〈Original Article〉

Effects of coronary artery bypass graft surgery on the abnormality of O_2 transport caused by myocardial ischemia during exercise

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Summary

Background: There have been no reports describing the extent of normalization in O_2 transport dynamics in patients with myocardial ischemia following treatment with coronary artery bypass grafting (CABG) or, percutaneous transluminal coronary angioplasty. The purpose of this study was to determine the extent of normalization of the abnormal O_2 transport dynamics and other abnormalities in exercise gas exchange, after surgery in patients with CAD who underwent coronary revascularization by CABG.

Methods: The subjects were 8 males who underwent CABG. All subjects underwent cardiopulmonary symptom-limited exercise testing with a cycle ergometer in a sitting position before and three months after the CABG surgery. In patients with CAD, $\Delta VO_2/\Delta WR$ can be divided into two linear components, a steep component with a slope of approximately 10 ml/min/W and an upper shallower slope. For both the pre and post CABG studies, we calculated the slope of $\Delta VO_2/\Delta WR$ over a two minute period before AT ($\Delta 1$), and over a two minute period after AT ($\Delta 2$), and their ratio of the two slopes ($\Delta 2/\Delta 1$).

Results: $\Delta 1$ did not change significantly, $\Delta 2$ significantly improved from 8.6 $\pm$ 2.2 ml/min/W, before, to 11.3 $\pm$ 2.2 ml/min/W, after the CABG surgery. Therefore, $\Delta 2/\Delta 1$ significantly improved from 0.99 $\pm$ 0.30 (before the operation) to 1.24 $\pm$ 0.31 (after the operation) ($p<0.05$).

Conclusions: Coronary revascularization by CABG was likely to improve the dynamic state of O_2 transport during exercise and other measures of aerobic function reflecting improved exercise tolerance.

Key words: Coronary artery bypass grafting, Exercise, O_2 transport, Myocardial ischemia, ST depression

1.Introduction

It has been reported that cardiac pump function decreases as work rate increases (failure to increase cardiac output appropriately) above the ischemic threshold during a progressive-exercise stress in patients with coronary artery diseases[1-3]. The oxygen uptake (VO_2) obtained by the analysis of expired gas is the product of cardiac output and the arterial-mixed venous oxygen difference. Therefore, the failure of

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cardiac output to increase appropriately during an increasing work rate test can be estimated by the slowing of VO_2 dynamics as work rate is increased.

In 2002, Itoh et al[4] performed a cardiopulmonary exercise test (CPX) combined with an analysis of the expired gas on patients suspected of effort angina and discussed the relationship between the occurrence of myocardial ischemia and changes in the dynamic state of the O_2 transport capacity during exercise. They reported that the O_2 uptake increase relative to the work rate increase significantly deteriorated above the ischemic threshold, as the severity of the coronary lesion rose. The objective of this study was to determine if the impairment in O_2 uptake and the abnormality in O_2 uptake dynamics in response to the work rate increase improves following coronary artery bypass grafting (CABG) in patients with ischemic heart diseases.

2. Methods

2.1. Study patients

The subjects in this study were 8 males who underwent CABG from 2008 to 2010 in our institution (average age: 61.2 ± 7.8) (Table 1). Each had a test followed by coronary angiography which showed significant stenosis in one or more coronary vessels. The presence of significant coronary stenosis was defined as >=75% reduction in the luminal diameter of the coronary vessels. Cases such as old myocardial infarction, hypertrophic cardiomyopathy, dilated cardiomyopathy, significant valvular disease, complications with atrial fibrillations, heart failures of class Ⅱ or higher by the New York Heart Association functional class (NYHA) and pulmonary diseases were excluded. The purposes and risks of the study were explained to the patients, and written informed consent was obtained from each.

2.2. Exercise stress testing

We performed the cardiopulmonary exercise stress test (CPX) with a cycle ergometer in a sitting position for all cases before and three months after the CABG. We used a Cycle⁻ ergometer (Fukuda Denshi Co. Ltd., Tokyo, Japan). We applied four minutes of rest, four minutes of warm-up exercise, and then, a ramp load that gradually increased by 10 W per minute. We measured the VO_2, CO_2 output (VCO_2) and minute ventilation (VE), breath-by-breath, using the CPX-1 (Inter Reha Co. Ltd, Tokyo, Japan)[5, 6] metabolic cart. The expired gas data obtained were converted into time-series data every three seconds. Then, an eight point moving average was performed.

The electrocardiogram during exercise was recorded with the Stress Test System ML-9000 (Fukuda Denshi Co. Ltd., Tokyo, Japan). The heart rate (HR) and ST segment changes were monitored continuously. Blood pressure was measured with the

Table 1 Clinical characteristics

			Weight (kg)		No. of diseased coronary arteries	No. of grafts	LVEF (%)	
No	Sex	Age	Pre	Post			Pre	Poet
1	M	48	51.0	54.0	3	3	46	58
2	M	69	64.0	63.5	1	3	68	75
3	M	58	56.0	63.0	3	2	36	51
4	M	57	70.0	69.8	2	2	46	68
5	M	64	79.0	75.0	3	4	56	63
6	M	58	76.3	69.0	1	3	62	72
7	M	57	79.2	79.5	2	3	51	54
8	M	74	65.0	61.0	3	1	56	62
mean		**60.6**	**67.6**	**66.9**	**2.3**	**2.6**	**52.6**	**62.9***
SD		**8.1**	**10.5**	**8.2**	**0.9**	**0.9**	**10.1**	**8.5**

* $P < 0.01$ vs pre CABG. Left ventricular ejection fraction (LVEF) was determined by left ventriculography both before and approximately 3-6 month after CABG.

STBP-780 (Nippon Colin Co. Ltd., Aichi, Japan). The systolic blood pressure (SBP) and the diastolic blood pressure (DBP) were measured every minute.

From the expired gas analysis, the anaerobic threshold (AT) was determined by the V-slope method[7-9]. Peak VO_2 was defined as the average value obtained during the last 15 seconds of incremental exercise.

We quantified the slope of the increase in VO_2 with respect to the increase in work rate during exercise ($\Delta VO_2/\Delta WR$) for two minutes before AT ($\Delta 1$), and the $\Delta VO_2/\Delta WR$ for two minutes after AT ($\Delta 2$). The ratio $\Delta 2/\Delta 1$ established the relationship between VO_2 dynamics above the AT point compared to below the AT point, established by the CPX test. Following CABG surgery, we repeated the CPX and remeasured $\Delta 1$, $\Delta 2$ and $\Delta 2/\Delta 1$. with the same analysis interval as before the surgery. The VO_2 time constants at the onset of unloaded cycling exercise (τ on) and the recovery from exercise (τ off) were calculated by fitting a single-exponential function to the VO_2 responses[5, 6] before and after the CABG (Fig. 1).

2.3. Statistical analysis

The differences in various indexes before and after the CABG were tested by the paired t-test with a significance level at $p<0.05$.

3. Results

The end point of CPX before the CABG was an ST depression in 4 patients, chest pain in 2 patients, leg fatigue in 2 patients, and shortness of breath in 1 patients. Meanwhile, the end point after the CABG was leg fatigue in 7 patients, shortness of breath in 1 patient, and an elevation of blood pressure (SBP>250mmHg) in 1 patient. The body weights of the subjects did not significantly change during 3-6 months of the follow-up period. The HR during the CPX also showed no significant differences before and after the CABG (Fig 2). However, the SBP at maximum exercise post CABG showed a significantly higher value ($p<0.05$) (Fig. 2). The peak exercise O_2 pulse (VO_2/HR) values, reflecting the product of stroke volume X arteriovenous O_2 difference, were compared before and after CABG. The peak exercise O_2 pulse was significantly higher after

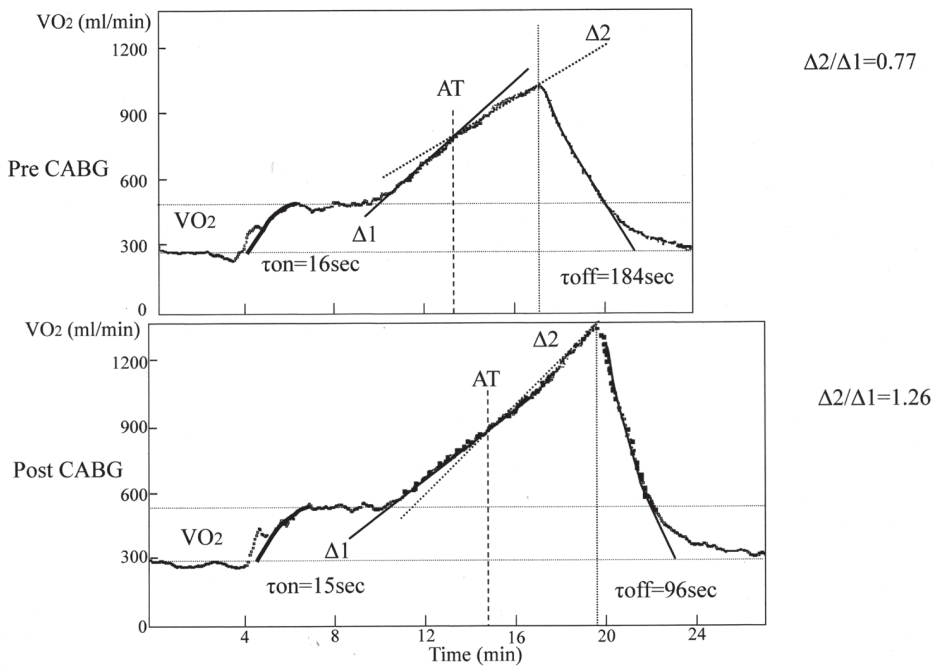

Fig. 1 Changes in VO_2 before and after the CABG in one subject (Patient # 6 in Table 1).
The $\Delta 2/\Delta 1$ before the CABG was 0.99, and improved to 1.24 after the CABG. The τ off was also improved from 139 seconds (before the CABG) to 96 seconds (after the CABG).

the CABG as compared to before the operation ($p<0.05$) (Fig. 2).

The AT significantly increased from 10.3 ± 1.7 ml/min/kg before compared to 12.0 ± 1.8 ml/min/kg after the CABG (three months after the operation) ($p<0.01$) (Fig. 3). As with the AT, the Peak VO_2 also increased significantly from 14.9 ± 2.4 ml/min/kg (before the operation) to 19.0 ± 3.1 ml/min/kg (three or six months after the operation) ($p<0.01$) (Fig. 3).

The Δ1 before and after the CABG was 8.9 ± 1.9 ml/min/W and 9.2 ± 1.1 ml/min/W, respectively, showing no significant difference. After the CABG, Δ2 significantly increased from 8.6 ± 2.2 ml/min/W before the CABG to 11.3 ± 2.2 ml/min/W ($p=0.03$). Therefore, Δ2/Δ1 improved significantly from 0.99 ± 0.30, before the CABG, to 1.24 ± 0.31, after the

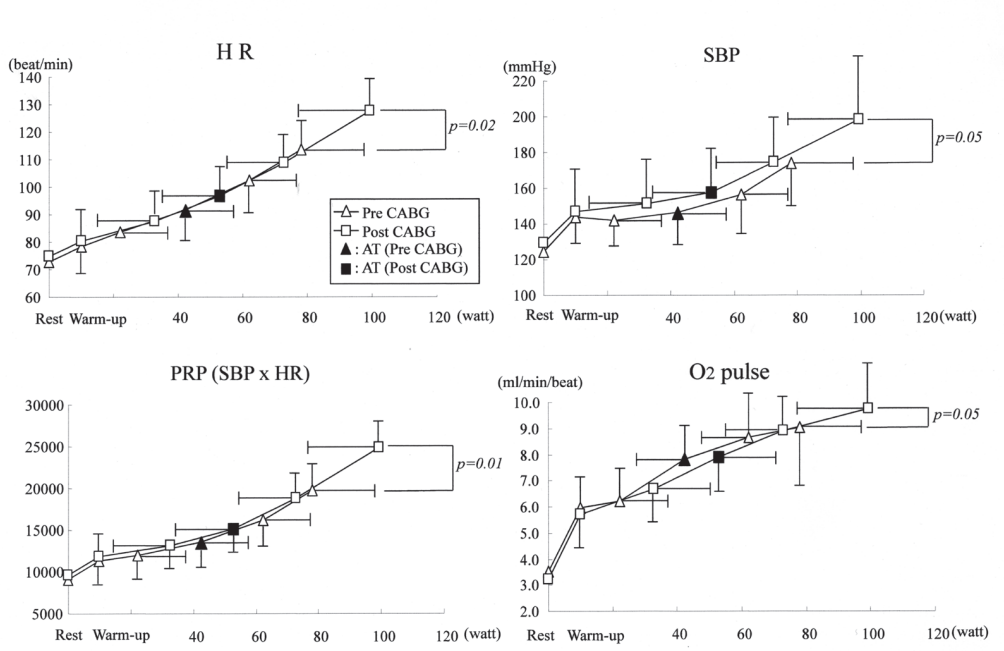

Fig. 2 Changes in the HR, SBP, PRP (HR×SBP), O_2 pulse and exercise intensity before and after the CABG.
There was no significant difference in HR before and after the CABG. However, the peak PRP, SBP and O_2 pulse three months after the operation showed significantly higher values.

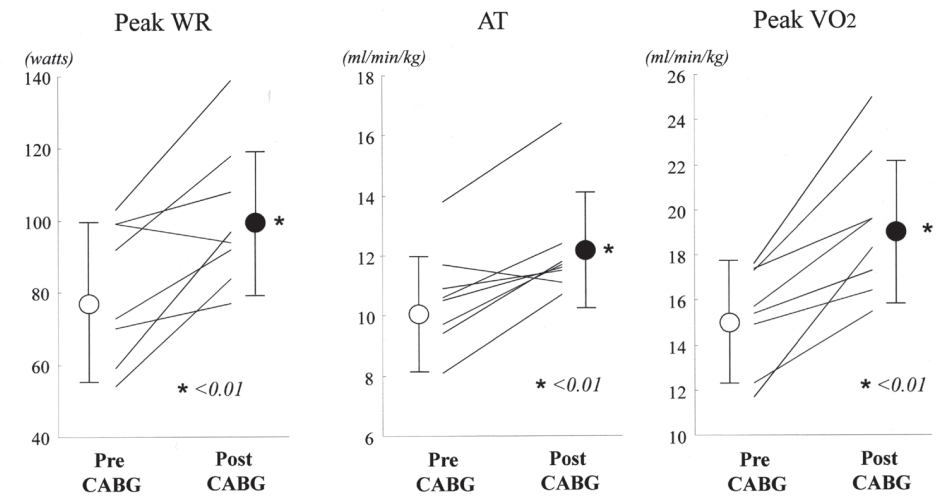

Fig. 3 Comparison of Peak WR, AT and Peak VO_2 before and after the CABG.
The Peak WR, AT and Peak VO_2 three months after the CABG both improved significantly compared to before the CABG.

CABG (p=0.04) (Fig. 4).

The preoperative and postoperative τ for the four minute of unloaded cycling (τ on) was 20.7 ± 6.7 seconds and 17.7 ± 5.0 seconds, respectively, showing no significant difference (Table 2). As with the τ on, the τ for recovery from the exercise (τ off) was significantly improved from 138.8 ± 35.7 seconds, before the operation, to 96.0 ± 18.8 seconds, after the operation, despite a higher peak VO_2, postoperatively ($p<0.01$) (Table 2)(Fig. 5).

4. Discussion

It had been reported that stroke volume and left ventricular ejection fraction decrease after a myocardial ischemia develops during exercise in patients with coronary stenosis[1-3]. It is also recognized from the Fick Principle that the increase in VO_2 in response to the increase in work rate during exercise is dependent on the increase in cardiac output during exercise[10].

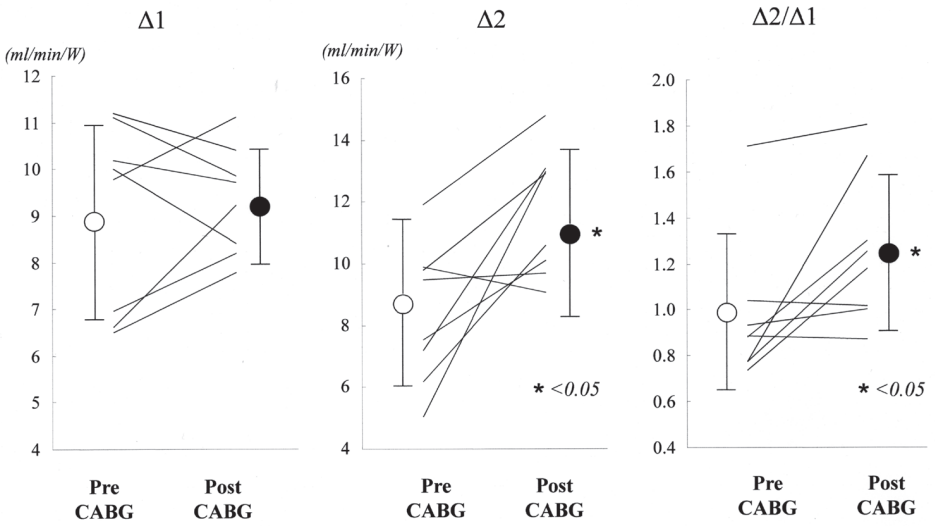

Fig. 4 Comparison of the Δ1, Δ2 and Δ2/Δ1 before and after the CABG.
Although the Δ1 showed no significant difference before and after the CABG, the Δ2 significantly improved. Accordingly, the Δ2/Δ1 improved significantly from 0.99 ± 0.30 to 1.24 ± 0.31.

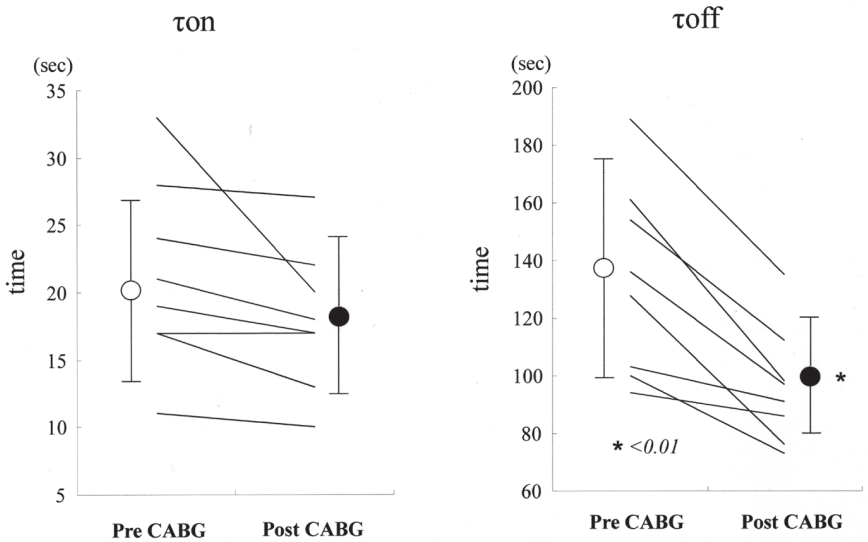

Fig. 5 Comparison of τ on and τ off before and after the CABG.
The τ on showed no significant difference before and after the CABG. On the other hand, the τ off significantly improved from 138.8 ± 35.7 seconds (before the operation) to 96.0 ± 18.8 seconds (three months after the operation).

Table 2 Exercise parameters and respiratory gas variables

	AT/kg		Peak VO_2/kg		Peak work rate (watt)		τ on (sec)		τ off (sec)		Δ 1		Δ 2		Δ 2/Δ 1	
No	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	11.7	11.1	15.7	19.6	54	84	21	18	103	91	11.2	10.4	9.9	9.1	0.88	0.87
2	13.8	16.4	17.3	22.6	92	118	17	13	128	76	11.1	9.9	9.8	12.9	0.88	1.30
3	8.1	10.7	11.7	18.3	59	97	11	10	136	97	6.6	9.2	7.5	10.1	1.14	1.09
4	9.7	11.7	14.9	16.4	70	77	24	22	189	135	10.0	8.4	10.4	8.5	1.04	1.02
5	10.9	11.5	12.3	15.5	73	92	28	27	154	112	6.5	7.8	5.0	13.0	0.78	1.67
6	10.6	12.4	17.6	25.0	103	139	33	20	94	86	9.8	11.1	7.2	13.1	0.74	1.18
7	10.5	11.6	15.4	17.3	99	108	19	17	161	98	7.0	8.2	11.9	14.8	1.71	1.80
8	9.4	11.8	17.4	19.6	99	94	17	17	100	73	10.2	9.7	9.5	9.7	0.93	1.00
mean	**10.6**	**12.2***	**15.3**	**19.3***	**81.1**	**101.1***	**21.3**	**18.0**	**133.1**	**96.0***	**9.0**	**9.3**	**8.9**	**11.4***	**1.01**	**1.24***
SD	**1.7**	**1.8**	**2.1**	**3.2**	**19.5**	**20.2**	**6.9**	**5.2**	**33.6**	**20.1**	**2.0**	**1.1**	**2.2**	**2.3**	**0.31**	**0.33**

*$P < 0.01$ vs Pre CABG.

Therefore, we investigated whether coronary flow, improved by CABG, also improved the reduced pre-surgery $\Delta VO_2/\Delta WR$. A normalization of $\Delta VO_2/\Delta WR$, after CABG surgery, would be predicted if myocardial contractility and cardiac output improved at the level of exercise which showed a reduced $\Delta VO_2/\Delta WR$, prior to CABG surgery. Indeed, we found that CABG surgery significantly improved the $\Delta VO_2/\Delta WR$ during higher intensity exercise, i.e., above the ischemic point.

4.1. Changes in AT and Peak VO_2 before and after the CABG

Generally, patients who undergo CABG often have multivessel diseases. It is believed that the larger the number of diseased vessels one has, the wider the range of abnormal wall motion abnormalities and cardiac functional disturbances[11-13].

The improvements in AT and peak VO_2 after CABG, are almost certainly due to reduced myocardial ischemia and improved cardiac output and muscle blood flow in response to exercise at the AT and peak exercise. The improved AT indicates an improvement of activity at the daily life level. The increased O_2 pulse at peak exercise after CABG surgery likey reflects an increased peak exercise stroke volume.

4.2. $\Delta VO_2/\Delta WR$ before and after CABG

In this research, we compared the $\Delta VO_2/\Delta WR$ before and after the CABG using a progressively increasing cycle ergometer exercise test. Normal people have a $\Delta VO_2/\Delta WR$ of about 10 ml/min/W [can add reference where it was reported]. Koike et al[14] reported that left ventricular ejection fraction and stroke volume decreased during exercise above the AT, after initially increasing, during a progressively increasing work rate exercise test in patients with ischemic heart diseases. They also reported that the cardiac output increased in almost a linear fashion to VO_2 in response to the exercise work rate. However, the rate of increase in VO_2 was reduced at an exercise intensity above the AT in patients with ischemic heart disease, likely due to the failure for cardiac output to increase appropriately for the increase in work rate[15]. Therefore the reduction in $\Delta VO_2/\Delta WR$ above the

ischemic point, reflected in ST changes, can also be seen as a more shallow $\Delta VO_2/\Delta WR$ above the AT.

It should be noted that $\Delta 1$ was not affected by CABG surgery. This is because $\Delta 1$ is already normal, On the other hand, above the AT, VO_2 is O_2 flow independent. Thus the failure to increase cardiac output and therefore muscle blood flow above the AT or ischemic point will only reduce $\Delta 2$. Improvement in cardiac output and O_2 flow to the skeletal muscle in the work rate domain above the ischemic point, improves $\Delta VO_2/\Delta WR$ and $\Delta 2$, after the operation.

4.3. VO_2 time constant at the start of exercise (τ on) and VO_2 time constant during recovery (τ off)

There was no significant change in the τ on during 3 or 6 months of the follow-up period. It was within the normal limit both before and after the operation[16]. This is consistant with normal cardiac pump function for low levels of exercise. On the other hand, post-CABG surgery, the τ off was significantly shortened, and exercise time was prolonged. Before the operation, as shown by the reduction of the $\Delta VO_2/\Delta WR$, the O_2 deficit was elevated. As a result, the O_2 debt during recovery after exercise was also elevated. The τ off may be shortened because the O_2 deficit was reduced, post-CABG[6].

The discussion shown above suggests that the CABG increases the oxygen supply to the cardiac and skeletal muscles during exercise. Thus $\Delta VO_2/\Delta WR$ is normalized somewhat, thereby reducing the O_2 deficit and improving exercise tolerance.

5. Study limitations

The mechanism of improvement of is presumably due to improved cardiac function (and skeletal muscle blood flow) resulting from the improved myocardial ischemia, rather than increased O_2 extraction. From the measurements of O_2 in venous blood sampled from the exercising leg (Koike) or mixed venous blood (Agostoni, and Weber), O_2 extraction in heart failure patients are about 75 to 80%, similar to that of normal subjects.

There was a three month delay before the post-CABG study was done. How much other factors than the CABG, such as medications and exercise training, might have caused $\Delta 2$ to increase is unknown. However it is largely irrelevant in that the objective was to demonstrate the break in the slope of $\Delta VO_2/\Delta WR$ reflecting myocardial ischemia, and its normalization with therapy.

6. Conclusions

$\Delta VO_2/\Delta WR$ normally increases linearly by 10 ml/min/watt to peak work rate. In contrast, patients with coronary artery disease who develop ischemia during exercise, slow their increase in cardiac output in response to the work rate increase. Consequently O_2 uptake also slows causing $\Delta VO_2/\Delta WR$ to decrease above the ischemic point. The change from the linear increase in $\Delta VO_2/\Delta WR$ to a more shallow increase in the domain of work rate above the ischemic point, can be reversed by coronary artery bypass graft surgery. These changes are complemented by improvements in peak VO_2, anaerobic threshold, O_2 pulse, work rate and exercise time.

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