Effect of Air Travel on Exercise-Induced Coagulatory and Fibrinolytic Activation in Marathon Runners

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Objective: Air travel and exercise change hemostatic parameters. This study investigated the effect of air travel on exercise-induced coagulation and fibrinolysis in endurance athletes.

Design: A prospective longitudinal study.

Setting: The 114th Boston Marathon (April 19, 2010).

Participants: Forty-one adults were divided into travel (T: 23 participants, living >4-hour plane flight from Boston) and nontravel (C: 18 participants, living <2-hour car trip from Boston) groups.

Independent Variables: Age, anthropometrics, vital signs, training mileage, and finishing time were collected.

Main Outcome Measures: Subjects provided venous blood samples the day before (PRE), immediately after (FINISH), and the day following the marathon after returning home (POST). Blood was analyzed for thrombin–antithrombin complex (TAT), tissue plasminogen activator (t-PA), hematocrit (Hct), and the presence of Factor V Leiden R506Q mutation.

Results: Thrombin–antithrombin complex increased more in T subjects in PRE to FINISH samples (5.0 ± 4.0 to 12.9 ± 15.6 μg/L) than in C subjects (4.0 ± 1.2 to 6.1 ± 1.2 μg/L; $P = 0.02$ for comparison). The t-PA increased in both the T (5.4 ± 2.3 to 25.1 ± 12.2 ng/mL) and C (5.6 ± 2.0 to 27.7 ± 11.3 ng/mL) groups in PRE to FINISH samples, and this response did not differ between groups ($P = 0.23$ for comparison). Both groups exhibited similar t-PA and TAT values at POST that were not different than PRE (all $P > 0.35$). Age was related to the FINISH TAT values in T ($r^2 = 0.19$; $P = 0.04$) but not in C ($r^2 = 0.03$; $P = 0.53$) subjects.

Conclusions: Results suggest that the combination of air travel and marathon running induces an acute hypercoaguable state; this hemostatic imbalance is exaggerated with increasing age.

Key Words: exercise, deep vein thrombosis, air travel, clot formation

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INTRODUCTION

Strenuous endurance exercise, such as marathon running, activates the coagulatory system, with an immediate increase in plasma levels of procoagulatory factors, such as thrombin–antithrombin complex (TAT) and prothrombin fragment 1 and 2.[1–3] However, the fibrinolytic system, including t-plasminogen activator (t-PA) antigen and t-PA activity, is also activated after exercise[1,4,5] so that both coagulation and fibrinolysis are augmented to preserve hemostatic balance.

There are several published cases and a large body of anecdotal evidence reporting deep vein thrombosis (DVT) and pulmonary embolism (PE) in otherwise healthy endurance athletes who have traveled via car or airplane to and from endurance competition.[6–8] Prolonged car, bus, train, or air travel activates the coagulatory system.[9,10] Therefore, the combination of endurance exercise and travel may shift the hemostatic balance in athletes after competition and disproportionately activate the coagulatory system.

The purpose of the present study was to test the hypothesis that strenuous endurance exercise, such as completing the 2010 Boston Marathon, in combination with cross-country air travel, increases coagulatory but not fibrinolytic activity in healthy runners compared with a nontravel control group.

METHODS

Subject Recruitment

Twenty-three travelers (12 men and 11 women) and 18 local controls (12 men and 6 women) were recruited through an e-mail sent to all participants registered for the 114th Boston Athletic Association Marathon held on April 19, 2010. Subjects were recruited based on either (1) residence in a geographic location that would require greater than 4 hours flight time to and from the Boston Marathon (California, Texas, or Colorado), or (2) residence in a geographic location that was less than a 2-hour car trip from the greater Boston area (Massachusetts or Connecticut). All subjects were nonsmokers between the ages of 20 and 51 years and free of known cardiovascular, metabolic, and/or coagulatory disease,

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including history of DVT/PE. Female subjects were all premenopausal and did not take any form of hormone therapy with the exception of 1 young woman who disclosed oral contraceptive use (norgestimate/ethinyl estradiol) after study completion. Additionally, subjects were not taking medicines known to affect coagulation (warfarin/Coumadin) and agreed to refrain from taking medications 24 hours before, during, or after the marathon that could affect coagulation, such as aspirin or nonsteroidal anti-inflammatories. All subjects provided written informed consent to participate as approved by the Institutional Review Board at the Hartford Hospital in agreement with the guidelines set forth by the Declaration of Helsinki.

Study Design

Subjects reported the day before the marathon (April 18, 2010). Resting blood pressure and heart rate (Welch Allyn 52000 Vital Signs Monitor; Skaneateles Falls, New York) as well as height and body mass were measured. Subjects provided a detailed medical and exercise history. Venous blood was obtained to measure TAT and t-PA, hematocrit (Hct), and the presence of Factor V Leiden R506Q mutation. Blood was also obtained immediately after the subjects completed the marathon in the main medical tent approximately 100 m from the finish line and the day after the race at a Quest Diagnostics Laboratory in the subject's home city of Texas, California, or Colorado or in the Boston/Hartford area. This last blood draw was conducted in subjects within 30 hours of the race finish, except for 1 traveler whose sample was obtained 40 hours after the finish.

Assessment of Physical Activity

Subjects completed a 24-hour physical activity recall for the 24-hour periods before and after the marathon using Question 8 from the Paffenbarger Physical Activity Questionnaire[11] to compare recent physical activity between control and travel groups. Subjects categorized their physical activity by hours of the day into sedentary, light, moderate, and vigorous activities.

Blood Sample Collection

Twenty-five milliliters of blood was collected from an antecubital vein without stasis by single venipuncture into tubes containing 3.2% sodium citrate for platelet-poor plasma measures of TAT and tPA and EDTA for measures of Hct and Factor V mutation. Tubes for TAT and t-PA analyses were centrifuged at 2000*g* for 10 minutes. A plastic pipette was used to remove plasma (avoiding the platelet layer) into a plastic tube, and the tube was recentrifuged for an additional 10 minutes. The plasma was then transferred into labeled cryovials and stored on dry ice (−80°C). Whole blood for the Hct and Factor V analyses was refrigerated.

All analyses for Hct and Factor V were performed at the Quest Diagnostics Nichols Institute, Chantilly, Virginia, whereas all analyses for TAT and t-PA were performed by the same company in San Juan Capistrano, California.

Blood Sample Analyses

Hematocrit was measured via colorimetric assay. Factor V Leiden R506Q mutation analysis was performed on baseline blood samples only using signal amplification of the gene by allele-specific hybridizations and chemilluminescent detection of hybridized probes. Subjects were characterized as being negative, heterozygous, or homozygous for Factor V Leiden mutation. Thrombin–antithrombin complex was measured by enzyme-linked immunosorbent assay and t-PA by colorimetric active site–specific immunoassay.

Statistical Analyses

Differences in baseline characteristics between control and travel groups were assessed with a 1-way analysis of variance with significance set at $P < 0.05$. To determine the effects of travel on changes in TAT and t-PA, we used a linear mixed model for repeated measurements with autoregressive variance–covariance structure, incorporating time as the within-subjects factor and group (control vs travel) as the between-subjects factor. Subjects were defined as the random factor; all other variables were fixed within the model. Potential categorical factors (eg, gender) that could affect the relation between the main effects and outcomes were added into the model to assess significance, and the effect of continuous variables (eg, age and finishing time) was investigated using analysis of covariance. *P* values for mean difference estimates between groups at various time points were adjusted using Tukey multiple comparison procedure to account for post hoc multiple comparison testing, thereby ensuring that the familywise type I error would be 5%. The repeated measures model was also used to assess group differences in physical activity before and after the marathon. Simple linear regression was used to assess the relation between age and TAT. Statistical analyses were performed with SAS 9.1 (SAS Institute Inc, Cary, North Carolina), and all data are expressed as group means ± SD.

RESULTS

Subject Characteristics

The travel and control groups exhibited similar baseline characteristics, although the travel group was approximately 10 years older than the control group (Table). One female

TABLE. Mean Physical and Performance Characteristics (±SD) of the Travel Versus Control Subjects (n = 41)

Characteristics	Control (n = 18)	Travel (n = 23)
Age, y	32 ± 8*	42 ± 7
Weight, kg	71.1 ± 10.7	67.2 ± 10.5
Height, cm	171.2 ± 14.2	165.1 ± 32.3
SBP, mm Hg	126 ± 8	123 ± 14
DBP, mm Hg	72 ± 7	73 ± 8
HR, beats/min	64 ± 9	62 ± 8
Training distance, km/wk	61 ± 23	63 ± 16
Taper distance, km/wk	37 ± 16	40 ± 13
Official finishing time, h:min:s	3:42:24 ± 0:28:14	3:34:23 ± 0:24:54

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; training distance, average kilometers run per week during training for the Boston Marathon; taper distance, kilometers run in the week preceding the marathon.

*$P < 0.001$; control versus travel groups.

control subject and 4 travel-group subjects (1 woman and 3 men) were heterozygous for Factor V Leiden.

Travel and Race Characteristics

Average in-air travel duration for the travel groups was 5.6 ± 1.4 hours to and 5.7 ± 1.4 hours from the marathon. The travel group arrived in Boston an average of 53.3 ± 12.2 hours (approximately 2 days) before the marathon. All participants (travel and control) arrived at the starting area on race day at least 2 hours before the start of the race. Race day weather was optimal with average temperature 10.6°C and relative humidity 59%.

Physical Activity

There were no group differences in hours spent in vigorous, moderate, and light activities, as well as sitting or sleeping time; however, both groups spent less time in vigorous exercise and more time sitting the day following the marathon relative to the day before the marathon (Figure 1).

Markers of Coagulation and Fibrinolysis

There were no group differences in TAT and t-PA at baseline. There was a significantly greater increase in TAT immediately after the marathon in the travel group relative to the control group (Figure 2; $P = 0.04$ for group effect and 0.02 for time effect); this group difference was not observed in t-PA because both groups exhibited an equal increase in t-PA immediately after the marathon (Figure 3; $P < 0.01$ for time effect). Thrombin–antithrombin complex and t-PA returned to baseline in both groups the day after the marathon. Due to laboratory error, Hct was not measured in the baseline samples. Hct decreased significantly between the second and third time points (control, 42.5 ± 3.4 vs 40.0 ± 2.9% and travel, 43.8 ± 3.1 vs 40.7 ± 2.7%; both $P < 0.01$), indicative of an increase in plasma volume from immediate post-exercise to the following day. However, there were no group differences in changes in Hct, and adjusting TAT and t-PA for Hct to account for these changes in plasma volume did not change the nature of the results between the second and third time points (group and time effects still significant for TAT at $P = 0.04$ and $P < 0.05$, respectively, and time effect still significant for t-PA at $P < 0.01$). In addition, characteristics such as gender, body mass index (BMI), Factor V Leiden mutation (heterozygous vs negative), distance run the week before the race, and finishing time were not significant factors or covariates in the repeated measures model for either TAT or t-PA. Notably, there was a significant age × group × time interaction for TAT ($P < 0.05$), such that there was a positive relationship between age and post-marathon TAT in the travel group but not in the control group that persisted even when 2 travel group individuals classified as outliers were removed from analysis (Figure 4). The accompanying age × group × time interaction for tPA was not significant ($P = 0.97$).

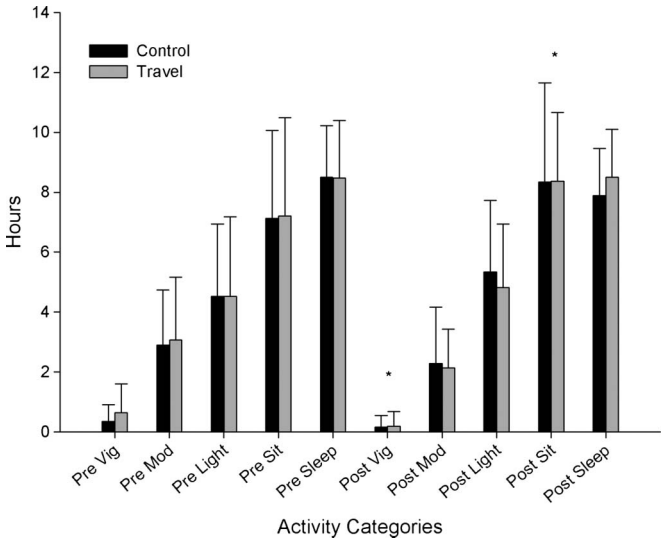

FIGURE 1. Group means (±SD) of hours spent in activity categories during the 24-hour period before the marathon (Pre) versus the 24-hour period after the marathon (Post). *Significant effect of time (Pre vs Post) in both groups at $P < 0.01$. Vig, vigorous physical activity; mod, moderate physical activity; light, light physical activity; sit, sitting; sleep, sleeping.

DISCUSSION

This study is, to our knowledge, the first to examine the effect of endurance exercise and air travel on markers of coagulation and fibrinolysis. Results suggest that the combination of air travel and marathon running disrupts the hemostatic balance such that immediate post-race changes in coagulation are greater in athletes who fly cross-country to participate in a marathon versus athletes who travel locally. Moreover, these findings appear to be age specific, such that acute coagulatory activation following air travel and endurance exercise is greater with advancing age.

Effect of Endurance Exercise on Hemostasis

Several previous studies have investigated the effect of marathon running on markers of hemostatic activation. Siegel

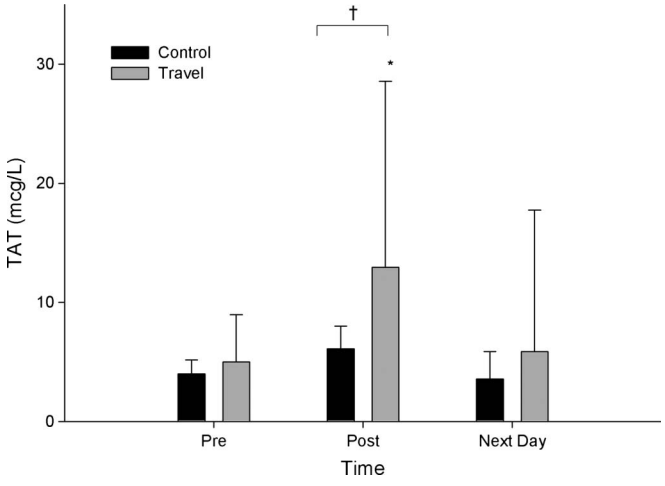

FIGURE 2. Group means (±SD) of thrombin-antithrombin complex (TAT) before (Pre), immediately after (Post), and the day after the marathon (Next Day). *Significant effect change relative to the baseline (Pre) value at $P < 0.05$ within each group. †Significant difference between the groups at $P < 0.05$.

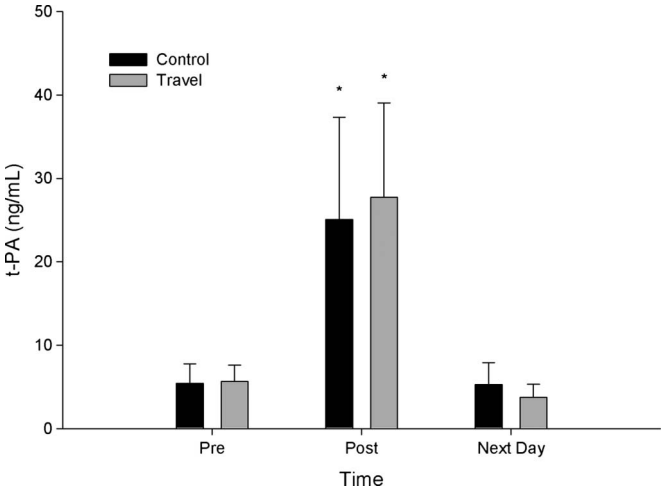

FIGURE 3. Group means (±SD) of tissue plasminogen activator (t-PA) before (Pre), immediately after (Post), and the day after the marathon (Next Day). *Significant effect change relative to the baseline (Pre) value at $P < 0.05$ within each group.

et al assessed hemostatic markers in healthy individuals before and after the Boston Marathon from 1996 to 2001. Phlebotomy was performed before, within 4 hours after the race, and 24 hours after the race. Compared with baseline values, von Willebrand Factor, D-dimer, and fibrinolytic activity were elevated after the marathon, indicative of augmented activation, yet a maintained hemostatic balance.[3] These findings of acute parallel coagulatory and fibrinolytic activation have been replicated in other marathon studies.[2,4]

Effect of Travel on Hemostasis

Previous studies on the effects of exercise on hemostatic activation have not controlled for travel patterns of the participants. This is important because prolonged travel also induces activation of the coagulatory system and could influence exercise-induced hemostatic alterations. Schreijer et al measured markers of coagulatory and fibrinolytic activities, before, during, and after an 8-hour plane flight. The median TAT concentration increased 30% in subjects after the plane flight, indicative of an acute hypercoagulable state unaccompanied by fibrinolytic activation.[9] Long-distance bus travel (ie, a 10-hour bus trip) also activates the coagulatory system,[10] and the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis or MEGA study suggests that car, bus, train, or plane travel >4 hours in duration increases the risk of venous thrombosis 2-fold.[12]

Effect of Combined Endurance Exercise and Travel on Hemostasis

In the current study, the travel group increased TAT, but not t-PA, immediately after the marathon significantly more than the control group (Figures 2, 3). This effect was not attributable to travel alone because there were no group differences in TAT or t-PA observed the day before the marathon, in agreement with previous findings that acute alterations in the hemostatic balance after plane flight are not present the day after travel.[13] There were no reported differences in acute physical activity before or after the marathon that could explain the greater TAT response in the travelers (Figure 1). Nor were the results altered by correcting for gender, BMI, and hematocrit as a surrogate for plasma volume, or by excluding 1 woman in the travel group who used oral contraceptives. Coagulatory and fibrinolytic parameters in both groups returned to baseline by 24 hours after marathon, a finding consistent with the previous studies.[2,4] This suggests that the hemostatic imbalance in the travel group was transient and did not evoke sustained coagulatory activation.

Additionally, the increase in TAT was greater in the travel group, but not in the controls, with increasing age (Figure 4). There were 2 individuals in the travel group whose response after marathon was >2 SDs above the mean. The relationship between age and TAT in the travel group was even stronger when these subjects were excluded from the analysis. It is unlikely that the greater TAT response with travel was attributable to the slightly greater age of the travel group because previous acute exercise studies show parallel activation of coagulatory and fibrinolytic systems in adults up to 60 years of age.[14,15] Rather, the interaction between cross-country plane fight and endurance exercise on coagulation seems to be exacerbated with increasing age.

Contribution of Factor V Leiden Mutation

Individuals heterozygous for the Factor V Leiden mutation did not exhibit significantly different coagulatory and fibrinolytic responses to exercise and travel, although the sample size of heterozygous individuals included only

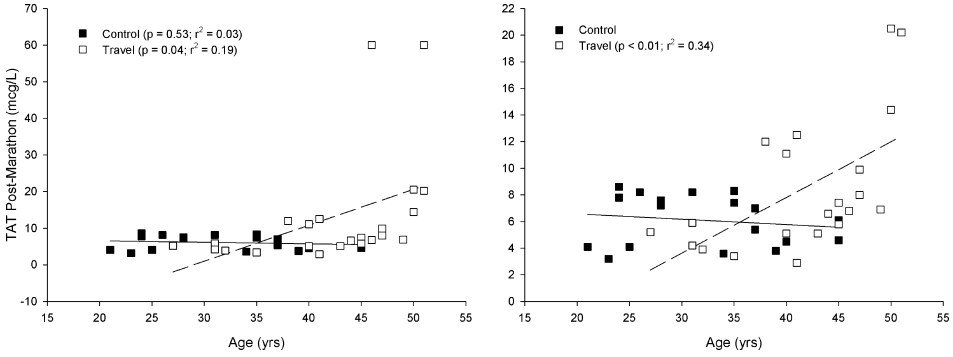

FIGURE 4. Relationship between thrombin-antithrombin complex (TAT) immediately after the marathon and age in control group (black squares with solid regression line) versus the complete travel group (gray squares with dashed regression line; left graph) and versus the travel group with 2 outliers removed (right graph).

4 travelers and 1 control. Although 1 heterozygote had the highest observed TAT value immediately after the marathon (60 μg/L), the 2 other individuals with similarly high values (also 60 μg/L) were negative for Factor V Leiden. Schreijer et al[9] also found no effect of Factor V Leiden mutation on the TAT response to air travel, although female Factor V Leiden heterozygotes who were also using oral contraceptives exhibited exaggerated TAT values after the plane flight. It is possible that a combination of genetic propensity and environmental factors may produce an exaggerated hemostatic imbalance after endurance exercise and travel.

Implications

There are several published case reports of athletes developing DVT and PE after athletic events and travel.[6] Tao and Davenport[16] reported a female triathlete presenting with DVT and PE after completing a half-Ironman triathlon and driving 5 hours. Kiell[17] reported a man who developed DVT after the Honolulu Marathon and a 6000-mile plane flight. An online registry (www.airhealth.org) details numerous reports of athletes who developed DVT after plane flight. Our results suggest that the hemostatic balance immediately after marathon is altered in individuals who travel >4 hours via plane to compete in a marathon, particularly in subjects with advancing age. Therefore, individuals who travel substantial distances to compete in endurance events may be at an increased risk for DVT immediately after the marathon if additional factors (age, history of DVT, use of oral contraceptives, presence of additional thrombophilias, combined oral contraceptives with Factor V Leiden mutation) are superimposed on travel and exercise. Future studies confirming these findings, using additional clinical markers to assess DVT risk (eg, D-dimer measurements and/or venous ultrasound) are necessary to support this hypothesis and develop recommendations for prevention.

Limitations

We did not perform a comprehensive analysis of factors involved in thrombus formation/degradation or platelet activation because of financial constraints. It is possible that these additional factors are affected by the combination of plane travel and endurance exercise, which might also influence the hemostatic balance. Future studies should be aimed at confirming the results of the present study and investigating additional thrombotic factors to determine the interaction among exercise, prolonged travel, and thromboembolic risk.

We also did not evaluate the effect of diurnal variation on our results. Coagulatory activation may be greater in the morning because activated factor VII, F1+2, and PAI-1 significantly decrease across the morning hours.[18] We could not control diurnal variation because phlebotomy was predetermined by marathon and travel schedules, although there was an equal distribution of control and travel subjects receiving morning and afternoon phlebotomy for both the first and third time points.

CONCLUSIONS

Our preliminary results suggest that prolonged air travel before a marathon disrupts the parallel activation of coagulation and fibrinolysis usually observed with endurance exercise such that an acute hypercoagulable state is observed immediately after the race. This hemostatic imbalance is exaggerated with increasing age. This novel finding may in part explain the reports of DVT in endurance athletes after exercise and travel, particularly if additional factors augment thromboembolic risk.

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REFERENCES

1. Cerneca E, Simeone R, Bruno G, et al. Coagulation parameters in senior athletes practicing endurance sporting activity. *J Sports Med Phys Fitness*. 2005;45:576–579.
2. Prisco D, Paniccia R, Bandinelli B, et al. Evaluation of clotting and fibrinolytic activation after protracted physical exercise. *Thromb Res*. 1998;89:73–78.
3. Siegel AJ, Stec JJ, Lipinska I, et al. Effect of marathon running on inflammatory and hemostatic markers. *Am J Cardiol*. 2001;88:918–920, A9.
4. Sumann G, Fries D, Griesmacher A, et al. Blood coagulation activation and fibrinolysis during a downhill marathon run. *Blood Coagul Fibrinolysis*. 2007;18:435–440.
5. Rocker L, Taenzer M, Drygas WK, et al. Effect of prolonged physical exercise on the fibrinolytic system. *Eur J Appl Physiol Occup Physiol*. 1990;60:478–481.
6. Eichner ER. Blood clots and plane flights. *Curr Sports Med Rep*. 2009;8:106–107.
7. Randall K. On The Mend [Kikkan Randall blog]. April 4, 2008. http://blogs.fasterskier.com/kikkanrandall/2008/04. Accessed July 20, 2010.
8. Lehman S. Blood Clots and the Endurance Athlete. 2009. http://pressurepositive.wordpress.com/2009/03/30/blood-clots-and-the-endurance-athlete/2009. Accessed July 20, 2010.
9. Schreijer AJ, Cannegieter SC, Meijers JC, et al. Activation of coagulation system during air travel: a crossover study. *Lancet*. 2006;367:832–838.
10. Schobersberger W, Mittermayr M, Innerhofer P, et al. Coagulation changes and edema formation during long-distance bus travel. *Blood Coagul Fibrinolysis*. 2004;15:419–425.
11. Matthews CE, Freedson PS, Hebert JR, et al. Comparing physical activity assessment methods in the Seasonal Variation of Blood Cholesterol Study. *Med Sci Sports Exerc*. 2000;32:976–984.
12. Cannegieter SC, Doggen CJ, van Houwelingen HC, et al. Travel-related venous thrombosis: results from a large population-based case control study (MEGA study). *PLoS Med*. 2006;3:e307.
13. Schobersberger W, Fries D, Mittermayr M, et al. Changes of biochemical markers and functional tests for clot formation during long-haul flights. *Thromb Res*. 2002;108:19–24.
14. van den Burg PJ, Hospers JE, van VM, et al. Changes in haemostatic factors and activation products after exercise in healthy subjects with different ages. *Thromb Haemost*. 1995;74:1457–1464.
15. Menzel K, Hilberg T. Coagulation and fibrinolysis are in balance after moderate exercise in middle-aged participants. *Clin Appl Thromb Hemost*. 2009;15:348–355.
16. Tao K, Davenport M. Deep venous thromboembolism in a triathlete. *J Emerg Med*. 2010;28:351–353.
17. Kiell PA. Marathon is an injury. *AMAA Quarterly*. 1988;1:16–17.
18. Kapiotis S, Jilma B, Quehenberger P, et al. Morning hypercoagulability and hypofibrinolysis. Diurnal variations in circulating activated factor VII, prothrombin fragment F1+2, and plasmin-plasmin inhibitor complex. *Circulation*. 1997;96:19–21.

