CLINICAL RESEARCH

Abnormal cardiac enzyme responses after strenuous exercise: alternative diagnostic aids

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Abstract

Serial estimations of activities of creatine kinase and its MB isoenzyme, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase and of concentrations of alpha$_1$-acid glycoprotein were performed in 15 healthy well-trained male marathon runners. Estimations were made initially within three days before a race and then one, 24, and 96 hours after the race. Technetium-99m pyrophosphate myocardial scintigraphy was carried out at the initial prerace assessment and repeated 48 to 96 hours after the race. None of the subjects developed cardiac symptoms during or after the race.

Activities of creatine kinase and creatine kinase MB became maximal 24 hours after the race. One and 96 hours after the race two and five subjects, respectively, showed amounts of creatine kinase MB totalling 5% or more of total creatine kinase. Lactate dehydrogenase activity peaked at one hour after the race, and activities of aspartate and alanine aminotransferases peaked at 24 and 96 hours after the race, respectively. Activities of all these enzymes showed a significant increase from prerace values during the rest of the study. Electrocardiographic features noted were similar to those reported elsewhere in athletes under similar conditions. They included first-degree heart block, incomplete right bundle-branch block, left ventricular hypertrophy, pseudoischaemic T-wave changes, and early repolarisation of variant ST-segment elevations in precordial leads. Technetium-99m pyrophosphate myocardial scintigraphy did not show evidence of myocardial damage before or after the race. Alpha$_1$-acid glycoprotein concentrations were normal throughout.

These data suggest that reliance on standard enzyme estimations and electrocardiographic criteria may yield false-positive indicators of myocardial injury during prolonged strenuous exercise. Technetium-99m pyrophosphate scintigraphy and alpha$_1$-acid glycoprotein measurements offer additional information and may usefully be employed in evaluating circulatory collapse associated with such exercise.

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Introduction

Finding critically raised serum activities of creatine kinase MB isoenzyme is widely held to be the most sensitive and specific indicator of acute myocardial infarction[1-3] even in the absence of diagnostic electrocardiographic changes.[1] Creatine kinase MB values exceeding 5% of total creatine kinase activity measured at the same time are considered to indicate myocardium as the source of this isoenzyme.[4,5] Blood values of creatine kinase MB may rise in the presence of skeletal muscle damage, however, due to a small quantity of this isoenzyme which has been detected in type II skeletal muscle fibres.[6-8] Varying activities of creatine kinase MB after exercise have been reported.[5-9] The detection of this isoenzyme after strenuous exercise could therefore indicate injury either to the myocardium or to skeletal muscle.

Marathon running has rapidly gained popularity and entails prolonged strenuous exertion. ST and T-wave changes in the electrocardiogram simulating pericarditis or myocardial ischaemia in asymptomatic subjects have been recognised for many years and remain without adequate explanation.[10-13] Such changes accompanied by increased creatine kinase MB activity will

present considerable diagnostic difficulty when cardiac symptoms ensue or are associated with strenuous exertion. Hence additional diagnostic techniques may be required to clarify the aetiology of such symptoms. Myocardial scintigraphy with technetium-99m pyrophosphate is a non-invasive technique widely used to increase the specificity of diagnosis in myocardial infarction.[14 15] Circulating α_1-acid glycoprotein, one of the acute-phase proteins, has been suggested by various reports to increase in myocardial infarction.[16-19] This study reports on the sequential changes in marathon runners of creatine kinase MB and the other cardiac enzymes commonly used in the diagnosis of myocardial injury —namely, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. Technetium-99m pyrophosphate myocardial scintigraphy and α_1-acid glycoprotein estimations were performed to determine the presence or absence of such damage and to test the hypothesis that such enzyme changes could arise from a non-cardiac source.

Methods

Fifteen well-trained white male athletes aged 25-53 years were selected before the 1981 Dublin City Marathon. Selection criteria were that they had no history of cardiovascular disease and that they were capable of completing the race (42 km) within three hours. Weights ranged from 55·5 to 80·0 kg, and the subjects had been in training for two to 29 years. Weekly distances covered in training varied from 64 to 224 km. All were non-smokers and none was taking any medication. Nine of the 15 had a family history of cardiovascular disease.

Prerace evaluations were carried out within three days before the race with the subjects abstaining from running for at least 24 hours. Evaluations consisted of complete physical examination, resting supine standard 12-lead electrocardiogram, chest radiography, and technetium-99m pyrophosphate myocardial scintigraphy. Venous blood was taken from the antecubital vein for estimation of serum enzyme activities. Blood was immediately refrigerated at 4°C, centrifuged, and assayed within 24 hours. Activities of creatine kinase, aspartate and alanine aminotransferases, and lactate dehydrogenase were measured at 25°C by optimised spectrometric methods (Boehringer-Mannheim GmbH Diagnostica). The MB fraction of creatine kinase was obtained by an ion-exchange chromatographic method modified according to Mercer.[4] α_1-Acid glycoprotein concentration was measured by immunodiffusion as described by Mancini *et al*[20] using partigen plates (Behringwerke AG, Marburg, FRG). To exclude abnormal liver metabolism influencing the results, serum bilirubin concentration and alkaline phosphatase and γ-glutamyltransferase activities were measured.

Technetium-99m pyrophosphate myocardial scintigraphy was performed 40 to 45 minutes after the intravenous administration of 15 mCi technetium-99m stannous pyrophosphate. The images were obtained using a Phocan scanner and reproduced on film. A relative measure of quantitative uptake of pyrophosphate was made comparing the heart area with the background area (right hemithorax) using a Siemens gamma-camera computer. Repeat scintiscans were taken 48 to 96 hours after the race, this being the optimal time to detect any myocardial damage sustained during the race.

Repeat evaluations were done one and 24 hours after the race, consisting of physical examination, 12-lead electrocardiogram, and blood estimations. Final evaluations were at 96 hours after the race.

Differences between values obtained before and after the race were analysed by paired *t* tests.

Results

All 15 subjects completed the race, and finishing times were between two hours 23 minutes and three hours 26 minutes. None developed cardiac symptoms during or after the race. No abnormality was noted on physical examination. All chest radiographs were normal.

Creatine kinase and MB isoenzyme—One and 96 hours after the race two and five subjects, respectively, showed creatine kinase MB percentages equal to or greater than 5% of the total creatine kinase value, though the means of these percentages were all within the normal range throughout. Mean total creatine kinase activity of 102 ± SEM 22 IU/l before the race rose to 325 ± 80 IU/l one hour after the race. Activity became maximal (1399 ± 348 IU/l) at 24 hours, and at 96 hours it was still raised (287 ± 55 IU/l) (significance of difference from values before race: $p < 0.05$ at one hour; $p < 0.001$ at 24 hours; $p < 0.01$ at 96 hours). All mean values were significantly above the upper limits of normal. Mean creatine kinase MB activities followed the same pattern, being 2·7 ± SEM 1·0 IU/l before the race and 9·3 ± 2·7, 27·7 ± 5·9, and 12·1 ± 3·1 IU/l one hour, 24 hours, and 96 hours after the race, respectively ($p < 0.05$; $p < 0.001$; $p < 0.01$) (fig 1; table).

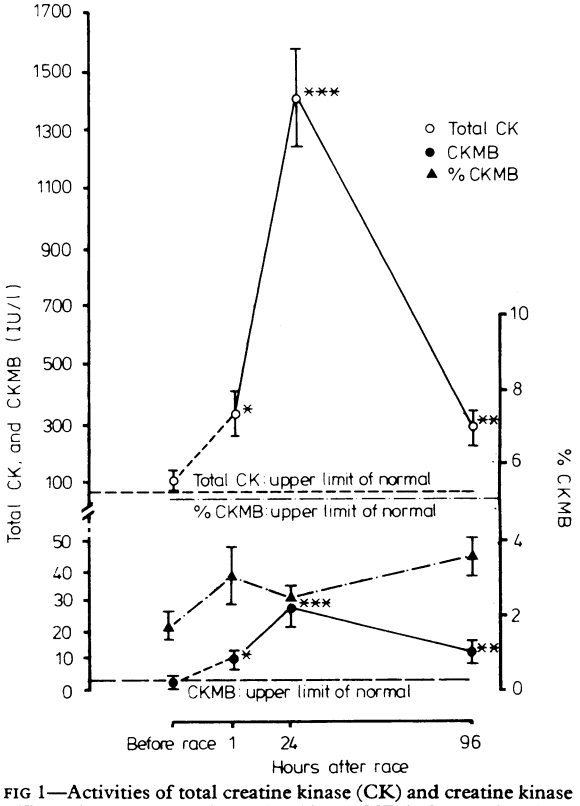

FIG 1—Activities of total creatine kinase (CK) and creatine kinase MB, and percentage of creatine kinase MB before and serially after marathon race. Values are means ± SEM.

Significance of difference from value before race: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Creatine kinase MB percentages in six subjects with values equal to or greater than 5% of total creatinine kinase value

Time after race (h)	Subject No					
	1	2	3	4	5	6
1				5·4	10·6	
24						
96	5·2	5·0	5·1	5·1		6·0

Lactate dehydrogenase—The ratio of lactate dehydrogenase isoenzyme I to isoenzyme II exceeded 0·8 in six subjects at one hour and three subjects at 96 hours after the race. Before the race the mean lactate dehydrogenase activity was 234 ± SEM 9 IU/l. Activity then peaked at one hour (1129 ± 110 IU/l), decreased to 375 ± 20 IU/l at 24 hours, and was 406 ± 39 IU/l at 96 hours after the race (comparison with values before race: $p < 0.001$ at one hour; $p < 0.001$ at 24 hours; $p < 0.01$ at 96 hours) (fig 2).

Aspartate and alanine aminotransferases—Mean aspartate aminotransferase activity was just above the upper limit of normal before the race (18·4 ± SEM 1·8 IU/l). Values then increased to 33·9 ± 2·6 IU/l at one hour, were maximally raised at 24 hours (68·3 ± 13·2 IU/l), and remained above normal 96 hours after the race (43·0 ± 5·7 IU/l) ($p < 0.01$ at one hour; $p < 0.001$ at 24 hours; $p < 0.01$ at 96 hours). Mean alanine aminotransferase activity was normal before the race (15·7 ± 1·5 IU/l). At one hour it was 18·9 ± 1·3 IU/l, at 24 hours

31·8±3·9 IU/l, and at 96 hours (maximal activity) 33·8±3·4 IU/l ($p < 0·05$ at one hour; $p < 0·001$ at 24 and 96 hours) (fig 3).

α_1-Acid glycoprotein—Mean and individual concentrations of α_1-acid glycoprotein remained within the normal range of 0·6-1·4 g/l throughout the study period.

Technetium-99m pyrophosphate scintiscans were normal before the race and showed no uptake indicative of myocardial damage or the diffused uptake pattern indicative of unstable angina pectoris. The quantitative uptake ratio of the heart area to the background area showed a mean of 0·9 (expected value 1·0; coefficient of variance 8·35%).

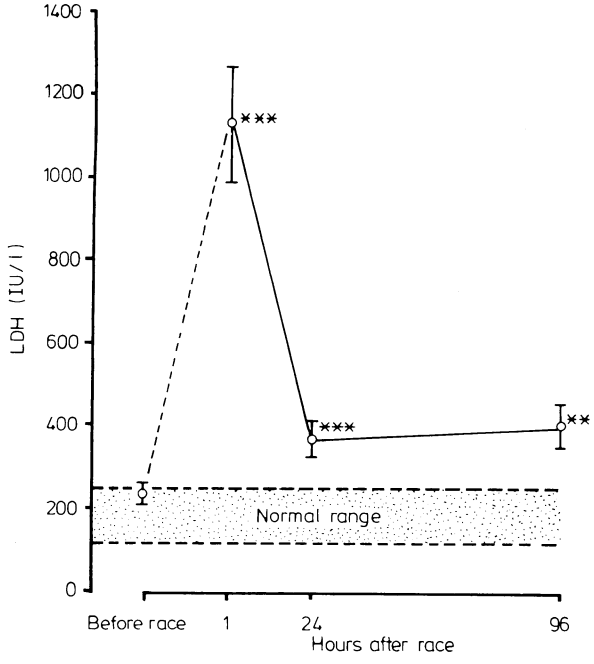

FIG 2—Activities of lactate dehydrogenase (LDH) before and serially after marathon race. Values are means±SEM.
Significance of difference from value before race: **$p < 0·01$; ***$p < 0·001$.

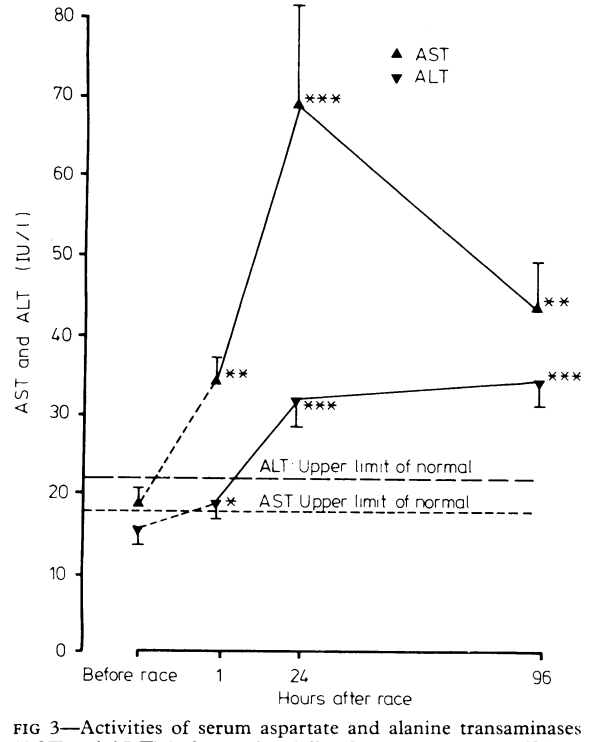

FIG 3—Activities of serum aspartate and alanine transaminases (AST and ALT) before and serially after marathon race. Values are means ± SEM.
Significance of difference from value before race: *$p < 0·05$; **$p < 0·01$; ***$p < 0·001$.

Electrocardiograms—All electrocardiographic axes and Q-T_c intervals were normal before the race and not significantly changed after the race. One subject with a resting heart rate of 43 beats/min before the race showed a P-R interval of 0·28 s, and this remained unchanged after the race. Similarly, three others had P-R intervals of 0·20 s. Incomplete right bundle-branch block pattern was found in six subjects both before and after the race. Five subjects showed definite left ventricular hypertrophy and three probable left ventricular hypertrophy, according to the criteria of Romhilt and Estes.[21] Pseudo-ischaemic T-wave changes in the anteroseptal leads were present in two prerace electrocardiograms; both became normal one hour after the race but were clearly abnormal again at 96 hours. Twelve subjects exhibited posteroinferior ischaemic patterns both before and after the race. Twelve showed early repolarisation variant ST-segment elevations of 2 and 3 mm in the precordial leads; these persisted and in 10 cases became more pronounced after the race. Five subjects showed terminal P-wave negativity in lead V1 both before and after the race, while six others developed this change only one hour after the race. Premature ventricular extrasystoles were seen in two resting electrocardiograms.

Liver metabolism—Serum bilirubin concentrations and alkaline phosphatase and γ-glutamyltransferase activities were normal throughout.

Discussion

This study shows the diagnostic difficulty in distinguishing myocardial damage from other muscular injury by enzymatic means in subjects after prolonged strenuous exertion. The pattern of enzyme changes after acute myocardial infarction is well known. Total creatine kinase and creatine kinase MB activities show significant increases four to six hours after the onset of symptoms.[1 2] The time taken to reach maximal values varies, but an average of 18 hours for total creatine kinase and 17·4 hours for the MB isoenzyme have been reported.[1] Creatine kinase MB has a higher elimination constant than creatine kinase MM, and the activity of MB therefore remains raised for a shorter time than that of total creatine kinase.[1] It has been suggested that when there is no increase in total creatine kinase activity an elevation of MB by itself is of diagnostic significance.[22] Furthermore, an increase in MB equal to or greater than 5% of the total creatine value increases the specificity and sensitivity of the MB isoenzyme in the diagnosis of myocardial damage.[1 4] The initial rise in activities of creatine kinase and creatine kinase MB in this study followed a pattern similar to that after myocardial infarction. Twenty-four hours after the race there was a maximal rise with a greater than 12-fold increase in total creatine kinase activity and a threefold increase in creatine kinase MB activity. Two subjects showed MB values equal to or greater than 5% of the total creatine kinase value at one hour, and five subjects showed such values at 96 hours.

Lactate dehydrogenase activity rises slowly after myocardial infarction and becomes maximal 30-78 hours after the event[2] and later than creatine kinase and creatine kinase MB. In this study total lactate dehydrogenase activity became maximal one hour after the race, which is not typical in myocardial infarction.[23] Lactate dehydrogenase I is cardiac specific and has a longer half life than lactate dehydrogenase II,[2] and a ratio of I:II of greater than 0·8 indicates myocardium as the source of the enzyme.[24] Three subjects with MB values greater than 5% of the total creatine kinase value also had a lactate dehydrogenase I:II ratio greater than 0·8.

Both aspartate aminotransferase activity and alanine aminotransferase activity rise after an acute myocardial infarction. In our study they showed increases after the race similar to the pattern in myocardial infarction.

The wide variety of electrocardiographic changes in our subjects have all been noted before in similar circumstances. Major repolarisation disorders have been reported in 4-18% of athletes.[10 11] These changes are thought to be neurogenic[25] due

to a decrease in resting vagal and sympathetic tone.[26] This may produce a latent functional asymmetry of cardiac sympathetic nerves and bring about an inequality of ventricular repolarisation resulting in T-wave abnormalities.[27] Mitral valve prolapse has been found in some athletes showing these electrocardiographic changes.[28] Nevertheless, while this explanation may be acceptable in the routine evaluation of athletes found to have electrocardiographic changes they must be interpreted with care when accompanied by a rise in aminotransferase activity.

Technetium-99m pyrophosphate myocardial scintigraphy is an established technique in the diagnosis of myocardial infarction,[14 15] the optimal time for scanning being two to five days after the onset of the event.[14 15] The specificity and sensitivity of this method approaches that of measuring creatine kinase MB. It is used to diagnose acute myocardial infarction after cardiac surgery in which there is procedure-related skeletal muscle damage.[15] None of our subjects showed any evidence of increased uptake indicative of myocardial necrosis. Furthermore, the diffuse uptake pattern compatible with unstable angina pectoris and non-transmural myocardial infarction[15] was not seen.

The concentration of α_1-acid glycoprotein has been shown to be raised after acute myocardial infarction,[16-19] increasing steadily to a peak between the fourth and eighth days.[19] A strong positive correlation between the infarct size as determined by creatine kinase estimations and measurements of α_1-acid glycoprotein has been shown.[18] An increase of this acute-phase protein occurs in inflammatory states as part of an immunochemical response in the liver and other organs.[29] In the absence of any inflammatory condition, measurement of α_1-acid glycoprotein may serve as a corroborative test in myocardial infarction. Snyder *et al*[29] further suggested that there exists a persistent increase in α_1-acid glycoprotein and other protein-bound carbohydrates in patients suffering from atherosclerotic cardiovascular disease. We therefore suggest that an α_1-acid glycoprotein concentration within the normal range refutes the presence of myocardial damage and in the absence of evidence from more specific techniques indicates the absence of coronary artery disease.

The continuing enthusiasm for long-distance running among established athletes and other members of the population, with and without cardiac disease, requires the establishment of diagnostic tools of definite value to obviate erroneous diagnosis of myocardial damage. Our data suggest that reliance on standard enzyme estimations and electrocardiographic criteria may yield false-positive indicators of myocardial injury. Technetium-99m pyrophosphate myocardial scintigraphy and α_1-acid glycoprotein measurement offer additional information and should be employed in the evaluation of circulatory collapse associated with strenuous exercise.

Requests for reprints should be sent to Dr J H Horgan.

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Correction

Comparison of whole-blood eosinophil counts in extrinsic asthmatics with acute and chronic asthma

An error occurred in the paper by A R Luksza and D K Jones (30 October, p 1229). The correction factor for eosinophil counts should have read $\times 10^6$/l and not $\times 10^9$/l. This alteration does not influence the significance of the results.