Plasma Levels of Cardiac Troponin I After Prolonged Strenuous Endurance Exercise

Guenther Neumayr, MD, Hannes Gaenzer, MD, Rudolf Pfister, MD, Wolfgang Sturm, MD, Severin P. Schwarzacher, MD, Guenther Eibl, PhD, Guenther Mitterbauer, PhD, and Helmut Hoertnagl, MD

Extreme exercise poses a variety of health hazards. It is well documented that endurance athletes can experience exercise-induced skeletal muscle damage when they expose their muscles to loads that they are not accustomed to. Whether strenuous ultraendurance exercise may even cause cardiomyocyte injury is uncertain at present. So far, the evidence for exercise-induced myocardial damage is small[1–4] and is based mainly on elevation of postexercise plasma concentrations of various "cardiac-specific" enzymes known to show considerable residual cross-reactivity to skeletal muscle proteins as described for the standard measurement of the creatine kinase-MB isoenzyme (CK-MB) and the "first generation" assays of cardiac troponin T (cTnT).[5–8] Currently, cardiac troponin I (cTnI) is the most sensitive and specific marker for the detection of cardiomyocyte necrosis, even in the presence of skeletal muscle damage. The currently applied assays for determining cTnI use monoclonal antibodies showing no, or at least very low (<0.005%), cross-reactivity with the skeletal troponin isoforms.[9] This study investigates whether strenuous ultraendurance exercise can induce myocardial cell injury as assessed by the determination of plasma concentrations of cTnI in well-trained cyclists who participated in an Alpine bicycle ultramarathon.

• • •

Thirty-eight male volunteers out of 1,420 participants of the Tyrolean Ötztaler Radmarathon 1999 were subjects of the study. The workload of this race (total distance, 230 km; altitude difference, 5,500 m) is comparable to that of the hardest mountain stages of the Tour de France. All 38 study participants were experienced and well-trained amateur cyclists. They were free of cardiovascular risk factors and without evidence for any heart disease according to case history and clinical investigation. Blood specimens of all participants were taken the day before, immediately after, and 1 day after competition. Plasma concentrations of cTnI, CK, and CK-MB were measured. cTnI was determined by means of a 2-step sandwich microparticle enzyme-immunoassay method on an AxSYM analyzer (Abbott Diagnostika, Wiesbaden, Germany). The upper reference limit was 0.5 μg/L. The activity of CK was measured colorimetrically at 25°C (NAC, Roche Diagnostics, Hoffmann-LaRoche Inc., Basel, Switzerland) by using the standard method of the "Deutsche Gesellschaft für Klinische Chemie" (reference range 10 to 80 U/L) and CK-MB by an immunoinhibition assay with reagents from Roche Diagnostics (reference range <10 U/L, <6% of total CK activity). The differences in baseline characteristics between athletes with and without exercise-induced cTnI levels were calculated by using the Mann-Whitney test. Changes in biochemical markers during the observation period were calculated by the Wilcoxon test and correlations between them were computed by a simple linear regression analysis using the SPSS software package, version 9.0 (Chicago, Illinois). Statistical significance was assumed at a level of $p < 0.05$.

Cardiac TnI values, negative in all athletes before competition, increased in 13 cyclists (34%) immediately afterward and significantly decreased in 12 on the following day (Figure 1). In one 42-year-old participant without symptoms, cTnI increased from 1.3 μg/L after exercise to 4.0 μg/L on the following day. The increased postexercise levels ranged from 0.9 to 4.9 μg/L. The highest individual level of 4.9 μg/L was measured in a 29-year-old athlete who had achieved the best performance among the study participants (race time, 8.1 hours; place, 24; training distance, 5,500 km). On the following day, cTnI was not detectable in 4 athletes any longer and had decreased to levels of 0.5 to 0.9 μg/L in all the others. The differences in age, race time, and total training distance were significant ($p < 0.05$) between athletes with and without increased postrace cTnI (Table 1).

Baseline activity of total CK ranged from 17 to 328 U/L before competition. In 33 athletes (87%) it was within the gender-specific normal reference range, in 5 (13%) it was already elevated in the prerace sample, most likely due to preceding cycling training the days before. In 3 of these 33 participants (8%) the CK-MB/CK ratio was higher than 6%. In all the others the baseline activity of CK-MB was below the upper limit of the normal range. Immediately after competition there was a pronounced increase in CK in 35 cyclists (92%), with a further increase on the following day. There was no significant change in total CK after exercise in only 3 athletes (8%). CK-MB/CK ratios >6%, considered to indicate myocardial damage, were seen in 23 subjects (60.5%) immediately after the race and in 10 (26%) the day after. There was no correlation between the increase in cTnI and the changes in CK and CK-MB. Pre- and postrace values of all markers are listed in Table 2.

From the Institute of Sports Medicine, and the Departments of Internal Medicine, Cardiology, and Biostatistics, University of Innsbruck, Innsbruck, Austria. Dr. Neumayr's address is: Institute of Sports Medicine, University Clinics of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. E-mail: guenther.neumayr@uklibk.ac.at. Manuscript received May 1, 2000; revised manuscript received and accepted August 8, 2000.

0002-9149/01/$–see front matter
PII S0002-9149(00)01382-5

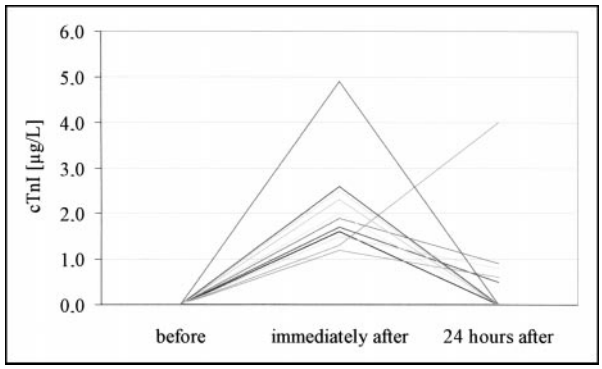

FIGURE 1. Plasma levels of cTnI before, immediately after, and 24 hours after competition

TABLE 1 Characteristics of Athletes With and Without Positive Postrace cTnI Levels

	Positive Postrace cTnI	Negative Postrace cTnI
Age (yrs)*	33.7	36.3
Height (cm)	180	179
Weight (kg) before race	74.4	72.8
Weight (kg) after race	73.4	71.7
Race time (h)*	9.3	9.8
Training distance before race (km)*	8,000	5,300

*$p < 0.05$ (Mann-Whitney test).

TABLE 2 Biochemical Markers Before and After Competition

	Before	Immediately After	24 Hours After
cTnI (>0.05 µg/L)*	0/38	13/38 (34%)	9/38 (24%)
CK (U/L)†	79 ± 58 (17–328)	160 ± 121 (40–569)	245 ± 165 (48–548)
CK-MB/CK (>6%)*	3/38 (8%)	23/38 (60.5%)	10/38 (26%)

*Values presented as number of positive observations/total observations.
†Values presented as mean ± SD (range).

• • •

The major finding of this study is that plasma levels of cTnI, negative before competition, increased after ultraendurance exercise, indicating that extraordinary long-term strains may induce subclinical cardiac injury even in well-trained athletes. The most popular hypothesis explaining this exercise-induced cardiac injury is that under the stress of increased myocardial oxygen consumption, high concentrations of catecholamines cause coronary vasospasm and endothelial injury resulting in asymptomatic focal myocardial necrosis and fibrosis.[10]

Previous studies, however, have consistently shown that prolonged aerobic exercise does not cause myocardial damage.[9,11–15] Only since the introduction of cardiac troponins as novel cardiac markers did a few reports emerge providing biochemical evidence for the opposite.[1–4] In 2 of 23 participants (9%) of the Hawaii Ironman Triathlon, Rifai et al[1] found marked postexercise plasma increases in cTnI and cTnT, and only moderate increases in cTnT in an additional 4 athletes (17%).[1] Because they also detected depressed ejection fractions and abnormal wall motions in their echocardiographic analyses, which correlated with positive cTnT levels after the race, they concluded that abnormal segmental wall motion is not only "cardiac fatigue" but cardiac injury. Recently, further evidence was provided by Koller et al,[2] who detected moderate postexercise cTnT increases in 4 of 36 participants (11%) in an Alpine cross-country marathon.

In our study we found positive postexercise cTnI values in 13 of 38 cyclists (34%)—representing a prevalence comparable to the 26% found by Rifai et al.[1] The athletes with positive cTnI values had a higher training level and were significantly younger and faster than their competitors. It is unknown whether these results indicate that cyclists with a better cardiac performance capacity are more likely to be exposed to an increased risk for minor cardiac injury because they eventually put more stress on their hearts by fighting harder and longer on their cardiovascular limits. These findings, however, contrast with the conclusions recently drawn by Koller et al[2] that transient subclinical myocardial damage may predominately occur in persons who usually perform physical activity only on a modest scale and that regular high levels of exercise would protect against cardiac injury.

The cTnI levels observed after the race lay between 0.9 and 4.9 µg/L, representing a range of elevation which usually means minor but significant cardiac injury. In clinical cardiology, comparable values are seen in patients with an acute coronary syndrome in whom cTnI serves as a reliable predictor of short-term prognosis.[16] Cardiac TnI is not detectable in the serum of healthy persons. So far, increased cTnI concentrations have predominantly been found positive in settings of myocardial damage such as infarction, severe congestive heart failure, myocarditis, after cardiotoxic treatment, and so forth. In contrast, acute and chronic peripheral muscle diseases, noncardiac surgery, polytrauma, electrical cardioversion, and burns have not caused elevations in cTnI.[9,17,18]

The question of whether the positive cTnI levels observed after exercise in asymptomatic athletes actually represent significant myocardial damage is difficult to answer in the absence of available tissue for histologic analysis and for the following reasons. In this study all evidence for exercise-induced cardiomyocyte injury is only based on positive postexercise cTnI levels. Although the applied assay for determining cTnI has a very high specifity and sensitivity and false-positive results due to a cross-reactivity with skeletal isoforms seem to be very unlikely, false-positive results due to unknown or not yet identified interferences with the assay cannot completely be excluded.[14] No follow-up studies >24 hours after the race could be conducted because they would have been logistically difficult to perform and comparable preexaminations did not exist. Neither echocardiogra-

phy nor electrocardiography were performed because they are too unspecific for detecting minor cardiac injury, and potential abnormalities are shown to be very temporary.[1,19,20]

As expected, the enormous physical strains during this ultramarathon did cause skeletal muscle damage manifested as a postrace increase in total CK whose extent was comparable to that of previous studies. The missing correlation between elevations in CK-MB/CK and cTnI confirms previous data that in the presence of skeletal muscle damage, the determination of CK-MB/CK lacks sufficient specificity for the diagnosis of myocardial damage.[6–8]

As long as the clinical significance and potential long-term consequences of positive postexercise cTnI values are uncertain, they must be considered as biochemical evidence for minor cardiomyocyte injury. Endurance athletes, therefore, should at least undergo serial cardiovascular examinations looking for subtle evidence of myocardial dysfunction.

1. Rifai N, Douglas PS, O'Toole M, Rimm E, Ginsburg GS. Cardiac troponin T and I, electrocardiographic wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman Triathlon. *Am J Cardiol* 1999;83:1085–1089.
2. Koller A, Summer P, Moser H. Regular exercise and subclinical myocardial injury during prolonged aerobic exercise [letter]. *JAMA* 1999;282:19.
3. Koller A, Mair J, Mayr M, Calzolari C, Larue C, Puschendorf B. Diagnosis of myocardial injury in marathon runners [letter]. *Ann N Y Acad Sci* 1995;752:234–235.
4. Laslett L, Eisenbud E, Lind R. Evidence for myocardial injury during prolonged strenuous exercise. *Am J Cardiol* 1996;78:488–490.
5. Adams JE III, Sicard GA, Allen BT, Bridwell KH, Lenke LG, Davila-Roman VG, Bodor GS, Ladenson JH, Jaffe AS. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med* 1994;330:670–674.
6. Siegel AJ, Silverman LM, Holman BL. Elevated creatine kinase MB isoenzyme levels in marathon runners: normal myocardial scintigrams suggest noncardiac source. *JAMA* 1981;246:2049–2051.
7. Riley WJ, Pike FS, Roberts AD. The effect of long-distance running on some biochemical variables. *Clin Chim Acta* 1975;65:83–89.
8. Siegel AL, Silverman LM, Lopez RE. Creatine kinase elevations in marathon runners: relationship to training and competition. *Yale J Biol Med* 1975;53:275–279.
9. Adams JE III, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS. Cardiac troponin I: a marker with a high specifity for cardiac injury. *Circulation* 1993;88:101–106.
10. Rowe WJ. Extraordinary unremitting endurance exercise and permanent injury to normal heart. *Lancet* 1992;340:712–714.
11. Cummins P, Young A, Auckland ML, Michie CA, Stone PC, Shepstone BJ. Comparison of serum cardiac specific troponin I with creatine kinase, creatine kinase-MB isoenzyme, tropomyosin, myoglobin, and C-reactive protein release in marathon runners: cardiac or skeletal muscle trauma? *Eur J Clin Invest* 1987;17:317–324.
12. Laslett L, Eisenbud E. Lack of detection of myocardial injury during competitive races of 100 miles lasting 18 to 30 hours. *Am J Cardiol* 1997;80:379–380.
13. Koller A, Mair J, Schobersberger W, Wohlfarter T, Haid C, Mair M, Villinger B, Frey W, Puschendorf B. Effects of prolonged strenuous endurance exercise on plasma myosin heavy chain fragments and other muscular proteins. *J Sports Med Phys Fitness* 1998;38:10–17.
14. Bonetti A, Tirelli F, Albertini R, Monica C, Monica M, Tredici G. Serum cardiac troponin T after repeated endurance exercise events. *Int J Sports Med* 1996;17:259–262.
15. Sorichter S, Mair J, Calzolari C, Rama D, Puschendorf B, Berg A. Changes in skeletal and cardiac troponin I serum levels in 42 athletes after a sprint marathon. *Int J Sports Med* 1996;17(suppl1):S11.
16. Antman EM, Tanasijeevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fisher GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac specific troponin I to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342–1349.
17. Trinquier S, Flecheux O, Bullenger M, Castex F. Highly specific immunoassay for cardiac troponin I assessed in non-infarct patients with chronic renal failure or severe polytrauma [letter]. *Clin Chem* 1995;41:1675–1676.
18. Bonnefoy E, Chevalier P, Kirkorian G, Guidolet J, Marchand A, Touboul P. Cardiac troponin does not increase after cardioversion. *Chest* 1997;111:15–18.
19. Douglas PS, O'Toole ML, Hiller WDB, Hackney K, Reichek N. Cardiac fatigue after prolonged exercise. *Circulation* 1987;76:1206–1213.
20. Douglas PS, O'Toole ML, Woolard J. Regional wall motion abnormalities after prolonged exercise in the normal left ventricle. *Circulation* 1990;82:2108–2114.

Effect of Increased Body Mass Index on Accuracy of Two-Dimensional Echocardiography for Measurement of Left Ventricular Volume, Ejection Fraction, and Mass

Michael L. Chuang, MS, Peter G. Danias, MD, PhD, Marilyn F. Riley, BS, Mark G. Hibberd, MD, PhD, Warren J. Manning, MD, and Pamela S. Douglas, MD

Transthoracic 2-dimensional echocardiography (2DE) is widely used to assess left ventricular (LV) mass and ejection fraction, both of which are important predictors of cardiovascular risk.[1–3] However, patient obesity or overweight, which are risk factors for cardiac disease,[4,5] are associated with poor study quality in transthoracic 2DE.[6–8] Overweight, defined as body mass index (BMI) $\geq$25 but $<$30 kg/m^2, and obesity (BMI $\geq$30 kg/m^2)[9] are highly prevalent in the USA; more than one third of adults are estimated to be obese.[10] However, the quantitative effect of overweight and obesity on 2DE accuracy in measurement of LV volumes, mass, and ejection fraction has not been explicitly investigated. We sought to evaluate the effect of increased BMI on 2DE in assessing LV volumes, mass, and ejection fraction using magnetic resonance imaging (MRI) as a reference standard, and to compare 2DE with transthoracic 3DE.

• • •

Twenty-four adults (8 women and 16 men) underwent 2DE, 3DE, and cardiac MRI after providing written informed consent in accordance with the policies of the hospital institutional review board. Twelve

From the Cardiovascular Division, Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of the Department of Medicine, and the Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts. Dr. Douglas's address is: University of Wisconsin School of Medicine, H6/352 Clinical Science Center, 600 Highland Avenue, Madison, Wisconsin 53792-3248. E-mail: psd@medicine.wisc.edu.

This study was supported in part by a grant from the Hewlett-Packard Company, Andover, Massachusetts. Michael Chuang was supported in part by a fellowship from the Stanley J. Sarnoff Endowment for Cardiovascular Science, Inc., Great Falls, Virginia. Manuscript received April 24, 2000; revised manuscript received and accepted August 14, 2000.

0002-9149/01/$–see front matter
PII S0002-9149(00)01383-7