

Overshoot phenomenon of oxygen uptake during recovery from maximal exercise in patients with previous myocardial infarction

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Abstract The overshoot in oxygen uptake ($\dot{V}O_2$ overshoot) during recovery from maximal exercise is thought to reflect an overshoot in cardiac output. We investigated whether this phenomenon is related to cardiopulmonary function during exercise in cardiac patients. A total of 201 consecutive patients with previous myocardial infarction underwent cardiopulmonary exercise testing (CPX). An apparent $\dot{V}O_2$ overshoot during the recovery from CPX ($6.5 \pm 8.1\%$ increase relative to the peak $\dot{V}O_2$) was observed in ten patients. A comparison of patients with the $\dot{V}O_2$ overshoot to those without the $\dot{V}O_2$ overshoot revealed that the former had a significantly lower left ventricular ejection fraction (40.1 ± 19.1 vs. $55.2 \pm 14.9\%$, respectively, $p = 0.002$) and larger left ventricular diastolic and systolic dimensions. Patients with the $\dot{V}O_2$ overshoot also had a significantly lower peak $\dot{V}O_2$ (13.1 ± 6.1 vs. 18.1 ± 4.5 ml/min/kg, $p < 0.001$), lower $\Delta\dot{V}O_2/\Delta WR$ (work rate) (6.6 ± 3.8 vs. 9.5 ± 1.7 mL/min/W, $p < 0.0001$), and a higher $\dot{V}E$ (minute ventilation)/ $\dot{V}CO_2$ (carbon dioxide output) slope (45.0 ± 18.6 vs. 32.6 ± 6.6 , $p < 0.0001$) than those without the overshoot. A $\dot{V}O_2$ overshoot during recovery from maximal exercise

was found in 5% of patients with previous myocardial infarction. This condition, which suggests a transient mismatch between cardiac contractility and afterload reduction, was found to be related to impaired cardiopulmonary function during exercise.

Keywords Exercise recovery · Exercise testing · Oxygen uptake · Previous myocardial infarction

Introduction

The response of cardiopulmonary function to exercise regardless of the mode of the exercise, including maximal incremental exercise and submaximal constant work rate exercise, has been studied [1–3]. However, the time-course of cardiopulmonary function during recovery from exercise is not yet fully understood. In patients with left ventricular dysfunction, the response of cardiac output during incremental exercise is impaired, resulting in lower peak cardiac output [4]. During recovery from the exercise, cardiac output declines towards a resting value. The speed of the recovery of cardiac output is known to be slower in patients with left ventricular dysfunction than in normal subjects [5]. The delayed recovery of cardiac output after exercise results in the delayed kinetics of oxygen uptake ($\dot{V}O_2$) [5], with $\dot{V}O_2 = (\text{cardiac output}) \times (\text{the arterial} - \text{mixed venous } O_2 \text{ difference}) (C[a-v]O_2)$.

In 2000, Tanabe et al. [5] reported that patients with left ventricular dysfunction have an overshoot phenomenon of cardiac output during the early phase of recovery. This overshoot of cardiac output after exercise is characterized by the cardiac output being transiently higher following exercise than at peak exercise for approximately 1 min [5]. This phenomenon is assumed to be due to the overshoot of

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stroke volume during recovery [6]. Thus, if the overshoot of cardiac output exists, the overshoot of $\dot{V}O_2$ may also exist in patients with left ventricular dysfunction.

Cardiopulmonary exercise testing (CPX) with respiratory gas measurements has been recognized as a useful tool for evaluating both the severity of disease and the factors limiting activities of daily living in cardiac patients [7, 8]. CPX is becoming one of the standard tests in the field of clinical cardiology. In the study reported here, we focused on the change in $\dot{V}O_2$ during recovery from maximal exercise and investigated the prevalence of the overshoot phenomenon of $\dot{V}O_2$ during recovery from maximal exercise and its clinical significance in patients with previous myocardial infarction.

Methods

Study patients

A total of 201 consecutive patients with previous myocardial infarction who performed CPX at the Cardiovascular Institute were enrolled in the study (Table 1). CPX was performed in order to evaluate the severity of the heart failure with the indices of CPX. The presence of myocardial infarction was diagnosed according to World Health Organization criteria [9]. Patients with critical coronary

stenosis, a condition considered to be inappropriate for CPX, had been treated by percutaneous coronary intervention and/or coronary artery bypass graft surgery prior to the CPX according to current therapeutic guidelines. Patients with orthopedic difficulty in pedaling a cycle ergometer were excluded from the study. The protocol was approved by the human subjects committee of the Cardiovascular Institute. The aims and risks of the study were explained to the patients, and informed consent was obtained from each patient.

Cardiopulmonary exercise testing

An incremental symptom-limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Rehcor; Lode, Groningen, The Netherlands). Exercise began with a 4-min warm-up at 0 or 20 W at 60 rpm, and the load was then increased incrementally by 1 W every 6 s (10 W/min). The work rate of the warm-up exercise was selected as 0 or 20 W depending on the subject's daily activity. During the test, we measured breath-by-breath $\dot{V}O_2$, CO_2 output ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) through a rubber mask attached to the subject's face using an AE-300S Respiromonitor (Minato Medical Science, Osaka, Japan), as previously described [3, 10]. The system was carefully calibrated before each testing.

Table 1 Clinical characteristics of the patients

Patient characteristics	All patients (<i>n</i> = 201)	Patients with $\dot{V}O_2$ overshoot (<i>n</i> = 10)	Patients without $\dot{V}O_2$ overshoot (<i>n</i> = 191)	<i>p</i> value
Male/female gender, <i>n</i>	188/13	9/1	179/12	NS
Age (year)	64.2 ± 9.3	61.7 ± 10.5	64.4 ± 9.3	NS
Height (cm)	164.7 ± 6.8	160.8 ± 5.2	164.9 ± 6.8	NS
Weight (kg)	64.7 ± 10.1	60.8 ± 6.7	64.9 ± 10.3	NS
Medication				
Nitrates	137 (68.2)	7 (70.0)	130 (68.1)	NS
Calcium-channel blockers	93 (46.3)	2 (20.0)	91 (47.6)	NS
β -blockers	92 (45.8)	5 (50.0)	87 (45.5)	NS
Angiotensin receptor blockers	50 (24.9)	4 (40.0)	46 (24.1)	NS
Angiotensin-converting enzyme inhibitors	48 (23.9)	3 (30.0)	45 (23.6)	NS
Diuretics	32 (15.9)	6 (60.0)	26 (13.6)	0.001
Digitalis	10 (5.0)	2 (20.0)	8 (4.2)	NS
Coronary risk factors				
Hypertension	110 (54.7)	6 (60.0)	104 (54.5)	NS
Dyslipidemia	109 (54.2)	6 (60.0)	103 (53.9)	NS
Diabetes mellitus	59 (29.4)	4 (40.0)	55 (28.8)	NS
Current or history of smoking	135 (67.2)	6 (60.0)	129 (67.5)	NS

Data are presented as the mean ± standard deviation (SD) or as the number of patients, with the percentage in parenthesis, unless otherwise indicated

NS Not significant

A five-point moving average of the breath-by-breath data was performed prior to any calculation of the parameters from the respiratory gas analysis. The peak $\dot{V}O_2$ was defined as the average value obtained during the last 30 s of incremental exercise. The ratio of the increase in $\dot{V}O_2$ to the increase in work rate (WR; $\Delta\dot{V}O_2/\Delta WR$) was calculated by a least-squares linear regression from the data recorded between 30 s after the start of incremental exercise and 30 s before the end of the exercise [11]. The $\dot{V}E/\dot{V}CO_2$ slope was calculated from the start of incremental exercise to the respiratory compensation point by the least-squares linear regression [11]. The respiratory compensation point was determined using the following criteria: (1) the ratio of $\dot{V}E$ to $\dot{V}CO_2$ starts to increase after a period of decrease or stasis, and (2) the end-tidal PCO_2 (partial pressure CO_2) starts to decrease after a period of stasis. When the respiratory compensation point could not be clearly identified, the $\dot{V}E/\dot{V}CO_2$ slope was calculated from the data recorded between the start of incremental exercise to the end of the exercise [11].

The overshoot phenomenon was defined as follows: (1) the overshoot of $\dot{V}O_2$, i.e., the higher value of $\dot{V}O_2$ relative to $\dot{V}O_2$ at peak exercise, was visually identified, and (2) the average value of $\dot{V}O_2$ from 0 to 60 s after the termination of exercise was higher than the peak $\dot{V}O_2$, which was determined as the average value during the last 30 s of exercise. The magnitude of the $\dot{V}O_2$ overshoot was calculated as the percentage of the increase in $\dot{V}O_2$ during the first minute of exercise recovery relative to peak $\dot{V}O_2$. The presence of $\dot{V}O_2$ flattening, which was defined as the absence of any increase in $\dot{V}O_2$ for at least 45 s despite an increase in WR just before the termination of exercise, was also identified.

Statistics

Data are presented as the mean \pm standard deviation (SD). The subjects were divided into two groups: patients with the $\dot{V}O_2$ overshoot ($n = 10$) and those without ($n = 191$). Intergroup differences for variables were compared using the unpaired t test or Fisher's exact test, where appropriate. A stepwise multivariate regression model was used to select an independent predictor of $\dot{V}O_2$ overshoot. In this analysis, a variable with an F value <4.0 was excluded.

Results

$\dot{V}O_2$ overshoot during recovery from exercise was identified in ten patients, and its magnitude was $6.5 \pm 8.1\%$. Comparisons of the clinical characteristics between patients with the $\dot{V}O_2$ overshoot during the recovery from exercise and those without it are presented in Table 1.

There were no significant differences in gender, age, height or weight between the two groups. The use of diuretics was more frequent in patients with the $\dot{V}O_2$ overshoot.

In all the patients ($n = 201$), the end-point of exercise testing was leg fatigue in 149 patients (74.1%) and shortness of breath in 16 patients (8.0%); the proportion did not differ between the two groups. No patient in either group experienced chest pain during CPX. Table 2 demonstrates hemodynamic and respiratory gas variables in patients with the $\dot{V}O_2$ overshoot and those without it. A comparison of patients with the $\dot{V}O_2$ overshoot to those without the $\dot{V}O_2$ overshoot revealed that the former had a significantly lower LVEF (40.1 ± 19.1 vs. $55.2 \pm 14.9\%$, respectively, $p = 0.002$) and larger left ventricular diastolic (61.9 ± 13.4 vs. 51.2 ± 7.2 mm, $p < 0.0001$) and systolic dimensions (50.3 ± 17.0 vs. 36.5 ± 9.5 mm, $p < 0.0001$). Patients with the $\dot{V}O_2$ overshoot also had a significantly lower systolic blood pressure at peak exercise, a significantly lower peak $\dot{V}O_2$ (13.1 ± 6.1 vs. 18.1 ± 4.5 ml/min/kg, $p < 0.001$), and a significantly lower $\Delta\dot{V}O_2/\Delta WR$ (6.6 ± 3.8 vs. 9.5 ± 1.7 ml/min/W, $p < 0.0001$), reflecting their decreased exercise capacity. The patients with the $\dot{V}O_2$ overshoot had a significantly higher $\dot{V}E/\dot{V}CO_2$ slope than those without the overshoot (45.0 ± 18.6 vs. 32.6 ± 6.6 , respectively, $p < 0.0001$). Flattening of the $\dot{V}O_2$ just before the termination of exercise was noted in three patients (30.0%) among those with the $\dot{V}O_2$ overshoot and nine patients (4.7%) among those without the $\dot{V}O_2$ overshoot (Table 2).

In order to select an independent predictor of $\dot{V}O_2$ overshoot, we performed a stepwise multivariate regression analysis on the variables gender, age, height, weight, LVEF, peak $\dot{V}O_2$, $\Delta\dot{V}O_2/\Delta WR$, $\dot{V}E/\dot{V}CO_2$ slope, and the presence of $\dot{V}O_2$ flattening. Among these, age, $\Delta\dot{V}O_2/\Delta WR$, $\dot{V}E/\dot{V}CO_2$ slope, and the presence of $\dot{V}O_2$ flattening were found to be statistically significant independent indices determining $\dot{V}O_2$ overshoot during recovery from exercise (standard regression coefficient of each index was -0.18 , -0.23 , 0.20 , and 0.20 , respectively).

Discussion

In our study, we found that the overshoot phenomenon of $\dot{V}O_2$ during recovery from maximal exercise occurred in approximately 5% of patients with previous myocardial infarction. As compared to patients without the $\dot{V}O_2$ overshoot, those with the $\dot{V}O_2$ overshoot had a lower peak $\dot{V}O_2$, lower $\Delta\dot{V}O_2/\Delta WR$, and higher $\dot{V}E/\dot{V}CO_2$ slope. Peak $\dot{V}O_2$ in cardiac patients globally reflects maximal cardiac output, i.e., the heart's pumping reserve. $\Delta\dot{V}O_2/\Delta WR$, which is approximately 10 ml/min/W in normal subjects, also reflects the rate of the increase in cardiac output during

Table 2 Hemodynamic and respiratory gas variables of the subjects

Variable	All patients (<i>n</i> = 201)	Patients with $\dot{V}O_2$ overshoot (<i>n</i> = 10)	Patients without $\dot{V}O_2$ overshoot (<i>n</i> = 191)	<i>p</i> value
At rest				
LVEF (%)	54.5 ± 15.4	40.1 ± 19.1	55.2 ± 14.9	0.002
Left ventricular diastolic dimension (mm)	51.7 ± 7.8	61.9 ± 13.4	51.2 ± 7.2	<0.0001
Left ventricular systolic dimension (mm)	37.1 ± 10.4	50.3 ± 17.0	36.5 ± 9.5	<0.0001
Heart rate (beats/min)	75.4 ± 12.2	74.1 ± 14.6	75.5 ± 12.1	NS
Systolic blood pressure (mmHg)	122.7 ± 18.7	122.3 ± 21.5	122.7 ± 18.6	NS
Diastolic blood pressure (mmHg)	70.9 ± 11.1	69.9 ± 16.6	71.0 ± 10.8	NS
Peak exercise				
Heart rate (beats/min)	124.8 ± 19.7	114.5 ± 23.6	125.3 ± 19.4	NS
Systolic blood pressure (mmHg)	185.4 ± 33.4	164.3 ± 45.5	186.5 ± 32.5	0.040
Diastolic blood pressure (mmHg)	86.3 ± 15.7	91.7 ± 27.4	86.0 ± 14.9	NS
Respiratory exchange ratio	1.09 ± 0.09	1.08 ± 0.14	1.09 ± 0.08	NS
$\dot{V}O_2$ flattening	12 (6.0)	3 (30.0)	9 (4.7)	0.020
Peak $\dot{V}O_2$ (ml/min/kg)	17.8 ± 4.7	13.1 ± 6.1	18.1 ± 4.5	<0.001
$\Delta\dot{V}O_2/\Delta WR$ (ml/min/W)	9.3 ± 2.0	6.6 ± 3.8	9.5 ± 1.7	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	33.3 ± 8.0	45.0 ± 18.6	32.6 ± 6.6	<0.0001
Magnitude of $\dot{V}O_2$ overshoot (%)		6.5 ± 8.1		

Data are presented as the mean ± SD or as the number of patients, with the percentage in parenthesis, unless otherwise indicated

LVEF Left ventricular ejection fraction, $\dot{V}O_2$ oxygen uptake, WR work rate, $\dot{V}E$ minute ventilation, $\dot{V}CO_2$ carbon dioxide output, NS not significant

incremental exercise [12]. The $\dot{V}E/\dot{V}CO_2$ slope is known to become steeper in cardiac patients in relation to the severity of heart failure [13–15]. Therefore, the findings of our study suggest that those patients with the $\dot{V}O_2$ overshoot during recovery from exercise have a more impaired cardiopulmonary function during exercise than those without the $\dot{V}O_2$ overshoot.

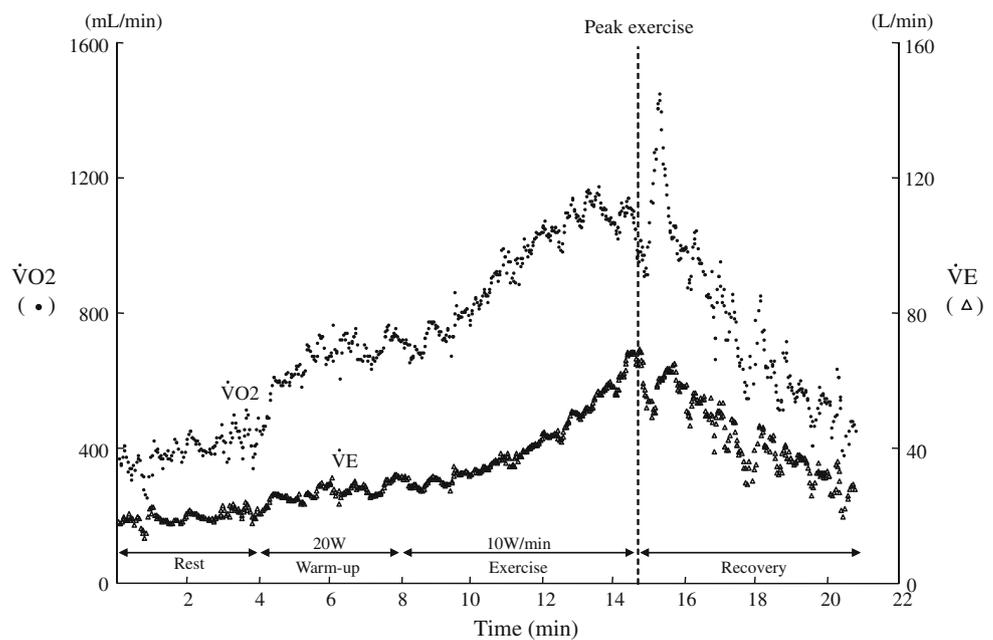
Mechanisms of the $\dot{V}O_2$ overshoot

Given that $\dot{V}O_2$ is the product of cardiac output and $C[a-v]O_2$, the $\dot{V}O_2$ overshoot during recovery from exercise probably results from the overshoot of cardiac output. An overshoot of cardiac function during recovery from exercise has been reported in patients with coronary artery disease [6] and in those with chronic heart failure [5, 16]. In 2000, Tanabe et al. [5] evaluated the time-courses of cardiac output, stroke volume, and heart rate during recovery from maximal exercise at 1-min intervals in patients with LVEF of <45%. Although their sampling interval was rather long, these researchers found the overshoot phenomenon of cardiac output in 11 of the 30 patients, based on the definition of a further increase in cardiac output at 1 min of recovery above the cardiac output at peak exercise [5]. They noted a similar overshoot phenomenon of stroke volume despite a smooth decline in heart rate during recovery after exercise [5]. The O_2 -pulse ($\dot{V}O_2$ /heart rate) obtained from CPX is

known as a noninvasive estimate of stroke volume. In our study, the overshoot of O_2 -pulse during recovery from exercise was noted more frequently in patients with $\dot{V}O_2$ overshoot: eight patients (80.0%) of those with $\dot{V}O_2$ overshoot and 41 patients (21.5%) of those without $\dot{V}O_2$ overshoot ($p < 0.0001$). Thus, the overshoot of $\dot{V}O_2$ resulting from the overshoot of cardiac output can be attributed to the overshoot of stroke volume. In patients with coronary artery disease, the overshoot of stroke volume has been reported to occur chiefly from a significant decrease in end-systolic volume along with a relatively constant value of end-diastolic volume [6].

Stroke volume during recovery after exercise is controlled by several factors associated with cardiac contractility and afterload reduction, such as the sympathetic and parasympathetic nervous systems and the production of nitric oxide [17–20]. Perini et al. [18] demonstrated that the blood norepinephrine concentration maintained a similar level during a 50-s recovery period from moderate- to high-intensity exercise as that attained during the maximal exercise; thereafter, the norepinephrine concentration decreased exponentially. Exhaled nitric oxide output increases proportionally with exercise intensity and decreases rapidly during recovery in normal subjects [20]. Nitric oxide plays a significant role in vasodilation [20]. Thus, a relatively slow decrease in norepinephrine and an immediate afterload reduction associated with the

Fig. 1 Oxygen uptake ($\dot{V}O_2$) and minute ventilation ($\dot{V}E$) during exercise and during recovery from exercise in a patient (46-year-old male subject) who had a $\dot{V}O_2$ overshoot during recovery. The magnitude of the $\dot{V}O_2$ overshoot was 9.2% in this subject



production of nitric oxide during the early phase of recovery may have contributed to the overshoots of stroke volume and cardiac output and, subsequently, to the overshoot of $\dot{V}O_2$. Those patients with the $\dot{V}O_2$ overshoot had a lower peak $\dot{V}O_2$, lower $\Delta\dot{V}O_2/\Delta WR$, and higher $\dot{V}E/\dot{V}CO_2$ slope than those without it. We therefore suggest that the mismatch between cardiac contractility and afterload reduction is associated with impaired cardiopulmonary function during exercise.

Another factor relating to the overshoot of $\dot{V}O_2$ may be the increased oxygen debt during recovery from exercise arising from a high oxygen deficit during exercise in patients with left ventricular dysfunction. The increase in $\dot{V}O_2$ during exercise is impaired in patients with left ventricular dysfunction because of the insufficient increase in cardiac output. The continuance of exercise under this condition can only be accomplished through the body's utilization of oxygen stored in tissues and blood and preformed chemical energy stores in muscle cells as well as by the formation of ATP by the nonoxidative metabolism of carbohydrate substrates [21–24]. The impaired increase in $\dot{V}O_2$, which is reflected in low $\Delta\dot{V}O_2/\Delta WR$ and in $\dot{V}O_2$ flattening before the end of exercise, is accompanied by an increased oxygen requirement during recovery. This increased oxygen requirement during recovery is probably due to a compensatory mechanism in response to the excessive use of stored oxygen or preformed chemical energy stores during exercise; that is, the greater oxygen deficit developed during exercise is repaid during recovery [24]. This increased oxygen requirement during recovery from exercise may be partly responsible for the overshoot phenomenon of $\dot{V}O_2$ in patients with left ventricular dysfunction.

Study limitations

The prevalence of the $\dot{V}O_2$ overshoot depends partly on the constraints of the definition. Based on our experience, an overshoot of $\dot{V}O_2$ usually lasts approximately 1 min after the termination of exercise, with the peak value occurring at approximately 30 s into the recovery period, as is shown in Fig. 1 for a representative subject. Thus, here, we defined the overshoot phenomenon of $\dot{V}O_2$ when the average $\dot{V}O_2$ from 0 to 60 s after the termination of exercise was higher than the peak $\dot{V}O_2$ as well as by the visually identified overshoot of $\dot{V}O_2$.

In cardiac patients, the major populations who undergo exercise testing are those with coronary artery disease. Thus, we enrolled only patients with previous myocardial infarction in our study in an attempt to exclude those with normal left ventricular function. In all subjects, the duration from the onset of myocardial infarction to the day of CPX was 1808 days on average, which did not differ between the patients with $\dot{V}O_2$ overshoot and those without it. At the time of exercise testing, 19 patients among those without $\dot{V}O_2$ overshoot had significant coronary stenosis, and no patient with $\dot{V}O_2$ overshoot had significant coronary stenosis. The severity of heart failure among our patients was relatively mild: most of our patients were classified as the New York Heart Association functional class I or II. However, there was a wide variation in left ventricular function and other medical backgrounds among our patients, which would certainly have influenced the prevalence of overshoot phenomenon of $\dot{V}O_2$.

The overshoot of $\dot{V}O_2$ seems to be related to a mismatch between cardiac contractility and afterload reduction. Thus, we assume that the overshoot phenomenon of $\dot{V}O_2$ is not

specific to the etiology of cardiac disease—rather it would be observed in patients with impaired left ventricular dysfunction regardless of the types of cardiac disease, as reported by Daida et al. [25] and Cohen-Solal et al. [26]. In our study, cool-down pedaling at 0 W was performed after the cessation of exercise for 1 min in 53 of the 201 patients in order to prevent a sudden decrease in blood pressure and other adverse effects related to the parasympathetic reflex. This cool-down pedaling could have influenced, to some unknown degree, the magnitude and prevalence of the $\dot{V}O_2$ overshoot [27].

Conclusion

The $\dot{V}O_2$ overshoot during recovery from maximal exercise was found in 5% of patients with previous myocardial infarction. This phenomenon appears to be related to impaired cardiopulmonary function during exercise, possibly suggesting a transient mismatch between cardiac contractility and afterload reduction during exercise recovery in patients with left ventricular dysfunction.

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