
Objective: To compare the effects of nicorandil (a hybrid ATP sensitive potassium channel (K\textsubscript{ATP} channel) opener/nitric oxide donor) with those of isosorbide dinitrate (ISDN) on myocardial microcirculation and cardiac function in patients with acute myocardial infarction (AMI) who had undergone reperfusion treatment by direct balloon angioplasty.

Design: Double blind randomised study.

Patients: 60 patients with AMI in Killip class I.

Interventions: Patients were assigned into two treatment groups: a nicorandil group (n = 30) and an ISDN group (n = 30). Each drug was infused intravenously at 6 mg/h for 72 hours starting at admission and was administered directly to the treated coronary artery immediately after angioplasty.

Results: Compared with ISDN, nicorandil more frequently caused recovery of ST segment elevation just after reperfusion (15 of 27 (55.5%) in the nicorandil group v 5 of 26 (19.2%) in the ISDN group, \(p = 0.006\)). The nicorandil group had higher values of averaged peak velocity 40 minutes after reperfusion (mean (SD) 24.8 (13.3) cm/s v 16.0 (11.1) cm/s, \(p = 0.045\)) and higher values of regional wall motion of the infarcted area three weeks after onset of AMI (–1.78 (1.11) SD/chord, \(p = 0.046\)).

Conclusions: A combination of nicorandil drip infusion starting before reperfusion and intracoronary injection immediately after reperfusion is more effective than a similarly performed infusion of ISDN in preserving myocardial microcirculation in the reperfused AMI area. The nicorandil regimen resulted in better left ventricular regional wall motion.

Coronary reperfusion is now widely used to restore blood flow to the jeopardised myocardium in patients with acute myocardial infarction (AMI). However, several studies have shown that about 20% to 35% of angiographically successful recanalisations of an infarct related artery fail to salvage ischaemic myocardium. This unfavourable outcome is related to a discrepancy between an open epicardial coronary artery and the absence of blood flow (no reflow) in the damaged distal microvessels.

Nicorandil, a hybrid molecule comprising an ATP sensitive potassium channel (K\textsubscript{ATP} channel) opener and a nitric oxide donor, has been approved as a treatment for angina pectoris in Japan and Europe. Recently, a large clinical trial, the IONA (impact of nicorandil on angina) study, showed that nicorandil reduces the frequency of cardiovascular events in patients with stable effort angina compared with placebo. Nicorandil promotes the recovery of post-ischaemic contractile dysfunction and reduces infarct size in animals. Numerous mechanisms for the salutary actions of nicorandil include the ATP channel, TIMI, thrombolysis in myocardial infarction.
and intracoronary artery infusion immediately after angioplasty to elicit maximal effects of the study drugs as adjunctive treatments. Because abrupt activation of $K_{ATP}$ channels has been shown to be proarrhythmic,18 we slowly injected both drugs into the treated coronary artery over a period of 60 seconds. Heparin infusion was continued for 72 hours and systolic blood pressure was kept below 150 mm Hg by intravenous drip infusion of nicardipine after angioplasty. Systemic blood pressure and the pulse in the left arm were measured by specially trained nurses at 7 am, noon, 5 pm, and 9 pm every day during the first seven days. The results of all 28 measurements were averaged. Serum concentrations of creatine kinase were measured every four hours from admission until they peaked and began to fall. The decision of whether to administer angiotensin converting enzyme inhibitors and $\beta$ blockers was left to the attending physician. Cardiac catheterisation was repeated three weeks after onset of AMI.

### Outcome assessment

The total ST segment elevation excluding aVR (defined as $\sum_{ST}$) was measured when TIMI 0 or 1 flow was confirmed before reperfusion. The $\sum_{ST}$ was also examined when TIMI 2 or 3 flow was confirmed for the first time after reperfusion by angioplasty. The isoelectric line was selected at the level of the PQ junction and ST segment elevation was measured at the J point. Posterior and lateral AMIs ($n = 7$) were excluded from the electrocardiographic analysis. The change in $\sum_{ST}$ at reperfusion was classified into one of the following two groups according to degree: decrease of $\geq$ 20% (ST recovered); and decrease of < 20% or increase (ST not recovered) as described previously.19

The status of the collateral circulation was defined as reported by Rentrop and colleagues.20 Left ventriculography was performed about 30 minutes (21–40 minutes) after the reperfusion and three weeks after the onset of AMI. One observer without knowledge of the patients’ data carefully traced all left ventricular end diastolic and end systolic endocardial contours. Left ventricular end diastolic volume index and end systolic volume index were determined. Global left ventricular ejection fraction was determined by the area-length method. Regional left ventricular wall motion was measured by the centre line method and expressed as SD/chord, as described elsewhere.19 21 Posterior and lateral AMIs were excluded from regional wall motion analysis.

Coronary blood flow velocity was measured about 40 minutes (31–60 minutes) after the reperfusion with a
Doppler guidewire connected to a real time spectrum analyser, as described elsewhere.\(^2\) Time averaged peak velocity was computed on line and continuously recorded on videotape. The peak systolic antegrade flow velocity and frequency of early systolic retrograde flow were also analysed.

### Statistical analysis

Data are presented as mean (SD). Groups were compared with Student’s \(t\) test or analysis of variance with Fisher’s post hoc test for continuous variables and \(\chi^2\) test for categorical values, as appropriate. A probability value of \(p < 0.05\) was considered to indicate significance.

### RESULTS

#### Baseline characteristics

There were no significant differences between the nicorandil and ISDN group with regard to age, sex, diabetes, preinfarction angina, infarction site, TIMI grade before and after angioplasty, collateral grade, time from onset to reperfusion, blood pressure, heart rate, use of stents, administration of angiotensin converting enzyme inhibitors and \(\beta\) blockers, or maximum serum concentrations of creatine kinase (table 1).

#### Electrocardiogram

Nicorandil more frequently caused recovery of ST segment elevation just after reperfusion (15 of 27 (55.5%)) than did ISDN (5 of 26 (19.2%), \(p = 0.006\)).

#### Left ventriculography

Regional wall motion of the infarct area 30 minutes after reperfusion was significantly greater in the nicorandil group than in the ISDN group (mean (SD) \(-1.75 (1.03)\) \(v\) 2.66 (1.16) SD/chord, \(p = 0.015\)). This effect continued for the three weeks after the onset of AMI (\(-1.78 (1.11)\) \(v\) 2.50 (1.04) SD/chord, \(p = 0.046\)) (fig 1). There were no differences in left ventricular volume between the two treatment groups (fig 2).

#### Coronary flow measurements

Of the coronary flow velocity variables measured 40 minutes after reperfusion, averaged peak velocity (APV) and peak systolic antegrade flow velocity (PVS) were higher in the NIC group than in the ISDN group. Frequency of early systolic retrograde flow (ESRF) was lower in the NIC group.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Major complications</th>
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<tbody>
<tr>
<td></td>
<td>Nicorandil (n = 30)</td>
</tr>
<tr>
<td>Sustained VT (rate &gt; 100 beats/min)</td>
<td>1/30 (3.3%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>3/30 (10%)</td>
</tr>
<tr>
<td>Ventricular rupture</td>
<td>0/30 (0%)</td>
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VT, ventricular tachycardia.
Coronary flow velocity was measured with a Doppler guide-oxycardiovascular mediators. In a recent study we conducted leucocyte plugging in microvessels, and production of shear through mechanisms such as spasm of microvessels, arterioles with diameters such as ISDN do not dilate small arteries and injury ("stunned myocardium").

Restoration of myocardial perfusion immediately after coronary revasculatization is an important mechanism for salvaging the post-ischaemic myocardium. According to a double blind study of 300 patients with AMI who underwent coronary angiography, abiciximab, a glycoprotein IIb/IIIa antagonist, plus stenting improved the primary end point (a composite of death, reinfarction, or urgent revasculatization of the target vessel), TIMI flow classification before and after stenting, and left ventricular function six months after onset compared with placebo plus stenting. Abiciximab has not been approved in Japan yet and the cost effectiveness of this drug requires further study before it can be used routinely. In previous studies, salutary actions of nicorandil on the coronary microcirculation were assessed by myocardial contrast echocardiography. In the present study, coronary flow velocity was measured with a Doppler guide-wire to assess myocardial perfusion. Inakura and colleagues found a strong correlation between no reflow (shown by myocardial contrast echocardiography) and early systolic retrograde flow (measured by Doppler guidewire). The nicorandil group had a higher coronary flow velocity after reperfusion and a lower frequency of early systolic retrograde flow than the ISDN group. Dilatation of smaller arterioles is an important factor in the extent of myocardial stunning, and the size and functional recovery after ischaemia-reperfusion. KATP channel activators dilate resistant vessels (especially arterioles with diameters < 100 μm) and increase collateral blood flow. Contrast, pure nitric oxide donors such as ISDN do not dilate small arteries and arterioles with diameters < 100 μm. Leucocytes are key players in the aggravation of post-reperfusion microcirculation through mechanisms such as spasm of microvessels, leucocyte plugging in microvessels, and production of oxyradical mediators. In a recent study we conducted with in vivo and in vitro methods, nicorandil and a specific mitochondrial KATP channel opener (diazoxide) suppressed the following processes of leucocyte activation: leucocyte pseudopod formation in the presence of N-formyl-methionyl-leucyl-phenylalanine under shear stress; adhesion of leucocytes to postcapillary venular endothelial cells; and extravascular migration of leucocytes in rat mesenteric microvessels subjected to ischaemia-reperfusion. An increase in shear rate caused by increased microvessel flow induced by a KATP channel activator may also reduce neutrophil recruitment because leucocyte attachment to and migration through inflamed vessels is somewhat dependent on shear rate. In addition, Gross et al. and Pieper et al. found that the beneficial effects of nicorandil in recovery from ischaemia-reperfusion injury may be due partly to inhibition of free radical production by leucocytes.

In a recent large clinical trial (n = 5126), nicorandil significantly reduced the number of cardiovascular events in patients with stable effort angina compared with placebo (relative risk reduction 15%, p = 0.025) during a follow up period of up to three years. This supports the benefit of pharmacological preconditioning in the management of stable angina. In addition, recent experiments with knockout mice have clearly documented that KATP channel subunits Kir 6.2 and sulfonylurea receptor 2 have important roles in preventing fatal vasospastic angina.

Conclusion
Nicorandil administered in a combination of drip infusion starting during the ischaemic period and intracoronary injection immediately after reperfusion was more effective than a similarly performed infusion of ISDN in preserving the myocardial microcirculation in relatively low risk patients with AMI. The result was improved left ventricular wall motion in the infarction zone. The present results suggest the need for a large clinical trial to determine whether nicorandil should be recommended for patients with AMI.

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REFERENCES
Nicorandil versus ISDN for cardioprotection in AMI

FROM BMJ JOURNALS

Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study

Harry Hemingway, Martin Shipley, Annie Britton, Michael Page, Peter Macfarlane, Michael Marmot

Objective: To investigate the prognosis of angina among people with and without diagnosis by a doctor and an abnormal cardiovascular test result.

Design: Prospective cohort study with a median follow up of 11 years.

Setting: 20 civil service departments originally located in London.

Participants: 10 308 civil servants aged 35–55 years at baseline.

Main outcome measures: Recurrent reports of angina; quality of life (SF-36 physical functioning); non-fatal myocardial infarction; death from any cause (n = 344).

Results: 1158 (11.4%) participants developed angina, and 813 (70%) had no evidence of diagnosis by a doctor at the time of the initial report. Participants without a diagnosis had an increased risk of impaired physical functioning (age and sex adjusted odds ratio of 2.36 (95% confidence interval 1.91 to 2.90)) compared with those who had neither angina nor myocardial infarction throughout follow up. Among reported cases of angina without a diagnosis, the 15.5% with an abnormality on a study electrocardiogram had an increased risk of death (hazard ratio 2.37 (1.16 to 4.87)). These effects were similar in magnitude to those in participants with a diagnosis of angina.

Conclusion: Undiagnosed angina was common and had an adverse impact on prognosis comparable to that of diagnosed angina, particularly among people with electrocardiographic abnormalities. Efforts to improve prognosis among people with angina should take account of this submersed clinical iceberg.