ORIGINAL ARTICLE

Adenosine intracoronary bolus dose escalation versus intravenous infusion to induce maximum coronary hyperemia for fractional flow reserve assessment

Jacek Legutko, Paweł Kleczyński, Artur Dziewierz, Łukasz Rzeszutko, Dariusz Dudek

Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

KEY WORDS

adenosine, borderline lesion, coronary artery disease, fractional flow reserve, physiology

ABSTRACT

BACKGROUND Achievement of maximal hyperemia is mandatory for an accurate calculation of fractional flow reserve (FFR), and it is obtained with adenosine administered either as an intravenous infusion or intracoronary bolus.

AIMS The aim of this study was to compare the infusion of adenosine with intracoronary adenosine bolus dose escalation in the optimal assessment of peak FFR.

METHODS We enrolled consecutive patients with borderline coronary lesions that were assessed by FFR with the use of intracoronary adenosine bolus (100 µg, 200 µg, 400 µg, and 600 µg) and intravenous infusion of 140 µg/kg/min and 280 µg/kg/min. The FFR values obtained by the 2 different routes of administration were assessed and compared.

RESULTS A total of 50 patients with 125 borderline coronary artery lesions were enrolled. The mean (SD) physiologic severity of coronary artery stenosis was as follows: 0.82 (0.09) for intravenous adenosine infusion at 140 µg/kg/min; 0.81 (0.09) for intravenous adenosine infusion at 280 µg/kg/min; as well as 0.83 (0.09) for an intracoronary adenosine bolus of 100 µg, 200 µg, 400 µg, and 600 µg each. There was a strong linear correlation between FFR values obtained with 140-µg/kg/min adenosine infusion and intracoronary bolus injection of adenosine at a dose of 100 µg, 200 µg, 400 µg, and 600 µg (r = 0.99, r = 0.99, r = 0.99, r = 0.99, respectively, P <0.001 for all).

CONCLUSIONS The values of FFR achieved with an intracoronary bolus of adenosine are very similar, but not identical, to those obtained using intravenous adenosine administration. The values may vary between escalating doses of intracoronary boluses and intravenous infusion.

Correspondence to:
Jacek Legutko, MD, PhD, Institute of Cardiology, Jagiellonian University Medical College, ul. Prądnicka 80, 31-202 Kraków, Poland, phone: +48 12 614 35 01, email: jacek.legutko@uj.edu.pl

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INTRODUCTION When evidence of ischemia is not available, coronary pressure–derived fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is recommended to assess the hemodynamical significance of intermediate-grade stenosis (typically 40%–90% stenosis).[1] Hemodynamic relevance is defined as an FFR of 0.8 or lower or an iFR lower than 0.9, but the FFR threshold of 0.75 is also useful to define more severe ischemia that is of prognostic relevance.[2,3] Recently, 2 randomized trials showed comparable results between FFR-guided and iFR-guided revascularization strategies in patients with borderline coronary stenosis.[4,5] However, the measurement of iFR requires an access to a dedicated console, which is not available in every catheterization laboratory. Moreover, there are no randomized trials comparing iFR-based management of patients with intermediate-grade stenosis with medical therapy. Data supporting the use of iFR to assess ambiguous left main disease are also lacking.[1] Thus, FFR remains the current standard

WHAT'S NEW?

Achievement of maximal hyperemia is mandatory for an accurate calculation of fractional flow reserve (FFR), and it is most commonly achieved with adenosine given either as an intravenous infusion or intracoronary bolus. Intravenous infusion of adenosine requires larger amounts of adenosine; therefore, it is associated with higher costs, more frequent occurrence of systemic adverse effects, and, finally, may be more time consuming. The values of FFR may vary between escalating doses of intracoronary boluses. There might be no need for increasing an adenosine bolus dose from 400 µg to 600 µg. However, there seems to be a grey zone (0.81–0.83) for FFR assessed with boluses, which, in selected cases, may indicate the use of intravenous infusion to confirm the results.

of care for the functional assessment of lesion severity in patients with intermediate stenosis.

Importantly, the induction of maximal hyperemia is mandatory for an accurate calculation of FFR.[6] Maximal hyperemia is most commonly achieved with adenosine given either as an intracoronary bolus or intravenous infusion. Intracoronary bolus administration is more challenging as it requires stable intubation of the guiding catheter in the coronary ostium and a careful assessment of short-lasting hyperemia. On the other hand, intravenous infusion of adenosine provides more stable and predictable hyperemia. However, it requires additional venous access and a larger amount of adenosine; therefore, it is associated with higher costs, more frequent occurrence of systemic adverse effects, and, finally, it may be more time consuming.[7] An optimal algorithm for the induction of maximal hyperemia remains a subject of debate, with no clear advice from current guidelines on myocardial revascularization. Thus, it is generally left at the discretion of the operator.

The aim of this study was to compare an intravenous infusion of adenosine with intracoronary adenosine bolus dose escalation for the assessment of peak FFR, as well as to develop an optimal algorithm for maximal hyperemia induction for FFR assessment in the catheterization laboratory.

METHODS This was a prospective study on consecutive patients between 18 and 90 years of age, with stable angina and angiographically intermediate stenosis (>40% diameter stenosis by visual assessment) in a major epicardial coronary artery, who were scheduled for FFR. Baseline clinical data of patients were collected. Patients with acute myocardial infarction or contraindications to adenosine were excluded. Ethics approval was granted from the institutional ethics review board, and all patients gave written informed consent. Coronary angiography was performed with the standard femoral or radial approach based on individual operator preferences. All procedures were performed by experienced operators in a cardiac reference university center with more than 1500 FFR assessments performed before. For the femoral venous administration of adenosine, a 6-F venous sheath with a sidearm was used. The infusion system was filled with adenosine to exclude the washout period of the saline. A launcher coronary guide catheter (Medtronic, Minneapolis, Minnesota, United States) without side holes, the s5/s5i console, and the Verrata pressure guide wire (Philips Volcano Corporation, San Diego, California, United States) were used in all cases. Data acquisition included electrocardiographic signal recording. After intracoronary nitrates (300 µg) and acquisition of coronary angiograms, aortic pressure (Pa) and intracoronary distal pressure (Pd) were recorded in the following pattern: first, the pressure wire was zeroed and equalized, and its correct equalization (mean [SD] Pd/Pa ratio, 1.00 [0.01]) was confirmed during a 10-second acquisition in the ascending aorta in each case. Then, the pressure sensor was positioned distal to the index stenosis, and the guiding catheter was flushed with saline and disengaged from the coronary ostium. Baseline pressures were recorded for at least 20 seconds before inducing hyperemia.

Adenosine administration through a femoral vein at a rate of 140 or 280 µg/kg/min for a minimum of 3 minutes and pressure wire pullback maneuver to check for pressure drift were mandatory. Each borderline lesion was assessed in the same way each time. First, an adenosine infusion through the femoral vein at 140 µg/kg/min was performed. We repeated these steps for the femoral vein adenosine infusion at 280 µg/kg/min. In the same pressure recording, the bookmarks for core laboratory analyses were placed: 1) when adenosine infusion started; 2) when the pullback maneuver started; and 3) when the pressure sensor reached the tip of the guiding catheter. If a Pd/Pa ratio of less than 0.99 or more than 1.01 at the catheter tip was documented, the protocol mandated a repeat assessment. After waiting for the washout of adenosine and the return of the Pd/Pa ratio to its baseline value, the guiding catheter was again flushed with saline and multiple intracoronary adenosine boluses (100 µg, 200 µg, 400 µg, and 600 µg) were administered. Each bolus was followed by a flush of saline and then disengagement of the guiding catheter from the coronary ostium. Each bolus was administered at least 1 minute after the previous one (in all cases until pressure curves returned to baseline values). The measurement of FFR was performed continuously after bolus administration. The time of stable hyperemia was assessed, along with the FFR value. Each subsequent bolus of adenosine was administered at least 1 minute after the previous one (in all cases until pressure curves returned to baseline values). All boluses

TABLE 1 Study population (n = 50) and procedural data

Patients		Value
Age, y, mean (SD)		66 (9.3)
Male sex, n (%)		36 (72)
Height, cm, mean (SD)		169.9 (7.9)
Weight, kg, mean (SD)		80.4 (13.3)
Body mass index, kg/m^2, mean (SD)		27.8 (3.7)
Arterial hypertension, n (%)		50 (100)
Diabetes mellitus, n (%)		28 (56)
Previous myocardial infarction, n (%)		26 (52)
Previous PCI, n (%)		24 (48)
Previous CABG, n (%)		0 (0)
Peripheral arterial disease, n (%)		2 (4)
Chronic obstructive pulmonary disease, n (%)		1 (2)
Previous stroke / TIA, n (%)		0 (0)
Hyperlipidemia, n (%)		50 (100)
Smoking, n (%)		20 (40)
Serum creatinine, µmol/l, mean (SD)		91.1 (19.4)
LVEF, %, mean (SD)		52.8 (8.1)
Heart rate, bpm, mean (SD)		71.5 (9.7)
Angina symptoms – CCS class, n (%)	I	6 (12)
	II	40 (80)
	III	4 (8)
Heart failure symptoms – NYHA class, n (%)	I	43 (86)
	II	5 (10)
	III	1 (4)
	IV	1 (4)
Access, n (%)	Radial	35 (70)
	Femoral	15 (30)
Number of assessed vessels, median (IQR)		3 (2–4)
Scheduled treatment, n (%)	Conservative	21 (42)
	PCI	23 (46)
	CABG	6 (12)

Abbreviations: CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

were divided by saline flush and administration of intracoronary nitrates (300 µg). We prepared the drug with a dilution so that all doses could be administered with a 5-cc syringe.

The FFR was experimentally and clinically validated under conditions of maximum and stable hyperemia[7] and was automatically calculated by a software (ver. 2.4.1.2723, Volcano, Philips Volcano, Rancho Cordova, California, United States) as the minimum Pd / Pa ratio found in the pressure recording. However, during intravenous adenosine infusion, the minimum hyperemic Pd / Pa ratio might develop before stabilization of hyperemia. Hence, conforming to its original validation,[8] core laboratory analyses included a thorough review of pressure recordings to confirm that the FFR was calculated: 1) after initiation of adenosine infusion; 2) within stable hyperemia; and 3) before the pullback maneuver. Stable hyperemia was defined as the plateau in the mean Pa after stabilization of changing hemodynamics following the initiation of adenosine infusion and before the pullback maneuver.[7] If a plateau was not clearly observed, stable hyperemia was then defined as the period of pressure recording in which no further systematic fall in Pa was observed, following the initiation of adenosine infusion but before the initiation of the pullback.[7] Within stable hyperemia, the minimum Pd / Pa ratio was then labeled as FFR.

Core laboratory analyses included an evaluation of pressure waveforms to confirm that none of the following exclusion criteria were present: inappropriate normalization of the pressure wire (Pd / Pa ratio <0.99 or >1.01), electrocardiogram artifacts or significant arrhythmias in the first 20 seconds of the recording, loss of Pa or Pd signals at any point during the recording, automatic calculation pitfalls (eg, identification of FFR during ectopic beats, Pa or Pd noise, and wire whipping artifacts), dampening of Pa or Pd waveforms, pressure drift lower than 0.99 or higher than 1.01, and absence of electrocardiogram or pressure-pullback recording. The core laboratory also assessed the time to reaction defined as a time point from the beginning of adenosine infusion to initial drop of the Pd / Pa ratio, as well as the time to peak hyperemia defined as the time from the beginning of adenosine infusion to the lowest stable Pd / Pa value.

Quantitative coronary angiography was performed by an independent core laboratory analyst blinded to the results of FFR. Using the guide catheter for calibration and an edge detection system (CAAS 5.7 QCA system, Pie Medical, Maastricht, the Netherlands), the reference vessel diameter and minimum lumen diameter were measured, and the percent diameter stenosis was calculated.

Statistical analysis Categorical variables were expressed as number of patients (percentage). Continuous variables were expressed as mean (SD). Nonnormally distributed data were reported as median (interquartile range [IQR]). Agreement among tested methods was assessed by Bland-Altman plots and 95% limits of agreement. All tests were 2-tailed, and a *P* value of less than 0.05 was considered significant. All statistical analyses were performed using STATISTICA 12.0 (StatSoft Inc., Tulsa, Oklahoma, United States).

TABLE 2 Lesion characteristics

Lesions (n = 125)	Value
LAD, n (%)	48 (38.4)
Dg, n (%)	11 (8.8)
Cx, n (%)	32 (25.6)
Mg, n (%)	9 (7.2)
RCA, n (%)	25 (20)
Quantitative coronary angiography results (n = 125)	**Value**
Lesion length, mm, mean (SD)	21.7 (14)
RVD, mm, mean (SD)	2.6 (0.6)
MLD, mm, mean (SD)	1.4 (0.4)
DS, %, mean (SD)	44.2 (11.7)
Eccentric lesion, n (%)	67 (53.6)
Moderate / severe tortuosity, n (%)	52 (41.6)
Irregular contours, n (%)	11 (9.2)
Moderate / severe calcifications, n (%)	49 (40.8)
Ostial lesion, n (%)	11 (9.2)

Abbreviations: Cx, circumflex artery; Dg, diagonal branch; DS, diameter stenosis; LAD, left anterior descending artery; LMCA, left main coronary artery; Mg, marginal branch; MLD, minimal lumen diameter; RCA, right coronary artery; RVD, reference vessel diameter

RESULTS

Study population Fifty patients with 125 borderline coronary artery lesions were enrolled. The baseline characteristics of patients and lesions are presented in TABLES 1 and 2. Overall, the mean (SD) age was 66.0 (9.3) years, and 72% of patients were male. All patients presented with stable angina that was an indication for coronary angiography. The left anterior descending artery was the most commonly interrogated vessel (36.8%).

Procedural data Procedural success was 100% for advancing the pressure wire distally to the stenosis. There were no procedure-related complications. The distribution of the FFR values in the study is shown in FIGURE 1. In general, patients had coronary stenoses of intermediate angiographic severity (mean [SD] diameter stenosis, 44.2 [11.7] mm by qualitative angiographic assessment). Adenosine caused an asymptomatic transient third-degree atrioventricular block in 5.8% of patients. Chest pain occurred in 13.6% of patients. On the basis of FFR assessment, 42% of patients were scheduled for conservative treatment, 46% were treated with percutaneous coronary intervention (PCI), and 12% were scheduled for bypass surgery. In patients who had undergone FFR-guided PCI, the mean (SD) FFR after the procedure was 0.87 (0.02) (median, 0.87 [IQR, 0.86–0.9]).

Functional flow reserve findings and analysis The mean (SD) physiologic severity of coronary artery stenosis was 0.82 (0.09) (median, 0.83; [IQR, 0.77–0.88]) when assessed with femoral vein adenosine infusion at 140 µg/kg/min, and 0.82 (0.1) (median, 0.83 [IQR, 0.76–0.88]) when assessed with femoral vein adenosine infusion at 280 µg/kg/min. The mean (SD) physiologic severity for an intracoronary bolus of 100 µg was 0.83 (0.09) (median, 0.84 [IQR, 0.78–0.9]); of 200 µg, 0.83 (0.09) (median, 0.84 [IQR, 0.78–0.9]); of 400 µg, 0.83 (0.09)

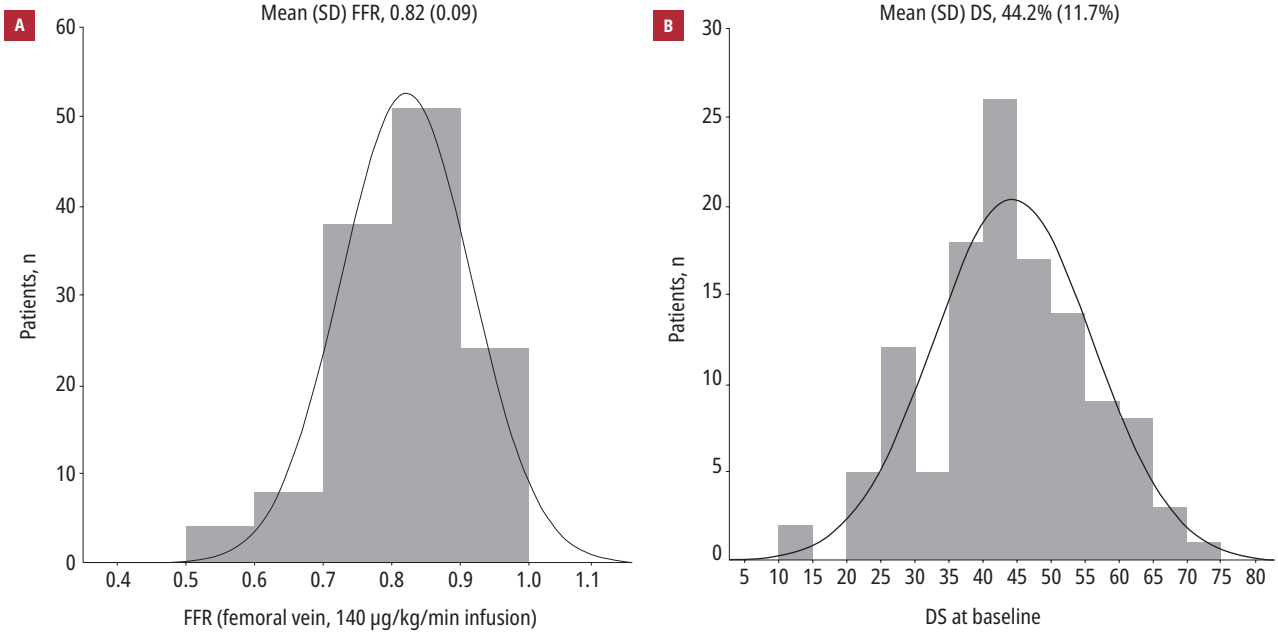

FIGURE 1 Distribution of the fractional flow reserve (**A**) and percent diameter stenosis (**B**) values in the study population
Abbreviations: FFR, fractional flow reserve; others see TABLE 1

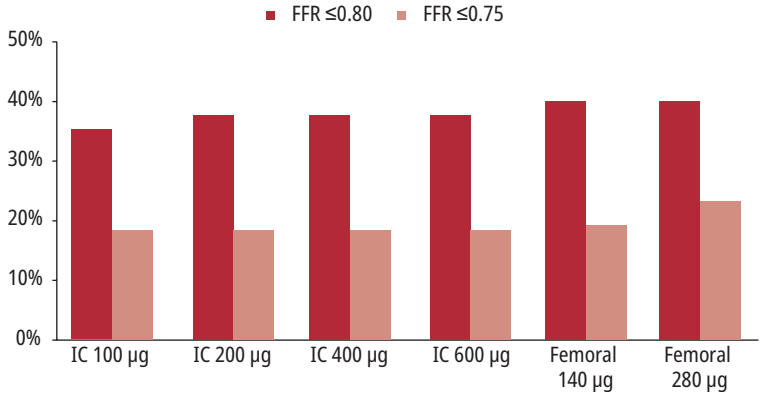

FIGURE 2 Percentage of functionally significant lesions according to different methods of adenosine administration
Abbreviations: IC, intracoronary; others, see FIGURE 1

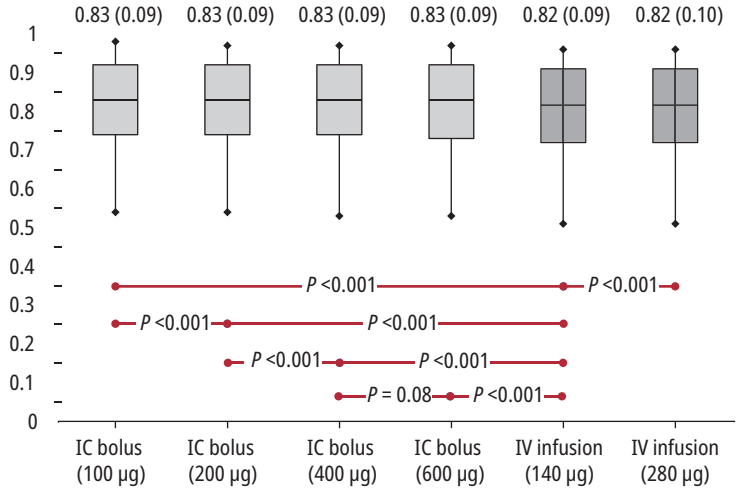

FIGURE 3 Mean (SD) fractional flow reserve values of adenosine intracoronary boluses of 100 µg, 200 µg, 400 µg, and 600 µg and femoral vein adenosine infusion 140 µg and 290 µg

(median, 0.84 [IQR, 0.78–0.9]); and of 600 µg, 0.83 (0.09) (median, 0.83 [IQR, 0.77–0.89]). Data are presented in FIGURE 3.

The time from initiation of adenosine infusion to beginning of pressure gradient drop was monitored and was shorter when measured during the 280-µg/kg/min femoral vein infusion compared with the 140-µg/kg/min infusion (mean [SD], 24 [10] seconds; median, 20 [IQR, 17–28] seconds vs mean [SD], 31 [14] seconds; median, 28 [IQR, 21–37] seconds; P <0.001).

The time from initiation of adenosine infusion to maximal stable hyperemia was shorter when assessed during the 280-µg/kg/min femoral vein infusion compared with the 140-µg/kg/min infusion (mean [SD], 36 [13] seconds; median, 33 [IQR, 27–40] vs mean [SD], 49 [19] seconds; median, 46 [IQR, 35–58]; P <0.001).

The time from saline flush after intracoronary adenosine bolus injection to maximal stable hyperemia was longer depending on the dose of adenosine used: mean (SD), 4.5 (1) seconds (median, 5 [IQR, 4–5] seconds) for 100-µg bolus; mean (SD), 6.2 (1.3) seconds (median, 6 [IQR, 5–7] seconds) for 200-µg bolus; mean (SD), 7.6 (1.6) seconds (median, 8 [IQR, 6–9] seconds) for 400-µg bolus; and mean (SD), 9.6 (2.2) seconds (median, 10 [IQR, 8–11] seconds) for 600-µg bolus. Percentage of functionally significant lesions according to different methods of adenosine administration is presented in FIGURE 2. The mean FFR values for femoral vein adenosine infusion at 140 µg/kg/min and 280 µg/kg/min as well as for intracoronary adenosine boluses of 100 µg, 200 µg, 400 µg, and 600 µg are shown in FIGURE 3. There was a strong linear correlation between FFR values obtained from 140 µg/kg/min femoral vein infusion and intracoronary adenosine bolus of 100 µg, 200 µg, 400 µg, and 600 µg (r = 0.99, P <0.001 for all; FIGURE 4).

Additionally, we performed a paired difference test comparing 140 µg/kg/min femoral vein infusion with an intracoronary bolus of 100 µg, 200 µg, 400 µg, and 600 µg in terms of FFR values and found numerically higher values for boluses, with a mean difference of 0.008 for 600-µg bolus (95% CI, –0.01 to –0.006; P <0.0001), 0.008 for 400-µg bolus (95% CI, –0.01 to –0.006; P <0.0001), 0.01 for 200-µg bolus (95% CI, –0.012 to –0.007; P <0.0001), and 0.015 for 100-µg bolus (95% CI, –0.016 to –0.01; P <0.0001).

Moreover, we compared differences in FFR values obtained from escalating intracoronary adenosine boluses between each other. The mean FFR difference between boluses was as follows: 100 µg vs 200 µg, 0.0034 (95% CI, 0.002–0.004; P <0.0001); 100 µg vs 400 µg, 0.005 (95% CI, 0.004–0.006; P <0.0001); 100 µg vs 600 µg, 0.0055 (95% CI, 0.004–0.007; P <0.0001); 200 µg vs 400 µg, 0.0017 (95% CI, 0.001–0002; P <0.0001); 200 µg vs 600 µg, 0.0022 (95% CI, 0.001–0.003; P <0.0001); and 400 µg vs 600 µg, 0.0005 (95% CI –0.0006 to –0.001; P = 0.08).

DISCUSSION

The results of the study identified the optimal adenosine administration and dose for the reliable assessment of coronary FFR in evaluating the hemodynamic severity of coronary stenosis. Intravenous infusion and escalating intracoronary boluses of adenosine showed a close, but not identical, agreement of FFR values after achieving maximal stable hyperemia and no systematic direction of bias was evident from the Bland–Altman analysis. However, there seems to be a grey zone for FFR assessed with boluses, which, in selected cases, may indicate the use of intravenous infusion to confirm the results. On the basis of our results, we propose that FFR values of 0.81 to 0.83 achieved with intracoronary adenosine boluses should be confirmed with an infusion of adenosine in order to obtain absolutely maximal stable hyperemia and true FFR values.

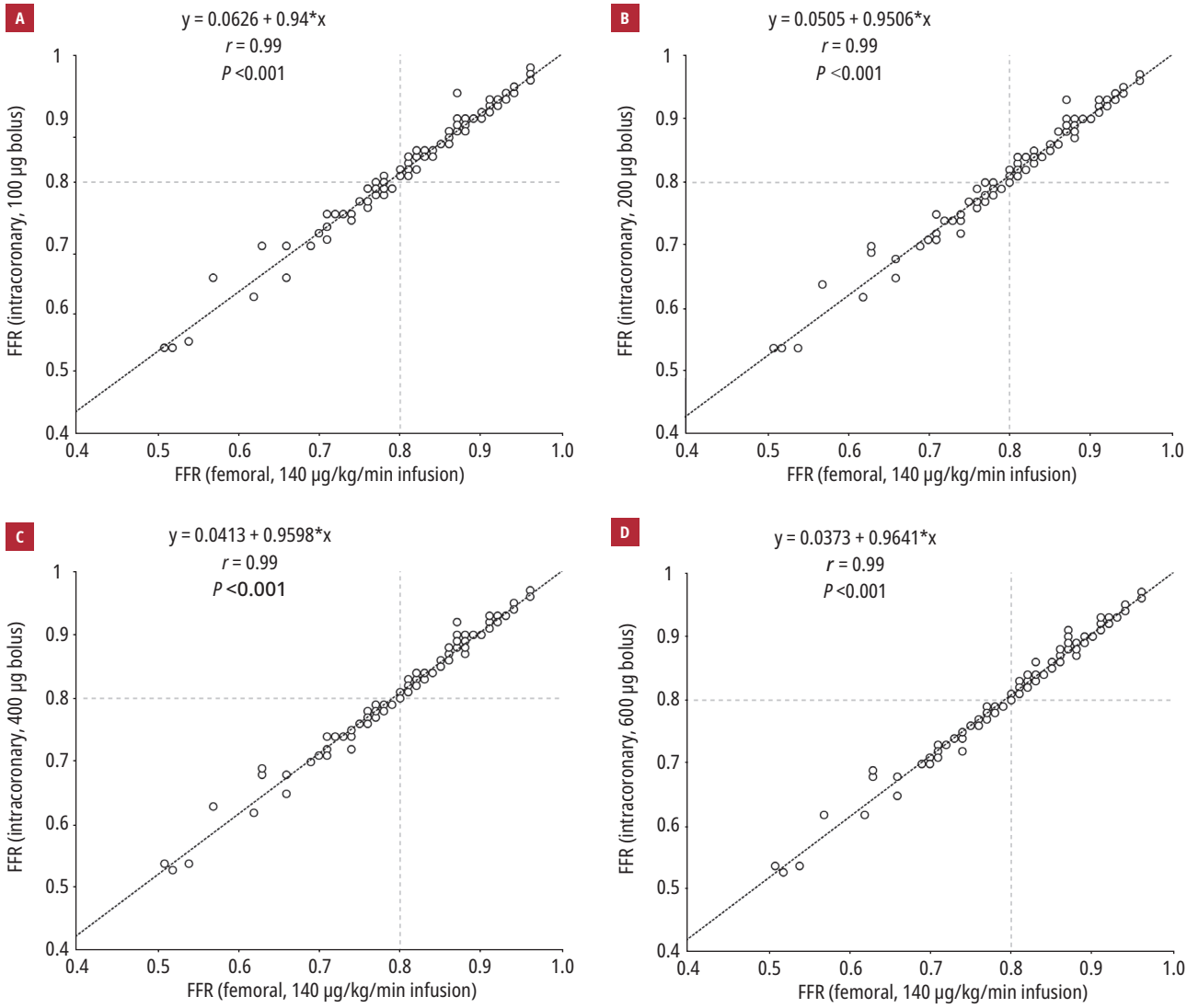

FIGURE 4 Correlation of fractional flow reserve values between 140 µg/kg/min femoral vein adenosine infusion and intracoronary bolus of adenosine (**A** – 100 µg; **B** – 200 µg; **C** – 400 µg; **D** – 600 µg)
Abbreviations: see FIGURE 1

Intravenous infusion of adenosine has been the gold standard method for obtaining hyperemia for FFR measurement,[6,9-15] and it can induce hyperemia with more reliable hyperemic efficacy than intracoronary bolus injection.[16-18] Moreover, intravenous adenosine may result in more stable vasodilation and therefore may be more appropriate for tandem or diffuse lesion assessment. However, it requires an additional procedure for venous access, which may increase the risk of vascular complications and is not so convenient to use in transradial approach. Therefore, in the era of radial approach as a common access for coronary angiography and intervention, an increasing frequency of intracoronary bolus of adenosine for FFR assessment has been noted. Intracoronary bolus can generate adequate and sufficiently stable coronary hyperemia, similar to a central venous infusion. In our study, escalating doses of an intracoronary bolus of adenosine from 100 µg to 400 µg were associated with significantly lower peak FFR values. However, we found that the FFR values achieved after 400 µg and 600 µg did not differ between each other, so there might be no need to increase the adenosine dose after a 400-µg bolus. This finding remains in contrast to the results obtained by de Luca et al,[19] who showed that high doses of intracoronary adenosine (up to 720 µg) increased the sensitivity of FFR in the detection of hemodynamically relevant coronary stenosis.

Our study presents a comprehensive approach directly comparing different doses of adenosine administered as intracoronary boluses (100 µg, 200 µg, 400 µg, and 600 µg) with intravenous adenosine infusion (140 µg/kg/min and 280 µg/kg/min) for 2 FFR cutoff values, namely, 0.80 and 0.75. According to current guidelines, hemodynamic significance of the lesion is confirmed by FFR of 0.80 or lower. However, the FFR threshold of 0.75 is also useful to define

more severe ischemia that is of prognostic relevance and is thus more convincing to support revascularization, even in high-risk lesions and patient subsets.[2,3] Escalating doses of intracoronary boluses as well as intravenous infusion of adenosine resulted in numerically higher rate of achieving significant FFR values, especially for the cutoff value of 0.75. In the study by de Luca et al,[19] the authors compared escalating adenosine boluses with only one dose of intravenous adenosine infusion and tested only one cutoff FFR value (0.8). In a study by Schlundt et al,[20] 114 patients with an intermediate degree of stenosis on coronary angiography were included. Two FFR assessments were performed during an intracoronary bolus injection (40 µg and 80 µg) and compared with continuous intravenous infusion of adenosine (140 µg/kg/min). They concluded that bolus injection of adenosine showed identical FFR results obtained with intravenous infusion while requiring less time. The doses were again tested only for a cutoff FFR value of 0.8. Khashaba et al[21] assessed borderline coronary lesions for ischemia only with one intracoronary bolus of adenosine (150 µg) and compared it with intravenous adenosine infusion over 3 minutes at a dose of 140 µg/kg/min. Their results suggested that intracoronary adenosine might be an alternative to intravenous adenosine with a cutoff FFR value of 0.8 recognized as significant. López-Palop et al[22] used intracoronary adenosine bolus doses of 60 µg, 180 µg, 300 µg, and 600 µg and intravenous administration of 140 µg/kg/min and 200 µg/kg/min, and concluded that an intracoronary bolus dose exceeding 300 µg can be equal to or more effective than an intravenous infusion of adenosine in achieving maximum hyperemia when calculating the FFR (with a cutoff FFR value again of 0.8).[22]

It was reported that intravenous administration of adenosine was better in inducing hyperemia than intracoronary bolus in some patients.[16,17] In our study, we compared intracoronary adenosine bolus injection to intravenous infusion and found numerically higher values (0.008-0.015) for boluses. Therefore, when sufficient hyperemia is doubtful during intracoronary bolus of adenosine, especially with FFR values of 0.81 to 0.83, the results should be confirmed with adenosine venous infusion (FIGURE 5).

Our study has several limitations. The FFR procedures were performed by 2 experienced operators at a single center, but interobserver variability was not assessed. Patients with ostial lesions of the right coronary artery or left main coronary artery as well as tandem lesions were not enrolled. We did not have any crossovers in the study.

In conclusion, FFR values achieved with intracoronary boluses of adenosine are very similar, but not identical, to those obtained using intravenous adenosine administration. The values of FFR may vary between escalating doses of intracoronary boluses and intravenous infusion.

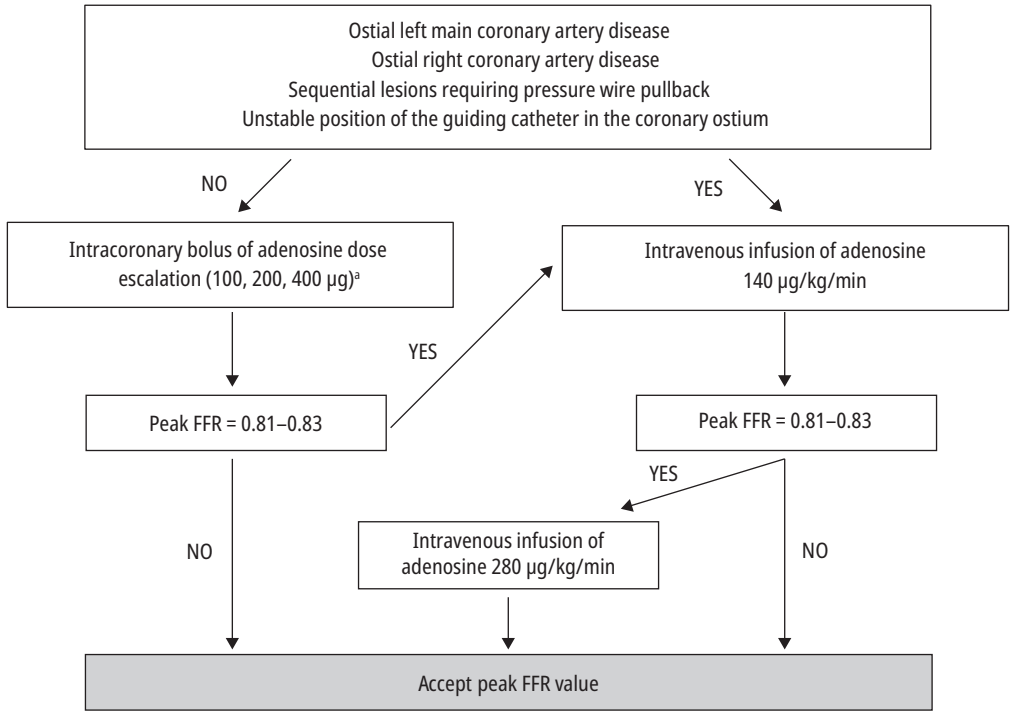

FIGURE 5 Suggested algorithm for maximal hyperemia induction with intracoronary boluses or infusion of adenosine for fractional flow reserve assessment

a If peak fractional flow reserve is below or equals 0.80 with 2 consecutive boluses, accept peak fractional flow reserve value.
Abbreviations: see FIGURE 1

There might be no need for increasing adenosine bolus dose from 400 μg to 600 μg.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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