Impact of Statin Use on Exercise-Induced Cardiac Troponin Elevations

Thijs M.H. Eijsvogels, PhD[a,b], James L. Januzzi, MD[c], Beth A. Taylor, PhD[a,d], Stephanie K. Isaacs, BS[c], Pierre D'Hemecourt, MD[e], Amanda Zaleski, MS[a], Sophia Dyer, MD[e], Chris Troyanos, ATC[e], Rory B. Weiner, MD[c], Paul D. Thompson, MD[a], and Aaron L. Baggish, MD[c,e,*]

Marathon running commonly causes a transient elevation of creatine kinase and cardiac troponin I (cTnI). The use of statins before marathon running exacerbates the release of creatine kinase from skeletal muscle, but the effect of statin use on exercise-induced cTnI release is unknown. We therefore measured cTnI concentrations in statin-using (n = 30) and nonstatin-using (n = 41) runners who participated in the 2011 Boston Marathon. All runners provided venous blood samples the day before, within an hour of finishing, and 24 hours after the marathon. cTnI was assessed at each time point via both a contemporary cTnI and high-sensitivity cTnI (hsTnI) assay. Before the marathon, cTnI was detectable in 99% of runners with the use of the hsTnI assay. All participants completed the marathon (finish time: 4:04:09 ± 0:41:10), and none had symptoms of an acute coronary syndrome. cTnI increased in all runners (p <0.001) immediately after the marathon, and half (hsTnI = 54% vs contemporary cTnI = 47%) exceeded the diagnostic cut-point for an acute myocardial infarction. Statin use did not affect the magnitude of cTnI release (group*time p = 0.47) or the incidence of runners with cTnI elevation greater than the diagnostic cut-point for myocardial infarction (57% vs 51%, p = 0.65). In addition, there was no significant association between statin potency and cTnI release (r = 0.09, p = 0.65). In conclusion, marathon-induced cTnI increases are not altered by statin use. **(Am J Cardiol 2014;114:624–628)**

Cardiac troponin I (cTnI) is a sensitive and specific marker of myocardial injury,[1] but serum cTnI increases may occur after strenuous physical exercise in healthy individuals.[2–4] Marathon participants often demonstrate cTnI elevations after racing that are similar to those characteristic of an acute coronary syndrome.[5–7] The mechanism mediating exercise-induced cTnI release remains uncertain, and it is unclear why some runners demonstrate increased cTnI concentrations and others do not. Skeletal muscle injury, documented by an increase in serum creatine kinase (CK) concentrations, commonly occurs after a marathon run. The use of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (i.e., statins) before a marathon increases the magnitude of CK release from skeletal muscle,[8] but the effect of statin use on myocardial cTnI release after prolonged aerobic exercise has not to our knowledge been examined. We measured serial cTnI concentrations by using both a contemporary cTnI and high-sensitivity cTnI assay (hsTnI) in statin-using and nonstatin-using runners who participated in the 2011 Boston Marathon. We hypothesized that statin-using runners would demonstrate greater cTnI elevations than otherwise-matched, nonstatin-using runners.

Methods

We recruited 30 statin-using runners (statin group) and 41 nonstatin-using runners (control group) participating in the 2011 Boston Marathon. All participants provided written, informed consent (Institutional Review Board, Hartford Hospital, Hartford, Connecticut). Participants were nonsmokers, aged >35 years, and free of known cardiovascular or metabolic disease except for dyslipidemia for the statin group.

The day before the marathon (PRE), participants provided their medical history and training mileage for the 3 months and 1 week preceding the marathon. Resting blood pressure, heart rate (Welch Allen 52000 Vital Signs Monitor, Skaneateles Falls, New York), height, and body mass were measured. Venous blood samples (25 ml) were obtained before (PRE), within 1 hour after (FINISH), and ∼24 hours after the race (POST-24H).

Venous blood was collected in serum-gel Vacutainer tubes (BD, Franklin Lakes, New Jersey) and allowed to clot for ∼45 minutes. Serum was separated by centrifugation, aliquoted, frozen, and stored at −80°C for later analysis. Cholesterol and triglycerides, hemoglobin, hematocrit,

[a]Henry Low Heart Center, Department of Cardiology, Hartford Hospital, Hartford, Connecticut; [b]Department of Physiology, Radboud University Medical Center, Nijmegen, The Netherlands; [c]Cardiovascular Performance Program, Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts; [d]Department of Health Sciences, University of Hartford, West Hartford, Connecticut; and [e]Boston Athletic Association, Boston, Massachusetts. Manuscript received April 7, 2014; revised manuscript received and accepted May 27, 2014.

This study was funded by research grants from the Massachusetts General Hospital (Boston, Massachusetts) and Hartford Hospital (Hartford, Connecticut). T.M.H.E is financially supported by the Netherlands Organization for Scientific Research (Rubicon Grant 825.12.016).

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*Corresponding author: Tel: (617) 643-7117; fax: (617) 643-7222.

E-mail address: abaggish@partners.org (A.L. Baggish).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.05.047

Table 1
Subject characteristics

Groups	Total (n = 71)	Statin (n = 30)	Control (n = 41)	Statin vs. Control (p-Value)
Men:women (number)	51:20	23:7	28:13	0.44
Age (years)	53 ± 8	56 ± 8	51 ± 7	0.003
Height (meters)	1.73 ± 0.10	1.74 ± 0.09	1.73 ± 0.11	0.70
Weight (kg)	70.0 ± 12.2	71.1 ± 11.1	69.4 ± 13.0	0.56
Body mass index (kg/m^2)	23.1 ± 2.7	23.3 ± 2.5	23.1 ± 2.9	0.71
Resting heart rate (bpm)	59 ± 11	59 ± 13	59 ± 10	0.99
Systolic blood pressure (mmHg)	138 ± 18	141 ± 17	137 ± 17	0.41
Diastolic blood pressure (mmHg)	79 ± 11	78 ± 16	79 ± 11	0.77
Average running distance (miles/week)	38 ± 16	39 ± 19	39 ± 13	0.85
Running distance week premarathon (miles)	20 ± 13	22 ± 17	19 ± 10	0.29
Total cholesterol (mg/dl)	183 ± 35	169 ± 32	193 ± 32	0.003
High-density lipoprotein cholesterol (mg/dl)	71 ± 19	65 ± 13	74 ± 21	0.04
Low-density lipoprotein cholesterol (mg/dl)	97 ± 27	87 ± 28	104 ± 25	0.01
Triglycerides (mg/dl)	77 ± 34	82 ± 41	75 ± 29	0.45
Hemoglobin (g/dL)	14.4 ± 1.1	14.5 ± 1.3	14.4 ± 1.0	0.73
Hematocrit (%)	41.8 ± 3.2	41.8 ± 3.7	41.8 ± 2.9	0.96
Albumin (g/dL)	4.5 ± 0.2	4.5 ± 0.2	4.6 ± 0.2	0.02
Total bilirubin (mg/dL)	0.83 ± 0.41	0.84 ± 0.45	0.82 ± 0.39	0.90
Direct bilirubin (mg/dL)	0.17 ± 0.08	0.18 ± 0.09	0.16 ± 0.07	0.34
Alkaline phosphatase (IU/L)	56.7 ± 16.6	58 ± 16	56 ± 17	0.50
Alanine aminotransferase (IU/L)	24.3 ± 14.3	28 ± 18	22 ± 11	0.07
Aspartate aminotransferase (IU/L)	27.9 ± 22.7	28 ± 12	28 ± 28	0.87

Table 2
Type and dose of statins

Statin (Dose in mg)	Number of Runners
Fluvastatin	
80	1
Atorvastatin	
5	2
10	2
20	5
80	1
Rosuvastatin	
10	2
Simvastatin	
10	2
20	5
40	5
Lovastatin	
20	2
Pravastatin	
10	2

albumin, bilirubin (total and direct), alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase were determined after a 12-hour fast at PRE only (Quest Diagnostics, Nichols Institute, Chantilly, Virginia). Lipid and hepatic panels were performed with a spectrophotometric assay. The hematocrit and hemoglobin were measured with a colorimetric assay. Muscle myoglobin was assessed with a nephelometric assay.

cTnI was analyzed with a contemporary assay (Siemens Dimension Vista cTnI; Siemens Healthcare Diagnostics Inc., Newark, New Jersey) and a precommercial, high-sensitivity assay (i.e., hsTnI; Siemens Vista hsTnI, Siemens Healthcare Diagnostics Inc.).[9] The limit of detection (LOD) of the contemporary cTnI assay was 15 ng/L, with a 10% coefficient of variation (CV) at 40 ng/L. A concentration of 45 ng/L (10% CV) has been reported as the 99th percentile upper reference limit for the contemporary cTnI assay[10] and has been proposed as the clinical cut-point for the diagnosis of acute myocardial infarction.[1] The LOD of the hsTnI assay was 0.8 ng/L, with an 8.5% CV at 4.4 ng/L and a 99th percentile of 48 ng/L (5.0% CV).[11] All samples were analyzed in duplicate and mean values calculated. We also measured complementary cardiovascular biomarkers (Siemens Dimension Vista Intelligen Lab System, Siemens Healthcare Diagnostics Inc.): N-terminal pro−B-type natriuretic peptide (NT-proBNP), myoglobin, and cystatin C at PRE, FINISH, and POST-24H.

All data were reported as mean ± SD unless stated otherwise, and statistical significance was set at a p-value <0.05. Statistical analyses were performed with the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, New York). The normality of the data was examined by the Kolmogorov-Smirnov test. When data demonstrated a non-Gaussian distribution, natural logarithmic transformation was applied. Changes in contemporary cTnI and hsTnI concentrations over time were assessed with a repeated measurements analysis of variance, with post-hoc Bonferroni corrections. The difference in the number of participants greater than the LOD and the 99th percentile with the contemporary cTnI and hsTnI assays was tested for significance by chi-square analysis. To determine the cardiac specificity of the contemporary cTnI and hsTnI assays, FINISH TnI concentrations were correlated with a Spearman correlation coefficient. Differences between the statin and control group were assessed with a Student *t* test and chi-square test for continuous and nominal parameters,

Table 3
Prevalence of cTnI samples above greater than the LOD and the 99th percentile using conventional and hsTnI

Variable	Conventional cTnI Assay		High Sensitive cTnI Assay	
	Statin	Control	Statin	Control
cTnI concentration >LOD				
PRE	7%	17%	100%	98%
FINISH	87%	71%	100%	100%
POST-24 hours	53%	56%	100%	100%
cTnI concentration >99th percentile				
PRE	3%	10%	3%	10%
FINISH	47%	46%	57%	51%
POST-24 hours	20%	29%	30%	24%

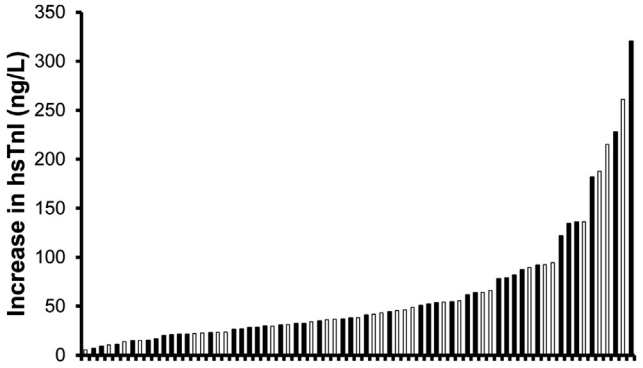

Figure 1. Exercise increases cTnI concentrations. Each *bar* represents 1 subject in the statin (*white bars*) or control group (*black bars*). All individuals demonstrated an exercise-induced increase in hsTnI.

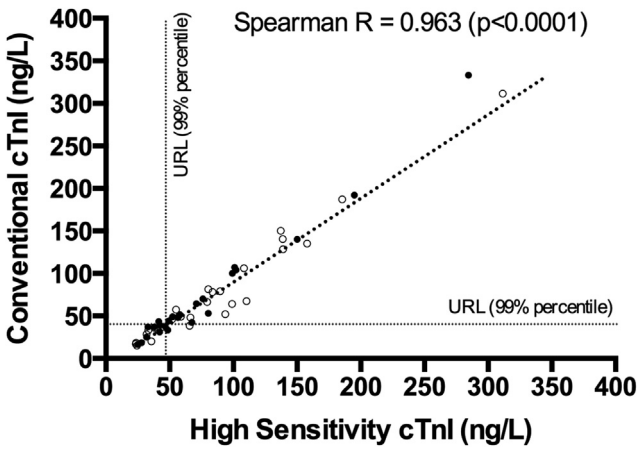

Figure 2. cTnI concentrations of the contemporary and high-sensitive assays are strongly correlated at FINISH (Spearman $R^2 = 0.96$, $p < 0.001$). Open circles represent FINISH cTnI concentrations of statin-using runners. Black circles represent cTnI concentrations of nonstatin-using runners.

respectively. To investigate the effect of statin dose on contemporary cTnI and hsTnI release (Spearman correlations), the statins were classified by the expected potency of cholesterol reduction according to dose equivalencies: rosuvastatin 2.5 mg = atorvastatin 5 mg = simvastatin 10 mg = lovastatin 20 mg = pravastatin 20 mg = fluvastatin 40 mg.[12,13]

Results

All athletes (Tables 1, 2) completed the marathon with an average race time of 4:04:09 ± 0:41:10 (range, 2:48:58−5:46:41 minutes). No runners had symptoms suggestive of an acute coronary syndrome within 24 hours of race completion.

cTnI could be detected in 13% and 99% of the runners before the race via the contemporary cTnI and hsTnI assay, respectively ($p < 0.001$), with an average of 7% of the participants exceeding the 99th percentile value with both assays (Table 3). Contemporary cTnI and hsTnI concentrations were increased at FINISH (both $p < 0.001$), with detectable cTnI concentrations in 78% and 100% for the 2 assays, respectively ($p < 0.001$). Notably, 100% of participants demonstrated an increase in hsTnI concentrations (Figure 1), with 47% and 54% of the runners exceeding the 99th percentile for the contemporary cTnI and hsTnI assays, respectively ($p = 0.40$). Contemporary cTnI and hsTnI concentrations were highly correlated at FINISH ($r^2 = 0.96$, $p < 0.001$; Figure 2). cTnI concentrations remained increased at POST-24H and detectable in 52% and 100% of the participants with the contemporary cTnI and hsTnI assay, respectively ($p < 0.001$). At POST-24H, the number of participants exceeding the 99th percentile was comparable for the contemporary cTnI (25%) and hsTnI (27%) assay ($p = 0.85$). The exercise-induced changes in CK concentrations in statin-using and nonstatin-using runners were published previously.[8] NT-proBNP ($p < 0.001$) myoglobin ($p < 0.001$), and cystatin C concentrations ($p < 0.001$) also were significantly increased at FINISH and POST-24H.

The magnitude of exercise-induced cTnI release was similar between the statin and control group when both the contemporary cTnI and hsTnI assay were used (group*time $p > 0.05$ for both assays, Figure 3). Our findings did not change after correction for age (contemporary cTnI: group*time: $p = 0.43$, hsTnI: group*time: $p = 0.44$). Statin potency was not significantly correlated to FINISH contemporary cTnI ($r = -0.102$, $p = 0.63$) or hsTnI concentrations ($r = 0.09$, $p = 0.65$). The incidence of runners greater than the hsTnI 99th percentile was similar between the statin and control group at PRE (3% vs 10%, $p = 0.30$), FINISH (57% vs 51%, $p = 0.65$), and POST-24H (30% vs 24%, $p = 0.60$) (Table 2). Similarly, changes in myoglobin ($p = 0.90$), NT-proBNP ($p = 0.10$), and cystatin C ($p = 0.38$) were not different between the statin users and nonstatin users (Figure 3).

Discussion

We compared cTnI concentrations at rest and after a marathon by using both a contemporary cTnI and hsTnI assay in statin-using and nonstatin-using recreational runners. Our results indicate that statin use does not affect the magnitude of cTnI release that occurs with marathon running. Thus, statin use does not contribute to the variability in the cTnI response to exercise observed in this study and in previous reports. The hsTnI assay data demonstrate that all runners experience an increase in cTnI

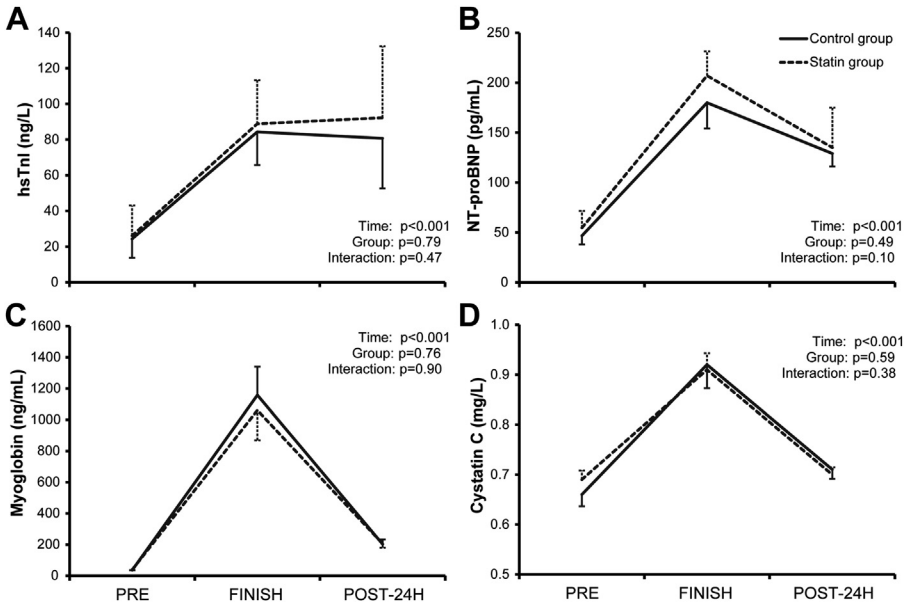

Figure 3. Concentrations of *(A)* hsTnI, *(B)* NT-proBNP, *(C)* myoglobin, and *(D)* cystatin C PRE, FINISH, POST-24 h the marathon in the statin (*dashed line*) and control group (*solid line*). Data are presented as mean ± SEM.

concentrations after exercise. This finding confirms the notion that exercise-induced cTnI release is a ubiquitous finding among recreational marathon runners. Approximately 50% of runners, all without clinical evidence of an acute coronary syndrome, demonstrated cTnI concentrations exceeding the recommended cut-point for the diagnosis of acute myocardial infarction. The prevalence of cTnI elevation consistent with acute myocardial infarction did not differ between the contemporary cTnI (47%) and hsTnI assays (54%).

In previous studies, authors suggest that the increase in cTnI after running a marathon, defined as a cTnI level greater than the assay-specific recommended upper reference limit, occurs in approximately 50% of runners.[14,15] Factors affecting the heterogeneity of the cTnI response, including age, gender, previous running experience, exercise characteristics, and troponin assay performance have been proposed but inconsistently duplicated.[16–20] The use of statins for the prevention of atherosclerotic vascular disease is widespread among athletic patients.

Recently, we have shown that exercise-induced CK release, a marker of skeletal muscle damage, is significantly greater in statin-using versus nonusing marathon runners, suggesting that statins potentiate exercise-induced skeletal muscle damage.[8] Contrary to CK release, the magnitude of cTnI release did not differ between statin-using and nonstatin-using runners, which is consistent with the concept that statin potentiate skeletal but not cardiac muscle injury. This finding is also consistent with the concept that cTnI increases after exercise are not caused by the release of cTnI from skeletal muscle. Some have hypothesized that the cardiac troponin increases are the result of repetitive injury and the breakdown of satellite repair cells, which have the capacity to produce cardiac troponin T (cTnT), the predominant troponin in fetal skeletal muscle.[21–23]

Most previous studies in which researchers have examined the release of cTnI during exercise have used contemporary cTnI assays. These assays have revolutionized the diagnostic evaluation of patients with suspected acute coronary syndromes but lack the sensitivity to detect small changes in cTnI concentrations. Newer assays facilitate measurement of cTnI at considerably lesser concentrations. Few studies have used these hsTnI/high-sensitivity cTnT (hsTnT) assays to examine exercise-induced cTnI release. Baker et al[24] used a hsTnT assay and found no difference in cTnT concentrations among runners in the London marathon who did (n = 5) or did not (n = 57) have structural heart disease. Mingels et al[18] used contemporary cTnI and cTnT assays and a precommercial hsTnT assay to assess cTnI and cTnT concentrations in runners at the Maas Marathon. The hsTnT assay detected low concentrations of premarathon cTnT, allowing the authors to document that cTnT release occurred in a greater percentage of runners than previously thought. Notably, 86% of runners exceeded the diagnostic cut-point for myocardial infarction with the hsTnT assay versus 45% with the contemporary cTnT assay.

Our data demonstrate for the first time that statin use does not increase exercise-induced cTnI release with strenuous exercise. These findings are in line with a recent clinical trial in which statin therapy did not impact cTnI release after a percutaneous coronary intervention.[25] cTnI increases occur in most healthy marathon runners, as documented by either contemporary cTnI or hsTnI assays. In contrast to other authors,[18] we did not observe a greater prevalence of runners meeting diagnostic criteria for acute myocardial infarction with the hsTnI versus contemporary cTnI assay probably because we used we used the 99th percentile as the diagnostic thresholds for both assays and not the upper reference limit used by others. We did observe a greater prevalence of runners with detectable hsTnI than

contemporary cTnI concentrations before the race, probably because of the low concentrations of these participants and the greater sensitivity of the assay. After exercise, however, cTnI concentrations increased to a range equally detectable by either method. In aggregate, these findings suggest that hsTnI assays provider novel insight into the physiology of exercise-induced cTnI release compared with contemporary cTnI assays and their use does not appear to increase the prevalence of runners with cTnI concentrations exceeding diagnostic thresholds for myocardial infarction after running a marathon.

This study has several limitations. The study cohort is relatively small but similar in size to other studies in which investigators examined the effect of statin use on muscle injury.[26] The study did not use a randomized design, and the statin-users were older than nonusers (51 ± 7 vs 56 ± 8, $p = 0.003$). Age may increase cTnI concentrations in marathon runners,[17] although correction for age did not alter the results in our study. Although we did not find a relationship between statin potency and cTnI release, we cannot exclude the possibility that greater doses of statins or a longer time on statin therapy would increase cTnI concentrations.

Acknowledgment: The authors thank Kevin Ballard, PhD, Jeffry Caprizzi, MS, Charles d'Hemecourt, BS, Lindsay Lorson, BS, and William Roman, BS, for assistance with data collection and Siemens Healthcare Diagnostics for assistance with blood sample analysis.

Disclosures

Dr. Januzzi has received grant support from DiagnosticsRoche, Siemens, Critical Diagnostics, Singulex, BG Medicine, and Thermo Fisher. Dr. Thompson reports receiving research grants from the National Institutes of Health, GlaxoSmithKline, Anthera, Genomas, Roche, Aventis, Novartis, Regeneron, and Sanolf; serves as a consultant for AstraZeneca, Regeneron, Merck, Roche, Genomas, Abbott, Runner's World, Genzyme, Sanolfi, Pfizer, and GlaxoSmithKline; receives speaker honoraria from Merck, Abbott, AstraZeneca, GlaxoSmithKline, and Kowa: and owns stock in General Electric, JA Wiley Publishing, J&J, and Abbott.

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