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Original article

Effects of intravenous bolus injection of nicorandil on renal artery flow velocity assessed by color Doppler ultrasound

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ABSTRACT

Background: Previous animal studies have shown that a potassium channel opener, nicorandil, provokes vasodilation in renal microvasculature and increases renal blood flow. We conducted a clinical study that aimed to evaluate the effect of nicorandil on renal artery blood flow in comparison with nitroglycerin by using color Doppler ultrasound.

Methods: The present study enrolled 40 patients with stable coronary artery disease who had no renal arterial stenosis and renal parenchymal disease. The patients received intravenous administration of nicorandil ($n = 20$) or nitroglycerin ($n = 20$). Before and after the administration, renal artery blood flow velocity was measured by color-guided pulsed-wave Doppler.

Results: The peak-systolic, end-diastolic, and mean renal artery blood flow velocities before the administration were not different between the nicorandil group and the nitroglycerin group. The peak-systolic (79 ± 15 cm/s to 99 ± 21 cm/s, $p < 0.001$; and 78 ± 19 cm/s to 85 ± 19 cm/s, $p = 0.004$), end-diastolic (22 ± 5 cm/s to 28 ± 8 cm/s, $p < 0.001$; and 24 ± 6 cm/s to 26 ± 6 cm/s, $p = 0.005$) and mean (41 ± 6 cm/s to 49 ± 9 cm/s, $p < 0.001$; and 43 ± 9 cm/s to 45 ± 9 cm/s, $p = 0.009$) renal artery flow velocities increased significantly in either group. The nominal changes in the peak-systolic (20 ± 10 cm/s vs. 7 ± 8 cm/s, $p < 0.001$), end-diastolic (5 ± 4 cm/s vs. 2 ± 3 cm/s, $p = 0.001$), and mean (8 ± 5 cm/s vs. 2 ± 2 cm/s, $p < 0.001$) renal artery blood flow velocities were significantly greater in the nicorandil group compared with the nitroglycerin group.

Conclusion: Intravenous nicorandil increased renal artery blood flow velocity in comparison with nitroglycerin. Nicorandil has a significant effect on renal hemodynamics.

Introduction

Nicorandil is a vasoactive agent that has dual properties of a nitric oxide donor and adenosine triphosphate (ATP)-sensitive potassium channel opener. The action of nicorandil on nitrate-mediated channels causes vasodilation of systemic veins and distributing arteries (i.e. muscular arteries or medium-sized arteries) [1,2]. The opening of ATP-sensitive potassium channels induces vasodilation of resistance vessels including small arteries and arterioles [1,2]. Nicorandil is used primarily to improve coronary blood flow for the treatment of ischemic heart disease [1,2]. In addition, this agent has the potential to provoke vasodilation in renal microvasculature and increase renal blood flow. Previous animal studies have shown that the ATP-sensitive potassium channel openers dilated renal afferent and efferent arterioles [3,4]. However, human data concerning the effects of nicorandil on the renal blood flow are limited. The color Doppler ultrasound is a noninvasive diagnostic method in evaluating blood

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flow through the renal arteries. The renal artery Doppler flow profile analysis provides a unique opportunity to understand renal hemodynamics in clinical settings [5,6]. We therefore conducted a clinical study that aimed to evaluate the effect of nicorandil on renal artery blood flow in comparison with nitroglycerin by using color Doppler ultrasound.

Methods

Study protocol

Between August 2014 and February 2015, we prospectively screened 249 patients with stable coronary artery disease at Wakayama-Minami Radiology Clinic, Wakayama, Japan. Inclusion criteria of the present study were (1) normal cardiac function with a left ventricular ejection fraction >60% on echocardiography and (2) normal renal function with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m^2 and no proteinuria. Exclusion criteria were (1) prior myocardial infarction, (2) prior percutaneous coronary intervention, (3) prior coronary artery bypass graft, (4) renal artery stenosis, and (5) renal parenchymal disease. A total of 66 patients satisfied all of the inclusion criteria and none of the exclusion criteria. Of these, 26 patients rejected to participate in the present study. Thus, we investigated the remaining 40 patients in the present study. The enrolled patients were assigned to the nicorandil group (n = 20) or the nitroglycerin group (n = 20) on the basis of clinician's decision. Following 10 min rest in a decubitus position, blood pressure and heart rate were measured in the upper arm by automated sphygmomanometer, and renal artery blood flow velocity was assessed by color guided pulsed wave Doppler. Subsequently, patients received intravenous injection of nicorandil at a dose of 0.1 mg/kg for 5 min or nitroglycerin at a dose of 0.25 mg for 5 min as reported in a previous study [7]. Immediately after the injection, blood pressure, heart rate, and renal artery blood flow were assessed again. The present study was approved by the hospital ethics committee, and all patients signed an informed consent form before participation in the study.

Color Doppler ultrasound

The color Doppler ultrasound examinations were conducted with Aplio Artida Ultrasound Diagnostic System SSH-880CV (Toshiba Medical System Inc., Tokyo, Japan) using a 3.5-MHz convex transducer. The examinations were performed by an experienced ultrasonographer (K.T.) who was blinded to the treatment with intravenous nicorandil or nitroglycerin. Patients were examined after an overnight fast in dorsal or left lateral decubitus positions. Right renal arteries were evaluated by flank coronal scanning or right intercostal or subcostal transverse scanning when possible. The angle of insonation was set at 60° or less, and the smallest possible Doppler angle was achieved by adjusting scanning sections to gain a more substantial peak systolic velocity. The sample gate was placed in the center of the arterial lumen with a width of 1–3 mm. Doppler sampling and velocity waveforms were obtained from the proximal renal arteries (Fig. 1). The peak-systolic, end-diastolic, and mean velocities were measured in 3 beats and the average values were used for analysis [8].

Statistical analysis

Statistical analysis was performed with Stat View 5.0J (SAS Institute, Cary, NC, USA). Categorical variables were presented as frequencies, with comparison using chi square statistics or Fisher's exact test (if there was an expected cell value <5). Continuous variables were presented as the mean ± standard deviation and were compared using unpaired Student's t tests (if variables were compared between the two groups) or paired t tests (if variables were compared between the pre- and post-administration of nicorandil or nitroglycerin). A p-value <0.05 was considered statistically significant.

Results

Patient clinical characteristics are shown in Table 1. Age, gender, eGFR, and prevalence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking were not different between the nicorandil group and the nitroglycerin group. Blood pressure and heart rate between pre- and post-administration of nicorandil or nitroglycerin are shown in Table 2. The systolic and diastolic blood pressure and heart rate at pre-administration were not different between the nicorandil group and the nitroglycerin group. The systolic (123 ± 15 mmHg to 111 ± 14 mmHg, $p < 0.001$; and 123 ± 8 mmHg to 111 ± 15 mmHg, $p < 0.001$) and diastolic blood pressure (70 ± 10 mmHg to 63 ± 8 mmHg, $p < 0.001$; and 72 ± 5 mmHg to 68 ± 8 mmHg, $p = 0.003$) decreased significantly and the heart rate (63 ± 9 bpm to 70 ± 10 bpm, $p < 0.001$; and 60 ± 8 bpm to 68 ± 11 bpm, $p < 0.001$) increased significantly between pre- and post-administration in the 2 group. The nominal and percent changes in those parameters were comparable between the 2 groups.

Renal artery blood flow velocities at pre- and post-administration of nicorandil or nitroglycerin are shown in Fig. 2. The peak-systolic, end-diastolic, and mean renal artery blood flow velocities at pre-administration were not different between the nicorandil group and the nitroglycerin group. The peak-systolic (79 ± 15 cm/s to 99 ± 21 cm/s, $p < 0.001$; and 78 ± 19 cm/s to 85 ± 19 cm/s, $p = 0.004$), end-diastolic (22 ± 5 cm/s to 28 ± 8 cm/s, $p < 0.001$; and 24 ± 6 cm/s to 26 ± 6 cm/s, $p = 0.005$) and mean (41 ± 6 cm/s to 49 ± 9 cm/s, $p < 0.001$; and 43 ± 9 cm/s to 45 ± 9 cm/s, $p = 0.009$) renal artery flow velocities increased significantly between pre- and post-administration in the 2 groups. Nominal and percent changes in the renal artery blood flow velocities are shown in Fig. 3. The nominal and percent changes in the peak-systolic (20 ± 10 cm/s vs. 7 ± 8 cm/s, $p < 0.001$; and 25 ± 10% vs. 10 ± 12%, $p < 0.001$), end-diastolic (5 ± 4 cm/s vs. 2 ± 3 cm/s, $p = 0.001$; and 24 ± 16% vs. 8 ± 14%, $p = 0.002$), and mean (8 ± 5 cm/s vs. 2 ± 2 cm/s, $p < 0.001$; and 20 ± 9% vs. 4 ± 7%, $p < 0.001$) renal artery blood flow velocities were significantly greater in the nicorandil group compared with the nitroglycerin group.

Discussion

The major finding of the present study was that intravenous nicorandil provided greater increase of renal artery blood flow velocity in comparison with intravenous nitroglycerin. Nicorandil had a significant effect on renal hemodynamics in the clinical setting.

Table 1
Patient clinical characteristics.

	Nicorandil (n = 20)	Nitroglycerin (n = 20)	p-value
Age (years)	67 ± 11	71 ± 5	0.223
Male	10 (50)	10 (50)	1.000
eGFR (ml/min/1.73 m^2)	77 ± 13	73 ± 10	0.282
Hypertension	9(45)	6(30)	0.327
Dyslipidemia	4(20)	2(10)	0.658
Diabetes mellitus	4(20)	1(5)	0.339
Smoking	1(5)	0	0.999

Values are given as n (%) or mean ± standard deviation. eGFR, estimated glomerular filtration rate.

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