



## Original Article

# Diagnostic utility and safety of intracoronary nicorandil as a hyperemic agent for the measurement of fractional flow reserve

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## ABSTRACT

We investigated the diagnostic utility and safety of intracoronary bolus administration of nicorandil compared with intravenous administration of adenosine for evaluating FFR in patients with intermediate (40–70%) coronary stenosis. The FFR values obtained with nicorandil and adenosine showed linear relationship. This correlation is statistically significant with regression coefficient of 0.932 ( $R^2 = 0.834$ ,  $p < 0.001$ ). The side effects such as bronchospasm, hypotension, and bradycardia were significantly higher after administration of adenosine compared to nicorandil (20% vs. 1.66%,  $p = 0.001$ ). Intracoronary use of nicorandil seems to be promising in offering the advantages of lesser side effects, similar efficacy, and lesser cost as compared to adenosine.

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## 1. Introduction

Measurement of FFR for evaluating intermediate coronary artery lesions (40–70%), has become an important tool for deciding the need for revascularization. Optimal hyperemia is absolute prerequisite and failure to achieve this would result in in-accurate diagnosis. For inducing hyperemia, traditionally vasodilator drugs, such as intravenous adenosine, adenosine 5'-triphosphate (ATP), and papaverine are used. However, intravenous bolus administration of adenosine sometimes results in transient atrioventricular (AV) block, transient dyspnea, hypotension, or chest pain.<sup>1–3</sup> Intracoronary nicorandil (Dual agonist of nitrate and ATP-sensitive K<sup>+</sup> channel) could be an attractive option as a hyperemic agent and may be used as a possible alternative to adenosine.<sup>4</sup> We therefore decided to evaluate the safety and efficacy of intracoronary administration of nicorandil for FFR measurement as compared to adenosine.

## 2. Materials and methods

This single center prospective study enrolled 46 consecutive patients who underwent coronary angiography and found to have intermediately stenosed lesions, with 40–70% severity, as judged by visual impression by two independent operators. The patients

who met the inclusion criteria of having intermediate lesions (40–70%) were subjected to FFR measurement after informed consent.

The exclusion criteria for the patients were as follows:

- A. Age less than 18 years,
- B. Non -ST/Sinus Tachycardia elevation Acute coronary syndrome in the preceding one week,
- C. Heart failure in preceding one week.
- D. Contraindication/allergy to nicorandil or adenosine, or patient already taking nicorandil
- E. Severe Renal or liver insufficiency,
- F. Severe valvular heart disease,
- G. Second or third-degree AV block,
- H. Open-angle glaucoma,
- I. Patient in cardiogenic shock,
- J. History of asthma/chronic obstructive pulmonary disease,
- K. Tandem, diffuse, or Instent coronary lesions,
- L. Left Main/ostial Right coronary lesions.
- M. Left ventricular ejection fraction less than 35%,
- N. Pregnancy

The study was approved by the Institutional Ethics Committee and conducted as per the Declaration of Helsinki.

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### 2.1. Measurement of fractional flow reserve

Standard technique was used to obtain FFR readings. An FFR value of 0.80 was considered to be the significant ischemic threshold. The hyperemia was induced by administering first adenosine and then nicorandil. The patients were subjected to FFR measurement initially with adenosine 140 µg/kg/min continuous infusion for 3 min through a peripheral or central venous line, and FFR readings were documented. After 5 min of wash-out period 2 mg nicorandil injection was given as a single intracoronary bolus and again FFR with nicorandil was recorded. The wash-out period is given to ensure that the changed hemodynamic parameters return to normal. The correlation between FFR values obtained after adenosine and nicorandil administration was studied. The data was statistically analyzed by SPSS version 2.0. A *p* value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

The study enrolled 46 patients having 60 intermediate severity coronary lesions. The baseline patient and lesion characteristics are outlined in Table 1.

### 3.2. Co-relation between FFR values after administration of adenosine and nicorandil

As shown in Table 2, the FFR values obtained with nicorandil and adenosine showed linear relationship. This correlation is statistically significant with regression coefficient of 0.932 ( $R^2 = 0.834$ ,  $p < 0.001$ ) (Fig. 1). As shown in Table 2, the value of FFR obtained with Nicorandil were numerically higher than those obtained with adenosine. However, the difference was not statistically significant. The relationship between FFR values obtained after adenosine and nicorandil was independent of any vessel.

The side effects such as bronchospasm, hypotension, and bradycardia were significantly higher after administration of adenosine as compared to nicorandil (20% vs. 1.66%,  $p = 0.001$ ) (Table 2). However, all the side effects observed with both the agents were transient and self-limiting.

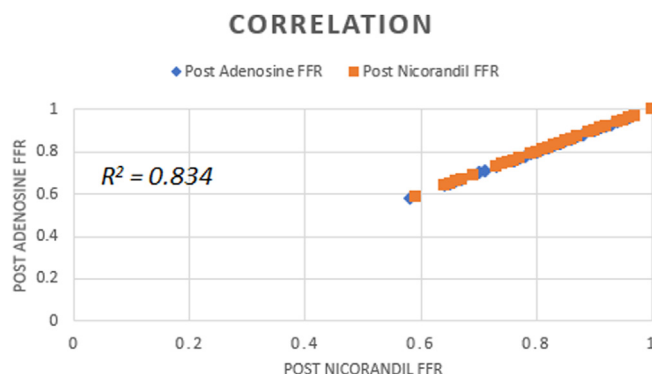
**Table 1**  
Showing the baseline patient and lesion characteristics. (*n* – number of patients; SD – Standard Deviation; BMI- Body Mass Index).

Variables	<i>n</i> = 60
Age, years, Mean ± SD	59.32 ± 11.20
<b>Gender,</b>	<b><i>n</i> (%)</b>
Female	15 (25)
Male	45 (75)
<b>History</b>	<b><i>n</i> (%)</b>
Family history of Ischemic Heart disease.	17 (28.3)
Past history of Ischemic heart disease.	20 (33.33)
Diabetes Mellitus	32 (53.33)
Hypertension	42 (70)
Obesity (BMI >25)	23 (38.33)
Asthma	Nil
Smoking	05 (8.33)
Tobacco chewing	12 (20)
Alcohol	10 (16.67)
<b>2D-Echocardiography (Left Ventricular Ejection Fraction %), Mean ± SD</b>	<b>48.35 ± 9.28</b>
<b>Lesion characteristics</b>	<b><i>n</i> (%)</b>
Left Anterior Descending artery.	31 (51.66)
Diagonal artery	01 (1.66)
Left Circumflex Artery.	12 (20)
Obtuse Marginal artery	04 (6.66)
Ramus artery	01 (1.66)
Right Coronary Artery.	11 (18.33)

**Table 2**  
Showing comparison between hyperemia with adenosine versus nicorandil. *n* – number of patients; FFR – Fractional Flow reserve.

Variables	Post Adenosine	Post Nicorandil	<i>P</i> -Value
Positive FFR ( <i>n</i> )	40	44	0.357
Negative FFR( <i>n</i> )	20	16	0.357
Drop in FFR	0.116 ± 0.075	0.106 ± 0.077	0.225
<b>Side effects (<i>n</i>)</b>	<b>12</b>	<b>1</b>	<b>0.001</b>

Bold values signifies *p* value < 0.05.



**Fig. 1.** Showing correlation of FFR post adenosine and FFR post nicorandil (FFR – Fractional Flow Reserve).

## 4. Discussion

The present study shows that hyperemia obtained with bolus intracoronary nicorandil was comparable to the hyperemia induced after intravenous adenosine. Nicorandil was associated with the lower side effects compared to the adenosine such as bronchospasm, hypotension, and bradycardia in the current study.

Previous studies have demonstrated the usefulness and safety of nicorandil over ATP. Tanaka et al. has shown effective safe dose of nicorandil to induce optimal hyperemia.<sup>5</sup> They showed that 2 mg intracoronary nicorandil bolus, induces optimal hyperemia comparable to ATP. Furthermore, they found that side effects were less with nicorandil and peak hyperemic response was quicker.<sup>5</sup> Similar findings were observed by Takashima et al.<sup>6</sup> and Lim et al.<sup>7</sup> concluding that nicorandil derived FFR correlated quite well with ATP, FFR in patients with intermediate lesions ( $R = 0.9541$  and  $R = 0.962$ , respectively). However, both of them found that ATP was associated with more frequent side effects. The incidence of AV block was significantly higher after ATP than nicorandil ( $p = 0.024$  and  $p < 0.001$ ). Additionally, Takashima et al.<sup>6</sup> also noted significant ( $P < 0.001$ ) fluctuations in FFR after ATP administration.

Another advantage of using intracoronary nicorandil is that the cost of the drug is substantially less as compared the cost of adenosine.

The current study has some limitations. The single-center study and relatively small sample size are major limitations. Moreover, limitation of intracoronary nicorandil is the inability to deliver a reliable dose in presence of ostial lesions. Additionally, also its inability to take pullback readings.

## 5. Conclusion

An ideal hyperemic agent needed for FFR study should be effective in producing maximal hyperemia, should be free from any significant side effects, should be transient and evanescent; moreover, it should be cost effective. Intracoronary use of nicorandil seems to

be promising. It has advantages of lesser side effects, similar efficacy, and lesser cost as compared to adenosine. Thus, we conclude that nicorandil could be as effective as and safer than IV adenosine in standard doses for inducing hyperemia during FFR estimation. However, larger studies are needed to confirm this hypothesis.

#### Declaration of competing interest

All authors have none to declare.

#### References

1. Pijls NH, Tonino PA. The crux of maximum hyperemia: the last remaining barrier for routine use of fractional flow reserve. *JACC Cardiovasc Interv.* 2011;4(10):1093–1095.
2. De Bruyne B, Pijls NH, Barbato E, et al. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation.* 2003;107(14):1877–1883.
3. Kern MJ, Deligonul U, Tatineni S, Serota H, Aguirre F, Hilton TC. Intravenous adenosine: continuous infusion and low dose bolus administration for determination of coronary vasodilator reserve in patients with and without coronary artery disease. *J Am Coll Cardiol.* 1991;18(3):718–729.
4. Nakae I, Matsumoto T, Horie H, et al. Effects of intravenous nicorandil on coronary circulation in humans: plasma concentration and action mechanism. *J Cardiovasc Pharmacol.* 2000;35(6):919–925.
5. Tanaka N, Takahashi Y, Ishihara H, Kawakami T, Ono H. Usefulness and safety of intracoronary administration of nicorandil for evaluating fractional flow reserve in Japanese patients. *Clin Cardiol.* 2015;38(1):20–24.
6. Takashima H. Clinical impact of intracoronary nicorandil infusion compared to intravenous adenosine triphosphate on measurement of fractional flow reserve in intermediate coronary lesions. *JACC.* March 2013;61(Issue 10 Supplement).
7. Lim W-H, Koo BK, Nam C-W, et al. Safety and efficacy of novel hyperemic agent, nicorandil, for Fractional flow reserve measurement. *J Am Coll Cardiol.* 2014;63(12 Supplement):A1782.