Comparison of Intracoronary Versus Intravenous Administration of Adenosine for Measurement of Coronary Fractional Flow Reserve

Christian Schlundt, MD; Christian Bietau, MD; Lutz Klinghammer, MD; Ricarda Wiedemann; Harald Rittger, MD; Josef Ludwig, MD; Stephan Achenbach, MD

Background—Measurement of fractional flow reserve (FFR) constitutes the current gold standard to evaluate the hemodynamic significance of coronary stenoses. Limited data validate the intracoronary application of adenosine against standard intravenous infusion. We systematically compared FFR measurements during intracoronary and intravenous application of adenosine about agreement and reproducibility.

Methods and Results—We included 114 patients with an intermediate degree of stenosis in coronary angiography. Two FFR measurements were performed during intracoronary bolus injection (40 μg for the right and 80 μg for the left coronary artery, FFRic), and 2 FFR measurements during continuous intravenous infusion of adenosine (140 μg/kg per minute, FFRiv). FFR value, the time to reach FFR and patient discomfort (on a subjective scale from 0 for no symptoms to 5 for maximal discomfort) were recorded for each measurement. Mean time to FFR was 100±27 s for continuous intravenous infusion versus 23±14 s for intracoronary bolus administration of adenosine (P<0.001). Reported discomfort after intracoronary application was significantly lower compared with intravenous adenosine (subjective scale >0 in 35.1% versus 87.7% of the patients; P<0.001). Correlation between FFRic and FFRiv was extremely close (r=0.99; P<0.001) with no systematic bias in Bland–Altman analysis (bias 0.002 [confidence interval, −0.001 to 0.005]) and low intermethod variability (1.56%). Intramethod variability was not different between intravenous and intracoronary administration (1.47% versus 1.33%; P=0.5).

Conclusions—Intracoronary bolus injection of adenosine (40 μg for the right and 80 μg for the left coronary artery) yields identical FFR results compared with intravenous infusion (140 μg/kg per minute), while requiring less time and offering superior patient comfort. (Circ Cardiovasc Interv. 2015;8:e001781. DOI: 10.1161/CIRCINTERVENTIONS.114.001781.)

Key Word: myocardial fractional flow reserve

Pressure-derived determination of fractional flow reserve (FFR) is the gold standard to invasively assess the hemodynamic relevance of coronary artery stenosis.1,2 FFR is determined by the ratio of the mean arterial pressures proximal (P<sub>a</sub>) and distal (P<sub>d</sub>) to a coronary stenosis. According to clinical trials, patients do not benefit from revascularization of coronary artery lesions with an FFR value >0.80,3 whereas revascularization is associated with reduced event rates as compared with medical therapy alone if FFR is ≤0.80.4 FFR measurements require maximal coronary vasodilatation. This is typically achieved by continuous intravenous infusion of adenosine at a rate of 140 μg/kg per minute. Alternatively, intracoronary injection of adenosine has been described. Suggested dosages for intracoronary adenosine ranged from 6 to 720 μg.1,5–7 Most frequently, a bolus injection of 40 μg adenosine for the right coronary artery and 80 μg for the left coronary artery has been used.8–10 There is only limited data, which validates the intracoronary application of adenosine against standard intravenous infusion. We therefore systematically compared FFR measurements during intracoronary and intravenous application of adenosine in 114 consecutive patients and evaluated both the agreement between the 2 application routes as well as the intrapatient variability of each method.

Study Population

One hundred fourteen consecutive patients met the inclusion criteria for this prospective single-center study, the recruitment period was from February to October 2013 (Figure 1). Patients were eligible for study inclusion if they underwent elective invasive coronary angiography for diagnostic purposes, were at least 18 years of age, and had at least 1 coronary artery stenosis of intermediate angiographic severity (maximum diameter stenosis 50% to 75% as determined by quantitative coronary analysis) in a segment suitable for FFR measurement.
WHAT IS KNOWN

• A fractional flow reserve value ≤0.8 indicates downstream ischemia and identifies lesions that benefit from revascularization.
• Currently fractional flow reserve measurements are typically performed with a continuous intravenous infusion of adenosine at a rate of 140 μg/kg per minute.
• Intracoronary bolus injection of adenosine substantially facilitates fractional flow reserve measurement in clinical practice but is insufficiently validated against continuous intravenous infusion.

WHAT THE STUDY ADDS

• Intracoronary bolus adenosine in fixed doses (40 μg for the right and 80 μg for the left coronary artery) is as safe and effective as the standard continuous infusion for assessment of fractional flow reserve.
• Advantages of the bolus approach include reduced patient discomfort, faster measurement, reduced logistic effort in the catheterization laboratory and lower cost.

Exclusion criteria were contraindications for adenosine application (chronic obstructive pulmonary disease, asthma, atrioventricular block>1st degree in resting ECG), primary percutaneous coronary intervention for acute coronary syndrome, and an unstable hemodynamic condition. Patients with ostial stenoses of the left main or the right coronary artery were also excluded because the inability to obtain stable guiding catheter positioning for intracoronary adenosine injection would preclude reliable assessment of FFR with intracoronary bolus injection. Patients were randomized about the sequence of intracoronary versus intravenous adenosine application. Informed consent was obtained from all patients. The research protocol was approved by the Institutional Review Board and the study complies with the Declaration of Helsinki.

Coronary Angiography

Selective coronary angiography was performed via either the radial or femoral approach, using 6-French diagnostic or guiding catheters. A intracoronary bolus injection of 0.2 mg nitroglycerin was administered routinely before angiography of the left and right coronary artery. The stenosis degree of all lesions included in the analysis was evaluated by contour-based quantitative coronary analysis after catheter-based calibration.

FFR Protocol

Adenosine Administration

Adenosine was administered either as a continuous intravenous infusion (FFRiv) or intracoronary bolus injection (FFRic). For intravenous infusion, 150 mg adenosine were diluted in 50 mL saline solution. An injection pump was used and the flow rate was individually adapted to achieve a dose of 140 μg/kg per minute. Intravenous infusion was performed through a 5-French sheath placed in the femoral vein. For intracoronary bolus injection, either 80 μg adenosine (left coronary artery) or 40 μg adenosine (right coronary artery) were diluted in 10 mL saline solution, which was rapidly injected manually through the guiding catheter, immediately followed by 10 mL pure saline solution. Stable guiding catheter position in the coronary ostium was ascertained to ensure complete delivery of adenosine to the artery.

Statistical Analyses

Categorical variables are shown in proportions, continuous data as mean±SD or as quartiles. For basic statistical analyses, SPSS Statistics (version 21.0, IBM, New York, NY) was used. P<0.05 was defined as significant. Intraindividual agreements between the 2 consecutive measurements of pressure-derived FFR, as well as between the 2 methods (intravenous and intracoronary) were analyzed using the Bland–Altman method and McNemar test for paired data. Mean difference between 2 measurements (bias), 95% limits of agreement, which are defined as the mean difference±1.96 SD of the differences, and confidence intervals (CIs) for the bias were calculated.

For comparison between intravenous and intracoronary FFR results, mean FFR was calculated for the 2 particular intravenous and intracoronary measurements and variability was defined as mean absolute difference, reported in percent.

To test for equivalence of the intracoronary and the intravenous approach, the two one-sided test was used.11,12 A difference of δ=0.005 between 2 FFR results was predefined. Such a small difference was considered not to have a clinically relevant impact on interpretation and classification of FFR results. To compare paired binary data for intravenous and intracoronary adenosine administration, we used McNemar χ² test.

Comparison of means for intraindividual variability and time to FFR was calculated using the paired t test. To compare discomfort rating during adenosine application McNemar χ² test for paired data was applied.

Figure 1. Flowchart of patient recruitment.
Results

Patient Characteristics

Of the 114 consecutive patients, 75% were men. Mean age was 67±10 years (Tables 1 and 2). Twenty-six patients (23%) had undergone previous percutaneous coronary intervention. Eleven percent of the patients had a left ventricular ejection fraction ≤35% and 7% were in atrial fibrillation.

Mean stenosis degree of the target lesion was 67±10%. Of all target lesions, 4% were located in the distal left main coronary artery, 50% in the left anterior descending, 17% in the left circumflex, and 18% in the right coronary artery.

FFR Measurements

Intravenous Adenosine Infusion

Mean resting $P_d/P_a$ was 0.93±0.07 with a range from 0.63 to 1.0. Mean difference between the 2 baseline measurements was −0.003 (95% CI, −0.006 to −0.001) with a variability of 1%. The mean FFR value determined by intravenous infusion of adenosine was 0.84±0.11. In 34 patients, FFR during the first intravenous infusion of adenosine was $\leq$0.80 (mean, 0.70±0.10), whereas in 80 patients, FFR was >0.80 (mean, 0.90±0.05). The 2 consecutive FFR measurements during intravenous infusion agreed closely with a mean difference of −0.003±0.016 (95% CI, −0.006 to 0), a mean absolute difference of 0.01±0.01, variability of 1.47%, and a correlation coefficient of $r=0.99$ (Figure 2). Three patients (2.6%) were classified differently based on the 2 independent FFR measurements during intravenous adenosine infusion.

Intracoronary Adenosine Injection

Mean baseline $P_d/P_a$ was 0.93±0.07 with a range from 0.61 to 1.0. Intrapatient agreement between the 2 intracoronary

Table 1.  Study Population and Procedural Data

<table>
<thead>
<tr>
<th>Patients</th>
<th>n=114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.1±10.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>86 (75)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81±14</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>27±4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53±11</td>
</tr>
<tr>
<td>Previous Q wave infarction</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>47 (42)</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (29)</td>
</tr>
<tr>
<td>Smoking</td>
<td>50 (44)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (82)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>84 (74)</td>
</tr>
<tr>
<td>Family history</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Procedural data</td>
<td></td>
</tr>
<tr>
<td>Approach</td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>41 (36)</td>
</tr>
<tr>
<td>Radial</td>
<td>73 (64)</td>
</tr>
<tr>
<td>Values are mean±SD or n (%). BMI indicates body mass index; and LVEF, left ventricle ejection fraction.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.  Fractional Flow Reserve Target Vessel and Segment

<table>
<thead>
<tr>
<th>FFR Target Vessel</th>
<th>FFR Target Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM (distal)</td>
<td>5 4 (4)*</td>
</tr>
<tr>
<td>LAD</td>
<td>57 (50)*</td>
</tr>
<tr>
<td>6 32 (28)</td>
<td></td>
</tr>
<tr>
<td>7 22 (19)</td>
<td></td>
</tr>
<tr>
<td>8 3 (3)</td>
<td></td>
</tr>
<tr>
<td>RD</td>
<td>9 8 (7)</td>
</tr>
<tr>
<td>LCX</td>
<td>19 (17)*</td>
</tr>
<tr>
<td>11 8 (7)</td>
<td></td>
</tr>
<tr>
<td>13 11 (10)</td>
<td></td>
</tr>
<tr>
<td>Obtuse marginal</td>
<td>14/15 3 (3)</td>
</tr>
<tr>
<td>RIM</td>
<td>12 1 (1)</td>
</tr>
<tr>
<td>RCA</td>
<td>21 (18)*</td>
</tr>
<tr>
<td>1 6 (5)</td>
<td></td>
</tr>
<tr>
<td>2 9 (8)</td>
<td></td>
</tr>
<tr>
<td>3 6 (5)</td>
<td></td>
</tr>
<tr>
<td>RPLD</td>
<td>4 1 (1)</td>
</tr>
<tr>
<td>Values are mean±SD or n (%). FFR indicates fractional flow reserve; LAD, left anterior descending; LCX, circumflex artery; LM, left main; RCA, right coronary artery; RD, diagonal branch; RIM, intermediate branch; and RPLD, right posterolateral branch.</td>
<td></td>
</tr>
</tbody>
</table>

baseline $P_d/P_a$ was close with a mean difference between the 2 baseline measurements of 0.003 (95% CI, 0–0.007) and a variability of 1.4%. The mean FFR value determined by intracoronary injection of adenosine was 0.84±0.11. In 33 patients, FFR was $\leq$0.80 (mean, 0.70±0.10), whereas in 81 patients, FFR was >0.80 (mean, 0.90±0.05). The 2 consecutive FFR measurements during intracoronary bolus injection agreed closely with a mean difference of 0.002±0.018 (95% CI, −0.002 to 0.005), a mean absolute difference of 0.011±0.015, variability of 1.33%, and a correlation coefficient of $r=0.99$ (Figure 3). Two patients (1.8%) were classified differently based on the 2 independent FFR measurements during intracoronary adenosine injection.

Comparison of Intravenous and Intracoronary Administration of Adenosine

FFR measurements with intravenous infusion and intracoronary injection of adenosine correlated closely ($r=0.99$; Figure 4). Bias was 0.002±0.017 (95% CI, −0.001 to 0.005). Variability was 1.56%. With regard to an FFR threshold of 0.80, 3 patients (2.6%) were classified differently based on intravenous and intracoronary administration of adenosine. The mean intraventricular variability between the 2 intravenous measurements was $−0.35±2.23\%$ with a mean absolute difference of 1.47±1.71% and a range from −4.55% to 3.08%. The mean intraventricular variability between the 2 repeated intracoronary measurements was 0.14±2.26%, with a mean absolute value of 1.33±1.82% and a range from −4.49% to 4.38%. The absolute variabilities of intravenous measurements and of intracoronary measurements were not significantly different.
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(P=0.50; t test for paired samples). Using McNemar χ² test to compare paired binary data for intravenous and intracoronary adenosine administration, there was no significant difference between the 2 methods of drug application (P=0.62). Using two one-sided test and a 90% CI for bias between intravenous and intracoronary measurements, equivalence between the 2 methods was established for a δ<0.0039 (Figure 4).

The mean time to FFR for intravenous adenosine was longer compared with intracoronary bolus injection (100±27 s versus 23±14 s; P<0.001). Patients more frequently reported any subjective discomfort after intravenous application of adenosine (frequency of a rating >0: 88% versus 35%; P<0.001).

Patients With Highly Reduced Left Ventricular Ejection Fraction

Severely reduced left ventricular ejection fraction may affect FFR measurements because of elevated diastolic pressure. Thirteen patients (11.3%) had a left ventricular ejection fraction ≤35% and were analyzed as a separate subgroup. In these patients, correlations between intravenous and intracoronary measurements of FFR were as close as for the entire cohort: mean baseline $P_d/P_a$ was 0.93±0.09 before the 2 intravenous measurements and 0.92±0.09 before the 2 intracoronary measurements. Mean hyperemia FFR was 0.84±0.13 for both intravenous and intracoronary application of adenosine. Variability between the 2 respective measurements was low: the mean difference was −0.005±0.008 (95% CI, −0.009 to 0) before the 2 intravenous measurements and −0.001±0.016 (95% CI, −0.009 to 0.007) before the 2 intracoronary measurements with a variability of 0.78% and 1%, respectively. Intravenous FFR measurements differed with a mean of −0.007±0.017 (95% CI, −0.016 to 0.001) and had a variability of 1.66%. FFR values obtained after intracoronary bolus injection differed with a mean of 0.003±0.001 (95% CI, −0.002 to 0.007) and had a variability of 0.8% (P=n.s.).

Discussion

FFR-guided percutaneous coronary intervention represents an increasingly important diagnostic tool for revascularization
Intracoronary vs Intravenous Adenosine for FFR

Figure 4. Comparison between fractional flow reserve (FFR) measurements after intravenous (i.v.) and intracoronary (i.c.) administration of adenosine. A, Correlation between mean FFR after i.v. (FFRv) and i.c. (FFRc) administration of adenosine. B, Bland–Altman plot for the intrapatient agreement of FFR after continuous i.v. and i.c. bolus administration of adenosine. Lines in Bland–Altman plot: black dashed line, mean difference (bias); brown solid line, ±1.96 SD; bold black dashed lines, ± 95% confidence interval. C, Box-plot of two one-sided test for ΔFFR. Equivalence between i.v. and i.c. FFR measurements is established for a >0.0039.

Current guidelines recommend intravenous infusion of adenosine at a rate of 140 μg/kg per minute to determine FFR of intermediate coronary artery stenosis.2,20,21 Intracoronary application of adenosine is a possible alternative, but the optimal dose has not been clarified and intracoronary bolus injection has not been systematically compared with intravenous administration on a large scale. In a series of 114 consecutive patients, we systematically compared intravenous and intracoronary adenosine application to induce hyperemia and found a close correlation between FFR measurements performed by intravenous infusion or intracoronary injection of adenosine at a dose of 80 μg for the right and 40 μg for the right coronary artery. Also, the variability of repeated measurements with either method was low and there was no difference about reproducibility with intracoronary and intravenous administration of adenosine. FFR measurements based on intracoronary bolus injection of adenosine were faster and induced less patient discomfort than intravenous infusion.

In previous trials, intracoronary adenosine has been administered in doses ranging from 6 to 720 μg, and the results suggest a dose–response relationship for the induction of maximum hyperemia and determination of functional severity of a coronary stenosis.6–8,22

In a cohort of 52 patients with 60 lesions, Jeremias et al23 described an underestimation of FFR after intracoronary injection of adenosine in 8.3% of patients, with the intracoronary FFR value differing by >0.05 compared with intravenous FFR. However, the trial was performed with substantially lower doses of intracoronary adenosine (15–24 μg) than the dose we used in our investigation. However, 2 trials used substantially higher intracoronary doses and reported that intracoronary injection may be more sensitive to detect functional ischemia than intravenous administration of adenosine: López-Palop et al24 used intracoronary bolus of 60 to −600 μg in 102 patients with 108 lesions and while a dose of 60 μg rendered fewer hemodynamically relevant classifications than intravenous administration of adenosine (27.5% versus 31.5%; P<0.001), ≈20% more pathological FFR results were observed with 300 and 600 μg intracoronary bolus compared with intravenous infusion (36.2% and 37.6% versus 31.5%, respectively; P<0.05 for each). De Luca et al9 used similar doses of 60 to 720 μg as intracoronary bolus in 46 patients (50 lesions) and, using an FFR threshold of 0.75, showed substantially more frequent detection of ischemia with higher doses of adenosine (51.2% with 720 μg IC versus 30% with 60 μg IC).

In some early validation studies, central venous pressure (Pv) was included in the FFR equation as follows: FFR=(P−Pd)/(Pv−Pd).25,26 Pv depends on end-diastolic left ventricular pressure and might be higher in patients with reduced systolic left ventricular function. We assumed right atrial pressure to be equal during all FFR measurements performed in 1 patient. We repeated intravenous measurements as well as intracoronary measurements and showed stable FFR values for both routes of adenosine application suggesting stable hemodynamic condition throughout the procedure. Taking into account that high atrial pressure (supposed to be present in 11.3% of our study population with left ventricular ejection fraction ≤35%) alters FFR results, decision making on percutaneous coronary intervention might have been different.27 Whether the results of FFR in patients with impaired left ventricular function are reliable, the correlation of the FFR values between the 2 routes of administration of adenosine was even as close as in patients with normal left ventricular function in our cohort.

Adenosine bolus of 40 μg for the right and 80 μg for the left coronary artery are the suggested dosages for intracoronary bolus injection of adenosine26–30 and our data support these doses by demonstrating a close agreement of FFR results obtained with this regimen compared with a continuous
adenosine infusion at a dose of 140 μg/kg per minute—the dose that was used in the major randomized outcome trials.\textsuperscript{3,4,11} Measurement variability of both the methods was not different, results were obtained faster by intracoronary administration, and subjective patient discomfort was less so that the results of our trial support the use of intracoronary adenosine to measure FFR and make revascularization decisions for intermediate coronary artery stenoses. A potential caveat is the fact that ostial lesions cannot be reliably assessed by intracoronary injection and were excluded from our analysis.

Recently, the potential use of \( P/P_a \) measurements to estimate FFR without any administration or adenosine or other drugs has been suggested. They include the instantaneous wave-free ratio and the simple assessment of \( P/P_a \) at rest during the entire cardiac cycle.\textsuperscript{2,11} However, such measurements can only eliminate the need for hyperemia in a subset of patients with high or low resting values, whereas medication remains necessary in patients whose adenosine-free measurements are in a gray zone. Thus, our study results remain pertinent even if adenosine-free measurements are performed first to limit the number of patients requiring maximum vasodilatation.

**Limitations**

Our trial has several limitations. For example, only one standard dose of intracoronary adenosine was used for all patients, and we did not compare the effect of increasing intracoronary adenosine dosages on FFR results. By necessity, operators were not blinded to the mode of adenosine administration. We did not include a sufficiently large number of patients to identify subgroups, for example, patients after revascularization or patients in atrial fibrillation, in whom intracoronary and intravenous administration of adenosine might display larger differences than in the overall patient cohort. The most important limitation may be that we directly compared FFR measurements obtained by intravenous and intracoronary administration of adenosine, but we did not compare patient outcome of an FFR-based revascularization strategy after randomization to either intravenous or intracoronary based determination of FFR—neither about symptom relief nor about cardiovascular events during follow-up. However, when considering the extremely close agreement of FFR values during intravenous and intracoronary adenosine administration, and the relatively low event rates after coronary revascularization, the number of included patients would need to be extremely high to identify, or rule out, systematic differences. In our opinion, the close agreement between FFR values obtained after intracoronary adenosine injection and FFR values obtained during intravenous infusion at the dosage that was used in the major outcome trials constitutes a sufficiently strong foundation to soundly justify the clinical use of intracoronary adenosine injection for clinical purposes. A potential downside for clinical applications may be the fact that mapping of the coronary vessels by slow pullback of the FFR wire during continuous hyperemia is not possible when intracoronary bolus injection is used. However, such a pullback is not required in all patients and clinicians can make a case-by-case decision, on which method to use in a given individual.

About the cardiovascular risk factors, detailed information about lipid status, waist circumference and metabolic syndrome unfortunately was not available.

**Conclusions**

Our data convincingly demonstrate that both about the obtained FFR values, as well as about intrapatient variability, intracoronary administration of adenosine is not inferior to intravenous infusion. Given the logistic advantages of intracoronary bolus injection, as well as increased patient comfort and lower cost, intracoronary adenosine injection may become the preferred route of administration in the future.

**Disclosures**

Dr Achenbach obtained research grants from Siemens and Abbott. Dr Schlundt is speaker honoraria of Siemens and Abbott. Dr Ritter is speaker honoraria and obtained proctor Lecture Fees from St Jude Medical. The other authors report no conflicts.

**References**


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Circ Cardiovasc Interv. 2015;8:
doi: 10.1161/CIRCINTERVENTIONS.114.001781
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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