosine until FFR would not have further decreased in a classical dose-finding fashion. Therefore, we cannot exclude the possibility that at doses higher than 720 μg, a further decrease in FFR may be

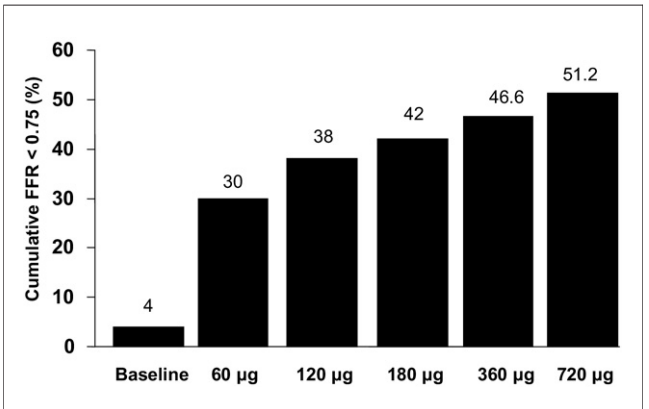

Figure 4. Cumulative Percentage of Patients With FFR ≤0.75

Bar graph shows the cumulative percentage of patients with fractional flow reserve (FFR) ≤0.75 with increasing dose of adenosine.

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observed. Finally, although CVR was not measured in this study, it is reasonable to assume a similar dose–response relationship on hyperemia for CVR assessment as well.

Conclusions

This study shows that high-dose intracoronary adenosine (up to 720 μg) increased the sensitivity of FFR in the detection of hemodynamically relevant coronary stenoses. Furthermore, lesion length and stenosis severity were independent angiographic determinants of FFR.

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Key Words: adenosine ■ FFR ■ myocardial ischemia.