Continuous Administration of Nicorandil Decreases QT Dispersion During the Chronic Phase of Acute Myocardial Infarction

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SUMMARY

We previously reported that continuous intravenous (IV) administration of nicorandil (NIC) inhibits QT dispersion (QTd). However, no prior study has evaluated the efficacy of NIC when administered orally to acute myocardial infarction (AMI) patients following continuous IV administration.

Thirty patients with anteroseptal infarction in whom revascularization was performed successfully within 6 hours of AMI onset were included in the study and assigned to one of 3 groups: group A (continuous IV administration of NIC), group B (continuous IV and oral administration of NIC), and group C (no treatment with NIC). After 24 hours, QTd in groups A and B was significantly decreased compared to QTd in group C ($P < 0.01$) (group A, 58.1; group B, 58.2; and group C, 81.3). The QTd obtained 3 months later was significantly shorter in group B subjects who were orally administered NIC, and QTd before percutaneous coronary intervention (PCI) was restored in group A, in which no NIC had been administered orally [group A, 66.7; group B, 54.1; and group C, 73.9; $P < 0.05$ (group A versus group B) and $P < 0.01$ (group B versus group C)].

The effects were evaluated by comparing different routes of administration. Continuous IV and subsequent oral administration of NIC inhibited prolongation of QTd, suggesting that these effects may prevent the occurrence of cardiac events during both the acute and chronic phases of AMI. (Int Heart J 2006; 47: 351-361)

Key words: QT interval, Electrocardiography, Potassium channel opener, Oral administration

EARLY reperfusion reportedly determines the prognosis for acute myocardial infarction (AMI).1-3 However, according to previous reports, myocardial contrast...
echocardiography has been used to detect a no-reflow phenomenon induced by a microcirculation disorder, although cardiac angiographic thrombolysis in myocardial infarction (TIMI) grade 3 was achieved by early reperfusion.\(^4\text{-}^6\) Since the no-reflow phenomenon was a factor reported to contribute to left ventricular remodeling and hospital complications,\(^7\) both improved blood flow through the infarct-related artery and microcirculation may be significant.

Several approaches have been used to determine the prognosis of AMI, among them the noninvasive approach of QT dispersion (QTd) in standard 12-lead electrocardiography (ECG). Various hypotheses have been advanced regarding the relationship between AMI and QTd and its implications for left ventricular function, occurrence of arrhythmia, and mortality rates.\(^8\text{-}^{11}\)

Nicorandil (NIC) exhibits a dual mechanism of action, functioning as both a nitrate and an adenosine triphosphate (ATP)-sensitive potassium channel opener.\(^12\) Attention has focused on reperfusion injury prevention or myocardial protection resulting from its potassium channel-opening action.\(^13\text{-}^{15}\) NIC has also been reported to inhibit QTd in patients with AMI\(^16\) and patients undergoing palliative PCI.\(^17,18\) Based on our study of AMI patients, we previously reported that continuous IV administration of NIC inhibits QTd.\(^17,19\)

However, no prior study has evaluated the efficacy of NIC when administered orally to AMI patients following continuous intravenous (IV) administration. This comparative study was undertaken to confirm the significance of continuous IV administration of NIC during the acute phase of AMI and subsequent oral administration beginning in the subacute phase.

The aim of the present study was to clarify whether the effects of NIC were induced by continuous IV administration during the acute phase or by oral administration during the chronic phase, using QTd as a surrogate marker.

**METHODS**

**Study subjects:** Among 98 AMI patients transferred to Rakuwakai Otowa Hospital between April 2002 and March 2004, 30 patients with anteroseptal infarction were enrolled in this study. Successful revascularization (achievement of TIMI grade 3) had been performed within 6 hours of the onset of AMI in all 30 patients. In addition, no antiarrhythmic drugs or β-blockers with the potential to affect QTd were used, except for aspirin, heparin, nitrates, and angiotensin-converting enzyme inhibitors. Prior to commencing the study, the objectives of the study were explained in detail and informed consent was obtained from all subjects.

**Protocol:** Following the diagnosis of AMI, 30 AMI patients were randomly divided into 3 groups (Table I). Group A consisted of 10 AMI patients who were
continuously treated by IV administration of NIC (4 mg/hr) before percutaneous coronary intervention (PCI) and subsequent intracoronary administration of NIC (2 mg) immediately after reperfusion (However, continuous IV administration of NIC was discontinued 48 hours later). Group B consisted of 10 AMI patients who were treated by continuous IV drip infusion and intracoronary administration of NIC before PCI, as in group A. In group B, oral administration of NIC (15 mg/day) was initiated from the third day of hospitalization. Group C was a control group consisting of 10 AMI patients to whom no NIC was administered. ECGs were recorded for all patients (with patients resting on their backs) at the 4 following points in time: on admission (Pre), at 24 hours after PCI (24H), at the 1-month point (1M), and at the 3-month point (3M).

In addition, the time course changes in cardiac function were recorded by echocardiography. Ejection fraction (EF), left ventricular diastolic dimension

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<th>Table I. Profile of Patients</th>
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<tr>
<td>Number (M/F)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Time to revascularization (min)</td>
</tr>
<tr>
<td>Maximum CPK level (mg/dL)</td>
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<tr>
<td>Echocardiography on admission EF (%)</td>
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<tr>
<td>LVDD (mm)</td>
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<td>LVDS (mm)</td>
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Values are mean (± SD). CPK indicates creatine phosphokinase; EF, echocardiographic ejection fraction; LVDD, left ventricular diastolic dimension; and LVDS, left ventricular systolic dimension.

<table>
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<th>Table II. Echocardiographic Measurements</th>
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<td>On admission</td>
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<td>Group A</td>
</tr>
<tr>
<td>EF</td>
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<td>LVDD</td>
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<td>LVDS</td>
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<td>Group B</td>
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<td>EF</td>
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<td>LVDS</td>
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<tr>
<td>Group C</td>
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<tr>
<td>EF</td>
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<td>LVDD</td>
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Values are mean (± SD). 24H indicates 24 hours later; 1M, month later; 3M, 3 months later; EF, echocardiographic ejection fraction; LVDD, left ventricular diastolic dimension; and LVDS, left ventricular systolic dimension.
(LVDD), and left ventricular systolic dimension (LVDS) were measured at the 4 specified time points.

**ECG analysis:** Recorded ECG data were digitized and the QT was analyzed automatically using QT analysis software (QTD-1 versus 01-02, Fukuda Denshi Co., Ltd.) to evaluate changes in QTd. All measurements of values were entirely mechanical and free of subjective compensation. A single ECG recording consisted of 10 heart beats. The mean value of QTd was used as the value for QTd in individual patients.

**Statistical analysis:** All measured values are expressed as the mean ± standard deviation (SD). The time course of variables was analyzed by analysis of variance. If significant differences emerged, multiple comparisons between the 2 groups were performed using Fisher's protected least significant difference post-hoc test. A value of $P < 0.05$ was considered significant.

**RESULTS**

1) **Baseline characteristics:** Table I shows a profile of patients enrolled in the study. No significant differences were observed among the 3 groups with respect to age, time to revascularization, maximum creatine phosphokinase level, EF, LVDD or LVDS obtained on admission.

2) **Time course changes in cardiac function measured by echocardiography:** Table II shows the time course changes in EF, LVDD, and LVDS measured by echocardiography. Though small differences were noted among the 3 groups at the 4 time points, no statistically significant difference was observed.

3) **Comparison of QTd:** Since analysis showed that the time course of QTd differed significantly among the 3 groups ($P < 0.01$), the time course of QTd in each group and intergroup differences at the respective time points were evaluated. Table III shows the measured values.

   Figure 1 and Table III show the changes in QTd in groups A, B, and C. In group A, although the value for QTd obtained at 24 hours (24H) was lower than the value obtained before PCI (Pre), the QTd values obtained at 1 and 3 months were similar to the Pre value for QTd. In group B, the value for QTd obtained at 24 hours was lower than the Pre value, an effect found to persist at 1 and 3 months. In group C, the 24H value for QTd increased, and QTd remained elevated at 1 and 3 months, despite a slight decrease.

   Figure 2 and Table III show the changes in QTd obtained before PCI (Pre), at 24 hours, at 1 month, and at 3 months after PCI. Pre values for QTd did not differ significantly among the 3 groups. Although the 24H value of QTd did not differ significantly between groups A and B, it was significantly higher in group C than in groups A or B ($P < 0.01$). One month after PCI, group B showed the low-
est QTd, and the 1M value for QTd differed significantly between groups A and B ($P < 0.05$), groups B and C ($P < 0.01$), and groups A and C ($P < 0.05$). Three months later, group B still showed the lowest QTd, while the 3M value for QTd differed significantly between groups A and B ($P < 0.05$) and between groups B and C ($P < 0.01$). However, there was no significant difference in the 3M value for QTd between groups A and C.

In patients treated by continuous IV administration of NIC during the acute phase of AMI (groups A and B), the value for QTd decreased significantly 24 hours after PCI, though the 24H value for QTd increased in group C. Patients in
group A, who were not treated orally with NIC, showed a 1M value for QTd similar to the Pre value. However, the 1M values for QTd remained at lower levels in group B patients, who were treated orally with NIC.
These findings suggest that oral administration of NIC following continuous IV administration may help maintain lower QTd, once reduced during the acute phase of AMI.

4) **Comparison of QT interval**: Figure 3 shows the time courses of maximal and minimal QT interval values in groups A, B and C. In all 3 groups, both the maximum and minimum values obtained at 24 hours, 1 month, and 3 months did not differ significantly from the Pre values.

5) **Example of standard 12-lead electrocardiogram (ECG)**: Figure 4 shows typical ECG wave forms in groups A, B and C. There appeared to be no significant differences in the T wave, QT interval, and ST segment between groups A and B. However, in group C, prolongation of the QT interval was observed at all time points compared to the other 2 groups, and of note, a negative T wave was observed in leads V₁ to V₄ at 1 month. Furthermore, a diphasic T wave or a U wave was observed at 3 months.
DISCUSSION

1) Pharmacological action of NIC: NIC is a hybrid chemical compound that exhibits a dual mechanism of action, functioning as both a potassium channel opener and a nitrate. Its nitrate-like action on large coronary arteries opens ATP-sensitive potassium channels, dilating coronary resistance vessels and increasing coronary blood flow. However, NIC has also been reported to reduce the extent of experimentally induced myocardial infarctions. Since the effects of NIC do not depend on increased coronary blood flow, a direct effect on the myocardium may be associated with these effects (pharmacological preconditioning). Furthermore, NIC prevents ischemic myocardial cell necrosis, an effect reportedly attributable primarily to the opening of mitochondrial potassium channels. Thus, NIC may dilate coronary arteries as well as protecting the myocardium.

2) AMI and QTd: Several previous studies have reported a relationship between AMI and QTd. To be more specific, QTd obtained 4 weeks after reperfusion was reported to predict 5-year mortality rates, although this was not found to be true for early QTd. In addition, the association of QTd with myocardial viability was also reported, and the salvaging of regions at risk before the development of infarction may inhibit QTd. A relationship between NIC and QTd has been reported in patients undergoing palliative PCI who were treated with oral medications and injections. In a recent report, continuous IV administration of NIC inhibited QTd 48 hours after PCI, as well as preventing the development of lethal arrhythmia.

In this study, NIC improved QTd during both the acute and chronic phases of AMI. However, the major mechanism of this action remains unclear. Since all patients in this study were treated with a nitrate, differences in QTd among the 3 groups may have been induced primarily by the potassium channel-opening action of NIC. From this point, we will discuss the effects of NIC during the acute and chronic phases separately.

3) Effects of NIC in the acute phase: In this study, NIC was continuously administered to AMI patients during the acute phase, resulting in a significant decline in QTd 24 hours after PCI compared to the control group.

Adequate myocardial reperfusion could not be obtained in certain AMI patients, even after successful revascularization by early reperfusion. This may have been due to the no-reflow phenomenon associated with microcirculation disorders, such as reperfusion injury in myocardial cells caused by Ca overload.

Continuous administration of NIC in AMI patients initiated before reperfusion has been reported to prevent the no-reflow phenomenon and to improve regional wall motion, mean coronary flow rate, and ST-resolution.

With regard to the effects of NIC during the acute phase, potassium channels opened after IV administration of NIC decreased the extent of the stunned myo-
cardium by improving microcirculation, likely preserving myocardial viability and subsequently inhibiting the prolongation of QTd.

In addition, NIC may have reduced the duration of active potentials by opening potassium channels, thereby likely decreasing the maximal QT interval.\textsuperscript{28} Unfortunately, due to the limited number of subjects enrolled in this study, the maximum value for the QT interval did not differ among the 3 groups, although a declining trend was observed.

Thus, the acute phase effects of NIC may have been induced by the direct action of potassium channels on QT and the preservation of myocardial viability after inhibition of reperfusion injury.

4) Effects of NIC in the chronic phase: Following continuous IV administration, NIC was administered orally, resulting in persistent inhibition of the prolongation of QTd. However, the prolongation of QTd was not inhibited in AMI patients who were treated solely by continuous IV administration of NIC.

The mechanism of this action may involve pharmacological preconditioning by NIC.\textsuperscript{29} During the chronic phase, since prolonged ischemia can increase QTd, NIC may return QTd to normal levels by inducing ischemic preconditioning immediately after reperfusion and thereafter.

Moreover, a basic study has reported that oral administration of NIC initiated from the day after the onset of AMI inhibited the development of myocardial fibrosis.\textsuperscript{30} Furthermore, inhibition of remodeling,\textsuperscript{31} induction of anti-inflammatory reactions,\textsuperscript{32,33} and prevention of apoptosis\textsuperscript{34,35} after the administration of NIC have also been reported. The chronic phase effects of NIC may have been induced by these mechanisms.

The results of this study suggest that continuous oral administration of NIC following continuous IV administration inhibits the prolongation of QTd at 1 and 3 months after PCI. As described previously, QTd obtained at 1 month was reported to reflect the prognosis of AMI more precisely than that obtained during the acute phase. Thus, oral administration of NIC may improve AMI prognosis. A study using patients with stable angina, 66\% of whom had a history of AMI, reported that NIC inhibited the occurrence of cardiovascular events.\textsuperscript{36} This study also indicated the efficacy of orally administered NIC in AMI patients.

**Conclusions:**

1. This study evaluated the effects of NIC in AMI patients by comparing routes of administration. Continuous IV administration of NIC initiated from the early stages after the onset of AMI inhibited the prolongation of QTd during the acute phase. Oral administration of NIC following continuous IV administration also inhibited the prolongation of QTd during the chronic phase of AMI.

2. These findings suggest that continuous IV and oral administration of NIC may help safeguard against cardiac events during both the acute and chronic
phases of AMI.

**Limitations:** Although the results of this study suggested the usefulness of orally administered NIC in AMI patients beginning in the subacute phase, certain study limitations must be noted. First, the number of subjects enrolled was limited. Second, the clinical significance of QTd as used in this study remains controversial. Third, the clinical effects of NIC, including improved cardiac function or protection against sudden death or lethal arrhythmia, have yet to be confirmed. Nevertheless, since oral administration of NIC maintained the above acute phase effects, we plan to continue evaluating the clinical significance of this finding after increasing the number of enrolled subjects.

**REFERENCES**


