特 集 (special edition)

# Myocardial ischemia and sympathetic activity

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## Introduction

It has been emphasized that the balance of myocardial oxygen demand and supply should be maintained for the prevention of myocardial ischemia during anesthesia in the patients with coronary artery disease.

Recently, using transesophageal echocardiography or longterm ECG monitoring in the perioperative period, new myocardial ischemia was shown to occur in 20-40% of patients undergoing coronary artery bypass graft surgery[1,2]. Since myocardial ischemia is accompanied by no remarkable hemodynamic changes, the decreased coronary blood flow in the ischemic myocardium rather than the increased myocardial oxygen consumption appears to be responsible for the development of new myocardial ischemia.

Stimulation of sympathetic nerves was reported to contract the coronary artery. Alpha adrenoreceptors may be subdivided into types 1 and 2. Coronary vascular smooth muscle has postjunctional alpha 1 and alpha 2 receptors, both of which induce vasoconstriction. Adrenergic vasoconstriction of epicardial large coronary artery is predominantly mediated via alpha 1 receptors in contrast to resistant small arteries where both alpha 1 and alpha 2 receptors are involved. Coronary arteries also have beta receptors that cause vasodilation directly or metabolically. These vasoconstriction due to sympathetic alpha action and vasodilation due to beta action may control the coronary blood flow and distribution in the myocardium. Whether sympathetic action aggravates or improves the myocardial ischemia is still controversial[3,4,5].

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## Methods

The effects of stimulation of cardiac sympathetic nerve on ischemic heart were studied in thoracotomized dogs. Anesthesia was maintained with continuous intravenous administration of fentanyl keeping the heart rate around 100 beats·minutes$^{-1}$. Stenosis was produced by 50% reduction of blood flow through the circumflex branch of the left coronary artery. The sympathetic nerve was electrically stimulated at anterior branch of the left stellate ganglion to increase the arterial blood pressure by 10-15 mmHg.

## Results and discussion

Changes in parameteres of myocardial oxygen demand and supply, and subendocardial pH in ischemic region during stimulation of cardiac sympathetic nerve were summarized (Table 1).

In control state, the stimulation of cardiac sympathetic nerve increased both myocardial oxygen demand and supply, but subendocardial pH did not show any change, suggesting the balance of demand and supply was maintained.

In stenosis, the increase in myocardial oxygen demand during stimulation of cardiac sym-

**Table 1** Changes in parameters of myocardial oxgen demand and supply, and subendocardial pH during stimulation of cardiac sympathetic nerve

| | HR | LVP | LV dp/dt max | CBF | CVR | pH endo |
|---|---|---|---|---|---|---|
| No stenosis | → | ↑ | ↑↑ | ↑ | ↗ | → |
| Stenosis | → | ↑ | ↑↑ | ↗ | ↗ | ↘ |
| Stenosis +propranolol | → | ↑ | ↑ | → | ↑ | → |
| Stenosis +proranolol +Halothane | → | ↑ | ↑ | ↑ | → | ↓ |

↑ or ↓: increase or decrease significantly with p value less than 0.05. Abbreviations: HR=heart rate; LVP=left ventricular pressure; LV dp/dt max=maximum rate of rise of left ventricular pressure; CBF=coronary blood flow distal to the stenosis; CVR=coranary vascular resistance distal to the stenosis; pH endo=intramyocardial pH in subendocardium distal to the stenosis.

pathetic nerve was equivalent to that in control. However the increase in oxygen supply, that is coronary blood flow, was not sufficient so that myocardial ischemia was worsened, especially in the inner layer of stenosed area.

With 50% reduction of coronary blood flow, the dilatory reserve of coronary artery could be almost lost. Even when the dilatory reserve was thought to have disappeared due to stenosis, the sympathetic nerve stimulation was reported to contract the coronary artery and decrease blood flow[3]. However, the increase of coronary blood flow in response to alpha receptor blocker during reactive hyperemia following the release from coronary artery occulusion was demonstrated. The dilatory reserve of the blood vessel distal to the stenosis can disappear in the inner layer, but persist in the outer layer[4,5]. Sympathetic nerve stimulation may result in dilation of the coronary artery through the beta receptor, simultaneously through the effect on metabolism. It is possible that the vasodilation in response to beta-receptor stimulation rivaled the effect of alpha stimulation and the vascular resistance distal to the stenosis failed to rise.

The tendency of aggravation of myocardial ischemia distal to the stenosis might be explained by first, failure of the increase of coronary blood flow relative to the increase of myocardial oxygen consumption. Secondly, a possibility of the decrease of blood flow in the inner layer of the myocardium along with the increase of blood flow through the outer layer due to coronary vasodilatation caused by sympathetic nerve stimulation. Which of these possibility was responsible for the aggravation of ischemia has not been clarified as yet.

After administration of propranolol, myocardial oxygen demand increased, but slightly, during the stimulation of cardiac sympathetic nerve. Even though coronary artery blood pressure increased, coronary blood flow did not increase. The coronary vascular resistance distal to the stenosis increased, nevertheless subendocardial pH did not decrease. It can be speculated that alpha-mediated coronary vasoconstriction in the outer layer distal to the stenosis lessened the transmular steal.

On the stimulation of cardiac sympathetic nerve after propranolol administration, the beta-action of the sympathetic nerve was blocked, causing only a mild increase of the myocardial contractility, so that myocardial oxygen consumption was low in comparison with that in control state. The increase of myocardial contractility in response to sympathetic nerve stimulation was minimal, and no vasodilation

due to metabolic change or beta action occured. The increase of blood pressure distal to the stenosis probably did not cause the aggravation of myocardial ischemia despite no change of the blood flow. No abnormality of the blood flow distribution through the myocardium was noted.

After supplementation with low concentration of halothane, myocardial oxygen demand increased only slightly during stimulation of cardiac sympathetic nerve similar to in propranolol. The coronary blood flow increased significantly in the ischemic area, nevertheless subendocardial pH decreased. Both blood flow and blood pressure distal to the stenosis increased, and the vascular resistance distal to the stenosis tended to fall in consequence. Since the influence of beta-action in sympathetic nerve stimulation was minimal, such decrease of vascular resistance was probably due to the block of alpha-action of the sympathetic nerve by halothane[6].

The aggravation of myocardial ischemia may be explained by the decrease of blood flow through the inner layer of the myocardium, in spite of the increase of the blood flow through the site of stenosis and mainly through the outer layer of the myocardium in response to sympathetic nerve stimulation. Halothane could cause the vertical, intramural, coronary steal by attenuating alpha-receptor mediated coronary vasoconstriction in the outer layer of ventricle distal to the stenosis.

These results in this experiment suggested that myocardial ischemia may be caused by the interaction with vasoconstriction of coronary artery due to sympathetic alpha stimulation and vasodilation due to beta stimulation rather than by the increase of myocardial oxygen consumption.

In the heart with coronary artery stenosis, the blood vessels in the outer layer of left ventricle distal to the stenosis contract in response to sympathetic nerve stimulation, influencing the blood flow distribution especially during the use of beta-blocker. While these sympathetic vasoconstriction was blocked by halothane. Despite of the increasing of coronary blood flow, myocardial ischemia may be occured in the inner layer of ventricle distal to the stenosis. The sympathetic vasoconstriction of coronary arteries was beneficial on the area of ischemia in this study. Intraoperative myocardial ischemia may be caused by the modification of anesthetics on these sympathetic vasoconstriction as well as the effects on the coronary perfusion pressure and myocardial oxygen consumption.

The findings of current work should be cautiously transferred to the clinical setting with realization of the study limitations. The acutely induced myocardial ischemia in animal model is different from the myocardial ischemia in human with coronary artery desease. In clinical circumstances, unlike experimentally induced fixed stenosis, the site of stenosis may reserve contractile and dilatory responses, so that the contraction in the site of stenosis may decrease the blood flow to aggravate the myocardial ischemia. Further studies are required with regards to this points.

In conclusion, even if coronary blood flow does not decrease, the stimulation of cardiac sympathetic nerve may cause the abnormality of the blood flow distribution through the myocardium and worsen the myocardial ischemia.

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