High Index of Microcirculatory Resistance Level After Successful Primary Percutaneous Coronary Intervention Can Be Improved by Intracoronary Administration of Nicorandil

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Background: Although microvascular dysfunction following percutaneous coronary intervention (PCI) can be evaluated with the index of microcirculatory resistance (IMR), no method of treatment has been established. We hypothesized that intracoronary administration of nicorandil can improve IMR after successful primary PCI in patients with ST-segment elevation myocardial infarction (STEMI).

Methods and Results: In 40 patients with first STEMI after successful primary PCI, IMR was measured using PressureWire™ Certus (St. Jude Medical, MN, USA). In 20 of the patients (Group N), IMR was measured at baseline and after intracoronary nicorandil (2 mg/10 ml). In the other 20 patients (Control), IMR was measured at baseline, after intracoronary saline (10 ml) and after intracoronary nicorandil (2 mg/10 ml). In Group N, IMR significantly decreased after intracoronary nicorandil (median IMR, 27.7–18.7 U, P<0.0001). In the Control group, IMR did not change after saline administration (median IMR, 24.3–23.8 U, P=0.8193), but was significantly decreased after intracoronary nicorandil (median IMR, 23.8–14.9 U, P<0.0001). Next, all 40 patients were divided into subgroups by tertile of baseline IMR. In those with intermediate to high IMR (baseline IMR ≥21), intracoronary nicorandil significantly decreased IMR, although it did not change IMR in those with low IMR (baseline IMR <21).

Conclusions: High IMR levels in patients with STEMI after successful primary PCI can be improved by intracoronary administration of nicorandil. (Circ J 2010; 74: 909–915)

Key Words: Acute myocardial infarction; Index of microcirculatory resistance; Microcirculation; Nicorandil
tricular function after ST-segment elevation MI (STEMI). Although microvascular injury following PCI can be evaluated with IMR, no method of treatment has been established. Several groups have shown that coronary microvascular resistance is predominantly regulated by adenosine triphosphate-sensitive potassium (K-ATP) channels. Nicorandil is a vasodilator that exerts effects both as a nitrate and a K-ATP channel activator. It has been reported that nicorandil dilates coronary resistance vessels less than 100 μm in diameter by opening K-ATP channels, which increases coronary blood flow and improves microcirculation. Although intravenous and intracoronary administrations of nicorandil prior to PCI have been reported to prevent no-reflow/slow-flow phenomenon after PCI, they have not yet been clearly proven to improve abnormal coronary microcirculation after PCI. In the present study, intracoronary administration of nicorandil was performed in patients with STEMI after successful primary PCI to determine whether nicorandil can improve IMR.

Methods

A total of 40 patients (age >18 years) admitted to Osaka Saiseikai Senri Hospital between February 2008 and February 2009 for their first episode of STEMI after successful primary PCI within 24 h of symptom onset were included in the study population. The diagnosis of STEMI was made on the basis of chest pain for more than 30 min and 0.1 mV ST-segment elevation in 2 continuous ECG leads. Exclusion criteria were cardiac shock, history of old MI, severe liver and/or renal dysfunction, history of allergic response to drugs and severe hypovolemia. The study was approved by the Osaka Saiseikai Senri Hospital Ethics Committee. All patients provided informed written consent.

Following arrival, all patients diagnosed with first STEMI received a bolus administration of nicorandil at 0.067 mg/kg followed by 24-h intravenous infusion at 1.67 μg·kg⁻¹·min⁻¹. Antiplatelet therapy was administered with a loading dose of 300 mg of clopidogrel or 200 mg of ticlopidine and 200 mg of aspirin before primary PCI regardless of background therapy. Prior to coronary angiography, all patients received intravenous heparin (8,000 U before PCI) and intracoronary nitroglycerin (200 μg).

Following urgent coronary angiography, repulsion was achieved by passing a guidewire through the infarct-related artery (IRA) and then all patients underwent aspiration thrombectomy with several repetitions of aspiration. Balloon pre-dilatation was performed for patients in whom an extraction catheter could not be advanced into the lesion. Distal protection was performed at the discretion of the operator.

Coronary Physiological Measurements

After successful stenting of the culprit lesion, PressureWire™ Certus (St. Jude Medical, MN, USA) was advanced through the guiding catheter and positioned in the distal two-thirds of the IRA, which was beyond the stented region. This wire has a microsensor at 3 cm from the floppy tip, which enables simultaneous high-fidelity recording of coronary pressure and temperature with accuracies of 1 mmHg and 0.02°C. The shaft of the wire, acting as additional electric resistance, can be used as a second thermistor, recording the input signal at the coronary ostium of any fluid injection with a temperature different from blood. Proximal aortic and distal coronary pressures were recorded simultaneously. A single bolus of 12 mg intracoronary papaverine was used as a hyperemic agent. Hyperemic mean transit time was determined by averaging the transit times after 3 injections of 3 ml of room-temperature saline through the guiding catheter as previously described.

Study Protocols

This study was a non-randomized, prospective, single-center study. Patients were divided into 2 groups. One group was given nicorandil (Group N) and the other was given saline as a control (Control group).

Group N

Between February 2008 and September 2008, 20 consecutive patients underwent baseline IMR measurement immediately after successful primary PCI for first STEMI, then received intracoronary administration of nicorandil 2 mg diluted with physiological saline 10 ml over 30 s and underwent IMR measurement again (Figure 1).

Control Group

Between October 2008 and February 2009, 20 consecutive patients underwent baseline IMR measurement immediately after successful primary PCI for first STEMI, then received intracoronary administration of physiological saline (10 ml) 5 min after baseline IMR and underwent IMR measurement again.

To examine how long the effect of intracoronary administration of nicorandil persists, following the above-described session, patients received nicorandil 2 mg and underwent IMR measurement again.
Nicorandil Improves Microvascular Dysfunction in AMI

measurements immediately after and 10 min after nicorandil administration (Figure 1).

Other Measures of Microvascular Function and Infarct Size
Myocardial blush grade (MBG) was categorized into 4 classes densitometrically, based on visual assessment of contrast opacification of the IRA area. The corrected TIMI frame count (cTFC) was defined as the number of frames required for the dye to reach standardized distal landmarks. The images were independently analyzed offline by 2 experienced interventional cardiologists blind to IMR results. Blood samples for creatine kinase (CK) and CK-MB measurements were drawn before PCI and at 1, 2, 6, 9, 12, 18, 24, 36, 48 and 72 h after reperfusion. Peak CK and peak CK-MB were defined as the highest CK and highest CK-MB values measured, respectively.

Coronary Risk Factors
Coronary risk factors were determined as follows: diabetes, a history of diabetes and/or a fasting plasma glucose concentration ≥126 mg/dl and/or a glycosylated hemoglobin level ≥6.5% detected during the hospital stay; hypertension, a history of hypertension and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; dyslipidemia, a history of dyslipidemia and/or LDL cholesterol ≥140 mg/dl and/or HDL cholesterol <40 mg/dl and/or triglyceride ≥150 mg/dl.

Statistical Analysis
Values are the mean±standard deviation, percentages, or medians (interquartile ranges). The Wilcoxon signed-rank test was used for paired comparisons. The unpaired t-test or the Mann–Whitney test was used for unpaired comparisons. The Fisher’s exact or chi-squared test was used to examine differences between categorical variables. Spearman correlation analysis was performed to assess correlations. P-values <0.05 were considered significant. Statistical analysis was performed using JMP 7.0.1 (SAS Institute Inc, NY, USA).

Results
Baseline Patient Characteristics
Between February 2008 and February 2009, a total of 40 patients were divided into the 2 groups described above.

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<tr>
<th>Table 1. Baseline Characteristics of the Patients</th>
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<td>Age (years)</td>
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<td>Male gender</td>
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<td>Multivessel disease</td>
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<td>Peak CK-MB (IU/L)</td>
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<td>Onset-to-balloon time (min)</td>
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<td>Door-to-balloon-time (min)</td>
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Values are numbers (%), mean (SD) or median (interquartile ranges).

<table>
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<th>Table 2. Changes in IMR in Patients in Group N and Control</th>
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<td>IMR</td>
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<td>Baseline (U)</td>
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<td>Post (U)</td>
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<td>Absolute changes (U)</td>
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<td>Relative changes (%)</td>
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Values are median (interquartile ranges).

IMR, index of microcirculatory resistance; Baseline, immediately after percutaneous coronary intervention; Post, immediately after administration of nicorandil or saline.

Absolute changes were calculated as Baseline IMR–Post IMR. Relative changes were calculated as 100 [(Baseline IMR–Post IMR)/Baseline IMR].
Patient and lesion characteristics are shown in Table 1. No significant difference was found between the study groups with respect to age, sex, prevalence of coronary risk factors, prevalence of angina pectoris, type of IRA, initial TIMI flow grade, collateral flow grade, prevalence of multivessel diseases, Killip class, time from onset to balloon, or time from door to balloon.

**Effects of Nicorandil on Coronary Microcirculation**

Table 2 shows IMR at baseline and following intracoronary administration of nicorandil or saline and Figure 2 shows changes in IMR. No significant difference was observed in baseline IMR between Group N and the Control. In Group N, IMR significantly decreased after intracoronary administration of nicorandil (median IMR, 27.7–18.7 U, P<0.0001). IMR did not change after intracoronary administration of saline (median IMR, 24.3–23.8 U, P=0.8193). In the Control group, IMR values at baseline and after saline administration were very strongly correlated (ρ=0.98, y=0.99x+0.30, P<0.0001). Absolute changes (Baseline IMR – Post IMR) in Group N were significantly larger than those in the Control group (10.0U vs –0.05U, P<0.0001). The relative changes (100×(Baseline IMR – Post IMR)/Baseline IMR) in Group N were thus also significantly larger than those in the Control group (33.4% vs 0.4%, P<0.0001).

**Duration of Effects of Nicorandil**

In the Control group, patients received intracoronary administration of nicorandil following measurement of IMR after intracoronary administration of saline. IMR was decreased significantly from 23.8(11.5–49.6) U after saline administration to 14.9(11.1–18.5) U after nicorandil administration (P<0.0001). When IMR measurement was repeated 10 min after nicorandil administration to determine whether the effect of nicorandil persisted, IMR at 10 min after nicorandil administration was 14.9(10.5–17.0) U, and did not differ significantly from the value immediately after nicorandil administration (P=0.6150).
Stratified Analysis of the Effect of Nicorandil

In the 40 patients, baseline IMR approximately 15 min after reperfusion was 26.5 (18.1–48.3) U, with a mean value of 35.7 U. Following administration of nicorandil, IMR was significantly decreased to 16.8 (13.5–21.9) U, with a mean value of 19.8 U (P<0.0001). Absolute change in IMR after administration of nicorandil (8.9 [2.2–21.4] U) was strongly correlated with baseline IMR (\(\rho=0.95\), \(y=0.72x–9.68\), P< 0.0001) (Figure 3).

Change in IMR after intracoronary administration of nicorandil was examined in subgroups of patients by tertile of baseline IMR. In the patients with intermediate IMR (baseline IMR 21–<37) and those with high IMR (baseline IMR \(\geq 37\)), intracoronary administration of nicorandil decreased IMR significantly (intermediate IMR group: 25.9 [23.5–28.7] U to 15.9 [14.5–21.4] U, P=0.0002; high IMR group: 67.1 [43.1–82.9] U to 29.0 [20.6–40.8] U, P=0.0001) (Figures 4B, C). However, in the low IMR group (baseline IMR <21), no significant change in IMR due to intracoronary administration of nicorandil was observed (13.5 [8.4–
Based on the results of tertile analysis, a subanalysis of patients with baseline IMR ≥21 was conducted between Group N (n=14) and the Control group (n=13). Baseline IMR did not differ significantly between the groups (33.4 [26.6–68.0] U in group N vs 37.8 [24.3–67.3] U in Control, P=0.9420). IMR after intracoronary administration was significantly lower in Group N (21.3 [17.4–31.4] U) than in the Control group (38.7 [23.8–68.0] U) (P=0.0071) (Figure 5). These findings suggest that although the effect of nicorandil is larger in patients with more severe coronary microvascular dysfunction as indicated by high IMR, complete normalization of IMR cannot be achieved in such patients. In contrast, IMR may be completely normalized with nicorandil in patients with intermediate degrees of coronary microvascular dysfunction.

Relationships Between IMR and Measures of Microvascular Function and Infarct Size
After all patients received intracoronary administration of nicorandil, 17 of 40 patients achieved a final MBG of 3. Median cTFC after intracoronary administration of nicorandil was 23.8 (19.8–28.6). Median peak CK and peak CK-MB were 2,040 (1,319–2,968) IU/L and 224 (148–339) IU/L, respectively.

Correlations of these factors with IMR after intracoronary administration of nicorandil were evaluated. For the 40 patients evaluated, significant correlations were observed between IMR after administration of nicorandil and MBG (ρ=−0.32, P=0.0456), cTFC (ρ=−0.44, P=0.0044), peak CK (ρ=−0.33, P=0.0399) and peak CK-MB (ρ=−0.32, P=0.0477).

Discussion
Determination of IMR immediately after PCI is a real-time method enabling quantification of the severity of coronary microcirculatory disorder. IMR can also be used to confirm the importance of adjunctive therapy performed with PCI. In the present study, determination of baseline IMR after successful primary PCI revealed that intracoronary administration of nicorandil, a K-ATP channel opener, decreased IMR significantly, and that the decrease in this index was larger in patients with higher coronary vascular resistance (ie, patients with higher IMR).

In the Control group, intracoronary administration of physiological saline in the same volume as nicorandil solution did not induce changes in IMR. The change in IMR in patients receiving nicorandil was thus confirmed to be an effect of nicorandil rather than the volume of carrier solution. The absence of changes in IMR from baseline to after administration of saline, which was carried out 5 min after baseline IMR, indicated excellent reproducibility of IMR determination even during the acute phase (approximately 15 min) after reperfusion in lesions of acute MI.

Evaluation Using IMR
Many researchers are interested in the finding that abnormal coronary microcirculation persists in patients with STEMI in whom reperfusion has been achieved after primary PCI and its effect on long-term prognosis. Fearon et al reported that the mean IMR in patients with STEMI following primary PCI was 39 U, similar to the mean IMR, 35.7 U, observed in the present study in patients immediately after primary PCI. These values were substantially higher than the mean IMR (21.9–23.0 U) in patients with stable coronary artery disease without obvious microvascular dysfunction. These findings suggest the presence of abnormal coronary microcirculation immediately after reperfusion in patients with STEMI.

In the present study, a substantial decrease in IMR was observed following intracoronary administration of nicorandil at 2 mg in patients with STEMI. To our knowledge, this is the first report of induction of a decrease in IMR following PCI by pharmacological treatment. Following administration of nicorandil, mean IMR was decreased to 19.8 U, a level similar to that observed in patients with stable coronary artery disease (21.9–23.0 U). The absence of effect of nicorandil on IMR in patients in the lowest tertile of baseline IMR (IMR <21) suggests that the normal IMR level can be considered less than 21 U. The absence of a significant difference between Group N and the Control group post-IMR may be due to the fact that baseline IMR was less than 21 U as considered in the Control group. In fact, a subanalysis of patients with an IMR ≥21 revealed that the post-IMR value was significantly lower in Group N than in the Control group.

Because the decrease in IMR after nicorandil administration might have been caused by a washout effect of the intracoronary saline infusion or may have represented the natural course of change in IMR over time, we administered an intracoronary saline injection after determination of baseline IMR at the same volume and with the same timing as the nicorandil administration. Intracoronary administration of saline did not affect IMR, and the absence of effects of carrier solution and time (over at least 5 min) indicated that nicorandil itself affected IMR.

Repeated measurement of IMR 10 min after intracoronary administration of nicorandil did not reveal significant changes. It has been reported that the increase in coronary blood flow induced by bolus injection of nicorandil is only transient, and that coronary blood flow peaks at 1–2 min and returns to baseline 5 min after administration. Because the decrease in IMR induced by nicorandil lasted for at least 10 min, improvement of abnormal coronary microcirculation may be prolonged once nicorandil normalizes the coronary microcirculation. Patients with high IMR following PCI should receive additional pharmacotherapy with agents such as nicorandil to decrease IMR.

Improvement of Coronary Microcirculation by Nicorandil
Several mechanisms to improve coronary microcirculation using nicorandil have been proposed. The first is to dilate coronary microvessels (<100 μm) so that coronary blood flow increases as a result of the K-ATP channel-opening effect. A second mechanism is to relieve microvascular spasm caused by vasopressors. An increase in the blood flow through microvessels may improve the function of a stunned myocardium. A third hypothesis is based on a report that demonstrates nicorandil acting as a direct radical scavenger. Because reperfusion disorder resulting from polymorphonuclear leukocyte activation and free radical production is believed to play a role in the progression of microcirculatory disorder after reperfusion, nicorandil can be expected to control this type of disorder.

Safety
It has been reported that intracoronary administration of nicorandil may cause arrhythmia therefore appropriate measures should be taken to prevent this from occurring in the treatment for acute MI. In the present study, nicorandil 2 mg
was infused in an intracoronary fashion for 30 s. No patients experienced arrhythmia and nicorandil could thus be given safely to them.

**Study Limitation**

A limitation of this study is the absence of follow-up data. Although the decrease in IMR induced by nicorandil can be expected to improve cardiac function and clinical outcome, this could not be confirmed because follow-up data were not available. In this context, a prospective double-blind study of nicorandil should be performed to examine whether a decrease in IMR using nicorandil improves cardiac function and clinical outcome.

**Conclusion**

High IMR levels in patients with first STEMI after successful primary PCI can be improved by intracoronary administration of nicorandil.

**Disclosures**

There were no funding sources or conflicts of interest.

**References**