原 著 (Original article)

Effects of Sympathetic Nerve Stimulation after Propranolol Administration on Coronary Artery and Myocardial Metabolism in the Dog with Coronary Stenosis

Arifumi Kohyama* Shozo Kaji* Satoshi Yasumoto*
Hideyuki Kimura* Hiroshi Kitahara* Takao Saito*

ABSTRACT

The effects of cardiac sympathetic nerve stimulation after propranolol administration on coronary vascular resistance and myocardial metabolism were studied in 21 dogs with coronary artery stenosis.

After administration of propranolol in the heart with stenosis, heart rate and maximal rate of rise of left ventricular pressure significantly decreased, whereas systolic left ventricular pressure did not change. Mean coronary arterial pressure and coronary vascular resistance distal to the stenosis significantly increased, while coronary blood flow through the stenosis tended to decrease. Intramyocardial pH tended to increase. Myocardial oxygen consumption significantly decreased. Cardiac sympathetic nerve stimulation after propranolol administration significantly increased mean aortic blood pressure, mean coronary arterial pressure and coronary vascular resistance distal to the stenosis. Coronary blood flow distal to the stenosis tended to increase. Intramyocardial pH did not change.

These results suggest that propranolol appears to improve myocardial ischemia by decreasing myocardial oxygen consumption and increasing coronary perfusion pressure in the ischemic region, and that, even when in addition of cardiac sympathetic nerve stimulation, propranolol may not decrease coronary blood flow and prevent myocardial ischemia.

Key words : Sympathetic nerve stimulation, Propranolol, Myocardial Metabolism, Coronary Stenosis

Introduction

In patients with ischemic heart disease, beta-blocking agents are used extensively to reduce the episodes of angina pectoris and increase exercise ability[1,2]. They improve ischemia by decreasing the heart rate and myocardial oxygen consumption, in addition, by promoting redistribution of blood flow into the inner layer of the myocardium in ischemic region through increase of diastolic period and contraction of the coronary artery[3)~5)]. Sympathetic vasoconstriction, however, as well as increase of myocardial oxygen consumption, may aggravate ischemia[6,7]. Beta-blocking agents is thought to contract the coronary artery and to cause coronary artery spasm.[8)] Furthermore, sympathetic nerve stimulation after beta-blocking agents worsens ischemia by causing contraction of the stenotic site of superficial coronary artery and/or coronary arterioles in the ischemic myocardium[9,10], and may facilitate the appearance of angina during the cold pressor test and hand grip test[11,12]. On the other hand, vasoconstrictive reaction due to sympathetic nerve sti-

*Department of Anesthesiology, Tokushima University School of Medicine, Tokushima, Japan

Presented by Medical*Online

mulation after beta-blocking agents is thought to occur only in the normal region and to improve the myocardial ischemia by maintaining the blood flow to the ischemic region[13~15]. The precise effects of the beta-blocking agents on the coronary vessels are still not clear.

In the present study, we investigated whether propranolol constricts coronary artery in the ischemic region and whether cardiac sympathetic nerve stimulation after propranolol reduces coronary blood flow and aggravates the inner layer of myocardium in the ischemic region in fentanyl anesthetized dogs with severe coronary stenosis.

Methods

Anesthesia was induced with 25 $mg \cdot kg^{-1}$ thiamylal in 21 mongrel dogs, followed by intratracheal intubation and artificial ventilation using Harvard respirator to maintain the $PaCO_2$ at 40 mmHg approximately. Anesthesia was maintained with intravenous infusion of 50-100 μg fentanyl followed by a continuous infusion of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the experiment. Thoracotomy was performed through the left 5th 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) was placed proximal to the snare. One catheter-tip pressure transducer (Mikro Tip SPC-370, Miller) 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 transducer (Statham P23, Gould) was inserted into the artery at the branch of circumflex distal to the stenosis to measure coronary artery pressure and another 23 gauge catheter for blood sampling into the vein in the same region. A pH electrode (pH sensor, Kurare) was inserted and fixed in the inner layer of the myocardium distal to the stenosis.

The heart rate (HR), left ventricular pressure (LVP), maximal rate of LVP rise (LV dp/dt max), aortic pressure (AoP), coronary arterial pressure distal to the stenosis (CoAP), coronary blood flow through circumflex artery (CBF), and left ventricular end-diastolic pressure (LVEDP) were measured. These data were put in and recorded with multipurpose 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). Blood gas analysis was conducted with a gas analyzer (ABL-3, Radiometer). Oxygen content and hemoglobin were determined with a oximeter (CO-oximeter-2500, Corning). Blood lactate was measured with a auto-chemical analyzer (ACA-SX, Dupon). Myocardial oxygen uptake, oxygen uptake ratio, lactate uptake, lactate uptake ratio, and coronary venous-arterial blood CO_2 partial pressure difference ($cv\text{-}aPco_2$) were calculated as the followings;

Myocardial oxygen uptake = (arterial oxygen content − regional venous oxygen content) × CBF

Oxygen uptake ratio = (arterial oxygen content − regional venous oxygen content) / arterial oxygen content

Lactate uptake = (arerial lactate fraction − rgional venous lactate fraction) × CBF

Lactate uptake ratio = (arerial lactate fraction − regional venous lactate fraction) / arerial lactate fraction

$cv\text{-}aPco_2$ = regional venous Pco_2 − arterial Pco_2

The experiment consisted of sympathetic nerve stimulation in the heart with coronary artery stenosis before and after propranolol administration. Coronary artery stenosis was instituted with a 50% decrease of CBF. A bolus of 0.5 $mg \cdot kg^{-1}$ prop-

Presented by Medical*Online

ranolol was administered intravenously. Sympathetic nerve stimulation was performed on the anterior branch of the left stellate ganglion at 2-5 Hz, 2 msec duration, 5-10 mV with electrical stimulator (S7272A, Nihon Kohden) to increase mean aortic pressure about 10mmHg and maintain this state for 90 sec. Hemodynamic, intramyocardial pH, and myocardial metabolic data were obtained before and after 90 sec sympathetic nerve stimulation. During experiment, normal saline was infused at a rate of $10 m\ell \cdot kg^{-1} \cdot hr^{-1}$

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 (table 1)

1. Effects of sympathetic nerve stimulation in the heart with stenosis

In the heart with stenosis, during sympathetic nerve stimulation, LVP and LV dp/dt max increased significantly. Mean CoAP and CBF increased significantly (Fig.1), whereas CVR did not increase (Fig.2). Intramyocardial pH and lactate uptake ratio tended to decrease. Myocardial oxygen uptake in the myocardium distal to the stenosis increased significantly.

2. Effects of sympathetic nerve stimulation after propranolol

Table 1 Effects of Sympathetic Nerve Stimulation on Hemodynamics and Myocardial Metabolics in the Heart with stenotic coronary artery (Stenosis) and after propranolol administration (Propranolol).

		Stenosis		Propranolol	
		control	SN stimulation	control	SN stimulation
HR	beats/min	77±25	77±24	60±19#	63±19#
LVP	mmHg	119±20	135±17*	118±15	133±17*#
LV dp/dt max	mmHg/sec	2306±559	3025±654*	1708±353#	1836±336*#
m AoP	mmHg	93±16	105±19*	91±14	102±18*#
LVEDP	mmHg	7.2±3.1	7.2±3.2	8.2±2.4	8.8±2.7*#
mCoAP	mmHg	44±19	56±28*	57±21#	69±2.7
CBF	ml/min/100g	47.9±18.6	56.0±24.3*	42.4±18.3	44.9±19.4
CVR	mmHg/ml/min/100g	0.96±0.40	1.07±0.46	1.44±0.57#	1.67±0.73*#
RPP	beats·mmHg/min	9081±3167	10376±3446*	7031±2525#	8326±2734*
PaC_2	mmHg	404.4±125.4	407.1±122.7	417.6±113.8	411.7±113.8
$PaCO_2$	mmHg	41.5±4.1	44.2±4.3	39.9±5.0#	43.1±6.3*
$PcvO_2$	mmHg	33.1±6.23	33.3±6.4	34.4±7.8	34.1±7.2
$cv-aPCO_2$	mmHg	13.2±3.9	14.9±4.8*	13.8±4.6	14.8±5.3
pH t		7.12±0.10	7.10±0.11	7.15±0.12	7.15±0.11
LA	mMol/L	1.5±0.5	1.3±0.7*	1.5±0.6	1.3±0.5*#
uptake	μMol/min	5.19±16.83	0.89±25.58	9.31±17.74	11.52±14.82
uptake ratio	%	2.5±30.5	−27.4±100.8*	−3.1±72.9	13.3±42.1
O_2 uptake ratio	%	60.8±9.4	62.3±10.1	57.2±11.7#	60.2±10.9
$M\dot{V}O_2$	ml/min	5.62±2.11	6.72±2.69*	4.62±2.00#	5.20±1.99*

Values are mean ± SD n = 21

: $p<0.05$ versus control value of stenotic coronary artery

* : $p<0.05$ versus preceded value

HR = heart rate ; LVP = left ventricular pressure ; LV dp/dt max = maximal rate of rise of left ventricular pressure ; m AoP = mean aortic pressure ; LVEDP = Left ventricular end-diastolic pressure ; mCoAP = mean circumflex coronary artery pressure ; CBF = circumflex coronary blood flow ; CVR = coronary vascular resistance ; RPP = Rate Pressure Product ; $cv-aPCO_2$ = coronary vein-artery CO_2 partial pressure difference ; pH t = intramyocardial pH ; LA = lactic acid ; O_2 uptake ratio = myocardial oxygen uptake ratio ; MVO_2 = myocardial oxygen consumption.

Presented by Medical*Online

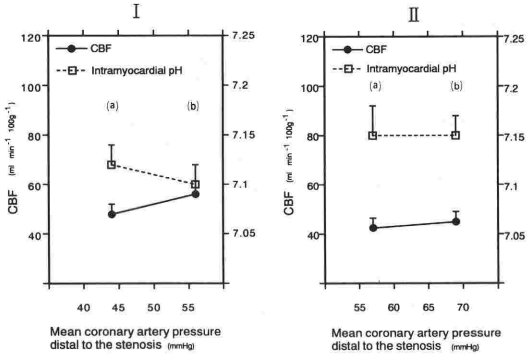

Fig. 1 Relationship between coronary artery pressure distal to the stenosis and intramyocardial pH in the inner layer of myocardium distal to the stenosis and coronary blood flow through the stenosis.

These data are indicated in the heart with stenotic coronary artery before (I) and after propranolol administration (II) at control state (a) and during cardiac sympathetic never stimulation (b). Coronary artery pressure distal to the stenosis and coronary blood flow through the stenosis increased during cardiac sympathetic nerve stimulation in both groups, while intramyocardial pH did not change after propranolol administration but tended to decrease before propranolol.

Data are presented as mean ± SEM ; n =21.

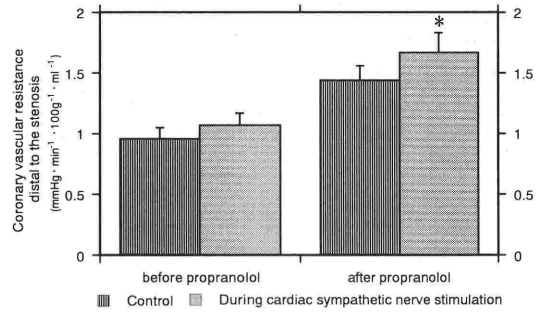

FIg 2. Effects of cardiac sympathetic never stimulation on the coronary vascular resistance distal to the stenosis before and after propranolol administation.

During cardiac sympathetic never stimulation, coronary artery resistance distal to the stenosis markedly increased after propranolol administration but, before propranolol, did not increase.

Data are presented as mean ± SEM ; n =21.
*Significant difference from control at $P < 0.05$.

Propranolol administration caused a significant decrease in HR and LV dp/dt max, and no change in LVP in the heart with stenosis. In the ischemic region, CBF decreased slightly, but not significantly, while mean CoAP and CVR increased significantly. The intramyocardial pH tended to increase, and myocardial oxygen uptake and uptake ratio decreased significantly, while lactake uptake and uptake ratio did not change.

Sympathetic nerve stimulation after propranolol significantly increased LVP and LV dp/dt max, but increase of LV dp/dt max was slight. In the ischemic region, mean CoAP and CVR significantly increased, while CBF increased slightly but not significantly (Fig.1, 2). Intramyocardial pH and lactate uptake ratio did not change. Myocardial oxygen uptake increased significantly.

Discussion

The increase in intramyocardial pH indicates an improvement of the balance of myocardial oxygen supply and demand, which is influenced also by the myocardial blood flow distribution, as well as coronary blood flow and myocardial oxygen consumption. With propranolol administration, decreasing heart rate and lowering myocardial contractility cause a reduction of oxygen demand, and, at the same time, increased LVEDP is expected to increase oxygen demand due to enhancing myocardial wall tension. In the present study, myocardial oxygen uptake and uptake ratio after propranolol administration were lower than the control value in the heart with stenosis. These findings indicate that the effect of the decrease in heart rate and myocardial contractility was more dominant than that of the increase in myocardial wall tension, thus resulting in a net decrease in myocardial oxygen consumption. On the other hand, the coronary blood flow was decreased, yet myocardial ischemia tended to improve as shown by the decrease of myocardial oxygen uptake ratio

Presented by Medical*Online

and increase of intramyocardial pH. The decrease in coronary blood flow can be considered a result of reduction of myocardial oxygen consumption. Moreover, the improvement in myocardial metabolism implies increased blood flow to the inner layer of myocardium relative to the oxygen demand. Propranolol may improve myocardial blood flow distribution and increase blood flow to the inner layer of myocardium by the following mechanism: 1. decreased heart rate and prolonged diastolic period[3,4,9]; and 2. diminished metabolic vascular dilation by beta-receptor blockade; and 3. coronary artery contraction, especially in the outer layer of myocardium, due to the dominance of alpha-receptor relative to beta−receptor blockade [17~19]. The improvement in myocardial blood flow distribution of myocardium, however, may be lost by the increase of the heart rate to the control level[9,14,16]. In this study, although the coronary blood flow through the stenosis was lowered by propranolol, coronary artery pressure distal to the stenosis was increased and pressure difference of aorto-coronary artery distal to the stenosis was decreased, and the coronary vascular resistance in the ischemic region was significantly increased. These findings indicate the possibility that propranolol contracts the coronary arterioles, not the stenotic site of the superficial coronary artery. Furthermore the increase in intramyocardial pH strongly indicates a possibility of an improvement of blood flow in the inner layer of myocardium due to contraction of the coronary artery, especially the arterioles in the outer layer of myocardium.

The sympathetic nerve stimulation after propranolol did not reduce coronary blood flow and did not decrease the intramyocardial pH. Sympathetic nerve stimulation after propranolol is thought to enhance the alpha-receptor action more than without propranolol and to cause contraction of the superficial coronary artery or peripheral arterioles, leading to reduce coronary blood flow through the stenosis, thus aggravating the myocardial ischemia[8)11)12)]. In the present study, the coronary blood flow was virtually unchanged, and marked increase in coronary artery pressure and coronary resistance distal to the stenosis was observed. These observations may indicate coronary contraction. Pressure difference of aorto-coronary artery distal to the stenosis and coronary vascular resistance in the stenotic site did not increase. Moreover, the coronary blood flow did not decrease, and intramyocardial pH did not lower, implying that the stenotic segment in superficial coronary artery did not contract, although the peripheral vessels did. Propranolol may prevent the contraction of the superficial coronary artery due to the sympathetic stimulation[19)]. Compared with sympathetic nerve stimulation in untreated heart with stenosis, the aortic pressure and rate pressure product increased equivalently, whereas the myocardial contratility was virtually unchanged and myocardial oxygen uptake obtained by calculation was only slightly increased. These findings indicate that the increase in myocardial oxygen demand was slight after propranolol compared with in the untreated heart. Therefore inhibition of increase of myocardial oxygen demand after propranolol is thought to prevent metabolic coronary dilation and markedly increase in coronary resistance bears a significant contraction with alpha-receptor stimulation[20~22)]. Especially, by the inhibition of metabolic vascular dilation in the outer layer of myocardium, the coronary artery pressure distal to the stenosis was increased markedly, maintaining blood flow to the inner layer of myocardium. In the inner layer, the blood flow increased in response to myocardial oxygen consumption, so that intramyocardial pH did not change and myocardial ischemia in distal to the stenosis did not worsen. These findings showed that sympathetic nerve stimulation after propranolol results in only slight vascular dilation in the outer layer of myocardium in the stenotic region and does not aggravate myocardial ischemia by the so-called reverse steal effect[14,20,23)].

In the ischemic heart, propranolol may improve myocardial ischemia by reducing myocardial ox-

Presented by Medical*Online

ygen demand and increasing coronary perfusion pressure in the ischemic myocardium, and moreover, sympathetic nerve stimulation after propranolol may not reduce coronary blood flow, but markedly increase the coronary artery pressure, maintaining blood flow to the inner layer of myocardium.

References

1) Alderman EL, Davies RO, Crowley JJ, et al : Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 51 : 964-975, 1975
2) Rainwater J, Steele P, Kirch D, et al : Effect of propranolol on myocardial perfusion images and exercise ejection fraction in men with coronary artery disease. Circulation 65 : 77-81, 1982
3) Becker LG, Fortuin NJ, Pitt B : Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle. Circ Res 28 : 263-269, 1971
4) Gross GJ, Winbury MM : Beta adrenergic blockade on intramyocardial distribution of coronary blood flow. J. Pharmcol. Exp Therap 187 : 451-465, 1973
5) Sakata S, Toriumi S, Takata K, et al : Effect of Propranolol on regional oxygen balance in the ischemic canine myocardium. Masui 36 : 39-45, 1987
6) Mudge GH, Goldberg S, Gunther S, et al : Comparison of metabolic and vasoconstrictor stimuli on coronary vascular resistance in man. Circulation 59 : 544-550, 1979
7) Brown BG, Lee AB, Bolson EL, et al : Reflex constriction of significant coronary stenosis as a mechanism contributing to ischemic left ventricular dysfunction during isometric exercise. Circulation 70 : 18-24, 1984
8) Yasue H, Omote S, Takizawa A, et al : Circadian variation of exercise capacity in patients with prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation 59 : 938-948, 1979
9) Guth BD, Heusch G, Seitelberger R, et al : Mechanism of beneficial effect of β -adrenergic blockade on exercise-induced myocardial ischemia in conscious dogs. Circ Res 60 : 738-746, 1987
10) Heusch G, Deussen A : The effects of cardiac sympathetic nerve stimulation on perfusion of stenotic coronary arteries in the dog. Circ Res 53 : 8-15, 1983
11) Kern MJ, Ganz P, Horowitz JD, et al : Potentiation of coronary vasoconstriction by beta-adrenergic blockade in patients with coronary artery disease. Circulation 67 : 1178-1185, 1983
12) Robertson RM, Wood AJJ, Vaughn WK, et al : Exacerbation of vasotonic angina pectoris by propranolol. Circulation 65 : 281-285, 1982
13) Feigl EO : The paradox of adrenergic coronary vasoconstriction. Circulation 76 : 737-745, 1987
14) Giudicelli J, Berdeaux A, Tato F, et al : Left stellate stimulation: regional myocardial flows and ischemic injury in dogs. Am J Physiol 239 : H359-H364, 1980
15) Matsuzaki M, Patritti J, Tajima T, et al : Effects of β-blockade on regional myocardial flow and function during exercise Am J Physiol 247 : H52-H60, 1984
16) Thuillex C, Berdeaux A, Bonhenry C, et al : Effects of propranolol on regional myocardial blood flow and function during severe coronary stenosis in dogs. Eur J Pharmacol 92 : 171-179, 1983
17) Berdeaux A, Drieu La Rochelle C, Richard V, et al : Opposed responses of large and small coronary arteries to propranolol during exercise in dogs. Am J Physiol 261 : H265-H270, 1991
18) Turlapaty PDM, Altura BM : Propranolol induces contractions of canine small and large coronary arteries. Basic Res Cardiol 77 : 68-81, 1982
19) Bortone AS, Hess OM, Gaglione A, et al : Effect of intravenous propranolol on coronary vasomotion at rest and during dynamic exercise in patients with coronary artery disease. Circulation 81 : 1225-1235, 1990
20) Ertl G, Fuchs M : Alpha-adrenergic vasoconstriction in arterial and arteriolar sections of the canine coronary circulation. Basic Res Cardiol 75 : 600-614, 1980
21) Vatner SF : Alpha-adrenergic regulation of the coronary circulation in the conscious dog. Am J Cardiol 52 : 15A-21A, 1983
22) Johannsen UJ, Mark AL, Mercus ML : Responsiveness to cardiac sympathetic nerve stimulation during maximal coronary dilation produced by adenosine. Circ Res 50 : 510-517, 1982
23) Gewirtz H, Most AS, Williams DO : The effect of generalized alpha-receptor stimulation on regional myocardial blood flow distal to a severe coronary artery stenosis. Circulation 65 : 1329-1336, 1981

(Circ Cont 15 : 415～420, 1994)

Presented by Medical*Online