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# The Time Course of Phosphorylcreatine Resynthesis during Recovery of the Quadriceps Muscle in Man

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*Summary.* The time course of phosphorylcreatine (PC) resynthesis in the human m. quadriceps femoris was studied during recovery from exhaustive dynamic exercise and from isometric contraction sustained to fatigue. The immediate postexercise muscle PC content after either form of exercise was 15–16% of the resting muscle content. The time course of PC resynthesis during recovery was biphasic exhibiting a fast and a slow recovery component. The half-time for the fast component was 21–22 s but this accounted for a smaller fraction of the total PC restored during recovery from the isometric contraction than after the dynamic exercise. The half-time for the slow component was in each case more than 170 s. After 2 and 4 min recovery the total amounts of PC resynthesized after the isometric exercise were significantly lower than from the dynamic exercise.

Occlusion of the circulation to the quadriceps completely abolished the resynthesis of PC. Restoration of resynthesis occurred only after release of occlusion.

*Key words:* Man – Muscle – Exercise – Recovery – Phosphorylcreatine – Phosphagen.

## INTRODUCTION

Physical exercise in man results in a marked decrease in the musle content of phosphorylcreatine (PC) but only a slight change in that of ATP [4, 10, 12, 18, 22, 23]. The magnitude of the decrease in PC varies both with the type and intensity of the exercise performed and under certain circumstances can be correlated with the increase in muscle lactate content [16]. At fatigue following isometric exercise at 66% of a subject's maximum voluntary contraction force (MVC) the decrease in PC can be as much as 95% [10].

The resynthesis of the muscle PC store during recovery after exercise has been studied in a number of different laboratory animals [2, 27, 29, 30, 36]. In general resynthesis appears to proceed exponentially with respect to time. Estimates of the half-time ($t_{1/2}$) of resynthesis, however, when calculated from [ref. 2, 27, 29, 30 and 36] show considerable variation, ranging from as little as 20 s in pectorialis muscle of pigeon to as high as 300 s in gastrocnemius of rabbit. In man a $t_{1/2}$ of 30–40 s for the resynthesis of high energy phosphates (mainly PC) hydrolyzed during dynamic exercise was calculated by Di Prampero and Margaria [9] from data of Hultman et al. [18]. Recent results of Karlsson and co-workers [19, 20] are in accord with this though other reports [5, 23, 31, 34, 39] have indicated much slower rates of resynthesis suggesting that the conditions of the preceeding exercise itself might be of importance to the rate. In order to examine this further the present study was undertaken in which the rates of PC resynthesis in the m. quadriceps femoris after an isometric or dynamic exercise were examined. In each case the exercise was sustained to fatigue. This resulted in a decrease of the muscle PC content to approximately 15% of the resting muscle content.

## METHODS

The present data are taken from two studies; one of metabolic recovery following dynamic exercise and the other of metabolic recovery following isometric contraction. In either study subjects exercised using principally the m. quadriceps femoris at a predetermined load. The exercise was continued until the load could no longer be maintained i.e. to exhaustion or fatigue. Immediately following release of muscle tension a muscle biopsy was taken from the lateral portion of the quadriceps by the method of Bergström [3] and was frozen whilst still in the biopsy needle [14]. The average time between release of tension and freezing of the sample was 5–6 s. Because of the delay the results obtained from these biopsies are

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considered to describe the metabolic state of the muscle 6 s after termination of the exercise. In all subjects a further 2 or 3 muscle biopsies were taken from the same leg during the period of recovery, and in most cases a muscle biopsy was also taken at rest before exercise. Anaesthetization and preliminary incision of the skin for all biopsies was made before the start of the exercise. Muscle biopsies were subsequently freeze-dried and analyzed for ATP, PC and creatine (Cr) as previously described [14].

All subjects were males and were aged between 18–30 years. As a group they were not especially well trained but each subject did participate in some form of physical activity.

The nature and purpose of each study was explained to the subjects before their voluntary consent was obtained.

*Study I – Recovery Following Dynamic Exercise.* Four subjects exercised on an electrically braked ergometer (Elema, Sweden) at a continuous pedalling rate of 60 rev. per min, and with a load calculated to lead to exhaustion after approximately 6 min. The exercise load for each subject was determined in previous sessions according to the method of Tornvall [38] and was as a mean 301 ± S.D. 23 watts. Each subject performed two exercise tests (mean endurance of the 4×2 tests was 8.7 ± S.D. 0.7 min) separated by a space of 1 week. Muscle biopsies were taken from one leg only on each occasion. One biopsy was taken immediately after exhaustion while the subject was still sitting on the ergometer. The subject then lay on a couch where further biopsies were taken after 2 or 4 min and 8 and 20 min recovery.

*Study II – Recovery Following Isometric Exercise.* In this the subjects sustained an isometric contraction of the knee extensors, chiefly the m. quadriceps femoris, in a chair of the type described by Tornvall [38]. In every case the contraction was sustained with a force of 66% of the subject's maximum voluntary contraction force (MVC). Determination of MVC and preliminary testing at 66% MVC were as previously described [1]. MVC of all subjects ranged from 45–62 kp, and endurance at 66% MVC from 40–55 s.

*Study IIa.* Five subjects sustained one isometric contraction with either leg with an interval of 4–7 days. One muscle biopsy was taken from each leg immediately after fatigue and two others during the following 4 min of recovery.

*Study IIb.* This was similar to study IIa but with the difference that 1 min prior to the start of contraction the blood flow to the quadriceps was occluded by mens of a pneumatic cuff placed around the upper thigh and inflated to a pressure of 240 mm Hg [15]. The cuff was left in place during both the contraction and recovery period. Three muscle biopsies were taken during the first 6 min of recovery.

*Study IIc.* Six subjects contracted to fatigue after occlusion of the circulation as in study IIb. One min after termination of the contraction a muscle biopsy was taken. At 1 min 30 s the pneumatic cuff was deflated and was reinflated 25 s later. 2 min 55 s after the end of the contraction a second biopsy was taken.

## RESULTS

*General.* As in other studies the PC content of the muscle biopsies taken immediately after exercise were greatly decreased below the content at rest. In contrast the ATP content showed only a minor decrease in a few subjects and at most accounted for only 5% of the total phosphagen decrease (i.e. $\Delta$ATP + $\Delta$PC). A more usual figure was 1–2%.

Mean total creatine (TCr = PC + Cr) at rest of all subjects did not differ significantly from that determined previously [14]. Immediately after exercise TCr was significantly lower in groups I and IIa but not in IIb or IIc. At the end of the experimental recovery period TCr was again normal in groups I and IIa. The fall in TCr is believed to have been due to an increase in the average blood content of the biopsies taken immediately after exercise, and this was supported by visual examination of the biopsies made at the time of dissection. For this reason values of PC have been adjusted to a normal mean TCr content of 124.4 mmol per kg dry muscle (d.m.) [14] to compensate for changes in the reference base.

*Study I.* The muscle PC content 6 s after the end of the exhaustive dynamic exercise was 16% of rest content of 75.0 mmol per kg d.m. During recovery the PC content increased rapidly (Fig. 1). As far as could be judged resynthesis appeared to be complete after 20 min. At this time the muscle PC contents tended to be higher in some subjects than the normal content before exercise, though the difference was not significant.

The general form of the data in Figure 1, viewed in context with earlier results of Hultman et al. [18] and the findings of Di Prampero and Margaria [9], appeared at first to be consistent with the hypothesis that the resynthsis of the PC store during recovery proceeded exponentially with respect to time. However, attempts to derive a single exponential equation to describe the data were not successful and it was found that a two component exponential equation was required. The general form of this equation was:

$$PC_t = a - b\,(c_1 e^{-k_1 t} + c_2 e^{-k_2 t})$$

in which.

$PC_t$ is the PC content (in mmol per kg d.m.) of the muscle $t$ min after termination of the exercise.

$a$ is a constant and has the units mmol per kg d.m. $a$ is in fact the PC content of the muscle at infinite time and this has been assumed to be the same as that determined at rest before exercise.

$b$ is a constant and has the units mmol per kg d.m. At the instant of termination of the exercise (i.e. when $t = 0$) $b$ predicts what the absolute decrease in the PC store below the rest content was.

$c_1$ and $c_2$ are dimensionless constants. $c_1 + c_2 = 1$.

$k_1$ and $k_2$ are the rate constants (in $min^{-1}$) of the two exponential components.

$t$ is the time (in min) after termination of the exercise.

In Table 1 are given the values of the constants which were used to calculate the time course of PC resynthesis after the dynamic exercise (Fig. 1 – continuous line). The equation used estimates that at the instant the exercise stopped the muscle PC content was of the order of 2.0 mmol per kg d.m., though extra-

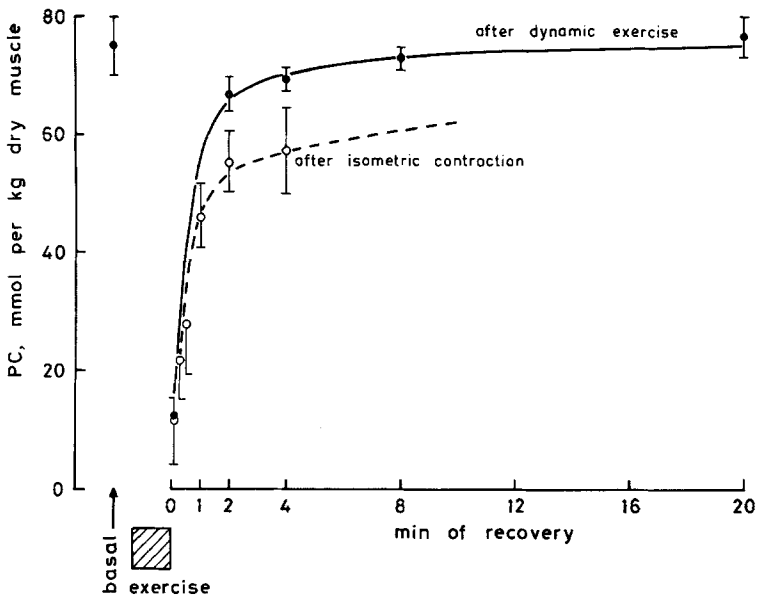


Fig. 1
The time courses of PC resynthesis during recovery from 6 min exhaustive dynamic exercise (filled circles and continuous line) and isometric contraction sustained at 66% MVC to fatigue (open circles and dashed line). The number of observations made during recovery from the dynamic exercise was 7 at 6 s, 4 at 2 min, 4 at 4 min, 6 at 8 min and 7 at 20 min; and during recovery from the isometric exercise was 6 at 6 s, 3 at 15 s, 4 at 30 s, 6 at 1 min, 5 at 2 min and 5 at 4 min. The vertical bars (where shown) indicate ± one S.D. about the mean

Table 1. Resynthesis curve parameters for calculation of $PC_t = a - b(c_1 e^{-k_1 t} + c_2 e^{-k_2 t})$

| | $a$ (mmol per kg d.m.) | $b$ (mmol per kg d.m.) | $c_1$ | $k_1$ ($min^{-1}$) | $c_2$ | $k_2$ ($min^{-1}$) |
|---|---|---|---|---|---|---|
| Dynamic | 75.0 | 73.0 | 0.822 | 1.98 | 0.178 | 0.24 |
| Isometric | 74.1 | 71.0 | 0.690 | 1.86 | 0.310 | 0.06 |

polation of the data beyond the range observed is always hazardous. During the first 2 min of recovery most of the resynthesis in the PC store can be accounted for by the first exponential term.

*Study IIa.* The muscle PC content 6 s after fatigue at 66% MVC was 15% of the rest content of 74.1 mmol per kg d.m. The deficit in the PC store at 6 s was thus almost exactly the same as in study I. After 2 and 4 min recovery 68 and 72% of the 6 s deficit had been restored compared to 84 and 89%, respectively, during recovery from the dynamic exercise. The difference in the amounts restored between the two studies was significant ($P < 0.01$) at 2 min, though only probably significant ($P < 0.05$) at 4 min.

In Table 1 are given the values of the constants which were used to calculate the time course of resynthesis after isometric contraction (Fig. 1 – dashed line). $k_1$ was found to be of the same order as in study I, but $c_1$ was slightly lower causing an earlier decline in the influence of the first exponential. Nevertheless the absolute increases in PC content during the first 30 s of recovery after either type of exercise were probably about the same. The formulae used predict that the maximum absolute difference between the muscle PC contents during recovery from the two types of exercise occurred between 2–8 min after termination of the exercise.

It should be noted that although the between-individual variance in PC content at any time during recovery from the isometric contraction was quite high, individual PC resynthesis curves approximated very closely to the one computed (i.e. the dashed line in Fig. 1). Because no measurements of PC resynthesis were made after 4 min little reliance can be placed on the estimate of $k_2$ presented in Table 1, though $c_2$ is probably of the correct order. As the equation stands it predicts that resynthesis was 99.9% complete after 95 min and that at the instant the contraction creased the PC content was 3.1 mmol per kg d.m.

*Studies IIb and IIc.* When the circulation to the quadriceps during the recovery period was occluded, resynthesis of PC was completely abolished (Fig. 2). The lowest muscle contents of PC were recorded in this study, and in two subjects ranged from 1–3 mmol per kg d.m. during the entire occlusion period of 6 min.

Release of occlusion for 25 s resulted in some resynthesis as judged from the analysis of muscle biopsies taken one minute later (Fig. 2). The increase in PC was about that which would have occurred during 25 s with normal circulation.

## DISCUSSION

In the study of Di Prampero and Margaria [9] it was assumed that the repayment of the deficit in the muscle

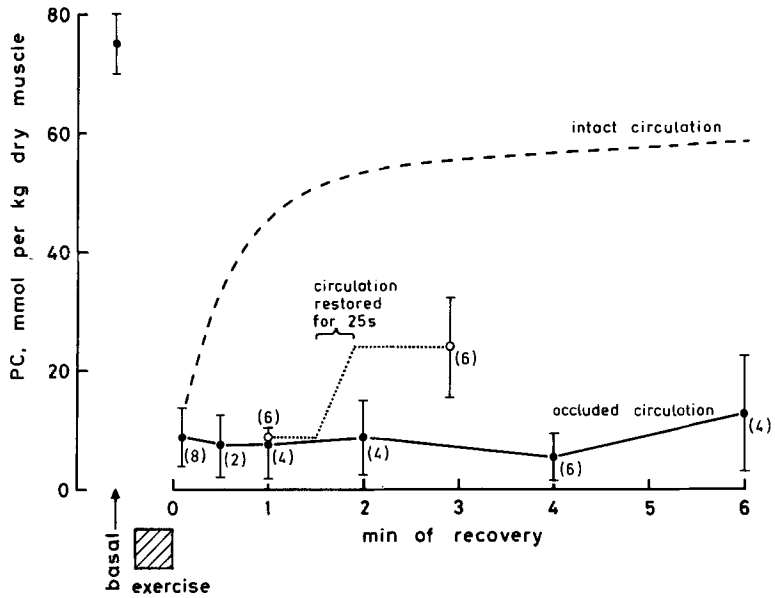


Fig. 2
PC resynthesis during recovery from an isometric contraction sustained at 66% MVC to fatigue: dashed line (from Fig. 1) – with intact circulation (study IIa); continuous line – with occluded circulation (study IIb); dotted line – with occluded circulation for the first 1 min. 30 s of recovery, after which the circulation was restored for 25 s and re-occluded at 1 min 55 s (study IIc). The line has been drawn with the assumption that the increase in PC observed between the two sets of biopsies occured during the period when the circulation was restored. Vertical bars indicate ± one S.D. about the mean. The figures in parenthesis are the number of observations

phosphagen store (mostly PC) proceeded in accordance with the law of exponential decay. Although a satisfactory fit to the data was obtained with a single exponential function it needs to be noted that the experimental observations on which they based their conclusion were confined to a relatively early period of recovery. From the present study it can be seen that when the period of observation is extended a more complex mathematical model is required.

By using a double exponential equation the post-exercise deficit in the muscle PC store (constant $b$ in Table 1) has in effect been divided into two fractions, a fast component $c_1$, and a slow component $c_2$. Division of the deficit in this way has been made for reasons of mathematical convenience and not out of consideration of any pre-supposed chemical or physiological model. $t_{1/2}$ for the repayment of $c_1$ was 21 s after dynamic exercise and 22.5 s after isometric exercise whilst that for $c_2$ was in both cases more than 170 s. Any attempt to obtain an estimate of $t_{1/2}$ covering repayment of the total deficit will thus result in an incorrect vlue lying between these extremes, the actual value obtained being dependant upon the period of recovery in which the data was collected. The wide variation in the estimates of $t_{1/2}$ noted in the introduction can probably be accounted for in this way.

Considerable interest in the past has been focussed on the origin of the ATP used in the resynthesis of PC [6, 27, 28]. In this respect the present findings emphasize an observation made by Piiper and Spiller [27], namely that the kinetics of PC resynthesis during recovery are very similar to those of oxygen debt repayment. According to Margaria et al. [25] the fast component of $O_2$ debt repayment in man has a $t_{1/2}$ in the order of 25 s which is very close to $t_{1/2}$ calculated for the fast component in the present study. In dog muscle there is also a quantitative agreement between excess $O_2$ consumed during recovery and muscle PC restored [26] implying that the ATP used in resynthesis is derived from oxidative metabolism. Alternatively the ATP utilized may be derived from the anaerobic metabolism of hexose monophosphates, accumulated within the muscle by the end of exercise, to pyruvate. In a recent study (unpublished) it was found that immediately after isometric contraction sustained at 66% MVC to fatigue the muscle hexose monophosphate content (glucose 1-phosphate + glucose 6-phosphate + fructose 6-phosphate) was approximately 25 mmol per kg d.m., and after 4 min of recovery was 10 mmol per kg d.m. The decrease of 15 mmol per kg d.m. if metabolized to pyruvate would result in the synthesis of 45 mmol ATP per kg d.m. This is almost exactly equal to the amount of PC resynthesis during the first 4 min of recovery from isometric exercise (Fig. 1).

Some difference in the resynthesis rates of PC after the dynamic and isometric exercises was apparent in the present study. However, as earlier noted, this did not result in any major absolute difference in the PC contents of the muscles until after 100 or more s of recovery. On the other hand the studies with circulatory occlusion suggest that impairment of blood flow may be an important regulator of the rate of resynthesis. The absence of resynthesis during the 6 min of occlusion in spite of an almost normal muscle ATP content can best be explained on the basis that the creatine kinase (EC 2.7.3.2) reaction is at equilibrium at this time [31]. The equilibrium state of the reaction, however, is different from that at rest due to decreased

intramuscular pH resulting in the very low muscle PC contents observed. Partial recovery in intramuscular pH and therefore also the creatine kinase equilibrium state during the 25 s when the circulation was restored in study IIc, can probably account for the increase in PC in those biopsies which were taken 60 s later [31].

It can be calculated that in either study with intact circulation the initial velocity of PC resynthesis after exercise was 2–3 mmol per kg d.m. per s. This is only a small fraction of the theoretical rate calculated from in vitro studies of the $V_{max}$ of creatine kinase in skeletal muscle [24] and indicates that factors other than enzymic activity regulate the resynthesis rate during recovery. One possibility is that it is again intramuscular pH, through it's effect upon the creatine kinase equilibrium [31], which is the limiting factor. Recent studies have shown that the decrease in muscle pH at exhaustion after $W_{max}$ dynamic exercise is about the same as at fatigue after isometric contraction at 66% MCV [31, 32]. Recovery in muscle pH after $W_{max}$ dynamic exercise to the pre-exercise value takes approximately 20 min [17, 32] as does also recovery in PC (Fig. 1), however, there are differences in the form of the two time courses. Unlike PC, recovery in muscle pH does not show a fast and slow component. Recovery in muscle pH after isometric contraction has not been investigated.

Alternatively the availability of ATP during recovery could be the limiting factor to the rate of PC resynthesis. On this basis the faster rate of PC resynthesis found after dynamic exercise would imply a greater capacity for ATP synthesis than after isometric exercise, such as might result from a higher post-exercise muscle temperature.

Fundamental to the present studies is the question of the relationship between chemical recovery in muscle to that of recovery in muscle performance. In this context it is of interest to note that the present time courses of PC resynthesis resemble those of maximum strength recovery in man following exhaustive exercise [7, 8, 12, 37]. Both exhibit fast and slow recovery components which persist for similar periods of time, and there are indications that strength recovery proceeds more slowly after isometric contraction [7, 8]. Further, occlusion of the circulation during recovery, which in the present study prevented the resynthesis of PC and the maintenance of extremely low levels, has also been shown to inhibit muscle strength recovery [11, 26]. Obviously these similarities could be coincidental but on the other hand may reflect the importance of the size of the PC store in regulation of the rate of ATP production during maximum effort [c.f. ref 35], or the existence of a common regulatory factor such as recovery in intramuscular pH.

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