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Effects of Isoflurane Inhalation and Cardiac Sympathetic Nerve Stimulation on Myocardial Ischemia in the Canine Hearts with Severe Coronary Stenosis

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Abstract

The effects of isoflurane inhalation and cardiac sympathetic nerve stimulation on myocardial ischemia were studied in dogs with severe coronary artery stenosis (N=11).

After institution of severe coronary artery stenosis in fentanyl anesthetized dog, 0.5mg·kg^{-1} propranolol was administered. Isoflurane was inhaled at the inspiratory concentration of 0.8%. Cardiac sympathetic nerve was stimulated electrically before and during isoflurane inhalation.

By isoflurane inhalation, heart rate significantly increased, while left ventricular pressure, maximal rate of left ventricular pressure rise, and myocardial oxygen uptake decreased. Mean coronary artery pressure and coronary blood flow distal to the stenosis decreased and coronary vascular resistance distal to the stenosis tended to decrease. Aortic pressure decreased more than enlargement of pressure gradient of aorto-coronary artery distal to the stenosis. Intramyocardial pH in the inner layer of the ischemic region was decreased and myocardial lactate uptake ratio was worsened. With sympathetic nerve stimulation under isoflurane inhalation, mean coronary artery pressure and coronary blood flow increased and coronary vascular resistance tended to increase, while intramyocardial pH unchanged.

These results suggest that isoflurane can dilate coronary artery distal to the stenosis and may induce the transmular steal. However, vasodilation of isoflurane may be weak to produce myocardial ischemia by coronary steal and myocardial ischemia during isoflurane inhalation may not occur in the absence of marked hemodynamic changes.

Key words : Isoflurane, Cardiac sympathetic nerve, Myocardial ischemia, Coronary stenosis.

Introduction

Isoflurane has been reported to produce or exacerbate myocardial ischemia by a coronary steal mechanism due to coronary vasodilation[1)-6)]. On the other hand, coronary vasodilatory action of isoflurane is reported to be the same degree as that of other inhalation anesthetics[7)8)], or to be weaker than halothane in constricted coronary artery[9)], and moreover, not to cause coronary steal[10)-12)] because of decreasing myocardial oxygen consumption due to reduction of myocardial contractility[13)14)]. Furthermore, in patients with coronary artery disease, there is no difference between inhalation anesthetics and narcotics in the rate of mortality and occurrence of myocardial infarction and myocardial ischemia during and after surgery[15)-17)]. Precise effects of coronary vasodilatory property of isoflurane on myocardial ischemia are still not clear.

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In the present study, we investigated first; whether isoflurane inhalation aggravates the myocardial ischemia due to dilation of the coronary artery and secondly; whether sympathetic stimulation during isoflurane inhalation worsens myocardial ischemia.

Methods

Anesthesia was induced with intravenous administation of 25mg·kg^{-1} thiamylal in 11 mongrel dogs, followed by intratracheal intubation and artificial ventilation using Harvard respirator to maintain the $PaCO_2$ at 40mmHg approximately. Anesthesia was maintained with halothane (0.7%) until completion of surgical procedure. Thoracotomy was performed through the left 5 th intercostal space and pericardium was incised, and the heart was suspended in a pericardial cradle. The proximal left circumflex coronary artery was dissected free as far as the obtuse marginal branch and a snare for producing stenosis was placed around the circumflex coronary artery. An electromagnetic flow probe (MF-3200, Nihon Kohden, Japan) was placed proximal to the snare. One catheter-tip pressure transducer (Mikro Tip SPC-370, Miller, USA) was inserted into left ventricle via right carotid artery to measure left ventricular pressure. Another transducer was inserted into femoral artery and located in descending aorta to measure aortic pressure. The change in pressure with time was continuously derived from the left ventricular pressure signal. A 23 gauge catheter attached to the pressure transducer (Statham P23, Gould, USA) was inserted into the branch of circumflex artery distal to the stenosis to measure coronary artery pressure and another 23 gauge catheter for blood sampling was inserted into the coronary vein at the same region. A pH electrode (pH sensor, Kurare, Japan) was inserted and fixed in the inner layer of the myocardium (6-8mm depth) distal to the stenosis.

The heart rate (HR), left ventricular pressure (LVP), maximal rate of LVP rise (LV dp/dt max), left ventricular end-diastolic pressure (LVEDP), aortic pressure (AoP), coronary arterial pressure distal to the stenosis (CoAP), and coronary blood flow through circumflex artery (CBF) were measured. These data were put in and recorded with multi-purpose monitor (RMC-1000,Nihon Kohden). Coronary vascular resistance of circumflex artery (CVR) was calculated by the equation: CVR=mean CoAP/CBF. Intramyocardial pH was measured continuously with a pH/PCO_2 monitor (KR-500, Kurare) and recorded with multipurpose recorder (Multi Recorder T1-104, IT Giken, Japan). Blood gas analysis was conducted with a gas analyzer (ABL-3, Radiometer, Denmark). Oxygen content and hemoglobin were determined with an oximeter (CO-oximeter-2500, Corning, USA). Blood lactate was measured with an auto-chemical analyzer (ACA-SX, Dupon, USA). Myocardial oxygen uptake, myocardial oxygen uptake ratio, myocardial lactate uptake, myocardial lactate uptake ratio, and regional coronary venous-arterial blood CO_2 partial pressure difference (cv-aPco_2) in myocardium distal to the stenosis were calculated as the followings:

Myocardial oxygen uptake =
(arterial oxygen content - regional venous oxygen content) x CBF

Myocardial oxygen uptake ratio =
(arterial oxygen content - regional venous oxygen content) / arterial oxygen content

Myocardial lactate uptake =
(arterial lactate concentration - regional venous lactate concentration) x CBF

Myocardial lactate uptake ratio =
(arterial lactate concentration - regional venous lactate concentration) / arterial lactate concentration

cv-aPco_2 = regional coronary venous Pco_2-arterial Pco_2

After completion of surgical procedure, halothane was discontinued and fentanyl was continuously infused at the rate of 0.2 μg·kg^{-1}·min^{-1} during the experiment following a intravenous bolus infusion of 50-100μg. Over 60min later, coronary artery stenosis was instituted with a 50% decrease of CBF. Coronary stenosis decreased mCoAP (91 ± 17 to 41 ± 16mmHg) and tended to de-

crease CVR (1.12 ± 0.30 to 0.91 ± 0.31mmHg·ml^{-1}·min^{-1}·100g^{-1}). After the stabilization of CBF (30-40min), a bolus of 0.5mg·kg^{-1} propranolol was administered intravenously. propranolol decreased heart rate (83 ± 23 to 61 ± 14 beats·min^{-1}) and increased mCoAP (41 ± 16 to 54 ± 18mmHg) and CVR (0.91 ± 0.31 to 1.38 ± 0.05mmHg·ml^{-1}·min^{-1}·100g^{-1}).

The experiment consisted of sympathetic nerve stimulation in the heart with coronary artery stenosis before and after isoflurane inhalation. Control recordings of hemodynamics, intramyocardial pH, and myocardial metabolic data were obtained, and then cardiac sympathetic nerve was stimulated (without isoflurane). After hemodynamics had returned to control levels (30 to 40min), isoflurane was inhaled at the inspiratory concentration of 0.8%. This concentration was selected to decrease AoP 10-15mmHg. Measurements were repeated 15 min later and sympathetic nerve was stimulated (Isoflurane). Sympathetic nerve stimulation was performed on the anterior branch of the left stellate ganglion at 2-5Hz, 2 msec duration, 5-10mV with electrical stimulator (S7272A, Nihon Kohden) to increase mean AoP about 10mmHg and this state was maintained for 90sec. During the experiment, normal saline was infused at a rate of 10 ml·kg^{-1}·hr^{-1}.

The results were statistically analyzed by repeated analysis of variance followed by paired t-test, using $p<0.05$ as the level of significance.

Results

1. Effects of sympathetic nerve stimulation before isoflurane. (table 1 and Fig. 1, 2)

Table 1. Effects of Sympathetic Nerve Stimulation on Hemodynamics and Myocardial Metabolics in the Heart with Coronary Stenosis without and with Isoflurane Inhalation.

		Without Isoflurane		Isoflurane	
		control	SN stimulation	control	SN stimulation
HR	beats·min^{-1}	61±14	67±15	79±13#	81±14#
LVP	mmHg	119±12	132±14*	99±12#	115±11*
LV dp/dt max	mmHg·sec^{-1}	1817±386	1946±320*	1510±351#	1732±379*
m AoP	mmHg	90±13	100±17*	75±13#	90±12*
LVEDP	mmHg	7.8±1.3	8.3±2.1	6.2±1.3#	6.6±1.3*#
m CoAP	mmHg	54±18	68±24*	33±13#	49±18*#
AoP−CoAP	mmHg	36±14	33±15	42±10	42±12
CBF	ml·min^{-1}·100g^{-1}	40.9±17.1	44.1±19.3*	29.2±10.1#	37.2±13.3*
CVR	mmHg·ml^{-1}·min^{-1}·100g^{-1}	1.38±0.45	1.65±0.67*	1.16±0.42	1.35±0.45
RPP	beats·mmHg^{-1}·min^{-1}	7336±2070	8881±2523*	7597±1573	9187±1866*#
PaO_2	mmHg	420.3±115.4	408.8±114.2	418.0±111.9	409.1±116.0
$PaCO_2$	mmHg	40.9±6.0	42.9±6.2*	41.7±8.0	44.8±7.9*#
cv−aPCO_2	mmHg	13.6±4.3	17.1±4.4*	16.6±8.9	19.1±8.0*#
pH t		7.12±0.12	7.13±0.11	7.04±0.14#	7.04±0.16#
O_2 uptake	ml·min^{-1}	4.49±1.49	5.38±1.85*	3.12±0.74#	4.26±1.07*
O_2 uptake ratio	%	57.1±12.9	61.5±10.2	56.8±13.4#	59.2±12.0
LA uptake	μMol·min^{-1}	15.7±17.2	14.5±8.3	−1.2±17.7#	1.1±21.2#
LA uptake ratio	%	20.2±20.9	24.2±14.0	−9.4±44.4#	−6.9±49.1

Values are mean ± SD n=11

#: $p<0.05$ versus control value without isoflurane, *: $p<0.05$ versus preceded value

SN=sympathetic nerve; HR=heart rate; LVP=left ventricular pressure; LV dp/dt max=maximal rate of rise of left ventricular pressure; m AoP=mean aortic presssure; LVEDP=left ventricular end-diastolic pressssure; m CoAP=mean circumflex coronary artery presssure; AoP−CoAP=aorto−coronary artery pressure difference; CBF=circumflex coronary blood flow; CVR=coronary vascular resistance; RPP=rate presssure products; cv−aPCO_2=coronary venous−arterial CO_2 partial presssure difference; pH t=intramyocardial pH; O_2 uptake=myocardial oxygen uptake; LA uptake=lactic acid uptake.

Before isoflurane inhalation, sympathetic nerve stimulation increased LVP, LV dp/dt max, mean CoAP, CBF, and CVR, while intramyocardial pH, myocardial lactate uptake, myocardial lactate uptake ratio, and myocardial oxygen uptake ratio unchanged. Myocardial oxygen uptake increased.

2. Effects of isoflurane inhalation in the heart with stenosis (table 1)

Isoflurane decreased LVP and LV dp/dt max, but increased HR significantly. Rate pressure product (RPP) did not change. In the ischemic region, mean CoAP and CBF decreased and CVR tended to decrease. Intramyocardial pH and lactate uptake ratio decreased significantly. Myocardial oxygen uptake and myocardial oxygen uptake ratio decreased significantly.

3. Effects of sympathetic nerve stimulation under isoflurane inhalation. (table 1 and Fig. 1, 2)

Under isoflurane, sympathetic nerve stimulation increased LVP, LV dp/dt max, mean CoAP, CBF, and RPP. CVR tended to increase, but not significantly. Intramyocardial pH, myocardial lactate uptake, myocardial lactate uptake ratio, and myocardial oxygen uptake ratio unchanged. Myocardial oxygen uptake increased.

LVP and mean AoP during sympathetic nerve sti-

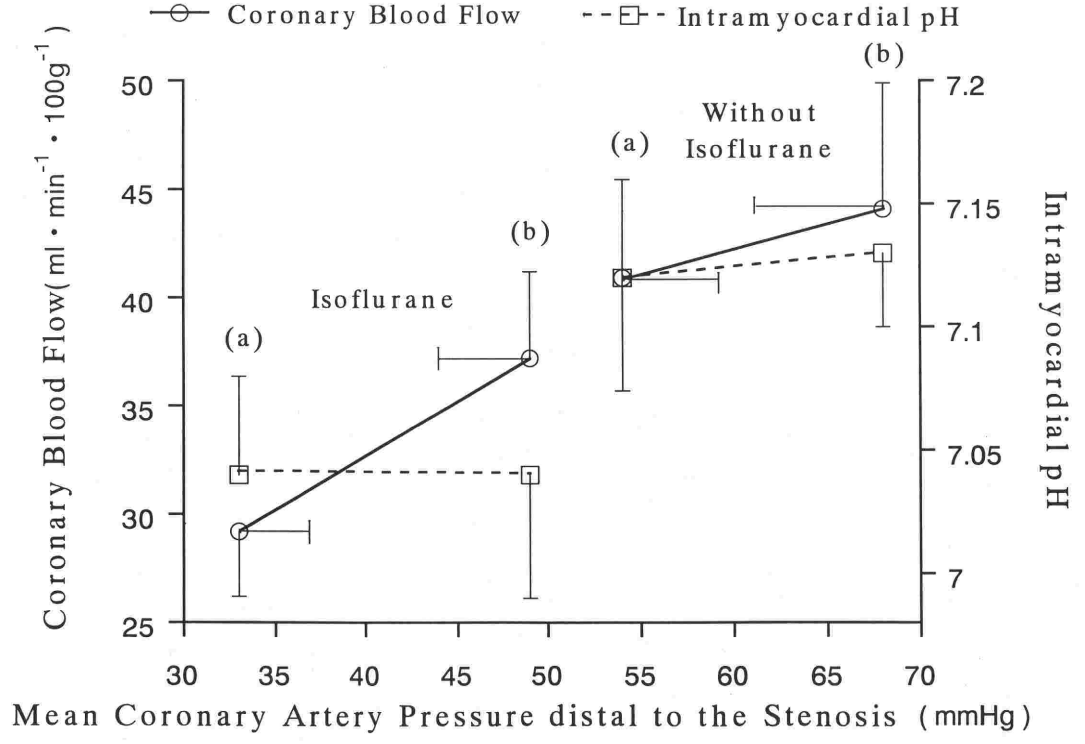

Fig 1. Relationship between coronary artery pressure distal to the stenosis or intramyocardial pH in the inner layer of myocardium distal to the stenosis and coronary blood flow (CBF) through the stenosis.

(a) indicates control state without cardiac sympathetic nerve stimulation and (b) is during cardiac sympathetic nerve stimulation. Coronary artery pressure distal to the stenosis and CBF through the stenosis increased during cardiac sympathetic nerve stimulation in both groups, while intramyocardial pH unchanged.

Data are presented as mean ± SEM; n=11.

mulation in the presence of isoflurane were the same level to the control value without isoflurane, whereas mean CoAP and intramyocardial pH were low.

Discussion

In an acute experiment stenosing coronary artery to mimic ischemic heart disease, basic hemodynamics should be kept stable as at rest, because hemodynamics can affect the severity of coronary artery stenosis and coronary reserve. Especially, heart rate should be kept in reasonable rate, because it influences on both myocardial oxygen supply and demand. In this study, as basal anesthesia we used a continuous infusion of fentanyl to keep heart rate less than 100beats·min^{-1}, thereafter instituted coronary stenosis. Propranolol was administered to minimize the metabolic vasodilatory effect on coronary artery. In this study, 0.5mg·kg^{-1} propranolol was administered although other experiments have used 2.0mg·kg^{-1} for this purpose, because 2.0mg·kg^{-1} was too high to keep heart rate over 50beats·min^{-1} under continuous infusion of fentanyl.

In patients with coronary artery disease, effect of coronary artery vasodilation of anesthetics on myocardial blood flow in ischemic region depends on the number, severity, and location of the diseased coronary arteries[18) -20)]. In the heart with single coronary artery stenosis like this study,

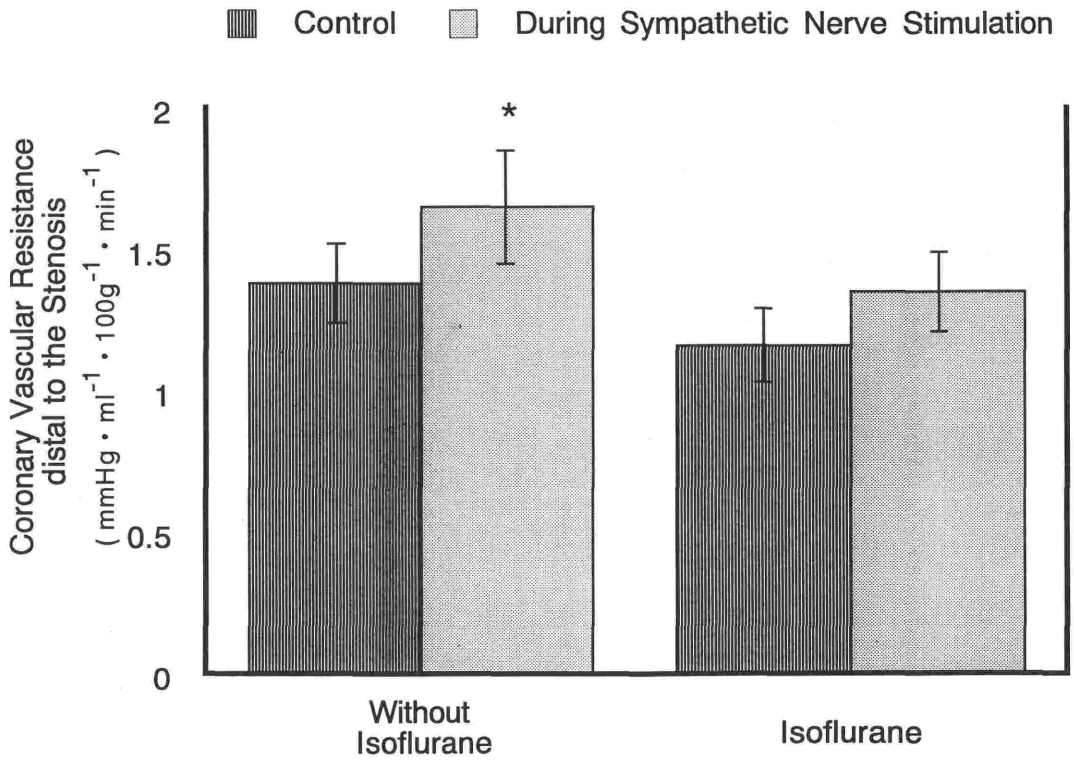

Fig 2. Effects of cardiac sympathetic nerve stimulation on the coronary vascular resistance before (Without Isoflurane) and after isofluran inhalation (Isoflurane).
The resistance before isoflurane inhalation increased during cardiac sympathetic nerve stimulation, while the resistance after isoflurane tended to increase, but not significantlly.
Data are presented as mean ± SEM; n=11. *Significant difference from control at $P<0.05$.

coronary artery in the inner layer of myocardium distal to the stenosis is thought to dilate maximally, thus losing dilatory reserve, resulting that myocardial blood flow in ischemic region may be dependent on the perfusion pressure. Vasodilation of coronary arterioles in outer layer of myocardium may cause myocardial ischemia in the inner layer of myocardium in ischemic region by vascular resistance difference; so-called transmural steal. These kinds of myocardial ischemia were reported to occur typically by dipyridamole and adenosine[19)-22)]. Isoflurane has been reported to have a possibility to cause transmural steal[1)-6)]. In this study, isoflurane decreased aortic pressure, coronary artery pressure distal to the stenosis and coronary blood flow through the stenosis, and coronary vascular resistance distal to the stenosis tended to decrease. Furthermore, intramyocardial pH in the inner layer of myocardium distal to the stenosis decreased and myocardial lactate production occurred. These results suggested a possibility that isoflurane dilated arterioles in the outer layer of myocardium distal to the stenosis and myocardial ischemia was worsened in the inner layer in the ischemic myocardium by transmural steal. On the other hand, myocardial ischemia could occur also by reduction of aortic pressure without steal through the decrease of coronary perfusion pressure, when mean aortic pressure decreases below 70-55mmHg[4)] or coronary perfusion pressure is lowered less than 50mmHg[23)]. In this study, mean aortic pressuer was relatively higher than that which was known to cause myocardial ischemia. However, aortic pressure does not represent the coronary perfusion pressure in the ischemic region. In this study, isoflurane inhalation severely lowered coronary artery pressure distal to the stenosis. In the severe coronary artery stenosis like this study, slight decrease of aortic pressure caused by isoflurane inhalation could reduce coronary artery pressure below critical level, therefore myocardial ischemia may be worsened simply by decrease of aortic pressure rather than the steal phenomenon induced by coronary artery dilation.

Even though isoflurane decreased coronary blood flow, myocardial ischemia could be prevented to worsen by reducing myocardial oxygen consumption due to isoflurane mediated decrease in myocardial contractility and myocardial wall tension[13)-14)]. In this study, however, despite of decrease of calculated myocardial oxygen uptake, anaerobic metabolism was accelerated (Fig. 1 , 3). Decrease of coronary artery pressure causes reduction of myocardial blood flow in ischemic region, resulted in decrease of oxygen delivery. Decrease of oxygen delivery below the critical level causes reduction of myocardial oxygen uptake and acceleration of anaerobic metabolism[24)], meaning decrease of myocardial oxygen uptake might be caused by decrease of oxygen delivery, not by decrease of myocardial oxygen demand.

Disturbance of increase in coronary perfusion pressure during sympathetic nerve stimulation may worsen myocardial ischemia in the inner layer of the myocardium in ischemic region because of unbalance of myocardial oxygen supply and demand relationship[25)26)]. Isoflurane was reported to diminish vasodilation due to hypoxia, ischemia or myocardial metabolism which is caused by enhancement of myocardial contractility with sympathetic nerve stimulation[27)]. In this study, during sympathetic nerve stimulation under isoflurane inhalation, coronary artery pressure and coronary blood flow significantly increased and coronary vascular resistance distal to the stenosis tended to increase (Fig. 2). Furthermore, myocardial lactate uptake and uptake ratio did not worsen and intramyocardial pH unchanged. These results suggested isoflurane did not disturb sympathetic nerve stimulation mediated increase in coronary perfusion pressure in this study[22)28)29)].

Despite of the increase of coronary blood flow by sympathetic nerve stimulation under isoflurane inhalation, intramyocardial pH did not improve to the control value without isoflurane inhalation (Fig. 1). Moreover, by cardiac sympathetic nerve stimulation, systolic left ventricular pressure, aortic pressure, and coronary blood flow were almost restored

to the control value observed before isoflurane inhalation. While coronary artery pressure did not recover to the control level and rate pressure product was higher than the control value without isoflurane inhalation (Fig. 3), suggesting that myocardial blood flow in the inner layer of ischemic region is lower and myocardial oxygen demand is higher than those of the control values without isoflurane inhalation, then intramyocardial pH could not improve to the control value. The situation like this study has been showed in the experiment of norepinephrine or phenylephrine infusion in the hearts with coronary stenosis. When norepinephrine or phenylephrine was used to correct the decrease of blood pressure and myocardial blood flow in the ischemic region caused by isoflurane inhalation, maldistribution of myocardial blood flow and regional myocardial dysfunction have been reported not to be improved[13) 14)] despite of the increase in myocardial blood flow in the inner layer[25) 26)]. This increase of myocardial blood flow in the inner layer of ischemic region might be correspondent to the increase of myocardial oxygen demand which is caused by administration of norepinephrine or phenyrephrine, so that the regional myocardial ischemia caused by isoflurane inhalation could not be improved[30) 31)].

In conclusion, this study showed that inhalation of isoflurane even in the low concentration might have a possibility to induce the transmural steal in

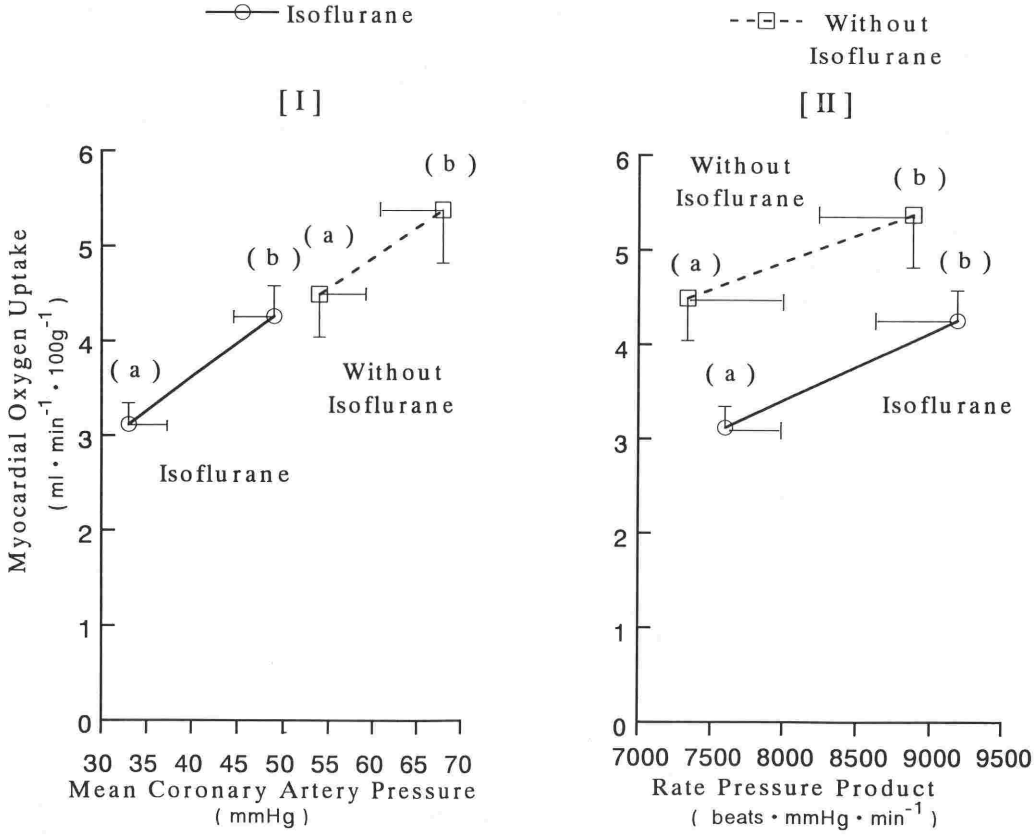

Fig 3. Relationship between myocardial oxygen uptake and mean coronary artery pressure distal to the stenosis [I], and rate pressure product [II] before (Without Isoflurane) and after isoflurane inhalation (Isoflurane) at control state (a) and during sympathetic nerve stimulation (b).

Myocardial oxygen uptake decreased corespondent with mean coronary artery pressure by isoflurane inhalation, whereas rate pressure product did not decrease.

Data are presented as mean ± SEM ; n=11.

the heart with severe coronary stenosis when decrease in blood pressure is accompanied. Cardiac sympathetic nerve stimulation during isoflurane inhalation dose not disturb the increase in coronary artery perfusion pressure and dose not worsen myocardial ischemia.

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