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Original Article

The impact of hepatitis B carrier on cardiac troponin I in 100-km ultramarathon runners

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Abstract

Background: Prolonged endurance exercise is known to cause elevation of cardiac troponin I (cTnI). Previous studies have reported the correlation of several factors with exercise-induced cTnI release. However, the investigation of the predictors for elevated cTnI and postrace kinetics of cTnI after ultramarathon running is lacking, especially in an Oriental population.

Methods: Twenty-six participants, including eight hepatitis B virus carrier (HBVc) runners, who finished a 100-km ultramarathon in Taiwan were enrolled. For each participant, blood samples were collected 1 week before the race, as well as immediately and 24 hours after the finish.

Results: The results showed that 19 runners (73.1%) had postrace elevated cTnI levels and eight (30.8%) had elevated cTnI values lasting more than 24 hours after the run. A multiple linear regression analysis demonstrated that the HBV status was a factor related to the high level of cTnI after 24 hours of running ($\beta = 0.03$, $p = 0.08$). The recovery of plasma cTnI levels was delayed in ultramarathon runners with latent HBV infection. Among HBVc runners, multiple linear regression analyses showed age ($\beta = -0.01$), previous running experience ($\beta = -0.06$), training distance ($\beta = 0.37$), and 4 hours of running distance ($\beta = -0.04$) as significant predictors of higher postrace cTnI levels.

Conclusion: For most athletes, cTnI values significantly increased immediately following the race in the absence of adverse clinical sequelae, and HBVc runners had higher and prolonged cTnI levels. While several factors are identified for such HBV effects, the specific causes need further elucidation.

Keywords: hepatitis B carrier; troponin I; ultramarathon

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Marathon running has a growing popularity worldwide.[1,2] This trend is also observed in Taiwan, where the number of races held has increased from a single race in 2005 to 13 races in 2014.[2] Such competitions not only test the resiliency and character of the marathon runners but also push them to a huge physical stress. Ultramarathon is defined as a race longer than an official marathon (42.195 km or 26.2 miles) and may vary in length or time duration.[1,2] Numerous reports have been published on changes in runners' physiological characteristics that occur during long-distance and 24-hour ultramarathons,[3,4] including hyponatremia, skeletal muscle breakdown, iron depletion, anemia, and possible hepatic damage. Our previous study showed that ultramarathon running is associated with a wide range of significant changes in hematological parameters, several of which can be associated with potentially serious renal and physiological abnormalities.[2]

Cardiac troponin I (cTnI) is a well-established, sensitive, and specific marker of myocardial injury. However, evidence indicates that unrecognized myocardial injury may be occurring with certain conditions such as sepsis without acute coronary ischemic event, which demonstrate elevated cTnI levels.[5] Like most prolonged endurance exercises, ultramarathon is known to cause elevation of cardiac markers, like cTnI.[6−10] Previous studies revealed the association of several factors with such exercise-induced cTnI release,[11−13] including age, exercise intensity, exercise duration and training levels,[1,6,12−15] in the absence of clinical symptoms of myocardial infraction.[6,13−15] However, those studies mainly focused on white populations.[14,15]

More than 240 million people globally are currently infected with hepatitis B virus (HBV).[16] At least 9.8% of the population are HBV chronic carriers in Asia-Pacific.[17] Among Oriental endurance athletes, many are HBV carrier (HBVc) runners. Previous literature had demonstrated that subclinical myocardial injury occurs more commonly than has been recognized in acute liver failure.[18] HBV has been associated with several extrahepatic manifestations.[19] Here, we wondered whether HBVc runners had different degree of impairment of myocardiocytes in comparison with that for other athletes. In addition, we examined the potential independent factors known to be relevant to exercise-induced cTnI release in this exertional exercise model.

2. Methods

2.1. Study design and population

Twenty-five males and one female experienced ultramarathon runners participating in the 2011 FLEX Power Cup National 100-km Ultra-Marathon in Taipei, Taiwan volunteered for this study. Approval was obtained from the Institutional Review Board of the Taipei Veterans General Hospital. All runners provided written consent to participate in the study. The competition began at 7 AM and ended at 9 PM on October 10, 2011. All runners ran around a 400-m oval track. They were permitted to rest and to ingest water and food freely. Before the competition, all runners were required to complete a questionnaire for demographic data and information on medical and training history. All participants with a medical history of heart disease including congenital heart disease, coronary heart disease, or heart failure were excluded.

2.2. Laboratory assessment

Blood (20 mL) was drawn from an antecubital vein, using sterile techniques, 1 week before, immediately following, and at least 24 hours after the race. All specimens were refrigerated and transported to the laboratory within 4 hours of sampling.

The participants were screened for hepatitis A, B, and C virus (HAV, HBV, and HCV, respectively) infections by electrochemiluminescent immunoassay with Vitro ECiQ Immunodiagnostic System (VITROS, Raritan, USA). All of them denied having been infected by HAV or HCV previously, and were negative for anti-HAV immunoglobulin M and anti-HCV antibodies. Among 26 participants, there were eight HBVc runners with a previous history of HBV infection and positive hepatitis B surface antigen (HBsAg). The eight HBVc runners were in an inactive state, with negative antihepatitis Be antigen (HBeAg) and positive antihepatitis Be antibody (anti-HBe).

Plasma samples of the two groups were assayed on the Siemens Dimension RXL Max Integrated Chemistry System using reagents supplied by the manufacturer. Analysis was directly performed on the same race day using the same calibration. Troponin I was analyzed using a high-sensitivity cTnI ASSAY (Siemens Healthcare Diagnostics, Germany). Creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), and myoglobin were analyzed with the Siemens Dimension RxL Max Integrated Chemistry System (Siemens Dimension RxL, Germany) using reagents supplied by the manufacturer. A cTnI value $\geq$ 0.05 ng/mL was considered an elevated level, representing a positive test indicative of myocardial injury. The lower limit of detection of the test was 0.01 ng/mL.

2.3. Statistical analysis

All data were reported as mean $\pm$ standard deviation and histogram was plotted to examine the normality of the data distribution. Statistical significance was assumed at $p < 0.05$. Statistical analyses were performed using a paired t test with R (3.1.2) statistics environment. A linear regression analysis was used to identify factors that significantly related to postrace cTnI levels in asymptomatic hepatitis carriers. Based on our hypothesis, we had age, running experience, training, and 4 hours of running distance in our model as potential determinants to predict postrace cTnI level. All predictors with $p < 0.05$ were retained in our final regression model.

3. Results

All 26 participants completed a 100-km ultramarathon. The training status of each participant and the completed 100-km

running time were described in previous reports.[2,20–22] The ultramarathon was held on a sunny day with temperatures between 24.9°C and 28.7°C, humidity between 66% and 87%, and wind speed ranging from 0 m/s to 6.5 m/s (information provided by Central Weather Bureau). None of these participants finished the race with any adverse medical event.

All participants with age 46.9 ± 9.0 years completed the ultramarathon in 670.0 ± 85.3 minutes. The average distance after 4 hours' running was 39.3 ± 5.2 km. The average experience in all runners was 5.4 ± 3.4 times, and the average best marathon time was 211.3 ± 21.2 minutes. For the runners in this study, four had weekly training of <40 km, 15 had weekly training of 40 km to 100 km, and seven had weekly training of >100 km (Table 1). There were no missing and undetectable data.

Similar to previous results, our data showed that cardiac biomarkers, including CK, CK-MB, and cTnI, had a statistically significant rise immediately after the race (Table 2). Specifically, CK levels showed a ~25-fold increase immediately after the run, and the levels may have become a little higher even after 24 hours. For CK-MB, there was an approximately sevenfold increase in plasma activity immediately following the run, and this increase might persist for 24 hours. Between postrace and prerace values, there were statistically significant rises after the race in cTnI, a sensitive and specific marker of myocardial injury. Nineteen runners (73.1%) had postrace elevated cTnI levels. Eight participants (30.8%) had elevated cTnI values lasting more than 24 hours after the run.

A multiple linear regression analysis was performed on the 26 participants to explore the association between cTnI levels and other potential factors, including HBV status, considering age, body mass index, performance record, training levels, and previous years of marathon running. We found that the HBV status was a factor related to the high level of cTnI after 24 hours of running ($\beta = 0.03$, $p = 0.08$) but it was not associated with the cTnI levels before and immediately after the ultramarathon. Other factors were not associated with cTnI levels at all three time points ($p > 0.1$).

The 26 participants were further divided into HBVc runners ($n = 8$) and non-HBVc runners ($n = 18$). The performances of the HBVc and non-HBVc runners in the race were largely similar (Table 1). For plasma cTnI, the levels before race showed no apparent difference between the two groups of runners. For non-HBVc runners, the cTnI levels increased from 0.02 ± 0.03 ng/mL to 0.08 ± 0.05 ng/mL immediately after the finish; 72% of these runners had elevated cTnI. By contrast, the cTnI levels in HBVc showed an increase from 0.01 ± 0.01 ng/mL to 0.10 ± 0.11 ng/mL after the race, and a similar percentage (75%) of these runners had elevated cTnI. Intriguingly, five (62.5%) of the HBVc runners had unusually high cTnI levels 24 hours after the run, in stark contrast to the low percentage (16.7%) for the non-HBVc runner group (Fig. 1). These data suggest that the recovery of plasma cTnI levels is delayed in ultramarathon runners with latent HBV infection. Multiple linear regression analysis was performed on a data set of HBVc and non-HBVc runners. We identified age ($\beta = -0.01$, $p = 0.03$), previous running experience

Table 1
Descriptive characteristics of the study groups.

Characteristic	Total participants ($N = 26$)	Non-HBVc runners ($N = 18$)	HBVc runners ($N = 8$)
Age (yr)	46.9 ± 9.0	46.3 ± 10.0	48.3 ± 6.6
Height (m)	1.68 ± 0.08	1.69 ± 0.07	1.66 ± 0.08
Weight (kg)	64.5 ± 9.2	65.9 ± 10.0	61.3 ± 6.5
Body mass index (kg/m^2)	22.9 ± 2.7	23.3 ± 3.0	22.1 ± 2.0
Ultramarathon PR (min)	670.0 ± 85.3	680.2 ± 84.6	674.1 ± 92.7
4 h of running distance (km)	39.3 ± 5.2	39.3 ± 5.5	34.1 ± 4.5
Previous marathon experience (times)	5.4 ± 3.4	5.2 ± 3.5	5.9 ± 3.2
Marathon PR (min)	211.3 ± 21.2	210.5 ± 20.9	213.0 ± 23.1
Training distance			
<40 km/wk	4	2	2
40–100 km/wk	15	11	4
>100 km/wk	7	5	2

Data are expressed as means ± standard deviation.
HBV = hepatitis B virus; PR = performance record.

Table 2
Markers of cardiac and skeletal muscle damage prerace, postrace, and post-24 hours after a 100-km ultramarathon in 26 runners.

Variable	URL	Prerace	Postrace	Post-24 h
CK (U/L)	168	172.3 ± 91.7	4274.8 ± 5903.8*	5530.2 ± 3398.4*
		42.3% (11/26)	100% (26/26)	100% (26/26)
CK-MB (U/L)	13	9.9 ± 3.4	69.8 ± 87.0*	72.5 ± 44.3*
		11.5% (3/26)	100% (26/26)	96.2% (25/26)
Troponin I (ng/mL)	0.05	0.02 ± 0.03	0.09 ± 0.05*	0.04 ± 0.02
		11.5% (3/26)	73.1% (19/26)	30.8% (8/26)

CK = creatine kinase; CK-MB = creatine kinase-MB isoenzyme; URL = upper reference limit.
* Benjamini and Hochberg corrected $p < 0.05$. Paired t tests were used to detect the mean difference between prerace and postrace or post-24 race.

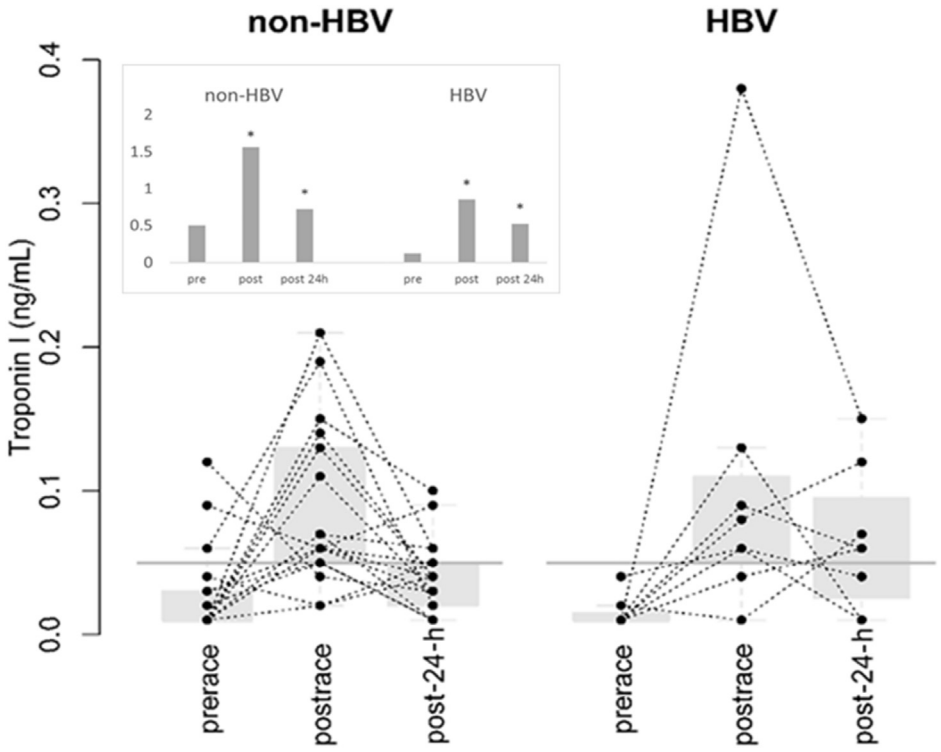

Fig. 1. Troponin I levels. Serum cardiac troponin I levels of eight asymptomatic hepatitis B and 18 non-hepatitis B runners at prerace, postrace, and post-24 hours after a marathon. The clinical cutoff of cardiac troponin I for myocardial injury (0.05 ng/mL) is shown as the horizontal lines. Dots represent the concentrations of troponin I of participants. The troponin I concentrations of the same participant at different time points are linked by dotted lines. Statistical significance was evaluated using the paired t test. * indicates a significant value ($p < 0.05$). HBV = hepatitis B virus.

($\beta = -0.06$, $p = 0.02$), training ($\beta = 0.37$, $p = 0.02$), and 4-hour running distance ($\beta = -0.04$, $p = 0.04$) as independent predictors of higher postrace cTnI levels in HBVc runners, whereas those parameters were not significant in non-HBVc runners. Our prediction model had an overall $r^2 = 0.8$.

4. Discussion

Similar to previous results, our data showed that cardiac biomarkers CK and CK-MB had a significant rise immediately after the race, and the increase persisted 24 hours after the run. Notably, this continuing elevation 24 hours after the run is also reported in marathon athletes, consistent with the notion that the muscle injury caused by ultramarathon may persist for at least a short while even when the endurance exercise is ended. When comparing these values with those of marathon runners, we found that the increase of CK or CK-MB in ultramarathon runners perhaps ranks among the highest among various endurance exercises. The difference in fold changes of CK and CK-MB probably indicates the sources of muscle injury. Increased creatine kinase-MM isoenzyme would be responsible for the great surge of CK activity in plasma. Specific creatine kinase-MM isoenzyme assay should help validate such a possibility.

Intriguingly, in a case report about elevation of skeletal enzymes in ultramarathon runners, the CK level reached its peak value one day after the run, had a ~4-day plateau, and began to decline after a few more days.[23] The sustained increase of plasma CK in this athlete was quite different from the peak pattern seen in patients with myocardial infarction. We do not know whether the athletes in this study follow the same kinetics, as more plasma samples collected at different time points need to be analyzed. Because it is likely that proteins leaked from stressed muscle cells, rather than being released from damaged tissues, these results together suggest that endurance exercises probably have a prolonged effect on membrane permeability, which is manifested as a multiple-day plateau for the CK or CK-MB level.

We examined how cTnI levels changed in ultramarathon runners. Our findings are very similar to those reported for one marathon athlete.[23] The cTnI level of this runner reached its peak value at 8−17 hours after the run, and returned to baseline within 48 hours. Thus, the cTnI level in endurance exercises dropped fairly quickly, which is in sharp contrast to the known cTnI profiles seen in myocardial injury. For patients with myocardial infarction, cTnI, among tested cardiac biomarkers, is supposed to be the last one to reach its peak level as well as to return to its baseline level. Thus, our results seem to confirm that the plasma cTnI profiles due to exertion-induced rhabdomyolysis are different from those caused by myocardial injury.

It is intriguing to see the rapid cTnI decline in such exertion-associated rhabdomyolysis. Based on the kinetic pattern and the minor increase, we propose two possibilities that may account for these findings. First, the cTnI measured in the current studies is indeed the troponin I from the heart

tissues of these athletes. cTnI (i.e., type 3 troponin I) is only present in cardiac muscle tissue; its release probably reflects myocardial injury during endurance exercise. It is very likely that this stress is minor and transient to cardiac tissue, as the increase is slightly above the reference limit and the decline occurs rapidly, within 24 hours after the run. Second, the troponin I detected here is due to the cross reactivity of antibodies against isoforms from skeletal muscles. With a molecular mass of ~24 kDa and consisting of 209 amino acid residues, type 3 troponin I is different from types 1 and 2 isoforms largely by its N-terminal extension of 26 amino acids. Because most of the cTnI immunogens have epitopes beyond this N-terminal domain, the antibodies produced may indeed react with other troponin I isoforms. Because the CK and CK-MB spikes predict extensive muscle stress, the observed low cTnI level is likely due to the ineffective detection by low cross-reactivity. The CK and troponin I kinetics here are also different from those due to myocardial infarction, because these profiles in these two health conditions likely reflect the fundamental distinction in the contractile systems between skeletal and cardiac muscles. It is a general belief that most proteins released by tissue leakage are cleared from the bloodstream in kidney. The filtration capacity of glomerular membrane, with an approximated limit of 40–60 kDa for globular proteins, likely determines how fast plasma proteins are cleared. To distinguish these two scenarios, we will repeat immunochemical analyses using antibodies against type 1 or type 2 troponins.

Furthermore, HBV latent infection appeared to cause some aberration in troponin kinetics in ultramarathon athletes. Our data suggest that the recovery of plasma cTnI levels is somehow delayed in ultramarathon runners with HBVc. Multiple linear regression analyses were performed to identify whether any factors were associated with this higher postrace cTnI level, which identified age, previous running experience, training, and 4-hour running distance as independent predictors for HBV carriers. By contrast, those parameters were not significantly different from those of non-HBVc runners, with an excellent correlation coefficient ($r^2 = 0.8$) for the overall prediction model.

We examined the potential independent factors previously reported to relate to postrace cTnI levels using linear regression analysis. We found that age, 4-hour running distance, previous running experience, and postrace cTnI levels demonstrated an inverse relationship in HBVc runners. This observation is in line with those of other studies.[6,7,11] Previously, Shave et al[24] had investigated whether higher cTnI release might relate to higher exercise intensity, and to higher work of the heart muscle, suggesting an age-dependent relationship. Eijsvogels et al,[13] however, reported an opposite relationship between postrace cTnI levels and exercise duration. However, in the present study, we observed that the 4-hour running distance was related to increase of cTnI levels. This is consistent with the model that longer exercise duration is usually related to exercise intensity-induced cTnI levels.[24,25] In addition, we also observed a positive relationship between training ($\beta = 0.37$, $p = 0.02$) and postrace cTnI levels in HBVc runners. This finding is in line with Shave et al[24] group's report that exercise-induced cTnI release was strongly related to training experience.[26] Thus, factors such as age, intensity of exercise, training, and running experience might be a potential relation to be explained by the exercise mode in the present study.

Taken together, 100-km ultramarathon seems not to have been the trigger for myocardial damage in our study. Meanwhile, our exercise model's predictive value is high ($r^2 = 0.8$), which indicates that a portion of cTnI levels can be explained due to those potential factors in the HBVc runners' group. However, a recent study by He et al[27] investigated whether autophagy is induced by exercise, which resulted in biochemical evidence of skeletal and cardiac muscle autophagy. In addition, exercise-induced autophagy in liver and heart involved glucose and energy homeostasis.[27] Thus, exercise is a newly defined stimulus that induces autophagy *in vivo*.[27,28]

We recognize several limitations in this small observational study, such as small sample size, no electrocardiography monitor, and single post-24-hour assessment of cTnI. In addition, we did not follow the participants' cardiac markers for long-term effects of the 100-km ultramarathon in both groups. We provide these data as a resource for additional studies, so a further investigation of long-term effects of the 100-km ultramarathon on cardiac markers is necessary to confirm and support the findings in this study.

In conclusion, for most athletes, cTnI values significantly increased immediately following the race in the absence of adverse clinical sequelae. HBVc runners had significantly higher cTnI levels immediately postrace and a prolonged cTnI increase 24 hours after the race. This response could be partly explained by age, running experience, training, and 4-hour running distance. The cause for different variations of cTnI in HBVc runners in response to ultramarathon needs further elucidation. While we observed rapid recovery of cTnI elevation for most non-HBVc participants, HBVc runners generally have a prolonged cTnI elevation. These results suggest that high cTnI levels can be a common variation seen for athletes in asymptomatic HBV.

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