Effects of Mild Hypoxia on Circadian Time Structure during Long Duration Flights in Man

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ABSTRACT

French Air Force is concerned by the frequent fatigue complaint reported after long duration flights in pressurized aircrafts. It may be partly explained by the hypoxic exposure resulting of the characteristics of the pressurization, through potential effects on circadian time structure even when no time zones are crossed. Indeed, cabin altitudes can reach 8000 ft (~2400 m) in civil aviation and 12,000 ft (~3600 m) in military Air carrying. The aim of the study was to evaluate the effects of a diurnal exposure (08:00-16:30 h) to prolonged mild hypobaric hypoxia on the human circadian time structure and on the recovery sleep, at 8000 and 12,000-ft altitudes simulated in a hypobaric chamber.

This controlled cross-over study, performed in 20 male young healthy volunteers (20-40 yr) showed significant alterations in the expression of the circadian markers (core body temperature, plasma melatonin and cortisol) in response to hypoxia. These circadian alterations were more important at 12,000 ft in association with an absence of sleep rebound after a significant physiologically penalizing proof. Part of these circadian alterations depended on the variations of the central autonomic balance in response to hypoxic exposure. The effects of mild hypoxia on circadian time structure may explain at least in part the fatigue complaint after a long duration flight, even when no time zones are crossed.

1.0 INTRODUCTION

1.1 Background

Crews and passengers often report a fatigue complaint after long duration flights in pressurized aircrafts. Most of the time it can be related to jet lag in case of transmeridian flights [1-10]. Jet lag is considered as a consequence of a desynchronization of circadian rhythms. The main clinical signs are a state of fatigue with sleep troubles, sleepiness, decrease of cognitive performance, and digestive signs sometimes.

Nevertheless, the complaint of fatigue is also reported when no time zones are crossed, i.e. after North-South flights [11, 12] and in some military missions (AWACS, Sea Patrol) [13]. Excessive workload, sleep deprivation and some environmental stressors may be involved in this phenomenon. Noise, vibrations and hypobaric hypoxia constitute the main aeronautical environmental factors leading to an increase of fatigue level. Amongst them hypoxia may play an important role through a depressive effect on the central nervous system and through potential effects on circadian time structure, independently of jet lag.

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1.2 Flight hypoxic exposure

Mild hypobaric hypoxia [14] is commonly experienced in aeronautics during flights in pressurized cabins. Indeed, pressurization consists in keeping the barometric pressure (P_B) higher inside the cabin than outside. Cabin pressure always remains below sea level P_B, i.e., ~1013 hectoPascals (hPa), at a level compatible with acceptable physiological tolerance [15]. International rules specify that cabin pressure must not fall below 753 hPa in civil aviation (FAR pt 25, JAR pt25) or below 644 hPa in NATO Air Carrying (NATO-STANAG 3198), corresponding to altitudes of 8000 ft and 12,000 ft, respectively. In other words, in normal flight conditions cabin altitudes must not exceed 8000 ft in civil and 12,000 ft in military aviation [15-19]. Healthy young subjects generally tolerate these altitudes without deleterious effects from hypoxia. They can compensate for the resulting decrease in arterial oxygen pressure by increasing their ventilation and cardiac output.

1.3 What is known about the effects of hypoxia on circadian time structure

Although the biological effects of hypoxia have been extensively studied in humans (review in [19]), little is known about the influence of hypoxia on circadian rhythms.

Recent controlled studies on rodents explored the effects of severe normobaric hypoxia ($F_I0_2 = 0.1$) on circadian rhythms [20-23]. The authors observed that the circadian rhythm of core body temperature and locomotor activity disappeared during continuous hypoxia and reappeared without any apparent phase shift when the animals returned to normal oxygen. The daily mean level of the studied rhythms was also decreased. They concluded that continuous acute hypoxia acted mainly on the thermoregulatory centers of the hypothalamus, rather than on the circadian clock. Nevertheless, a phase delay of the activity rhythm was reported when animals were placed in constant darkness (free-run) and exposed to intermittent hypoxia, i.e., 3 hours in the middle of the subjective day for 7 consecutive days.

In man, only one study reported that short exposure (2-3 min) to severe hypobaric hypoxia (25,000 ft) in a hypobaric chamber appeared to delay the peak time of several circadian rhythms (oral temperature, grip strength, and peak expiratory flow) [24]. This delaying effect persisted for four days before returning to initial values.

No previous published studies before ours dealt with the effects of prolonged mild hypoxia on human circadian time structure during long duration flights in pressurized planes.

2. EFFECTS OF MILD HYPOXIA ON HUMAN CIRCADIAN TIME STRUCTURE DURING SIMULATED LONG DURATION FLIGHTS

The aim of our study was therefore to evaluate the effects of a diurnal exposure to prolonged mild hypobaric hypoxia at 8000-ft and 12,000-ft altitudes simulated in a hypobaric chamber on the circadian markers, i.e., core body temperature (CBT), plasma melatonin and cortisol, and also on the recovery sleep.

2.1 Subjects

Twenty healthy young male volunteers (age: 20-40 years) were involved in this controlled cross-over study. Each subject served as his own control.

Lifestyle, physical health, and clinical status were assessed by routine clinical and laboratory examinations to determine eligibility for the study. Subjects had no notable medical history and no current acute or chronic diseases. No subject had a current or past depressive disorder or psychosis. None had a history of abusing or being dependent on alcohol, tobacco, or other addicting substances. All subjects had routine blood counts and blood chemistry in the normal range and negative tests for HIV and hepatitis B and C.

Subjects' synchronization was determined by questionnaire. They were all synchronized with diurnal activity and nocturnal rest. They took no medication known to alter circadian rhythms, worked no rotating shifts, and did no travel across times zones for at least two months before the experiment. They were neither evening nor morning types, according to the Horne and Östberg's questionnaire [25]. Physical fitness was determined by a validated questionnaire of sport practice.

2.2 Experimental design

The circadian markers were studied before, during and after 8-h exposure to two different simulated altitudes: 8000 ft followed by 12,000 ft. This order was chosen for safety reason. The higher altitude is indeed considered in aerospace medicine as a threshold of cognitive trouble appearance [26]. All subjects were studied at each altitude level for two consecutive 24-hour cycles: D_0, the control 24-hour cycle and D_1, the hypoxic exposure 24-hour cycle. In order to minimise possible seasonal variations the entire study took place in September (8000 ft) and October (12,000 ft) respectively, separated by a four week period for each subject to allow biological recovery. The work–rest schedule was identical on D_0 and D_1 for both sessions. The subjects were given standardized meals at 07:00, 11:30 and 19:00 h and mineral water ad libitum. They slept from 22:30 to 06:30 h.

2.3 Simulation of hypobaric hypoxia

Both altitudes were simulated in a 60-m^3 hypobaric chamber for 8 hours (08:00-16:30 h). The chamber was large enough for five subjects during each session. Ascent and descent speeds were maintained at minimal values (i.e., 900 ft/min) in order to simulate normal aircraft takeoff and landing. This descent speed also minimises the risk of barotraumatic otitis and sinusitis which is generally seen during the recompression phase. Intermittent fresh air ventilation was used to control the ambient temperature and the composition of inspired gases (F_IO_2 = 20-21 % and F_ICO_2 < 1 %). The hypobaric chamber was equipped with an airlock which allowed a subject to leave the hypobaric chamber if necessary without stopping the entire study session.

2.4 Variables under study

Core body temperature (CBT) was continuously recorded by telemetry (CorTemp™, Human Technologies, Palmetto, FL), with an accuracy of 0.01°C. Subjects swallowed a calibrated sensor embedded in a leak-proof silicone-coated capsule weighing 7 g once a day in the morning.

Plasma melatonin and cortisol were determined on venous blood samples withdrawn every two hours from an intravenous catheter, positioned in the subject's antecubital vein for 48 hours. The samples were taken

under standardised conditions, i.e. after sitting quietly for 15 min from 08:00 to 22:00 h and when recumbent during sleep from 00:00 to 06:00 h. Light intensity was controlled and ranged from 400 to 500 lux during the day. Light was maintained at low level (< 5 lux) at night in order to avoid the subjects waking up. A red lamp providing a minimal light was used when taking the night time blood samples in order to avoid inhibiting nocturnal melatonin secretion by the pineal gland which is seen with bright light exposure [27]. The tubes were centrifuged and stored at -20°C until assay, using respectively a highly specific radioimmunoassay for the melatonin and a specific competitive enzyme immunoassay for the cortisol.

Autonomic nervous reactivity to hypoxic exposure was studied by spectral analysis of heart rate variability from continuous ECG recordings (Embla™ & Somnologica™, Flaga, Reykjavik, Iceland) [28]. The proportion of high frequencies (HF) as a function of the total power (TP) of the spectrum (Hfn = HF/TP) was used as an index of vagal tone and the low-to-high frequency ratio (LF/HF) was used as an index of the level of sympathetic tone.

Sleep was studied by sleep logs filled by the subjects in the morning. Mean subjective sleep parameters taken into account were the sleep latency, the total sleep time (TST), the waking after sleep onset (WASO), i.e. the total amount of time spent awake between sleep onset at night and sleep offset in the morning, and the sleep efficiency index (SEI), i.e. the total sleep time-to-time in bed ratio (SEI = TST / TIB).

2.5 Data analysis

The variables were studied with conventional statistical methods (ANOVA, post-hoc tests, linear correlations) and with specific methods (Cosinor, Bingham test, moving average fitted profiles, mid range crossing time,…) [29-31].

2.6 Main results

2.6.1 Core body temperature rhythm

The 8000-ft exposure slightly altered the expression of CBT rhythm (Fig. 1) with a significant 90-min advance of peak time when compared with control ($p = 0.004$). This modification may be a result of an increase of CBT under hypoxia in relation with an increase of energy expenditure in order to compensate this hypoxia.

The 12,000-ft exposure led to greater perturbation of the CBT rhythm (Fig. 1). The ANOVA comparing D_1 and D_0 revealed a significant Day effect ($p < 0.001$) with a significant Day x Time interaction ($p = 0.048$). Post-hoc tests revealed significantly differences in each of the mean values between 08:00 to 01:00 h. The mean CBT was indeed higher during D_1 than D_0, but predominantly from 08:00 to 01:00 h. The study of the phase markers showed controversial results with a significant 70-min advance of the peak time, a significant 47-min delay of the Mid Range Crossing Time MRCT was delayed while the trough time remained the same. The advance of peak time was a probable consequence of the increase of CBT under hypoxia. This parameter could not therefore be considered as a reliable phase marker of the endogenous rhythm of CBT. As the MRCT and the trough time were less influenced by hypoxia in our study, they could be more reliable phase markers. The conclusion may be then that the 12,000-ft exposure led to a transient phase delay of the endogenous rhythm of CBT with a delayed evening decline of CBT.

2.6.2 Plasma melatonin rhythm

The expression of circadian melatonin rhythm was altered by hypoxia at both studied altitudes (Fig. 2).

A significant decrease of amplitude was found, but without any phase shift. The decreased rhythm amplitude was a consequence of a significantly lower mean nocturnal peak of melatonin.

This decrease depended on subjects' characteristics as age, physical fitness, and sympathetic reactivity to hypoxia (Fig. 3). The decrease was only seen in the younger subjects (23-28 yr) who presented in parallel a mild increase of sympathetic tone under hypoxia (+30 %). No decrease was detected in the older subjects (29-39 yr) who presented in parallel a strong increase of sympathetic tone under hypoxia (+90 %) in relation with a lower physical fitness.

The decrease in the nocturnal peak of melatonin after hypoxic exposure may be result of a decreased availability in serotonin in the pineal gland. Indeed, this monoamine constitutes the precursor of melatonin [27]. Its local concentration may have been decreased by hypoxic exposure, as it was shown in rats submitted to hypoxia [32]. Moreover, a strong sympathetic reactivity to hypoxia likely stimulates the synthesis of the N-acetyl transferase, the rate limiting enzyme for melatonin synthesis which is under noradrenergic control [27]. This last effect may increase melatonin synthesis and counterbalance the inhibitory effect of hypoxia. It may also explain the inter-individual differences we observed in our study.

2.6.3 Plasma cortisol rhythm

The expression of circadian cortisol rhythm was altered by hypoxia at both studied altitudes (Fig. 4).
Circadian rhythm was validated in each study situation (control and altitude sessions) using the Cosinor method. The well known circadian profile was found, with a peak in the morning (between 06:00 and 08:00 h) and a trough around midnight. In other words no phase shift could be detected. A significant decrease in amplitude was found by the Bingham test only at 8000-ft hypoxic exposure.

Biphasic modifications of plasma cortisol under hypoxia were shown by ANOVA for both studied altitudes. An initial fall of cortisol was seen during the first hours of hypoxic exposure by comparison to control values and then a rebound of secretion occurred in the evening just after the hypoxic exposure. The slight differences observed between 8000 and 12,000 ft were not significant.

This biphasic evolution can probably be explained by two different effects acting in opposite sense. On the one hand, hypoxia may exert a Nitric Oxide mediated inhibitory effect on adrenal gland with a decreased sensitivity to ACTH [33, 34], that may explain the initial fall of plasma cortisol concentration in the first part of the hypoxic proof. On the other hand, the increase of sympathetic tone during hypoxic exposure, found by the HRV spectral analysis (Fig. 5), may stimulate the secretion of ACTH and therefore explain the progressive return of cortisol to control values, the rebound of secretion in the evening after hypoxic exposure, and probably also the slight differences observed between 8000 ft and 12,000 ft.

2.6.4 Recovery sleep

During the first recovery night, a decrease in sleep latency was observed with an increase in sleep duration and sleep efficiency, only after the 8000-ft exposure (Table). These modifications may be interpreted as an increase of sleep pressure after a physiologically penalizing hypoxic proof, in accordance with Borbely's homeostatic theory [35].

On the contrary, no change was seen in sleep parameters after the 12,000-ft exposure (Table), although the physiological constraint was greater at this altitude. The lack of sleep rebound could be a consequence of the delayed decline of CBT, observed in the evening at this altitude. It is indeed more difficult to fall asleep when the CBT level is high [36, 37].

3. CONCLUSIONS AND OPERATIONAL CONSEQUENCES

Significant alterations of the expression of the circadian markers were induced by mild hypoxia at both studied altitudes. These alterations do not deal with a phase shift of the circadian system, except transiently for the CBT rhythm during the 12,000-ft exposure only. The alterations are therefore different from the desynchronization observed during jet lag.
Moreover the delayed evening decline of CBT observed during the 12,000-ft exposure seemed to impair the possibility of sleep rebound we observed at the lower altitude during the first recovery night.

The mechanisms of action of hypoxia, leading to these circadian alterations, are complex. The autonomic balance may play an important role: the level of sympathetic reactivity to hypoxia may especially explain some interindividual differences.

All the effects of mild hypobaric hypoxia on the circadian markers and on the recovery sleep may therefore contribute to an increased level of fatigue after a long duration flight, even when no time zones are crossed. In case of transmeridian flights, hypoxia may add its circadian effects to the desynchronization linked to the jet lag.

These data should be taken into account in military operations including long duration flights in pressurized planes in order to maintain combat readiness. The 12,000-ft cabin altitude, that can be reached in the Tactical Air Carrying, seems to reduce the capacity of sleep rebound during the first night of recovery in healthy young subjects. As there is a frequent physiological decrease of partial oxygen pressure with age, the same effect of hypoxia on the recovery sleep may appear for a lower cabin altitude. In other words, recommendations can be made to limit the time of exposure at the 12,000-ft cabin altitude in the planes on duty as far as possible to reduce the effects of hypoxia on circadian rhythms. From this point of view, it would be desirable to improve the pressurization in the future large aircrafts, so that cabin altitude do not exceed 8000 ft or perhaps less.

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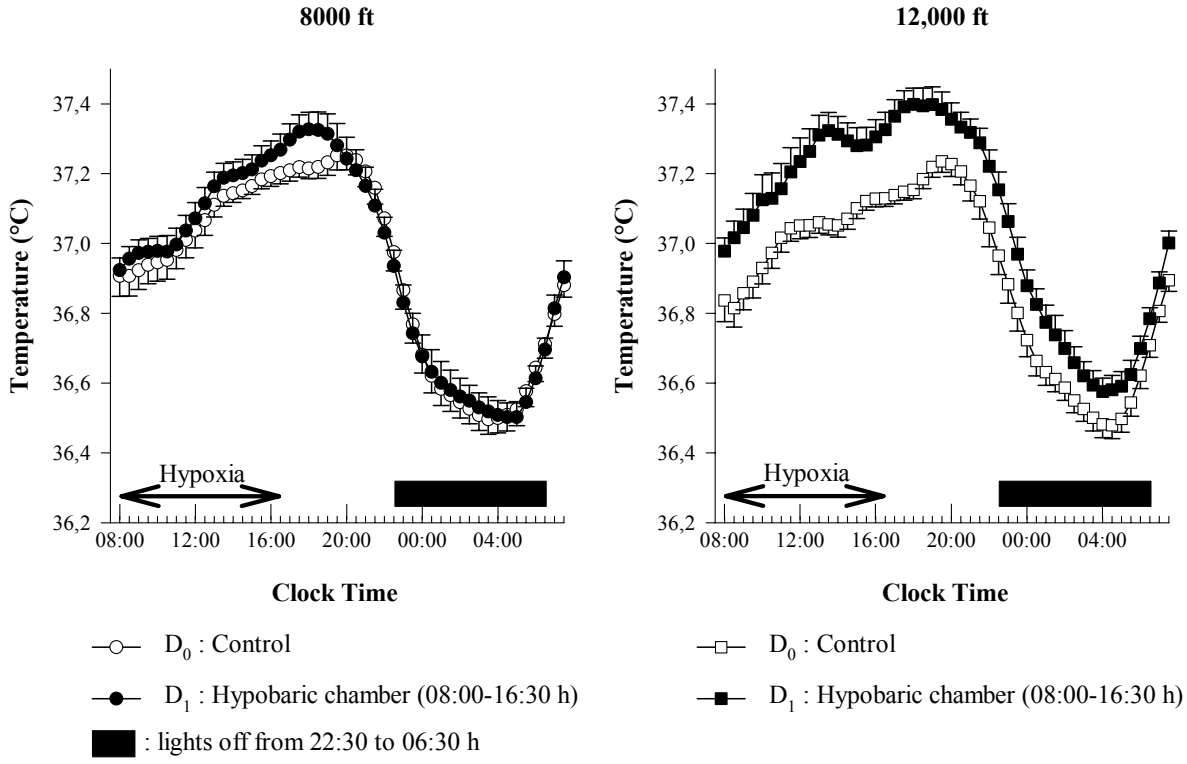

Figure 1: Circadian profiles of CBT at 8000-ft and 12,000 ft simulated altitudes

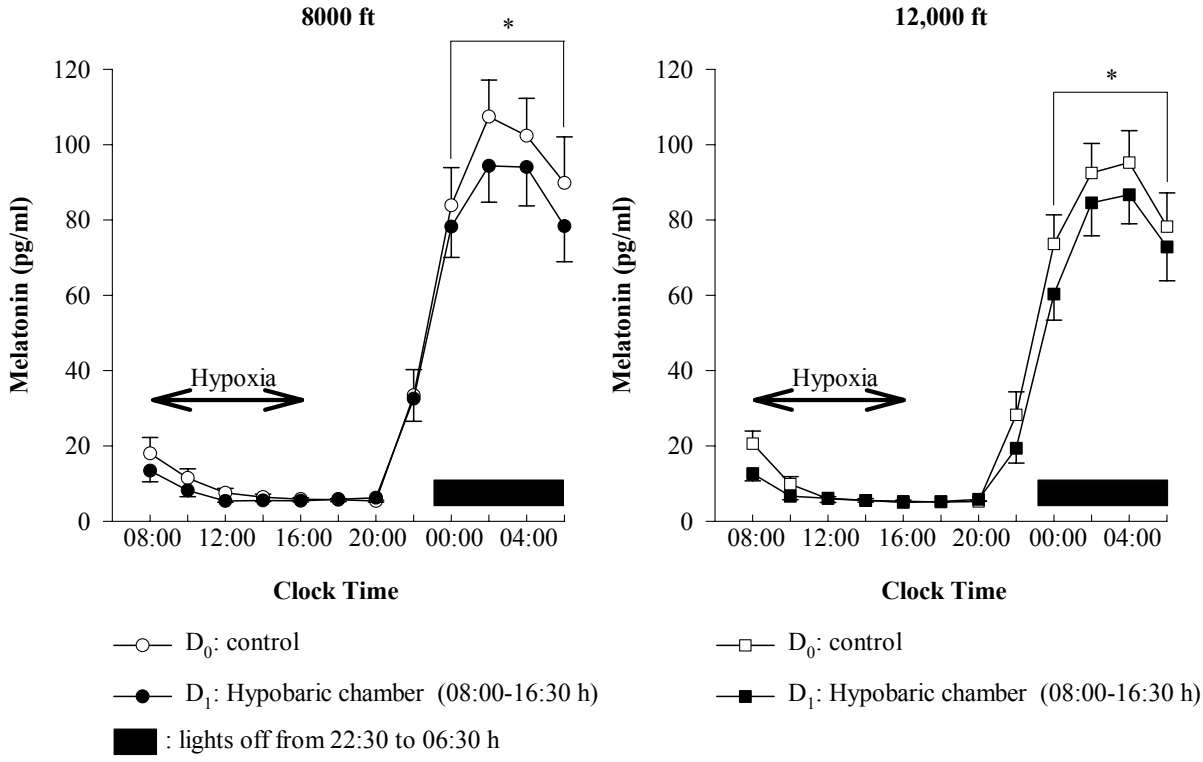

Figure 2: Circadian profiles of plasma melatonin at 8000-ft and 12,000 ft simulated altitudes

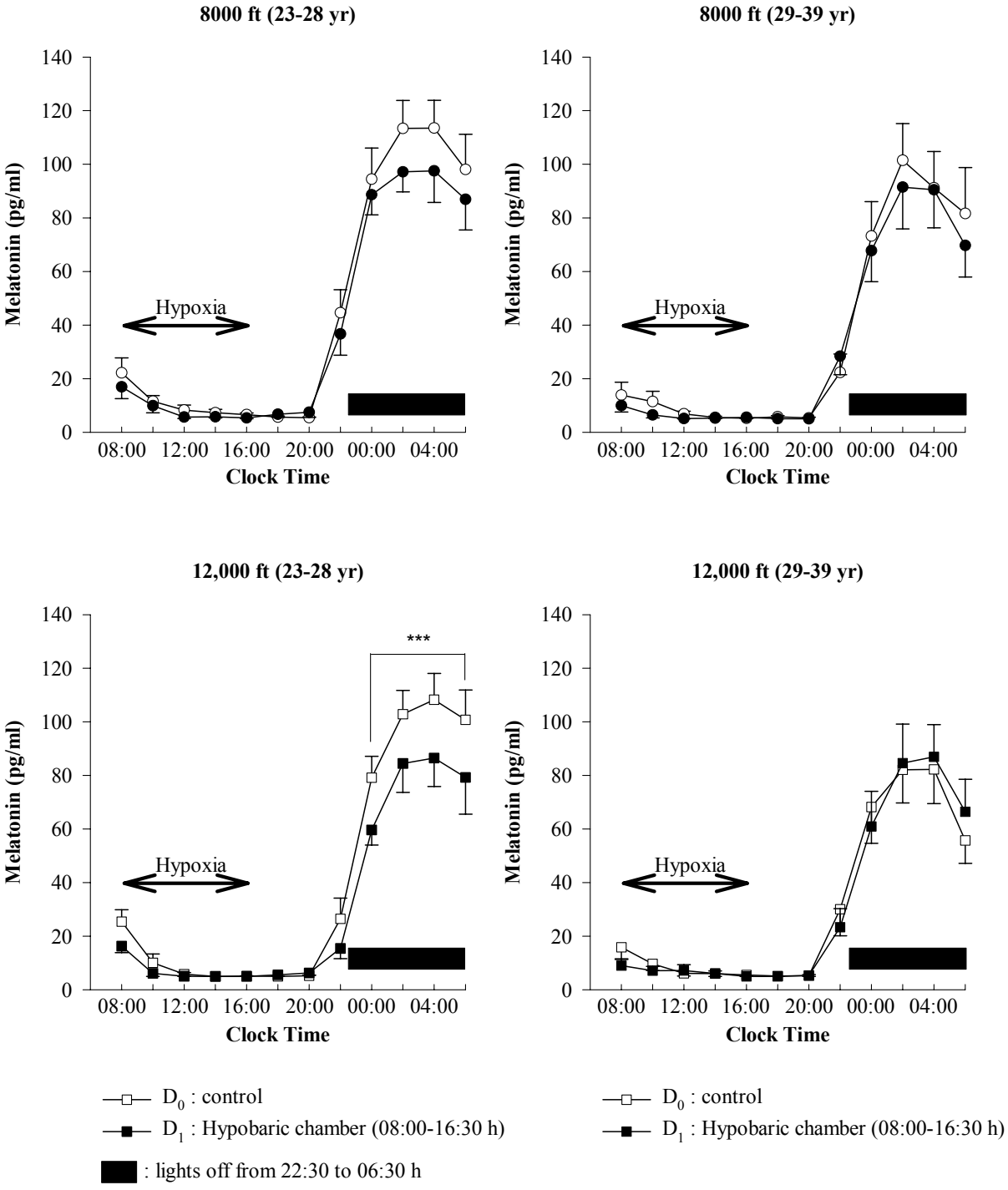

Figure 3: Plasma melatonin circadian profiles according to subjects' age at 8000-ft and 12,000 ft simulated altitudes

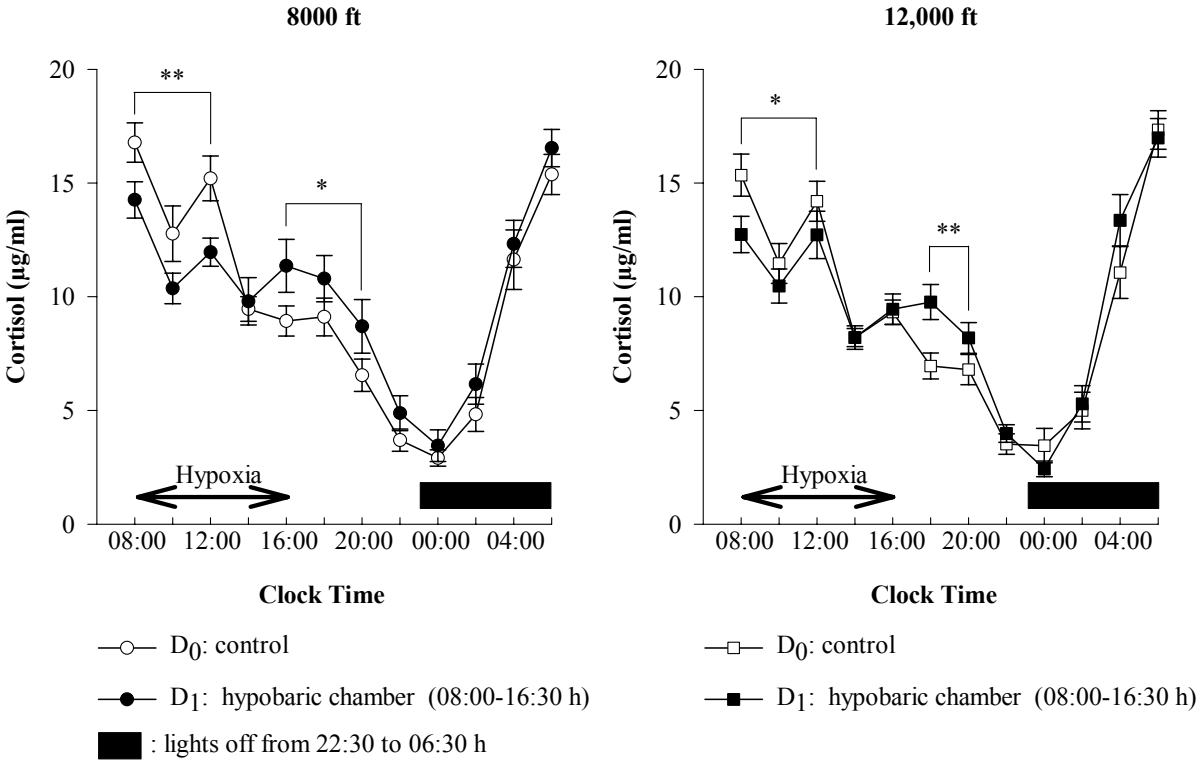

Figure 4: Circadian profiles of plasma cortisol at 8000-ft and 12,000 ft simulated altitudes

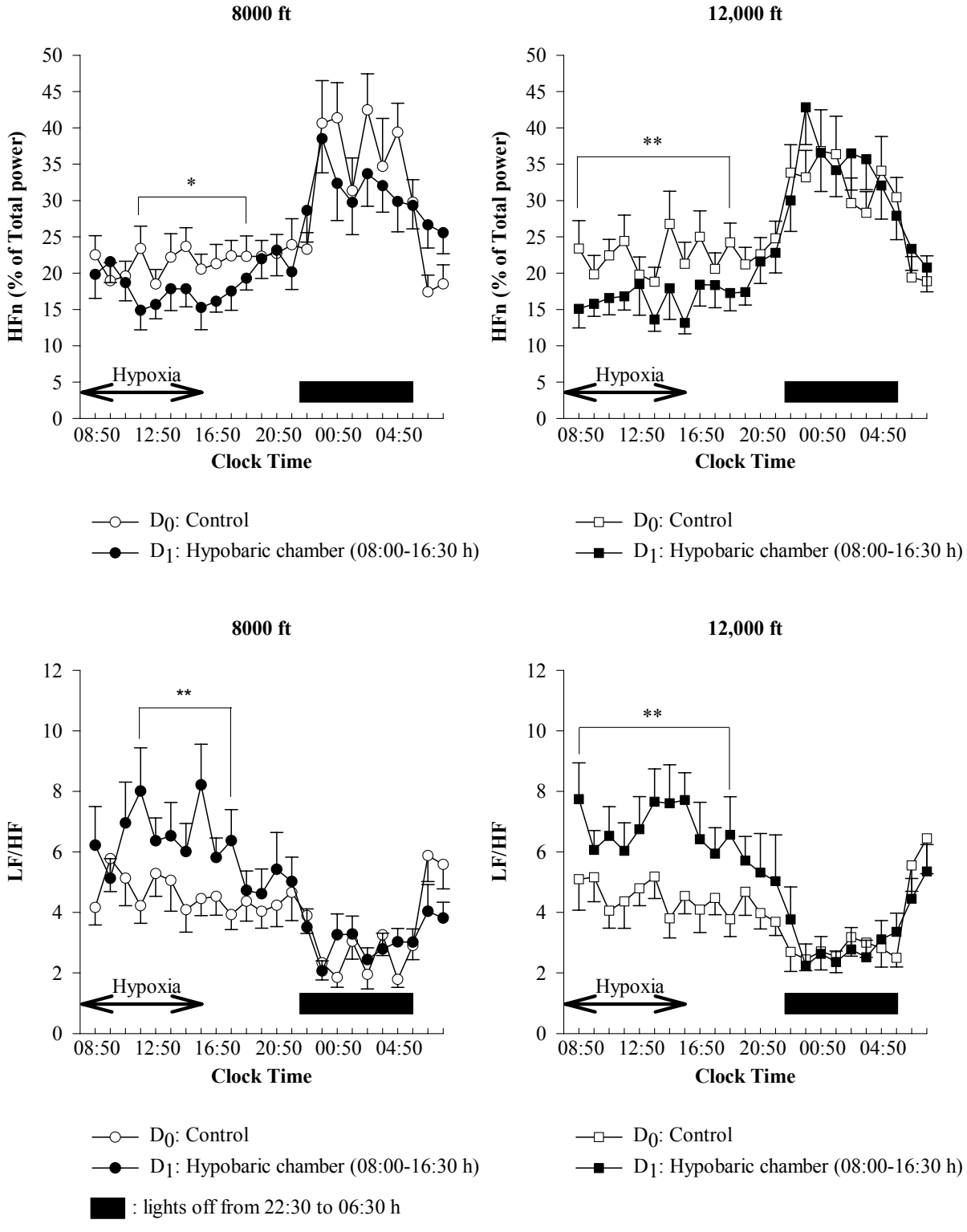

Figure 5: Circadian profiles of autonomic balance studied from HRV spectral analysis at 8000-ft and 12,000 ft simulated altitudes

Subjective sleep	8000 ft		12,000 ft	
	N_0	N_1	N_0	N_1
Duration of Wakefulness After Sleep Onset, WASO (min)	23 ± 9	23 ± 11	20 ± 9	14 ± 7
Sleep Latency, SL (min)	37 ± 7	**17 ± 7 ****	30 ± 8	30± 8
Total SleepTime, TST (h:mn)	06:38 ± 0:13	**07:08 ± 0:13 ***	06:45 ± 0:15	06:58 ± 0:11
Sleep Period Time, SPT (h:mn) SPT = TST + WASO	07:01 ± 0:10	**07:31 ± 0:07****	07:05 ± 0:11	07:12 ± 0:09
Sleep Efficiency Index, SEI (%)	0.83 ± 0.03	**0.89 ± 0.03 ***	0.84 ± 0.03	0.87 ± 0.02

(* p < 0.05; ** p <0.01)

Table: Sleep parameters during the first recovery night (N_1) after hypoxic exposure compared to the control night (N_0)

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