

Intracoronary Continuous Adenosine Infusion

— A Novel and Effective Way of Inducing Maximal Hyperemia for Fractional Flow Reserve Measurement —

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Background Various methods are used to induce maximal hyperemia for physiologic studies, but the feasibility and efficacy of continuous intracoronary (IC) infusion of adenosine for measurement of fractional flow reserve (FFR) has not been well-defined.

Methods and Results Patients with intermediate coronary artery stenosis were consecutively enrolled. In the phase I study, FFR was measured after 3 dosages of IC adenosine infusion (180, 240 and 300 µg/min) in 30 patients. The phase II study was performed to compare the hyperemic efficacy of IC infusion (240 µg/min) with IC bolus injection (40, 80 µg) and intravenous (IV) infusion (140 µg·kg⁻¹·min⁻¹) of adenosine in 20 patients. In the phase I study, no significant differences in FFR were observed with the 3 different doses of IC infusion (p=0.06). In the phase II study, FFR after an IC bolus injection (0.83±0.06) was significantly higher than with IV (0.79±0.07) or IC (0.78±0.09) infusion (p<0.01). However, no difference in FFR was observed for IC and IV infusions.

Conclusion IC infusion of adenosine seems to be a safe and effective method of inducing maximal hyperemia for FFR measurement. (Circ J 2005; 69: 908–912)

Key Words: Adenosine; Fractional flow reserve; Hyperemia

Fractional flow reserve (FFR) is an easily obtainable lesion-specific parameter for the physiological evaluation of epicardial coronary artery stenosis. This index is relatively independent of systemic blood pressure, heart rate, and contractility and is being increasingly used to assess the functional significance of intermediate lesions and the results of coronary interventions.^{1–8} FFR is the ratio of hyperemic flow in the presence of coronary artery stenosis to normal maximal flow, and it can be obtained by the ratio of the hyperemic distal coronary artery pressure to the aortic pressure.⁹ Because distal coronary artery pressure is determined by both epicardial stenosis and distal resistance, maximal hyperemia is a key determinant for FFR in a fixed epicardial stenosis. Various pharmacologic stimuli are used to induce maximal hyperemia for FFR measurement;^{10–12} however, the usefulness of continuous intracoronary (IC) infusion of adenosine has not been evaluated. Recent reports suggest that bolus adenosine administration is sometimes inadequate for the induction of maximal hyperemia^{10,12–14} and intravenous (IV) adenosine infusion requires a large venous access, a large amount of adenosine

and long procedural time. The present study was performed to assess the safety and efficacy of continuous IC adenosine infusion for the induction of maximal hyperemia for FFR measurement.

Methods

Patient Population

Patients with an angiographically intermediate lesion (visual estimation: 50–75%) in a major epicardial coronary artery were prospectively and consecutively enrolled. Clinical and angiographic data are shown in Table 1. There were no patients with angiographically visible collateral flow to the target vessel. Patients with myocardial infarction, unstable clinical condition, regional wall motion

Table 1 Clinical and Angiographic Characteristics of the Study Group (n=50)

Age, years	61.4±9.5
M/F	29/21
Body mass index (kg/m ²)	24.9±3.5
Clinical diagnosis	
Stable angina	30
Unstable angina	13
Silent ischemia	7
Lesion location	
LAD/LCX/RCA	25/7/18
Lesion length, mm	21.1±7.5
Diameter stenosis, %	61.9±16.4

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

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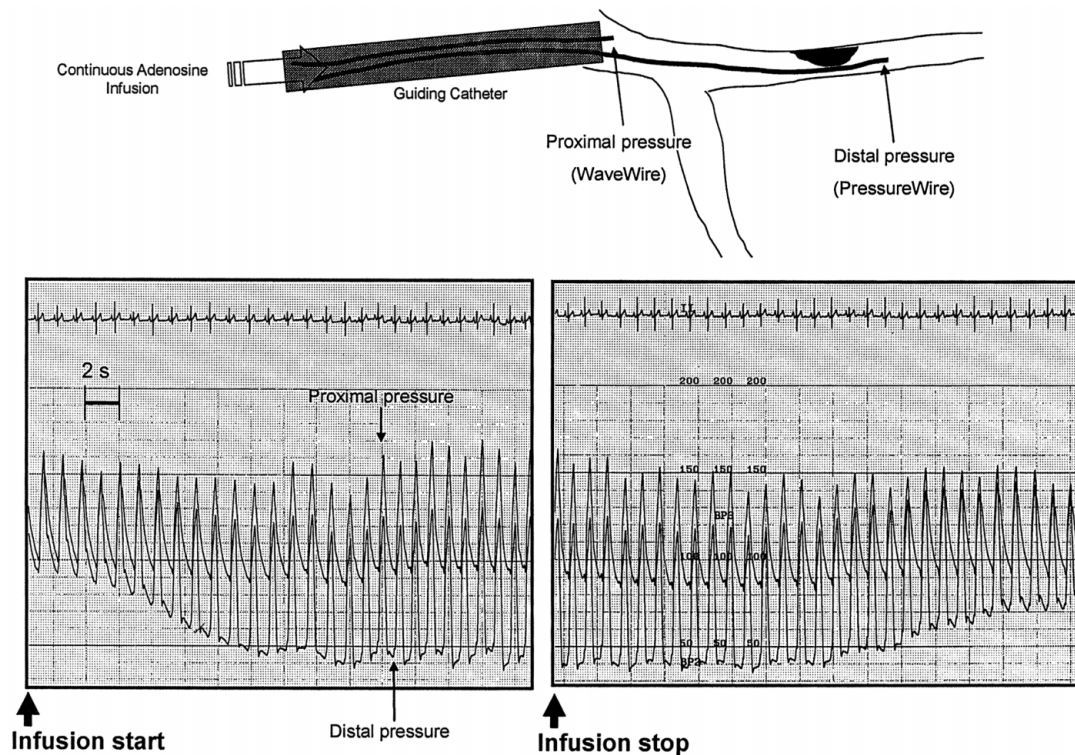


Fig 1. Continuous recording of proximal and distal pressures during the intracoronary continuous infusion of adenosine using 2 pressure wires. Fractional flow reserve was calculated by the ratio of the mean distal pressure to the mean proximal pressure in each beat.

abnormalities, reduced left ventricular systolic function, left ventricular hypertrophy, or arrhythmia were excluded. The institutional review board approved the study protocol and all patients gave informed consent.

Phase I Study

The phase I study was performed in 30 patients (17 men; mean age: 62.8 ± 9.0 years) to assess the safety and efficacy of continuous IC adenosine infusion. Target lesions were located in the left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) in 18, 2 and 10 patients, respectively. Mean lesion length was 22.0 ± 8.1 mm and the percent stenosis $58.3 \pm 15.3\%$. Basal pressure gradient across the stenosis was 5.1 ± 4.4 mmHg. In this study, FFR was measured after an IC adenosine bolus injection (LAD, LCX: $80 \mu\text{g}$, RCA: $40 \mu\text{g}$) and at 3 different IC adenosine infusion dosages: 180, 240 and $300 \mu\text{g}/\text{min}$.

Phase II Study

The phase II study was performed in 20 patients (12 men; mean age: 59.5 ± 10.1 years) to compare the hyperemic efficacy of IC adenosine infusion with bolus injection and IV infusion of adenosine. FFR was measured in the LAD, LCX and RCA in 7, 5 and 8 patients, respectively. Mean lesion length was 19.8 ± 6.4 mm and the %stenosis $66.8 \pm 17.1\%$. Basal pressure gradient across the stenosis was 5.4 ± 3.1 mmHg. Adenosine was administered in the following order: IC bolus injection, IC $240 \mu\text{g}/\text{min}$ continuous infusion and IV $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ continuous infusion.

Catheterization and FFR Measurement

All procedures were performed using 7Fr guiding catheters by a femoral approach. In the phase I study, a tem-

porary pacemaker was inserted in all patients. After positioning a guiding catheter in the coronary ostium, $200 \mu\text{g}$ of nitrate was administered and a reference image obtained. Pressure measurements were performed using 0.014-inch pressure guide wires (WaveWire, Endosonics Inc, Rancho Cordova, CA, USA; PressureWire, Radi Medical Systems, Uppsala, Sweden), as previously described!¹⁵

Phase I Study To record the changes in the proximal and distal pressures during continuous IC adenosine infusion, aortic pressure was measured using a WaveWire and distal pressure using a PressureWire in the first 10 patients (Fig 1). After locating the 2 wires in the correct positions, IC adenosine infusion was started through a 4-way coronary manifold. Proximal and distal pressures were continuously recorded during and after adenosine infusion. FFR, time to maximal hyperemia (time needed to reach $>90\%$ of the maximal hyperemic efficacy with adenosine infusion) and duration of the plateau phase (the time during hyperemic efficacy remained at $>90\%$ of its maximal value after adenosine infusion) were measured. In the other 20 patients, only the distal pressure was monitored using a PressureWire during adenosine infusion. Adenosine infusion was continued for 30 s after the distal pressure reached its minimum. Adenosine infusion was then stopped and the FFR and the duration of the plateau phase were measured. After the distal pressure had returned to its baseline value, the next dosage of adenosine infusion was started.

Phase II Study FFR was measured using only the PressureWire. First, $40 \mu\text{g}$ (RCA) or $80 \mu\text{g}$ (LAD, LCX) of adenosine was administered as a bolus. After proximal and distal pressures and the heart rate had returned to their baseline values, the IC adenosine infusion was started. The system was purged with 4 mL of mixed adenosine fluid and

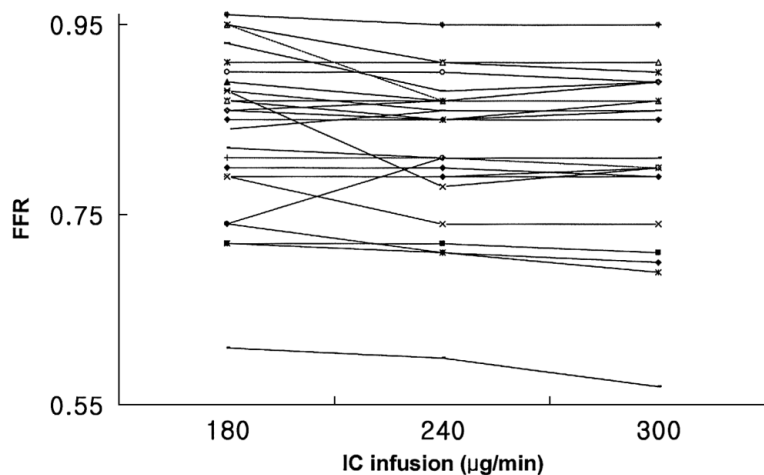


Fig 2. Individual fractional flow reserve (FFR) values of the 28 patients in the phase I study. IC, intracoronary.

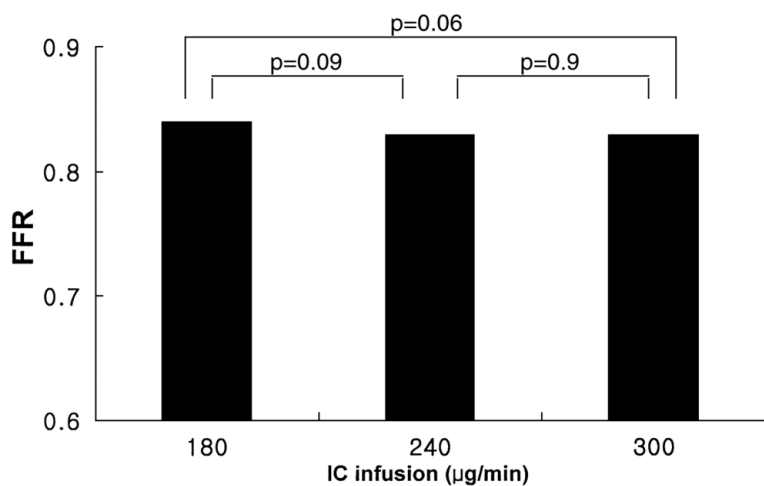


Fig 3. Fractional flow reserve (FFR) according to the 3 intracoronary adenosine infusion doses. Abbreviations as in Fig 1.

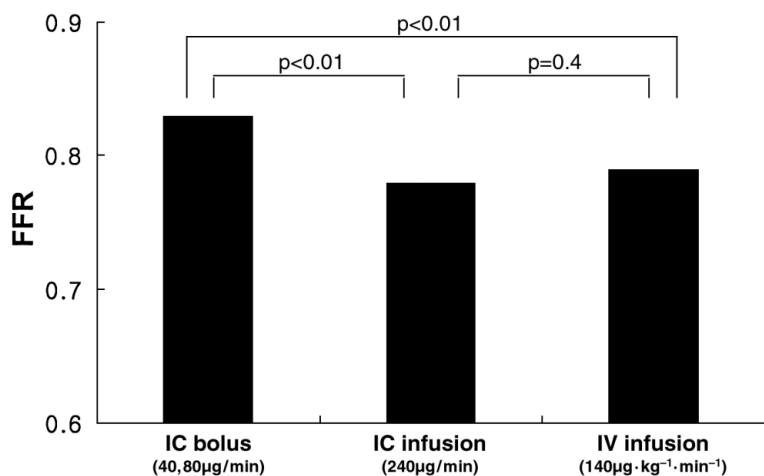


Fig 4. Fractional flow reserve (FFR) according to the different methods of adenosine administration. IV, intravenous; IC bolus, intracoronary bolus injection. Other abbreviations as in Fig 1.

followed by continuous infusion at a rate of 240 µg/min. The adenosine infusion was continued for 30 s after the distal pressure reached its minimum at which time the infusion was stopped and the FFR measured. IV continuous infusion of adenosine was done via a femoral vein at 140 µg·kg⁻¹·min⁻¹. IC nitrate (200 µg) was given prior to each method of adenosine administration.

Statistical Analysis

Data are presented as mean±SD. Differences between the FFR measured according to the 3 different methods of administration or dosages of adenosine were analyzed by repeated measures ANOVA. Differences between the 2 groups were analyzed using the paired t-test with Bonferroni correction. Student's t-test was used to assess FFR differences after IC bolus and IC infusion, and blood pressure

and heart rate differences with the IC and IV infusions. A p -value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 11.0 (Chicago, IL, USA).

Results

Hyperemic Efficacy of IC Adenosine Infusion at the 3 Different Doses

FFR was measured in all except 2 patients who showed complete atrioventricular (AV) block with IC adenosine infusion of $300\mu\text{g}/\text{min}$. Fig 2 shows the FFR changes in each patient according to the 3 different doses of adenosine. No significant differences in FFR were observed ($p=0.06$, Fig 3). However, there was a trend toward a lower FFR after an infusion of $240\mu\text{g}/\text{min}$ (0.83 ± 0.07 , $p=0.09$) or $300\mu\text{g}/\text{min}$ (0.83 ± 0.08 , $p=0.06$) vs an infusion of $180\mu\text{g}/\text{min}$ (0.84 ± 0.08).

In 3 patients (2 RCA, 1 LAD), AV block occurred during infusion at $300\mu\text{g}/\text{min}$ and 1 of them showed AV block at both $240\mu\text{g}/\text{min}$ IC infusion and $40\mu\text{g}$ IC bolus injection. There were no other complications related to IC adenosine infusion.

Comparison of IC Bolus Injection and IV Infusion of Adenosine

In all 20 patients, FFR measurements were completed using the 3 different methods of adenosine administration, and found to differ significantly ($p=0.001$, Fig 4). As compared with the FFR after IC bolus (0.83 ± 0.06), the FFR after IC infusion ($240\mu\text{g}/\text{min}$, 0.78 ± 0.09) or IV infusion ($140\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, 0.79 ± 0.07) was significantly lower ($p<0.01$). However, no difference was observed between the FFR measured after IC or IV infusion ($p=0.4$). FFR was <0.75 in 3 patients after bolus administration of adenosine and in 6 patients after both IC and IV continuous infusion.

Comparison of FFR After IC Bolus Injection and IC Infusion

Comparison of FFR after IC bolus and IC infusion ($240\mu\text{g}/\text{min}$) was available in 49 patients during the phase I and II studies, and FFR was significantly lower with IC infusion than after bolus injection (0.85 ± 0.07 vs 0.81 ± 0.08 , $p<0.001$). All 8 patients with an FFR between 0.75 and 0.8 after IC bolus injection had an FFR of less than 0.75 after IC infusion.

Hemodynamic Changes During Adenosine Infusion

Mean systemic blood pressure was significantly reduced from the baseline values with both IC and IV infusions (IC: -4.2 ± 6.9 mmHg; IV: -12.1 ± 13.4 mmHg). However, the change in systemic blood pressure was significantly larger after IV infusion than after IC infusion ($-11.3\pm 12.5\%$ vs $-4.1\pm 6.1\%$, $p=0.01$). A slight increase in heart rate was observed during IV and IC adenosine infusion (Table 2). The plateau phase was measured in 29 patients with IC $240\mu\text{g}/\text{min}$ infusion and it was 21.1 ± 7.3 s (range: 11–44 s). In 10 patients in the phase I study, proximal and distal pressures were continuously recorded during IC adenosine infusion and the mean time to maximal hyperemia in these patients was 8.5 ± 3.0 s (range: 4–13 s).

Discussion

Various pharmacologic stimuli are currently used to

Table 2 Percent Change in Blood Pressure and Heart Rate From Baseline Values During Adenosine Infusion

	IC infusion	IV infusion	<i>p</i> value
Δ Blood pressure (%)	-4.1 ± 6.1	-11.4 ± 12.5	0.03
Δ Heart rate (%)	4.1 ± 9.1	6.3 ± 10.7	0.5

IC, intracoronary; IV, intravenous.

induce maximal hyperemia for FFR measurements and the hyperemic efficacy and safety of adenosine have been validated in many studies.^{10,16–18} However, bolus administration of adenosine is sometimes inadequate for the induction of maximal hyperemia,^{10,13,14} and the duration of the hyperemia is too short for a pressure pullback maneuver or coronary flow reserve measurement by the thermodilution method.^{10,16} Moreover, IV adenosine infusion requires central or large vein access and a large amount of adenosine. Thus, we investigated the safety and efficacy of IC adenosine infusion for FFR measurement, and we found that this method can be performed safely and that it offers a hyperemic efficacy comparable to that of IV infusion.

Safety and Adequate Dose of IC Infusion

A previous study conducted in a small number of patients showed that IC adenosine infusion at $80\mu\text{g}/\text{min}$ induced maximal hyperemia.¹⁶ To define the adequate infusion rate of adenosine, we first performed a pilot study (data not shown) and found that stable hyperemia could be induced at the rate of $180\mu\text{g}/\text{min}$ in most patients. In the present study, although hyperemic efficacy did not differ significantly with the 3 different doses of IC infusion, there was a trend toward a lower FFR after an infusion of $240\mu\text{g}/\text{min}$ (0.83 ± 0.07 , $p=0.09$) or $300\mu\text{g}/\text{min}$ (0.83 ± 0.08 , $p=0.06$) vs an infusion of $180\mu\text{g}/\text{min}$ (0.84 ± 0.08); infusion of $300\mu\text{g}/\text{min}$ caused AV block in 10% of patients. These results suggest that $240\mu\text{g}/\text{min}$ is the advisable dose for FFR measurement during IC adenosine infusion, having taken both safety and efficacy into consideration.

Hyperemic Efficacy

As compared with IC bolus administration, IC adenosine infusion was found to be more effective at inducing maximal hyperemia. Furthermore, in all 9 patients with borderline FFR (0.75–0.80) after bolus injection of adenosine, FFR during IC infusion ($240\mu\text{g}/\text{min}$) was <0.75 . Recent studies have shown that the standard doses used for bolus adenosine do not always achieve maximal hyperemia. In a study by Lopez-Palop et al,⁴ the true FFR value was obtained in only 23% of lesions with a $30\mu\text{g}$ injection of adenosine. And in an excellent study by De Bruyne et al,¹⁰ a significantly lower FFR was obtained with IV infusion of adenosine in patients who had a borderline FFR (0.70–0.86) after $40\mu\text{g}$ bolus administration. In the present study the hyperemic efficacy of adenosine IV infusion ($240\mu\text{g}/\text{min}$) was comparable to IV infusion.

Although both methods of adenosine infusion reduced systemic pressure, IC infusion caused less hypotension than IV infusion. A previous study showed that the FFR is independent of heart rate and blood pressure, in contrast to coronary flow reserve, which is dependent on these factors.⁹ Therefore, we assumed that the difference in hemodynamic parameters between IV and IC infusion would not influence the FFR. However, the influence of the changes in central venous pressure could not be completely ruled out because

we did not measure central venous pressure after each method of adenosine administration. However, because we excluded the patients with clinical conditions likely to raise central venous pressure, we consider that the effect of a change in central venous pressure on measured FFR would have been negligible.

Because IC infusion can be performed without large vein or central vein access and with a relatively small amount of adenosine, this time-saving method would be particularly useful in patients who record a borderline FFR after IC bolus administration. This method would be also easily applicable to procedures via the radial artery.

Duration of Hyperemia

The pressure pullback maneuver is useful in patients with multiple or diffuse lesions, but requires steady-state hyperemia. Because the duration of the plateau phase is more than 10 s (mean: 21.1 ± 7.3 s), IC adenosine infusion also appears to be useful for performing this maneuver. Another way of performing pressure pullback is to record only the pullback curve of the distal pressure during continuous IC infusion.

In addition to FFR, coronary flow reserve can be measured using a pressure-temperature sensor-tipped guide wire!^{9–21} Repetitive manual injections of saline solution during maximal hyperemia are mandatory to obtain the coronary flow reserve by thermodilution method. The short time to maximal hyperemia and the relatively long plateau phase of IC adenosine infusion will enable experienced operators to measure coronary flow reserve.

Study Limitations

The main limitation of IC adenosine infusion is that it always requires a proper engagement of the guiding catheter and the infusion cannot be done with a catheter that has side holes. Second, the hyperemic efficacy of IC adenosine infusion was compared only with bolus injection and IV infusion. The relative efficacy of IC adenosine infusion compared with ATP or papaverine is unknown. However, considering the results of the study by De Bruyne et al,¹⁰ the efficacy of IC adenosine infusion would be expected to be comparable to that of other vasodilatory drugs. Third, IC adenosine infusion was performed only in patients with a stable condition and normal left ventricular function. Safety and efficacy in patients with an unstable condition and left ventricular dysfunction remain to be established. Fourth, all patients enrolled in our study had intermediate stenosis; further study is needed to define the plateau time in subjects with a normal coronary artery.

Conclusions

The IC infusion (240 μ g/min) of adenosine seems to be a safe and effective method of inducing maximal hyperemia for FFR measurement, and this method would be particularly helpful in patients with a borderline FFR after bolus adenosine injection.

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