Coronary Blood Flow and Lactate Metabolism during Isometric Handgrip Exercise in Heart Disease

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SUMMARY

Twenty-one patients with various heart diseases undergoing the coronary sinus catheterization had myocardial blood flow studies before and during isometric handgrip exercise. At 30% of the maximal voluntary contraction (MVC), handgrip increased both coronary sinus blood flow by 19.8% and myocardial O₂ consumption by 21.0% on the average as compared to those at rest. At 20% of MVC, the increase of the both was slight except for 1 case. The increase in coronary sinus blood flow significantly correlated to the increase of myocardial O₂ consumption. Lactate extraction ratio decreased to less than 10% during handgrip in 4 of 19 cases studied despite of normal values at rest. Lactate extraction ratio had significantly positive correlations with coronary sinus blood flow and myocardial O₂ consumption during handgrip, while there were not significant ones at rest. It is suggested that isometric handgrip exercise is useful as a stress test for detection of myocardial ischemia in the heart of coronary artery disease.

Additional Indexing Words:

Coronary sinus flow Dye-dilution method Myocardial ischemia
Myocardial oxygen consumption

ISOMETRIC handgrip exercise has been used as a stress test for estimating cardiac reserve of the left ventricle.¹⁾⁻¹⁰⁾ Since handgrip exercise results in increased heart rate, elevated systemic blood pressure, increased cardiac output and presumably enhanced myocardial contractility, myocardial oxygen consumption must be increased¹¹⁾⁻¹³⁾ and myocardial blood flow is inevitably augmented during the exercise. In this point, handgrip exercise might be considered as a useful stress test for detection of myocardial ischemia and diagnosis of ischemic heart disease in cases in whom coronary artery disease is suspected. There is a few reports^{14), 15)} concerning electrocardiographic

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study and occurrence of anginal pain during handgrip exercise, in which the authors¹⁴⁾⁻¹⁶⁾ pointed out that handgrip exercise was inferior to dynamic exercise regarding diagnosis of ischemic heart disease. Coronary circulation study including measurements of myocardial blood flow during handgrip exercise is to our knowledge, only made by Kivowitz et al.,²⁾ Lowe et al.,¹⁶⁾ and Nelson et al.¹⁷⁾

The purpose of this report is to describe the results of measurements of coronary sinus blood flow and lactate metabolism before and during isometric handgrip exercise in patients with heart diseases.

MATERIALS AND METHODS

Twenty-one patients listed in Table I underwent study. Diagnosis was made by clinical signs, laboratory findings, routine cardiac catheterization, angiocardiography, and selective coronary arteriography when needed.

Studies were performed under the postabsorptive state in supine position on

Table I. Subject

Subject	Age	Sex	Diagnosis	NYHA	BSA (m ²)	CTR (%)
F. O.	54	M	Angina Pectoris	2	1.60	45
J. S.	45	M	Angina Pectoris	2	1.51	44
Y. M.	46	F	Angina Pectoris	2	1.66	44
C. A.	32	M	PMD, COCM	2	1.63	50
M. H.	31	M	PMD, HCM	2	1.83	57
S. F.	49	F	Mitral Stenosis, AF	2	1.34	55
Se. S.	30	F	Mitral Stenosis	2	1.51	61
Si. S.	34	F	Mitral Stenosis, AF	2	1.37	53
H. T.	52	F	Mitral Stenosis	3	1.47	68
C. S.	54	M	Mitral Stenosis $\bar{c}$ Insufficiency	1	1.65	50
A. U.	29	F	Aortic Stenosis, Mitral Insuf.	2	1.28	56
H. H.	18	F	Ventricular Septal Defect	1	1.40	50
M. N.	24	M	Ventricular Septal Defect	1	1.70	46
N. K.	19	F	Atrial Septal Defect	2	1.60	51
S. O.	46	M	Essential Hypertension	2	1.68	46
M. M.	24	M	Normal	1	1.57	47
H. M.	61	F	Angina Pectoris	2	1.34	54
S. A.	59	M	Myocardial Infarction	3	1.53	64
K. I.	23	M	PMD, COCM	2	1.68	48
M. K.	44	M	Mitral Stenosis	2	1.68	50
R. A.	14	M	Ventricular Septal Defect	1	1.61	47

PMD: primary myocardial disease, COCM: congestive type, HCM: hypertrophic type, BSA: body surface area, CTR: cardio-thoracic ratio.

the X-ray table. Coronary sinus blood flow was measured as described previously.¹⁹⁾ The procedures are summarized as follows. A Gensini 9 F catheter was percutaneously introduced via the right femoral vein and advanced until its tip lay in the coronary sinus. A polyethylene tube (I.D., 0.58 mm; O.D., 0.97 mm) was introduced through the catheter and the tip of the tube was advanced more than 5 cm from the tip of the catheter. A solution of Cardiogreen 395 mg per liter dissolved in isotonic saline was injected into the great cardiac vein through the tube at a constant rate of 7.6 ml per minute with a Harvard infusion withdrawal pump (Model 600-915). While blood was drawn through the catheter with this pump at a constant rate of 20 ml per minute, the dye concentration curve was recorded with a Gilford densitometer (Model 103 IR). Calibration was made by passing known concentrations of dye-labelled blood through the densitometer. Coronary sinus blood flow was calculated from a dye concentration plateau constructed on the dye concentration curve from the coronary sinus using the following formula:

$$\text{Coronary sinus blood flow (ml/min)} = (C_i - C_p) \times f / C_p$$

where C_i represents the dye concentration (mg/L) of the injectate, C_p is the dye concentration of the plateau (mg/L), and f is the rate of injection (ml/min).

The position of the catheter was confirmed by injection of contrast medium through the catheter so that it was placed as near to the ostium of the coronary sinus as possible. Furthermore, in order to confirm that the blood drawn through the tip of the catheter was not contaminated with the blood from the right atrium, 5 mg of Cardiogreen was suddenly injected into the femoral vein while recording dye dilution curve from the catheter in the coronary sinus. If there was right atrium contamination, as evidenced by an early appearance of dye, the tip of the catheter was inserted about half a centimeter further into the coronary sinus and the contamination test was repeated. Measurement of coronary sinus blood flow was performed only when the presence of right atrium contamination was excluded.

A Kifa red catheter 25 cm in length was introduced in the right femoral artery for measurement of arterial blood pressure and cardiac output by the dye-dilution technique with a cuvette densitometer (Gilford Model 103 IR). Cardiac output was measured by injection of Cardiogreen 5 mg into the left antecubital vein and recording of the dye-dilution curve from the femoral artery. In cases with left-to-right shunt, shunted blood flow was calculated by Nakamura's method¹⁸⁾ and aortic blood flow was obtained by subtraction of shunted blood flow from pulmonary blood flow.

Isometric handgrip exercise was performed by the right hand at 30% (in 16 patients) or 20% (in 5 patients) of the maximal voluntary contraction (MVC) using a commercial handgrip dynamometer (Matsuyoshi, Type M, Tokyo) for 4 min. All patients were instructed to breathe normally to avoid performing the Valsalva maneuver. ECG was continuously monitored and systemic blood pressure was recorded at interval of 1 min. Coronary sinus blood flow was measured at 3 min after onset of the exercise, and subsequently cardiac output measurement and blood samplings from the coronary sinus and femoral artery were made. The bloods were analysed for O_2 content, O_2 saturation and lactate²⁰⁾ concentration. Myocardial O_2 consumption was calculated by the equation; coronary sinus blood flow $\times$ (arterial O_2 content - coronary sinus O_2 content). Myocardial lactate ex-

tration ratio was obtained by the equation; $[(\text{arterial blood lactate} - \text{coronary sinus blood lactate}) / \text{arterial blood lactate}] \times 100$.

RESULTS

I. 30% handgrip of MVC (Table II)

Heart rate and systemic blood pressure increased during handgrip in all cases. The average increase was 16 ± 11 beats/min (mean $\pm$ SD, $p < 0.001$) for heart rate, 22 ± 16 mmHg ($p < 0.001$) for systolic blood pressure, 18 ± 9 mmHg ($p < 0.001$) for diastolic blood pressure, and 22 ± 9 mmHg ($p < 0.001$) for mean blood pressure. Cardiac output did not change significantly. Coronary sinus blood flow increased in all cases, the average increase being 28 ± 26 ml/min (19.8%) ($p < 0.001$). Myocardial O_2 consumption increased in all cases except for 2 cases; the increase was 2.7 ± 2.9 ml/min (21.0%) on the average ($p < 0.001$). Myocardial O_2 extraction showed no significant change. Myocardial lactate extraction ratio decreased in 8 of 14 cases and showed lower values than 10% in 2 cases.

II. 20% handgrip of MVC (Table III)

Twenty % handgrip exercise resulted in less changes in heart rate and blood pressure than 30% handgrip did. The average increase during the exercise was 2 ± 2 beats/min for heart rate, 3 ± 3 mmHg for systolic pressure, 3 ± 7 mmHg for diastolic pressure, and 6 ± 8 mmHg for mean pressure. Cardiac output did not change significantly. Coronary sinus blood flow and myocardial O_2 consumption showed only small changes except for 1 (K.I.) who showed large increases in both. Myocardial lactate extraction ratio decreased in 3 cases, increased in 1, and was unchanged in the other one. Two cases had the extraction ratio less than 10% during handgrip.

III. Relationships between changes in coronary sinus blood flow and in other parameters in response to handgrip exercise (Table IV)

The increase in coronary sinus blood flow revealed a significantly positive correlation with the increase in myocardial O_2 consumption during handgrip exercise ($r = 0.546$, $p < 0.02$). Fig. 1 shows the relationship between coronary sinus blood flow and myocardial lactate extraction ratio. Fig. 2 indicates the relationship between myocardial O_2 consumption and the lactate extraction ratio. In both figures, the left panel shows the relation before the exercise and the right panel during the exercise. Coronary sinus blood flow was not significantly correlated to myocardial lactate extraction ratio before the exercise ($r = -0.295$, N.S.), while both positively correlated

Table II. Hemodynamic and Myocardial Blood Flow Response to Isometric Handgrip Exercise. I. 30% of Maximal Voluntary Contraction of Handgrip

Subject	HR	Aortic Pressure			CI (l/min/ m ²)	CSF (ml/min)	MVO ₂ (ml/min)	O ₂ Extr. (%)	Lactate Extr. (%)
		Syst. (mmHg)	Diast. (mmHg)	Mean (mmHg)					
F. O.	B 66	123	66	87	3.14	159	14.9	54	35
	D 76	141	78	98	3.24	184	14.3	48	18
J. S.	B 66	154	69	100	5.40	116	10.5	58	24
	D 83	195	89	134	6.36	171	17.1	60	28
Y. M.	B 91	144	67	89	3.99	204	12.4	69	31
	D 99	168	84	112	3.12	220	13.4	69	13
C. A.	B 107	126	69	90	3.62	176	15.9	52	21
	D 135	150	94	112	3.56	180	15.2	49	35
M. H.	B 70	123	63	89	3.93	200	19.8	54	21
	D 73	178	98	130	4.67	211	20.8	55	16
S. F.	B 114	170	100	116	2.57	91	8.9	69	38
	D 132	165	109	130	2.54	102	10.3	67	38
Sc. S.	B 80	154	67	97	2.26	121	9.6	73	66
	D 88	171	78	114	2.46	144	10.4	72	32
Si. S.	B 105	116	72	83	2.36	61	8.2	72	12
	D 143	126	81	103	2.04	66	9.6	76	-15
H. T.	B 75	135	86	95	1.96	62	6.2	71	37
	D 108	141	96	115	1.73	91	9.6	71	2
C. S.	B 72	126	77	96	2.78	175	17.9	54	39
	D 84	164	108	129	2.75	272	28.4	53	57
A. U.	B 77	105	57	77	3.82	146	12.3	65	17
	D 93	134	75	95	3.75	177	15.8	65	18
H. H.	D 84	124	62	87	5.36	181	15.5	57	38
	B 98	138	74	102	5.38	244	20.8	58	34
M. N.	B 69	105	60	75	2.94	238	23.4	55	28
	D 102	130	88	102	3.11	252	26.8	60	54
N. K.	B 72	118	71	82	2.30	93	8.7	72	
	D 83	123	77	92	2.03	104	9.4	72	
S. O.	B 62	180	93	125	3.13	78	7.9	59	53
	D 68	216	122	153	2.97	82	8.6	61	32
M. M.	B 70	105	58	74	3.57	157	11.9	61	
	D 76	116	77	96	3.60	212	16.0	62	
Mean±SD	B 80±16	132±23	71±12	91±14	3.32±1.02	141±54	12.8±4.8	62±8	33±14
	D 96±23	154±28	89±14	114±17	3.33±1.25	170±65	15.4±6.1	62±8	26±19
D-B (Mean±SD)	16±11	22±16	18±9	22±9	0.01±0.41	28±26	2.7±2.9	0±3	-7±19
p value	<0.001	<0.001	<0.001	<0.001	NS	<0.001	<0.005	NS	NS

HR: heart rate, CI: cardiac index, CSF: coronary sinus blood flow, MVO₂: myocardial oxygen consumption, O₂ Extr.: oxygen extraction ratio, Lactate Extr.: lactate extraction ratio, B: before handgrip exercise, D: during handgrip exercise.

Table III. Hemodynamic and Myocardial Blood Flow Response to Isometric Handgrip Exercise. II. 20% of Maximal Voluntary Contraction of Handgrip

Subject	HR	Aortic Pressure			CI (l/min/ m ²)	CSF (ml/min)	MVO ₂ (ml/min)	O ₂ Extr. (%)	Lactate Extr. (%)
		Syst. (mmHg)	Diast. (mmHg)	Mean (mmHg)					
H. M.	B 66	134	75	95	2.58	77	5.4	54	28
	D 70	137	71	93	2.85	82	7.1	63	-11
S. A.	B 100	165	86	106	2.55	120	12.0	61	14
	D 100	163	94	117	2.42	117	11.5	60	14
K. I.	B 79	131	68	90	5.63	298	24.2	47	11
	D 81	132	71	100	5.63	424	37.6	51	20
M. K.	B 102	136	82	100	4.20	127	13.5	55	26
	D 106	138	77	97	3.74	133	13.8	55	1
R. A.	B 64	161	80	102	3.72	112	13.6	67	41
	D 64	168	90	115	3.94	107	10.3	62	34
Mean±SD	B 82±18	145±16	78±7	99±6	3.74±1.28	147±87	13.7±6.7	57±8	24±12
	D 84±18	148±17	81±11	104±11	3.72±1.24	173±142	16.1±12.3	58±5	12±17
D-B (Mean±SD)	2±2	3±3	3±7	6±8	-0.02 ±0.29	26±56	2.3±6.5	1±5	-12±19
p value	NS	NS	NS	NS	NS	NS	NS	NS	NS

HR: heart rate, CI: cardiac index, CSF: coronary sinus blood flow, MVO₂: myocardial oxygen consumption, O₂ Extr.: oxygen extraction ratio, Lactate Extr.: lactate extraction ratio, B: before handgrip exercise, D: during handgrip exercise.

Table IV. Correlation Coefficients between the Increase in Coronary Sinus Flow and Changes in Other Parameters by Isometric Handgrip Exercise

Parameters	Correlation Coefficient	Significance (p value)
Heart Rate	0.055	NS
Arterial Systolic Pressure	0.337	NS
Arterial Diastolic Pressure	0.330	NS
Arterial Mean Pressure	0.378	NS
Cardiac Index	0.194	NS
Myocardial Oxygen Consumption	0.546	p<0.02
Myocardial O ₂ Extraction Ratio	-0.012	NS
Myocardial Lactate Extr. Ratio	0.331	NS
Effort Index	0.331	NS
Katz's Index	0.201	NS

Effort index=arterial systolic pressure×heart rate, Katz's index=arterial mean pressure×heart rate, NS: not significant.

Fig. 1. Relationship between coronary sinus blood flow and lactate extraction ratio before and during handgrip. Left panel is before handgrip, and right panel is during handgrip.

Fig. 2. Relationship between myocardial oxygen consumption and lactate extraction ratio before and during handgrip. Left panel is before handgrip, and right panel is during handgrip.

with each other during the exercise as shown in Fig. 1 ($r = 0.532$, $p < 0.05$). The similar relation was obtained between myocardial O₂ consumption and myocardial lactate extraction ratio as seen in Fig. 2. It was observed that most of patients with ischemic heart disease or ST depression on ECG tended to shift to lactate production during handgrip exercise.

DISCUSSION

Isometric handgrip exercise increases heart rate and systemic blood pres-

sure so that it enhances myocardial oxygen requirement and leads to an increase in myocardial blood flow.^{2),16),17)} In patients with ischemic heart disease who have a limitation in increasing coronary artery blood flow during exercise, therefore, handgrip exercise would induce ischemia in the myocardium and result in the impairment of left ventricular function due to ischemic changes. The latter is one of the reasons why handgrip exercise has been applied as a stress test for the evaluation of cardiac function.

It has been reported,^{14),15)} however, that handgrip exercise was less valuable than dynamic exercise, when myocardial ischemia was evaluated by ischemic ECG changes and occurrence of anginal chest pain during exercise. The advantage of handgrip exercise may be simplicity and clinical convenience because this is possible to perform at bedside whenever and wherever it is needed. Some authors^{4),22),23)} reported that occurrence of diastolic heart sound during hadgrip was related to ischemic impairment of left ventricular function. Cohn et al²³⁾ suggested that the emergence of diastolic heart sounds during handgrip exercise is a useful clinical adjunct in the diagnosis of coronary artery disease and these sounds are associated with significant elevations in left ventricular end-diastolic pressure in patients with coronary artery disease. Flessas et al²¹⁾ reported that all 8 patients with the increase in left ventricular end-diastolic pressure developed hypokinetic areas during handgrip exercise and the abnormal response to handgrip exercise in patients with coronary artery desease may result from the development of hypokinetic areas that decrease the distensibility of the left ventricle.

The measurement of coronary blood flow during handgrip exercise was for the first time performed by Kivowitz et al.²⁾ They reported that coronary sinus blood flow by means of the thermo-dilution technique increased from 123 ± 9.6 ml/min to 179 ± 13.4 ml/min by 5 min handgrip exercise at 25% of MVC in 7 patients with coronary artery disease and in one hypertensive. Lowe et al¹⁶⁾ measured myocardial blood flow before and during handgrip exercise at 33% of MVC by means of the ⁸⁴Rb coincidental counting method in patients with and without coronary artery disease. In their study, myocardial blood flow increased by 35% on the average in 7 patients without coronary artery disease and by 23% in 17 patients who had significant coronary disease, i.e., greater than 75% occlusion of at least one major coronary artery and no angina, while it decreased by 17% in 6 patients who had both significant coronary disease and angina. Nelson et al¹⁷⁾ measured myocardial blood flow during static (handgrip) and dynamic (ergometer) exercise by the N₂O method in 10 normal subjects, and mean myocardial blood flow increased from 181 ml/100 Gm LV/min during dynamic exercise only to 201 ml/100 Gm LV/min during combined static (at 17% of MVC) and dynamic exercise.

In the present study, coronary sinus blood flow increased by 19.8% at 30% of MVC and by 17.6% at 20% of MVC, respectively, although in the latter the increase was not significant. Increases in coronary sinus blood flow significantly correlated with increases in myocardial O_2 consumption as shown in Table IV, while these had no significant correlation with the other parameters. It has been reported^{(24), (25)} that myocardial blood flow and myocardial O_2 consumption increase in proportion to heart rate or the product of heart rate and blood pressure during dynamic exercise. The lack of the above-mentioned relations during handgrip exercise seems due to small increase of heart rate as compared to dynamic exercise.

Myocardial lactate extraction ratio showed no significant change during handgrip exercise as a whole. Kivowitz et al⁽²⁾ reported that there was no significant change of lactate extraction ratio during handgrip exercise at 25% of MVC in 5 patients with coronary artery disease although lactate concentration increased in both arterial blood and coronary sinus blood. Nakhjavan et al⁽²⁶⁾ reported myocardial lactate metabolic studies done during pacing tachycardia and isometric handgrip at 30% of MVC. They indicated that isometric handgrip even if performed during pacing tachycardia was not a sensitive test for detection of myocardial lactate abnormality and that the rising level of arterial lactate during isometric handgrip was the most likely mechanism of positive myocardial arteriovenous lactate difference.

There has been no report, to our knowledge, that revealed the relationship between myocardial lactate metabolism and coronary blood flow or myocardial O_2 consumption during handgrip exercise. In our study, it is noteworthy that 4 cases showed myocardial lactate production or decreased extraction (less than 10%) during handgrip exercise despite of normal lactate metabolism at rest. It is, furthermore, interesting that there were significant positive correlations between lactate extraction ratio and coronary sinus blood flow and myocardial O_2 consumption during handgrip exercise as shown in the right panel of Figs. 1 and 2. These indicate that isometric handgrip exercise induced myocardial ischemia in the cases who could not increase myocardial blood flow during the exercise. Thus, it may be concluded that isometric handgrip exercise is useful as a stress test for disclosing or aggravating myocardial ischemia in the heart.

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