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Prolonged Recovery of Cardiac Output After Maximal Exercise in Patients With Chronic Heart Failure

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OBJECTIVES The aim of this study was to characterize the kinetics of cardiac output during recovery from maximal exercise in patients with chronic heart failure (CHF).

BACKGROUND Recent studies have shown that oxygen uptake kinetics during recovery from exercise are delayed in patients with CHF. However, the kinetics of cardiac output during recovery from maximal exercise in CHF has not been examined.

METHODS Thirty patients with CHF performed maximal upright ergometer exercise with respiratory gas analysis. Kinetics of oxygen uptake (VO_2) and carbon dioxide output (VCO_2) during recovery were characterized by T1/2, the time to reach 50% of the peak values. Cardiac output was measured at 1-min intervals during exercise and recovery. Kinetics of cardiac output during recovery were characterized by the ratios of cardiac output during the first 4 min of recovery to cardiac output at peak exercise. Overshoot of cardiac output was defined as a further increase in cardiac output at 1 min of recovery above the cardiac output at peak exercise.

RESULTS Both T1/2 VO_2 and T1/2 VCO_2 increased as CHF worsened. The ratios of cardiac output during recovery to cardiac output at peak exercise were significantly correlated with T1/2 VO_2 ($r = 0.47$ to 0.62, $p < 0.05$) and T1/2 VCO_2 ($r = 0.40$ to 0.70, $p < 0.05$). There was a negative correlation between cardiac index at peak exercise and both T1/2 VO_2 ($r = -0.65$, $p < 0.001$) and T1/2 VCO_2 ($r = -0.60$, $p < 0.001$). Overshoot of cardiac output was recognized in 11 of 30 patients. Cardiac index at peak exercise was significantly lower in patients with overshoot (4.5 ± 0.9 L/min/m^2) than in those without overshoot (6.1 ± 2.1 L/min/m^2, $p < 0.05$). However, because of a continued increase in cardiac output at 1 min of recovery in patients with overshoot, there were no differences in cardiac index after the first minute of recovery. Heart rate at peak exercise and recovery of heart rate did not differ between these groups. Overshoot of cardiac output was caused by a rebound increase in stroke volume which was due to a reduction in systemic vascular resistance.

CONCLUSIONS Prolonged kinetics of VO_2 or VCO_2 during recovery from maximal exercise represent impairment of circulatory response to exercise and delayed recovery of cardiac output after exercise. Overshoot of cardiac output at 1 min of recovery was characteristic of severe CHF with poor cardiac output response to exercise. (J Am Coll Cardiol 2000;35:1228–36) © 2000 by the American College of Cardiology

In patients with chronic heart failure (CHF), exercise capacity is limited by inadequate oxygen transport to working skeletal muscle due to reduced exercise cardiac output (1–3). To assess the impairment of exercise capacity in patients with CHF, respiratory gas analysis during exercise has been used (1,2). Recently, studies have shown that oxygen uptake kinetics during recovery from exercise are delayed at more advanced stages of heart failure and that the kinetics of recovery oxygen uptake can be used to measure the functional capacity of CHF patients (4–9). However, the kinetics of recovery cardiac output and their relation to oxygen uptake kinetics during recovery have not been evaluated in CHF. We hypothesized that the time course of cardiac output during recovery is also slower in patients with severe CHF, and delayed recovery of oxygen uptake kinetics reflects the prolonged recovery of cardiac output after maximal exercise in severe CHF. Reddy et al. (10) have shown that increased cardiac output returned to its resting value at 90 s of recovery from light isometric exercise in normal subjects, but cardiac output increased further at 90 s of recovery in patients with severe CHF. However, cardiac output response during recovery from maximal exercise in

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Abbreviations and Acronyms

CHF = chronic heart failure
VCO_2 = carbon dioxide output
VO_2 = oxygen uptake
NYHA = New York Heart Association

patients with CHF has not been fully elucidated. The aims of the present study were as follows: 1) to elucidate the kinetics of cardiac output during recovery from maximal exercise and their relation to recovery ventilatory variables in patients with CHF; and 2) to examine whether a further increase in cardiac output during recovery above the cardiac output at peak exercise occurs in patients with CHF, and if so, to characterize the hemodynamics of patients who showed overshoot of cardiac output during recovery.

METHODS

Subjects. This study involved 30 patients (22 men and 8 women) aged 51 ± 10 years with a history of CHF at least six months in duration (Table 1). All patients had stable symptoms at least one month before entry into the study. The etiologic basis of CHF was dilated cardiomyopathy in 23 patients, old myocardial infarction in 6 patients and aortic regurgitation in 1 patient. All patients had reduced left ventricular ejection fraction (<45%) on contrast ventriculography or echocardiography. All patients except those with old myocardial infarction had normal or minimally sclerotic coronary arteries. No patients with old myocardial infarction showed scintigraphic evidence of exercise-induced myocardial ischemia. Twenty-one patients were in normal sinus rhythm and nine were in atrial fibrillation. Twenty-seven patients were being treated with angiotensin-converting enzyme inhibitors, 25 with diuretics, and 17 with digoxin. Patients were excluded if they had significant pulmonary disease, intermittent claudication or angina during exercise that could lead to nonmaximal exercise. Patients were classified into three groups according to the New York Heart Association (NYHA) functional classification (10 patients in class I, 10 in class II, and 10 in class III).

Exercise test. After written, informed consent was obtained, all patients performed a preliminary exercise test with respiratory gas analysis 2 to 14 days before the study to become familiar with the procedure. Patients performed maximal symptom-limited exercise tests while seated on an electronically braked ergometer. After a 3-min rest period on the ergometer, exercise began with a 3-min warm-up period at 10 W, followed by a continuous ramp protocol corresponding to increments of 10 W/min until the patient could no longer continue. After stopping the exercise, patients remained seated on the ergometer for 4 min. The electrocardiogram was monitored throughout exercise and recovery, and a 12-lead electrocardiogram was recorded at 1-min intervals.

Respiratory gas measurement. Respiratory gas analysis was performed on a breath-by-breath basis using an Aero Monitor AE-280 (Minato Medical Science, Osaka, Japan).

Table 1. Patient Characteristics and Results of Exercise Tests

	NYHA I	NYHA II	NYHA III
n	10	10	10
Gender (male/female)	8/2	7/3	7/3
Age (yrs)	48 ± 12	50 ± 11	53 ± 6
Body height (cm)	163.9 ± 11.3	164.2 ± 4.6	161.1 ± 8.4
Body weight (kg)	57.0 ± 8.9	58.8 ± 7.6	51.9 ± 6.3
BMI (kg/m^2)	22.2 ± 2.4	21.9 ± 2.8	20.0 ± 2.4
SR/AF	8/2	9/1	4/6
LVEDD (cm)	6.1 ± 1.1	6.6 ± 0.8	6.6 ± 0.6
LVESD (cm)	5.2 ± 1.1	5.5 ± 0.7	5.7 ± 0.7
EF (%)	31.9 ± 8.4	30.4 ± 6.4	24.1 ± 8.3
Etiology (DCM/OMI/AR)	6/3/1	7/3/0	10/0/0
Peak work rate (watts)	119 ± 28	87 ± 11*	62 ± 9*#
Peak VO_2 (ml/kg/min)	24.4 ± 2.8	18.7 ± 1.7*	15.2 ± 1.7*#
Peak VCO_2 (ml/kg/min)	30.0 ± 4.3	21.1 ± 2.2*	17.1 ± 2.6*#
RER at rest	0.84 ± 0.05	0.85 ± 0.06	0.87 ± 0.07
RER at peak exercise	1.21 ± 0.06	1.18 ± 0.07	1.17 ± 0.07
T1/2 VO_2 (s)	76.3 ± 10.8	93.1 ± 19.9	130.8 ± 23.9*#
T1/2 VCO_2 (s)	83.5 ± 11.3	122.5 ± 28.9*	154.3 ± 32.4*#

*$p < 0.05$ versus NYHA class I. #$p < 0.05$ versus NYHA II.

AF = atrial fibrillation; AR = aortic regurgitation; BMI = body mass index; DCM = dilated cardiomyopathy; EF = ejection fraction (determined by contrast ventriculography or echocardiography); LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; NYHA = New York Heart Association functional class; OMI = old myocardial infarction; RER = respiratory exchange ratio; SR = sinus rhythm; T1/2 VO_2 (VCO_2) = recovery half time, defined as the time needed for the peak value of VO_2 (VCO_2) to decrease by half; VCO_2 = carbon dioxide output; VO_2 = oxygen uptake.

The apparatus was calibrated before each study. Data were processed and the following parameters were calculated using an on-line computer system: expired minute ventilation, oxygen uptake (VO_2), and carbon dioxide output (VCO_2). Exercise capacity was assessed on the basis of peak VO_2, which was determined as the average of values obtained during the final 15 s of exercise.

Hemodynamic measurements. Before exercise, a 7F Swan-Ganz catheter was inserted into the pulmonary artery via an internal jugular vein and a cannula was introduced into a radial or brachial artery. Blood samples were drawn simultaneously from this artery and the pulmonary artery at rest, during the warm up period, at 1-min intervals during exercise, at peak exercise, and at 1-min intervals during a 4-min recovery period. The blood samples were used to measure oxygen saturation and hemoglobin concentration. Cardiac output was determined by the Fick principle. Pulmonary and systemic arterial pressure were monitored throughout the study periods, and right atrial pressure was recorded at 1-min intervals. Systemic vascular resistance was calculated by (mean arterial pressure − mean right atrial pressure) × 80 ÷ cardiac output.

Derived variables. The kinetics of VO_2 and VCO_2 during recovery were characterized by the recovery half-time (T1/2), defined as the time needed for the peak value to decrease by half (in seconds). Recovery cardiac output was calculated at 1-min intervals for 4 min. The kinetics of cardiac output during recovery were characterized by the ratios of cardiac output at 1, 2, 3 and 4 min of recovery to cardiac output at peak exercise. Overshoot of cardiac output was defined as a further increase in cardiac output at 1 min of recovery above the cardiac output at peak exercise.

Statistical analysis. All data are expressed as mean ± SD. Multiple comparisons among groups were performed by one-way analysis of variance (ANOVA) combined with Tukey honestly significant difference. Linear regression analysis was used to assess the relationship between recovery gas exchange variables and both cardiac index at peak exercise and kinetics of cardiac output during recovery. Fisher's exact probability test was used to compare the incidence of overshoot of cardiac output at 1 min of recovery. Comparisons of variables between patients with overshoot and patients without overshoot were made by unpaired *t*-test. Comparisons of the stroke volume or systemic vascular resistance at peak exercise and at 1 min of recovery were made by the paired *t*-test. A value of $p < 0.05$ was considered significant.

RESULTS

Peak VO_2 and peak VCO_2 decreased significantly as the NYHA functional class severity advanced (Table 1). After the end of exercise, ventilatory variables declined toward their resting values at various rates. The recovery half-times of VO_2 and VCO_2 increased progressively as the NYHA class worsened (Table 1).

Hemodynamic data are reported in Table 2. Mean arterial pressure at peak exercise was significantly lower in class III than in class I patients, but it did not differ among three groups during recovery. Cardiac index and stroke volume was significantly lower and systemic vascular resistance was significantly higher in class III than in class I patients at rest, at peak exercise and during recovery. Although mixed venous O_2 saturation at rest and during recovery was significantly lower in class III, it was not different among the three groups at peak exercise. Arterial oxygen saturation was controlled within the normal range in all patients throughout the study periods. The ratios of cardiac output during recovery to cardiac output at peak exercise were greater in symptomatic patients (class II and III) than in asymptomatic patients (class I) (0.97 ± 0.13 vs. 0.86 ± 0.13 [$p < 0.05$] at 1 min, 0.79 ± 0.17 vs. 0.65 ± 0.15 [$p < 0.05$] at 2 min, 0.68 ± 0.14 vs. 0.54 ± 0.14 [$p < 0.05$] at 3 min, and 0.61 ± 0.13 vs. 0.50 ± 0.12 [$p < 0.05$] at 4 min of recovery), which indicated that decrease in cardiac output from its peak exercise value was delayed in severe CHF. The ratios of cardiac output at 1, 2, 3 and 4 min of recovery to cardiac output at peak exercise were significantly correlated with recovery half-time of VO_2 ($r = 0.47$ [$p < 0.05$] at 1 min, $r = 0.62$ [$p < 0.001$] at 2 min, $r = 0.62$ [$p < 0.001$] at 3 min, and $r = 0.55$ [$p < 0.01$] at 4 min of recovery), and were also significantly correlated with recovery half-time of VCO_2 ($r = 0.40$ [$p < 0.05$] at 1 min, $r = 0.59$ [$p < 0.001$] at 2 min, $r = 0.68$ [$p < 0.001$] at 3 min, and $r = 0.70$ [$p < 0.001$] at 4 min of recovery).

Figure 1 shows the relationship between cardiac index at peak exercise and the recovery half-times of VO_2 and VCO_2. There was a negative correlation between the recovery half-times of VO_2 or VCO_2 and cardiac index at peak exercise.

Overshoot of cardiac output at 1 min of recovery above the cardiac output at peak exercise was noted in 11 patients (1 in class I, 4 in class II, and 6 in class III). The incidence of overshoot of cardiac output was significantly higher in symptomatic patients (class II and III) than in asymptomatic patients (class I) (50% vs. 10%, $p < 0.05$). In 11 patients with overshoot, 6 patients were in sinus rhythm and 5 in atrial fibrillation. In 19 patients without overshoot, 15 patients were in sinus rhythm and 4 in atrial fibrillation. Mean age (49 ± 9 years vs. 52 ± 11 years), body mass index (21.4 ± 2.7 kg/m^2 vs. 21.4 ± 2.7 kg/m^2), ejection fraction at rest ($25.2 \pm 7.0\%$ vs. $30.9 \pm 8.3\%$), left ventricular end–diastolic dimension (6.6 ± 0.9 cm vs. 6.4 ± 0.9 cm) and end–systolic dimension (5.7 ± 0.9 cm vs. 5.4 ± 0.8 cm) did not differ between patients with overshoot and those without overshoot. Peak VO_2 (17.6 ± 3.6 ml/kg/min vs. 20.3 ± 4.8 ml/kg/min, $p=0.11$) and respiratory exchange ratio at peak exercise (1.18 ± 0.07 vs. 1.19 ± 0.07) were not different in patients with overshoot compared with patients without overshoot. Table 3 shows comparisons of hemody-

Table 2. Hemodynamic Data in Patients at Rest, at Peak Exercise and during Recovery

				Recovery Time (min)			
	NYHA	Rest	Peak Exercise	1	2	3	4
Heart rate (beats/min)	I	76 ± 10	159 ± 19	124 ± 19	109 ± 17	102 ± 17	98 ± 16
	II	89 ± 13	147 ± 20	120 ± 21	111 ± 19	105 ± 17	103 ± 16
	III	96 ± 24	147 ± 32	117 ± 31	107 ± 27	103 ± 24	101 ± 25
Mean AP (mm Hg)	I	100 ± 7	125 ± 14	107 ± 14	99 ± 12	96 ± 9	94 ± 12
	II	88 ± 11	111 ± 16	101 ± 16	98 ± 15	94 ± 12	91 ± 11
	III	91 ± 12	107 ± 10*	98 ± 13	96 ± 11	98 ± 13	90 ± 15
Mean PA (mm Hg)	I	14 ± 3	31 ± 9	21 ± 6	19 ± 6	17 ± 5	17 ± 5
	II	16 ± 2	32 ± 9	25 ± 6	21 ± 4	19 ± 5	18 ± 4
	III	21 ± 5*#	42 ± 14	34 ± 16*	30 ± 12*	27 ± 12*	25 ± 10*
Mean RA (mm Hg)	I	3 ± 3	7 ± 5	2 ± 2	3 ± 2	3 ± 2	2 ± 2
	II	3 ± 3	8 ± 7	4 ± 5	3 ± 4	3 ± 3	3 ± 3
	III	4 ± 3	8 ± 5	5 ± 4	4 ± 3	3 ± 3	3 ± 3
Cardiac index (L/min/m^2)	I	2.3 ± 0.4	7.2 ± 1.8	6.2 ± 1.6	4.7 ± 1.7	3.9 ± 1.3	3.6 ± 1.1
	II	2.4 ± 0.6	5.6 ± 1.3*	5.2 ± 1.1	4.1 ± 0.6	3.5 ± 0.6	3.1 ± 0.5
	III	1.8 ± 0.4#	3.8 ± 0.7*#	3.7 ± 0.8*	3.1 ± 0.9*	2.5 ± 0.7*	2.3 ± 0.6*
Stroke volume (ml)	I	51 ± 13	77 ± 25	81 ± 21	69 ± 26	64 ± 27	60 ± 23
	II	44 ± 11	65 ± 18	72 ± 13	61 ± 9	56 ± 12	52 ± 12
	III	28 ± 6*#	38 ± 8*#	46 ± 6*#	41 ± 6*#	36 ± 7*#	32 ± 7*#
SVR (dynes · sec · cm^{-5})	I	2033 ± 433	873 ± 253	902 ± 306	1171 ± 470	1349 ± 497	1397 ± 480
	II	1837 ± 455	948 ± 253	948 ± 210	1160 ± 271	1283 ± 272	1411 ± 322
	III	2667 ± 535*#	1509 ± 285*#	1450 ± 342*#	1762 ± 419*#	2164 ± 505*#	2195 ± 431*#
SvO_2 (%)	I	59 ± 4	24 ± 5	49 ± 7	61 ± 4	62 ± 4	62 ± 4
	II	60 ± 4	29 ± 7	50 ± 7	62 ± 3	64 ± 3	64 ± 4
	III	52 ± 4*#	25 ± 7	40 ± 10*#	51 ± 7*#	54 ± 4*#	53 ± 3*#

*$p < 0.05$ versus NYHA I. #$p < 0.05$ versus NYHA II.
AP = arterial pressure; NYHA = New York Heart Association functional class; PA = pulmonary artery pressure; RA = right atrial pressure; SvO_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance.

namic variables in patients with overshoot and those without overshoot. Mean pulmonary artery pressure was significantly higher in patients with overshoot than in those without overshoot at rest, at peak exercise and during recovery. Mixed venous O_2 saturation at peak exercise was significantly lower in patients with overshoot than in patients without overshoot, but it did not differ at rest and during recovery.

Figure 2 shows comparisons of cardiac index in patients with overshoot and patients without overshoot. At rest, there was no difference in cardiac output between patients with overshoot and those without overshoot (2.1 ± 0.6 L/min/m^2 vs. 2.2 ± 0.5 L/min/m^2). Patients with overshoot showed significantly lower cardiac output at peak exercise (4.5 ± 0.9 L/min/m^2 vs. 6.1 ± 2.1 L/min/m^2, $p < 0.05$). But as a result of increased cardiac output at 1 min of recovery in patients with overshoot, there were no differences in cardiac output at 1 min of recovery (4.8 ± 0.9 L/min/m^2 in patients with overshoot vs. 5.1 ± 1.9 L/min/m^2 in patients without overshoot) or after the first minute of recovery.

Figure 3 shows comparisons of heart rate and percent change in heart rate from the peak exercise value between patients with overshoot and patients without overshoot. Heart rate at peak exercise (159 ± 20 beats/min vs. 148 ± 28 beats/min) and recovery of heart rate did not differ between patients with overshoot and patients without overshoot. Additionally, the data for 21 patients in sinus rhythm show that heart rate at peak exercise (152 ± 17 beats/min vs. 150 ± 22 beats/min) and recovery of heart rate were not different between patients with overshoot and those without overshoot.

Figure 4 shows comparisons of stroke volume and percent change in stroke volume from the peak exercise value between patients with overshoot and patients without overshoot. Stroke volume at peak exercise in patients with overshoot was significantly lower than that in patients without overshoot. A marked increase in stroke volume at 1 min of recovery was noted in patients with overshoot (from 43.8 ± 12.7 ml at peak exercise to 57.6 ± 16.6 ml at 1 min of recovery, $p < 0.001$), but stroke volume did not change significantly in patients without overshoot (from 69.0 ± 24.8 ml at peak exercise to 71.3 ± 21.2 ml at 1 min of recovery). Additionally, the data for 21 patients in sinus rhythm show that stroke volume significantly increased at 1 min of recovery in 6 patients with overshoot (from 47.8 ± 10.9 ml at peak exercise to 60.2 ± 16.5 ml at 1 min of recovery, $p < 0.001$), but that stroke volume did not change significantly in 15 patients without overshoot (from 75.4 ± 23.4 ml at peak exercise to 74.6 ± 22.2 ml at 1 min of

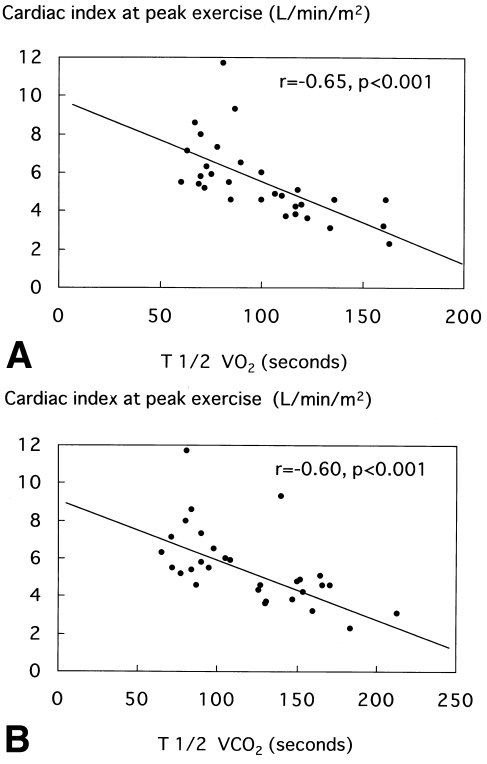

Figure 1. Scatterplots showing relationship between cardiac index at peak exercise and recovery half-times of oxygen uptake (T1/2 VO_2) and CO_2 output (T1/2 VCO_2).

recovery). There was no significant difference in stroke volume after the first minute of recovery.

Figure 5 shows comparisons of systemic vascular resistance and percent change in systemic vascular resistance from the peak exercise value between patients with overshoot and patients without overshoot. Systemic vascular resistance at peak exercise in patients with overshoot was significantly higher than in patients without overshoot. Systemic vascular resistance at 1 min of recovery significantly decreased in patients with overshoot (from 1341 ± 299 dynes · sec · cm^{-5} at peak exercise to 1184 ± 259 dynes · sec · cm^{-5} at 1 min of recovery, $p < 0.005$), but it increased significantly in patients without overshoot (from 976 ± 370 dynes · sec · cm^{-5} at peak exercise to 1051 ± 431 dynes · sec · cm^{-5} at 1 min of recovery, $p < 0.05$). As a result, there was no significant difference in systemic vascular resistance after the first minute of recovery.

DISCUSSION

The present study revealed that recovery of cardiac output, as well as ventilatory variables, after maximal exercise was delayed in advanced CHF. Overshoot of cardiac output at 1 min of recovery above the cardiac output at peak exercise due to a marked rise in stroke volume was characteristic of severe CHF, along with poor cardiac output response to exercise.

Recovery of oxygen uptake after maximal exercise in CHF. Recently, the kinetics of expired gas have been evaluated not only during exercise but also during recovery from exercise in patients with CHF (4–9). Cohen-Solal et al. (5) have shown that the recoveries of ventilation, O_2 uptake, and CO_2 output are prolonged in patients with CHF. They indicated that prolonged recovery of O_2 uptake is related to slow recovery of energy stores in skeletal muscle (5). Other studies also indicated that prolonged recovery of O_2 uptake during recovery from exercise can be used to evaluate functional capacity in patients with CHF (4,6–9). Although these recent studies showed that ventilatory kinetics during recovery from exercise is prolonged in CHF patients, to our knowledge, recovery of cardiac output from maximal exercise in patients with CHF has not been elucidated.

Table 3. Hemodynamic Data at Rest, at Peak Exercise, and during Recovery in Patients with Overshoot of Cardiac Output at One Minute of Recovery above the Peak Exercise Value and in Patients without Overshoot

				Recovery Time (min)			
	Overshoot	Rest	Peak Exercise	1	2	3	4
Mean AP	(+)	94 ± 15	114 ± 15	107 ± 19	102 ± 16	100 ± 13	95 ± 15
(mm Hg)	(−)	93 ± 9	114 ± 16	99 ± 11	95 ± 11	93 ± 9	90 ± 12
Mean PA	(+)	19 ± 4*	40 ± 11*	32 ± 11*	27 ± 9*	24 ± 9	22 ± 7*
(mm Hg)	(−)	15 ± 4	31 ± 11	23 ± 10	19 ± 8	18 ± 7	17 ± 5
Mean RA	(+)	4 ± 3	9 ± 7	5 ± 5	4 ± 3	4 ± 3	3 ± 3
(mm Hg)	(−)	3 ± 3	7 ± 4	3 ± 3	3 ± 3	3 ± 3	3 ± 3
SvO2 (%)	(+)	56 ± 6	22 ± 4*	45 ± 8	57 ± 6	59 ± 6	58 ± 5
	(−)	58 ± 5	28 ± 7	47 ± 10	59 ± 7	61 ± 6	61 ± 6

*$p < 0.05$ versus patients without overshoot of cardiac output.
AP = arterial pressure; PA = pulmonary artery pressure; RA = right atrial pressure; SvO_2 = mixed venous oxygen saturation; (+) = patients with overshoot of cardiac output at one minute of recovery above the cardiac output at peak exercise (n = 11); (−) = patients without overshoot (n = 19).

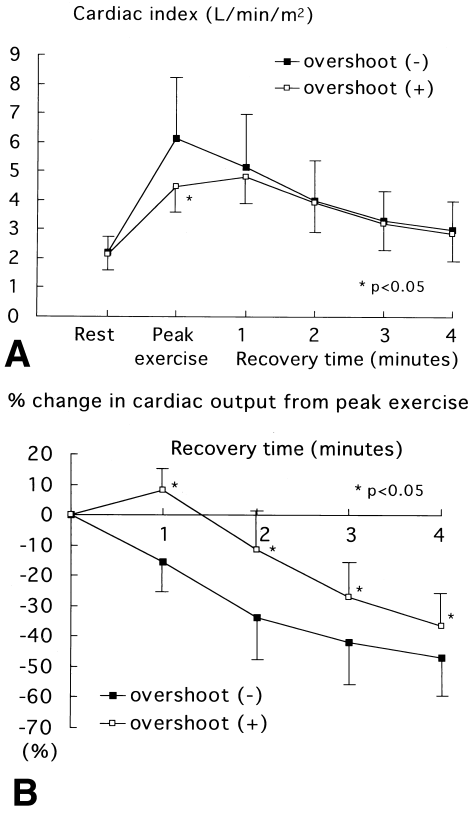

Figure 2. Line graphs showing cardiac index at rest, at peak exercise and during 4 min of recovery, and percent (%) change in cardiac output from the peak exercise value in patients with overshoot of cardiac output at 1 min of recovery above the cardiac output at peak exercise (open square) and in patients without overshoot (closed square). * $p < 0.05$ compared with patients without overshoot.

Recovery of cardiac output after maximal exercise in CHF. We found that not only O_2 uptake but also cardiac output fell much more slowly after maximal exercise as CHF worsened. The pathophysiologic basis of the delayed fall in cardiac output in severe CHF cannot be established from the results of this study, but it was closely related to reduced cardiac output response to exercise. In patients with CHF, O_2 uptake at identical work load is lower than in normal subjects (11). The lower O_2 uptake at identical work load results from a slower increase in O_2 uptake during exercise (8,12). Inadequate cardiac output increment during exercise probably accounts for the prolongation of O_2 uptake kinetics in CHF (12), thereby increasing the O_2 deficit during exercise. Koike et al. (8) have shown that the delayed kinetics of O_2 uptake during exercise (a reflection of the increased O_2 deficit) are closely related to prolonged recovery of O_2 uptake after exercise (a reflection of the increased O_2 debt) in patients with CHF. The delayed fall in cardiac output during recovery, in conjunction with the prolonged recovery of O_2 uptake, appears to act for the repayment of increased O_2 debt, at least in part.

Sumimoto et al. (13,14) have shown that cardiac output during recovery in CHF patients apparently exceeds the O_2 demand of whole body tissues, because mixed venous oxygen saturation increases above the resting value during the early recovery phase. They indicated that high cardiac output during recovery is predominantly responsible for CO_2 elimination (14). By any of these mechanisms, prolonged O_2 uptake or CO_2 output kinetics during recovery from exercise, which are closely related to reduced cardiac output at peak exercise and delayed fall in cardiac output during recovery, represent markers of circulatory impairment in CHF.

Overshoot of cardiac output during recovery. Reddy et al. (10) have shown that during light isometric exercise that requires 25% of maximal voluntary contraction, cardiac output increased in normal subjects but remained unchanged in severe CHF patients. At 90 s of recovery, cardiac output returned to resting values in normal subjects, whereas cardiac output increased in severe CHF (10). However, to our knowledge, the overshoot of cardiac output above the peak exercise value during recovery from maximal upright exercise has not been reported previously. Although left ventricular ejection fraction and cardiac output at rest were not different in patients with overshoot and in those without overshoot, patients with overshoot showed higher

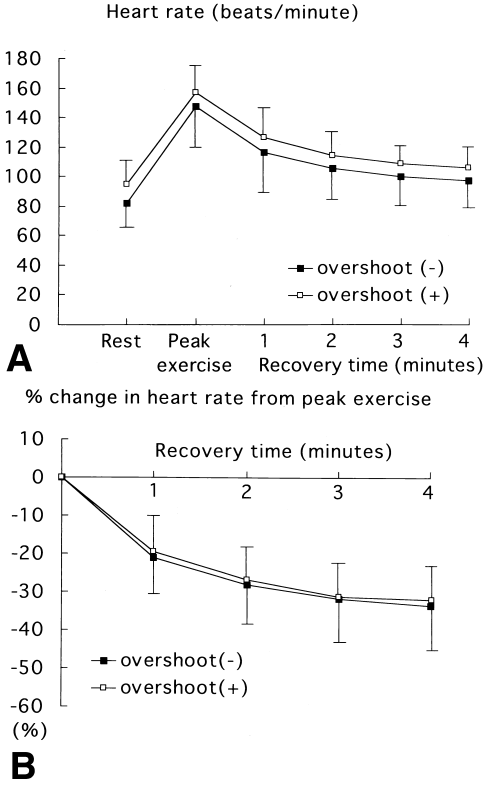

Figure 3. Line graphs showing heart rate at rest, at peak exercise and during 4 min of recovery, and percent (%) change in heart rate from the peak exercise value in patients with overshoot of cardiac output (open square) and in patients without overshoot (closed square).

systemic vascular resistance, lower stroke volume and cardiac output, and elevated mean pulmonary artery pressure at peak exercise. Reduced cardiac output reserve and severely attenuated vasodilator response to exercise characterized patients with overshoot of cardiac output during early recovery.

Overshoot of cardiac output was caused by a marked increase in stroke volume during recovery. A slight rebound in stroke volume after exercise has been reported in normal subjects, especially in the supine position, and in patients with coronary artery disease (15–17). Koike et al. have shown a marked rebound of stroke volume just after cessation of upright exercise in patients with old myocardial infarction. The rise in stroke volume is chiefly a result of a significant decrease in end–systolic volume and a significant increase in ejection fraction during several minutes of recovery (17). Previous studies have shown that minimal value of systemic vascular resistance is recognized at peak exercise, and that the systemic vascular resistance at peak exercise is significantly higher in severe CHF (18–20). Although the insufficient afterload reduction during exercise in CHF contributes to the impaired stroke volume response to exercise (18), systemic vascular resistance during early recovery has not been fully evaluated in patients with CHF.

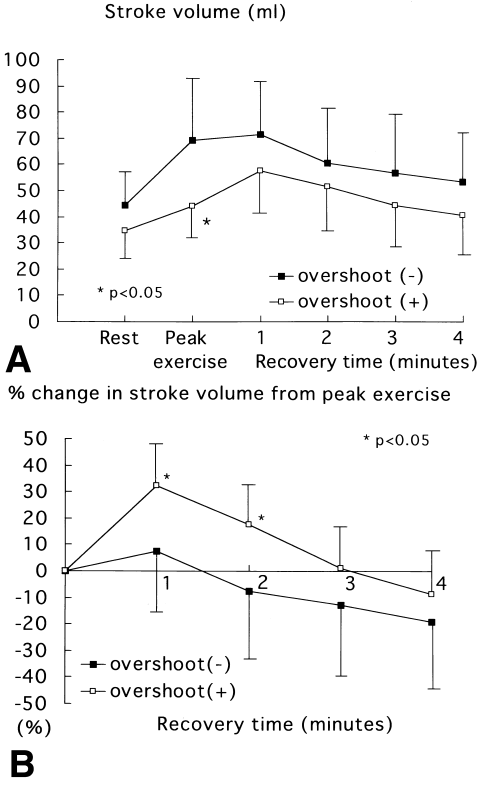

Figure 4. Line graph showing stroke volume at rest, at peak exercise and during 4 min of recovery, and percent (%) change in stroke volume from the peak exercise value in patients with overshoot of cardiac output (open square) and in patients without overshoot (closed square). * $p < 0.05$ compared with patients without overshoot.

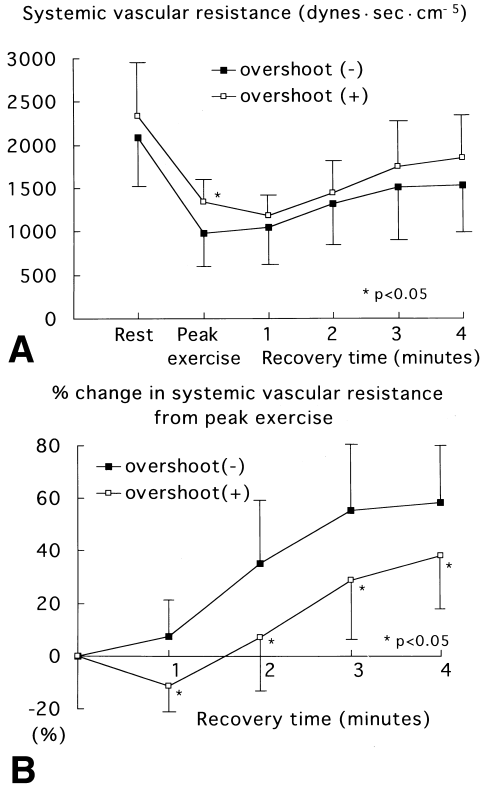

Figure 5. Line graphs showing systemic vascular resistance at rest, at peak exercise and during 4 min of recovery, and percent (%) change in systemic vascular resistance from the peak exercise value in patients with overshoot of cardiac output (open square) and in patients without overshoot (closed square). * $p < 0.05$ compared with patients without overshoot.

The present study showed, for the first time, that systemic vascular resistance at 1 min of recovery significantly decreased from that at peak exercise in patients with CHF who showed overshoot of cardiac output during recovery. Plasma catecholamines are still elevated above the resting value during this early phase of recovery (20,21). The marked increase in stroke volume during early recovery in patients with overshoot appears to result from both an immediate afterload reduction and a relatively slow decrease in cardiac sympathetic stimulation during recovery.

Possible mechanism of circulatory control during recovery in severe CHF. During exercise, increase in sympathetic activity serves to increase vascular resistance in nonworking tissues (22). In working skeletal muscle, local metabolic factors and endothelium-derived substances such as nitric oxide and prostaglandins override the neurohumoral vasoconstrictor stimuli and produce vasodilation (23–29). In patients with severe CHF, the minimal skeletal muscle vascular resistance in response to exercise is increased, thereby decreasing blood flow to working skeletal muscle compared with normal subjects (19,20). Increased renin–angiotensin–aldosterone system activity, rather than sympathetic activity, plays a predominant role for marked

elevation in vasoconstrictor activity during exercise in CHF (30,31). The attenuation of the nitric oxide-dependent vasodilation also contributes at least in part to the increased vascular resistance in patients with CHF (26,27,32,33)

The local control system of peripheral circulation during recovery has not been fully elucidated, especially in patients with CHF. However, the following mechanism may contribute to the reduction in systemic vascular resistance and the overshoot of cardiac output during early recovery in severe CHF. Previous studies showed that a reduction of blood flow to the splanchnic, renal and non-exercising skeletal muscle during exercise was recognized in severe CHF (22,34,35). If this redistribution of blood flow from non-exercising regions to exercising muscle occurs during exercise in severe CHF, reversal of the excessive vasoconstriction in the non-exercising area may induce a decrease in systemic vascular resistance and an increase in blood flow to non-working region during early recovery. However, recent studies have shown that blood flow to non-exercising regions does not decrease during exercise in patients with severe CHF (19,31). The forearm blood flow or non-leg blood flow remains unchanged from the resting level during maximal leg exercise in patients with severe CHF and normal subjects (19,31). In the present study, patients with overshoot of cardiac output during early recovery showed lower cardiac output and lower mixed venous O_2 saturation at peak exercise, suggesting that more severe muscle underperfusion occurred and that O_2 deficit and regional ischemia thereby increased. Attenuation of intense vasoconstriction in the working skeletal muscle due to augmented local metabolic and endothelial vasodilator stimuli, coupled with reduced neurohumoral vasoconstrictor activities, may produce decreased vascular resistance and increased blood flow to the working skeletal muscle during early recovery. Therefore, increased cardiac output during early recovery may be distributed to exercised skeletal muscle to repay the higher O_2 deficit in patients with overshoot of cardiac output.

The local control of peripheral circulation is complex, and the role of neurohumoral factors, metabolic factors and endothelium-derived substances in the regulation of vascular resistance and blood flow distribution during exercise and recovery in severe CHF has not been established. Further studies are needed to clarify circulatory regulation during recovery.

Study limitations. In contrast to the measurement of O_2 uptake or CO_2 output using a breath-by-breath basis, continuous measurement of cardiac output during exercise or recovery is extremely difficult. We measured cardiac output at 1-min intervals and assessed the cardiac output kinetics during recovery by the ratios of cardiac output at 1, 2, 3, and 4 min of recovery to the cardiac output at peak exercise instead of determining the recovery half-time of cardiac output. However, our findings of an increased ratio of recovery cardiac output to cardiac output at peak exercise in severe CHF and a higher incidence of overshoot of cardiac output during early recovery in severe CHF indicate that delayed kinetics of cardiac output during recovery are characteristic of severe CHF.

There was no control group in this study. A recent study showed that recovery half-time of O_2 uptake is significantly shorter in normal subjects than in CHF patients (5). In the present study, prolonged O_2 uptake kinetics during recovery were closely correlated with a delayed fall in cardiac output during recovery. Cardiac output recovery must be rapid in normal subjects (36).

This study was performed on a somewhat heterogeneous patient population, but all patients had homogeneously depressed left ventricular systolic function without exercise-induced myocardial ischemia. There is no reason to believe that the kinetics of O_2 uptake or cardiac output during recovery are influenced by the etiology of CHF.

We evaluated overshoot of cardiac output at 1 min of recovery, and did not estimate overshoot of cardiac output during 0 to 60 s of recovery. However, our findings that the overshoot of cardiac output at 1 min of recovery above the peak exercise value is more common in severe CHF suggested that prolonged overshoot of cardiac output after exercise is characteristic of severe CHF.

Conclusions. The prolonged kinetics of O_2 uptake or CO_2 output during recovery from maximal exercise represent circulatory impairment during exercise and delayed recovery of cardiac output after exercise in CHF patients. The overshoot of cardiac output at 1 min of recovery above the cardiac output at peak exercise, which is caused by an increase in stroke volume due to a reduction in systemic vascular resistance, is characteristic of severe CHF with poor cardiac output response to exercise. The increased cardiac output during early recovery in patients with severe CHF may act as a compensation mechanism for insufficient cardiac output during exercise.

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