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Intracoronary administration of nicorandil during primary percutaneous coronary intervention: Impact on restoration of regional myocardial perfusion in reperfused myocardium during the subacute phase of myocardial infarction

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ABSTRACT

Background: The impact of nicorandil as adjunctive therapy for percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) is controversial. We performed ^{15}O-labeled water positron emission tomography (PET) to quantify regional myocardial perfusion in patients with STEMI who received nicorandil or no adjunctive therapy during PCI.

Methods: PCI was performed within 8 h after STEMI onset in 33 patients. 14 patients received intracoronary nicorandil 2 mg immediately after recanalization of the culprit lesion (Nico group). After 3–4 weeks, PET was performed in which myocardial blood flow (MBF) was measured at baseline and during adenosine triphosphate (ATP)-induced hyperemia. Myocardial vascular resistance (MVR) was calculated for all segments. Data were obtained from the reperfused (Rep) and normal segments (Cont) in each patient.

Results: In patients not given nicorandil (No-Nico group), the MBF was significantly lower in Rep than that in Cont at baseline and during hyperemia (Cont vs. Rep: 0.82 ± 0.14 vs. 0.68 ± 0.11, $P = 0.001$, ATP-Cont vs. ATP-Rep: 2.00 ± 0.72 vs. 1.52 ± 0.61, $P = 0.017$), which was restored in the Nico group (Cont vs. Rep: 0.79 ± 0.17 vs. 0.78 ± 0.20; ATP-Cont vs. ATP-Rep: 2.02 ± 0.84 vs. 1.84 ± 0.62). MVR was elevated in Rep at baseline and during hyperemia in the No-Nico group. MVR elevation in Rep was prevented in the Nico group.

Conclusions: ^{15}O-labeled water PET was feasible for segmental analysis of MBF during the subacute phase of STEMI. It revealed that intracoronary administration of nicorandil to STEMI patients who underwent PCI prevented MVR elevation and thus restored MBF in the reperfused segments to a level similar to that in the normal segments.

1. Introduction

Nicorandil is a potassium channel opener with nitrate-like actions that dilate coronary arteries. This agent is also known to prevent reperfusion injury and promote ischemic preconditioning [1]. It has been expected to reduce infarction size and improve clinical outcomes in patients with acute myocardial infarction [2,3]. The value of nicorandil as an adjunctive therapy to primary PCI, however, is still controversial. In fact, a randomized clinical trial showed that intravenous or intracoronary injection of nicorandil after coronary reperfusion did not reduce infarct size as assessed with a total creatine kinase leak [4,5]. In contrast, several reports have shown salutary effects on coronary perfusion and clinical outcomes by intravenous administration before reperfusion or intracoronary administration during primary PCI [6,7]. Sakata et al. have reported that intracoronary administration of nicorandil improved incomplete restoration of myocardial perfusion after coronary revascularization and functional recovery of the jeopardized myocardium, as shown by myocardial contrast echocardiography in convalescents [8]. Ishii et al. reported that single intravenous administration of nicorandil before reperfusion improved coronary flow as evaluated by the corrected thrombolysis in myocardial infarction

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frame count, leading to improved clinical outcomes and prevention of cardiovascular events and death in patients with ST-elevation myocardial infarction (STEMI) [9]. This may explain why the administration of nicorandil has shown inconsistent outcomes in patients with STEMI. The studies have provided different timing for nicorandil administration and/or different methods for evaluating myocardial perfusion.

Positron emission tomography (PET) with ^{15}O-labeled water is a noninvasive method for accurately quantifying regional myocardial blood flow (MBF) presented as the regional perfusion ($mL \cdot min^{-1}$) per gram of myocardium [10,11]. This method has been validated in previous reports [12,13]. Previous studies showed a reduction of basal MBF in patients who smoked or had diabetes mellitus. Furthermore, there are still concerns regarding confounding factors affecting MBF such as hypertension, dyslipidemia, sex, and age [14,15]. Therefore, to clarify the effect of nicorandil on MBF, it is important to measure the MBF in the normal segments to compare them with the reperfused segments of the left ventricle in each patient. This study was designed to estimate MBF in all segments at basal and during adenosine triphosphate disodium hydrate (ATP)-induced hyperemia. ATP is a short-acting drug that mainly dilates the coronary arterial smooth muscle. Therefore, ATP-induced hyperemic blood flow is used to evaluate the coronary vasculature [16].

Based on these previous studies, the main aim of this study is to evaluate the regional myocardial blood flow in the reperfused segments compared with those in the normal segments by ^{15}O-labeled water PET after intracoronary administration of nicorandil during percutaneous coronary intervention (PCI) procedures in patients with STEMI.

2. Materials and methods

The eligibility criteria were the presence of STEMI in a patient admitted to the hospital within 8 h of the onset of symptoms. The exclusion criteria were a history of myocardial infarction; left main trunk stenosis; severe liver or kidney dysfunction, or both; suspected aortic dissection; previous coronary artery bypass grafting; and/or a history of drug allergy. All patients gave written informed consent immediately after admission to the hospital.

The Institutional Review Board and Ethics Committee of Kagawa University Hospital approved the study protocol in accordance with the Declaration of Helsinki.

We introduced an adjunctive treatment with nicorandil to the standard PCI. Nicorandil 2 mg was given by intracoronary injection immediately after recanalization of the culprit lesion. We applied this treatment to 14 consecutive patients from June 2011, who comprised the nicorandil (Nico) group. An earlier group of 19 consecutive patients who underwent standard primary PCI only, served as the no-nicorandil (No-Nico) group. The difference between the two groups was the presence or absence of the adjunctive treatment with intracoronary administration of nicorandil. Standard PCI, including nitrate administration, was performed in all patients within 8 h after the onset of STEMI.

We evaluated the regional MBF and myocardial vascular resistance (MVR) by ^{15}O-labeled water PET between 3 and 4 weeks after PCI. MVR is calculated as the mean arterial blood pressure divided by the MBF. For the analysis of MBF, we performed segment-based measurements. As shown in Fig. 1, the left ventricle was divided into 16 segments according to the model recommended by the American Society of Echocardiography and American Heart Association [17]. These segments included the anterior, anteroseptal, septal, inferior, posterior, and lateral walls, where each was subdivided into basal and mid portions, as well as the anterior apex, septal apex, inferior apex, and lateral apex. Data were obtained from each segment, and MBF was calculated by mean value in each coronary artery territories [18]. Furthermore, to avoid the effect of ischemia on MBF, we categorized the myocardial segments into three groups according to the most recent coronary angiography before the ^{15}O-labeled water PET: those perfused insufficiently by a stenosed coronary artery (Ischemia group); those with a nonstenosed coronary artery (controls, Cont); and those reperfused by PCI (Rep). The definition of stenosis is more than 75% of stenosis according to the definition of the American Heart Association [19]. The Ischemia group was excluded from the analysis.

2.1. PET image processing.

PET image processing and analysis were accomplished as described previously [20]. PET was performed using a whole-body scanner (Siemens/CTI, Knoxville, TN, USA) equipped with germanium-68 retractable line sources for transmission scans. All emissions and transmissions were reconstructed using filtered back-projection. The full-width at half maximum at the center of the field of view was 4.7 mm. The optimal imaging positron was determined by a 5-min rectilinear scan after exposure of an external ^{68}Ga ring source. A 6-min transmission scan was then acquired for the purpose of attenuation correction of all subsequent emission scans.

Blood volume images were produced in the following manner. During the 5-min scanning period, venous blood samples were obtained every 2 min, and radioactivity in the whole blood was measured with an automatic gamma counter (Fukuda Electric Company, Saitama, Japan).

^{15}O radioactivity returned to background level 15 min after the blood volume scan. Then, ^{15}O-labeled water was slowly (over 2 min) infused into an antecubital vein. ^{15}O-labeled water was administered twice during the study. The administered dose of ^{15}O-labeled water was 500 MBq/min. A 20-frame dynamic PET scan was performed for 6 min consisting of six frames for 5 s, six frames for 15 s, and eight frames for 30 s.

The MBF (in milliliters per gram per minute) of the whole left ventricle was measured using ^{15}O-labeled water as the flow tracer and previously validated ^{15}O radioactivity. We repeated the MBF measurement during ATP-induced hyperemia. ATP was infused for 9 min at 0.16 mg/kg/min, according to a standard protocol. PET acquisition was started 3 min after beginning the ATP infusion. Blood pressure was recorded at 1-min intervals. The patient's electrocardiogram was monitored continuously throughout the procedure at baseline and every minute during ATP administration.

2.2. Production of ^{15}O-labeled water PET

A low-energy deuteron accelerator was used to produce the ^{15}O compounds (CYPRIS-HM18 cyclotron; Sumitomo Heavy Industries, Tokyo, Japan). ^{15}O-labeled water was produced with a dialysis technique in a continuously working water module. Sterility and pyrogen tests were performed daily to verify the purity of the product.

2.3. Statistical analysis

Data were analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). All data are expressed as the mean ± standard deviation. The baseline clinical and angiographic characteristic parameters between the Nico group and the No-Nico group in all groups were compared with an unpaired t-test. The MBF and MVR at baseline and during ATP-induced hyperemia were compared in each group with the unpaired t-test. The PET-derived parameters (MBF and MVR) were compared between the two groups by repeated-measures analysis of variance. $P < 0.05$ was considered statistically significant.

3. Results

The baseline characteristics of the patients and the baseline and PET procedure drug information are shown in Table 1 and 2. There were no differences between the two groups in PCI procedure. The ratio of patients with obesity and hyperlipidemia in the No-Nico were significantly higher than that in the Non-Nico group.