Safety and efficacy of a novel hyperaemic agent, intracoronary nicorandil, for invasive physiological assessments in the cardiac catheterization laboratory

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Received 3 September 2012; revised 5 January 2013; accepted 20 January 2013; online publish-ahead-of-print 8 February 2013

Aims

Maximal hyperaemia is a key element of invasive physiological studies and adenosine is the most commonly used agent. However, infusion of adenosine requires additional venous access and can cause chest discomfort, bronchial hyper-reactivity, and atrioventricular conduction block. The aim of this study was to evaluate the feasibility and efficacy of intracoronary (IC) nicorandil as a novel hyperaemic agent for invasive physiological studies.

Methods and results

We enrolled 210 patients who underwent fractional flow reserve (FFR) measurement. Hyperaemic efficacy of the following methods was compared: IC bolus injection of adenosine; intravenous (i.v.) infusion of adenosine (140 μg/kg/min); and IC bolus of nicorandil (1 and 2 mg). In 70 patients, the index of microcirculatory resistance was also measured. Hyperaemic efficacy of IC nicorandil 2 mg was non-inferior to that of i.v. adenosine infusion (FFR: 0.82 ± 0.10 vs. 0.82 ± 0.10; P for non-inferiority, 0.001). There was a strong correlation between FFRs measured by i.v. adenosine and IC nicorandil (R² = 0.934). Nicorandil produced fewer changes in blood pressure, heart rate and PR interval, and less chest pain than adenosine (all P-values < 0.05). Atrioventricular block occurred in 12 patients with IC adenosine, 4 patients with i.v. adenosine and none with IC nicorandil. The index of microcirculatory resistance was 18.3 ± 8.7 with i.v. adenosine and 17.2 ± 7.6 with IC nicorandil (P = 0.126).

Conclusion

This study suggests that IC bolus injection of nicorandil is a simple, safe, and effective way to induce steady-state hyperaemia for invasive physiological evaluations.

Clinicaltrials.gov number: NCT01331902.

Keywords

Fractional flow reserve • Hyperaemia • Nicorandil

Introduction

The fractional flow reserve (FFR) is an epicardial lesion-specific parameter for the invasive physiological evaluation of coronary artery stenosis. An FFR-guided revascularization strategy has been reported to be better than an angiography-guided strategy in the management of patients with coronary artery disease.¹–³ FFR is calculated by the ratio of the distal coronary artery pressure (Pd) to the aortic pressure (Pa) obtained during hyperaemia.⁴ As Pd is determined by both epicardial stenosis and microvascular resistance, maximal hyperaemia is a critical prerequisite for the accurate measurement of the FFR. Intravenous (i.v.) infusion of

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adenosine through the central vein is a gold standard method for the induction of hyperaemia for invasive physiological assessment. However, this method requires additional venous access and the infusion of adenosine can cause chest discomfort, bronchial hyperreactivity, and atroventricular (AV) conduction delay. Therefore, a more convenient and safer hyperaemic agent may facilitate the use of FFR measurement in the cardiac catheterization laboratory. Nicorandil (Sigmart®, Chugai Pharmaceutical, Japan), a coronary vasodilator which acts on both macro- and microvascular systems, was reported to be safe and cardioprotective via intracoronary (IC) administration in patients with coronary artery disease. We performed this study to evaluate the feasibility and efficacy of IC nicorandil as a hyperaemic agent for invasive physiological assessment using a coronary pressure wire.

Methods

Study population

Patients with an angiographically intermediate lesion (visual estimation: 40–70%) 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 (<40%), primary valvular or myocardial disease, and contraindication to adenosine were excluded. The study protocol was approved by the institutional review board of each participating centre. All patients were properly informed prior to the procedure and gave their written consent to participate in the study.

Study protocol

Fractional flow reserve measurement

Coronary angiography was performed using 5–7 French guide catheters without side holes by a femoral or radial approach. Pressure measurements were performed using a 0.014-inch pressure guide wire (St Jude Medical, Minneapolis, MN, USA). Pd and Pa were recorded from baseline to maximal hyperaemia and then to the recovery. Maximal hyperaemia was presumed to be occurring when the maximal drop in distal pressure was identified. FFR was calculated by dividing the mean Pd by the mean Pa obtained during maximal hyperaemia. The time to the lowest FFR (time needed to reach >90% of the minimal value of Pd/Pa) and the plateau time (the time during FFR remained at >90% of its lowest value) were measured. The visual analogue scale pain score was assessed during i.v. infusion of adenosine and IC bolus of nicorandil. The hyperaemic mean transit time and the index of microcirculatory resistance (IMR) were measured using three injections of 3 mL of room temperature saline under maximal hyperaemia. IMR was calculated as Pd at maximal hyperaemia multiplied by the hyperaemic mean transit time. A 12-lead electrocardiogram (ECG) was performed at baseline, during i.v. infusion of adenosine and IC bolus of nicorandil. The PR interval was measured in Lead II by an independent cardiologist in a blinded fashion. IMR and ECG substudies were performed in 70 patients.

Protocol of hyperaemic stimuli

The hyperaemic efficacy of the following four successive methods was compared as illustrated in Figure 1: IC bolus injection of adenosine (80 µg in the left coronary artery; 40 µg in the right coronary artery); continuous i.v. infusion of adenosine (140 µg/kg/min); and IC bolus injection of nicorandil (1 and 2 mg). Continuous i.v. infusion of adenosine was performed via either a large forearm vein or a femoral vein. To exclude the possible influence of the sequence of pharmacological agents, the IC bolus and i.v. infusion of adenosine was followed by nicorandil IC bolus in the first half of the patients, and vice versa in the second half. A bolus of IC nitroglycerine (0.2 mg) was administered before each FFR measurement. Each hyperaemic stimulus was given after confirming that the Pa, Pd, and heart rate had recovered to their baseline values. An additional IC bolus of nicorandil 2 mg was given during maximal hyperaemia with i.v. infusion of adenosine in the patients included in the IMR and ECG substudies.

Quantitative coronary angiography

Quantitative coronary angiography (QCA) was performed by an independent analyser blinded to the results of the FFR. The external diameter of the contrast-filled guide catheter was used as a calibration standard. Using an edge detection system (CAAS 5.7 QCA system, Pie Medical, Maastricht, the Netherlands), the minimal luminal diameter and the reference diameter were measured and the percent diameter stenosis was calculated.

Statistical analysis

Based on the results of a previous study, the FFR in patients with angiographically intermediate stenosis was assumed to be 0.79 ± 0.07 with i.v. infusion of adenosine. Using a non-inferiority design with a non-inferiority margin of 0.02 (i.v. adenosine vs. IC nicorandil 2 mg) and an alpha value of 0.05, 193 patients would be required to gain 80% power. To allow for a 10% dropout rate, we included a total of 210 patients in this study.

Continuous variables were expressed as mean ± standard deviation or median and inter-quartile range (25–75th). Discrete variables were expressed as a frequency and a percentage. Differences in continuous variables with two different methods of hyperaemia were assessed by the paired t-test or by the Wilcoxon signed-rank test. Differences in FFR with three or more different methods of hyperaemia were analysed by repeated measures ANOVA. Comparison in the number of functionally significant stenoses with two different methods was conducted by McNemar’s test. A P-value <0.05 (two-sided) was considered statistically significant. All statistical analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL, USA).

Results

Between December 2010 and October 2011, 210 patients were prospectively enrolled from three university hospitals. Sixteen patients were excluded owing to the following reason: incomplete pressure recording in six patients, guide catheter instability in five patients, pressure drift in three patients, prolonged AV block after the first dose of adenosine in one patient and, wiring failure in one patient. FFR comparisons were finally available in 194 patients. Clinical and angiographic characteristics of study subjects are summarized in Table 1.

Hyperaemic efficacy

The hyperaemic efficacy among different methods of hyperaemia is summarized in Table 2 and Figure 2. The FFR with an IC bolus of nicorandil 2 mg (0.82 ± 0.09) was non-inferior to that with continuous i.v. infusion of adenosine (0.82 ± 0.10) (P for non-inferiority <0.001). Nicorandil 1 mg showed less hyperaemic efficacy than 2 mg (FFR: 0.84 ± 0.09 vs. 0.82 ± 0.09, P < 0.001). A strong and linear correlation was observed between FFRs with i.v. infusion
of adenosine and an IC bolus of nicorandil 2 mg ($R^2 = 0.967, y = x, P < 0.001$) (Figure 3). The agreement between the two sets of measurements was good with a mean difference of 0.002 and a standard deviation of 0.024 (Figure 4). In five patients, FFR with adenosine i.v. infusion exceeded the FFR with nicorandil 2 mg IC bolus by >0.05, and in three vice versa. The time to the lowest FFR was shorter with an IC bolus of nicorandil than with i.v. infusion of adenosine [17.5 ± 4.6 (median 17.0) vs. 43.0 ± 15.9 (median 40.5) s, $P < 0.001$] and the plateau time of an IC bolus of nicorandil was 26.1 ± 10.4 (median 27.3) s.

The number of functionally significant stenoses under four different methods of hyperaemia is shown in Table 3. The FFR was 0.75 in 37 (19.1%) patients with an IC bolus of nicorandil 2 mg and 40 (20.6%) patients with i.v. infusion of adenosine ($P = 0.453$ by McNemar’s test). The number of patients with FFR <0.80 was 67 (34.5%) with IC nicorandil and 60 (30.9%) with i.v. infusion of adenosine ($P = 0.210$ by McNemar’s test).

An additional IC bolus of nicorandil 2 mg was injected during continuous i.v. infusion of adenosine in 70 patients who did not have AV block with adenosine administration. Figure 5 demonstrates the FFR in each of the 70 patients with three different methods of adenosine administration. Adding a nicorandil bolus injection to adenosine continuous i.v. infusion did not have an additive hyperaemic effect when compared with adenosine i.v. or nicorandil bolus alone (nicorandil + adenosine vs. nicorandil vs. adenosine: 0.82 ± 0.10 vs. 0.82 ± 0.10 vs. 0.82 ± 0.10, respectively; $P = 0.361$ by repeated measures ANOVA). The index of

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**Table 1** Baseline characteristics ($n = 194$)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.0 (56.3–70.0)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>129 (66.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.5 (23.1–26.7)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>121 (62.4)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>53 (27.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>137 (70.6)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>35 (18.0)</td>
</tr>
<tr>
<td>Clinical diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>122 (62.9)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>22 (11.3)</td>
</tr>
<tr>
<td>Silent ischaemia</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>64.0 (58.0–68.0)</td>
</tr>
<tr>
<td>Studied artery</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA</td>
<td>152/19/23</td>
</tr>
<tr>
<td>Quantitative coronary angiography</td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter, mm</td>
<td>1.6 (1.2–2.1)</td>
</tr>
<tr>
<td>Percent diameter stenosis, %</td>
<td>54.3 (42.0–70.0)</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>3.0 (2.7–3.2)</td>
</tr>
</tbody>
</table>

Values given are medians (inter-quartile range, 25–75th) or n (%).
LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

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**Figure 1** Outline of the hyperaemic stimuli protocol. In protocol 1, an intracoronary bolus and intravenous infusion of adenosine was followed by intracoronary bolus of nicorandil. In protocol 2, intracoronary bolus of nicorandil was followed by the intracoronary bolus and intravenous infusion of adenosine. Pa, Pd, and ECG were obtained during each hyperaemic stimulus. The index of microcirculatory resistance was measured with intravenous infusion of adenosine and intracoronary bolus of nicorandil. ADO, adenosine; ECG, electrocardiogram; IC, intracoronary; IMR, index of microcirculatory resistance; i.v., intravenous; NCR, nicorandil; NTG, nitroglycerine; Pa, aortic pressure; Pd, distal coronary pressure.
microcirculatory resistance was $18.3 \pm 8.7$ (median 16.7) with i.v. infusion of adenosine and $17.2 \pm 7.6$ (median 14.5) after IC bolus of nicorandil.

### Table 2  Hyperaemic efficacy between two different methods of induction of hyperaemia

<table>
<thead>
<tr>
<th></th>
<th>Adenosine infusion</th>
<th>Nicorandil bolus, 2 mg</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 194$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.83 (0.77–0.89)</td>
<td>0.84 (0.77–0.89)</td>
<td>0.327</td>
</tr>
<tr>
<td>Time to the lowest FFR, s</td>
<td>40.5 (33.5–49.0)</td>
<td>17.0 (15.0–19.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plateau time, s</td>
<td>27.3 (17.0–33.3)</td>
<td></td>
<td></td>
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<tr>
<td>$n = 70$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperaemic mean transit time, s</td>
<td>0.21 (0.16–0.28)</td>
<td>0.18 (0.15–0.28)</td>
<td>0.137</td>
</tr>
<tr>
<td>Index of microcirculatory resistance</td>
<td>16.7 (13.0–20.0)</td>
<td>14.5 (11.7–20.7)</td>
<td>0.126</td>
</tr>
</tbody>
</table>

Values given are medians (inter-quartile range, 25–75th). FFR, fractional flow reserve.
*P-value for superiority, by the Wilcoxon signed-rank test.

### Figure 2  Comparison of fractional flow reserve among four different methods of induction of hyperaemia. FFR, fractional flow reserve; IC, intracoronary; i.v., intravenous.

### Discussion

Various pharmacological stimuli to induce maximal hyperaemia for an invasive physiological study have been evaluated,\(^{14–16}\) and the continuous infusion of adenosine via a central vein has been considered as the gold-standard method of hyperaemia.\(^{14,17}\) However, this method requires relatively large doses of adenosine,\(^{15,18}\) and requires an additional procedure for femoral vein access. While the IC bolus injection of adenosine is easy and simple, the hyperaemic efficacy of this method is suboptimal in some patients.\(^{19,20}\) Moreover, this method cannot provide sufficient hyperaemic duration for pressure pullback tracing and IMR measurement. Adenosine administration is associated with adverse effects such as AV block, bronchial hyper-reactivity, and chest pain.\(^{15,18}\) In a recent study,\(^{21}\) a single i.v. bolus of
regadenoson, a selective A2A receptor agonist, showed a similar hyperaemic effect to i.v. adenosine infusion for FFR measurement. However, the study population was small and therefore further studies are needed to validate its clinical applicability for invasive physiological assessments.5

Nicorandil is a nicotinamide ester and has a dual mechanism of action. This agent opens ATP-sensitive potassium channels, thereby causing dilatation of coronary resistant arterioles and possesses a nitrate moiety which dilates epicardial coronary arteries.22 Nicorandil has been approved as an anti-anginal drug that possesses cardioprotective properties.23 The safety and cardioprotective effect of IC administration of nicorandil has been confirmed by several studies.6–11 However, its feasibility and efficacy to induce maximal hyperaemia for various invasive physiological studies has not yet been fully evaluated.

**Hyperaemic efficacy**

The hyperaemic efficacy of IC bolus of nicorandil 2 mg was not inferior to continuous i.v. infusion of adenosine, and the number of functionally significant stenoses was not different between the two methods although there were numerical differences. As the usual dosage of an IC nicorandil bolus in many clinical studies was 1–2 mg,6,9,24 we compared the hyperaemic efficacy of 1 and 2 mg of nicorandil, finding that nicorandil 1 mg did not achieve adequate hyperaemic efficacy. Although we did not investigate the hyperaemic efficacy of doses >2 mg, the appropriate dosage of IC nicorandil to induce maximal hyperaemia seems to be 2 mg as there was no difference in the FFR with i.v. infusion of adenosine.

**Nicorandil for index of microcirculatory resistance measurement**

The IMR is a physiological parameter used to assess microvascular function.12 In our study, there were no differences in the mean hyperaemic transit time and the IMR between an IC bolus of nicorandil and i.v. infusion of adenosine. IC bolus of nicorandil was faster in reaching the lowest FFR than i.v. infusion of adenosine and provided longer hyperaemic duration than an IC bolus of adenosine. Therefore, IC nicorandil can be used for IMR measurement as well as for pressure pullback tracing. However, the plateau time of 26 s may be insufficient to measure the IMR for the less experienced operators and to perform pressure pullback tracings in complex lesions. Therefore, IC nicorandil may be less suitable than i.v. infusion of adenosine in those circumstances.

**Safety**

Casella et al.25 reported that transient AV block rate by IC bolus adenosine 60 μg was 8% and the incidence of AV block was reported to have a positive correlation with the dosage of adenosine. In our study, i.v. infusion of adenosine caused more prolongation of the PR interval than IC bolus of nicorandil. A transient AV block occurred in 12 patients with an IC bolus of adenosine and in 4 patients with i.v. infusion of adenosine. However, no patients...

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**Figure 3** Correlation of fractional flow reserve between intracoronary bolus of nicorandil (2 mg) and intravenous infusion of adenosine (140 μg/kg/min).
experienced an AV block with nicorandil administration. The influence on systemic blood pressure and heart rate was smaller with IC nicorandil than with i.v. adenosine. Therefore, nicorandil seems to be safer than adenosine and can be used in patients with contraindications to adenosine.

Limitation
First, continuous i.v. infusion of adenosine was performed through both the femoral vein and the large forearm vein in our study. Therefore, the possibility of suboptimal hyperaemia with i.v. infusion of adenosine cannot be completely excluded. However, a recent study reported that the hyperaemic efficacy of i.v. infusion of adenosine using a forearm vein was comparable with that using a femoral vein. Secondly, the hyperaemic efficacy of a higher dosage of nicorandil was not evaluated in this study. Although the appropriate dosage of IC nicorandil to induce maximal hyperaemia seems to be 2 mg as we have previously described, this may need to be confirmed in future studies. Thirdly, as this was not a blinded study, there could have been a small amount of subjectivity in the interpretation of pressure tracings. Fourthly, nicorandil is not available in all countries. With evidence of its benefit in patients with myocardial infarction or slow flow and this study showing the possibility of its novel indication, this situation may well change in the near future.

Conclusion
The hyperaemic efficacy of the administration of an IC bolus of nicorandil 2 mg was comparable with continuous i.v. infusion of adenosine for FFR and IMR measurements. This study suggests that an IC bolus injection of nicorandil is a simple, safe, and effective way to induce steady-state hyperaemia for invasive physiological evaluations in patients undergoing angiography in a cardiac catheterization laboratory. The use of this novel agent may encourage
interventional cardiologists to perform FFR measurement in their patients to optimize interventional procedures.

Funding
This work was supported by grants from the Innovative Research Institute for Cell Therapy and the Clinical Research Center for Ischemic Heart Disease (0412-CR02-0704-0001) sponsored by the Ministry of Health & Welfare, Republic of Korea.

Conflict of interest: none declared.

References

Figure 5 Individual values of the fractional flow reserve among three different methods of hyperaemic induction (n = 70). See Figure 1 for abbreviations.

Table 4 Haemodynamic changes and pain score according to hyperaemic agents

<table>
<thead>
<tr>
<th></th>
<th>Adenosine infusion</th>
<th>Nicorandil bolus, 2 mg</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔBlood pressure, mmHg</td>
<td>−16.0 (−21.0 to −11.0)</td>
<td>−12.0 (−15.0 to −10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔHeart rate, /min</td>
<td>5.0 (1.0–8.0)</td>
<td>2.0 (1.0–5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔPR interval, ms</td>
<td>8.0 (3.0–17.0)</td>
<td>4.0 (0–10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n = 194</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS pain score</td>
<td>0 (0–4.0)</td>
<td>0 (0–0.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values given are medians (inter-quartile range, 25–75th). VAS, visual analogue scale.
*P-value for superiority by the Wilcoxon signed-rank test.