Comparison of Hyperemic Efficacy Between Central and Peripheral Venous Adenosine Infusion for Fractional Flow Reserve Measurement

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Background—Maximal hyperemia is a prerequisite for the accurate measurement of fractional flow reserve (FFR). Although continuous infusion of adenosine via the femoral vein is considered to be the gold standard, this requires an additional invasive procedure for femoral vein access and is difficult to use during transradial coronary catheterization. We performed this prospective study to evaluate the feasibility and efficacy of peripheral intravenous infusion of adenosine for FFR measurement.

Methods and Results—Seventy-one patients were prospectively enrolled, and FFR was measured using a 0.014-inch coronary pressure wire. Hyperemic efficacy of adenosine was compared among intracoronary bolus injection and continuous IV infusion (140 μg/min/kg) via the femoral and via the forearm vein. In 20 patients, hyperemic mean transit time and index of microcirculatory resistance were also measured. Mean FFR after bolus administration of adenosine was 0.81 ± 0.10. As compared with femoral vein infusion (FFR: 0.80 ± 0.10), hyperemic efficacy of forearm vein infusion of adenosine (FFR: 0.80 ± 0.11) was not inferior (P for noninferiority = 0.01). The number of functionally significant stenoses (FFR < 0.75) was also not different between the 2 methods (femoral vein versus forearm vein; 17 (25.0%) versus 17 (25.0%), P = 1.0). Both hyperemic mean transit time and index of microcirculatory resistance were not different between the 2 routes of adenosine infusion. Additional bolus injection of adenosine during IV infusion did not improve the hyperemic efficacy but increased the risk of atrioventricular block.

Conclusions—This study suggests that continuous intravenous infusion of adenosine via the forearm vein is a convenient and effective way to induce steady-state hyperemia for invasive physiological measurements.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01070420.

Key Words: adenosine ■ fractional flow reserve ■ hyperemia

Fractional flow reserve (FFR) is an invasive method used to evaluate the functional significance of coronary stenosis, and FFR-guided revascularization strategy is reported to be better than angiography-guided strategy in patients with coronary artery disease.1–4 FFR is obtained by the ratio of the hyperemic distal coronary artery pressure to the aortic pressure. As the distal coronary artery pressure is determined by epicardial stenosis and microvascular resistance, achievement of maximal hyperemia is a prerequisite for the accurate measurement of FFR.

Continuous intravenous (IV) infusion of adenosine through the femoral vein has been used as a standard method for the induction of hyperemia for FFR measurement,5–8 however, this method needs a large central venous access, which requires additional time, cost, and risk of complication. Moreover, this method is very difficult to use during transradial coronary catheterization procedures, which have become more popular in recent years.9–11

Therefore, we sought to evaluate the feasibility and efficacy of continuous peripheral IV infusion of adenosine in the achievement of steady-state maximal coronary hyperemia for the measurements of FFR and index of microcirculatory resistance. We also tested the safety and efficacy of additional bolus injection of adenosine during IV fusion of adenosine.
WHAT IS KNOWN

- Intravenous infusion of adenosine through the central vein is recommended to induce steady-state hyperemia for invasive physiological measurements; however, this method requires an additional procedure for femoral vein access and is difficult to use during transradial coronary catheterization procedures.

WHAT THE STUDY ADDS

- Intravenous infusion of adenosine via the forearm vein is a convenient and effective way to induce steady-state hyperemia for invasive physiological measurements.
- Additional bolus injection of adenosine during intravenous infusion increases the risk of prolonged atrioventricular block. Also, adding the bolus injection does not induce additional hyperemic efficacy.

Methods

Study Population

Patients with angiographically intermediate stenosis in a major epicardial coronary artery were prospectively and consecutively enrolled. Patients with acute myocardial infarction, regional wall motion abnormalities, reduced left ventricular systolic function (<50%), primary valvular or myocardial disease, or contraindication to adenosine were excluded. The study protocol was approved by the institutional review board of Seoul National University Hospital, and all patients gave informed consent to participate in the study.

Study Protocol

FFR Measurement

Coronary angiography was performed with the standard femoral approach. For adenosine infusion, the femoral vein was accessed by a 6-French sheath and the forearm vein by an 18-gauge IV catheter. A 0.014-inch pressure guide wire (St. Jude Medical) was advanced distal to the stenosis through a 6F or 7F guide catheter without side holes. Intracoronary (IC) nitroglycerin (0.1 to 0.2 mg) was administered before each FFR measurement. Distal coronary pressure (Pd) and proximal coronary pressure (Pa) were measured at baseline and at maximal hyperemia, and then, FFR was calculated by dividing mean Pd by mean Pa during maximal hyperemia. Maximal hyperemia was presumed to be occurring at the same time the maximal drop in distal pressure was identified. The time to maximal hyperemia (time needed to reach >90% of the minimal value of Pd/Pa with adenosine infusion) and plateau time (the time hyperemic efficacy remained at >90% of its maximal value after stopping of adenosine infusion) were also measured.6 Hyperemic mean transit time was measured using 3 injections of 3 mL of room temperature saline under maximal hyperemia in 20 patients. The index of microcirculatory resistance was calculated as Pd at maximal hyperemia multiplied by the hyperemic mean transit time.12-14

Protocol of Hyperemic Stimuli

The following hyperemic stimuli using adenosine were successively administered: IC bolus administration (80 μg in left coronary artery and 40 μg in right coronary artery), continuous IV infusion (140 μg/min/kg) via femoral vein, and IV infusion via forearm vein. To evaluate the safety and efficacy of an additional IC bolus injection during continuous IV infusion of adenosine, IC bolus of adenosine was given during maximal hyperemia with continuous IV infusion of adenosine. To measure plateau time, Pa and Pd were continuously recorded after stopping the infusion. Each hyperemic stimulus was given when Pa, Pd, and heart rate had returned to their baseline values. To exclude the possible influence of the sequence of infusion, the forearm vein infusion was followed by femoral vein infusion in the second half of patients. Visual analog scale pain score was assessed during the continuous infusion of adenosine.

Quantitative Coronary Angiography

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

Statistical Analysis

From results of a previous study,15 we assumed FFR in patients with intermediate stenosis to be 0.79±0.07 with femoral vein infusion of adenosine. The difference in FFRs between femoral and peripheral vein infusion was assumed to be 0.0±0.0098. Using a noninferiority design with a noninferiority margin of 0.03 and an alpha value of 0.05, 68 patients would be required for enrollment to have 80% power. To allow for an estimated dropout rate of 5%, a total of 71 patients were included in this study.

Continuous variables were expressed as mean±SD, and categorical variables as a frequency and a percentage. Categorical variables were analyzed by the use of Cochran’s Q test with Bonferroni correction, while continuous variables were assessed by paired t test. FFR with 3 different methods of adenosine administrations were compared by repeated measures ANOVA. Linear regression was calculated for FFR with central and peripheral infusion of adenosine. The mean±standard deviation of the signed differences between measurements of FFR with central and peripheral infusion of adenosine was used as an index of agreement between measurements.16 A P value of <0.05 was considered statistically significant, and all statistical analyses were performed using SPSS, version 15.0 (SPSS).

Results

Between June 2009 and July 2010, 71 patients were enrolled, and FFR comparisons were available in 68 patients. Two patients were excluded owing to prolonged AV block with IC bolus injection of adenosine and 1 owing to a protocol violation. Clinical and angiographic characteristics of study subjects are presented in Table 1.
of 0.02 (Figure 3). Two cases with forearm vein infusion yielded a difference in FFR of 0.03 compared with femoral vein infusion.

The number of functionally significant stenoses is shown in Table 3, and there were no significant between-group differences. FFR was 0.75 in 14 (20.1%) patients after IC bolus administration and in 17 (25.0%) patients after both femoral and forearm vein infusion of adenosine. FFR was 0.80 in 28 (41.2%), 32 (47.1%), and 30 (44.1%) lesions with IC bolus, femoral vein infusion, and forearm vein infusion, respectively. Among 30 lesions with an FFR range of 0.75 to 0.85 with femoral vein infusion, FFR was 0.80 in 16 lesions with femoral vein infusion and 14 lesions with forearm vein infusion.

Table 1. Baseline Characteristics (n=68)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.1±8.9</td>
</tr>
<tr>
<td>Male (%)</td>
<td>47 (75.8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.9±9.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.2±8.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8±2.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>35 (56.5)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>25 (40.3)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>Clinical diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>42 (67.7)</td>
</tr>
<tr>
<td>Silent ischemia</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>61.1±6.6</td>
</tr>
<tr>
<td>Studied artery</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA</td>
<td>44/9/15</td>
</tr>
<tr>
<td>Quantitative coronary angiography</td>
<td></td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>Percent diameter stenosis, %</td>
<td>57.2±10.6</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>3.0±0.5</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LV, left ventricular; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2. Hyperemic Efficacy Among 3 Different Methods of Adenosine Administration

<table>
<thead>
<tr>
<th>Method</th>
<th>Bolus</th>
<th>Central Infusion</th>
<th>Peripheral Infusion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.81±0.10</td>
<td>0.80±0.10</td>
<td>0.80±0.11</td>
<td>0.22*</td>
</tr>
<tr>
<td>Time to maximal hyperemia, s</td>
<td>NA</td>
<td>38.7±17.9</td>
<td>53.7±22.8</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Plateau time, s</td>
<td>NA</td>
<td>16.6±13.5</td>
<td>17.4±12.9</td>
<td>0.46†</td>
</tr>
<tr>
<td>N=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemic mean transit time, s</td>
<td>NA</td>
<td>0.23±0.14</td>
<td>0.22±0.13</td>
<td>0.55†</td>
</tr>
<tr>
<td>IMR</td>
<td>NA</td>
<td>11.8±10.9</td>
<td>11.3±9.2</td>
<td>0.58†</td>
</tr>
</tbody>
</table>

FFR indicates fractional flow reserve; IMR, index of microcirculatory resistance; NA, not available.

*By repeated measures ANOVA.
†By paired t test.

Additional Bolus Injection During IV Infusion of Adenosine

Additional bolus injection of adenosine during IV infusion was performed in 22 patients. It was not used in the other patients owing to the risk of AV block, as this method caused prolonged AV block (>3 seconds) in 2 patients. Neither of these patients had AV block with bolus injection alone. Figure 4 shows the FFR in each of the 20 patients, with 5 different methods of adenosine administration. Adding the bolus injection to the continuous IV infusion did not have additional hyperemic efficacy (femoral vein IV versus IV: 0.78±0.14 versus 0.78±0.12 (P=0.52) and forearm vein IV versus IV+IC; 0.78±0.14 versus 0.77±0.12 (P=0.22)).

Hemodynamic Changes and Adverse Events During IV Infusion of Adenosine

The percent changes in systemic blood pressure and in heart rate were not different between femoral vein and forearm vein infusions of adenosine (Table 4). There was a slight difference in visual analog scale pain score in the 2 groups (femoral

Figure 1. Individual values of fractional flow reserve with 3 different methods of adenosine administration.

Figure 2. Correlation of fractional flow reserve between central and peripheral adenosine administration.
vein versus forearm vein: 2.2±2.5 versus 2.1±2.4, *P*=0.01). Only 1 patient had transient AV block during adenosine infusion.

**Discussion**

Central venous infusion of adenosine has been the gold standard method of hyperemia induction for FFR measurement. This method can induce steady-state hyperemia and has more reliable hyperemic efficacy than IC bolus injection; however, it requires an additional procedure for femoral vein access and is difficult to use during transradial coronary catheterization procedures.

Yoon et al described IC continuous infusion of adenosine through the microcatheter and found that its hyperemic efficacy is comparable to IV infusion of adenosine via the femoral vein; however, this method requires insertion of an additional catheter into the coronary artery, and the catheter itself can reduce the proximal pressure when a small caliber guide catheter is used. Another alternative access for adenosine infusion can be a large peripheral vein. Lindstaedt et al compared the hyperemic efficacy of adenosine infusion between the femoral vein and the antecubital vein. They found that a 140 μg/kg/min infusion of adenosine via the antecubital vein was slightly less effective than the femoral vein infusion; however, the mean difference of FFR between the antecubital vein and femoral vein infusions was just 0.0126. In a study by de Bruyne et al, hyperemic efficacy of adenosine was not different between the central vein and peripheral vein infusions, and increasing the dose to 240 μg/kg/min did not improve the vasodilatory action of adenosine.

We selected the forearm vein as a route of adenosine infusion, as this site is the most common IV site in patients undergoing coronary catheterization. To avoid inadequate hyperemia, we used only an 18-gauge needle and did not use the access around and distal to the wrist, as the flow from this site can be influenced by position of wrist and external compression. In our study, forearm vein infusion of adenosine was as effective as femoral vein infusion in the induction of maximal hyperemia. There was no difference in mean FFR between these 2 methods of adenosine administration and the number of functionally significant stenoses was not different between femoral vein and forearm vein infusions of adenosine; however, in patients with gray-zone FFR, there seems to be a possibility of underestimation of lesion severity with forearm vein infusion. In our study, among 30 lesions with an FFR range of 0.75 to 0.85 with femoral vein infusion, FFR was <0.80 in 16 lesions with femoral vein infusion and 14 lesions with forearm vein infusion; however, this difference was not statistically significant.

In addition to FFR, the mean hyperemic transit time and index of microcirculatory resistance were also compared, as these indices are now commonly used to assess microvascular function. We found that there was no difference in these indices between either method of adenosine administration. The time to maximal hyperemia was longer with forearm vein infusion of adenosine than with the femoral vein infusion. In our study, the mean difference of time to maximal hyperemia was 15 seconds, comparable to that in a study by de Bruyne.

**Table 3. No. of Functionally Significant Lesions According to 3 Different Methods of Adenosine Administration**

<table>
<thead>
<tr>
<th>Bolus</th>
<th>Central Infusion</th>
<th>Peripheral Infusion</th>
<th>Cochran Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR&lt;0.8</td>
<td>28 (41.2%)</td>
<td>32 (47.1%)</td>
<td>30 (44.1%)</td>
</tr>
<tr>
<td>FFR&lt;0.75</td>
<td>14 (20.6%)</td>
<td>17 (25.0%)</td>
<td>17 (25.0%)</td>
</tr>
</tbody>
</table>

FFR indicates fractional flow reserve.

*No significant between-group differences by Cochran Q test.

**Table 4. Hemodynamic Changes and Pain Score With Adenosine Administration**

<table>
<thead>
<tr>
<th></th>
<th>Central Infusion</th>
<th>Peripheral Infusion</th>
<th><em>P</em> Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ Blood or blood pressure (%)</td>
<td>−9.8±8.0</td>
<td>−9.6±6.3</td>
<td>0.86</td>
</tr>
<tr>
<td>∆ Heart of heart rate (%)</td>
<td>5.5±6.7</td>
<td>7.0±7.2</td>
<td>0.07</td>
</tr>
<tr>
<td>VAS pain score</td>
<td>2.2±2.5</td>
<td>2.1±2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>AV block (%)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

VAS indicates visual analog scale; AV, atrioventricular.

*By paired *t* test.
et al. These results suggest that the infusion time should be long enough (>1 minute) when the forearm vein is selected as a route of adenosine infusion for invasive physiological measurements.

It was reported that IC administration of adenosine induced better hyperemia than IV infusion in some patients. In our study, FFR was lower by >0.1 with IC bolus administration than with IV infusion in 2 patients. Therefore, when sufficient hyperemia is doubtful during IV infusion of adenosine, adding an IC bolus injection can be a possible option. We initially included this method (IC bolus+IV infusion) in our study protocol but decided not to continue after having 2 (out of 22) patients develop prolonged AV block. Moreover, adding a bolus injection to the continuous infusion did not improve hyperemic efficacy. Therefore, the combination of bolus injection and IV infusion of adenosine may not be recommended in terms of safety and efficacy; however, considering the small number of patients included in our study, further studies are needed.

**Limitations**

There are some limitations to our study. First, even though an intracoronary nitrate was given before each method of adenosine administration, the possible influence of minor changes in epicardial vessels could not be completely excluded. Second, as this was not a blinded study, there could have been a small subjectivity in the interpretation of pressure tracings. Third, while various doses of adenosine are used to induce maximal hyperemia for invasive physiological studies, the main purpose of this study was to compare the hyperemic efficacy between peripheral and central IV infusion of adenosine; therefore, we did not use the higher doses of adenosine in our study. Fourth, as this study was performed in Korean patients of relatively low body mass index, the results might not be applied to a Western population or to patients with higher body mass index.

In conclusion, the results of our study suggest that IV infusion of adenosine using a forearm vein is a convenient and effective way to induce steady-state hyperemia for invasive physiological measurements. This method may be especially useful during transradial coronary catheterization procedures. Adding an IC bolus injection to the continuous IV infusion of adenosine may not be recommended owing to the risk of prolonged AV block.

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**Disclosures**

None.

**References**

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