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Short communication

Blood Pressure Dipping and Salivary Cortisol as Markers of Fatigue and Sleep Deprivation in Staff Anesthesiologists

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A B S T R A C T

Anesthesiologists often work extended duty shifts that result in acute and chronic sleep loss and circadian disruption. Stress caused by sleep deprivation, together with excessive workload could contribute to acute increases in blood pressure (BP) and sympathetic nervous system activity. Non-dipping pattern of BP is considered an additional risk factor for cardiovascular events and target organ damage. We hypothesized that there would be significant changes of cardiovascular parameters when comparing work on call during the 24-hour in-hospital shift (24-HD) versus ordinary working day (8-HD) combined with changes of dipping pattern and altered diurnal cortisol secretion, measured by salivary cortisol (SC). Following local Medical Ethics Committee approval, 12 out of 36 staff anesthesiologists (8 male, 4 female), 33–61 years old, participated in this study. Ambulatory BP monitor was used for noninvasive 24-hour ambulatory BP and heart rate (HR) monitoring. Each participant was monitored continuously during the 8-HD, as well as during the 24--HD. Saliva for analysis of cortisol levels was collected six times a day (at 8 am, 11 am, 2 pm, 5 pm, 8 pm, and 11 pm) both during 8-HD and on 24-HD. There was a significant decrease in number of diastolic dippers on call vs. diastolic dippers on ordinary working day (4/12 vs. 10/12, p=0.036), and non significant decrease of systolic dippers (3/12 vs. 7/12, p=0.214). There were no significant differences in SC values between 8-HD and 24-HD at all observed time points. However, the SC values measured during the night were markedly elevated on both days compared with reference values and the shapes of SC curves were altered. The lack of diastolic BP dipping could be more sensitive indicator of stress among staff anesthesiologists than systolic BP dipping. The shape of SC diurnal curve in terms of elevated night values could be another indicator of their chronic fatigue.

***Key words**: anesthesiologists, sleep deprivation, shift work, blood pressure, ambulatory blood pressure monitoring, fatigue, salivary cortisol*

Introduction

Anesthesiologists often work extended duty shifts that result in acute and chronic sleep loss and circadian disruption. Fatigue caused by sleep loss and circadian disruption can degrade performance and reduce many aspects of human capability[1]. Stress caused by sleep deprivation, together with excessive volume of work, requirements to work quickly and lack of opportunity for consultation could contribute to health problems in anesthesiologists[2,3].

Sleep has undoubtedly important homeostatic functions, and sleep deprivation is a well-known stressor that has consequences for the brain, as well as many body systems[4]. Depriving healthy subjects of sleep has been shown to acutely increase blood pressure (BP) and sympathetic nervous system activity. Prolonged short sleep durations could lead to hypertension through extended exposure to raised 24-hour BP and heart rate (HR) values, elevated sympathetic nervous system activity, and

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increased salt retention[5]. The chronic sleep deprivation is also associated with cardiovascular events[6], and usual sleep duration below the median of 6 hours *per* night is associated with an increased prevalence of hypertension[7].

Blood pressure dipping is a nocturnal decrease in blood pressure, described by following equation; Dipping = [1-(BP sleeping/BP awake)] × 100%. The subjects who exhibit a nocturnal BP fall of at least 10% are called dippers, and between 0–10% are non-dippers. There are also extreme dippers (more than 20%), and reverse dippers (<0%)[8–10]. Several studies have investigated the relationship between the lack of or reduction of nocturnal BP fall (non-dipping pattern) and cardiovascular risks, showing not only an increase of target-organ damage (heart, brain, kidney), but a greater frequency of cardiovascular events (stroke, myocardial infarction) and higher cardiovascular mortality in non-dippers, both hypertensive and normotensive subjects. Therefore, a non-dipping pattern may be considered an additional risk factor[11,12]. It seems that deeper and less-fragmented sleep is associated with more blood pressure dipping in normal subjects[13].

Adrenocorticotropic (ACTH) and other pituitary hormones rhythms are associated with sleep and the circadian cycle, generating reproducible patterns that are repeated approximately every 24h. The hypothalamic-pituitary-adrenal (HPA) axis exhibits characteristic peaks of ACTH and cortisol production in the early morning, with a nadir during the night[14]. The high workload and much stress increases sleepiness, impairs sleep, and affects the pattern of diurnal cortisol secretion[15]. It seems that decreased diurnal variation in cortisol is associated with decreased diurnal variation in BP[16]. Besides, in the chronic fatigue syndrome the functioning of HPA-axis has previously been found to be altered[17], and salivary cortisol changes were used as biochemical markers of this syndrome[18].

Until recently[19], the potential impact of sleep loss, fatigue and stress, particularly among staff anesthesiologists, has received only sporadic attention and researches involved principally medical students, residents and younger physicians[1,20].

The aim of this study was to compare cardiovascular parameters and diurnal cortisol secretion measured by salivary cortisol (SC) in staff anesthesiologists while on call during the 24-hour in-hospital shift (24-HD) *versus* ordinary 8-hour working day (8-HD), and to test for possible reduction in exhibiting BP dipping pattern as an indirect measure of fatigue and sleep deprivation.

Subjects and Methods

Participants

Following Biomedical Research Ethics Committee of both University of Split School of Medicine and Split University Hospital Center approvals, as well as Split University Hospital Center management approval, 12 out of 36 (8 male, 4 female) staff anesthesiologists, 33–61 years old, filled in the informed consent (flow chart, Figure 1). The anesthesiologists were declared healthy by passing their physical, and considered capable of practicing their job by their physicians. The exclusion criteria included cardiovascular disease – high levels of hypertension (systolic BP >200 mmHg, or diastolic BP >120 mmHg), chronic obstructive pulmonary disease, diabetes, and depression. Besides, they were taking no psychoactive drugs (Table 1). The anesthesiologists had to sleep normally before 24-HD or 8-HD, and not to be on call at least 3 days before testing, to avoid possible influence of acute fatigue and sleep deprivation.

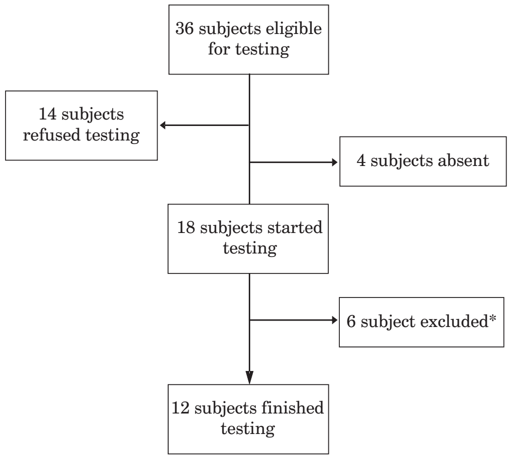

*Fig 1. Flow chart of participants. (*Due to the violation of protocol for salivary cortisol testing).*

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS IN THE STUDY

Gender (male/female)	8/4
Age (median, range)	45.5 (33–61)
Height (cm) – mean±SEM	174.7±1.9
Weight (kg) – mean±SEM	80.9±3.5
BMI (kg/m^2) – mean±SEM	26.4±0.8
Smokers (yes/no)	3/9
Hypertension (yes/no)*	4/8
Other diseases (yes/no)	0/12

* controlled BP values, 3 anesthesiologists taking beta-blockers, 1 taking diuretic

Settings

This study was performed in the University Hospital Split, having 1500 beds, the only one in the county of approximately 500,000 inhabitants. There are approximately 160–180 physical exams *per* day and 2.300 operations *per* year in the surgical emergency department. Type of patients: from neonatal to geriatric. Type of surgery: polytrauma including burn injury; neurosurgical, abdominal, thoracic, vascular, and pediatric surgery (neonates to 18 yrs old). There are two anesthesiologists on call in the surgical emergency department, caring for all patients scheduled for emergent surgery, as well as taking part in diagnostics or interventions, especially in critically ill or injured patients, including resuscitations.

Blood pressure monitoring

Ambulatory blood pressure monitor SpaceLabs 90207 (Spacelabs Medical, Washington, USA) was used for non-invasive 24-hour ambulatory BP and heart rate (HR) monitoring. It uses oscillometry, the most widely accepted and validated method of automatic non-invasive BP determination and measures systolic, diastolic and mean BP, as well as heart rate over the period of 24 hours. Measurement ranges for this device are as follows: HR 40–180 min^{-1}, systolic blood pressure (SBP) 70–285 mmHg, diastolic blood pressure (DBP) 40–200 mm Hg, mean arterial pressure (MAP) 60–240 mmHg. Automatic measurement intervals are adjustable from 6 minutes to 120 minutes. One measurement usually lasts between 35 and 50 seconds. The device itself weighs 346 grams, and the dimensions are 2.8×11.4×8.6 centimeters (height, depth, width). The device was equipped also with waist-belt to facilitate daily activities of participants and with standard adult cuff (24–32 cm). Specially designed Spacelabs Medical Recorder software v2.0 was used to analyze automatic blood pressure and heart rate monitoring data[21,22].

The following parameters were recorded, analyzed and subsequently printed in each subject: a) personal data: name, ID, age, gender, height, weight; b) duration of test (+ scan start, scan end), percentage of successful readings; c) overall test summary (all data with minimum, average and maximum values, as well as standard deviation; SBP, DBP, MAP, Pulse pressure, and HR). All aforementioned data were re-analyzed in the same manner in regard to wake period (defined as 6 am – 10 pm) and sleep period (10 pm – 6 am). Blood pressure dipping was calculated in both absolute and relative values.

Each participant was monitored for two 24-hour periods; *i.e.* one during the regular 8-hours day work shift, and the other during the 24-hours in-hospital service. Each monitoring started at the beginning of the work day (between 7.30 am and 8 am). The 24-hour period was divided into a wake period (from 6 am to 10 pm) and a sleep period (from 10 pm to 6 am). The SBP, DBP, MAP, and HR readings were obtained in 20 minute-intervals during the wake period and in 30 minute-intervals during the sleep period. The subjects were asked to keep the diary concerning their activities and sleeping time during the service.

Salivary cortisol

Saliva samples for analysis of cortisol levels were collected in three hours intervals, starting at 8 am and lasting till 11 pm. Each subject collected 12 saliva samples in total: six samples of saliva (at 8 am, 11 am, 2 pm, 5 pm, 8 pm, and 11 pm) were collected during 24 hours shift, and six during the regular 8 hours day shift at same time points.

The saliva was collected in sterile, pre-marked 2 mL glass vials. Prior to sampling, subjects were instructed not to eat or drink for at least 15 minutes. The sampling procedure was as follows: the subject opened a sterile, pre-marked glass vial, filled it with approximately 1 mL of saliva, according to graduation on the vial, and closed the rubber cap. Samples were then stored at –20 °C in the refrigerator for further analysis. When saliva samples were collected at home (control testing), vials with samples were stored at home refrigerators.

After sample collection, saliva was prepared for analysis with salivary cortisol analyzing kit (Active Cortisol EIA (for saliva), DSLabs, Webster, USA). Samples were thawed on ice and moved into 1.5 mL micro-centrifuge eppendorf tube. They were centrifuged on 9000 rpm/ +4 °C (7880 g) for 10 minutes. Supernatant was moved to a new, sterile 1.5 mL eppendorf tube and analyzed for cortisol concentration.

The results were expressed in nmol/L. Normal values for salivary cortisol are between 1.4 and 27 nmol/L, and the concentration vary according to the cortisol circadian rhythm: a) referent morning values: 5–27 nmol/L; b) referent afternoon values: 2.7–7.2 nmol/L; c) referent midnight values: 1.4–4.7 nmol/L[23,24].

Statistical analysis

Statistica 7.1™ software package (StatSoft, Inc., Tulsa, USA) was used to perform statistical analysis of the data. GLM ANOVA was used to test the differences in averaged blood pressures, heart rates, and salivary cortisol values from all subjects' pooled data, along with Bonferroni post-hoc correction to obtain multiple comparisons. Fischer's exact test was applied to test for dippers and non-dippers subjects at 8-HD *vs.* 24-HD. Results were presented as mean±SEM, and $p<0.05$ was considered statistically significant.

Results

There were 12 subjects (8 male, 4 female) participating in this study (Table 1, Figure 1).

During on call the subjects slept 5 hours (median, range 2–7 hours), whereas before ordinary working day they slept for 8 hours (median, range 7–9 hours). The average percentage of successful readings of ambulatory BP monitoring among participants were 84.8% (range 64–98%) during 24-hours on call and 80.6% (range 47–100%) during ordinary working day.

There were no significant changes in systolic and diastolic blood pressure curves between on call and ordinary working day (Table 2). However, there was a significant decrease of diastolic dippers on call *vs.* diastolic dippers on ordinary working day (4 *vs.* 10, $p=0.036$) (Table 3), and not significant decrease in number of systolic dippers on call *vs.* systolic dippers on ordinary working day (3 *vs.* 7, $p=0.214$) (Table 3).

TABLE 2
POOLED HEMODYNAMIC PARAMETERS OF THE SUBJECTS IN THE STUDY (N=12)

Parameter	Control 8-HD[1]	On Call 24-HD[2]
SBP (mmHg)	127.8±17	126.0±16.8
DBP (mmHg)	78.6±14.3	77.1±14.3
MAP (mmHg)	94.9±14.7	93.7±14.7
PP (mmHg)	49.2±11.5	48.9±10.4
HR (beats/min)	71.4±10.9	71.3±12.0

[1] during the control ordinary working day
[2] during the 24-hour in-hospital shift

TABLE 3
PRESENCE OF DIPPING IN INDIVIDUAL SUBJECTS IN THE STUDY

Subject	Control 8-HD[1]			On Call 24-HD[2]		
	SBP DIPP*	MAP DIPP†	DBP DIPP**	SBP DIPP*	MAP DIPP†	DBP DIPP**
1	NO	NO	YES	NO	NO	NO
2	YES	YES	YES	NO	NO	NO
3	NO	YES	YES	NO	NO	YES
4	NO	NO	NO	NO	NO	NO
5	YES	YES	YES	YES	YES	YES
6	YES	YES	YES	NO	NO	NO
7	YES	YES	YES	YES	YES	YES
8	YES	YES	YES	NO	NO	NO
9	NO	YES	YES	NO	NO	NO
10	YES	YES	YES	NO	YES	NO
11	YES	YES	YES	YES	YES	YES
12	NO	NO	NO	NO	NO	NO

[1] during control ordinary working day
[2] during the 24-hour in-hospital shift
SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, DIPP – dipping, YES – dipping was present, NO – there was no dipping
*the two-tailed p=0.214 (Fischer's exact test), † the two-tailed p=0.0995 (Fischer's exact test), **the two-tailed p=0.036 (Fischer's exact test)

During on call maximal and minimal SC values of all participants were 48.3 and 1.4 nmol/L, respectively. During ordinary working day, this range was between 46.9 and 1.4 nmol/L. There were no significant differences in salivary cortisol values between on call and ordinary working day (p=1.0). However, the salivary cortisol values measured during the evening/night were markedly elevated both during 8-HD and 24-HD compared with reference values (see Methods) and consequently the shape of both salivary cortisol curves was changed (Figure 2).

Blood pressure changes associated with diurnal salivary cortisol changes are shown in Figure 3. There was a significant decrease of averaged nocturnal diastolic blood pressures compared to morning values during 8 hour-working day (84.7 *vs.* 71.9 mmHg, p=0.016), but not during 24-hour on-call (84.3 *vs.* 79.9 mmHg, p=1.0).

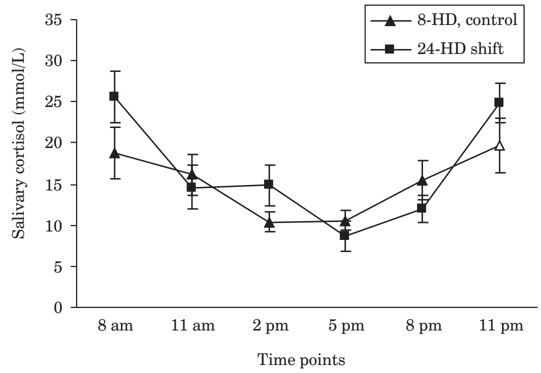

Fig. 2. Diurnal pattern of salivary cortisol (SC) values during control ordinary working day (8-HD) and during 24-hour in-hospital on call (24-HD shift). There were no significant differences between the two curves, but both curves exhibit increases in SC values at evening/night especially at 11 pm time point.

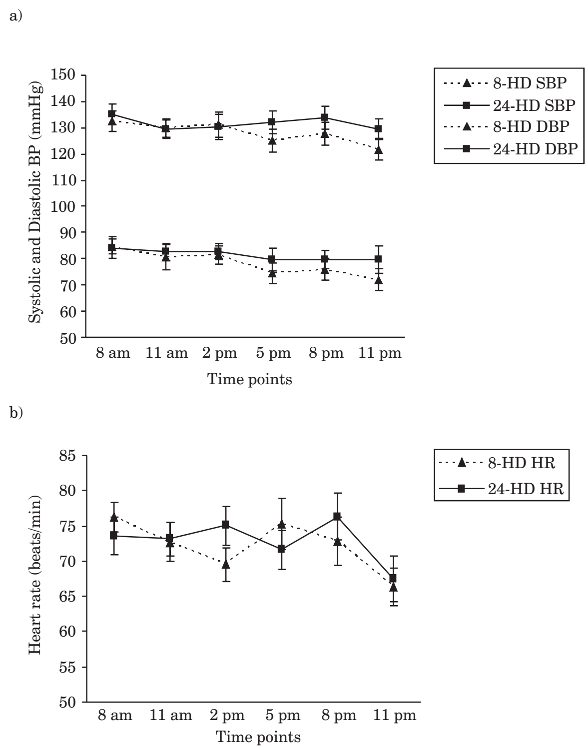

Fig. 3. Systolic and diastolic blood pressure (A) and heart rate(B) values at specific time points during the ordinary working day (control, 8-HD), as well as during the 24-hour in-hospital shift (24-HD). 8-HD SBP – systolic blood pressure during 8-hour working day, 24-HD SBP – systolic blood pressure during 24-hour in-hospital shift, 8-HD DBP – diastolic blood pressure during 8-hour working day, 24-HD DBP – diastolic blood pressure during 24-hour in-hospital shift, 8-HD HR – heart rate during 8-hour working day, 24-HD HR – heart rate during 24-hour in-hospital shift.

There were no significant changes of averaged systolic blood pressure and heart rate during 8 hour-working day, as well as during 24-hour on call at these time points.

Discussion

This self-controlled study showed that there were no differences between hemodynamic variables of staff anesthesiologists' pooled data (blood pressure, pulse pressure, heart rate) when comparing work on call 24-HD *versus* ordinary 8-hour working day, as measured by ambulatory continuous BP and HR monitoring. However, there were significant changes in the nocturnal diastolic blood pressure pattern, and the decreased number of diastolic non-dippers during on call compared with control days. There were no significant differences in salivary cortisol value curves between on call and ordinary working day, but the shape of salivary cortisol diurnal curves was changed in both testing days, in terms of elevated night values compared with the reference values.

The studies researching the fatigue and work stress in staff anesthesiologists are very rare, so we decided to undertake this type of study because of subjective and objective opinion of work overload of anesthesia personnel in emergency surgical departments and possible health problems arising from it. We considered the ambulatory BP monitoring as the most appropriate method for this type of testing, together with a salivary cortisol sampling, because they are not too aggressive for researched subjects and nevertheless they would probably not disturb their usual activities.

The ambulatory continuous BP monitoring is well-established method in the diagnosis and treatment of hypertension and cardiovascular events. The devices are modern, nowadays of markedly reduced weight and the compliance of patients is improving. It is emphasized that ambulatory BP monitoring is superior to clinical BP monitoring in predicting cardiovascular morbidity and mortality, and it is considered that 24-hour BP control may be necessary to gain complete benefit from blood pressure-lowering therapy[25–27].

The concept of dippers and non-dippers is broadly explained in literature and it clearly showed that non-dippers, *i.e.* the subjects in whom blood pressure decreases during the night have less damage to their brain, kidneys, heart, and blood vessels than people with elevated nocturnal BP[9,11,12].

In this study we found the significant decrease of diastolic, but not of systolic blood pressure dipping during on call. We did not find references in the literature distinguishing between systolic and diastolic dippers. However, there is a review discussing only the elevated diastolic BP night/day ratio in normoalbuminuric normotensive type I diabetic patients, associated with an increased glomerular filtration rate and an increased extracellular volume[28].

There is evidence that a work-week with a high workload and much stress increases sleepiness, impairs sleep, and affects the pattern of diurnal cortisol secretion[15]. A reduced secretion of cortisol has been proposed as a possible explanation of the symptoms in chronic fatigue syndrome, although the evidence of hypocortisolism in this syndrome is conflicting[29]. Diurnal cortisol variation was a significant predictor of BP dipping and was found to have a strong relationship with BP dipping[16].

Measurement of salivary cortisol is an excellent indicator of free cortisol concentration in human serum[23,30–32]. In this study there were not significant changes in salivary cortisol levels comparing 24-HD and 8-HD, but the shape of cortisol diurnal curve was altered (Figure 2). This is in accordance with some studies that found significantly reduced diurnal variation of SC in exhausted subjects[33]. The diurnal profile of concentrations of SC for construction workers with extended work-weeks differed from the diurnal profile of SC for those with regular work schedules[34]. Poor sleep quality could also contribute to blunted SC diurnal curve[35]. People with chronic fatigue syndrome demonstrated lower SC concentrations in the morning and higher SC concentrations in the evening indicating a flattening of the diurnal cortisol profile, which is similar to results of our study[36]. The diurnal variations of SC were found also in subjects with depression[37].

There are some limitations to our study. The sample of tested doctors was rather small, and we were disappointed because of very low response rate of our colleagues. The idea of repeating these tests one or more times was evenly rejected by almost all physicians. However, this could also be an indicator of work overload and stress of anesthesia personnel in emergency surgical departments that was also found in another study from our group[38]. Among the multiple factors contributing to regulation of SC levels, there could be marked gender differences. Female gender, menstrual cycle phase and usage of oral contraceptives or hormone replacement therapy should also be taken into consideration, because all of them could have important effects on the HPA responsiveness to stress in healthy subjects[39,40]. There was a small number of females participating in this study and without obtained data of aforementioned variables, we could not provide reliable conclusions regarding sexual dimorphism and possible outcome on regulation of SC levels.

In conclusion, non-dipping pattern of diastolic blood pressure could be an indicator of stress and chronic fatigue among staff anesthesiologist and may be considered as a risk factor for future cardiovascular events. Although there were no significant changes in salivary cortisol levels between 24-hour in-hospital shift and ordinary working day, the shape of salivary cortisol diurnal curve was altered in terms of elevated night values, which could also be an indicator of chronic fatigue and stress in staff anesthesiologists.

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NOĆNO SNIŽENJE ARTERIJSKOG KRVNOG TLAKA I KORTIZOL U SLINI KAO MOGUĆI POKAZATELJI UMORA I NEDOSTATKA SPAVANJA U ANESTEZIOLOGA

SAŽETAK

Anesteziolozi su izloženi čestim dežurstvima, koja dovode do akutnog i kroničnog gubitka spavanja i poremećaja cirkadijanog ritma. Stres koji nastaje zbog nedostatnog spavanja, a u kombinaciji s radnim opterećenjem, mogao bi dovoditi do akutnog povećanja arterijskoga krvnog tlaka (BP) i simpatičke živčane aktivnosti. Izostanak noćnog sniženja BP (tzv. »non-dipping obrazac«) je možebitni dodatni čimbenik rizika za srčanožilne događaje i oštećenje ciljnih organa. Prepostavili smo da će postojati znakovite promjene hemodinamskih parametara između redovnog 8-satnog radnog dana (8-HD) i 24-satnog dežurstva (24-HD), praćene promjenama »dipping« obrasca i dnevnog lučenja kortizola, mjerenog putem kortizola u slini (SC). Nakon odobrenja Etičkog povjerenstva, 12 od 36 specijalista anesteziologa (8 muškaraca i 4 žene), u dobi od 33–61 godine, sudjelovalo je u ovom istraživanju. Ambulantni monitor arterijskoga krvnog tlaka korišten je za neinvazivno 24-satno praćenje arterijskog krvnog tlaka i srčane frekvencije (HR). Svaki liječnik bio je nadziran cijeli dan kako za vrijeme 8-HD, tako i za vrijeme 24-HD. Slina za analizu razine kortizola skupljala se šest puta dnevno (svakih 3 sata od 08:00 do 23:00) za vrijeme 8-HD i 24-HD. Za vrijeme 24-satnog dežurstva bilo je znakovito manje dijastoličkih »dippera« u usporedbi s 8-satnim radnim danom (4 *vs.* 10, p=0,036), ali ne i sistoličkih »dippera« (3 *vs.* 7, p=0,214). Nije bilo znakovitih razlika u vrijednostima SC između 8-HD i 24-HD u svim promatranim vremenskim točkama (p=1,0). Noćni SC bio je višestruko povišen u odnosu na referentne vrijednosti, te je posljedično izmijenjen izgled krivulje SC. »Non-dipping« obrazac mogao bi biti pokazateljem umora i nedostatka spavanja u anesteziologa, a samim tim i čimbenik rizika za buduće srčanožilne bolesti. Dijastolički »non-dipping« obrazac mogao bi biti još osjetljiviji pokazatelj umora i stresa, kao i promjena izgleda krivulje SC, prvenstveno u smislu povećanja noćnih vrijednosti.