

## Original Article

# Efficiencies of intracoronary sodium nitroprusside on fractional flow reserve measurement

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**Abstract:** Background: Fractional flow reserve (FFR) has certain advantages of assessing functional severity of coronary stenosis. Adenosine(AD) is the most widely used agents in FFR measurement but has the disadvantages of higher rate of complications. Sodium Nitroprusside (SNP) represents a valuable alternative. Methods and results: In 75 patients with 86 moderate coronary stenosis, FFR values, heart rate and blood pressure were measured at baseline, after 0.6 µg boluses of intracoronary (IC) SNP, and after 140 µg/kg/min of continuous intravenous (IV) AD. FFR values decreased significantly after administering IV AD and IC SNP compared with the baseline Pd/Pa values ( $P < 0.001$ ). Mean FFR induced by IV AD was not significantly different from that by IC SNP ( $t = 0.577$ ,  $P = 0.566$ ). The mean kappa value in the evaluation of two methods was 0.973 for FFR. There was a significant correlation between the FFR values of IV AD and IC SNP ( $R = 0.911$ ,  $P < 0.001$ ). Significant decreases in the blood pressures were found after agents were given compared to the baseline. No significant difference was found between AD and SNP. In addition, immediate complications occurred in 60.5% patients of IV AD in contrast to no adverse events after IC SNP. Conclusion: SNP is a safe and effective agent and easy to use for the FFR measurement. Maximal hyperemia by IC SNP is equivalent to that by IV AD. IC SNP could be considered a potential alternative in patients with contraindications to AD administration.

**Keywords:** Fractional flow reserve, coronary artery disease, coronary angiography

## Introduction

Accurate evaluation of the severity of moderate coronary stenosis is a challenge for interventional cardiologist. Quantitative coronary angiography (QCA) is a poor predictor of functional significance of coronary lesions [1]. In the last decade, fractional flow reserve has emerged as a good diagnostic and prognostic tool [2]. The patients with a FFR value of  $< 0.75$  almost always presents with myocardial ischemia [3]. Nowadays, Defer, FAME1 and FAME2 have proved that FFR has become the best functional parameter for evaluation borderline stenosis severity of diseased coronary artery [4-6]. It is crucial to achieve a maximum steady state hyperemia for an accurate FFR. The most used agent is adenosine. However, it is associated with more side effects, either by intracoronary or intravenous routes [7-9]. Therefore, SNP represents a valuable alternative in everyday clinical practice.

We had previously tested that IC SNP are equivalent in inducing maximal coronary hyperemia compared with IC AD [7]. However we did not directly compared IC SNP with IV AD. The latter is considered the standard method to achieve maximal hyperemia on FFR measurement. And IC AD may not last long enough to achieve a steady hyperemia because of short half-life. About 81% of patients occurred side effects by IV AD, of which the most severe was AV block occurring 7.6% from a multicenter trial [9]. Therefore, the aim of this study was to compare the FFR response of IC SNP with IV AD in patients with moderate coronary artery stenosis identified by coronary angiography.

## Patients and methods

75 patients (86 coronary arteries with moderate stenosis) aged from 48 to 79 were enrolled in this study to compare the FFR induced by IC SNP and IV AD. Major exclusion criteria included

**Table 1.** Characteristics of target arteries

Characteristics	n
Left anterior descending artery	41 (47.7%)
Left Circumflex artery	19 (22.1%)
Right coronary artery	26 (30.2%)
Length of diseased artery	
< 10 mm	47 (54.7%)
10-20 mm	22 (25.6%)
> 20 mm	17 (19.7%)

cardiomyopathy, congestive heart failure with a left ventricular ejection fraction < 40%, myocardial infarction, significant valvular or congestive heart disease and renal failure. The study was approved by the Institutional Review Board of the Shenyang Northern Hospital.

*Practicalities in measuring FFR*

CAG was performed according to the standard procedure as previous [10]. Based on QCA assessment, the severity of each stenosis was defined as < 40% of stenosis, 40-70% of stenosis and > 70% of stenosis.

After administration of heparin 100 IU/kg IV, a 0.014-inch pressure monitoring guidewire (Pressure wire™ Certus, ST Jude Medical, Sweden) was calibrated and introduced into the guiding catheter. The pressure transducer was advanced just outside the tip of the guiding catheter, and the pressure measured by the sensor was then equalized to that of the guiding catheter. Subsequently, the pressure wire was advanced in the coronary artery with the pressure sensor placed distal to the target lesion site. Distal coronary and aortic pressures were measured at baseline. FFR was calculated as the distal coronary/aortic pressure (Pd/Pa) during maximal hyperemia.

The study consisted of 2 sequential steps.

1. A bolus of IC SNP at the dose 0.6 µg/kg was given over at less 5 s via the guiding catheter.
2. Continuous IV AD at the dose of 140 µg/kg/min was administered through a major arm vein with the use of rate-controlled infusion pump to calculate FFR.

At baseline and after an IV AD and IC SNP, detail medical data were recorded, including FFR value, change of systolic and diastolic blood

pressure, change of heart rate, patient's symptoms (namely, an angina sensation, dyspnea, or flushing), and any other complications. The electrocardiogram was simultaneously recorded.

*Statistical analysis*

Continuous data are expressed as the means ± SDs. Differences in the mean values of the FFR values, time to peak value of FFR, duration of the plateau phase, change of systolic and diastolic blood pressure, and change in heart rate were compared using paired student's t test. A Z-test was used to test for significant linear trends in the association of the FFR values with the stimuli. The Cohen's kappa coefficient was calculated to measure intra-observer (comparison of FFR between two times by the same doctor) and inter-observer (comparison of FFR by different doctors) variability. All statistics were two-tailed, and a p value of < 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, Illinois). A p value of 0.05 was considered significant.

**Results**

*Characteristics of target arteries*

The study was performed with a total of 86 coronary arteries in 75 patients with moderate stenosis. The characteristics of target arteries are shown in **Table 1**. The mean percentage of stenosis measured was 64.5 ± 7.7%.

*FFR values after IV AD and IC SNP*

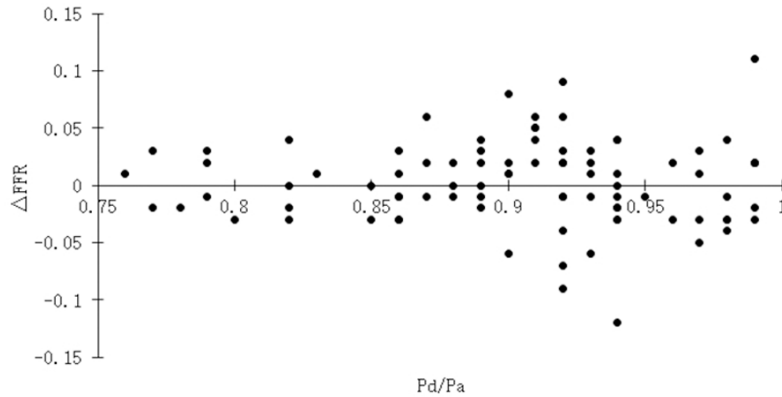
As shown in **Table 2**, the FFR values decreased significantly after administering IV AD and IC SNP compared with the baseline Pd/Pa values ( $P < 0.001$ ). Mean FFR induced by IV AD was not significantly different from that by IC SNP ( $P = 0.566$ ). Mean difference between IV AD and IC SNP-induced FFR was  $0.002 \pm 0.037$ . **Figure 1** depicts individual difference between FFR induced by IV AD and IC SNP. The mean kappa value in the evaluation of two methods was 0.973 for FFR.

The rates of an FFR measurement of < 0.75 in stenotic arteries were 29.01% (n = 25) and 27.91% (n = 24) in IV AD and IC SNP ( $P = 0.846$ )

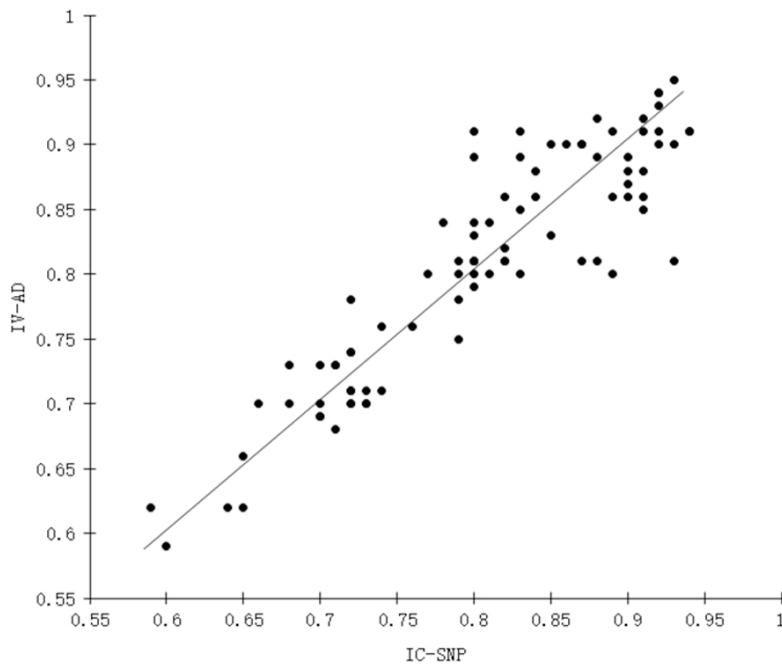
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**Table 2.** Change of Parameters by IC AD and IV SNP

	FFR (or Pd/Pa)	Sbp (mmHg)	Dbp (mmHg)	HR (bpm)
Baseline	0.904 ± 0.059	134.91 ± 21.19	72.72 ± 13.02	74.73 ± 10.90
IV AD	0.805 ± 0.089	120.76 ± 15.75	61.95 ± 10.09	75.74 ± 11.70
IC SNP	0.808 ± 0.088	118.80 ± 15.13	60.34 ± 9.55	75.80 ± 10.66



**Figure 1.** Difference of FFR induced by IV AD and IC SNP ( $\Delta$ FFR).



**Figure 2.** Correlation analysis of FFR between IV AD and IC SNP.

respectively. As shown in **Figure 2**, there was a significant correlation between the FFR values of IV AD and IC SNP ( $R = 0.911$ ,  $P < 0.001$ ).

### *Homodynamic effects of IV AD and IC SNP*

As can be seen from **Table 2**. Significant decreases in the systolic blood pressures were

found after agents were given compared to the baseline (decrease of 10.20% and 11.63% in AD and SNP,  $P$  all  $< 0.001$ ). No significant difference was found between AD and SNP ( $P = 0.075$ ). Compared with baseline, the diastolic blood pressure significantly decreased by 14.82% and 16.42%, respectively ( $P < 0.001$ ). There was no significant difference between AD and SNP ( $P = 0.073$ ). The heart rate increased by 0.98% and 1.90% in AD and SNP, respectively ( $P > 0.05$ ).

### *Side effect profile*

During IV AD infusion, 52 patients (60.5%) reported at least one side effect. 35 patients (40.7%) reported shortness of breath, 10 patients (11.6%) developed flushing, 19 patients (22.1%) reported headache, and 6 patients (7.0%) developed transient second degree AVB. All symptoms promptly disappeared after the treatments were discontinued. No patients reported unpleasant symptoms after SNP injection.

### **Discussion**

FFR is a more reliable indicator for assessing stenosis severity and necessity of intervention than CAG alone. In patients with coronary stenosis based on CAG and an FFR of  $\geq 0.75$ ,

deferral of percutaneous coronary intervention (PCI) is safe and reduces costs [11]. However its diagnostic value depends on the ability to achieve maximal, stable, and sustained coronary hyperemia. With sub-maximal hyperemia, FFR will be artificially high, and therefore, it underestimates the functional severity of the lesion. AD is the widest agent on FFR assess-

ment. And SNP is another alternative. A recent study showed that IC SNP at dose of 1.25 µg/kg is as effective as IV AD on FFR assessment. Furthermore, IC SNP also has several advantages compared with IV AD in the catheterization laboratory. It is much easier to administer, has a very rapid onset of action [12]. However, we had previously tested that doses higher than 0.6 µg/kg of IC SNP do not increase coronary hyperemia for FFR measurement and increase the propensity for hypotension [7]. So in the present study, we thus compared efficacy of IC SNP (0.6 µg/kg) with IV AD (140 mg/min/kg).

The result showed that the FFR values decreased significantly after a bolus of IC SNP at a dose of 0.6 µg/kg was given, which is similar with that produced by IV AD at a dose of 140 mg/kg/min. And IC SNP produces FFR response that strongly correlates with FFR induced by IV AD. In addition, the rate of stenosed arteries with FFR values < 0.75 showed no significant difference between two methods. So our study suggests that the effects of IC SNP on coronary microcirculation were similar to IV AD and that the maximal coronary hyperemia, equivalent to that induced by IV AD, could be achieved by IC SNP at a dose of 0.6 µg/kg.

SNP can directly relax arterial and venous muscle vasodilatation by producing nitric oxide without affecting other type of smooth muscles or producing myocardial contractility. It dilates the coronary microcirculation and induces the hyperemic response, and reduces the systemic pressure at the same time when SNP was administered. IC SNP at a dose of 0.6 µg/kg lowered systemic pressure, which was similar with IV AD at dose of 140 mg/kg/min. It suggests that the effect of SNP affects epicardial vasodilatation to a similar degree with AD.

IC bolus of SNP was well tolerated because patients reported no subjective symptoms after SNP was given. Especially, no patients developed AVB.

Limitation: we used only one dose of SNP our precious study showed.

### Conclusion

This study indicated that SNP is a safe and effective agent and easy to use for the FFR

measurement. Maximal hyperemia by IC SNP is equivalent to that by IV AD. IC SNP could be considered a potential alternative in patients with contraindications to AD administration.

### Disclosure of conflict of interest

None.

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