Impact of renin-angiotensin-aldosterone system activation and body weight change on N-terminal pro-B-type natriuretic peptide variation in 100-km ultramarathon runners

Li-Hua Li[a,b], Wei-Fong Kao[c,d], Yu-Hui Chiu[c,e], Sen-Kuang Hou[c,d], Chen Meng[f], Chorng-Kuang How[g,h,*]

[a] Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b] PhD Program of Medical Biotechnology, Taipei Medical University, Taipei, Taiwan, ROC; [c] Department of Emergency Medicine, School of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [d] Department of Emergency and Critical Care Medicine, Taipei Medical University Hospital, Taipei, Taiwan, ROC; [e] Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan, ROC; [f] Department of Proteomics and Bioanalyticas, Techinsche Universitaet Muechen, Freising, Germany; [g] Department of Emergency, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [h] Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC

Abstract

Background: The change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels follows a paradox imposed by strenuous endurance exercise. Previous reports showed significant body weight (BW) loss was common in ultramarathon runners. This study investigated whether the BW change and renin–angiotensin–aldosterone system activation contribute to exercise-induced NT-proBNP release.

Methods: A total of 26 participants who finished a 100 km ultramarathon in Taiwan were enrolled. For each participant, blood samples and spot urine samples were collected 1 week before the race, as well as immediately and 24 hours after the finish. BW change was recorded to monitor the hydration status.

Results: Prolonged endurance exercise led to a substantial increase in NT-proBNP. Compared with prerace values, NT-proBNP levels significantly increased immediately after the race (24.3 ± 20.2 pg/mL to 402.9 ± 305.9 pg/mL, $p < 0.05$) and maintained high levels until 24 hours after the race (143.7 ± 126.1 pg/mL, $p < 0.05$). The fractional excretion of sodium values was below 1% in three different time points. The 100 km ultramarathon resulted in significant BW loss and elevated renin and aldosterone levels. However, only 24 hours after the race, a positive significant relationship was found between NT-proBNP and aldosterone levels ($p = 0.007$, $r^2 = 0.267$), but a negative significant relationship between NT-proBNP and BW increased during the recovery phase ($p < 0.001$, $r^2 = 0.372$).

Conclusion: The mechanism of NT-proBNP release immediately following the race was multifaceted. During the recovery phase, rehydration might lead to the decrease of NT-proBNP. Our observations with regard to aldosterone and NT-proBNP might be in response to help the body maintains hydration state.

Keywords: Aldosterone; Mass balance; NT-proBNP; Rennin; Ultramarathon

1. INTRODUCTION

Ultramarathon, which is a running race longer than an official marathon (42.195 km or 26.2 miles), has gained increased popularity in recent decades worldwide.[1,2] During this long-distance event, the participants excite a huge physiological and metabolic responses to finish the competition.[3] Ultramarathon running is associated with a wide range of considerable changes in hematological parameters.[1,2,4] In addition, the high physiological demands required during an ultramarathon running may be associated with an increased risk for health, as electrolyte imbalance,[5] rhabdomyolysis, acute kidney injury,[2,6] and cardiac arrest.[7] Hence, understanding of athletes' hematological, physiological and cardiovascular consequences during these exhaustive exercise are becoming more important.

Taiwan is not an exception to these events. The number of races held in Taiwan has increased from a single race in 2005 to 124 races in 2018.[8] However, the increasing popularity of extreme endurance exercise necessitates a clear understanding of the cardiovascular consequences associated with such races. The prolonged duration of exercise performed during ultramarathon events is particularly important, considering that these races require increased cardiac work. In our previous study, up to 80.7% of finishers exhibited detectable levels of cardiac

*Address correspondence. Dr. Chorng-Kuang How, Emergency Department, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: ckhow@vghtpe.gov.tw (C.-K. How).

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

Journal of Chinese Medical Association. (2020) 83: 48-54.

Received May 14, 2019; accepted August 5, 2019.

doi: 10.1097/JCMA.0000000000000227.

troponin I after 100 km ultramarathon.[4] Long-distance running stimulates an increase in cardiac biomarkers, not only cardiac troponin but also N-terminal pro-B-type natriuretic peptide (NT-proBNP).[9,10]

NT-proBNP belongs to the cardiac natriuretic peptide family that is released from the heart in response to overloaded volume and pressure.[11] NT-proBNP level increases with the severity of left ventricular dysfunction and/or hypertrophy; therefore, it has become a useful biomarker for the diagnosis and prognosis of heart failure.[12] The change in NT-proBNP levels is associated with this kind of strenuous exercise-imposed paradox. Running a half marathon and a marathon induced slight changes in NT-proBNP levels, with no data exceeding the upper range limit of 125 pg/mL.[13,14] Meanwhile, NT-proBNP increment after endurance exercise had been revealed by some marathoners.[10,15] Serrano-Osta and colleagues reported that NT-proBNP increase is associated with exercise duration but not exercise intensity.[16] NT-proBNP expression is related to extreme exercise, increases vasodilatation, and inhibits sympathetic nerves to protect the cardiac myocytes.[10] During a 246 km ultramarathon foot race event, NT-proBNP increased remarkably.[17] Scott and colleagues demonstrated that a 160 km ultramarathon resulted in a mild decrease of left ventricular function and a significant NT-proBNP release.[18] However, the mechanisms related to these responses have not been extensively explained.

The release of NT-proBNP has been associated with various physiological functions, such as vasodilatation, diuresis, sodium excretion, inhibition of renin secretion, and suppression of aldosterone synthesis.[19,20] The disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ might induce acute or chronic dysfunction of the other.[21] A weak but significant correlation was found among the fluctuating parameters representing the cardiac and renal system in ultramarathon runners.[1,2,22] Furthermore, a substantial body weight (BW) loss is common in 100 km ultramarathon runners.[2] The renin-angiotensin-aldosterone system (RAAS) can be activated when blood volume loss is manifested, such as in dehydration. The RAAS is a group of related hormones that regulates blood pressure and fluid and electrolyte balance. Therefore, the purpose of the present study was to investigate the relationship between BW change, serum renin, aldosterone, and NT-proBNP levels. It was hypothezied that BW loss and RAAS activation possibly contribute to exercise-induced NT-proBNP release.

2. METHODS

2.1. Study population

Institutional Review Board approval (VGHIRB No: 2011-01-061IC) was obtained from the Ethics Committee of Taipei Veterans General Hospital. The protocol was approved by the Chinese Taipei Association of Ultrarunners. Amateur runners were scheduled to participate in the 2011 Soochow University 100 km ultramarathon in Taipei, Taiwan. Athletes volunteered for the study and provided written consent before participation. We excluded subjects with a history of cardiovascular disease (including congenital heart disease, coronary heart disease, and congestive heart failure). Subject characteristics and medical and training history were collected using predesigned clinical questionnaire forms that were personally filled out by the subjects. Variables included subject height, training load, previous marathon completion times, medical history, and medicine used within the past week. The route was based on the university stadium track (400m track circumference). Food and drink stations were set up and accessible along the route. BW change, fluid intake, and urine excretion were recorded to monitor the hydration status. To improve the accuracy of BW measurements, we maintained calibration and verification logs for our scale. Furthermore, we used the same scale and performed all scale measurements twice. BW was measured right before the competition, immediately following the race, and 24 hours after the race. All runners were allowed to have a short period to towel-dry before making BW measurements immediately after the race. BW change was the difference between prerace and immediate or 24 hours postrace and shown as percentage change from prerace measurements.

A total of 26 runners (25 male and 1 female) were recruited into our study. The training load of each subject and the completed 100 km running time are described in previous reports.[1,2] The ultramarathon was held in a sunny day, with temperature range of 24.9–28.7 °C, humidity of 66%–87%, and wind speed range of 0–6.5 m/s (Central Weather Bureau). All subjects have previous marathon experience, as well as training schedule. The average experience of running marathon was 5.4 ± 3.4 times, and the average best marathon time was 211.3 ± 21.2 minutes. Moreover, 4 runners (15%) had a weekly training of <40 km, 15 runners (58%) had a weekly training of 40–100 km, and 7 runners (27%) had a weekly training of >100 km.

2.2. Data collection

Blood (20 mL) was drawn from the antecubital vein by sterile techniques 1 week before, immediately following, and at least 24 hours after the race, as well as urine samples. All specimens were refrigerated and transported to the laboratory within 4 hours of sampling. None of the specimens demonstrated signs of hemolysis. Plasma samples were assayed on the Cobas 6000 analyzer. NT-proBNP levels were measured with an electrochemiluminescence sandwich immunoassay (Elecsys ProBNP, Roche Diagnostics) using the Roche e601 system. For subjects aged <75 years, the upper normal range limit was 125 pg/mL. Aldosterone and renin levels were determined by Architect I-2000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA), which demonstrates a chemiluminescent microparticle immunoassay. Other serum samples were assayed on the Siemen Dimension RXL Max Integrated Chemistry System using reagents supplied by the manufacturer. Spot urine samples were also collected to analyze the electrolyte levels and specific gravity.

2.3. Fractional excretion of sodium

Fractional excretion of sodium (FeNa) calculation predicts the likelihood of patient of acquiring acute renal failure due to prerenal, intrinsic, or postrenal pathology.[23] The following formula calculates the FeNa by using plasma sodium and creatinine concentrations (P[Na] and P[Cr]) and spot urine sodium and creatinine levels (U[Na] and U[Cr]) obtained simultaneously.

$$\text{FeNa} = (\text{U[Na]} \times \text{P[Cr]}) / (\text{P[Na]} \times \text{U[Cr]}) \times 100$$

FeNa > 2% suggests post-glomerular failure, whereas FeNa < 1% suggests prerenal azotemia (volume depletion). We then measured the FeNa levels of ultramarathon runners at prerace, immediate, and 24 hours postrace.

2.4. Statistical analysis

All data were shown as mean ± standard deviation. NT-proBNP, renin, and aldosterone levels were analyzed. We used Shapiro-Wilk normality test to test whether the measured values of parameters followed normal distribution. The results suggested 11 parameters out of 15 (3 time points × weight, NT-proBNP, aldosterone, renin, and FeNa) were significantly different with normal distribution ($p < 0.05$). Therefore, all statistical analyses were compared using the Wilcoxon signed-rank test with R (3.5.1) statistics environment. The Pearson correlation coefficient was used to evaluate the association of NT-proBNP /renin/aldosterone/BW changes. Differences were

statistically significant when $p < 0.05$. In addition, the coefficient of determination calculated from linear regression was reported to evaluate the proportion of the variance explained by the linear model.

3. RESULTS

3.1. Clinical variables of subjects

A total of 26 runners were enrolled in this study. All of them completed a 100-km ultramarathon. None had relevant medical problems during or 24 hours after the race. Table 1 shows the clinical variables of the 26 participants. The average age of the participants was 46.9 ± 9.0 years. Their BMI was 23.0 ± 2.2 kg/m^2. All 26 subjects completed a 100-km ultramarathon and finished the race in 670.0 ± 85.3 minutes. No missing data, as well as undetectable data, were noted.

Table1.

Demographic data and outcome measurement of 100 km ultramarathon runners

Variable	n = 26
Age (y)	46.9 ± 9.0
Gender, n (%)	
Males	25 (96.2%)
Females	1 (3.8%)
Height (cm)	167.9 ± 7.5
BW (kg)	65.0 ± 9.4
BMI (kg/m^2)	23.0 ± 2.2
Outcomes	
Finished time (min)	670.0 ± 85.3
Total drinking consumed (mL)	6906 ± 2687
Amount of urine excreted (mL)	252.5±166.6
BW change (immediate postrace), %	−2.6 ± 1.6%
BW change (24 hours postrace), %	−1.1 ± 2.0%

BW = body weight; BMI = body mass index.

3.2. Serum NT-proBNP levels

The prerace values of NT-proBNP were placed within the lower and middle ranges of normal distribution. Compared with the prerace values, NT-proBNP levels significantly increased immediately after the race (24.3 ± 20.2 pg/mL to 402.9 ± 305.9 pg/mL, $p < 0.05$) and maintained the lasting high levels until 24 hours after the race (143.7 ± 126.1 pg/mL, $p < 0.05$). Overall, 24 (92.3%) out of the 26 participants had NT-proBNP levels above the upper normal range limit immediately after the race without adverse clinical sequelae (Fig. 1).

3.3. Hydration status evaluation

Hydration status evaluation was based on BW change. During the race, subjects consumed an average of 6906 ± 2687 mL of fluid. However, BW was significantly decreased from prerace measurements to all postrace measurements. We observed that BW changes were −2.6% ± 1.6% immediately following the race. Furthermore, −1.1% ± 2.0% of BW change was found 24 hours after the race, as shown in Table 1.

3.4. FeNa evaluation

FeNa typically decreases (<1%) as the volume depletes. The FeNa levels were all below 1% in the prerace, immediate, and 24 hours postrace (Fig. 2).

3.5. Correlation of NT-proBNP with renin and aldosterone

Postexercise serum aldosterone and renin values were significantly ($p < 0.05$) increased compared with the prerace values (Table 2). NT-proBNP did not correlate with renin and aldosterone before the race and immediately after the race, whereas NT-proBNP did not correlate with renin 24 hours after the race. However, a positive significant relationship was found between

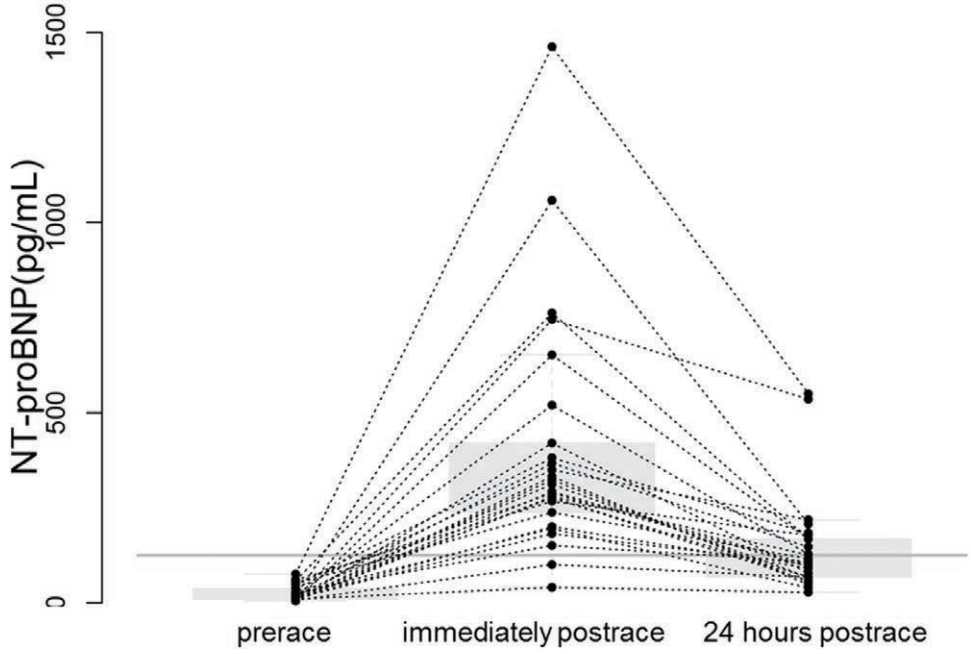

Fig. 1. Serum NT-proBNP levels of ultramarathon runners at prerace, immediate postrace, and 24 hours postrace. The horizontal lines denote the upper normal range limit of NT-proBNP (125 pg/mL). Dots represent the NT-proBNP concentrations of the participants. The NT-proBNP concentrations of the same participant at different time points are linked by dotted lines. Statistical significance was evaluated using the paired *t* test. * indicates a significant value ($p < 0.05$).

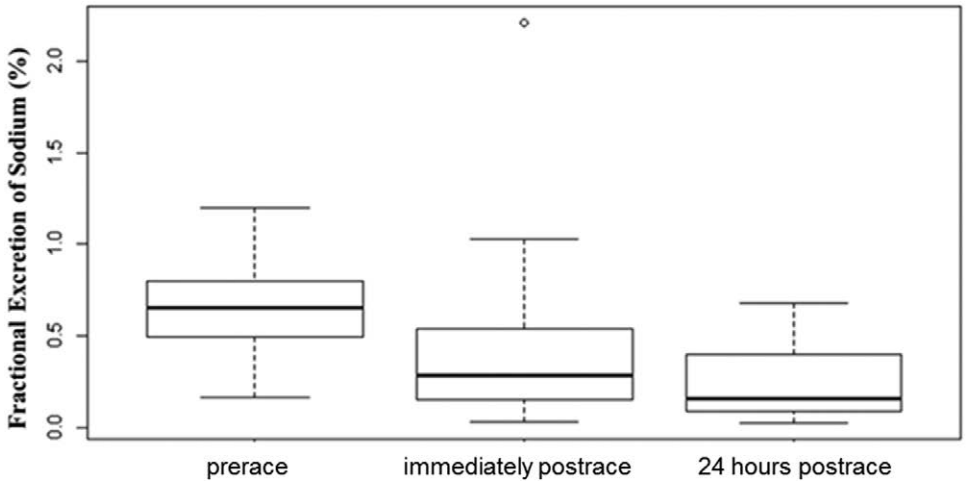

Fig. 2. Time course of the fractional excretion of sodium (FeNa) levels of ultramarathon runners at prerace, immediate postrace, and 24 hours postrace. Data are expressed as median value, interquartile range, and 5 and 95 percentile range.

Table 2.

Clinical and laboratory parameters throughout the 100-km ultramarathon race (n = 26)

Parameter	Prerace	Immediate postrace	24 hours postrace
NT-proBNP (pg/mL)	24.3 ± 20.2	402.9 ± 305.9[a]	143.7 ± 126.1[a]
Aldosterone (pg/mL)	118.1 ± 48.8	717.0 ± 301.9[a]	201.4 ± 169.0[a]
Renin (ng/L)	13.3 ± 5.3	84.3 ± 48.5[a]	26.4 ± 16.6[a]
BW (kg)	65.0 ± 9.4	63.3 ± 9.1[a]	64.2 ± 8.9[a]

*$p < 0.05$ versus prerace values.
BW = body weight.

NT-proBNP and aldosterone levels 24 hours after the race ($p = 0.007$, $r^2 = 0.267$) (Fig. 3).

3.6. Correlation between NT-proBNP and BW changes

BW immediately after the race (63.3 ± 9.1 kg) and 24 hours after the race (64.2 ± 8.9 kg) was significantly lower than the prerace values (65.0 ± 9.4 kg). We then analyzed the correlation between the BW changes and serum NT-proBNP levels. No correlation existed between the two abovementioned parameters immediately after the race. However, 24 hours after the race, a negative significant relationship existed between the NT-proBNP values and BW increase ($p \leq 0.001$, $r^2 = 0.372$) (Fig. 4).

4. DISCUSSION

Similar to previous results,[17,18] our data showed that a prolonged endurance exercise can lead to a substantial increase in NT-proBNP levels immediately after the race and lasted for 24 hours after the race. Furthermore, 100-km ultramarathon resulted in significant BW loss and RAAS activation immediately and 24 hours after the race. There was no correlation between NT-proBNP and renin, aldosterone, or BW changes immediately after the race. Also, NT-proBNP levels did not significantly correlate with renin values 24 hours after the race. However, a positive significant relationship existed between NT-proBNP and aldosterone levels 24 hours after the race, and a negative significant relationship existed between the NT-proBNP values and BW increase during the recovery phase. Our results indicated that changes in the aldosterone concentrations and BW increase were associated with the changes in the NT-proBNP levels only in the 24 hours after the race.

Our study showed that 92.3% of the subjects had elevated NT-proBNP levels above the upper normal range limit immediately after the race without adverse clinical sequelae. NT-proBNP increase is associated with exercise duration.[14,16] Furthermore, NT-proBNP expression is related to extreme exercise, increases vasodilatation, and inhibits the sympathetic nerves to protect the cardiac myocytes.[10] The average time for the studied subjects to complete the 100 km course was 670 minutes (10+ hours). Our results in terms of extent and changes over time support the recent reports following a 246-km ultramarathon foot race and a 160-km ultramarathon.[17,18] In both publications, NT-proBNP changes occurred during the exercise.

Ultramarathon runners developed a significant BW loss and subsequently induced RAAS activation immediately after the race. RAAS is associated with the acute and chronic defense of plasma volume, blood pressure, and fluid and electrolyte balance during exercise and recovery.[24] Dehydration induced by diuretic administration led to an increase in renin activity and aldosterone concentrations.[25] Our results demonstrated that serum renin and aldosterone concentrations were significantly increased immediately after the race. Cardiac and renal systems communicate and cooperate with each other precisely to maintain hemodynamic stability and perfect perfusion in essential organs. Their interaction is bidirectional, and cardiorenal syndrome is defined as the simultaneous dysfunction of both the heart and the kidney.[26] However, changes in serum renin and aldosterone concentrations were not associated with changes in the NT-proBNP levels immediately after the race. NT-proBNP release is associated with various physiological functions, such as vasodilatation, diuresis, sodium excretion, inhibition of renin secretion, and suppression of aldosterone synthesis.[19,20] The 100-km ultramarathon resulted in an immediate large-scale stimulation of cytokine storms and sympathetic activation.[27] Endurance-induced hypoxia exerts a tremendous stress on the heart, resulting in NT-proBNP release.[28] The RAAS activation might be one of the multifaceted mechanisms of NT-proBNP release immediately following the race.

During the recovery phase, NT-proBNP levels dropped but maintained the lasting high levels for 24 hours after the race. In addition, BW increased, and serum renin and aldosterone levels decreased. Notably, NT-proBNP levels had a negative significant relationship with BW increase and a positive significant relationship with aldosterone levels 24 hours after the race. Thus, rehydration might lead to the decrease of NT-proBNP in the

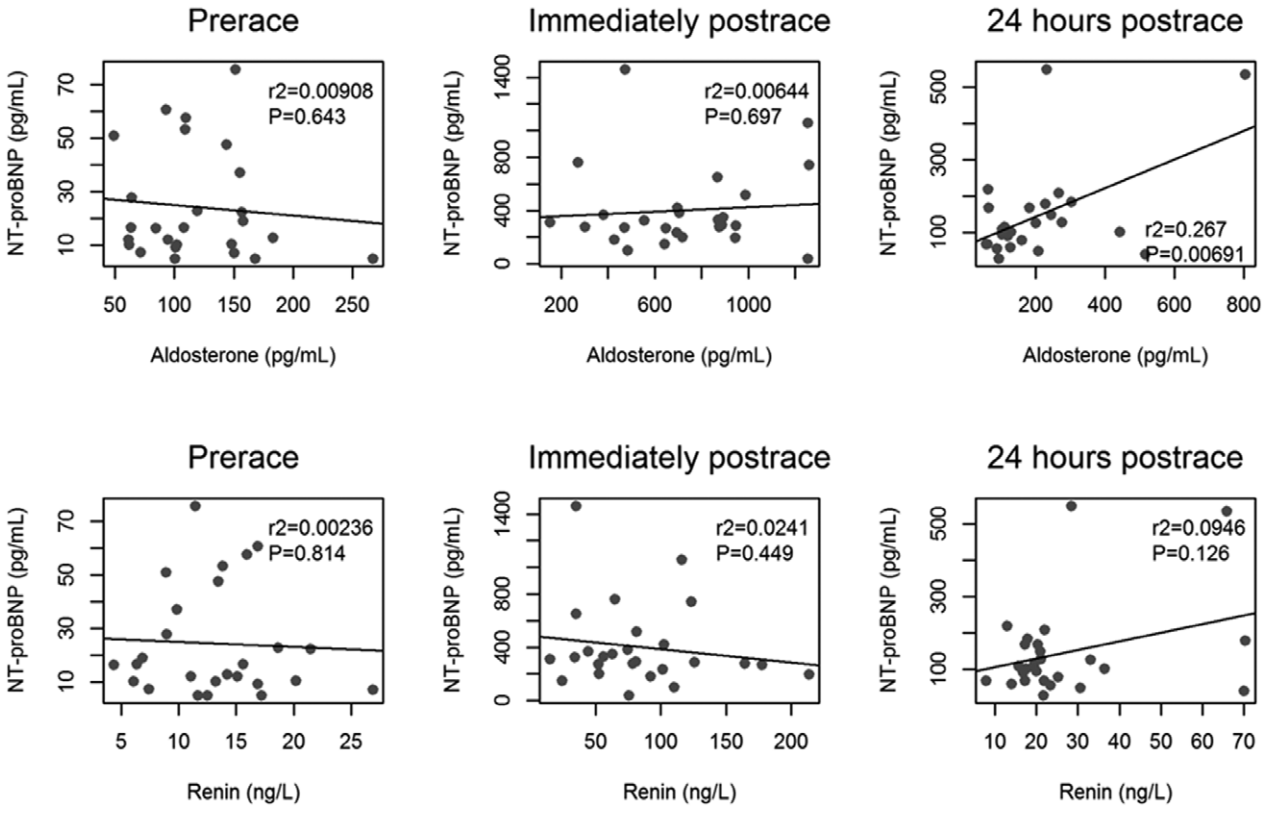

Fig. 3. Relationship of serum NT-proBNP and aldosterone or renin in prerace, immediate postrace, and 24 hours postrace.

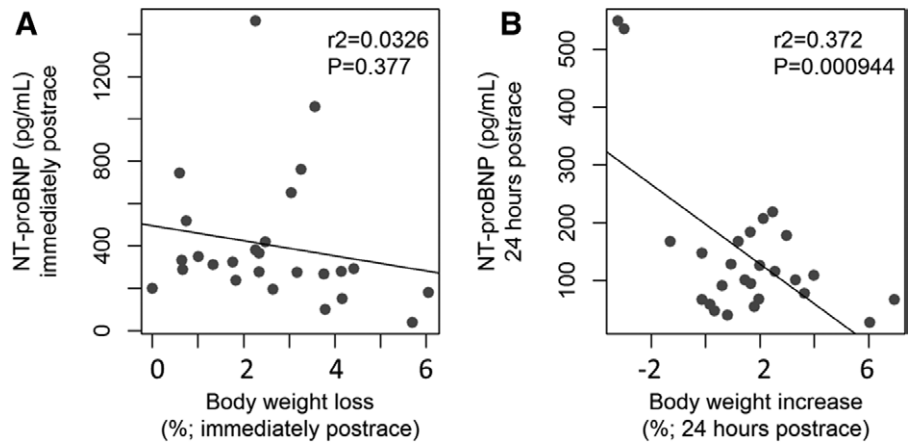

Fig. 4. Correlation between body weight changes and NT-proBNP. (A) immediate postrace. (B) 24 hours postrace.

recovery state. Alzand et al[29] had presented a case with dehydration with high NT-proBNP levels. Normalization of NT-proBNP level was achieved by the cessation of diuretics and the administration of normal saline.[29]

A change in BW might not be equal to the change in hydration status during a prolonged exercise.[30,31] The effects of BW loss from substrate use, release of water bound with muscle and liver glycogen, and production of water during substrate metabolism required to maintain body water balance for an ultramarathon runner.[31] As much as 2%–3% of BW should have been lost to maintain euhydration in the participants of this event.[32] However, the amount of BW loss would vary among individuals, largely depending on the individual energy cost and energy intake. The BW loss for the runners in this study could be <1% BW immediately after the race. Possibly, 24-hour BW loss may comprise a substrate that has remained unreplenished to a large degree. Given these theoretical calculations for the substrate loss alone, the volunteers were possibly not dehydrated to any extent following the 100-km ultramarathon event, considering that they consumed ~6 L of fluid and more fluid may have come from any food consumed. When considering that some body mass should be lost to maintain euhydration, our observations with regard to aldosterone and NT-proBNP might be in response to help the bodies maintain hydration status.

We recognize several limitations to this noninterventional study. First, the sample size is limited. Some small sample biases may be present. Second, considering the paucity of the long-term data >24 hours after the race, the integral variation of this heart failure marker in response to ultramarathon cannot be well recognized. Third, hydration status was calculated from pre- to postrace BW measures. However, these measures were not corrected for fluid/food intake or sweat/urine/feces excretion. The 100 km ultramarathon event was long enough such that substrate losses would be appreciable and would alter the post-BW measures. These views might alter the findings and conclusions of this study. Finally, the amount of individual sweating was not recorded in this study. We do not know whether it is possible that the increase of NT-proBNP is due to the sweating instead of diuresis and vasodilatation. Further study is needed.

In our study, we highlight the findings of the contribution of the RAAS activation and BW change to endurance exercise-induced NT-proBNP release. A positive significant relationship was found between NT-proBNP and aldosterone levels at 24 hours after the race, but a negative significant relationship between NT-proBNP and BW increased during the recovery phase. Our study represented the confluence of heart-kidney interactions across several interfaces during an ultramarathon run. These include alterations in hydration status, neurohormonal, and inflammatory pathways, central to which are activation of the sympathetic nervous system, inflammatory storms, and RAAS activation. Our study also provided biomarkers of aldosterone and NT-proBNP may provide valuable information to indicate early cardiovascular responses and the repair process during this long-distance event. A previous study regarding "heart-gut-brain" axis found that exogenous BNP administration modulated ghrelin, hunger, and satiety in healthy men,[33] while ghrelin comprised acyl ghrelin and des-acyl ghrelin which might exert distinct biological actions.[34,35] In our study, we did not measure this hungry gastric hormone in ultramarathon runners. Further study is needed to clarify this issue.

In conclusion, 100-km ultramarathon resulted in elevated NT-proBNP levels, BW loss, and RAAS activation immediately and 24 hours after the race. The mechanisms of immediate NT-proBNP release following the race were multifaceted. During the recovery phase, rehydration might lead to the decrease of NT-proBNP. Our observations with regard to aldosterone and NT-proBNP might be in response to help the bodies maintain hydration state.

ACKNOWLEDGMENTS

We thank all the ultramarathon runners who participated in this study and all the doctors, nurses, and emergency medical technicians who provided professional care at this ultramarathon race. We also thank our colleagues at Soochow University, Taipei, Taiwan, and the Chinese Taipei Association of Ultrarunners (Taipei, Taiwan) who assisted at the ultramarathon event. Finally, the grant of this study was supported by Taipei Veterans General Hospital in Taipei, Taiwan (V100C-202, V106C-130, and V108C-189).

REFERENCES

1. Hou SK, Chiu YH, Tsai YF, Tai LC, Hou PC, How CK, et al. Clinical impact of speed variability to identify ultramarathon runners at risk for acute kidney injury. *PLOS ONE* 2015;**10**:e0133146.
2. Kao WF, Hou SK, Chiu YH, Chou SL, Kuo FC, Wang SH, et al. Effects of 100-km ultramarathon on acute kidney injury. *Clin J Sport Med* 2015;**25**:49–54.
3. Waśkiewicz Z, Kłapcińska B, Sadowska-Krępa E, Czuba M, Kempa K, Kimsa E, et al. Acute metabolic responses to a 24-h ultra-marathon race in male amateur runners. *Eur J Appl Physiol* 2012;**112**:1679–88.
4. Li LH, How CK, Kao WF, Chiu YH, Meng C, Hsu CC, et al. The impact of hepatitis B carrier on cardiac troponin I in 100-km ultramarathon runners. *J Chin Med Assoc* 2017;**80**:347–52.
5. Hoffman MD, Fogard K, Winger J, Hew-Butler T, Stuempfle KJ. Characteristics of 161-km ultramarathon finishers developing exercise-associated hyponatremia. *Res Sports Med* 2013;**21**:164–75.
6. Fallon KE, Sivyer G, Sivyer K, Dare A. The biochemistry of runners in a 1600 km ultramarathon. *Br J Sports Med* 1999;**33**:264–9.
7. Maisch B. Exercise and sports in cardiac patients and athletes at risk: balance between benefit and harm. *Herz* 2015;**40**:395–401.
8. Race Events in Taiwan, Available at http://www.taipeimarathon.org.tw/contest.aspx?lang=en-US
9. Scharhag J, Herrmann M, Urhausen A, Haschke M, Herrmann W, Kindermann W. Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. *Am Heart J* 2005;**150**:1128–34.
10. Herrmann M, Scharhag J, Miclea M, Urhausen A, Herrmann W, Kindermann W. Post-race kinetics of cardiac troponin T and I and N-terminal pro-brain natriuretic peptide in marathon runners. *Clin Chem* 2003;**49**:831–4.
11. Gardner DG, Chen S, Glenn DJ, Grigsby CL. Molecular biology of the natriuretic peptide system: implications for physiology and hypertension. *Hypertension* 2007;**49**:419–26.
12. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;**350**:655–63.
13. Lippi G, Schena F, Salvagno GL, Montagnana M, Gelati M, Tarperi C, et al. Influence of a half-marathon run on NT-probnp and troponin T. *Clin Lab* 2008;**54**:251–4.
14. Legaz-Arrese A, George K, Carranza-García LE, Munguía-Izquierdo D, Moros-García T, Serrano-Ostáriz E. The impact of exercise intensity on the release of cardiac biomarkers in marathon runners. *Eur J Appl Physiol* 2011;**111**:2961–7.
15. Scharhag J, Urhausen A, Schneider G, Herrmann M, Schumacher K, Haschke M, et al. Reproducibility and clinical significance of exercise-induced increases in cardiac troponins and N-terminal pro brain natriuretic peptide in endurance athletes. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:388–97.
16. Serrano-Ostáriz E, Terreros-Blanco JL, Legaz-Arrese A, George K, Shave R, Bocos-Terraz P, et al. The impact of exercise duration and intensity on the release of cardiac biomarkers. *Scand J Med Sci Sports* 2011;**21**:244–9.
17. Tchou I, Margeli A, Tsironi M, Skenderi K, Barnet M, Kanaka-Gantenbein C, et al. Growth-differentiation factor-15, endoglin and N-terminal pro-brain natriuretic peptide induction in athletes participating in an ultramarathon foot race. *Biomarkers* 2009;**14**:418–22.
18. Scott JM, Esch BT, Shave R, Warburton DE, Gaze D, George K. Cardiovascular consequences of completing a 160-km ultramarathon. *Med Sci Sports Exerc* 2009;**41**:26–34.
19. Rock PB, Kraemer WJ, Fulco CS, Trad LA, Malconian MK, Rose MS, et al. Effects of altitude acclimatization on fluid regulatory hormone response to submaximal exercise. *J Appl Physiol* 1993;**75**:1208–15.
20. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-probnp in clinical routine. *Heart* 2006;**92**:843–9.
21. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al; Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010;**31**:703–11.
22. Hewing B, Schattke S, Spethmann S, Sanad W, Schroeckh S, Schimke I, et al. Cardiac and renal function in a large cohort of amateur marathon runners. *Cardiovasc Ultrasound* 2015;**13**:13.
23. Koyner JL, Vaidya VS, Bennett MR, Ma Q, Worcester E, Akhter SA, et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin J Am Soc Nephrol* 2010;**5**:2154–65.
24. Shim CY, Ha JW, Park S, Choi EY, Choi D, Rim SJ, et al. Exaggerated blood pressure response to exercise is associated with augmented rise of angiotensin II during exercise. *J Am Coll Cardiol* 2008;**52**:287–92.
25. Roy BD, Green HJ, Burnett M. Prolonged exercise following diuretic-induced hypohydration effects on fluid and electrolyte hormones. *Horm Metab Res* 2001;**33**:540–7.
26. Ronco C, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin* 2014;**10**:251–80.
27. Li LH, Chen CT, Kao WF, Chiu YH, Meng C, Hsu CC, et al. Procalcitonin variation before and after 100-km ultramarathon. *Clin Chem Lab Med* 2017;**55**:e110–2.

28. Mellor A, Boos C, Holdsworth D, Begley J, Hall D, Lumley A, et al. Cardiac biomarkers at high altitude. *High Alt Med Biol* 2014;**15**:452–8.
29. Alzand BS, Mihl C, Brunner La Rocca HP. Dehydration with high natriuretic peptide levels! A word of caution. *Cardiology* 2011;**118**:75–8.
30. Cheuvront SN, Montain SJ. Myths and methodologies: making sense of exercise mass and water balance. *Exp Physiol* 2017;**102**:1047–53.
31. Hoffman MD, Goulet EDB, Maughan RJ. Considerations in the use of body mass change to estimate change in hydration status during a 161-kilometer ultramarathon running competition. *Sports Med* 2018;**48**:243–50.
32. Cheuvront SN, Kenefick RW. CORP: improving the status quo for measuring whole body sweat losses. *J Appl Physiol* 2017;**123**:632–6.
33. Vila G, Grimm G, Resl M, Heinisch B, Einwallner E, Esterbauer H, et al. B-type natriuretic peptide modulates ghrelin, hunger, and satiety in healthy men. *Diabetes* 2012;**61**:2592–6.
34. Chen CY, Fujimiya M, Laviano A, Chang FY, Lin HC, Lee SD. Modulation of ingestive behavior and gastrointestinal motility by ghrelin in diabetic animals and humans. *J Chin Med Assoc* 2010;**73**:225–9.
35. Chen CY, Inui A, Asakawa A, Fujino K, Kato I, Chen CC, et al. Des-acyl ghrelin acts by CRF type 2 receptors to disrupt fasted stomach motility in conscious rats. *Gastroenterology* 2005;**129**:8–25.