Prevention of endothelial dysfunction by nicorandil through reduction of oxidative stress in diabetic rats

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Introduction and Objective
• Diabetes is thought as an independent major risk factor for the cardiovascular disease mortality.
• Endothelial dysfunction plays a central role in diabetic cardiovascular diseases.
• Nicorandil, an anti-anginal drug, was reported to have cardioprotective effect in diabetes patients (1). Nicorandil also have an endothelial protective effect in both basic and clinical studies (2,3).
• The purpose of this study was to evaluate the protective effect of nicorandil on endothelial function in streptozotocin (STZ)-induced diabetic rats.

Methods
Animals
Male SD rats (6 weeks old) were intraperitoneally administered STZ (40 mg/kg, once a day for 3 days) to induce diabetes.

Treatments
Nicorandil (15 mg/kg/day) and tempol (radical scavenger, 20 mg/kg/day) were administered by drinking water for a week from 3 weeks after STZ administration.

Flow-mediated dilation (FMD)
Four weeks after STZ administration, FMD was measured as an indicator of endothelial function. Diameter change of femoral artery after 5 min occlusion of iliac artery was measured by high-resolution ultrasound system (4) (Vevo 770, Visual Sonics).

Protein analysis
Four weeks after STZ administration, femoral artery was harvested for analysis by western blotting for p47phox, a NADPH oxidase subunit, and eNOS. NOx analysis
For the measurement of NO production, the serum concentration of NOx (nitrate + nitrite) was measured by Griess method.

Reactive oxygen species (ROS) analysis
Normal human coronary artery endothelial cells (HCAECs) were exposed to high glucose (30 mM) with or without nicorandil (100 μM) or L-NAME (300 μM) for 24 hour. The production level of ROS was monitored using the fluorescent probe 2′,7′-dichlorodihydrofluorescein diacetate (H2DCFDA).

Conclusion
Nicorandil prevents diabetes-induced endothelial dysfunction via the reduction of oxidative stress. Endothelial protective effect of nicorandil may partly contribute to the reduction of cardiovascular events in diabetic patients.

Result 1
Nicorandil prevented diabetes-induced FMD reduction without changes in reactive hyperemia and NTG-induced vasodilation.

Result 2
Tempol prevented FMD reduction in STZ rats.

Result 3
In STZ rats, nicorandil inhibited the increased expression of p47phox and eNOS in femoral artery.

Result 4
Serum NOx levels was not increased in STZ rats. Nicorandil did not affect it.

Result 5
In HCAECs, nicorandil or L-NAME inhibited high glucose-induced ROS production.

Result 6
Nicorandil did not change in body weight, blood glucose, blood pressure and heart rate in STZ rats.

Disclosure of conflict of interest
All presenters earn salary from Chugai Pharmaceutical Co., Ltd.