



Original Article

Safety and efficacy of intracoronary sodium nitroprusside for the assessment of coronary fractional flow reserve

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ABSTRACT

Background: Coronary fractional flow reserve (FFR) determination is a valuable tool for the assessment of stenosis significance in intermediate coronary obstructions. Maximal hyperemia is mandatory for this determination. Although intravenous (IV) Adenosine is the standard agent used, its use carries an elevated incidence of side effects. Intracoronary sodium nitroprusside (IC NTP) is a very well-known coronary vasodilator, but it is not routinely used for FFR determinations.

Objectives: The purpose of the present study was to compare FFR determinations and side effect profile of IC NTP with IV Adenosine.

Methods: We prospectively assessed FFR determinations in a total of 20 intermediate coronary artery stenotic lesions in 18 consecutive patients with the administration of IV Adenosine (140 µg/kg/min) and IC NTP (100 µg). The appearance of side effects was registered.

Results: The mean age was 55.5 ± 7.5 years. Fifteen (83%) of the patients were male. Mean FFR values with IC NTP were similar to those obtained with IV Adenosine (0.82 ± 0.07 vs 0.82 ± 0.06, respectively, $r = 0.775$, $p < 0.0001$). Intravenous Adenosine induced side effects in 45% of patients (shortness of breath 30%, flushing 5%, headache 5%, angina pectoris 5%, and transient conduction disturbances 10%). No side effects were reported with IC NTP.

Conclusions: IC NTP at a dose of 100 µg is as effective as IV Adenosine for FFR assessment. Besides, it is better tolerated and should be considered as a vasodilator agent in the assessment of FFR.

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1. Introduction

Fractional flow reserve (FFR) is a valuable tool for the assessment of intermediate coronary artery stenosis.^{1,2} Maximal, stable and sustained coronary vasodilation to perform the desired measurements plays a key role to obtain accurate results.^{3–5} Adenosine is considered the standard pharmacological agent to achieve maximal coronary hyperemia.^{6,7} However, the administration of adenosine either as an intracoronary bolus or peripheral continuous intravenous infusion has several disadvantages. The former produces very short lasting hyperemia leading to inaccurate results and may be associated with severe ventricular arrhythmias.^{4,8,9} The latter requires a central venous access or a large bore peripheral vein, higher doses of the drug, and may lead to frequent unpleasant systemic side effects, which limits its use,

especially in patients with reactive airway disease and advanced conduction disorders.^{10–13}

Sodium nitroprusside is a potent vasodilator which has no effect on myocardial contractility, nonvascular smooth muscles,^{14–16} and has been extensively used during the non-reflow phenomenon complicating percutaneous coronary angioplasty.^{17,18} It has several advantages over adenosine. First, Intracoronary Sodium Nitroprusside (IC NTP) has fewer adverse effects than Adenosine and besides it is inexpensive.¹⁹ Moreover, Parham et al found that IC NTP (at doses 0.3–0.6 µg/kg) produces similar and more sustained hyperemia than Adenosine, so it can be easily administered as an intracoronary bolus. They have also observed a good correlation between FFR values induced by IC NTP and those obtained by Adenosine.²⁰

The purpose of the present study was to compare FFR determinations of IV Adenosine and IC NTP in patients with single vessel and multivessel intermediate coronary artery stenosis. We also aimed to compare the side effects profile of both agents.

Abbreviations: FFR, fractional flow reserve; IV, intravenous; µg, micrograms; IC NTP, Intracoronary Sodium Nitroprusside.

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2. Methods

2.1. Patients

From March 2016 to July 2017, we routinely used IV Adenosine and IC NTP to assess FFR. If FFR values obtained with IC NTP and IV Adenosine are discrepant, we consider the latter to make a decision regarding coronary intervention. We prospectively assessed a total of 20 coronary artery stenotic lesions in 18 consecutive patients who underwent clinically indicated FFR at our Institution. Patients with ages between 20 and 75 years old, with stable coronary artery disease, and who had coronary artery obstructions of intermediate severity (30–70%) on angiography were considered for the study. Patients with conduction disturbances, history of reactive airway disease, arterial hypotension (systolic blood pressure lower than 90 mmHg), acute coronary syndromes, signs of heart failure or previous CABG were excluded.

The study was approved by the local ethical committee and conformed to the Declaration of Helsinki on human research, and informed consent was obtained after complete explanation of the protocol and potential risks.

2.2. Coronary angiography

Arterial access was performed using radial or femoral percutaneous approach. Diagnostic coronary angiography was performed by the Judkins technique with a 6 French right and left coronary catheters. The electrocardiogram, arterial blood pressure, and arterial oxygen saturation were monitored throughout the procedure. Decision to perform FFR measurements was based on visual assessment of the stenotic lesion.

2.3. Pressure measurements

After administration of IV heparin (80 UI/kg), a guiding catheter was inserted in coronary ostia. A 0.014-inch high fidelity pressure-recording guidewire (Primewire PRESTIGE, Volcano, San Diego, CA) was externally calibrated and then the wire was advanced to the tip of 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. Then, 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 and maximal hyperemia. Pressure signal were continuously recorded at baseline speed of 25 mm/s and a beat to beat analysis of mean pressure was automatically performed. Once stable pressure signal was obtained, measurements were recorded. FFR was calculated as a ratio of distal pressure (Pd) to aortic pressure (Pa) obtained during maximal hyperemia. A fractional flow reserve value <0.80 was considered hemodynamically significant.²

2.4. Pharmacological protocol

Once pressure wire was positioned distal to the interrogated lesion, a bolus of 100 µg of nitroglycerin intracoronary was administered. Special attention was paid to avoid pressure damping in the guiding catheter or unselective catheterization of the coronary ostia. Intravenous Adenosine or IC NTP was administered as the first agent, according to a random chart. Sodium nitroprusside was injected at a dose of 100 µg over less than 3 s via the guiding catheter. Pd/Pa ratio, blood pressure and heart rate were monitored during maximal hyperemia and until all parameters returned to the baseline level. Subsequently, a peripheral IV infusion of Adenosine at a dose of 140 µg/kg/min was administered through a major arm vein with the use of a rate-

controlled infusion pump. Infusion was continued for 180 s and FFR was measured when steady state hyperemia was achieved.

2.5. Statistical analysis

All analysis was performed using Primer program by Stanton A. Glanz (McGraw-Hill Inc. 1992).²¹ Data are presented as mean ± SD. Continuous variables were compared using paired Student's *t*-test. Sensitivity was defined as the ratio of true positives/true positives + false negatives. Specificity was defined as the ratio of true negatives/true negatives + false positives. Correlations were calculated using Pearson's correlation coefficient. A *p* value of <0.05 was considered significant.

3. Results

3.1. Baseline characteristics

During the study period, 22 consecutive patients with stable coronary artery disease and intermediate coronary stenosis were screened. Four patients were excluded. Three of them because of history of obstructive airway disease and 1 patient because of second degree atrio-ventricular block. Population consisted of 18 patients (15 males and 3 females) with a mean age of 55.5 ± 7.59 years. Baseline heart rate was 69.05 ± 15.24 beats/min. Mean arterial pressure was 93.4 ± 10.75 mmHg. All patients were in sinus rhythm. Baseline angiographic characteristics are reported in Table 1. Most of the lesions were 50–60%, (mean 56%, minimum stenosis 30%, maximum stenosis 70%) (Table 1).

3.2. Comparison of FFR induced by Intracoronary Sodium Nitroprusside and Intravenous Adenosine

Mean FFR value obtained after IC NTP injections was not different from FFR obtained after Adenosine infusion (0.82 ± 0.07 vs 0.82 ± 0.06, respectively (*p* = 0.756)). Mean time between both infusions was 4.9 min. Fig. 1 also depicts individual values comparing hyperemia induced by both agents. There was a strong correlation between FFR values induced by IC NTP and IV Adenosine (*r* = 0.775, *p* < 0.0001) (Fig. 2). Sensitivity and specificity for IC NTP were 87.5% and 91.66%, respectively. Individual differences in FFR measurements between both drugs is shown in Fig. 3.

3.3. Effects of Intracoronary Sodium Nitroprusside and Intravenous Adenosine on Hemodynamic Parameters

Compared to baseline blood pressure, IC NTP reduced mean blood pressure by 20% (93 ± 10 vs. 75 ± 10 mmHg), (*p* < 0.001). No patient reported any symptoms related to hypotension and blood pressure consistently returned to baseline levels within 60 s. Adenosine produced a mild reduction in baseline mean pressure

Table 1
Clinical and angiographic characteristics.

Patient characteristics	n
Total Number of patients	18
Male gender	15
Age	55.5 ± 7.5
Number of vessels interrogated	20
LAD	16
LCX	1
RCA	3
Mean% stenosis (range)	56 (30–70)

Reported values are total numbers. n: number. %: percentage. Age is expressed as mean ± 1 SD in years. LAD: Left anterior descending artery. LCX: Left circumflex artery. RCA: Right coronary artery.

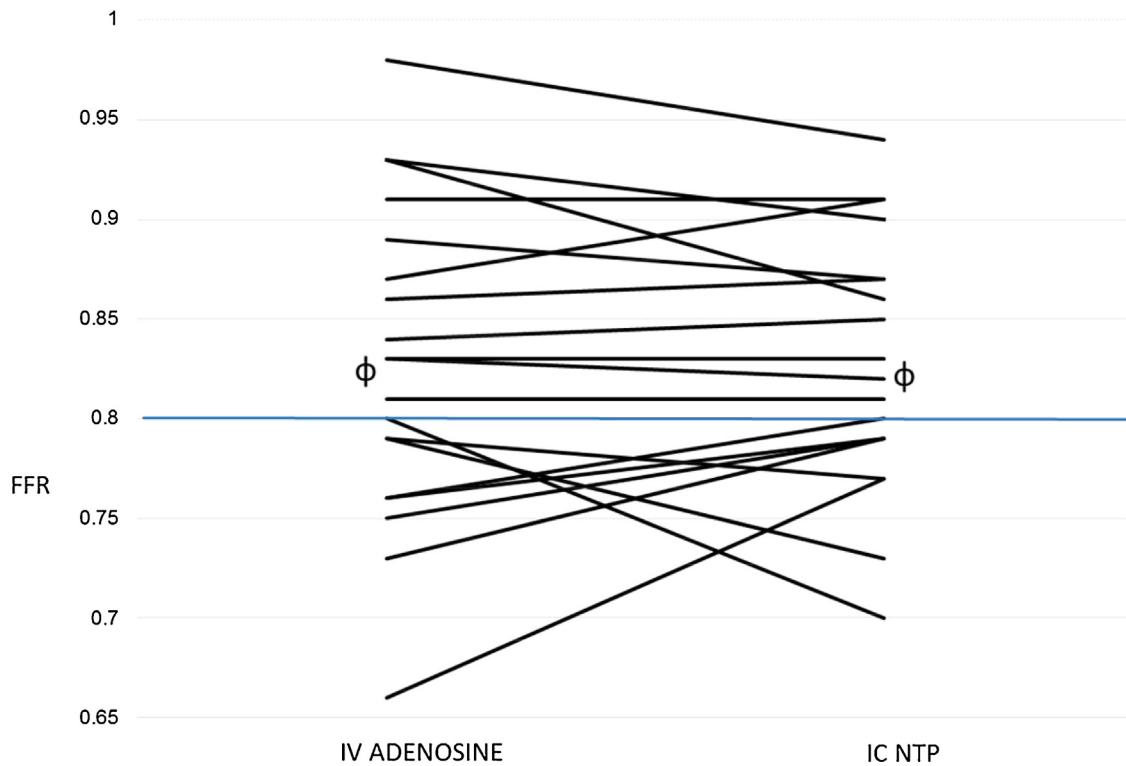


Fig. 1. Individual values of FFR induced by Adenosine and Sodium Nitroprusside. FFR: Fractional flow reserve. IV: intravenous. IC NTP: intracoronary sodium nitroprusside. Solid line depicts FFR cut off value of 0.80. Means \pm 1SD are shown as circles plus horizontal bars. $p = 0,756$.

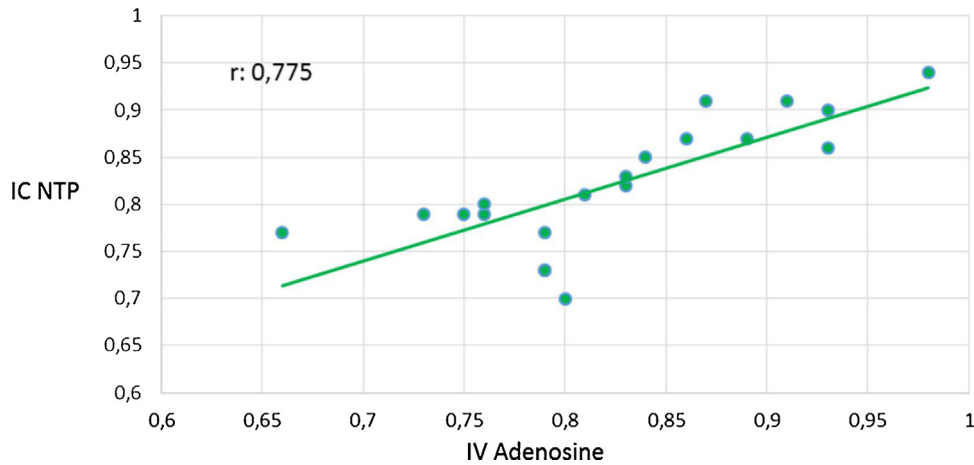


Fig. 2. Correlation between FFR induced by Adenosine and Sodium Nitroprusside. FFR: fractional flow reserve. IC NTP: intracoronary sodium nitroprusside. IV Adenosine: intravenous adenosine. r: Pearson's correlation coefficient.

(93 ± 10 vs 85 ± 11 mmHg), ($p = 0.003$). Baseline heart rate was not significantly increased by IC NTP (69 ± 15 beats/min vs 73 ± 11 beats/min), ($p = 0.25$). Although heart rate increase with IV Adenosine was not clinically relevant, it was statistically significant (69 ± 15 beats/min vs 75 ± 16 beats/min), ($p = 0.005$).

3.4. Side effects profile

During adenosine infusion 9 patients (45%) reported at least one side effect. Six patients reported shortness of breath, one patient developed flushing, one patient reported headache, and one patient reported angina pectoris. Two patients developed transient

conduction disturbances. No patients reported unpleasant symptoms after NTP injection.

4. Discussion

Our study has shown that FFR determinations obtained with IC NTP at a fixed dose of $100 \mu\text{g}$ has a strong correlation with that obtained with the current gold standard infusion of intravenous adenosine (Figs. 1 and 2). These results are in agreement with data previously reported by Parham et al and Rudzinski et al.^{20,22}

This study provides more evidence regarding the usefulness of IC NTP for the assessment of FFR, as other authors have shown, having the largest metanalysis evaluated only 173 patients.²³

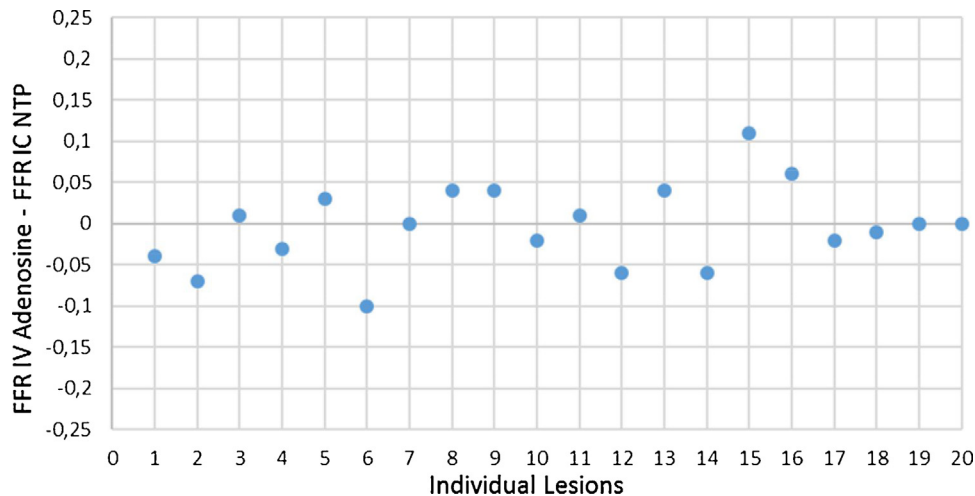


Fig. 3. Differences between FFR induced by IV Adenosine and IC NTP.

Individual differences between FFR induced by Intravenous Adenosine and Intracoronary Nitroprusside. FFR = Fractional Flow Reserve. IC NTP = Intracoronary Sodium Nitroprusside. IV Adenosine = Intravenous Adenosine.

Only one patient who had a negative FFR value with IC NTP (FFR = 0.80) was positive with IV Adenosine (FFR = 0.76), so sensitivity obtained with IC NTP was almost 88%. On the other hand, another patient who had a positive FFR value with IC NTP (FFR = 0.70) was negative with IV Adenosine (FFR = 0.80). Specificity for IC NTP was 91%. Note that both results were near the cut-off point value of 0.80 selected for this and other studies.^{1–3,19} FFR values obtained with both vasodilators agents had shown a good correlation in patients with multivessel disease and lesions between 30% to 70% of diameter stenosis. This was also shown by Rudzinski et al.²²

Our study evaluated stenotic lesions between 30% to 70%. Only 4 out of 20 lesions were below 50% of diameter stenosis (Mean FFR value: 0,88 with IV Adenosine and 0,86 with IC NTP). One of this patients with a 40% stenosis had FFR values below 0,80 with both drugs. Park et al have shown that up to 17% of lesions <50% have an FFR value lower than 0,80.²⁴

Intracoronary bolus of Sodium Nitroprusside was very well tolerated by patients who reported no subjective symptoms after drug injection. The effects of IC NTP on blood pressure although significant, were short-lasting, not clinically significant, and patients remained asymptomatic.

Although Parham et al found similar increases in average peak velocity determined with a Doppler Flow Wire with 0,3 µg/kg, 0,6 µg/kg and 0,9 µg/kg of IC NTP,²⁰ Leone et al demonstrated that doses of IC NTP of 0,6 µg/kg resulted in lower FFR values compared to IV Adenosine.¹⁹

We used the same fixed dose of 100 µg for FFR determination as well as Rudzinski et al did, without having clinically relevant side effects.²²

Using IC NTP as vasodilator agent for FFR measurements is more simple and time saving. The most important advantage of IC NTP over IV Adenosine is its cost and the absence of serious side effects, making IC NTP the agent of choice in patients with conduction disturbances and those with reactive airway disease, features found in 18% of our patients.

4.1. Study limitations

Although our study enrolled patients prospectively and consecutively, the number of lesions assessed was small. This is due to the fact that FFR was measured only in patients presenting for a coronary angiogram without a test for ischemia detection, or with discordant results between the stress test findings and those

obtained during the angiogram. Decision of which lesions should be assessed by FFR was made by operator.

Our primary objective was to compare the correlation between ICNTP and IV Adenosine and side effects profile of both drugs. Although sensitivity and specificity were calculated, our study was underpowered for guiding clinical decisions based on such analysis.

As most of our patients were male, and 80% of the lesions were located in the left anterior descending coronary artery, this findings may only apply in these subset of patients.

Ventricular function was not analyzed in this study. Kobayashi et al have demonstrated that reduced ejection fraction has no influence on FFR value.²⁵

5. Conclusions

This study demonstrates that IC NTP at a dose of 100 µg is as effective as IV Adenosine for the assessment of hemodynamic significance of intermediate coronary artery stenosis. In addition, IC NTP has fewer adverse events, is easier to use, and less expensive than Adenosine.

Disclosures

None.

Sources of funding

None.

Potential conflicts of interest

None to declare.

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