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Cardioprotective effect of substance P in a porcine model of acute myocardial infarction

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ABSTRACT

Background: Substance P (SP) may attenuate ischemia-reperfusion injury by reducing inflammation. We assessed cardioprotective effect of SP in a porcine model of acute myocardial infarction (AMI).
Methods: AMI was induced by occlusion of the left anterior descending artery on 28 swine, randomized to SP 5 nmol/kg (group 1, n = 14) and normal saline (group 2, n = 14) given intravenously 5 min before reperfusion. Blood samples were collected at baseline, 3 days and 4 weeks. Echocardiography and myocardial perfusion single photon emission computed tomography (SPECT) were performed at 1 week and 4 weeks. Histomorphometric infarct size assessment was done at 4 weeks.
Results: Left ventricular (LV) ejection fraction (EF) (LVEF) after AMI induction was higher in group 1 than group 2 (37.9 ± 4.6% vs. 29.4 ± 3.2%, $p = 0.001$) but not different at 4 weeks. No significant difference was observed in perfusion defect extent and total perfusion defect on SPECT at 1 week and 4 weeks. Pathologic infarct size (% LV) was significantly smaller in group 1 than group 2 (2.4 ± 2.3% vs. 5.7 ± 2.5%, $p = 0.020$). The ratio of neutrophil to lymphocyte on day 3 and serum creatinine concentration at 4 weeks after AMI were lower in group 1.
Conclusions: In a porcine model of AMI, SP improved LVEF early post-MI and reduced infarct size. SP may be beneficial in reducing inflammation and ischemia-reperfusion injury after AMI.

1. Introduction

Acute myocardial infarction (AMI) remains a leading cause of mortality in the world. Restoring blood flow to the myocardium suffering ischemic insult as early as possible is the key to salvaging myocardium and limiting infarct size. Reperfusion may, however, give rise to ischemia-reperfusion (IR) injury, a phenomenon of paradoxical cardiomyocyte death and dysfunction.

Substance P (SP) is a tachykinin, located primarily in sensory nerves. In the heart, SP-containing nerve fibers are commonly found surrounding coronary vessels [1]. SP is also present in coronary endothelial cells [2], which make SP ideally situated to sense changes in the myocardial environment and to be released under conditions of altered coronary flow or pressure, such as myocardial ischemia [3]. There has been a body of evidence suggesting that SP plays a cardioprotective role in IR injury through its potent coronary vasodilator actions [4–7] as well as its direct actions on myocardial cells, which involves activation of the AKT pathway [8].

Currently, however, there is a paucity of data on the cardioprotective effect of SP in an AMI setting, especially in large animals. Thus, in the present study, we sought to evaluate the benefit of SP in a porcine model of AMI.

2. Materials and methods

2.1. Induction of AMI

This study was conducted on a total of 28 swine at the animal catheterization laboratory of Chonnam National University Hospital in Gwangju, Republic of Korea. Yorkshire X Landrace F1 crossbred castrated male swine (20–25 kg) were provided from Chuwol grandparent farm located in the southwest of the Republic of Korea and observed in the animal breeding house of Chonnam National University Medical Institute for 3–5 days

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before the experiment. All swine were given loading doses of aspirin (300 mg) and clopidogrel (300 mg) on the morning of the experiment, followed by aspirin 100 mg and clopidogrel 75 mg daily throughout the study period of 4 weeks. Experiment was done under anesthesia with zolazepam (2.5 mg/kg, intramuscular), tiletamine (2.5 mg/kg, intramuscular), xylazine (3 mg/kg, intramuscular), and azaperone (6 mg/kg, intramuscular). A 7F arterial sheath was placed in the left carotid artery under local anesthesia with 2% lidocaine. After infusion of 5000 units of heparin, a 7F coronary artery guiding catheter was placed within the opening of the coronary artery and baseline coronary angiogram was obtained under the fluoroscopic guidance by mobile C-arm (Phillips BV-25 Gold). AMI model was induced with inflation of a balloon (3.0*20 mm, Terumo Co. Tokyo, Japan) just distal to the first diagonal branch or the septal branch of the left anterior descending coronary artery. Complete occlusion was maintained by balloon dilatation (up to 8 atm) for 50 min. During the experiment oxygen and normal saline were supplied continuously and the anesthesia maintained with an additional administration of anesthetic regimens. Continuous electrocardiographic monitoring was performed to confirm normal ST segment at baseline and ST elevation during the ischemic period and to monitor occurrence of cardiac arrhythmia. After induction of AMI, each swine was closely observed for 1 h for development of ventricular tachycardia or fibrillation, and then the swine was carried back to the breeding house and monitored until recovery.

2.2. Compliance with ethical standards

This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1985). All animals received humane care and all procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Chonnam National University Hospital (IACUC approval No. CNU IACUC-H-2013-18).

2.3. Study groups and medications

The scheme of the study was shown in Fig. 1. The swine were randomly divided into 2 groups: group 1 (SP, n = 14) and group 2 (AMI control, n = 14). Group 1 received SP (5 nmol/kg) intravenously and group 2 placebo (saline) intravenously 5 min before reperfusion by deflating the balloon catheter occluding the left anterior descending coronary artery. SP was intravenously injected as a bolus (5 nmol/kg). To reduce hypotensive effect of exogenous SP, diluted SP was administered via the ear vein at a speed of 10 mL/min. Total volume of SP subjected to porcine (20–25 kg) was in the range of 20–25 mL according to the weight of the experimental animals. SP administration was started at 45 min after AMI induction (5 min before reperfusion).

2.4. Imaging studies

2.4.1. Two-dimensional echocardiography

All swine underwent 2-dimensional transthoracic echocardiographic examination at baseline (before the procedure), post-AMI induction, and 4 weeks after the procedure (Fig. 1). LV ejection fraction (EF), LV end-diastolic and end-systolic dimensions, and LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) were determined by modified biplane Simpson's rule in the 2- and 4 chamber views [9]. Considering the rapid growth of the animal, LVESV and LVEDV were normalized to the animal's body surface area in order to more adequately present the data over time, as both volumes naturally increase with growth of the animal [10]. A global diastolic function was assessed using transmitral inflow parameters: peak early (E) and peak late (A) velocities, E-wave deceleration time (DT) and E/A ratio. In addition, tissue Doppler imaging of mitral annular velocities (E', A') was measured. For the prediction of LV filling pressures, E/E' was calculated [11].

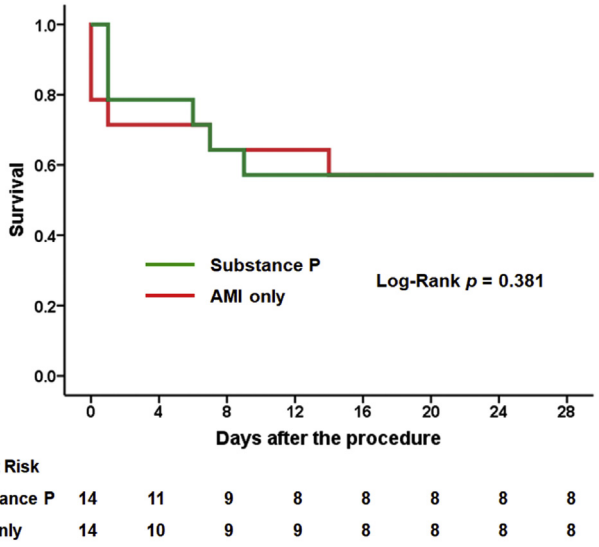

Fig. 2. Kaplan–Meier estimate of the survival function between SP and AMI only groups. AMI = acute myocardial infarction; SP = substance P.

2.4.2. Tc-99m sestamibi myocardial perfusion SPECT

All swine underwent technetium (Tc)-99m sestamibi myocardial perfusion single photon emission computed tomography (perfusion SPECT) at resting state twice at 1 week and 4 weeks after the procedure. Resting ECG-gated Tc-99m sestamibi SPECT imaging was performed in concordance with standards of the American Society of Nuclear Cardiology [12]. The swine were fasted overnight, Tc-99m sestamibi 111 MBq was injected intravenously at rest. Forty minutes after the injection, the planar and SPECT images were acquired in the supine position with ECG-gated technique using eight frames for a cardiac cycle. The SPECT data was acquired using a dual-headed SMV DST-XLi gamma camera (GE Medical systems) with low-energy, all purpose (LEAP) collimator, setting the energy photo-peak at 140 keV with a 20% symmetric window and a 90° acquisition arc. The SPECT acquisition was undertaken in 16 steps (32 projections) and each step collect counts for 30 s. Reconstruction of the images was performed by filtered back projection using butterworth filter. After reconstruction by filtered back projection using butterworth filter, transaxial slices along the vertical long axis, the horizontal long axis, and the short axis were generated.

2.5. SPECT data analysis

Perfusion SPECT data were evaluated on the consensus of 2 independent nuclear physicians. LVEF was derived from the ECG-gated images from perfusion SPECT [13]. Static tomographic images and polar maps were normalized to their maximum and used for visual analysis of regional perfusion/metabolism patterns using the American Heart Association 17-segment model. Perfusion defect size was quantified on polar maps according to a method described earlier [14]. Visual classification was done for classification of normal or defect segments. Perfusion defect assessment on SPECT was performed using an automated quantification of total perfusion defect that was calculated as the percentage of the total surface area of the LV below the predefined uniform average deviation threshold

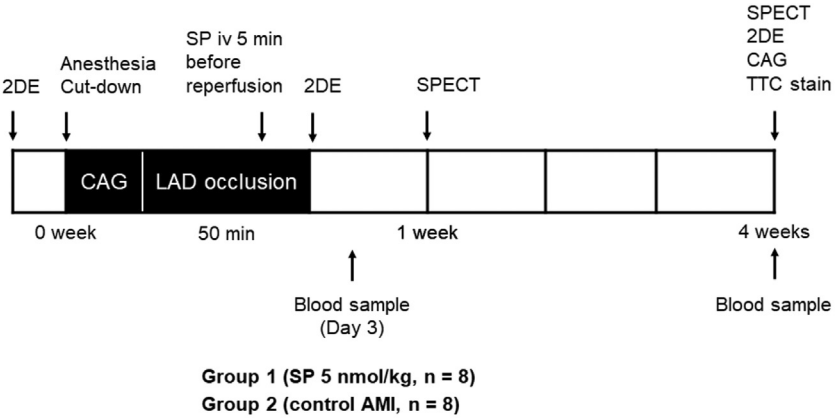

Fig. 1. Scheme of the study protocol. CAG = coronary angiography; 2DE = 2-dimensional echocardiography; SP = substance P; SPECT = Tc-99m sestamibi myocardial perfusion single photon emission computed tomography; TTC = 2,3,5-triphenyl tetrazolium chloride.

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