Autonomic Nervous System Modulation During Accidental Syncope Induced by Heat and Orthostatic Stress

Andres E. Carrillo, Stephen S. Cheung, and Andreas D. Flouris

Carrillo AE, Cheung SS, Flouris AD. ***Autonomic nervous system modulation during accidental syncope induced by heat and orthostatic stress.*** **Aviat Space Environ Med 2013; 84:722–5.**

Background: Heart rate variability (HRV) indices (LF, HF, LF/HF, RMSSD, and pNN50) under combined heat and orthostatic stress leading up to and during accidental syncope (EXP group: one man, two women; age: 23.7 ± 2.9 yr) were compared with data collected from subjects who did not experience syncope (CON group: one man, two women; age: 22.3 ± 1.5 yr). ***Methods:*** Minute averages of HRV indices were collected during 5 min at baseline (Base), 5 min leading up to syncope (PRE), and 5 min during syncope (Syncope) (i.e., 2 min leading up to, 1 min during, and 2 min post-syncope). Data were individually analyzed as 1-min means during Syncope as well as 5-min means during Base, PRE, and Syncope. ***Results:*** Between-group results revealed that LF and LF/HF were significantly higher and HF was significantly lower in EXP compared to CON subjects at minutes 1, 2, and 3 during Syncope. Further, RMSSD (CON: 161.1 ± 37.0 ms; EXP: 17.5 ± 13.3 ms) and pNN50 (CON: 26.4 ± 36.3%; EXP: 1.3 ± 1.2%) were significantly lower in EXP compared to CON subjects at minute 3 during Syncope. During Syncope, 5-min averages of LF (CON: 46.1 ± 13.9 nu; EXP: 77.5 ± 6.6 nu) and LF/HF (CON: 1.0 ± 0.5; EXP: 3.8 ± 1.7) were significantly higher, and HF (CON: 53.9 ± 13.9 nu; EXP: 22.5 ± 6.6 nu) was significantly lower in EXP subjects compared to CON. ***Discussion:*** Our findings show that autonomic nervous system modulation leading up to and during accidental syncope induced by heat and orthostatic stress is characterized by an exaggerated suppression of parasympathetic and elevation of sympathetic activity. Thus, elevated LF and LF/HF, and lower HF, RMSSD, and pNN50 may represent risk factors for accidental syncope.

Keywords: heart rate variability, parasympathetic nervous system, sympathetic nervous system, hot conditions, orthostatic intolerance, fainting.

SYNCOPE IS A spontaneous temporary loss of consciousness resulting from a reduction in cerebral perfusion and is quickly reversible with minimal intervention (9). Approximately 1 to 3% of visits to the emergency room and 6% of total hospital admissions are syncope related (6). Syncope has a lifetime cumulative incidence of > 35%, it is associated with significant costs to the healthcare system (4), and its risk is particularly high during heat and orthostatic stress due to hemodynamic alterations that result in hypotension (10). Indeed, combining heat and orthostatic stresses creates a competition between cutaneous vasodilation for heat dissipation and cutaneous vasoconstriction for blood pressure regulation; a recent study using a protocol designed to induce symptoms of syncope suggested that heat dissipation takes priority over blood pressure regulation (1).

The mechanism responsible for inadequate blood pressure regulation during orthostatic challenges in heat-stressed individuals remains unknown. Moreover, the changes in autonomic nervous system (ANS) modulation that, ultimately, regulates heat dissipation and blood pressure have not been examined during the occurrence of accidental syncope. Thus, the investigation of changes in the activity of ANS subsystems (i.e., parasympathetic and sympathetic nervous systems) during accidental syncope is a logical progression toward understanding the cardiovascular complications that occur during syncope induced by heat and orthostatic stress. In this retrospective investigation we examined ANS modulation via heart rate variability (HRV) under combined heat and orthostatic stress leading up to and during accidental syncope. Given that combined heat and orthostatic stress is a model of acute hemorrhage (5), these results will also have important implications for heat loss and blood pressure regulation in hyperthermic or hemorrhagic patients.

METHODS

Subjects

Previously obtained data (2) were examined to assess HRV indices in subjects who experienced accidental syncope (EXP group: one man, two women) compared to three randomly selected sex-matched subjects who did not experience syncope (CON group: one man, two women). All procedures were approved by the Dalhousie University Ethical Review Board and are described in detail elsewhere (2). Written informed consent was obtained from all subjects. Subjects were screened for Raynaud's phenomenon and high blood pressure. Female subjects were also screened for pregnancy and their testing was conducted during the early follicular phase of the menstrual cycle.

From the FAME Laboratory, Centre for Research and Technology Thessaly, Trikala, Greece.

This manuscript was received for review in November 2012. It was accepted for publication in December 2012.

Address correspondence and reprint requests to: Andreas D. Flouris, FAME Laboratory, Centre for Research and Technology Thessaly, Karies, Trikala 42100, Greece; andreasflouris@gmail.com.

DOI: 10.3357/ASEM.3573.2013

Procedures

Prior to water immersion, all subjects were asked to sit for 15 min in a ventilated and air-conditioned thermoneutral environment (ambient temperature: 25°C; relative humidity: 40%). Following baseline data collection, subjects entered a water tank maintained at 42°C and passively rested until their rectal temperature increased by 0.5°C above baseline. Thereafter, they exited the water tank and entered another water bath maintained at 12°C until their rectal temperature decreased by 0.5°C below baseline. During each immersion, subjects were rested in a semisupine position up to their chest. Their arms and head were not immersed in the water at any time. The procedure was repeated twice (i.e., hot-cold-hot-cold). Accidental syncope occurred in all EXP subjects while exiting from the second 'hot' condition.

Equipment

HRV data were continuously collected via Polar S810 (Kempele, Finland), previously validated for HRV measurements (3). Examined HRV indices included the low frequency (LF) band in the range of 0.04–0.15 Hz, high frequency (HF) band in the range of 0.15–0.4 Hz, their ratio (LF/HF), the square root of the mean of squared differences between successive RR intervals (RMSSD), and the percentage of successive normal-to-normal intervals greater than 50 ms (pNN50). HRV indices were analyzed using the HRV Analysis Software V1.1 (Biomedical Signal Analysis Group, University of Kuopio, Finland; 2002).

Cutaneous finger blood flow was assessed using laser-Doppler velocimetry (PeriFlux System 5000, main control unit; PF5010-LDPM, function unit; Perimed, Stockholm, Sweden) at the pulp of the right-hand index finger. Cutaneous finger blood flow data sampled at 32 Hz were averaged per minute and expressed in perfusion units. Rectal temperature was measured using a self-inserted flexible probe [2 mm in diameter (Mon-A-Therm Core, Mallinkrodt Medical, St. Louis, MO)] to a depth of 15 cm beyond the anal sphincter.

Statistical Analysis

Group differences in anthropometric variables were assessed using the Mann–Whitney U-test of two independent samples. Two separate data analyses were conducted to assess the current research question. The first part of data analysis used 1-min means while syncope occurred (i.e., 2 min leading up to, 1 min during, and 2 min post-syncope), a time period henceforth referred to as Syncope (**Fig. 1A**). Specifically, syncope occurred at the beginning of the third minute during the Syncope time period. Between-group differences were assessed using the Mann–Whitney U-test of two independent samples, while within-group differences (i.e., change across time) were examined via Friedman test of k related samples.

In order to confirm the findings of the first data analysis and to comply with the recently proposed requirement of 4 min of HRV recording (7), the second part of data analysis used three sets of 5-min HRV data: 5 min at baseline (Base), 5 min leading up to syncope (PRE), and Syncope (**Fig. 1B**). Between- and within-group differences were assessed using the Mann–Whitney U-test of two independent samples and the Friedman test of k related samples, respectively. Post hoc tests were conducted using the Wilcoxon signed-rank test in which a Bonferroni adjustment was applied. All statistical analyses were completed using PASW Statistics (version 18, SPSS Inc., Chicago, IL) statistical software package with the level of significance set at $P < 0.05$.

RESULTS

Age (CON: 22.3 ± 1.5 yr; EXP: 23.7 ± 2.9 yr), height (CON: 168.0 ± 5.6 cm; EXP: 173.7 ± 9.0 cm), bodyweight (CON: 64.3 ± 4.0 kg; EXP: 70.2 ± 6.8 kg), and percent body fat (CON: 16.9 ± 2.5%; EXP: 18.9 ± 12.5%) were similar between groups ($P > 0.05$). Furthermore, immersion time during the second 'hot' condition (CON: 37.3 ± 10.6 min; EXP: 40.7 ± 5.5 min) was not significantly different between groups ($P > 0.05$). For the first part of data analysis, between-group results revealed that LF, HF, and LF/HF were significantly different during Syncope at minutes 1, 2, and 3 ($P < 0.05$; **Fig. 2**). Further, RMSSD (CON: 161.1 ± 37.0 ms; EXP: 17.5 ± 13.3 ms) and pNN50 (CON: 26.4 ± 36.3%; EXP: 1.3 ± 1.2%) were significantly different between groups at minute 3 ($P < 0.05$). Within-group analysis during Syncope demonstrated a statistically significant main effect of time for heart rate [$\chi^2(2) = 9.867$, $P = 0.04$] in EXP. Post hoc tests, however, revealed no differences between minutes in either group ($P > 0.05$).

Table I illustrates between-group and within-group results for rectal temperature, heart rate, finger blood flow, and respiratory rate. Rectal temperature was different between groups at baseline ($P = 0.05$). No other between-group differences ($P > 0.05$) were observed

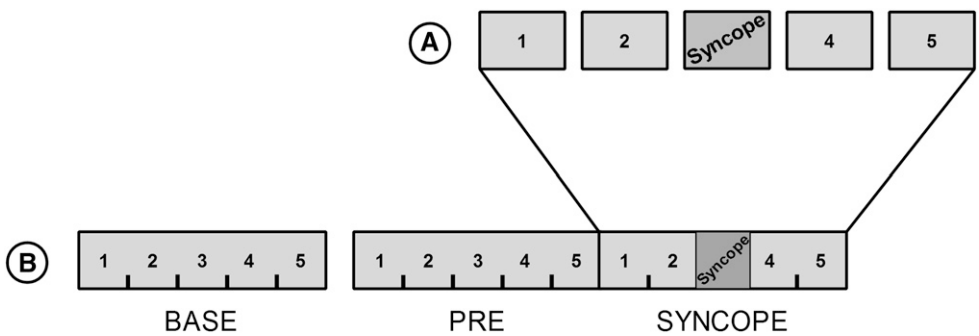

Fig. 1. The experimental protocol showing: A) the 5-min period of Syncope; and B) the 5-min periods for Base, PRE, and Syncope.

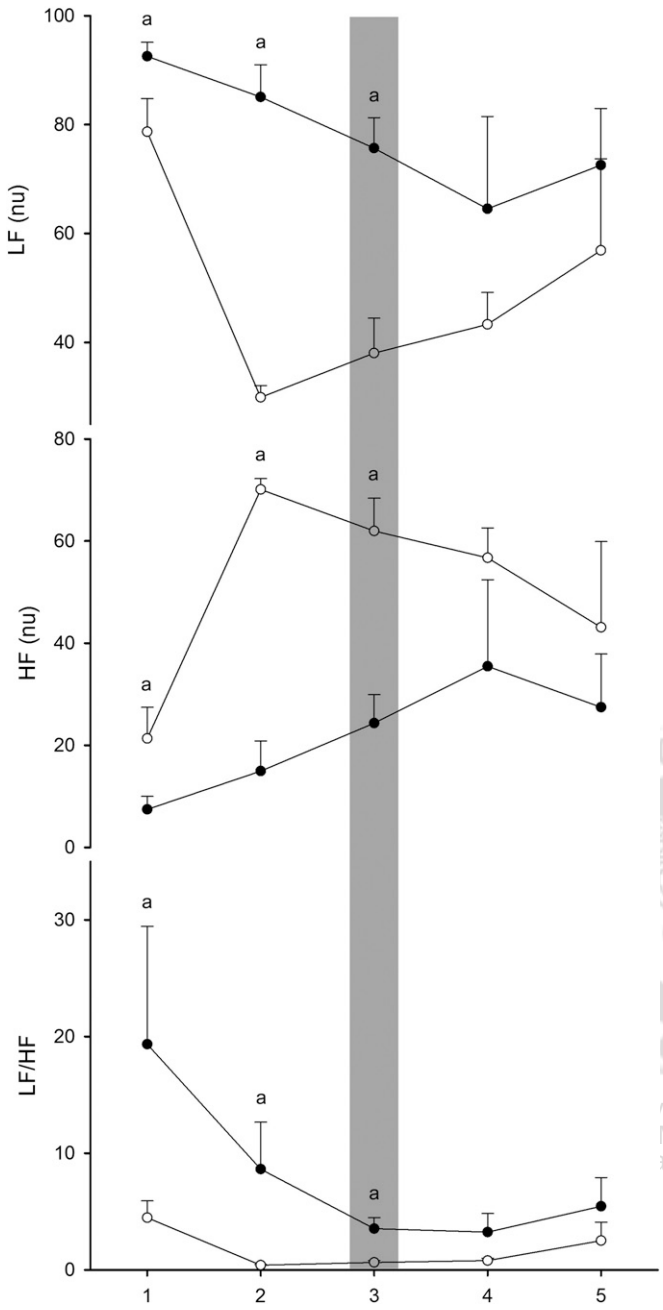

Fig. 2. Means ± SEM of 1-min low (LF) and high (HF) frequency bands, and their ratio (LF/HF) at Syncope (i.e., 2 min leading up to, 1 min during, and 2 min post-syncope). [a]Significant difference between groups, $P < 0.05$. Time of accidental syncope is shown by the gray bar; the white circle represents the CON group and the black circle the EXP group.

during Base and Syncope, while a significantly lower heart rate was observed in the CON subjects during PRE ($P < 0.05$). Between-group comparisons of HRV indices (**Fig. 3**) demonstrated higher LF and LF/HF as well as lower HF in EXP compared to CON ($P < 0.05$). Within-group comparisons revealed a statistically significant main effect of time for rectal temperature in CON [$\chi^2(2) = 6.000$, $P = 0.05$] and EXP [$\chi^2(2) = 6.000$, $P = 0.05$] subjects as well as heart rate [$\chi^2(2) = 6.000$, $P = 0.05$] in EXP subjects only. Post hoc tests, however, did not detect differences in rectal temperature or heart rate between time points in either group ($P > 0.05$).

DISCUSSION

We found that the ANS modulation of individuals experiencing accidental syncope induced by heat and orthostatic stress is characterized by elevated sympathetic and suppressed parasympathetic activity. More importantly, despite noticeable within-group differences in ANS modulation, we did not observe any statistically significant changes across time leading up to, during, and following accidental syncope. Combining heat and orthostatic stress leads to a greater risk of syncope because positional changes can cause a 300- to 800-ml redistribution of blood volume to the lower extremities, reducing cerebral perfusion (11). Recent evidence suggests that cutaneous vasodilation for heat dissipation takes priority over cutaneous vasoconstriction for blood pressure regulation during a heat and orthostatic challenge designed to induce symptoms of syncope (1). Interestingly, the latter study (1) also reported no paradoxical cutaneous vasodilation at the onset of syncopal symptoms that would indicate a suppression of sympathetic activity, unlike what is often reported in normothermic subjects (11). Our data collected during actual accidental syncope confirm that no changes in sympathetic nerve activity take place during baroreceptor unloading in heat stressed individuals. Thus, it may be cautiously postulated that the heat-induced increased risk for accidental syncope during orthostatic stress is due to an inadequate neural response to the skin relative to the hypotensive perturbation, resulting in no adjustments to cutaneous vasoconstriction.

Our results suggest that characterization of individuals who are at risk for accidental syncope due to heat and orthostatic stress may be improved with the inclusion of HRV measurements. Such guidelines, however, should be confirmed in larger groups of subjects given the low sample size and intra- and interindividual variability related to the clinical utility of HRV measurements (7,8). Furthermore, in the current study, subjects from each group were only matched for sex. Future studies should consider also matching for height and overall body surface area, which may influence the intensity of orthostatic stress, water immersion time, and body heat content. All nonsyncopal subjects from the previous study (2) were not included in this analysis due to some variation in anthropometry (e.g., bodyweight) as well as age. Water immersion time, however, was similar between the nonsyncopal subjects included in the current study versus the nonsyncopal subjects who were not included. Moreover, given that combined heat and orthostatic stress has often been used as a model of acute hemorrhage (5), the present findings may be beneficial toward the treatment of hemorrhagic heat-stressed individuals, as can occur in athletic events, military combat, or industrial accidents. Our data suggest that treatment to stabilize blood pressure in hyperthermic patients will be more challenging compared to normothermic or cooled patients.

In conclusion, the ANS modulation of individuals experiencing accidental syncope induced by heat and

TABLE I. RESULTS (MEAN ± SD) FOR HEART RATE, BLOOD FLOW, AND RESPIRATORY RATE FOR BOTH GROUPS DURING BASE, PRE, AND SYNCOPE.

Group	Time Point	Rectal Temperature (°C)	Heart Rate (bpm)	Blood flow (PU)	Respiratory rate (breaths · min^{-1})
CON (*N* = 3)	Base	37.1 ± 0.1†	75.8 ± 5.2	202.5 ± 134.3	15.8 ± 2.2
	PRE	38.1 ± 0.3†	103.7 ± 6.9	381.7 ± 37.8	16.5 ± 4.6
	Syncope	38.4 ± 0.3†	114.3 ± 43.5	355.1 ± 57.1	15.8 ± 3.9
EXP (*N* = 3)	Base	37.5 ± 0.1*†	86.1 ± 6.0†	171.2 ± 139.1	17.2 ± 2.8
	PRE	38.3 ± 0.6†	111.6 ± 2.8*†	414.9 ± 98.9	12.6 ± 4.1
	Syncope	38.6 ± 0.4†	133.2 ± 15.6†	400.1 ± 44.8	15.5 ± 6.1

* Significant group difference ($P < 0.05$). †Significant main effect of time ($P < 0.05$). PU, perfusion units; Base, 5 min at baseline; PRE, 5 min leading up to syncope; Syncope, 2 min leading up to, 1 min during, and 2 min post-syncope.

orthostatic stress is characterized by elevated sympathetic and suppressed parasympathetic activity with no changes across time leading up to, during, and following accidental syncope. Moreover, our findings suggest that, during heat stress, elevated LF and LF/HF, and lower HF, RMSSD, and pNN50 may represent risk factors for accidental syncope and should be investigated in future patients to refine preventative strategies.

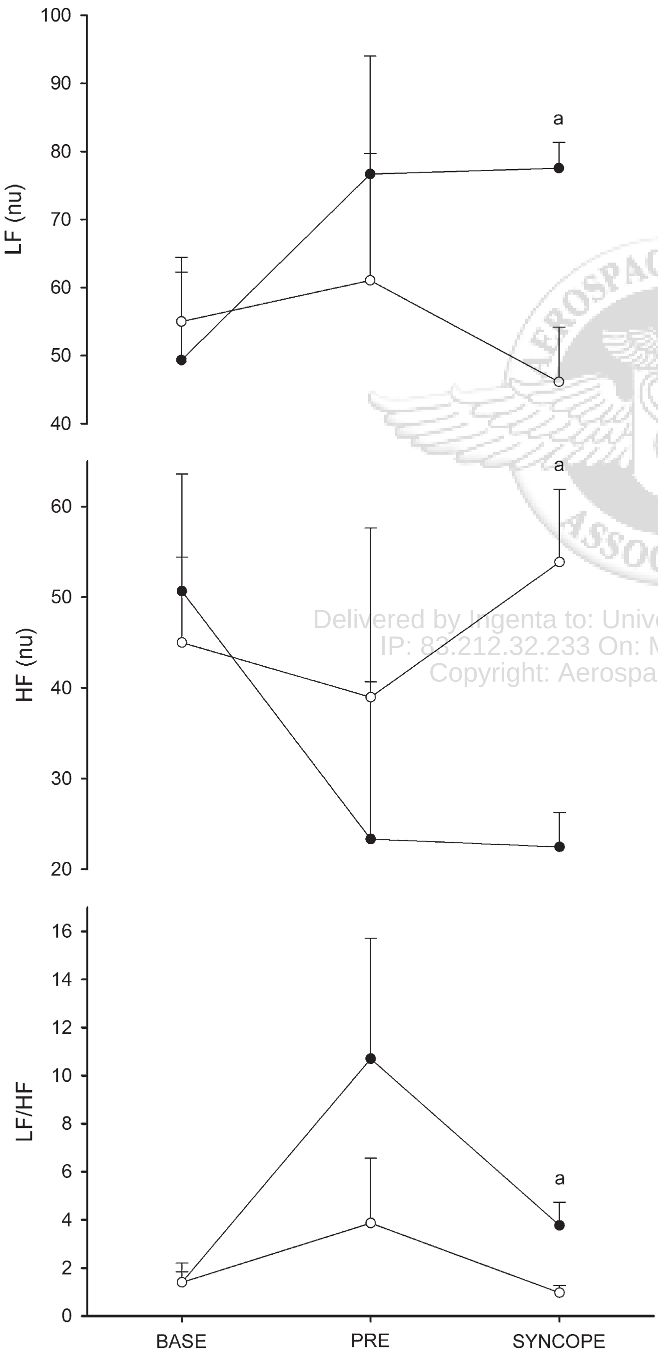

Fig. 3. Means ± SEM of 5-min low (LF) and high (HF) frequency bands, and their ratio (LF/HF) at Base, PRE, and Syncope. [a]Significant difference between groups, $P < 0.05$. The white circles represent the CON group and the black circles the EXP group.

ACKNOWLEDGMENTS

The project was supported by the Canadian Natural Sciences and Engineering Research Council and the Canadian Space Agency. The authors declare that they have no competing interests.

Authors and affiliations: Andres E. Carrillo, M.Sc., Ph.D., Department of Exercise Science, Chatham University, Pittsburgh, PA; Stephen S. Cheung, M.Sc., Ph.D., Department of Kinesiology, Brock University, St. Catherines, Ontario, Canada; and Andreas D. Flouris, M.Sc., Ph.D., FAME Laboratory, Centre for Research and Technology Thessaly, Trikala, Greece.

REFERENCES

1. Crandall CG, Shibasaki M, Wilson TE. Insufficient cutaneous vasoconstriction leading up to and during syncopal symptoms in the heat stressed human. Am J Physiol Heart Circ Physiol 2010; 299:H1168–73.
2. Flouris AD, Cheung SS. Influence of thermal balance on cold-induced vasodilation. J Appl Physiol 2009; 106:1264–71.
3. Gamelin FX, Berthoin S, Bosquet L. Validity of the polar S810 heart rate monitor to measure R-R intervals at rest. Med Sci Sports Exerc 2006; 38:887–93.
4. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. J Cardiovasc Electrophysiol 2006; 17:1172–6.
5. Keller DM, Low DA, Wingo JE, Brothers RM, Hastings J, et al. Acute volume expansion preserves orthostatic tolerance during whole-body heat stress in humans. J Physiol 2009; 587:1131–9.
6. Miller TH, Kruse JE. Evaluation of syncope. Am Fam Physician 2005; 72:1492–500.
7. Rickards CA, Ryan KL, Convertino VA. Characterization of common measures of heart period variability in healthy human subjects: implications for patient monitoring. J Clin Monit Comput 2010; 24:61–70.
8. Ryan KL, Rickards CA, Ludwig DA, Convertino VA. Tracking central hypovolemia with ecg in humans: cautions for the use of heart period variability in patient monitoring. Shock 2010; 33:583–9.
9. Vaddadi G, Lambert E, Corcoran SJ, Esler MD. Postural syncope: mechanisms and management. Med J Aust 2007; 187:299–304.
10. Wilson TE, Crandall CG. Effect of thermal stress on cardiac function. Exerc Sport Sci Rev 2011; 39:12–7.
11. Zaqqa M, Massumi A. Neurally mediated syncope. Tex Heart Inst J 2000; 27:268–72.