

Dissociation between muscle metabolism and oxygen kinetics during recovery from exercise in patients with chronic heart failure

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Abstract

Objective—To estimate muscle metabolism and oxygen delivery to skeletal muscle in patients with chronic heart failure.

Methods—13 patients with chronic heart failure and 15 controls performed calf plantar flexion for six minutes at a constant workload of 50% of one repetition maximum. During recovery from exercise, skeletal muscle content of oxygenated haemoglobin (oxy-Hb) and the level of phosphocreatine (PCr) were measured by near-infrared spectroscopy and ^{31}P -magnetic resonance spectroscopy, respectively.

Results—The mean (SD) time constants of PCr and oxy-Hb during recovery from exercise were significantly greater in patients with chronic heart failure than in normal subjects (τ PCr: 76.3 (30.2) s v 36.5 (5.8) s; τ oxy-Hb: 48.3 (7.3) s v 30.1 (7.7) s; $p < 0.01$). Both time constants were similar in normal subjects, while the τ PCr was significantly greater than the τ oxy-Hb in patients with chronic heart failure.

Conclusions—The slower recovery of PCr compared with oxy-Hb in patients with chronic heart failure indicates that haemoglobin resaturation is not a major rate limiting factor of PCr resynthesis. It is suggested that muscle metabolic recovery may depend more on oxygen utilisation than on haemoglobin resaturation or oxygen delivery in patients with chronic heart failure. (*Heart* 2000;83:161-166)

Keywords: near-infrared spectroscopy; ^{31}P -magnetic resonance spectroscopy; chronic heart failure; exercise tolerance

Studies have shown that the degree of exercise intolerance in patients with chronic heart failure is not significantly correlated with the extent of the central haemodynamic disturbance.^{1,2} This means that exercise capacity is not limited only by haemodynamics but also by peripheral abnormality. Studies using phosphorus-31 nuclear magnetic resonance spectroscopy (^{31}P -MRS) have shown that peripheral muscle metabolic abnormalities during exercise are important contributors to exercise intolerance in patients with chronic heart failure.³⁻⁸ Recent studies using near-infrared spectroscopy (NIRS) to evaluate skeletal muscle oxygen kinetics have shown that peripheral muscle oxygenation is impaired during systemic exercise in patients with chronic heart failure.^{9,10} Both muscle metabolism and muscle oxygen kinetics are important determinants of exercise capacity and these factors have been separately evaluated in patients with chronic heart failure. In normal subjects, only a few studies have assessed both muscle metabolism and oxygen kinetics. McCully *et al* simultaneously measured oxygenated haemoglobin (oxy-Hb) and phosphocreatine (PCr) recovery after submaximal exercise in normal subjects using NIRS and ^{31}P -MRS respectively, and found that the time constants of these indices were similar.¹¹ They suggested that oxy-Hb recovery is rate limiting for ATP synthesis, evaluated as the rate of PCr recovery after submaximal exercise. In patients with chronic heart failure, both skeletal muscle

metabolism and oxygen delivery are impaired and these abnormalities are potential contributors to exercise intolerance. Therefore the combination of ^{31}P -MRS and NIRS would appear to be useful for assessing exercise intolerance. However, these methods have not been used in combination in patients with chronic heart failure during exercise.

To elucidate the relation between muscle metabolism and oxygen kinetics, we measured PCr and oxy-Hb during recovery from submaximal constant load exercise in patients with chronic heart failure and in normal subjects. We also investigated the relations between these factors and systemic exercise capacity.

Methods

SUBJECTS

We studied 15 patients with chronic heart failure, mean (SD) age 58 (8) years, and 16 age matched normal subjects. The mean ejection fraction of the patients with chronic heart failure measured by radioisotope scintigraphy was 29 (13)%. Eight had symptoms consistent with New York Heart Association class II and seven with class III. Heart failure was attributed to idiopathic dilated cardiomyopathy in all patients. At the time of the study all patients were receiving diuretics, seven were receiving β blockers, and 11 were receiving angiotensin converting enzyme inhibiting agents. Six patients were taking digitalis. Patients with peripheral vascular disease were excluded from the study. The normal subjects were sedentary

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healthy volunteers, mean age 49 (11) years, with no known medical problems. Written informed consent was obtained from each subject.

SYSTEMIC EXERCISE

Upright bicycle exercise was performed with a ramp protocol (15 W/min after a three minute warm up at 0 W) using an electromechanical bicycle ergometer (Corval 400, Lode, Groningen, Holland). During exercise, respiratory gas analysis was performed by a breath by breath apparatus (Aeromonitor AE-280, Minato Medical Science, Osaka, Japan). Peak oxygen uptake (peak $\dot{V}O_2$) and the ventilatory anaerobic threshold were determined by the V slope method described by Beaver and Wasserman.¹²

LOCAL EXERCISE

Subjects performed supine plantar flexion of the right calf muscle. Their right foot was fixed on a pedal shaped lever attached to a basket in which appropriate weights were placed. The subjects were immobilised on the platform by a system of Velcro straps at the knee, ankle, chest, and shoulders. Before the study, muscle strength was measured in all subjects by the one repetition maximum (1 RM) method, which measures the maximum weight that can be lifted only once.

Using magnetic resonance imaging, the maximum calf flexor muscle cross sectional area (MCA) was determined. Conventionally there have been two ways to decide the workload in skeletal muscle exercise, as a function of MCA and MVC (maximal voluntary contraction). We used 1 RM as MVC and the workload was adjusted to 50% of 1 RM. Plantar flexion was performed once every 1.5 seconds for six minutes against a pedal. Measurements were obtained from the one minute rest period before exercise through the six minute recovery period after exercise.

PHOSPHORUS-31 nuclear magnetic resonance spectroscopy

We obtained ³¹P-MRS measurements using an 80 mm surface coil in a 55 cm bore, 1.5 Tesla superconducting magnet (Magnetom H15, Siemens, Erlangen, Germany). Shimming was adjusted using a proton signal from water. Spectra were obtained with a pulse width of 500 ms, a transmitter voltage of 20 V, and a repetition time of 1000 ms, and four scans were performed and averaged for each spectrum. PCr is expressed as $[PCr]/([PCr] + [Pi])$, where Pi is inorganic phosphate. The degree of PCr change (PCr depletion) was calculated as: PCr depletion = (rest PCr - peak PCr) / rest PCr.

The muscle pH was calculated from the changes in the chemical shifts of Pi relative to PCr as previously described.¹³ As previous studies have shown the appropriateness of using monoexponential fitting to describe the rate of PCr recovery,^{14,15} we estimated it using time constants. PCr recovery after exercise was fitted to a single exponential curve obtained by least squares regression, and the time constant for PCr recovery (τ PCr) was calculated as follows: $[PCr] = C1 + C2(1 - e^{-t/\tau})$, where [PCr] is

the PCr concentration, C1 is the initial [PCr], C2 is the difference between the final and initial [PCr], t is time, and k is the rate constant ($1/k = \tau$).

NEAR-INFRARED SPECTROSCOPY

NIRS was performed with a dual wave spectrometer (HEO100, Omron, Tokyo, Japan), a tissue oximeter that uses a two wavelength light emitting diode (LED), with wavelengths of 760 and 840 nm, as a light source. The basic principles of NIRS¹⁶ and in vitro results¹⁷ obtained with this tissue oximeter have been described previously. The NIRS probe, which has a photodiode in the centre and a near-infrared LED on each side, was attached to the medial portion of the calf muscle and fixed with a rubber strap to prevent displacement during exercise. All studies were performed using the same auto gain settings on the spectrometer. Subjects rested during the one minute gain setting. After exercise begins, oxy-Hb saturation is depleted from the stable baseline and then reaches a plateau indicating the balance of oxygen demand and supply in muscle tissue. After exercise is completed, the oxy-Hb saturation increases until it reaches a plateau. Data sampled every 0.5 seconds were fed into a personal computer and saved as a file. As in previous studies discussing recovery rate of oxy-Hb,^{11,18} we evaluated the recovery kinetics by means of time constants. The oxy-Hb recovery was fitted to a single exponential curve and the time constant for oxy-Hb recovery (τ oxy-Hb) was calculated as the τ PCr. Measurements by ³¹P-MRS and NIRS were obtained with the same protocol on alternate days within a week.

REPRODUCIBILITY

We have already reported the reproducibility of MRS data during local muscle exercise.¹⁹ Furthermore, we confirmed the reproducibility of PCr recovery with the same protocol in seven patients with chronic heart failure (coefficient of variation 8%). Walter *et al* also reported the good reproducibility of τ of PCr recovery.²⁰ To investigate the reproducibility of the NIRS data, five subjects underwent two tests within a one week period. The coefficient of variation between the two tests was 14%, which was small enough for the present study.

STATISTICAL ANALYSIS

All data were entered into a database on a personal computer and analysed with a commercial statistical package (Stat View-J 4.21, Abacus Concepts Inc and Igor, Wave Metrics). Significant differences between group means were analysed by a non-paired *t* test. Differences among the τ PCr and the τ oxy-Hb were analysed by analysis of variance for within and between patients with chronic heart failure and normal subjects. A level of $p < 0.05$ was considered statistically significant. Data are expressed as means (SD).

Table 1 Haemodynamic and respiratory gas responses to maximal bicycle exercise

	Normal subjects (n = 15)	Patients with CHF (n = 13)
Peak heart rate (beats/min)	169 (15)	146 (23)*
Peak $\dot{V}O_2$ (ml/min/kg)	30.0 (6.7)	19.2 (2.7)*
AT (ml/min/kg)	18.8 (3.9)	12.8 (1.8)*
Peak workload (W)	185 (53)	106 (15)*

Values are means (SD).

* $p < 0.01$ v normal subjects.

AT, anaerobic threshold; CHF, chronic heart failure; $\dot{V}O_2$, oxygen consumption.

Table 2 Indices of local exercise

	Normal subjects (n = 15)	Patients with CHF (n = 13)
1 RM (kg)	43.5 (9.6)	35.9 (10.7)
MCA (cm ²)	52.9 (9.2)	45.5 (5.9)*
1 RM/MCA	0.78 (0.34)	0.82 (0.18)
Muscle PCr		
Rest	0.95 (0.02)	0.91 (0.05)
Peak	0.48 (0.06)	0.40 (0.01)*
PCr depletion	0.50 (0.06)	0.56 (0.09)*
τ PCr (s)	36.5 (5.8)	76.3 (30.2)*
Muscle pH		
Rest	7.00 (0.10)	7.05 (0.08)
Peak	6.75 (0.03)	6.56 (0.01)*
τ Oxy-Hb (s)	30.1 (7.7)	48.3 (7.3)*

Values are means (SD).

* $p < 0.05$ v normal subjects.

CHF, chronic heart failure; MCA, maximum muscle cross sectional area; oxy-Hb, oxyhaemoglobin; PCr, phosphocreatine; 1 RM, one repetition maximum method.

Results

SYSTEMIC EXERCISE

The peak heart rate, peak $\dot{V}O_2$, and anaerobic threshold were significantly greater in the normal subjects than in the patients with chronic heart failure (table 1). The maximum workload was also greater in the normal subjects than in the patients with chronic heart failure.

LOCAL EXERCISE

Three subjects (two patients and one normal subject) could not complete the six minute exercise and they were excluded from the statistical analysis. As shown in table 2,

1 RM tended to be greater in normal subjects than in patients with chronic heart failure but there was no statistical difference. The MCA was significantly greater in normal subjects. The 1 RM/MCA was similar in both groups.

³¹P-MRS MEASUREMENTS

The resting muscle PCr and pH value were similar in both groups (table 2). Peak muscle PCr and peak pH were significantly lower in patients with chronic heart failure than in normal subjects. Representative data of ³¹P-MRS and NIRS spectra after exercise in a patient and a normal subject are shown in fig 1. The rate of PCr recovery, evaluated as the τ PCr, was significantly greater in patients with chronic heart failure than in normal subjects (table 2), indicating that PCr recovery was impaired in patients with chronic heart failure.

In fig 2, normal subjects showed a significantly smaller value of the τ PCr and greater anaerobic threshold, while patients with chronic heart failure showed greater τ PCr and lower anaerobic threshold (left panel). The τ PCr was significantly correlated with anaerobic threshold when both groups were included ($R = 0.54$, $p < 0.01$).

NIRS MEASUREMENTS

The rate of oxy-Hb recovery evaluated as the τ oxy-Hb was significantly greater in patients with chronic heart failure than in normal subjects (table 2). As well as the τ PCr, normal subjects showed significantly smaller τ oxy-Hb and greater anaerobic threshold, while patients with chronic heart failure showed greater τ oxy-Hb and lower anaerobic threshold (fig 2, right panel). The τ oxy-Hb was correlated with the anaerobic threshold when both groups were included ($R = 0.70$, $p < 0.01$).

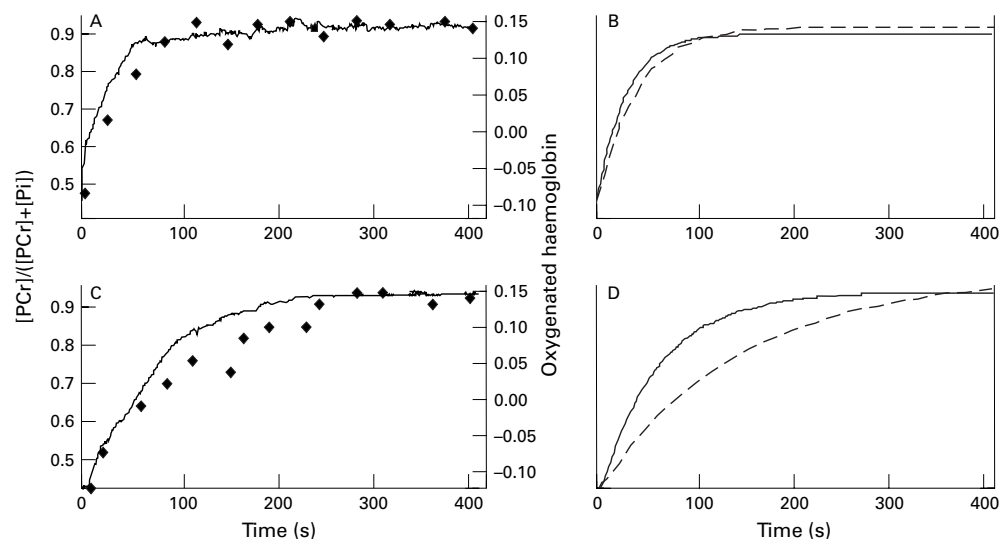


Figure 1 Representative spectra showing recovery of phosphocreatine (PCr, filled symbols) and oxygenated haemoglobin (oxy-Hb, solid line) in normal subjects (A) and patients with chronic heart failure (C). Each dataset is fitted with a single exponential curve (B and D). A dotted line indicates the fitting curve of PCr and a solid line shows that of oxy-Hb. The time constants are as follows: B (normal subject): τ oxy-Hb = 28 s; τ PCr = 33 s. D (patient with chronic heart failure): τ oxy-Hb = 53 s; τ PCr = 110 s. τ oxy-Hb, time constant for oxy-Hb resaturation; τ PCr, time constant for PCr resynthesis.

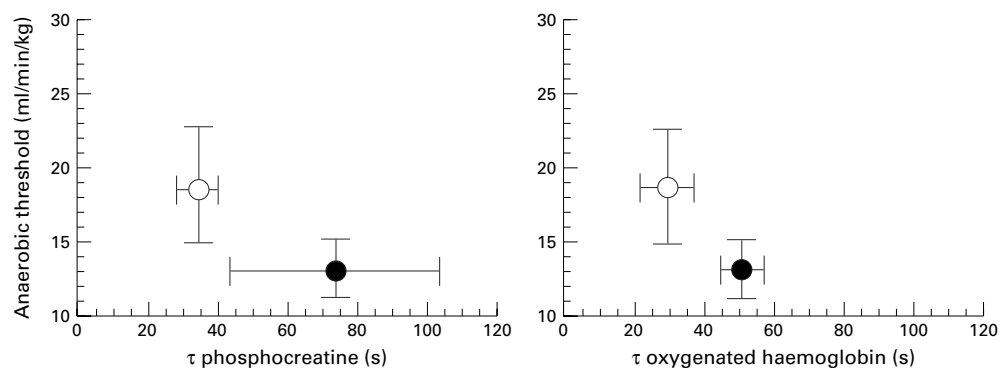


Figure 2 Relation between the time constants and the anaerobic threshold in patients with chronic heart failure (filled circles) and normal subjects (empty circles). Left panel shows correlation between anaerobic threshold and τ PCr and right panel shows anaerobic threshold and τ oxy-Hb.

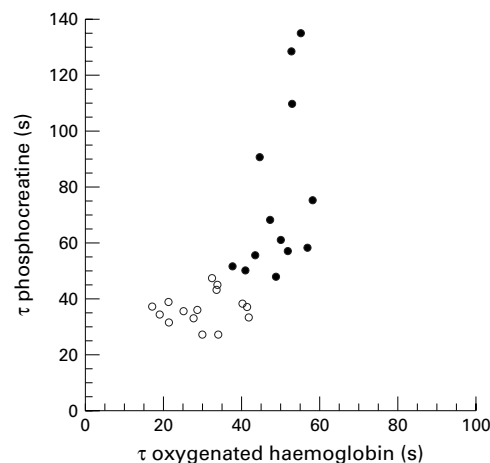


Figure 3 The relation between τ PCr and τ oxy-Hb presented by two dimensional plotting. Empty circles indicate normal subjects and filled circles indicate patients with chronic heart failure.

COMPARISON BETWEEN ^{31}P -MRS AND NIRS MEASUREMENTS

These results are shown in fig 3. The τ PCr and the τ oxy-Hb was similar in normal subjects. In patients with chronic heart failure, however, the τ PCr was significantly greater than the τ oxy-Hb. Moreover, the difference in the τ PCr between the two groups was remarkably greater than the difference in the τ oxy-Hb. The τ PCr in patients with chronic heart failure showed a wide variance.

Discussion

MAJOR FINDINGS

Both the τ PCr and the τ oxy-Hb after exercise were greater in patients with chronic heart failure than in normal subjects. These time constants correspond to PCr resynthesis and haemoglobin resaturation.¹¹ Thus our present findings indicate that PCr resynthesis and haemoglobin resaturation were impaired after exercise in patients with chronic heart failure. In normal subjects, the τ oxy-Hb was similar to the τ PCr, which was consistent with previous findings.¹¹ It suggested that the rate of haemoglobin resaturation matches the rate of oxygen utilisation after exercise to resynthesise PCr in skeletal muscle in normal subjects. However, the τ PCr was significantly greater than the τ oxy-Hb in patients with chronic heart failure in

the present study, indicating that PCr resynthesis was significantly delayed compared with haemoglobin resaturation. Therefore the rate of haemoglobin resaturation does not appear to be a major determinant of muscle metabolic recovery, evaluated as PCr resynthesis in patients with chronic heart failure.

A possible reason for the significant delay in PCr resynthesis in muscles is impaired oxygen utilisation in muscle mitochondria or impaired oxygen diffusion to mitochondria from capillaries. In other words, muscle metabolic recovery may depend to a greater extent on the capacity of oxygen utilisation rather than on haemoglobin resaturation or oxygen delivery in patients with chronic heart failure.

^{31}P -MRS MEASUREMENTS

During recovery period after exercise, the rate of PCr recovery represents the maximum oxidative capacity.^{6, 16} In the present study, PCr resynthesis was impaired after submaximal exercise in patients with chronic heart failure, and the rate of PCr resynthesis, evaluated as the τ PCr, may contribute to the anaerobic threshold. These findings suggest that the oxidative capacity in skeletal muscle is impaired and may affect performance during systemic exercise in patients with chronic heart failure.

Another possible reason for the greater τ PCr is more intense exercise in patients with chronic heart failure. However, we corrected the workload using 1 RM. There was no significant difference in 1 RM per MCA in normal subjects and patients with chronic heart failure, which means that the intensities of workloads per muscle area in both groups were similar (table 2). In addition, table 2 shows that the difference in the τ PCr between two groups is much greater than the difference in the PCr depletion. This suggests that the contribution of greater PCr depletion to the delayed τ PCr was small in patients with chronic heart failure. McCully *et al* also reported that low muscle pH (under 7.0) slowed the rate of PCr recovery as a result of the effect of H^+ concentration.¹¹ Therefore a greater decrease in muscle pH may affect the delayed τ PCr in patients with chronic heart failure. However, in the present study all

patients showed a greater τ PCr than did normal subjects within the pH range 6.58 to 6.75.

NIRS MEASUREMENTS

Our study showed that haemoglobin resaturation was impaired after submaximal exercise in patients with chronic heart failure. What is the meaning of this impaired haemoglobin resaturation? The rate of haemoglobin resaturation after exercise is believed to be determined by oxygenated blood flow in muscles and muscle oxygen uptake. Accelerated postexercise oxygen uptake (oxygen debt) may have been responsible for the delayed haemoglobin resaturation in patients with chronic heart failure. Belardinelli *et al* reported similar findings.¹⁰ Furthermore, previous studies have shown that cardiovascular stress is minimal and muscle perfusion is similar during small muscle mass exercise in patients with chronic heart failure and in normal subjects.^{1-4, 21} Thus the rate of haemoglobin resaturation might be determined mainly by excessive muscle oxygen uptake rather than by reduced blood flow in patients with chronic heart failure. However, if the τ oxy-Hb is determined by muscle oxygen uptake, the rate of haemoglobin resaturation should be consistent with the rate of PCr resynthesis because the major source of oxygen debt is PCr depletion.¹³ The present study showed a significant delay in PCr resynthesis compared with haemoglobin resaturation in patients with chronic heart failure.

One possible explanation for the delayed haemoglobin resaturation is that the resaturation may be affected by the oxygen debt but may occur earlier than repayment of the oxygen debt or PCr depletion, because of impaired oxygen utilisation of muscle mitochondria or impaired oxygen diffusion to mitochondria from capillaries. The second possible reason for the delayed haemoglobin resaturation is that it may mainly reflect an impaired oxygenated blood flow after exercise in patients with chronic heart failure. It has been shown that muscle blood flow remains normal even in patients with chronic heart failure during small muscle mass exercise. However, measurements in previous studies were performed by venous occlusion plethysmography or catheter based measurements, which evaluate non-selective blood flow. Plethysmography measures the whole limb blood flow, including the flow in skin and non-exercising muscles. A catheter is usually inserted into the femoral vein and also provides the whole limb blood flow measurement. In contrast, NIRS provides information about the flow in localised exercising muscle. It is possible that perfusion to exercising muscle is selectively impaired in patients with chronic heart failure.

CLINICAL IMPLICATIONS

Our study showed that muscle metabolism and oxygen delivery are two important factors that determine muscle function in patients with chronic heart failure. Estimating both variables with ³¹P-MRS and NIRS independently, we could acquire detailed information about the

mechanism that predominantly determined the exercise capacity in each patient. We could assume that different kinds of treatment may have a differential effect on muscle metabolism or oxygen delivery, for example, muscle training,²² medication, and so on. This may help us to plan better treatments to improve their exercise intolerance and enable us to evaluate their effects appropriately.

STUDY LIMITATIONS

Although reproducibility of the τ PCr and the τ oxy-Hb was proved, we could not acquire both measurements simultaneously because of the technical limitation of the NIRS device. Second, we have included patients treated with and without β blocker agents. This might affect the muscle metabolism. However, τ PCr and τ oxy-Hb in this study were not significantly different between patients with and without β blocker treatment ($p = 0.33$ and $p = 0.38$, τ PCr and τ oxy-Hb, respectively).

CONCLUSIONS

Both PCr resynthesis and haemoglobin resaturation during recovery from exercise were impaired in patients with chronic heart failure. Remarkably, the recovery of PCr was slower than haemoglobin resaturation in patients with chronic heart failure. Furthermore the τ PCr and the τ oxy-Hb in normal subjects were similar, whereas the τ PCr in patients with chronic heart failure was significantly slower than the τ oxy-Hb. Our results suggest that haemoglobin resaturation is not the only rate limiting factor for PCr resynthesis in patients with chronic heart failure. Muscle metabolic recovery may depend on the capacity of oxygen utilisation rather than on haemoglobin resaturation or oxygen delivery in the presence of chronic heart failure.

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