Nicardipine Augments Local Myocardial Perfusion after Coronary Artery Reperfusion in Dogs

Nicardipine is a potent coronary and systemic vasodilator without depression of ventricular function. We investigated the changes in local myocardial perfusion (LMP) according to the nicardipine administration after coronary reperfusion in a beating canine model. A Doppler probe was placed around the left anterior descending coronary artery (LAD) and thermal diffusion microprobe was implanted in the myocardium perfused by the exposed LAD. To define the nicardipine effects, we compared the two groups (control group, n=7 vs nicardipine group, n=7). In nicardipine group, 5 μg/kg/min nicardipine was infused continuously. After the release of the LAD occlusion, LAD blood flow were increased compared to the baseline of both groups. However, there was no difference between groups in the LAD blood flow. The LMP after LAD reperfusion did not recover to the baseline level until 30 min after LAD reperfusion in control group (74%, 52% and 70% at 10, 20 and 30 min after LAD reperfusion, respectively). In nicardipine group, however, the LMP recovered to the baseline level at 20 min (99%), and increased more than the baseline level at 30 min (141%) after LAD reperfusion. Our findings suggest that the nicardipine augments the LMP following the release of a coronary occlusion.

Key Words: Myocardial Reperfusion; Nicardipine

INTRODUCTION

The measurement of perfusion is very important to understand the physiology at the tissue level. And local myocardial perfusion (LMP) can identify hypoperfused myocardial tissue more precisely. In particular, during ischemia the myocardial layers of the left ventricle can be ischemic, while the epicardial blood flow is preserved. Many drugs have been used to improve the myocardial function in patients with coronary disease, and they may affect the LMP by various mechanisms (1-5). Nicardipine, a dihydropyridine calcium antagonist, is one of the most commonly used drugs to control the high blood pressure after coronary artery bypass graft. Nicardipine has relatively selective coronary vascular action (6). However, there has been no study of identifying the nicardipine effects in myocardium by using LMP after the coronary reperfusion.

Therefore, this study was undertaken to evaluate the nicardipine’s effect in myocardial layers after the coronary reperfusion. The LMP and left anterior descending coronary blood flow (BF-LAD) before and after left anterior descending coronary artery (LAD) occlusion were evaluated according to the nicardipine administration.

MATERIALS AND METHODS

This investigations were performed under a protocol approved by the Institutional Animal Investigation Committee, Keimyung University, Daegu, Korea. A total of 14 mongrel dogs, weighing 20-25 kg, were entered into the study. We divided the dogs into two groups, control group (n=7) and nicardipine group (n=7). The anesthesia was induced by 20 mg/kg thiopental sodium and 0.2 mg/kg vecuronium bromide followed by tracheal intubation after 2 min. Mechanical ventilation was done with 50% nitrous oxide in oxygen and 1-1.5 vol% isoflurane with a tidal volume of 15 mL/kg with a respiratory rate of 12/min.

A left thoracotomy was performed on the 5th or 6th intercostal space and LAD was exposed for occlusion and release. A thermal diffusion microprobe (TDM) was implanted in the myocardium perfused by the exposed LAD. To prevent the TDM displacement during cardiac contraction, the TDM was sutured in place. The TDM was then connected to QFlow™400 perfusion measurement system (Thermal technologies Inc., Cambridge, MA, U.S.A.) to measure LMP. The proximal LAD was dissected and the Doppler probe (HT107 medical
volume flowmeter, Transonic systems Inc., Ithaca, NY, U.S.A.) for measuring BF-LAD were placed around the LAD (Fig. 1).

After a sufficient stabilization period (30-60 min after surgical preparation), baseline LMP and BF-LAD were measured. The exposed coronary artery just proximal to the doppler probe was then occluded with an atraumatic clip for a period of 20 min, and all data were measured. We identified the appropriate TDM location by dusky region after LAD occlusion and by k-value. The k-value or tissue conductivity should not exceed 6.23 m·W/cm/℃ in this system. The k-value exceeding 6.23 m·W/cm/℃ indicates inappropriate microprobe positioning or other artifacts.

And then, LAD was reperfused following clip removal. In nicardipine group, 5 μg/kg/min nicardipine (Yamanouchi Co., Ltd. 1 mg/mL in 0.9% NaCl solution, Japan) was infused continuously, immediately before LAD reperfusion. The LMP and BF-LAD were also measured at 10, 20 and 30 min after the LAD reperfusion, respectively.

All data were presented as mean±SD. Comparisons between groups were performed by repeated measures ANOVA with SPSS program (version 10.0). Probability values < 0.05 were considered significant.

RESULTS

BF-LAD and LMP in two groups are presented in Table 1. The baseline BF-LAD in control group and nicardipine group were 17.5±6.7 mL/min and 18.4±7.3 mL/min, respectively. The BF-LAD decreased to 0 mL/min after LAD occlusion in both groups. Ten min after the coronary reperfusion, the BF-LAD were 66.2±13.4 mL/min in control group, and 64.5±11.6 mL/min in nicardipine group, respectively. And then, the BF-LAD at 20 and 30 min after the coronary reperfusion decreased, but did not return to the baseline level until 30 min after the coronary reperfusion. There was no statistical difference in BF-LAD between the two groups.

The baseline LMP in control group and nicardipine group were 52.0±18.3 mL/100 g/min and 49.6±2.9 mL/100 g/min, respectively. After the LAD occlusion, the LMP decreased to 18.4±17.0 mL/100 g/min in control group and 23.4±4.0 mL/100 g/min in nicardipine group. At the immediate reperfusion period, the LMP abruptly increased up to the 200-250 mL/100 g/min (the maximum range of QFlow™400 system is 250 mL/100 g/min) in both groups for 3 to 5 min after the LAD reperfusion. In nicardipine group, the LMP increased to the baseline level at 20 min after LAD reperfusion (49.1±7.9 mL/100 g/min) and increased more than the baseline value at 30 min after the LAD reperfusion (70.0±7.1 mL/100 g/min). In control group, however, the LMP did not recover to the baseline level at 20 and 30 min after the LAD reperfusion (27.2±17.4 mL/100 g/min and 36.2±17.2 mL/100 g/min at 20 and 30 min after LAD reperfusion, respectively).

**Table 1.** Changes in left anterior descending coronary artery blood flow and local myocardial perfusion according to the LAD reperfusion in dogs

| Blood flow (mL/min) | Baseline | LAD occlusion | Time after LAD reperfusion (min) |
|--------------------|----------|---------------|---------------------------------|
| Control            | 17.5±6.7 | 0             | 10  | 20   | 30   |
| Nicardipine        | 18.4±7.3 | 0             | 66.2±35.8* | 35.8±9.3* | 25.5±6.7* |
| LMP (mL/100 g/min) | 52.0±18.3| 18.4±17.0*    | 38.5±23.2 | 27.2±17.4* | 36.2±17.2* |
| Control            | 9.6±2.9  | 23.4±4.0*     | 30.6±5.3* | 49.1±7.9* | 70.0±7.1* |
| Nicardipine        |          |               |       |       |       |

Values are mean±SD. LMP: local myocardial perfusion; LAD: left anterior descending coronary artery; There was no statistically difference in blood flow change between two groups. *Significantly different from baseline; †Significantly different from control at each time.
Nicardipine and Myocardial Perfusion

DISCUSSION

The most important determinant of tissue oxygenation and substrate delivery is tissue perfusion. The measurement of tissue perfusion, therefore, is a key point to understand both normal and pathologic physiology. Many techniques, such as laser-Doppler flowmetry, radioactive microsphere technique, have been used to measure tissue blood flow (7-9). Previous methods, however, have been insufficient to measure local tissue perfusion (10, 11). In this study, we used TDM to measure LMP distal to the LAD, which validated many other organs (11-14).

Nicardipine has many properties of an ideal drug to control postoperative hypertension (15). The drug has a direct effect on vascular smooth muscle cells, and it causes vasodilation and reduction of blood pressure (16). Nicardipine also has the myocardial protective effect, and reduces the severity of myocardial ischemia (17). Nicardipine is a potent coronary and systemic vasodilator without evidence of depression of ventricular function. Therefore, we postulated that the nicardipine administration during coronary artery reperfusion may augment the LMP. In this study, the LMP after LAD occlusion were maintained to 35% and 48% of the baseline level in control group and nicardipine group, respectively. This phenomenon may suggest that other conduit coronary arteries, such as right coronary and circumflex artery, can normally supply some blood to LAD distributed myocardial area during the LAD occlusion. After immediate LAD reperfusion, we could find the hyperemic state in LMP. The duration of this state was about 3-5 min. One interesting result is that the LMP did not recover to the baseline level despite of BF-LAD increase after LAD reperfusion in control group. This phenomenon shows that impaired myocardial microcirculation occurs after coronary reperfusion in normal condition. Many substances such as free radical, cytokine, prostaglandins, and other peptides may play roles in this phenomenon (10). It is hence believed that the LMP is more reliable parameter than blood flow in ischemia or reperfusion state. This may suggest that it is not enough to measure blood flow in a coronary artery when trying to assess the adequacy of myocardial perfusion.

In nicardipine group, the LMP recovered to the baseline level at 20 min (99%) after LAD reperfusion and increased more than the baseline level at 30 min (141%) after LAD reperfusion. This result indicates that the nicardipine has an effect of LMP augmentation during the coronary reperfusion period.

We found that the LMP did not recover despite the increase of BF-LAD after coronary artery reperfusion in control group. However, the LMP can increase by using nicardipine during the coronary reperfusion period. In conclusion, nicardipine improves myocardial tissue perfusion following the release of a coronary occlusion in dogs.

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