Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K+ channel opener nicorandil

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Background It is not known whether pretreatment with nicorandil, an ATP-sensitive K+ channel (KATP channel) opener, induces a preconditioning effect independent of increased collateral recruitment.

Methods Forty-four patients with angina who underwent percutaneous transluminal coronary angioplasty (PTCA) to proximal left anterior descending artery (LAD) stenosis were randomly allocated for pretreatment with an intravenous injection of 80 g/kg nicorandil 5 min before initial ballooning (n=22) or saline (n=22). 99mTc tetrofosmin was injected during balloon inflation, quantitative analysis of occlusion images by SPECT was conducted, and the defect severity score (SS) was calculated. An ECG was recorded during the 2-min inflation to calculate the sum of ST elevation ($\Delta$ST).

Results $\Delta$ST levels were significantly reduced in patients with nicorandil pretreatment compared with control patients (control: 1.89±0.85 mV, nicorandil: 1.24±0.57 mV, p=0.0052). However, no difference was observed in defect severity (control: 79.0±32.5, nicorandil: 98.7±48.9 ns). A close correlation was observed between SS and $\Delta$ST in both groups (nicorandil group R²=0.505, control group R²=0.599). A multivariate regression model demonstrated that both defect severity ($p<0.0001$) and pretreatment with nicorandil ($p<0.001$) were significantly related to the level of $\Delta$ST, suggesting a cellular protective effect against ischaemia by nicorandil, independent of myocardial blood flow.

Conclusion Nicorandil pretreatment resulted in the induction of myocardial preconditioning independent of the severity of ischaemia.

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KEYWORDS
Angina pectoris; K+ channel opener; Ischemic preconditioning; Coronary angioplasty; Radionuclide imaging

Introduction
Animal studies suggest that repeated brief coronary occlusions render the heart resistant to subsequent episodes of myocardial ischaemia by a phenomenon known as ischaemic preconditioning. 1,2 Several studies suggest that this preconditioning effect is due to the activation of ATP-sensitive K+ channels (KATP channel). 3–5 A clinical study in humans involving percutaneous transluminal coronary angioplasty (PTCA) found that blockade of the KATP channel with glibenclamide prevented the preconditioning effect of PTCA.

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effect normally seen in this angioplasty model during repeated balloon inflation,6 suggesting that the KATP channel plays a central role in preconditioning in human. Nicorandil is an antianginal drug whose properties lie between those of nitrates and K+ channel openers.7,8 The IONA study, a recently completed randomized placebo control trial, clearly demonstrated a significant reduction in major coronary events after the oral administration of nicorandil to patients with stable angina.9 This drug has also been shown to be effective in the treatment of a variety of ischaemic heart diseases such as chronic stable angina, variant angina, and acute myocardial infarction.10–12

We previously demonstrated that nicorandil pre-treatment reduces ST segment elevation during transient coronary occlusion by PTCA model.13 However, it is unclear whether this antiischaemic property is the result of a cellular protective effect independent of the increased coronary blood flow to the ischaemic lesion. The purpose of this study was to demonstrate that nicorandil induces a cellular protective effect independent of increased collateral blood flow in humans.

Methods

Subjects

After obtaining informed consent, we studied 44 patients with angina who underwent elective PTCA to proximal left anterior descending artery (LAD) stenosis, with a normal electrocardiogram (ECG) at rest, normal left ventricular wall motion, and no severe stenosis (>75% stenosis) in the right coronary artery and the left circumflex artery. Patients who experienced antecedent anginal pain within 7 days before angioplasty were excluded because the anginal episode might induce the preconditioning state.14 Among the 44 patients, 22 were randomly allocated to nicorandil pretreatment, and 22 to saline. This study was not a double blind manner, but that instead, only the assessors were blinded to study treatment. The backgrounds of patients in each group are shown in Table 1.

Catheterization procedure: Coronary angioplasty was performed using 7F guiding catheters and the over-the-wire dilatation system according to standard procedures. Patients were pretreated with aspirin and ticlopidine at least 1 week before the procedure. Antianginal medication including Ca antagonists, nitrates, beta-blockers was not discontinued. No patients had been prescribed drugs affecting the potassium channels such as nicorandil, aminophylline, adenosine, and glibenclamide before this study. Seven thousands units of heparin were administered to all patients to prolong the activated clotting time beyond 300 s during the procedure. In the nicorandil pretreatment group, 80 g/kg of nicorandil was injected through the cubital vein 5 min prior to the initial balloon inflation. In the control group, 5 ml of saline was injected instead of nicorandil 5 min prior to balloon inflation. After placing the guiding catheter and guidewire, the balloon catheter was placed on the lesion just after the baseline ECG recording. Two minutes of balloon inflation was then initiated, and 740 MBq of 99mTc tetrofosmin was injected via the femoral vein for the quantification of ischaemic severity (Fig. 1).

The quantification of ST change

A 12-lead surface electrocardiogram was monitored throughout the study. Only ST levels in the leads with an ST elevation of more than 0.1 mV at 80 ms after J point at 1 min after ballooning, were measured and summed for the calculation of ∑ST by investigators who were blinded to the patients treatment (Fig. 2).

The quantification of ischaemia severity

99mTc tetrofosmin was injected during balloon inflation, and SPECT acquisition was performed after all PTCA procedures were completed. SPECT imaging was obtained with a wide field of view rotating a gamma camera (ZLC-7500, Siemens Co Ltd) equipped with a low energy, high resolution parallel hole collimator on the 140 KeV photo peak with a 30% window. The camera was rotated through 180° in an elliptical orbit around the patient’s
thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 each. The data were collected in a 64×64 array with a pixel size of 4.5 mm. Transaxial slices were reconstructed using a filtered back projection algorithm with a Butterworth filter without attenuation and scatter correction. Short axis tomograms were reconstructed from the transaxial slices and polar maps of regional tetrofosmin distribution were displayed. Each polar map was normalized for peak myocardial activity and compared with our normal limits: pixels with a tracer uptake <2.5 SD below the mean normal values were considered abnormal. Two types of polar maps were generated (Fig. 3). In the extent map, the abnormal area on each short axis slice was first multiplied by a factor that corrected the spatial distortion and allowed for differences in the myocardial slice mass from the apex to base. The corrected abnormal area was then summed to obtain the total extent of ischaemia, expressed as a percentage of the left ventricular surface. In the severity map, the value of each pixel was computed such that if the pixel was above the normal limit, it was assigned a value of 1. If below, it received a fractional value linearly dependent on how far it fell below the normal limit. The severity score is then calculated as the average pixel value in the abnormal area multiplied by the number of the abnormal pixels. Therefore, severity score specifically represents the severity of hypoperfusion during balloon occlusion. In this study, the severity score was used for the quantification of flow to the ischaemic zone during ballooning. This scintigraphical assessment of ischaemia was also performed by the investigators who were blinded to the patients’ treatment.

Statistical analysis
Statistical analysis was performed using Statview version 5.0. Comparison of continuous values
between the two groups were analysed using the non-paired t-test, and expressed as mean±standard deviation (SD). The change of heart rate, blood pressure, and rate pressure product by nicorandil or saline administration were analysed using paired t-test. Chi-square analysis was used to assess the distribution of categoric variables such as risk factors and coronary segment within the groups. Correlations between SS and ΣST were evaluated by Pearson's correlation analysis. A multivariate regression model was used to test the significance of nicorandil pretreatment independent of SS (as an index of oxygen supply to ischaemic lesion) and rate-pressure product (as an index of oxygen demand) by applying the following formula: \( \Sigma ST = a \times SS + b \times \text{rate-pressure product} + c \times \text{nicorandil} + d \). In this model, a value of 1 was applied to cases without nicorandil pretreatment, and a value of 0 was applied to cases with nicorandil pretreatment. \( p < 0.05 \) was considered statistically significant.

### Results

#### Patients characteristics in each group

The clinical and anatomical features of the two groups of patients are summarized and presented in Table 1. No significant difference was observed in their backgrounds including age, gender, the presence or absence of risk factors, and the severity of coronary stenosis assessed by quantitative coronary angiography. Coronary angioplasty was successfully performed in all 44 patients. All procedures were free of complications, with no ECG or enzymatic evidence of myocardial injury.

#### Haemodynamic effect of nicorandil

The haemodynamic effect of nicorandil is shown in Table 2. Nicorandil administration did not produce significant changes in systolic, diastolic, heart rate, or rate-pressure product at the time of balloon inflation. These values were not different from those of the control group, suggesting no difference in oxygen consumption between the two groups.

#### The difference of ST elevation (Fig. 4)

ΣST ranged from 0.25mV to 3.4 mV (mean: 1.89±0.85) in the group without nicorandil pretreatment, and from 0.54 to 1.7 mV (mean: 1.24±0.57) in the group with nicorandil. This difference was statistically significant (95% CI: lower 0.13, upper 0.95, \( p = 0.0052 \)).
The difference of ischaemia severity
(Fig. 5)

The severity score (SS) of $^{99m}$Tc tetrofosmin imaging ranged from 16.3 to 136.5 (mean: 79.0±32.5) in the group without nicorandil pretreatment, and from 16.0 to 170.9 (mean: 98.7±48.9) in the group with pretreatment. This difference was not statistically significant.

The relationship between ST elevation and ischaemia severity

A close correlation was observed between SS and $\Sigma$ST in both groups, and the regression line of the control group is steeper than that with the pretreatment of nicorandil as shown in Fig. 6. Multiple linear regression analysis yielded a significant relation between $\Sigma$ST and nicorandil pretreatment as well as SS and no significant relation with double product ($\Sigma$ST=0.010×SS+0.842×nicorandil+0.00004×double product−0.242, SE of regression coefficient, standardized correlation coefficient and p value; Severity score: SE 0.002, SCC 0.555 p<0.001, nicorandil: SE 0.187, SCC 0.595 p<0.0001, double product: SE 0.00005 SCC 0.102 p=0.4) suggesting a cellular protective effect against ischaemia with nicorandil pretreatment.

Discussion

This study clearly demonstrated that an intravenous administration of nicorandil produced a suppressed ST segment elevation during a brief period of ischaemia, and this effect was not entirely attributable to increased perfusion to the ischaemic bed as measured by nuclear method.

The relationship between myocardial perfusion abnormalities and ST segment shift

In clinical evaluation of preconditioning phenomenon particularly using PTCA model, ST level, which we used as the index of cellular response to ischaemia, is deeply influenced by the presence or absence of the flow to ischaemic bed. Experiments suggest that, during acute ischaemia, the magnitude of ST segment changes reflects the size of the ischaemic area. Pfisterer et al. studied 25 patients during elective PTCA of a single LAD lesion and found perfusion defects on the occlusion images obtained using $^{99m}$Tc sestamibi. They found a significant difference between proximal and distal lesions, and, most importantly, the only
factor relating to the presence or absence of the perfusion defect was the presence of collateral vessels. Furthermore, we recently demonstrated that the extent and severity of the defect at myocardial perfusion in the area of the occluded artery are highly correlated with the collateral flow reserve which is a theoretically and clinically well validated index of collateral circulation calculated from the coronary pressure during balloon occlusion, and can be used for quantitative assessment of the collateral blood flow in conscious humans. This study is consistent with these findings that angiographically-similar coronary lesions may differ in functional severity which is highly variable.

Assessment of myocardial perfusion during PTCA with $^{99m}$Tc tetrofosmin

$^{99m}$Tc tetrofosmin is a reliable myocardial flow tracer over a physiological range of flow with minimal redistribution, similar to $^{99m}$Tc sestamibi. Tracer uptake by myocytes is a metabolism-dependent process that may be inhibited by gross metabolic blocking, but is probably not related to adenosine triphosphate levels, and does not involve cation channel transport, including the K$_{ATP}$ channel, which is currently ascribed a pivotal role in ischaemic preconditioning. Therefore, the injection of $^{99m}$Tc tetrofosmin during angioplasty allows an accurate assessment of the effect of acute coronary occlusion on myocardial perfusion even under nicorandil pretreatment.

The mechanism of suppression of ST elevation by nicorandil pretreatment

Some of the mechanisms proposed to explain the differences in the perfusion and ST segment shift relationship with nicorandil could be discounted. Firstly, nicorandil at the dose used in this study changed neither the afterload nor the rate-pressure product, which is calculated as the index of myocardial oxygen consumption. Any decrease in the latter parameter would be expected to attenuate the total burden of ischaemia, however, this was not the case with nicorandil. The augmentation of oxygen delivery to the ischaemic myocardium could also be a potential mechanism for cardioprotection from acute ischaemia. Animal experiments and human studies have produced pharmacological evidence that nicorandil can induce coronary artery vasodilatation and stimulate the recruitment of collateral vessels. In the present study, no difference in ischaemic severity was observed between the two groups suggesting that the augmentation of oxygen delivery did not play a major role in the reduction of ST elevation. Thus, the main cardioprotective mechanism of nicorandil may be attributable to its direct effect on the myocyte probably via K$_{ATP}$ channel.

Comparison with previous studies of the induction of the cellular protective effect by nicorandil

Previous reports have clearly demonstrated the beneficial effect of nicorandil on the ventricular performance and ischaemia tolerance induced during exercise in patients with ischaemic heart disease. Our previous study using same PTCA model in human clearly demonstrated that the preconditioning effect of nicorandil pretreatment deserves in as much degree as the 3 min preceding ischaemia prior to reference ischaemia. However, none of these studies explained the confounding effect of collateral circulation on cellular protection against ischaemia, because no definitive data on myocardial blood flow at the time of ischaemia was available. Only two studies demonstrated that nicorandil prolongs the intrinsic ability of cardiac myocytes to withstand ischaemia in a clinical setting using a PTCA model. In these studies, the effect of collateral circulation is eliminated by using the coronary flow velocity of the lesion distal to the occlusion site and great cardiac vein oxygen saturation. As with our study, the ST elevation response was significantly reduced in patients with nicorandil pretreatment compared with the control regardless of no difference in the flow velocity or great cardiac vein oxygen saturation.

Conversely, inhibition of the K$_{ATP}$ channels with glibenclamide, a K$_{ATP}$ channel blocker, prevents nicorandil, aprikalim, and cromakalim from exerting a cardioprotective effect in animals. Furthermore, in human PTCA, Tomai et al. observed that patients undergoing PTCA procedures lose their ability to acquire progressive tolerance to ischaemia during successive balloon inflations when their potassium channels are pharmacologically blocked. These observations, including those of our study, clearly support the hypothesis that K$_{ATP}$ channels play a key role in this protective effect.

Study limitations

This study has several limitations. Firstly, double blind placebo control design was not employed. However, the selection and measurement of objective ECG, and the analysis of scintigraphical quantification of ischaemia severity were carried
out by examiners blinded to patient information regarding nicorandil pretreatment. Secondly, patients with recent angina were excluded to avoid a myocardium in which an ischaemic insult had occurred during daily activity. A previous report suggested that the majority of ischaemic episodes occurring during normal activities are asymptomatic. Although we excluded those patients suspected of having a defective anginal warning system, such as diabetes, old myocardial infarction, and severe multivessel disease sufferers (only patients with LAD stenosis without significant stenosis in other vessels were studied), this methodological limitation may have influenced our results. Thirdly, the presence of concomitant pharmacological agents-aspirin, ticlopidine, Ca channel blockers, and long-acting nitrates was an additional confounding factor. However, no difference was observed in terms of the level of pharmacological agents between the control and nicorandil groups, therefore it is unlikely that this influenced the results relative to the comparisons between nicorandil and the control.

**Conclusion**

The results of this study strongly support the hypothesis that nicorandil has a cardioprotective action, suggesting that the drug is effective for pharmacological preconditioning. The attenuation of ischaemic damage by pretreatment of nicorandil appears to confer protection in patients undergoing PTCA and CABG.

**References**


