

PLASMA CREATINE KINASE AFTER THE MARATHON — A DIAGNOSTIC DILEMMA

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ABSTRACT

The mechanism of the protein leak from exercised muscle remains obscure, but may be related to depletion of intracellular high-energy phosphate and/or to mechanical disruption. The high levels of creatine kinase (CK) and other muscle proteins found in plasma for several days after marathon running, especially downhill running, are due to protein efflux from skeletal muscle. There is no evidence that marathon running damages the healthy, well-perfused myocardium, despite the fact that the plasma levels of total creatine kinase (CK), the isoenzyme CK-MB, CK-MB/total CK (%), myoglobin, aspartate transaminase, lactate dehydrogenase and tropomyosin may be the same as after myocardial infarction. These indices must be interpreted with the greatest caution when found in anyone who habitually undertakes strenuous exercise, especially if they have done so within the previous week.

Key words: Marathon, Exercise, Creatine kinase, Myoglobin, Rhabdomyolysis, Myocardial infarction.

INTRODUCTION

Towards the end of a marathon, runners sometimes collapse. The usual cause of collapse is fluid depletion. The collapsed runner will then have a thready pulse and be hypotensive. Like other highly-trained endurance athletes, his electrocardiogram may show a variety of apparent abnormalities (e.g. Ohman et al, 1982). It would not be unusual, therefore, for a collapsed marathon runner to be considered for admission to the coronary care unit (CCU). This decision, and the decision when to discharge him from CCU, may be influenced strongly by the results of tests of plasma biochemistry usually considered indicative of myocardial damage. Circulating levels of creatine kinase (CK), aspartate transaminase (AsT), lactate dehydrogenase (LDH), myoglobin (Mgb) and tropomyosin (Tm) as high as those encountered following myocardial infarction are commonly observed after a marathon. Failure to recognise that this is a normal result of strenuous exercise may result in psychologically damaging and economically wasteful investigation and hospitalisation.

CREATINE KINASE POST-MARATHON

Muscle proteins are released into the circulation during and after strenuous exercise. Following a marathon run, plasma CK peaks some 6-24 hours after the end of the run (Ohman et al, 1982; Young et al, 1984; Rogers et al, 1984). Similar findings have been observed after pedalling (Ahlborg and Brohult, 1967), cross-country skiing (Stromme et al, 1978), and rowing (Nørregaard Hansen et al, 1982). Following a marathon run peak CK values may be many times the resting level and well within the range of values normally associated with myocardial infarction. For example, increases averaging 14-fold (Ohman et al, 1982), 17-fold in men and 9-fold in women (Rogers et al, 1984), and ranging from 3- to 29-fold (Young et al, 1984) have been reported. Levels may remain elevated for 4 or 5 days (Ahlborg and Brohult, 1967; Ohman et al, 1982; Young, Cummins, Michie and Auckland, unpublished). The habitually high level of activity of those who undertake marathons means that their pre-race levels are usually also above the limit of what is usually considered 'normal'.

OTHER MUSCLE PROTEINS POST-MARATHON

It is not just CK (molecular weight 81,000) that leaks from muscle. Larger molecules (e.g. LDH, molecular weight 140,000) and smaller molecules (e.g. Mgb, molecular weight 17,000) also leak from the stressed muscle cell. In vitro studies of exercised muscle do not suggest any selection according to molecular size in the efflux of proteins (Jones et al, 1983). Following a marathon run, both Mgb and LDH seem to peak rather earlier than CK, achieving mean peak elevations of 5-fold (LDH; Ohman et al, 1982) and 19-fold (Mgb; Young et al, 1984) some 1-6 hours post-race. The rapid renal clearance of myoglobin means that myoglobin levels fall faster than do

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the levels of muscle enzymes, so that CK levels may still be substantially elevated when myoglobin levels are within or close to the pre-race range.

AsT and Tm (a regulatory protein, forming part of the structure of the myofibril) reach their peak values 6-24 hours post-race, a 4-fold mean increase in AsT (Ohman et al, 1982) and a 6- to 43-fold increase in Tm (Young et al, 1984). The patterns of increase of CK and Tm are similar, with good correlation between the peak values obtained for the two proteins in individual runners (Young et al, 1984).

It has been suggested that the leakage of muscle proteins following exercise is greater if the subject is untrained (e.g. Ahlborg and Brohult, 1967; Nuttall and Jones, 1968; Maxwell and Bloor, 1981) but the studies are inconclusive since they failed to ensure that the provocation exercise was equally stressful pre- and post-training. After a period of training, the absolute intensity and the duration of the provocation exercise should both be greater. In one study, the stresses induced by the pre- and post-training exercise were partially matched (Hunter and Critz, 1971); testing maximal oxygen uptake (VO_2 max) induced a smaller increment in circulating levels of CK and AsT after a period of physical training.

EXERCISE-INDUCED DAMAGE TO SKELETAL MUSCLE

Degenerative and inflammatory damage to skeletal muscle, in muscular dystrophy and polymyositis, result in high circulating levels of CK, Mgb, AsT and LDH. The high levels seen in marathon runners are also associated with morphological evidence of structural and inflammatory damage (Hikida et al, 1983). Ultrastructural abnormalities were commonly present in needle biopsy specimens from the lateral gastrocnemius muscles of athletes training for a marathon. They were most prevalent at 1 and 3 days post-marathon, and at 7 days post-marathon tended still to be more prominent than in the pre-race specimens. Hikida concluded that "both the intensive training for, and the marathon itself, induce inflammation and fiber necrosis".

Exercise-induced muscle damage has also been demonstrated by technetium-99m pyrophosphate scintigraphy (Matin et al, 1983). Scintigrams collected within 48 hours after a 50 or 100 mile race showed extensively increased muscle radio-nuclide concentration, the pattern of uptake corresponding to the distribution of muscle pain.

Exercise-induced muscle soreness is known to be greater in muscles which were lengthened while they were active (eccentric contractions) than in muscles which were allowed to shorten while active (concentric contractions) (e.g. Asmussen, 1956; Talag, 1973; Edwards et al, 1981). Repeated downstairs-running

produced definite ultrastructural abnormalities (especially myofibrillar disruption) in the soleus muscles of normal subjects studied while suffering intense calf muscle discomfort two days later (Fridén et al, 1981). Both light- and electron-microscopic abnormalities were seen in needle biopsy specimens from the eccentrically exercised quadriceps muscles after a 20-minute step-test in which the quadriceps of one leg contracted concentrically throughout, by stepping up, and the other muscle contracted eccentrically, by controlling the step down (Newham et al, 1983b). The muscles which had contracted eccentrically showed some damage immediately after exercise and this was even more pronounced 24-48 hours later, by which time the muscles were also painful. This kind of stepping exercise may greatly increase plasma CK; 4 or 5 days later some subjects had peak values two orders of magnitude greater than their pre-exercise levels (Newham, Jones and Edwards, 1983). The rapid and forceful eccentric quadriceps contractions which provide the decelerating force in squat jumps explain why this exercise has given its name to the catastrophic and potentially lethal exercise-induced rhabdomyolysis sometimes seen in military recruits undergoing their initial training ("squat jump syndrome").

With running exercise too, the amount of eccentric activity influences the amount of muscle damage which occurs. For example, 45 minutes of running down a 10% incline (57% of VO_2 max) produced delayed-onset soreness in the glutei, the quadriceps, anterior and posterior lower-leg muscles and increased plasma CK activity (Schwane et al, 1983). In contrast, a similar period of running on the level (78% of VO_2 max) produced no muscle soreness and no elevation of plasma CK. Similarly, in the scintigraphic study the 100 mile runners (mostly downhill) showed involvement principally of the glutei, hamstrings and quadriceps whereas the 50 mile runners (mostly uphill) had most abnormalities in the thigh adductors (Matin et al, 1983).

There is good evidence, therefore, that the high circulating levels of muscle proteins after marathon running are due to skeletal muscle damage. But this does not exclude the important possibility that some of the protein efflux indicates simultaneous myocardial muscle damage.

CK-MB POST-MARATHON

Human tissues contain three dimers of CK (CK-MM, CK-MB, and CK-BB). There is relatively more of the MB isoenzyme in heart muscle than in any other tissue (15-25% of total CK activity: Sylvén, Jansson and Olin, 1983). It is generally considered that high plasma CK-MB activity is a specific indicator of myocardial damage, particularly useful in patients in whom other enzymatic indices of myocardial damage are already compromised, e.g. through trauma or hypoxia of other

tissues (Lancet Editorial, 1978). Elevated levels of CK-MB have been found in swimmers undergoing regular training (Strauss et al, 1982), in elite athletes after 15 and 30 kilometre track races (Nørregaard Hansen et al, 1982), and 10-fold (Ohman et al, 1982), 45-fold and 7-fold (Rogers et al, 1984) mean increases in CK-MB activity have been found after marathons. Does this imply that marathon running, by apparently healthy athletes, may produce a degree of silent myocardial damage?

CK-MB is not unique to heart muscle. A small amount of the CK activity in skeletal muscle is due to this isoenzyme. (The great majority is due to CK-MM). An elevated plasma CK-MB must be interpreted with caution in the presence of massive elevations of plasma total CK activity. Nevertheless, many athletes not only have high absolute values for circulating CK-MB post-marathon, they also have values for CK-MB/total CK (%) which are higher than normal, falling into the myocardial infarction range (Stansbie et al, 1982; Ohman et al, 1982; Rogers et al, 1984; Cummins et al, 1984). A further refinement of the criteria for detecting myocardial injury is to use a combination of total CK > 160 IU/l, CK-MB > 10 IU/l and CK-MB/total CK > 6%. Even applying these three criteria simultaneously, more than half of the subjects studied by Cummins et al (1984) had an abnormal result at some point during the five days following a marathon run.

The appropriateness of even these criteria, however, pre-supposes that CK-MB/total CK (%) in the skeletal muscles of marathon runners is the same as in normal subjects. Recent evidence, however, suggests that the muscles of trained endurance athletes contain a greater proportion of the MB isoenzyme (Table I) but have a normal total CK content (Sylvén et al, 1983b; Siegel, Silverman and Evans, 1983; Apple et al, 1984). A similar argument applies to the high plasma level of cardiac-specific LDH isoenzyme in trained runners after severe exercise (Ohman et al, 1982; Sylvén et al, 1983a).

In untrained muscle, type 1 muscle fibres contain a greater proportion of CK-MB than type 2 muscle fibres.

TABLE I

Isoenzyme CK-MB activity as a percentage of total creatine kinase (CK) activity in needle biopsy specimens of lateral gastrocnemius and lateral quadriceps muscles of trained endurance athletes and sedentary controls.

	Trained	Untrained
Quadriceps		
Sylvén et al, 1983	4.6	2.0
Gastrocnemius		
Siegel et al, 1983	8.9	3.3
Apple et al, 1984	7.7	< 1.0

CK-MB/total CK in the quadriceps may be directly related to the percentage of type 1 fibres in the muscle (Sylvén et al, 1983b; Apple et al, 1984) but such a relationship was not demonstrated in Sylvén's trained subjects, nor in Siegel's untrained subjects (Siegel et al, 1983). The increase in CK-MB/total CK (%) in runners' muscles may be related instead to the presence in their muscles of regenerating muscle fibres. The B sub-unit is synthesised in skeletal muscle before the M sub-unit and greatly increased relative levels of CK-MB may be found in muscles undergoing a continuous cycle of degeneration and regeneration, as in muscular dystrophy or polymyositis (Nanji, 1983). This probably also explains the fact that CK-BB (normally considered brain-specific) can be detected in homogenates of runners' muscle but not in those of controls (Apple et al, 1984). This, in turn, provides a reassuring interpretation for serum CK-BB levels after a marathon as high as those in patients with severe concussion (Phillips et al, 1982).

The circulating levels of CK-MB following marathon running, although initially suggestive of myocardial damage, may be adequately explained by the increased proportion of the isoenzyme in the endurance athlete's leg muscles. Further reassurance comes from studies using other methods for detecting myocardial damage.

ABSENCE OF OTHER EVIDENCE OF MYOCARDIAL DAMAGE

Technetium-99m pyrophosphate myocardial scintigraphy failed to detect any evidence of myocardial damage after a marathon (Siegel, Silverman and Holman, 1981; Ohman et al, 1982) and after 50 and 100 mile ultramarathons (Matin et al, 1983) despite the presence of increased circulating levels of the so-called "cardiac-specific" isoenzyme CK-MB. Siegel and his colleagues repeated this study in a further 5 runners, immediately after a marathon, using thallium-201 myocardial perfusion imaging, a highly sensitive technique for the detection of myocardial ischaemia. The findings were again normal (Siegel et al, 1984). These findings virtually exclude silent myocardial ischaemia as a factor in the elevated circulating levels of CK-MB seen after the marathon. Not everywhere, however, has access to myocardial scintigraphy and it would be useful to have a further, simpler test to assist the evaluation of the collapsed marathon runner.

Circulating levels of acute-phase proteins may be increased by myocardial infarction. The limited evidence currently available suggests that acute-phase proteins are not increased by strenuous exercise. Marathon running does not increase the circulating level of α_1 -acid glycoprotein (Ohman et al, 1982) and C-reactive protein is only minimally increased by prolonged running (Liesen, Dufaux and Hollmann, 1977; Cummins, Young, Michie and Auckland, unpublished). A further, potentially useful marker for myocardial

damage which would be applicable in this situation is offered by the radioimmunoassay for cardiac troponin-I (Cummins and Auckland, 1983). The primary sequence of this protein (part of the calcium regulatory troponin complex) differs markedly from its skeletal muscle isomorph so that a genuinely cardiospecific assay is possible. Specimens collected 1, 6, 24, 72 and 120 hours following a marathon had troponin-I levels which were below the limit of detection in most specimens and in every case remained well below the high levels typical of myocardial infarction (Cummins et al, 1984).

Addendum

Strachan et al (1984) have just reported minute changes in C-reactive protein after 15 and 21 km races and small increases after 56 km. After 88 km, however, C-reactive protein levels were similar to those seen after a small myocardial infarction.

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