The Effects of Antianginal Drugs on Energy Expenditure During Exercise in Normal Subjects

Susumu Asakuma, M.D., Mitsumasa Ohyanagi, M.D.
and Tadaaki Iwasaki, M.D.

The respiratory quotient ($RQ=\dot{V}CO_2/\dot{V}O_2$) provides important information (ie, the ratio of carbohydrate to fat utilization) concerning energy expenditure. We studied the effects of various antianginal drugs on energy expenditure during steady-state aerobic exercise in 9 healthy adult men. The drugs used were propranolol (a non-selective beta-blocker), metoprolol (a beta-1 selective blocker), amosulalol (an alpha- and beta-blocker), nicardipine (a calcium antagonist) and isosorbide dinitrate. Each drug was administered for 2 weeks, followed by a 2-week washout period. $\dot{V}O_2$, $\dot{V}CO_2$ and RQ were measured with an expired gas analyzer during treadmill exercise tests before and during the administration of each drug. Two protocols of constant-load exercise were performed: Protocol 1 lasted for 10 min at a speed of 5.5 km/h and a grade of 0%, (at a level of about 30% peak $\dot{V}O_2$), while Protocol 2 lasted for 10 min at a speed of 7 km/h and a grade of 0%, (at a level of about 40% peak $\dot{V}O_2$). RQ during exercise was significantly increased and $\dot{V}O_2$ was decreased after propranolol, metoprolol and amosulalol ($P<0.05$). Neither nicardipine nor isosorbide dinitrate produced significant changes in these values. These data suggest that propranolol, metoprolol and amosulalol increase the efficiency of energy expenditure during ordinary physical activity by increasing the utilization of carbohydrate and by decreasing the utilization of fat.

(*Jpn Circ J* 1995; **59:** 137–145)

It is generally accepted that antianginal drugs are efficacious mainly because they reduce myocardial O_2 consumption and increase coronary blood supply by reducing coronary resistance, inhibiting coronary artery spasms, reducing preload and afterload, and beta-adrenoceptor blocking effects[1–3] However, the reduced O_2 consumption by skeletal muscle may also increase the efficiency of energy expenditure during exercise. Therefore, elucidating the effects of antianginal drugs on energy expenditure during exercise is an important step in understanding antianginal actions. The effects of drugs on exercise capacity and energy expenditure during exercise have been previously reported for beta-blockers[4–9] but those reports evaluated energy expenditure at 60 to 100% of the peak $\dot{V}O_2$ level, and the results varied with differences in the exercise level. Thus, there have been no definitive reports. In addition, there have been no studies conducted with other antianginal drugs, or during ordinary physical activity at the aerobic level that is most crucial in the precipitation of angina. Therefore, the purpose of this study was to

Key words:
Antianginal drug
Exercise test
Respiratory quotient
Energy expenditure
Normal subject

(Received October 8, 1993; accepted July 23, 1994)
From the First Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho, 1-1, Nishinomiya 663, Japan
Mailing address: Susumu Asakuma M.D., First Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya 663, Japan

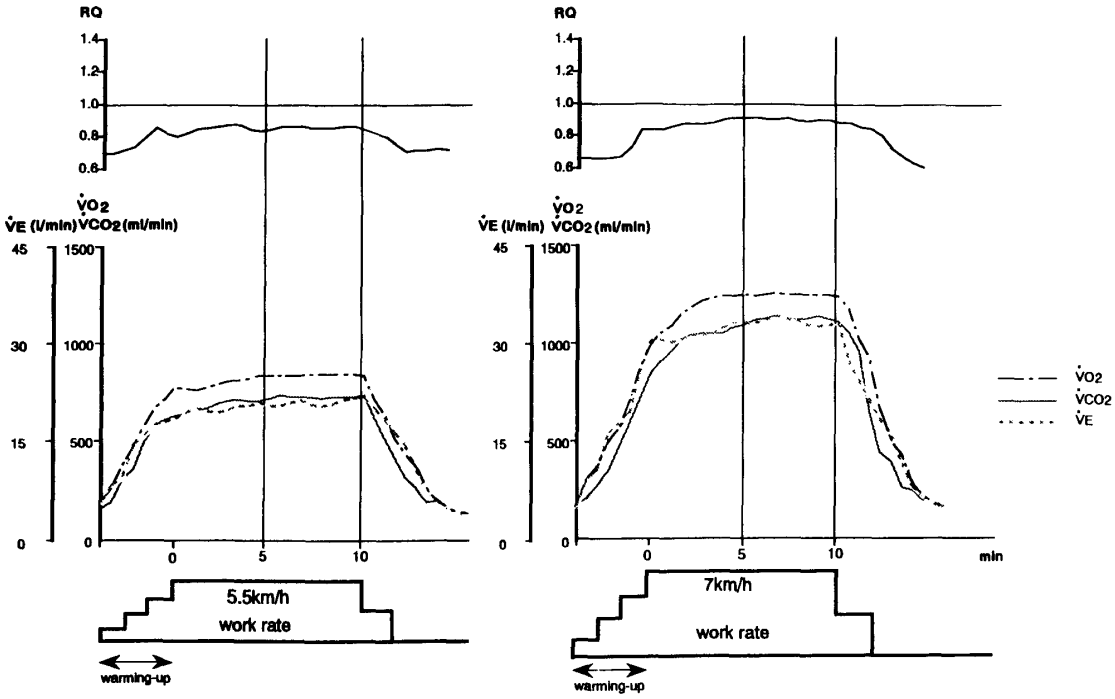


Fig.1. Determination of RQ and $\dot{V}O_2$.
Cardiopulmonary exercise tests were performed as described.
RQ and $\dot{V}O_2$ were determined by averaging the data from 5 to 10 min after the start of constant-load exercise.

examine the effects of a non-selective beta-blocker, a beta-1 selective blocker, an alpha- and beta-blocker, a calcium antagonist, and a nitrate on O_2 consumption at the aerobic level of ordinary physical activity (about 30% and 40% of the peak $\dot{V}O_2$), and on the utilization of carbohydrate and fat during exercise in normal subjects, through analysis of parameters obtained from a cardiopulmonary exercise test (CPX).

METHODS

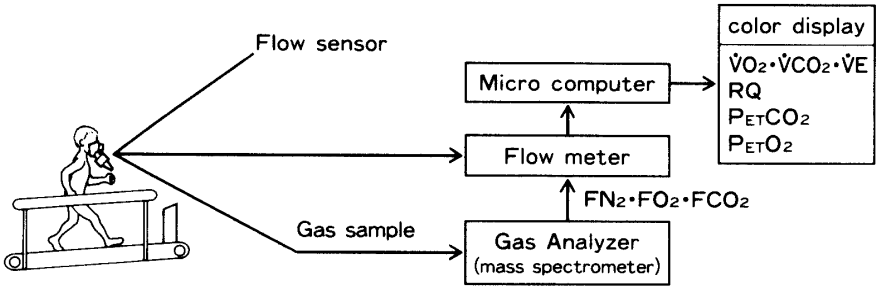
Subjects

Twelve nonsmoking healthy male volunteers (age 36–45 years) who were not on any medications participated in this study. Their average peak $\dot{V}O_2$, anaerobic threshold (AT) by Wasserman's method[10] and %AT were, respectively, 52.0 ± 3.5 ml/min /kg, 27.6 ± 3.2 ml/min/kg and 70.0 ± 3.1%. Informed consent for all testing was obtained from each subject. Each had a normal physical examination, resting electrocardiography and echocardiography. They were all physically active, but were not undergoing regular training. Three of 12 subjects withdrew from the study during the first drug test when they moved out of the area.

The drugs used in this study and their dosages were isosorbide dinitrate, 20 mg /day; nicardipine, 60 mg/day; propranolol, 60 mg/day; metoprolol, 80 mg/day; and amosulalol 80 mg/day. All of the drugs were administered orally. To minimize the effect of food intake, we administrated these drugs in a randomized, single-blind fashion.

Protocols

Treadmill exercise testing with respiratory gas analysis was performed before and after drug administration. Two protocols were adopted to compare the effects of energy expenditure at two different levels of physical activity. Protocol 1 consisted of 5.5 km /h, Grade 0%, and 10 min, while Protocol 2 consisted of 7.0 km/h, Grade 0%, and 10 min. Studies were performed between 3 pm and 5 pm. Both CPX data and circulatory data were obtained to serve as baseline values. After each drug had been administered for 14 days, the protocols were performed again under the same conditions as above, and the values obtained were compared with the baseline values. A washout period of more than 14 days, separated



CALCULATION OF RESPIRATORY QUOTIENT (R.Q.)

$$R.Q.=\dot{V}CO_2/\dot{V}O_2$$

$$\dot{V}O_2\ (STPD)=\frac{P_B-P_{H_2O}(Tr)}{760}\cdot\frac{273}{273+Tr}\cdot\int\left(\frac{F_{IO_2}}{F_{IN_2}}\cdot F_{EN_2}-F_{EO_2}\right)V_E(t-t_D)dt$$

for a breath

$$\dot{V}CO_2\ (STPD)=\frac{P_B-P_{H_2O}(Tr)}{760}\cdot\frac{273}{273+Tr}\cdot\int(F_{ECO_2}-F_{ICO_2})\cdot V_E(t-t_D)dt$$

for a breath

P_B : Barometric pressure (Torr)
P_{H_2O} : Vapor pressure (Torr)
Tr : Temperature (℃)
t_D : Time delay of expiratory flow (sec)

Fig.2. The system used in the cardiopulmonary exercise tests and the calculation of RQ.

the tests with each of the study drugs.

CPX was used to measure O_2 uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), the respiratory quotient (RQ), and the average $\dot{V}O_2$ and RQ values at steady-state during exercise, as in the example shown in Fig. 1. After a 3-min warm-up period, constant-load exercise was applied for 10 min. The values were calculated every 20 sec, and then averaged for a the 5- to 10-min period after the start of constant-load exercise. The work rates in Protocols 1 and 2 were below the subject's AT. There were no significant differences between the 5- to 10-min exercise values after the start of constant-load exercise in Protocols 1 and 2 during administration of each drug. The values before and after drug administration were compared. Furthermore, using the table of Zuntz Schumburg[11,12] the percentages of kcal derived from carbohydrate and fat were calculated from the RQ values. For the circulatory data, heart rate was measured for 1 min, both at rest and during exercise, with an ECG monitor, and blood pressure was measured with an automatic sphygmomanometer (Model STBP-680, Colin Co., Ltd, Tokyo, Japan). Heart rate at rest, systolic blood pressure at rest, systolic blood pressure-rate product at rest, and these same indexes at steady-state during exercise, were recorded.

The CPX system used in the present evaluation of energy expenditure during exercise, and the calculation of RQ, are shown in Fig. 2. The Stress System ML-600 (Fukuda Co., Ltd, Tokyo, Japan) treadmill exercise system, and a the WSMR-1400 respiratory gas analysis system (Westron Inc., Chiba, Japan) were used. Using the respiratory gas analysis system, which consisted of a flow meter, a mass spectrometer and an analyzing computer, we measured the fraction of end-tidal oxygen (FET O_2), the fraction of end-tidal carbon dioxide (FET CO_2) and the expiratory nitrogen concentration (FE N_2) breath-by-breath. These were fed, together with the minute ventilation ($\dot{V}E$) measured by the flow meter, into an analyzing computer (Model N-10, Data General Corp., Tokyo, Japan). The computer calculated $\dot{V}O_2$, $\dot{V}CO_2$ and the RQ, and then displayed the data on a monitor screen[13,14]

Data Analysis

The results are shown as the mean±SE. Analysis of variance was used to determine statistical significance. Student's paired t-test was applied to the data obtained before and after drug administration, with a P value of <0.05 considered significant.

TABLE I CIRCULATORY AND METABOLIC CHANGES IN PROTOCOL 1

		RQ	$\dot{V}O_2$ mL/min	Rest-HR beats/min	Steady-HR beats/min	Rest-BP mmHg	Steady-BP mmHg	Rest-RPP	Steady-RPP
B	Pre	0.84±0.01	822±55	65±3	92±1	113±3	125±4	7477±425	11604±516
	Post	0.89±0.01*	744±50*	56±2*	83±1*	111±3	119±4	6155±358*	9929±453*
B-1	Pre	0.83±0.01	886±40	68±2	95±2	116±4	128±6	7872±450	12004±432
	Post	0.87±0.01*	761±53*	54±2*	85±2*	100±3*	116±4*	5912±361*	9812±327*
AB	Pre	0.83±0.01*	849±54	66±1	92±2	114±5	127±5	7514±357	11722±658
	Post	0.90±0.01*	755±37*	66±2	91±2	113±4	127±5	7594±277	11632±559
C	Pre	0.83±0.01	825±43	71±3	94±3	118±5	129±5	7821±394	12120±529
	Post	0.85±0.02	770±57	66±3	93±2	116±4	124±6	7726±327	11587±429
N	Pre	0.84±0.01	880±51	68±3	93±3	116±3	126±5	7849±416	11913±532
	Post	0.86±0.02	889±64	68±3	92±3	118±8	124±6	7980±333	11598±641

Values are mean±SE; n=9 *$p<0.05$ vs Pre*

RQ: *Respiratory quotient during exercise*
$\dot{V}O_2$: *O_2 consumption during exercise*
Rest-HR: *Heart rate at rest*
Steady-HR: *Heart rate during exercise*
Rest-BP: *Systolic blood pressure at rest*
Steady-BP: *Systolic blood pressure during exercise*
Rest-RPP: *Resting rate-pressure products*
Steady-RPP: *Rate-pressure products during exercise*

B: *propranolol*
B-1: *metoprolol*
AB: *amosulalol*
C: *nicardipine*
N: *isosorbide dinitrate*

TABLE II CIRCULATORY AND METABOLIC CHANGES IN PROTOCOL 2

		RQ	$\dot{V}O_2$ mL/min	Rest-HR beats/min	Steady-HR beats/min	Rest-BP mmHg	Steady-BP mmHg	Rest-RPP	Steady-RPP
B	Pre	0.90±0.01	1146±69	66±3	117±3	113±3	140±3	7485±336	16330±796
	Post	0.94±0.01*	1004±69*	57±2*	101±1*	116±3	129±3*	6542±357*	13110±469*
B-1	Pre	0.89±0.01	1145±67	69±3	117±3	122±4	143±5	8262±371	16629±668
	Post	0.93±0.01*	1044±117*	56±2*	100±5*	109±5	128±5*	6285±378*	12958±530*
AB	Pre	0.90±0.03	1261±96	65±3	116±3	112±3	137±5	7220±310	15968±888
	Post	0.99±0.02*	1104±49*	60±2	115±3	111±3	140±4	6740±326	16153±784
C	Pre	0.88±0.01	1197±8.3	68±3	118±6	118±4	150±5	8021±368	17884±646
	Post	0.90±0.01	1170±105	71±3	120±3	116±3	153±3	8130±371	18578±741
N	Pre	0.89±0.01	1060±61	65±3	118±6	117±4	147±5	7850±293	17420±767
	Post	0.88±0.01	1100±67	68±3	119±5	119±4	143±5	8120±340	17120±733

Values are mean±SE; n=9 *$p<0.05$ vs Pre*
Abbreviations are the same in Table I

RESULTS

The average exercise level in Protocol 1 was 855±49 ml/min (at a level of 27.4 ±3.5% peak $\dot{V}O_2$). The results of Protocol 1 are shown in Table I. The analysis of variance did not show any significant differences in the values obtained before drug administration. The circulatory data showed a significant decrease during propranolol administration in heart rate at rest, heart rate during exercise, resting rate-pressure products and rate-pressure products during exercise. The data also showed a significant decrease in heart rate at rest, heart rate during exercise, systolic blood pressure during

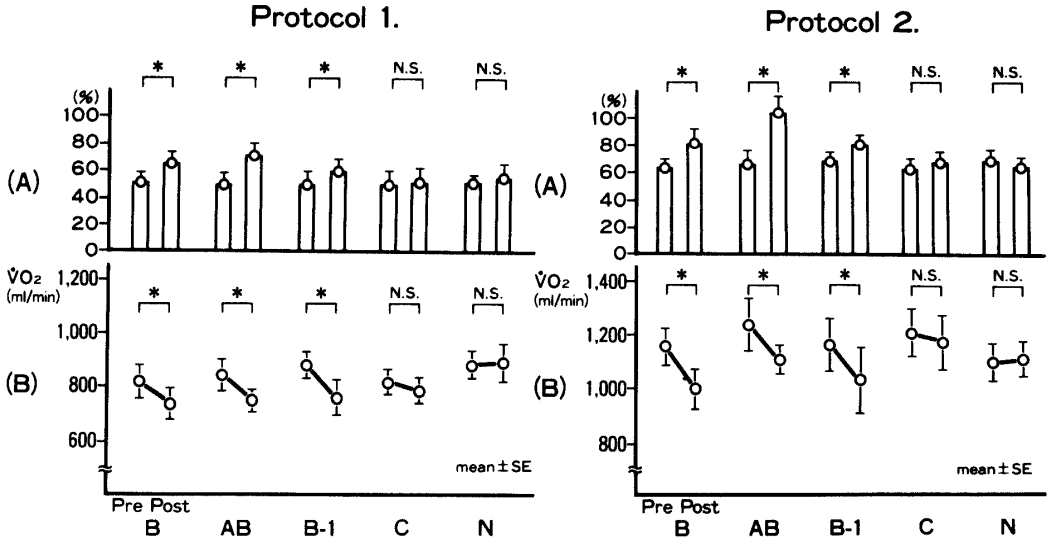


Fig.3. (A) Percentage of kcal from carbohydrate during drug administration in Protocols 1 and 2 (calculated from assumed RQ value). Percentage of kcal from carbohydrate was significantly increased during administration of propranolol, metoprolol and amosulalol in Protocols 1 and 2.
(B) Changes in $\dot{V}O_2$ during drug administration in Protocols 1 and 2.
$\dot{V}O_2$ was significantly decreased during the administration of propranolol, metoprolol and amosulalol in Protocols 1 and 2.
Pre: pre-drug administration, Post: post-drug administration.
B: propranolol, AB: amosulalol, B-1: metoprolol, C: nicardipine, N: isosorbide dinitrate.

exercise, resting rate-pressure products and rate-pressure products during exercise following metoprolol administration. However, the other drugs did not cause any significant circulatory changes. $\dot{V}O_2$ showed a significant decrease after the administration of propranolol, metoprolol or amosulalol. However, the other drugs did not cause any significant changes. The mean RQ in the nine subjects before drug administration was 0.83, and the percentage of kcal derived from carbohydrate was 43.8%, while that from fat was 56.2%. Therefore, energy expenditure appeared to be fat-dominant. The change in RQ after drug administration showed a significant increase from 0.84 ± 0.01 to 0.89 ± 0.01 during propranolol administration, from 0.83 ± 0.01 to 0.87 ± 0.01 during metoprolol administration, and from 0.83 ± 0.01 to 0.90 ± 0.01 during amosulalol administration. Neither nicardipine nor isosorbide dinitrate caused any significant changes.

The average exercise level in Protocol 2 was $1,173 \pm 76$ ml/min (at a level of $37.6 \pm 4.8\%$ peak $\dot{V}O_2$). The results of Protocol 2 are shown in Table II. The analysis of variance did not show any significant differences between pre- and post-drug values. The circulatory data showed a significant decrease in heart rate at rest, heart rate during exercise, systolic blood pressure during exercise, resting rate-pressure products and rate-pressure products during exercise following propranolol administration. The data also showed a significant decrease in heart rate at rest, heart rate during exercise, systolic blood pressure during exercise, resting rate-pressure products and rate-pressure products during exercise after metoprolol administration. However, neither amosulalol, nicardipine nor isosorbide dinitrate caused any significant changes in the circulatory data. The $\dot{V}O_2$ showed a decrease during propranolol, metoprolol and amosulalol administration. Neither nicardipine nor isosorbide dinitrate caused any significant changes. The mean RQ of the nine volunteers before drug administration was 0.90, and the percentage of kcal derived from carbohydrate was 67.5%, while that from fat was 32.5%. Therefore, energy expenditure appeared to be carbohydrate-dominant. The RQ after drug administration showed a significant increase from 0.90 ± 0.01 to 0.94 ± 0.01 during propranolol administration, from

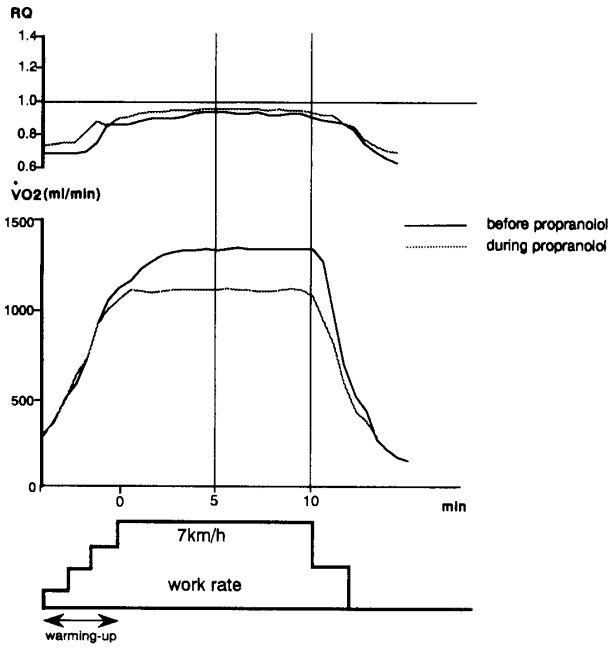


Fig.4. Changes in exercise values before and during propranolol administration. $\dot{V}O_2$ was significantly decreased and RQ was significantly increased, but there were no significant changes in $\dot{V}O_2$ kinetics or O_2 debt with propranolol administration.

0.90 ± 0.03 to 0.99 ± 0.02 during amosulalol administration, and from 0.89 ± 0.01 to 0.93 ± 0.01 during metoprolol administration. Neither nicardipine nor isosorbide dinitrate any significant changes.

The results of Protocols 1 and 2 are summarized in Fig. 3. Energy metabolism during exercise, as measured by RQ, was affected by propranolol, metoprolol and amosulalol. Administration of these drugs was accompanied by reduced $\dot{V}O_2$ during moderate exercise, and increased carbohydrate utilization. Neither nicardipine nor isosorbide dinitrate caused any significant changes.

Fig. 4 shows a representative data with propranolol administration. There were no significant differences between the 5- to 10-min exercise values after the start of constant-load exercise in Protocols 1 or 2 during each drug administration, because the work rates in Protocols 1 and 2 were below the subject's AT level. The increased post-exercise O_2 debt may be related to the slowing of $\dot{V}O_2$ kinetics after beta-blocker administration. In this study, however, no increase in post-exercise O_2 debt was observed after administration of propranolol, metoprolol, or amosulalol.

DISCUSSION

During activities such as complete bed rest or mild aerobic exercise such as walking or slow jogging, RQ reflects the metabolic mixture of carbohydrate and fat. The measurement of RQ values during rest and submaximal exercise provide a suitable guide for the nutrient mixture being catabolized for energy. RQ values range between 0.70 and 1.00, and increase with exercise intensity. In our study, the work rates used in Protocols 1 and 2 were 30% and 40% of peak $\dot{V}O_2$, respectively. RQ before drug administration in Protocol 1 was 0.83, and the utilization ratio of carbohydrate: fat was 42.2%: 57.8%. In Protocol 2, RQ was 0.90 and the carbohydrate: fat utilization ratio was 66.0%: 34.0%. Thus, even under different conditions, with fat utilization dominant in Protocol 1, and carbohydrate utilization dominant in Protocol 2, propranolol, metoprolol and amosulalol increased the utilization of carbohydrate and decreased that of fat. These results suggest that propranolol, metoprolol and amosulalol may increase the efficiency of energy expenditure. Accordingly, we postulate that the antianginal effects of propranolol, metoprolol and amosulalol in normal subjects are due not only to their action in decreasing myocardial O_2 consumption, but also to the increased efficiency of energy expenditure during exercise. In short, the administration of a non-selective beta-blocker suppresses the catabolism of fat in adipose tissue that results from activation of beta-1 and beta-2 receptors, thereby increasing the utilization of carbohydrate. In addition, $\dot{V}O_2$ significantly decreased during the administration of propranolol, metoprolol and amosulalol. This shows that the same amount of exercise was achieved with less consumption of oxygen, which suggests an increase in exercise efficiency. Depression of the circulatory response may have caused this decrease in $\dot{V}O_2$, but the circulatory response was not inhibited after administration of amosulalol, which resulted in a significant decrease in $\dot{V}O_2$ in Protocol 2. Therefore the possibility exists that the effects of propranolol, metoprolol and amosulalol on physical exercise are derived not only from

the circulatory response, but also from the increased efficiency of energy expenditure during exercise.

Carbohydrate, fat and protein provide the necessary energy to maintain body functions both at rest and during various forms of physical activity. The energy for exercise is supplied by the oxidation of carbohydrate, fat, and protein, but most of the human energy expenditure during physical activity is based on the utilization of carbohydrate and fat; the role of protein is so slight that it may be ignored![11] The amount of O_2 needed to use carbohydrate differs from that needed to use fat. For example, the oxidation of 1 gram of carbohydrate requires 810 ml of O_2, while 1 gram of fat requires 2,020 ml of O_2. Furthermore, carbohydrate provides 5.047 kcal per 1,000 ml of oxygen, while fat releases 4.686 kcal for the same amount of oxygen. Thus, utilization of carbohydrate requires less oxygen than fat and also releases a larger amount of energy for the same amount of oxygen. Therefore, it is more efficient to use carbohydrate than fat. In addition, energy metabolism during various activities can be expressed by measuring the utilization ratio of nutrients, using CPX to measure $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}CO_2$ /$\dot{V}O_2$ (non-protein RQ). The table of Zuntz Schumburg converts these values to the utilization ratios for carbohydrate and fat![12] This method enables the non-invasive measurement of energy expenditure during exercise. Normally, as the amount of exercise increases, RQ increases, and the utilization of carbohydrate exceeds that of fat![4,15–17] However, there is a problem in obtaining CPX data: ie, the inspiratory volume differs from the expiratory volume and $\dot{V}O_2$ is not equivalent to $\dot{V}CO_2$ in the lung. In this study, we could perform the analysis in real time more accurately using the system shown in Fig. 2![13,18] Using a mass spectrometer (with a lag and response time of 240 msec) as a gas analyzer enables us to measure the values breath-by-breath. Moreover, as shown in Fig. 2, we are able to measure expiratory O_2, CO_2, and N_2 simultaneously, and to correct the respective inspiratory volume by using N_2 as an inert gas. Therefore, the values of $\dot{V}O_2$, $\dot{V}CO_2$ and RQ obtained by this method can be considered very precise.

The most important energy sources for the muscles during exercise are glucose and free fatty acids (FFA)![19] It is known that insulin and catecholamines play important roles in the control of glucose metabolism![20,21] Before energy is release from fat, the triglyceride molecule is cleaved by hydrolysis into glycerol and three FFA molecules through the stimulation of beta receptors. Accordingly, it is thought that catecholamines play an important role in energy expenditure during exercise, and that alpha- and beta-receptor blockers may influence energy expenditure. Regarding the influence of alpha- and beta-receptor blockers on the metabolism of carbohydrate and fat, McLeod et al[5] reported that plasma glucose values rose after placebo or atenolol administration, but fell after propranolol administration, showing that there are differences in the metabolic responses to beta-1 selective blockers and non-selective beta-blockers, and that beta-2 adrenoceptors are important in providing carbohydrate as an energy source for exercising muscle. Koch et al[9] reported the influence of these drugs on the metabolism of carbohydrate and fat, stating that lipolysis was similarly inhibited by both selective and non-selective antagonists of adrenergic receptors while hypoglycemia occurred only with non-selective blockers. Moreover, the metabolic response to physical activity was altered by metoprolol, acebutolol (beta-1 selective blocker) and pindolol (non-selective). The reports described above were based on the examination of energy expenditure through the measurement of blood levels of glucose and FFA. Wilmore et al reported that neither atenolol nor propranolol caused a significant change in RQ during exercise at a level of 60% of the peak $\dot{V}O_2$![4] In this study, we found a significant increase in RQ after administration of propranolol, metoprolol, or amosulalol in both Protocols, at 30% and 40% of the peak $\dot{V}O_2$. Carbohydrate utilization was increased, while fat utilization was decreased. The different results between Wilmore's study and ours may have been caused by differences in the work rates.

To understand the influence of beta-blockers on physical exercise, the influence on $\dot{V}O_2$ kinetics and O_2 debt post-exercise must also be considered. Petersen et al[22] reported

that $\dot{V}O_2$ kinetics slow down at the level of AT after the administration of beta-blockers. Therefore, exercise values during the 5- to 10-min period after the start of the constant-load exercise in Protocols 1 or 2 following beta-blocker administration may not have reached the steady-state. Our data are consistent with those of Hazeki[23] He reported that propranolol decreased the $\dot{V}O_2$ of healthy men during exercise, and that the O_2 debt showed a tendency to increase after beta-blockers, but these changes were not significant. Beta-blockers affect exercise-induced lactic acidosis, which also affects the gas exchange analysis. However, since our protocols were conducted at a level of 30 or 40% of the subject's peak $\dot{V}O_2$, the amount of exercise was submaximal, and lactic acidosis during RQ measurements can be disregarded.

With respect to the action of nicardipine and isosorbide dinitrate, a few studies have examined their effects on exercise capacity, but there are none on their effects on energy expenditure. In this study, we did not detect any changes in RQ or hemodynamics during exercise. Therefore, any antianginal effects of nicardipine and isosorbide dinitrate would seem to be greatly dependent on increases in coronary blood flow and a decrease in myocardial oxygen demand.

Conclusion

The effects of antianginal drugs on energy expenditure at two different levels of physical activity (30% and 40% peak $\dot{V}O_2$) were investigated in 9 healthy adult men. Our results suggest that propranolol, metoprolol and amosulalol have antianginal effects not only by decreasing myocardial O_2 consumption, but also as a result of increased efficiency in energy expenditure during ordinary physical activity.

REFERENCES

1. Feldman RL, Conti CR: Relief of myocardial ischemia with nitroglycerin: What is the mechanism? *Circulation* 1981; **64:** 1098–1100
2. Braunwald E: Mechanism of action of calcium-channel-blocking agents. *N Engl J Med* 1982; **307:** 1618–1627
3. Chan P, Heo J, Garibian G, Askenase A, Segal BL, Iskandrian AS: The role of nitrates, beta-blockers, and calcium antagonists in stable angina pectoris. *Am Heart J* 1988; **116:** 838–848
4. Wilmore JH, Freund BJ, Joyner MJ, et al: Acute response to submaximal and maximal exercise consequent to beta-adrenergic blockade: Implication for the prescription of exercise. *Am J Cardiol* 1985; **55:** 135–141
5. Mcleod AA, Brown JE, Kuhn C, et al: Differentiation of hemodynamic, humoral, and metabolic responses to beta 1- and beta 2-adrenergic stimulation in man using atenolol and propranolol. *Circulation* 1983; **67:** 1076–1084
6. Mcleod AA, Brown JE, Kitchell B, et al; Hemodynamic and metabolic response to exercise after alpha 1-, beta 1 and non-selective beta- adrenoceptor blockade in man. *Am J Med* 1984; **27:** 97–100
7. Wolfel EE, Hiatt WK, Brammell HL, et al: Effects of selective and nonselective beta-adrenergic blockade on mechanisms of exercise conditioning. *Circulation* 1986; **74:** 664–674
8. Verstappen FTJ, Van Baak MA: Exercise capacity, energy metabolism, and beta-adrenoceptor blockade. *Eur J Appl Physiol* 1987; **56:** 712–718
9. Koch G, Franz IW, Gubba A, Lohmann FW: Beta-adrenoceptor blockade and physical activity: cardiovascular and metabolic aspects. *Acta Med Scand* 1983; **672**(Suppl): 55–62
10. Beaver WL, Wasserman K, Whipp BJ: A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60:** 2020–2027
11. McArdle WD, Katch FI, Katch VL: Measurement of human energy expenditure. *In:* Exercise Physiology. Philadelphia, Lea & Febiger. 1991, 145–157
12. Zuntz N, Schumburg WAEF: Studien zu einer Physiologie des Marsches. Berlin, Verlag von August, Hirschwald. 1901
13. Nishi I: A new method for multidimensional analysis of circulation and metabolism. *Proc Jpn Soc Med Mass Spect* 1984: **4:** 235–252
14. Nishi I, Tomizawa G, Shibuya H, et al: Estimation of sugar metabolism by means of simultaneous measurement of $\dot{V}O_2$, $\dot{V}CO_2$, RQ, and 13C/12C. *Proc Jpn Soc Med Mass Spect* 1983; **8:** 181–184
15. Jansson E: On the significance of the respiratory exchange ratio after different diets during exercise in man. *Acta Physiol Scand* 1982; **114:** 103–110
16. Kannagi T, Bruce RA, Hossack KF, Chang K, Kusumi F, Trimble S: An evaluation of the Beckman metabolic cart for measuring ventilation and aerobic requirements during exercise. *J Cardiac Rehab* 1983; **3:** 38–53
17. Aitken JC, Thompson J: The effects of previous severe exercise upon the respiratory $\dot{V}CO_2/\dot{V}O_2$ exchange ratio as a predictor of maximum oxygen uptake. *Eur J Appl Physiol* 1988; **57:** 720–725
18. Wilmore JH, Davis JA, Norton AC: An automatic system for assessing metabolic and respiratory function during exercise. *Eur J Appl Physiol* 1976; **40:** 619–624
19. Wahren J, Felig P, Hangenfeldt L: Physical exercise and fuel homeostasis. *Diabetologia* 1978; **14:** 213–222
20. Vranic M, Berger M: Exercise and diabetes mellitus. *Diabetes* 1979; **28:** 147–163

21. Berber M, Hagg S, Ruderman NB: Glucose metabolism in perfused skeletal muscle. *Biochem J* 1975; **146:** 231–238
22. Petersen ES, Whipp BJ, Davis JA, Huntsman DJ, Brown HV, Wasserman K: Effects of beta-adrenergic blockade on ventilation and gas exchange during exercise in humans. *J Appl Physiol Respirat Environ Exercise Physiol* 1983; **54:** 1306–1313
23. Hazeki T: Hemodynamic and metabolic effects of activities of the adrenergic beta receptor in physical exercise. *Jpn Circ J* 1973; **37:** 141–161