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# The Patterns of Exercise Limitation After Myocardial Infarction: Role of Cardiopulmonary Exercise Testing with Gas Exchange Measurements

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**CHU, ET AL.: *The Patterns of Exercise Limitation After Myocardial Infarction: Role of Cardiopulmonary Exercise Testing with Gas Exchange Measurements.*** Exercise limitation is a common problem after myocardial infarction (MI). This study aims to explore the patterns of exercise limitation in patients who suffer from myocardial infarction as assessed by cardiopulmonary exercise testing (CPEXT) with gas exchange measurements. Fifty two consecutive stable patients who suffered from MI were recruited into the study about one month post-MI. Progressive incremental exercise was performed on a treadmill. Electrocardiogram, pulse oximetry and gas exchange parameters were continuously monitored. Patients were encouraged to exercise to symptom limitation, unless there were significant ischaemic changes on ECG. The patho-physiological mechanism causing exercise limitation was analyzed by a widely used diagnostic algorithm. Thirty two patients (61.5%) have cardiovascular limitation, of which 17 (32.7%) had angina and/or significant ECG changes at peak exercise and 15 (28.8%) had low oxygen-pulse. Three (5.8%) have unequivocal ventilatory limitation due to chronic obstructive pulmonary disease. Seventeen (32.7%) were not limited by recognizable organic factors. Distinct patterns of exercise limitation emerged in our group of post-MI patients which may have significant implications for cardiac rehabilitation. CPEXT plays an important role in elucidating the patho-physiological mechanisms limiting exercise in post-MI patients. (*J HK Coll Cardiol* 1999; 7:xx-xx)

*Cardiopulmonary exercise testing, gas exchange measurements, myocardial infarction, cardiac rehabilitation*

## 摘要

心肌梗死(MI)後運動受限是一個常見問題。該研究旨在應用測量氣體交換的心肺運動實驗(CPEXT)評估患者運動限制的方式。52個心梗後持續穩定的患者梗後大約一個月入選該研究採用逐步增加運動量的蹬車實驗。持續監測心電圖、每搏血氧及氣體交換參數。鼓勵患者運動到產生症狀為止，除非心電圖上有顯著的缺血改變導致運動受限的病理生理機制通過廣泛應用的診斷規則予以分析。32個患者(61.5%)有心血管受限其中17個(32.7%)在運動高峰時有心絞痛及/或顯著的心電圖改變，15個(28.8%)每搏氧含量低3個(5.8%)由於慢性阻塞性肺疾病有明顯通氣受限，17個(32.7%)不受明顯的臟器因素限制。在我們研究的梗後病人中具有不同方式的運動受限，它們在心臟康復中具重要意義。CPEXT在闡述梗後病人的運動受限病理生理機制方面具重要意義。

關鍵詞:心肺運動實驗 氣體交換測量 心肌梗死 心臟康復

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## Introduction

Exercise limitation is a common problem after myocardial infarction (MI). In recent years, there is a growing enthusiasm in rehabilitating post-MI patients. One of the major foci in cardiac rehabilitation is exercise training. Exercise tolerance is an important outcome measure in a cardiac rehabilitation programme. The causes of exercise limitation in post-MI patients are usually a result of the development of signs and symptoms of myocardial ischaemia, such as anginal symptoms<sup>1</sup>. Some patients may have effort-related hypotension which reflects underlying significant coronary artery disease, left mainstem disease or left ventricular (LV) systolic dysfunction. After proper exercise endurance training, exercise capacity can be improved in patients with impaired LV function<sup>2</sup>. However, whether LV ejection fraction is improved as a result of aerobic training in these patients is controversial<sup>3</sup>. Little local data were published regarding the patho-physiology of exercise limitation in post-MI patients. The patho-physiology of exercise limitation in post-MI patients is likely to be of important implications as it might affect the strategy one employs for rehabilitating the patient. Moreover, a better understanding of the patho-physiology of exercise limitation allows us to interpret the outcome of rehabilitation in a more meaningful way.

Cardiopulmonary exercise testing (CPEXT) using continuous gas exchange measurements has been used to evaluate exercise limitation<sup>4,5</sup>. CPEXT has the unique advantage of being able to objectively evaluate exercise tolerance and also to give an indication of the patho-physiological mechanism causing exercise intolerance. CPEXT has been employed in the assessment of heart failure<sup>6,7,8</sup> and improves our understanding of exercise limitation in heart failure.

The aim of the present study is to describe, in a group of post-MI survivors, the mechanisms of exercise limitation and to explore if different patterns of limitation exist, using CPEXT with gas exchange measurements.

## Methods and Materials

From January to November 1998, consecutive patients who suffered from acute MI were continuously recruited if they survived the acute phase and consented to phase II cardiac rehabilitation. CPEXT was performed about 1 month after acute MI, when the patient was stabilized and was ready to undergo exercise

training. Patients with unstable heart failure or frequent angina were excluded.

Beta-blockers were stopped two days prior to CPEXT, all the other regular medications were continued at the usual dosages, including nitrates, angiotensin converting enzyme inhibitors, aspirin, diuretics, etc. Spirometry with measurements of forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC) and maximum voluntary ventilation (MVV) was performed prior to the test in each patient.

## Exercise protocol

The subjects performed incremental exercise testing on a treadmill (Series 2000; Marquette Electronics Inc; Milwaukee, Wisconsin) with the following exercise protocols<sup>9,10</sup>. Patients were divided into 2 groups according to their body weight (less than 60kg or greater than or equal to 60kg) before choosing the test protocol (Table 1a and 1b). After a resting period of at least 5 minutes, the exercise test would be started

**Table 1a. Treadmill exercise protocol for body weight less than 60kg**

Stage (2 minute interval)	Speed (mph)	Gradient (%)
1	1.8	0
2	1.8	5
3	2.6	7
4	3.0	9
5	3.3	11
6	3.5	13
7	3.7	15
8	3.8	17
9	3.9	19
10	3.9	21

**Table 1b. Treadmill exercise protocol for body weight equals to or greater than 60kg**

Stage (2 minute interval)	Speed (mph)	Gradient (%)
1	1.5	0
2	1.5	5
3	2.2	7
4	2.5	9
5	2.8	11
6	2.9	13
7	3.0	15
8	3.1	17
9	3.2	19
10	3.3	21

with a graded increase of the speed and gradient of the treadmill machine at 2 minute intervals at each stage. This corresponded to a steady and small increase in workload performed by the patient. At termination of the test, the patient would enter into a recovery period during which monitoring and measurements would be continued for at least 5 minutes.

Tests were terminated in the following situations: reaching maximal exercise capacity, severe chest pain, oxygen desaturation, dizziness, severe dyspnoea or fatigue, significant ST depression or elevation or T wave inversion, significant arrhythmias, appearance of advanced heart block, symptomatic claudication, systolic blood pressure (SBP) greater than 250mmHg, diastolic blood pressure (DBP) greater than 120mmHg, a sustained fall in SBP for more than 20mmHg or if the subject requested to stop.

### Monitoring and measurements

Pulse oximetry (Oxypleth; Novamatrix Medical Systems Inc; Wallingford, Connecticut) and 12-lead ECG (Case 16; Marquette Electronics Inc; Milwaukee, Wisconsin) were continuously monitored and recorded. Gas exchange was continuously monitored with pneumotachometer, zirconium oxygen analyzer and infrared carbon dioxide analyzer on a breath-by-breath basis (MedGraphics D-series CPX/MAX; Medical Graphics Corp; St. Paul, MN). The pneumotachometer was calibrated with a 3-litre syringe prior to each test and gas analyzers calibrated with standard test gases with two-point calibration. The following gas exchange and cardiovascular indices were obtained or derived: oxygen uptake ( $\text{VO}_2$ , STPD), carbon dioxide output ( $\text{VCO}_2$ , STPD), tidal volume (TV, BTPS), minute ventilation ( $\text{VE}$ , BTPS), respiratory rate (RR), heart rate (HR), breathing reserve ( $1 - \text{V}_E/\text{MVV}$ ), heart rate reserve (HRR), ventilatory equivalents ( $\text{V}_E/\text{VO}_2$ ,  $\text{V}_E/\text{VCO}_2$ ) and oxygen-pulse ( $\text{VO}_2/\text{HR}$ ). Anaerobic threshold (AT) were determined by the V-slope method<sup>11</sup>.

### Interpretation

The results were interpreted using widely adopted diagnostic algorithms<sup>12,13</sup>, compared to expected responses during exercise<sup>14,15</sup>. Multiple physiological parameters were analyzed in order to discern the most important limiting mechanism to exercise. Briefly, for example, cardiac limitation is characterized by a low peak  $\text{VO}_2$ , a slow rise of  $\text{VO}_2$  with respect to work rate, early AT, low oxygen-pulse and ECG changes with acute ischaemia<sup>7,8</sup>. Ventilatory and gas exchange limitation (e.g. chronic obstructive pulmonary disease, COPD) is characterized by low peak  $\text{VO}_2$ , high  $\text{V}_E/\text{MVV}$ , high HRR, high  $\text{V}_E/\text{VO}_2$  and  $\text{V}_E/\text{VCO}_2$ <sup>16,17</sup>.

Patients who did not reach any of the traditional limits despite coaching were considered not to have an organic limitation, but unaccustomed to exercise with submaximal test results<sup>18</sup>.

### Statistical analysis

Categorical data were expressed as frequencies and parametric data as mean and standard deviation (SD). Comparisons of parametric data between diagnostic subgroups were made with one-way analysis of variance (ANOVA) taking  $p < 0.05$  as significant; post hoc comparisons were made by Student's t-test with Bonferroni's correction. Comparison of non-parametric data between subgroups were made by Kruskal-Wallis test with significance level at  $p < 0.05$ , and post hoc analysis by Mann-Whitney test with Bonferroni's correction.

### Results

A total of 52 patients were recruited into the study. Ten (19.2%) were females and 42 (80.8%) were male. The mean age was 62.4 (SD 10.3) years and the mean body mass index (BMI) was 23.3 (SD 3.2)  $\text{kgm}^{-2}$ . All performed incremental exercise until symptom limitation or a stop-test criterion was met. Twenty-four (46.2%) stopped because of fatigue, 17 (32.7%) because of dyspnoea, 8 (15.4%) had angina with significant ECG changes, 3 (5.7%) had other miscellaneous symptoms (dry mouth or dizziness).

Exercise responses for the whole group were as follows. The mean  $\text{VO}_2$  at peak exercise achieved was 56.3% (SD 16.5%) of predicted maximum. Mean AT was 44.1% (SD 14.3%) of predicted maximal  $\text{VO}_2$  ( $\text{VO}_{2\text{max}}$ ). Breathing reserve (BRR) was 45.8% (SD 16.2%) of MVV and heart rate reserve (HRR) was 19.7% (SD 13.6%) of predicted maximum HR ( $\text{HR}_{\text{max}}$ ). Oxygen-pulse was 71.1% (SD 22.3%) of predicted maximum.

The key patho-physiological mechanisms limiting exercise were analyzed. Three (5.8%) had unequivocal ventilatory limitation due to co-existing COPD, and were classified as 'pulmonary limitation'. The limitation seemed to be mechanical rather than associated purely with gas exchange abnormality, with minute ventilation at peak exercise approaching the direct MVV. Seventeen (32.7%) did not have recognizable organic limitation at peak exercise, and were classified as the 'unaccustomed' group. Thirty-two (61.5%) had cardiovascular limitation (CVS limitation), 17 (32.7%) had either positive ECG changes or angina, 15 (28.8%) were thought to be limited by

low stroke volumes, as indicated by low oxygen-pulses.

Age did not differ significantly between the 'CVS'(mean 63.2 years; SD 8.9 years), 'pulmonary' (mean 67.7 years; SD 1.5 years) or 'unaccustomed' (mean 60.1 years; SD 13.2 years) groups (p=0.53). Peak exercise VO<sub>2</sub> also did not differ significantly between the 'CVS' (mean 55.2%; SD 16.9%), 'pulmonary' (mean 47.7%; SD 14.7%) or 'unaccustomed' (mean 59.9%; SD 15.8%) groups (p=0.42). AT did not show statistically significant difference (p=0.06) between 'CVS' (mean 40.7%; SD 13.7%), 'pulmonary' (mean 43.3%; SD 13.1%) and 'unaccustomed' (mean 51.8%; SD 13.9%), although there was a trend towards a higher AT in the 'unaccustomed' group.

Of all the physiological parameters assessed, significant differences existed between the three subgroups in BRR (p=0.01), HRR (p<0.001) and oxygen-pulse (p=0.002), as expected. Post hoc analysis confirmed that the 'pulmonary' group has significantly lower BRR (mean 4.3%; SD 7.5%) than the 'CVS' group (mean 46.3%; SD 13.2%) and the 'unaccustomed' group (mean 52.2%; SD 11.2%) with p < 0.001 and p=0.002 respectively. HRR was significantly lower (p<0.001) in the 'CVS' group (mean 13.8%; SD 12.7%) versus the 'unaccustomed' group (mean 30.8%; SD 7.9%). Oxygen-pulse at peak exercise was also significantly lower (p=0.002) in the 'CVS' group (mean 64.3%; SD 18.7%) versus the 'unaccustomed' group (mean 86.2%; SD 22.7%). Table 2 summarizes the results.

## Discussion

Our results show that it is common for patients who suffered an episode of acute MI to have exercise limitation, with a mean VO<sub>2</sub> of about 56% predicted. However, the mechanisms leading to exercise

intolerance are heterogeneous. In our group, closed to 40% of post-MI patients have exercise limitation resulting from factors other than cardiovascular limitation. Of those who have cardiovascular limitation, slightly more than half of them were limited by active ischaemia on exercise; the remaining have exercise limitation related to reduced oxygen-pulse, reflecting a reduction in stroke volume. Three of our patients had co-existing COPD which was the key limiting factor causing the exercise limitation, rather than ischaemia or low stroke volume. About 30% of our patients did not have an organic factor limiting exercise on CPEXT and we classified them as unaccustomed to exercise. The above mechanisms produce distinct pathophysiological patterns and can be delineated by CPEXT with gas exchange measurements.

Traditionally, cardiologists assess exercise capacity by performing exercise testing and estimate the aerobic capacity by the stage of exercise the patient reached. The capacity is expressed by multiples of metabolic equivalent (MET), which equals 3.5ml O<sub>2</sub>min<sup>-1</sup>kg<sup>-1</sup>. This is presumed to be the resting oxygen consumption of a 70kg, 40 year old man, which by no means reflect the resting metabolic rate of the individual patient. During 'cardiac' stress test, ECG and blood pressure were monitored, the rate-pressure product is used as a surrogate of the stress imposed on the heart. However, physical exercise does not only place stress on the heart. It also places stress on, and requires efficient coupling of the cardiovascular system and the respiratory systems to provide the necessary substrate (oxygen) to the exercising skeletal muscles, and to remove waste product (carbon dioxide). The ability of the cardiovascular and respiratory systems to respond to the stress of exercise (aerobic capacity) is a measure of their physiological competence, and the ability to sustain exercise depends on an integrated response from

**Table 2. Comparisons of cardiopulmonary and bioenergetic responses of three subgroups**

	Cardiovascular limitation	Pulmonary limitation	Unaccustomed to exercise	p-value*
VO <sub>2</sub>	55.2 (16.9) %	47.7 (14.7) %	59.9 (15.8) %	NS
AT	40.7 (13.7) %	43.3 (13.1) %	51.8 (13.9) %	NS
BRR	46.3 (13.2) %	4.3 (7.5) % <sup>a</sup>	52.2 (11.2) %	0.01
HRR	13.8 (12.7) % <sup>b</sup>	18.6 (9.5) %	30.8 (7.9) % <sup>b</sup>	<0.001
O <sub>2</sub> -pulse	64.3 (18.7) % <sup>b</sup>	57.7 (12.0) %	86.2 (22.7) % <sup>b</sup>	0.002

(Abbreviations: AT = anaerobic threshold; BRR = breathing reserve; HRR = heart rate reserve; O<sub>2</sub>-pulse = oxygen pulse; NS = not significant; \* = significance level with ANOVA or Kruskal-Wallis test; a = pulmonary group statistically different from the other two groups with post hoc analysis; b = cardiovascular group statistically different from unaccustomed group with post hoc analysis; figure in parenthesis = standard deviation)

the cardiopulmonary and musculoskeletal systems. Diseases affecting the heart, peripheral and pulmonary circulations, the lungs and the skeletal muscles may cause exercise intolerance and can affect gas exchange measured at the mouth. Excellent reviews of exercise physiology have been published<sup>12,19</sup>. CPEXT with gas exchange measurement has the unique advantage of being able to directly measure aerobic capacity and to delineate the mechanism of exercise limitation.

If only 'cardiac' stress test was performed in our group of post-MI patients, probably only those with exercise-induced ischaemia (33%) would be positively identified. CPEXT further breaks down the rest of the group into those with reduced stroke volumes, COPD and those unaccustomed to exercise. Aerobic capacity was also directly measured by CPEXT rather than estimated.

The current study has four implications. First, little local data were published on the causes of exercise limitations in post-MI patients before cardiac rehabilitation. It is a common experience that there is an improvement in aerobic capacity after cardiac rehabilitation. However, there is seldom a delineation of the patho-physiological mechanism underlying the impairment and the subsequent improvement. We caution against the use of  $VO_2$  alone in evaluating the success of a cardiac rehabilitation programme, without also examining the cause of limitation. The cause of exercise limitation is likely to be heterogeneous and the mechanisms for improvement heterogeneous too. An improvement in  $VO_2$  after cardiac rehabilitation may simply be obtained by getting a patient to accustom to exercising, rather than attributable to a specific training effect of the training programme.

Second, patients with multiple co-morbidities that might affect exercise tolerance can be evaluated by CPEXT to delineate the limiting factor to exercise. This is particularly relevant to post-MI patients as MI shares common risk factors for other diseases that might limit exercise, e.g., COPD or peripheral vascular disease. Distinct gas exchange and bioenergetic patterns can pinpoint the limiting factor<sup>20</sup> and hence allow prioritization of treatment in individual patient. The same is true for other processes complicating the exercise response, e.g., deconditioning<sup>13</sup>, psychological factors<sup>18</sup> or obesity<sup>21</sup>.

Third, CPEXT may help individualization of treatment plan and rehabilitation. For example, although patients who are limited either by low stroke volume or by cardiac ischaemia are 'cardiac limited', the management strategies are likely to be different. Patients with co-existing COPD who have predominant ventilatory limitation to exercise should be jointly

managed with a chest physician.

Fourth, CPEXT would be a very valuable research tool in evaluating various components of a rehabilitation programme as the mechanism of improvement in exercise capacity can be clearly elucidated by CPEXT. The core components of training which leads to improvement of exercise capacity can be more readily identified.

Our study has several limitations. First, the absolute number of patients was relatively small and we could only recruit those patients who consented to cardiac rehabilitation. Therefore the result may not be generalized to all post-MI patients. Second, the 'unaccustomed' group is likely a heterogeneous group. The reason why the patient did not exercise to any discernable physiological limit could be due to many factors (e.g., anxiety, poor motivation). Unfortunately, the use of CPEXT alone cannot further breakdown this subgroup. Third, we have attempted to classify the limiting mechanisms according to the key and unequivocal abnormalities detected. However, CPEXT can bring to light many co-existing abnormalities in individual patients, although not all of them are key limiting factors.

In conclusion, we have found CPEXT very helpful in delineating the mechanisms of exercise limitation in our group of post-MI patient before entering into phase II cardiac rehabilitation. It can potentially help individualization and prioritization of management. With more experience of its application, it would prove to be a valuable clinical and research tool.

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