Comparison of Effectiveness of High-Dose Intracoronary Adenosine Versus Intravenous Administration on the Assessment of Fractional Flow Reserve in Patients With Coronary Heart Disease

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Intravenous adenosine is considered the drug of choice to obtain maximum hyperemia in the measurement of the fractional flow reserve (FFR). However, comparative studies performed between intravenous and intracoronary administration have not used high doses of intracoronary adenosine. The present study compared the efficacy and safety of high doses of intracoronary adenosine to intravenous administration when calculating the FFR. Intracoronary bolus doses of 60, 180, 300, and 600 μg adenosine were compared to an intravenous administration of 140 μg/kg/min, 200 μg/kg/min, and 140 μg/kg/min plus an intracoronary bolus of 120 μg. All the cases were performed using the radial approach. FFR was assessed in 102 patients with 108 intermediate lesions by an intracoronary pressure wire. The intracoronary dose of 60 μg was associated with a significantly greater FFR compared to the intravenous infusion (0.02 ± 0.03, p = 0.001). The intracoronary doses of 300 (−0.01 ± 0.00; p = 0.006) and 600 μg (−0.02 ± 0.00; p <0.0005) were significantly associated with a smaller FFR compared to the intravenous infusion. An intracoronary dose of 600 μg revealed a significantly greater percentage of lesions with an FFR <0.80 compared to intravenous infusion at 140 μg/kg/min (37.6 vs 31.5%; p <0.05) and 200 μg/kg/min (37.6 vs 32.4%; p <0.05) and compared to intracoronary doses of 60 (26.9%) and 180 μg (31.5%). In conclusion, an intracoronary bolus dose >300 μg can be equal to or more effective than an intravenous infusion of adenosine in achieving maximum hyperemia when calculating the FFR. Its use could simplify these procedures without having an effect on safety. © 2013 Elsevier Inc. All rights reserved. **(Am J Cardiol 2013;111:1277−1283)**

Determining the fractional flow reserve (FFR) using a coronary pressure wire has been established as the preferred method to determine the functional repercussion of coronary lesions in the catheterization laboratory.[1−4] For the correct calculation of the FFR, it is indispensable to achieve maximum hyperemia.[5,6] Adenosine is the pharmacologic agent used most frequently to obtain maximum hyperemia. Its administration in bolus intracoronary doses is simple, inexpensive, and practically free of side effects. The use of intravenous adenosine is also safe but is more expensive and generally requires a longer preparation time and catheterization of a central vein, a limitation in procedures performed using a radial approach. However, the use of intravenous adenosine is considered the method of choice to obtain hyperemia.[1,6−8] The verification in recent studies that higher doses of intracoronary adenosine produce a greater grade of hyperemia without compromising safety[8−11] suggests that at greater doses, intracoronary adenosine could be as efficient as intravenous adenosine in obtaining maximum hyperemia. The aim of the present study was to compare the safety and efficacy of obtaining maximum hyperemia using high-dose intracoronary boluses of adenosine with intravenous administration.

Methods

From April 2011 to December 2011, all patients considered to have an indication for an intracoronary pressure wire study, because of a presentation with coronary stenosis of intermediate severity (visual estimation 40% to 70%) were included in the present study. The exclusion criteria were a procedure performed with a femoral approach and the lack of the capacity, or refusal, to provide written informed consent. All patients provided informed consent to participate in the present study, with a total of 102 patients with 108 lesions included.

All the procedures were performed using the radial approach. The left radial artery was preferred over the right, unless it was not possible to access it. Before the procedure, all patients were given aspirin (100 mg/day or a loading dose of 300 mg, if not taken previously). Immediately after catheterization, all patients received, by way of the radial artery, a "cocktail" of 5,000 IU of sodium heparin and 2.5 mg of verapamil. Before introducing the coronary pressure wire in the coronary artery, a corresponding dose of sodium heparin was administered to a total dose of 100 IU/kg. A nonionic contrast agent (iodixanol) was used in all procedures. All studies were performed through a 6F catheter

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See page 1282 for disclosure information.

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Table 1
Baseline demographic and clinical characteristics (n = 102)

Variable	Value
Age (yrs)	66.9 ± 10.5
Women	25 (24.5%)
Height (cm)	167.1 ± 7.2
Weight (kg)	79.0 ± 14.2
Body mass index (kg/m^2)	1.8 ± 0.2
Systolic blood pressure (mm Hg)	147.1 ± 29.5
Diastolic blood pressure (mm Hg)	78.7 ± 15.4
Heart rate (beats/min)	71.9 ± 14.2
Diabetes	37 (36.3%)
Hypertension	79 (77.5%)
Dyslipidemia	63 (61.8%)
Smoking	59 (57.8%)
Previous myocardial infarction	21 (20.6%)
Previous coronary revascularization	34 (33.3%)
Previous stroke	8 (7.8%)
Stable angina pectoris	27 (26.5%)
Acute coronary	57 (55.8%)
Valvulopathy	4 (3.9%)
Dilated myocardial cardiomyopathy	5 (4.9%)
Silent ischemia	9 (8.8%)
Left ventricular ejection fraction	52.96 ± 14.00
Arterial access	
Left radial artery	98 (96.3%)
Right radial artery	4 (3.7%)
Diseased vessels (n)*	0.80 ± 1.01
0	51 (50.0%)
1	26 (25.5%)
2	15 (14.7%)
3	10 (9.8%)
Lesions (n)*	1.06 ± 0.28

Data are presented as mean ± SD or n (%).

Study included patients considered to have indication for intracoronary pressure wire study because of presentation with coronary stenosis of intermediate severity.

* Angiographic stenosis >70% in lesions other than studied lesion.

Table 2
Angiographic characteristics of fractional flow reserve (FFR) studied coronary lesions (n = 108)

Characteristic	Value
Lesion type	
De novo lesion	103 (95.4%)
In-stent restenosis lesion	5 (4.6%)
Lesion type	
A	26 (24.1%)
B1	17 (15.7%)
B2	46 (42.6%)
C	19 (17.6%)
Studied vessel	
Left anterior descending	59 (54.6%)
Circumflex	29 (26.9%)
Right coronary	18 (16.7%)
Left main	2 (1.9%)
Localization	
Ostial	2 (1.9%)
Proximal	39 (36.1%)
Media	45 (41.7%)
Distal	22 (20.4%)
Quantitative analysis	
Reference diameter (mm)	2.96 ± 0.63
Minimum luminal diameter (mm)	1.55 ± 0.39
Lesion length (mm)	15.79 ± 8.62
Diameter stenosis (%)	52.60 ± 8.27

Data are presented as mean ± SD or n (%).

Coronary stenosis of intermediate severity (visual estimation 40−70%) included in present study.

guide. After the decision to perform the study with a pressure wire, an antebrachial vein (cephalic or basilic) of the ipsilateral or contralateral arm to the one with the radial access was catheterized. Through the venous catheter, a 5F arterial introducer was positioned, through which we introduced a diagnostic Judkins 4F catheter, until its distal end was localized in the right atrium. This catheter was connected to a continuous perfusion pump to ensure central administration of intravenous adenosine at the programmed dose.

The method to calculate FFR has been previously described.[12,13] Before initiating the functional study, 200 μg of intracoronary nitroglycerin was administered through the guide catheter. The functional evaluation was performed using a 0.014-in. Pressure-Wire Certus or Pressure-Wire Airis (St. Jude Medical Systems AB, Uppsala, Sweden) or Volcano Primewire (Volcano, Rancho Cordova, California) pressure wire. The pressure wire was externally calibrated and then advanced to the distal tip of the catheter to verify the equalization between the pressure curves recorded through the catheter and pressure wire. The pressure wire was subsequently advanced into the coronary artery, until its sensor was positioned ≥10 mm beyond the studied lesion. The FFR was measured after a beat-to-beat analysis between the mean aortic pressures (at the distal end of the guide catheter) and the pressure distal to the lesion (measured by the pressure wire) during maximum hyperemia. This calculation was performed, assuming that R in the maximum hyperemia conditions cancelled out in the equation and that the central venous pressure was negligible and generally ignored in the original formula: FFR = [(distal pressure − central venous pressure)/resistance]/[(aortic pressure − central venous pressure)/resistance].[14] At least 2 measurement of FFR were performed for each intracoronary dose. When measuring the FFR with intracoronary adenosine, special care was taken to avoid wedging the catheter in the coronary ostium after administration of the bolus drug. When damping was observed, the guiding catheter was pulled back a few millimeters into the aorta after the intracoronary injection. Intravenous infusion was performed with the distal end of the catheter guide outside the coronary ostium.

A protocol of increasing doses of intracoronary adenosine boluses (60, 180, 300, and 600 μg) was used for all patients. Two measurements of FFR were performed per dose. Each bolus was followed by a flush of saline. The beat-to-beat measurement of FFR was started 3 seconds after bolus administration. The administration of the next bolus was not performed until the pressure curves returned to the baseline values. After the end of the protocol for intracoronary bolus administration, intravenous infusion of adenosine was begun at 140 μg/kg/min. After the measurement of FFR 2 minutes after beginning the

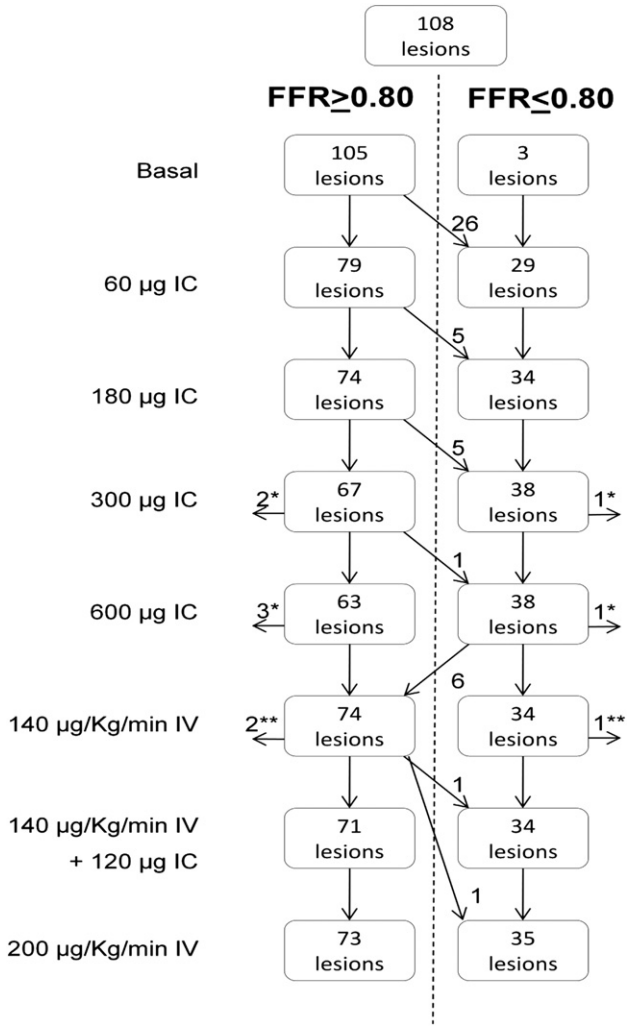

Figure 1. Change in number of lesions with FFR <0.80 in accordance with administration protocol of sequential doses of intracoronary adenosine. *Lesions not studied owing to pause >3 seconds with previous dose. **Lesions not studied because of pause >3 seconds with intracoronary dose of 180 µg/kg/min.

intravenous infusion, 2 intracoronary boluses of 120 µg adenosine were administered without stopping the intravenous infusion, using the same technique used with the initial boluses administered. The protocol was ended by increasing the intravenous infusion to 200 µg/kg/min. In the event of a pause of >3 seconds after an intracoronary bolus dose of adenosine, no additional doses were administered.

Quantitative analysis was performed offline by an experienced interventional cardiologist, who was unaware of the functional study results, using MEDIS QAngio XA, version 7.1 (Medis Medical Imaging Systems, Leiden, The Netherlands) software.

Continuous variables are presented as median ± SD and categorical variables as absolute values or percentages. The data for the mean arterial pressure and cardiac frequency, before and after adenosine intravenous infusion, and the FFR values measured at different doses of bolus intracoronary adenosine were analyzed using the Student *t* test

Table 3
Differences between fractional flow reserve (FFR) values according to adenosine doses

Variable	Standard Intravenous Perfusion (140 µg/kg/min)			Intravenous Perfusion (200 µg/kg/min)			Intravenous Perfusion (140 µg/kg/min) Plus 120-µg Intracoronary Adenosine		
	FFR Difference	95% CI	p Value	FFR Difference	95% CI	p Value	FFR Difference	95% CI	p Value
Intracoronary bolus dose (µg)									
60	0.02 ± 0.00	0.01–0.03	0.001	0.02 ± 0.00	0.01–0.03	0.000	0.03 ± 0.00	0.02–0.03	0.000
180	−0.00 ± 0.00	−0.01–0.00	0.256	−0.00 ± 0.00	−0.01–0.01	0.625	0.01 ± 0.00	0.00–0.01	0.049
300	−0.01 ± 0.00	−0.02–0.00	0.006	−0.01 ± 0.00	−0.02–0.00	0.035	0.00 ± 0.00	−0.00–0.01	0.902
600	−0.02 ± 0.00	−0.02–0.01	0.000	−0.01 ± 0.00	−0.02–0.01	0.000	−0.01 ± 0.00	−0.01–0.00	0.020
Intravenous perfusion									
Standard (140 µg/kg/min)	—	—	—	0.00 ± 0.00	−0.00–0.01	0.066	0.01 ± 0.00	0.01–0.02	0.000
200 µg/kg/min	−0.00 ± 0.00	−0.01–0.00	0.066	—	—	—	0.01 ± 0.00	0.00–0.01	0.005
Standard (140 µg/kg/min) plus 120-µg intracoronary adenosine	−0.01 ± 0.00	−0.02–0.01	0.000	−0.01 ± 0.00	−0.01–0.00	0.005	—	—	—

CI = confidence interval.

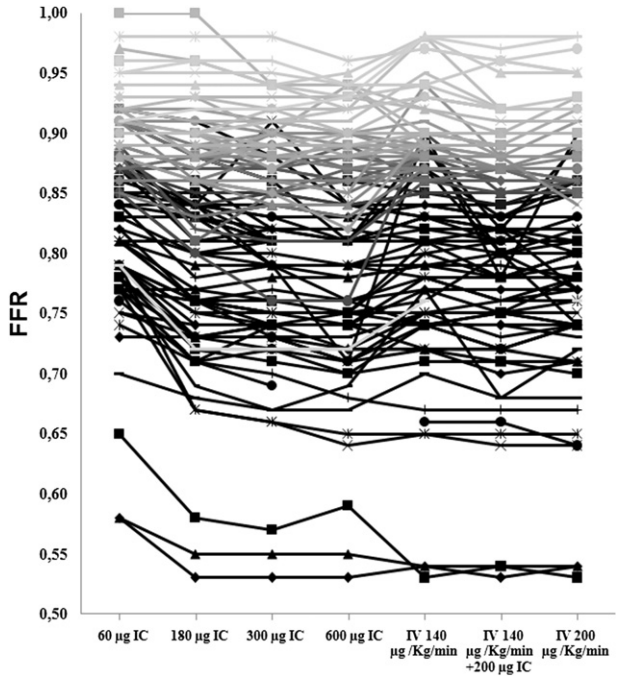

Figure 2. Individual values of FFR according to dose of adenosine. IC = intracoronary; IV = intravenous.

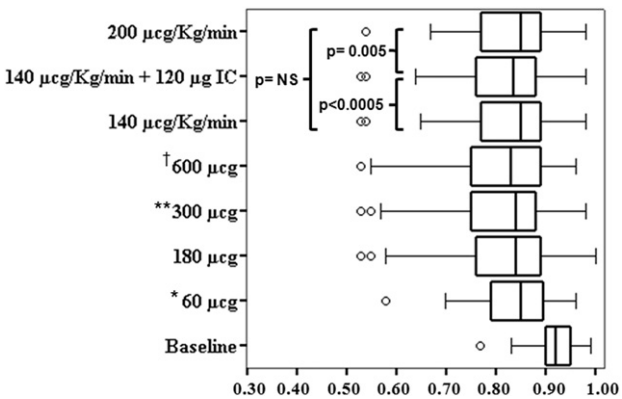

Figure 3. Distribution (box plot) of FFR values obtained in relation to adenosine dose administered. *FFR value significantly greater than with remaining doses. **FFR values significantly smaller with remaining doses, with exception of intravenous infusion at 140 µg/kg/min with added intracoronary bolus of 120 µg. †FFR values significantly smaller than with remaining doses of adenosine. NS = nonsignificant difference.

for paired multiple comparisons. The change in the percentage of patients with FFR <0.80 for each dose of adenosine was analyzed using the Cochran Q test for paired categorical measures. The results were considered statistically significant when p <0.05. The software SPSS, version 15.0 for Windows (SPSS, Chicago, Illinois) was used.

Results

In the present study, 108 lesions in 102 patients were included. The baseline patient characteristics and lesions studied are reported in Tables 1 and 2. In 94 patients (92.2%), the infusion was performed in the right atrium. In

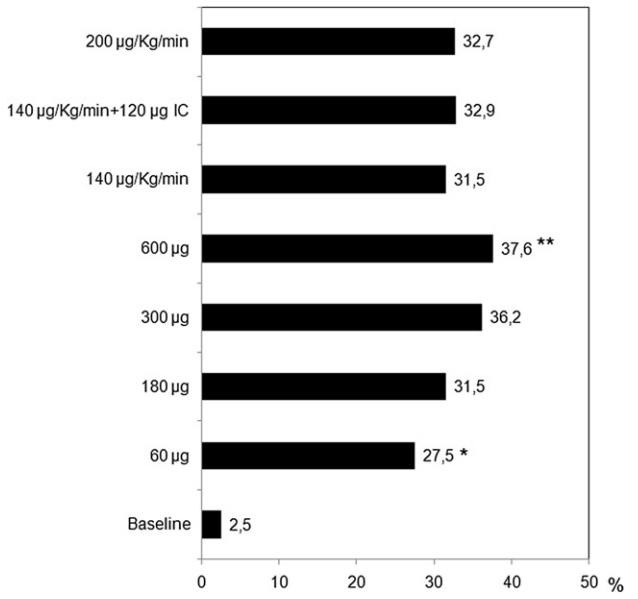

Figure 4. Distribution of percentage of lesions with FFR <0.80 in relation to dose administered. *Significant difference in relation to all doses of adenosine administered, intracoronary and intravenous. **Significant difference in relation to all intracoronary and intravenous doses, with exception of intracoronary bolus dose of 300 µg.

the remaining 8 patients (7.8%), the infusion was performed through an antebrachial vein. In 101 of the lesions (93.5%), all the doses of intracoronary adenosine were administered successfully. In 7 patients, the protocol of intracoronary adenosine administration could not be performed completely because of transient atrioventricular block of >3 seconds (mean 4.9 ± 1.2). The dosages causing an atrioventricular block of >3 seconds are reported in Figure 1. All episodes of atrioventricular block were spontaneously self-limiting or resolved by encouraging the patient to cough. All patients experienced some degree of thoracic discomfort with high-dose intracoronary adenosine. This discomfort was well tolerated by the patients and showed a very difficult possibility of evaluation because of the very short duration of the intracoronary adenosine effect. All cases (100%) reported some degree of thoracic discomfort with intravenous infusion of adenosine. In none of these cases was it necessary to discontinue the study before obtaining an FFR value. A significant decrease in systolic (141 ± 30 vs 129 ± 27 mm Hg; p <0.0005), diastolic (67 ± 15 vs 63 ± 15 mm Hg; p <0.0005), mean arterial pressure (92 ± 18 vs 86 ± 16 mm Hg; p <0.0005), and heart rate (71 ± 13 vs 80 ± 13 beats/min; p <0.0005) was observed with intravenous adenosine. These hemodynamic variations were not clinically relevant in any of the cases. One patient (0.98%) developed 1 episode of paroxysmal atrial fibrillation that was self-limiting, starting with the infusion of adenosine at 140 µg/kg/min. No complications were observed when advancing the guide or at the site of venous access, and no other complication was associated with the study with a pressure wire.

The intracoronary adenosine bolus dose of 60 µg obtained FFR values significantly greater than those obtained with the intravenous adenosine infusion (difference in

FFR 0.02 ± 0.03; 95% confidence interval 0.01 to 0.01; p = 0.001). Bolus doses of 300 and 600 μg resulted in FFR values significantly smaller than those obtained with intravenous adenosine. An intravenous adenosine infusion of 200 μg/kg/min was not associated with FFR values significantly smaller than those obtained with infusion at 140 μg/kg/min. The addition of a bolus intracoronary dose of adenosine during intravenous infusion did show an association with a significantly lower FFR than that observed with the 140-μg/kg/min and 200-μg/kg/min doses but significantly greater than that obtained with a bolus intracoronary dose of 600 μg (Table 3 and Figure 2).

The change in the number of cases with an FFR <0.80 is shown in Figures 1 and 3. The percentage of patients with an FFR <0.80 was significantly greater with the use of a bolus intracoronary dose of 600 μg of adenosine than that observed with the all other intravenous and intracoronary doses, with the exception of the intracoronary dose of 300 μg, for which no statistical significance was observed (37.2% vs 36.7%; p = 0.32; Figure 4).

Discussion

The results of the present study have shown that when determining the FFR using a pressure wire, the use of intracoronary adenosine at sufficiently high doses can obtain minimal FFR values at equal or greater frequencies than intravenous adenosine infusion at the standard (140 μg/kg/min) or greater (200 μg/kg/min) dose.

Intravenous adenosine through a central line is considered the reference standard in achieving maximum hyperemia for FFR determination.[5,15,16] Intracoronary adenosine has been associated with a failure percentage rate of 8% to 10% in obtaining maximum hyperemia compared to intravenous infusion.[7,8] The use of intracoronary boluses of adenosine is inexpensive and has few secondary side effects. Intravenous infusion is more expensive, results in a prolonged procedure time,[17] and requires catheterization of a central vein. The requirement of achieving maximum hyperemia and the aim of simplifying procedures has recently prompted the proposal of an alternative vasodilator stimulus[18] or estimations without administration of adenosine.[19]

Our study has demonstrated that with few secondary effects, intracoronary adenosine can be used with equivalent or superior results to those obtained with intravenous administration, simplifying the procedures. Recently, Seo et al[20] have demonstrated that peripheral administration of adenosine could be as effective as central administration to obtain steady-state hyperemia. Previous published studies have offered contradictory data. The most recent recommendations suggest administration through a large-bore cannula in a large vein for the study of FFR performance.[21] We believe 2 reasons might have contributed in our study to obtaining lower values of FFR with intracoronary administration of adenosine compared to the intravenous route: (1) the use of much higher doses than those recommended (20 to 60 μg), [6,22]and (2) the interventional cardiologists were especially careful when administering the intracoronary boluses. A very important issue is to verify that the catheter is sufficiently engaged in the coronary artery for the administration of adenosine and retracting the guide catheter from the coronary ostium to ensure the reliability of the measurements taken.

Several studies have analyzed the effect of incremental doses of adenosine on the FFR values achieved.[7,9–11,23] De Luca et al[11] tested a dose similar to the maximum dose used in our study (720 μg) and achieved FFR values inferior to those achieved with a dose of 360 μg, with no secondary effects. These doses are very superior to the maximum doses used to date in published studies for comparison with intravenous infusion (150 μg),[8,24] which might have been insufficient to ensure maximum hyperemia. More recently, in a study by Leone et al,[25] with a design similar to ours but including a reduced number of lesions (n = 50), no statistically significant difference was found between FFR values obtained with 600-μg intracoronary doses and intravenous infusion of 140 μg/kg/min; however, venous infusion was not performed in all cases using a central line. Although the investigators did not clarify whether some patients with an FFR <0.80 using intracoronary adenosine presented with an FFR >0.80 with intravenous infusion, they did report that 3 of 7 patients (30%) with an FFR <0.80 with intravenous adenosine presented with an FFR >0.80 with a 600-μg intracoronary dose. Our study findings have contradicted these results, given that although we included more than twice the number of lesions, we found no case in which a patient with an FFR >0.80 with 600-μg intracoronary adenosine had an FFR <0.80 with any of the intravenous doses used. We do not have a plausible physiologic explanation for this discrepancy. Differences in the lesions or patients included could provide a hypothetical explanation. The severity of stenosis was slightly greater (58% vs 53%), and neither the reference diameter nor the length of the lesions studied by Leone et al[25] was reported. We believe the difference between the 2 studies highlights the need for a stricter technique in the administration of intracoronary adenosine and the greater variability with intracoronary than with intravenous use. Special care should be taken to ensure that the adenosine is administered inside the coronary artery and to confirm that the position of the catheter tip in the coronary ostia does not cause a decrease in aortic pressure that might overestimate the FFR value obtained with the distal pressure/aortic pressure ratio.

The performance of coronary intervention using a radial approach has been associated with better clinical results.[26–28] The need to administer adenosine intravenously through a central line can be considered a limitation for determining the FFR in procedures using a radial approach. In the present study, the central line for intravenous infusion was obtained without complications using a brachial approach in 92% of the cases. Infusion using a peripheral vein has been tested in previous studies. Lindstaed et al[29] compared continuous intravenous administration of adenosine by accessing an antecubital vein to infusion using a femoral vein. They found that they required a greater dose of adenosine (170 μg/kg/min) through the peripheral line to obtain the same results using the femoral line. In our study, although the access was peripheral, the administration was given in the right atrium in almost all cases, avoiding femoral access. Thus, we believe the decision to determine the FFR (using intracoronary or

intravenous adenosine) should not be limited by a previous decision to use a radial approach.

The use of intracoronary adenosine requires a simple, but cautious, technique to ensure delivery of most of the drug into the coronary artery and that the pressure registered by the guide catheter is correct without artifacts caused by the presence of the catheter itself in the coronary ostium. The results observed in the present study might not be reproduced in each laboratory and each lesion, because the administration of intracoronary adenosine could be hampered by a less experienced operator or an ostial lesion location. These technical requirements must be considered a limitation of adenosine intracoronary administration versus intravenous infusion. The possible difficulty in advancing a catheter through an arm vein to the right atrial chamber could be considered another limitation.

Disclosures

The authors have no conflicts of interest to disclose.

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