特 集 (special edition)

Influence of Anesthesia on Ischemic Myocardium

Hideaki Tsuchida*, Satoshi Fujita*
and Akiyoshi Namiki*

There still remains a controversy whether anesthesia *per se* affects the course of myocardial ischemia.[1] Most anesthetics depress myocardial contractility and decrease blood pressure and heart rate in humans and in experimental animals. These changes can improve the myocardial oxygen supply/demand relationship and relieve myocardial ischemia in the compromised myocardium. For example, Bland et al. reported that halothane decreased the severity of experimentally-induced acute myocardial ischemia in non-failing canine heart, monitoring ST segment changes by epicardial ECG.[2] Vik-Mo et al. also demonstrated that thoracic epidural anesthesia (TEA) had a favorable effect on acute ischemic myocardium according to the same criterion.[3] Since the attenuation of the ST increase induced by the epidural anesthesia dissappeared after the decreased heart rate and blood pressure had been restored to the control, pre-TEA levels by atrial pacing and phenylephrine infusion, they concluded that reduced myocardial activity was the main factor in relieving myocardial ischemia. The question remains whether these hemodynamic changes are the only factors which influence myocardial ischemia during anesthesia. The authors have measured myocardial pH and metabolism in the canine heart to elucidate the effect of anesthesia on ischemic myocardium.

Experiments were carried out in open chest dogs anesthetized intravenously with urethane and α-chloralose (450:45 mg/kg iv, followed by 45:4.5 mg/kg/hr div). The trachea was intubated and the lung was ventilated with air to maintain $Paco_2$ between 30 and 40 mmHg and Pao_2 above 70 mmHg. Oxygen was added to the inspired gas when Pao_2 was less than 70 mmHg. Sodium bicarbonate was administered intravenously when the base excess was greater than −5 mEq/L. A left thoracotomy was performed at the fourth intercostal space. The left anterior descending coronary artery (LAD) was dissected free from the adjacent tissues distal to the first diagonal branch and an electromagnetic flow probe was placed on the LAD. Myocardial pH was measured by a micro glass pH electrode inserted in the area perfused by the dissected LAD at a depth of about 6 to 8 mm so as to place the tip within the endocardial layer.[4] The pH electrode was calibrated with standard pH solutions (pH 6.840 and 7.384) before each experiment. Myocardial metabolism was measured following an excision of the myocardium with scissors, which was immediately frozen with freezing clamps previously chilled with liquid nitrogen in such a way that the endocardial portion of the myocardium could be taken separately for analysis. The levels of ATP, ADP, AMP and lactate were

*Department of Anesthesiology, Sapporo Medical College, Sapporo, 060

determined according to standard enzymatic procedures. Energy charge potential was calculated from the equation of,

$$([ATP]+1/2[ADP])/([ATP]+[ADP]+[AMP])$$

In the first series of experiments, myocardial pH was measured continuously to evaluate the severity of myocardial ischemia.[5] Five minutes of complete LAD occlusion was repeated several times in a dog. During the control period, the LAD occlusion decreased myocardial pH from 7.46 to 6.99 (Fig. 1). After the occlusion was released, the pH was observed to recover to the pre-occlusion

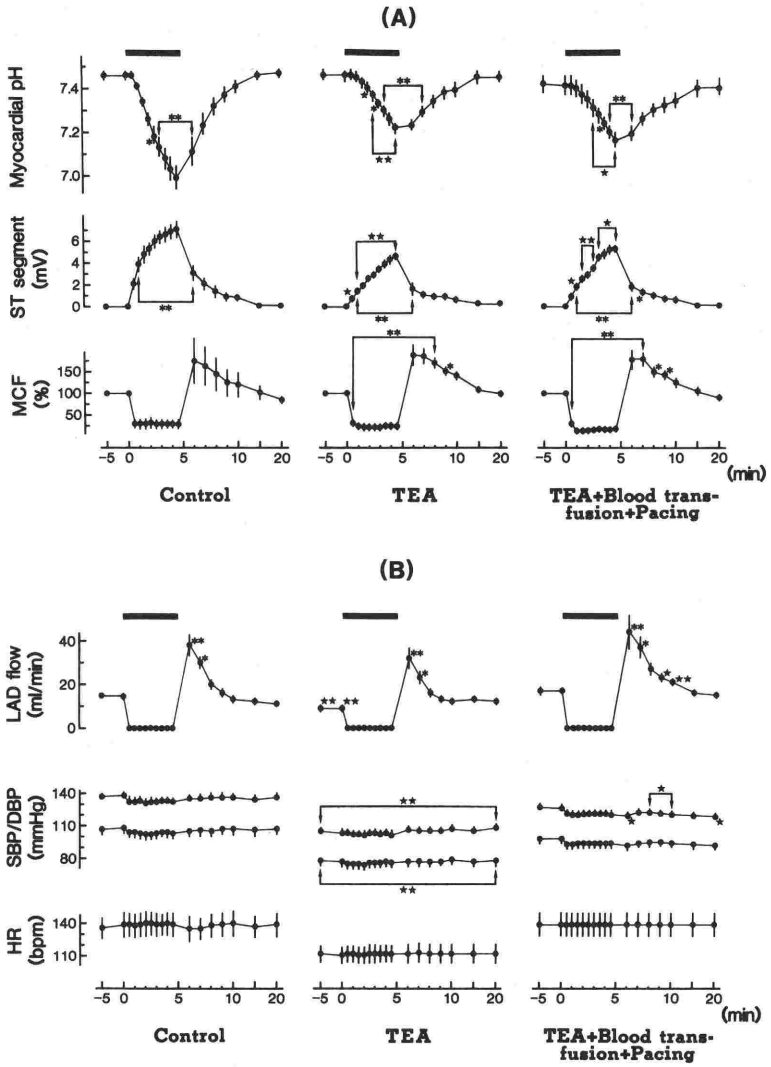

Fig. 1 **A.** Effect of LAD occlusion on myocardial pH, ST segment and myocardial contractile force (MCF); and **B.** LAD blood flow, systolic blood pressure/diastolic blood pressure (SBP/DBP) and heart rate (HR) during control, TEA, and TEA+blood transfusion+pacing. Horizontal bars at the top indicate the period for complete occlusion of the LAD. Values are expressed as mean±SEM. * $P<0.05$; ** $P<0.01$ vs. the values at 0 min within the group. ★ $P<0.05$; ★★ $P<0.01$ vs. control values at these times. Data between the two arrows show the same level of significance as indicated.

value. The ST segment of epicardial ECG elevated and myocardial contractile force decreased during the LAD occlusion, which indicated that myocardial ischemia had been elicited. Thoracic epidural anesthesia, which was induced by 0.15 m*l*/kg of 0.4% bupivacaine injection into the epidural space, significantly decreased arterial blood pressure, heart rate and LAD blood flow, but did not affect the myocardial pH. Five minutes of LAD occlusion again decreased myocardial pH from 7.46 to 7.22, but the decrement was significantly attenuated compared to the control value. Although the ST segment elevation during TEA was also less than that during the control period, the % change in myocardial contractile force was not altered. After the decreased blood pressure and heart rate induced by the TEA were restored to the pre-TEA levels by blood transfusion and atrial pacing, LAD blood flow also increased to the level observed during the control period. This suggests that myocardial oxygen demand might be comparable to that during the control experiment, where the acidosis induced by 5 minutes LAD occlusion was still attenuated to an extent similar to that during TEA.

Similar experiments were carried out during halothane and isoflurane anesthesia. Fig. 2 shows the effect of halothane anesthesia on myocardial pH. LAD occlusion was repeated three times in a dog, during control (C), 1 MAC halothane anesthesia (H) and halothane anesthesia with atrial pacing to restore heart rate to the control level (P). One MAC halothane anesthesia significantly attenuated the decrease in myocardial pH both in the absence and in the presence of atrial pacing of the heart. In the isoflurane trial, fentanyl was administered continuously during the control period as well as intravenous urethane and α-chloralose. The LAD occlusion decreased myocardial pH from 7.45 to 7.11 during the control period (Fig. 3). 1% to 1.5% isoflurane was then administered to decrease blood pressure by 30% of the control, pre-isoflurane value. This resulted in an increase of heart rate by 15% but the LAD blood flow remained unchanged. In spite of the decrease in blood pressure and increase in heart rate during isoflurane anesthesia, a significant attenuation was observed in the decrement of myocardial pH (from 7.43 to 7.25) in comparison to the control experiment.

In the second series of experiments, we employed another procedure to induce consistent myocardial ischemia[6] instead of a complete LAD occlusion. A 24 gauge catheter was

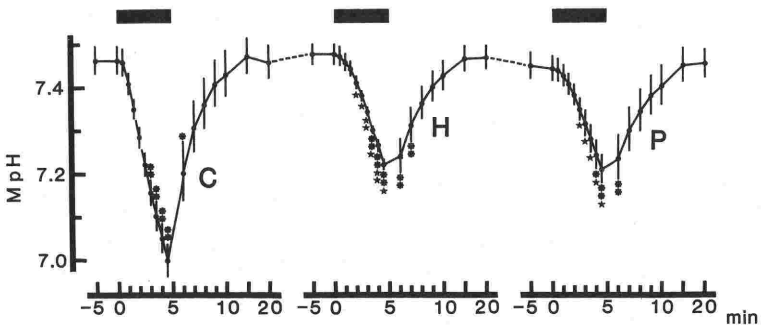

Fig. 2 Effect of LAD occlusion on myocardial pH (MpH) during control (C), 1 MAC halothane anesthesia (H), and halothane anesthesia+atrial pacing (P). Horizontal bars at the top indicate the period for complete occlusion of the LAD. Values are expressed as mean ±SEM. * $P<0.05$; ** $P<0.01$ vs. the values at 0 min within the group. ★ $P<0.05$; ★★ $P<0.01$ vs. control values at these times.

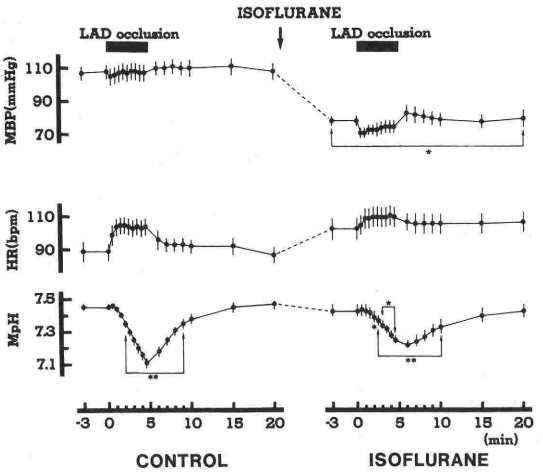

Fig. 3 Effect of LAD occlusion on mean arterial blood pressure (MBP), heart rate (HR), and myocardial pH (MpH) during control and isoflurane anesthesia. Values are expressed as mean±SEM. * $P<0.05$; * $P<0.01$ vs. the values at 0 min within the group. ★ $P<0.05$ vs. control values at these times.

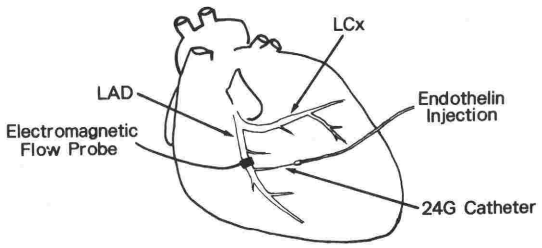

Fig. 4 Schematic illustration of the preparation of the heart.

inserted retrogradely into a small diagonal branch of the LAD just distal to the electromagnetic flow probe and 15 pM/kg dose of endothelin-1 was injected selectively into the LAD to produce myocardial ischemia (Fig. 4). The intracoronary injection of endothelin decreased LAD blood flow to approximately a third of its pre-injection value not only in the control and TEA groups but also in the controlled TEA group, in whom the decreased blood pressure and heart rate were restored to the control levels by aortic snare and atrial pacing. The endothelin injection decreased the level of ATP and increased the levels of AMP and lactate in the myocardium perfused by the LAD 3 minutes after the injection (Table 1). In contrast, these levels were kept within normal range in the myocardium perfused by the left circumflex coronary artery (LCx). Although endothelin injection produced myocardial ischemia in a group receiving thoracic epidural anesthesia, compromised myocardial metabolism was significantly alleviated as compared to the control group. This TEA-induced alleviation of the myocardial metabolism was observed even in the controlled TEA group.

In the third series of experiments, myocardial ischemia was compared under pentobarbital (25 mg/kg iv) and under morphine-urethane-α-chloralose (MUC) anesthesia,[7] both of which

Table 1 Effects of intracoronary injection of endothelin on adenine nucleotides and lactate levels in normal saline, TEA, and controlled TEA groups.

	ATP	ADP	AMP	lactate
Normal Saline				
LAD area	4.835±0.405**	1.005±0.127	0.257±0.079**	7.442±1.620**
LCx area	5.315±0.574	0.629±0.283	0.116±0.021	2.949±0.455
TEA				
LAD area	5.254±0.441*#	0.978±0.368	0.187±0.051#	5.761±1.160**#
LCx area	5.548±0.282	0.781±0.357	0.159±0.051#	2.707±1.767
Controlled TEA				
LAD area	5.222±0.228**#	1.045±0.047**	0.153±0.031**##	5.189±0.721**##
LCx area	5.548±0.107	0.824±0.103	0.110±0.022	3.161±0.706

Values are expressed as mean±SD.
* $P<0.05$; ** $P<0.01$ vs. LCx area. # $P<0.05$; ## $P<0.01$ vs. normal saline group.

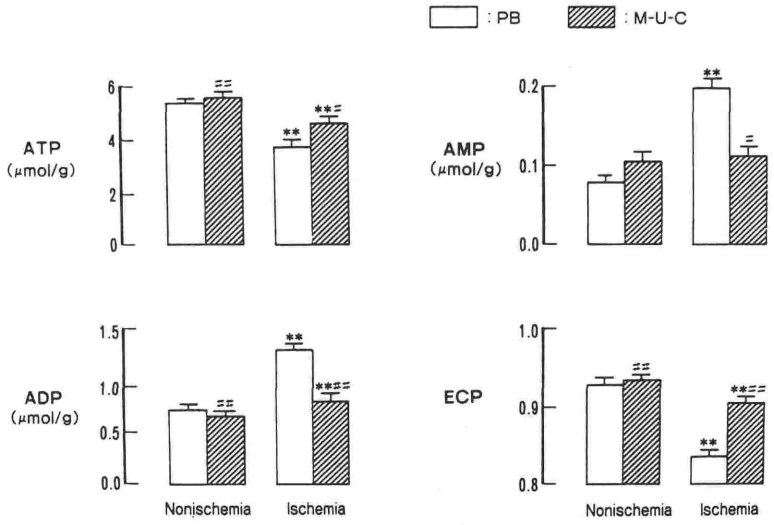

Fig. 5 Effect of pentobarbital (PB) and MUC anesthesia on adenine nucleotides levels and energy charge potential (ECP) during ischemia. Values are expressed as mean±SEM. $^{\#}P<0.05$; $^{\#\#}P<0.01$ vs. pentobarbital, $^{*}P<0.01$ vs. nonischemia.

are commonly used in animal experiments. Myocardial ischemia was produced by a complete ligation of the LAD for 3 minutes. Fig. 5 compares the metabolism in the myocardium obtained from the LAD area (ischemic region: the myocardium supplied by the LAD anatomically) and the LCx area (non-ischemic region: the myocardium supplied by the LCx anatomically). The LAD occlusion produced a consistant myocardial ischemia only in the LAD area during both pentobarbital and MUC anesthesia. However, the severity of ischemia under MUC anesthesia was less pronounced than that during pentobarbital anesthesia; this held true even after the lower heart rate observed during MUC anesthesia was increased by atrial pacing, but disappeared after either an ablation of bilateral stellate ganglia or cervical vagotomy. As shown in Fig. 6, the energy charge potential in the non-ischemic myocardium was comparable under both anesthesias, not only during the control experiment, but also after the stellectomy or vagotomy was carried out. Although the energy charge potential in the ischemic myocardium was significantly different between the two anesthesias during the control experiment, bilateral stellectomy or vagotomy completely abolished the difference.

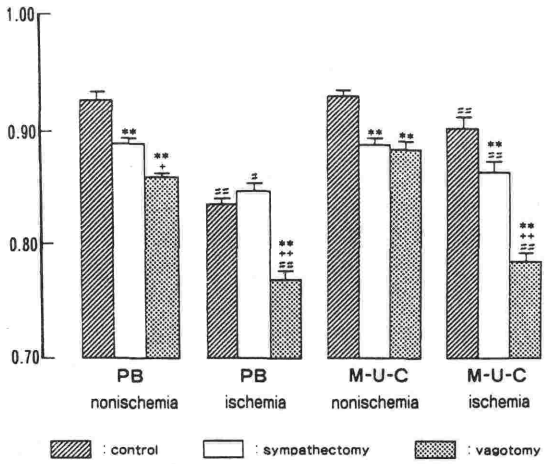

Fig. 6 Effect of sympathectomy and vagotomy on energy charge potential under pentobarbital (PB) and MUC anesthesia. Values are expressed as mean±SEM. $^{**}P<0.01$ vs. control, $^{+}P<0.05$; $^{++}P<0.01$ vs. sympathectomy, $^{\#}P<0.05$; $^{\#\#}P<0.01$ vs. nonischemia.

Our observations indicate that some process other than hemodynamic changes must be involved in the anesthesia-induced alleviation of myocardial ischemia. These may include, 1)

Ca^{2+} channel blocking property of the anesthetics, and 2) anesthesia-induced suppression of the sympathetic nerve activity.

Most inhalation anesthetics inhibit voltage-dependent Ca^{2+} channels and thus suppress increases in cytosolic Ca^{2+} levels in smooth muscle[8] and cardiac muscle.[9,10] This can induce dilation of the coronary arteries which supply blood flow to the ischemic myocardium. The Ca^{2+} channel blocking effect of the anesthetics could also suppress an increase in cytosolic Ca^{2+} levels in the ischemic myocardium.[11] Therefore, this property may partly explain the observed alleviation of myocardial ischemia by the inhalation anesthetics. However, the blocking of the voltage-dependent Ca^{2+} channel induced by the inhalation anesthetics is less than that induced by commonly used Ca^{2+} channel blockers such as verapamil and nifedipine.[12] Moreover, thoracic epidural anesthesia has no Ca^{2+} channel blocking activity.

Ichihara et al.[13] have reported that diltiazem, a Ca^{2+} entry blocker, has a favorable effect on the ischemic myocardium induced by a partial LAD occlusion. They reported, however, that not all Ca^{2+} channel blockers had identical properties with respect to the ischemic myocardium. For example, nifedipine, a powerful coronary dilator, could not alleviate the ischemic insult induced by a partial LAD occlusion.[14] These reports indicate that the coronary vasodilating effect of inhalation anesthetics is a minor, if present, contributing factor in relieving the ischemic myocardium.

Several experimental findings indicate an increased adrenergic activity in acutely ischemic myocardium.[15,16] A release of catecholamine may be mediated by increased nerve impulse flow to the heart, either as a part of general reflex sympathetic activation or by a local cardiac reflex. Catecholamine activates myocardial adrenoceptors and aggravates myocardial ischemia. Thoracic epidural anesthesia and inhalation anesthetics can blunt sympathetic control of the heart.[17,18] This anesthesia-induced suppression of sympathetic nerve activation seems likely to be included, at least partly, in the alleviation of ischemic myocardium. The fact that the difference between pentobarbital and MUC anesthesia on the myocardial metabolism was completely abolished after bilateral stellectomy also supports the involvement of sympathetic nerve activity in the anesthesia-induced alleviation of ischemic myocardium. Acute sympathetic blockade has also been hypothesized to inhibit lipolysis within the ischemic area, thereby decreasing regional myocardial oxygen comsumption and reducing the severity of ischemic injury.[19]

In conclusion, thoracic epidural anesthesia, halothane and isoflurane anesthesia alleviated the severity of experimental myocardial ischemia in open chest dogs. Pentobarbital and MUC anesthesia were observed to bring different metabolic effects in the ischemic region of the myocardium induced by 3 minutes of LAD occlusion. These differences could not be attributed solely to hemodynamic changes or individual differences such as blood pressure or heart rate alterations. The Ca^{2+} channel blocking properties of the anesthetics or anesthesia-induced suppression of sympathetic nerve activity must be involved in the alleviation of the myocardial ischemia.

References

1) Merin, R. G., Lowenstein, E., Gelman, S.: Is anesthesia benefical for the ischemic heart? III. Anesthesiology **64**:137-140, 1986.
2) Bland, J. H. L., Chir, B., Lowenstein, E.: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology **45**:287-293, 1976.
3) Vik-Mo, H., Ottesen, S., Renck, H.: Cardiac effect of thoracic epidural analgesia before and during coronary artery occlusion in open-heart dogs. Scand. J. Clin. Lab. Invest. **38**:737-746, 1978.
4) Abiko, Y., Ichihara, K., Sakai, K.: Myocardial pH: a useful indicator for evaluation of antianginal drugs. Trends Pharmacol. Sci. **5**: 513-517, 1984.

5) Tsuchida, H., Omote, T., Miyamoto, M., et al.: Effects of thoracic epidural anesthesia on myocardial pH and metabolism during ischemia. Acta Anaethesiol. Scand. **35**:508-512, 1991.
6) Fujita, S., Tsuchida, H., Kawamata, M., et al.: The effect of thoracic epidural anesthesia on the metabolism of ischemic myocardium induced by intracoronary injection of endothelin in dogs. Anesthesiology **75**:A515, 1991.
7) Fujita, S., Tsuchida, H.: The effects of pentobarbital anesthesia and morphine-urethane-α-chloralose anesthesia on hemodynamics and myocardial metabolism under experimental acute coronary artery ligation in dogs. Sapporo Med. J. **59**:481-492, 1990. (in Japanese)
8) Tsuchida, H., Notsuki, E., Yamakage, M., et al.: Inhibitory effect of halothane and isoflurane on cytosolic Ca^{2+} increase and contraction in vascular smooth muscle of rat aorta. Anesthesiology **75**:A531, 1991.
9) Bosnjak, Z. J., Supan, F. D., Rusch, N. J.: The effects of halothane, enflurane, and isoflurane on calcium current in isolated canine ventricular cells. Anesthesiology **74**:340-345, 1991.
10) Bosnjak, Z. J., Aggarwal, A., Turner, L. A., et al.: Differential effect of halothane, enflurane, and isoflurane on Ca^{2+} transients and muscle tension in guinea pigs. Anesthesiology **76**:123-131, 1992.
11) Hoka, S., Bosnjak, Z. J., Kampine, J. P.: Halothane inhibits calcium accumulation following myocardial ischemia and calcium paradox in guinea pig hearts. Anesthesiology **67**:197-202, 1987.
12) Blaise, G. A., Hughes, J. M., Sill, J. C., et al.: Attenuation of contraction of isolated canine coronary arteries by enflurane and halothane. Can. J. Anaesth. **38**:111-115, 1991.
13) Ichihara, K., Abiko, Y.: Effect of diltiazem, a calcium antagonist, on myocardial pH in ischemic canine heart. J. Pharmacol. Exp. Ther. **222**:720-725, 1982.
14) Ichihara, K., Sakai, K., Abiko, Y.: Effect of nifedipine and niludipine on myocardial pH in the ischemic canine heart. Arch. Int. Pharmacodyn. **280**:58-73, 1986.
15) Holmgren, S., Abrahamsson, T., Almgren, O., et al.: Effect of ischemia on the adrenergic neurons of the rat heart: a fluorescence histochemical and biochemical study. Cardiovasc. Res. **15**:680-689, 1981.
16) Heusch, G., Deussen, A., Schipke, J., et al.: Role of cardiac sympathetic nerves in the genesis of myocardial ischemia distal to coronary stenosis. J. Cardiovasc. Pharmacol. **7**:S13-S18, 1985.
17) Takeshima, R., Dohi, S.: Circulatory responses to baroreflexes, Valsalva maneuver, coughing, swallowing, and nasal stimulation during acute cardiac sympathectomy by epidural blockade in awake humans. Anesthesiology **63**:500-508, 1985.
18) Seagard, J. L., Hopp, F. A., Donegan, J. H., et al.: Halothane and the carotid sinus reflex: evidence for multiple sites of action. Anesthesiology **57**:191-202, 1982.
19) Rosenbaum, S. H., Barash, P. G.: Is anesthesia thrapeutic? Anesth. Analg. **69**:555-557, 1989.

(Circ Cont 13(3):405～411, 1992)