



# Arrhythmias and increased neuro-endocrine stress response during physicians' night shifts: a randomized cross-over trial

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## Aims

To evaluate the effects of a 24 h (h) physicians on-call duty (OCD) ('night shift') on 24 h electrocardiogram (ECG), heart rate variability, blood pressure (BP), and various biochemical serum and urine 'stress markers' compared with a 'regular' day at work.

## Methods and results

The study was designed as a prospective randomized cross-over trial with each physician completing a 24 h (h) OCD and a 24 h control period including a regular 8 h non-OCD. Thirty healthy physicians with a median age of 33.5 years (range 29.0–45.0) were analysed. Twenty-four hours ECG and BP monitoring were performed and participants were instructed to fill out an event diary and perform a 24 h urine collection. Furthermore, blood was drawn before and after OCD and control day. Twenty-four hours ECG showed a higher rate of ventricular premature beats (VPB) during early morning hours (VPB 0–6 h, 0.5 vs. 0.0,  $P = 0.047$ ) and increased low-frequency normalized units (29.3 vs. 25.5,  $P = 0.050$ ) during night shift when compared with respective control night at home. During OCD, BP monitoring revealed a greater diastolic BP throughout 24 h (83.5 vs. 80.2 mmHg,  $P = 0.025$ ) as well as during night-time (75.4 vs. 73.0,  $P = 0.028$ ) associated with a higher rate of systolic BP more than 125 mmHg during sleep time. Tumour necrosis factor alpha concentrations increased significantly during night shift (0.76 vs. 0.05 pg/mL,  $P = 0.045$ ). Urinary noradrenaline excretion was greater during OCD when compared with control day (46.0 vs. 36.0  $\mu\text{g}/24\text{ h}$ ,  $P = 0.007$ ).

## Conclusion

Our results highlight the association of OCD with an increased risk profile for cardiovascular disease. In addition to the acute effects observed, frequent night-calls over a longer period possibly elicit sustained alterations in cardiovascular homeostasis.

## Keywords

Night shift • Cardiovascular disease • Stress response • Arrhythmias • Hypertension

## Introduction

In several European countries, healthcare service during night time is usually provided by medical personnel working on night-call duty following a regular daytime shift. The overwhelming majority of physicians complete about three to five on-call duties (OCD) per month, representing a 24 h continuous attendance with OCD from 4.30 p.m. to 7.00 a.m. This specific kind of shift work includes frequent stressful situations, sleep deficit, and

desynchronization of circadian rhythms. Of great concern is the growing body of evidence that 'classical' shift work is associated with an increased rate of cardiovascular diseases (CVD) and other possible hazardous health effects.<sup>1–3</sup> Generally, it is assumed that irregular sleeping patterns cause fatigue and adversely affect physiological functions.<sup>4</sup> Changes in heart rate variability (HRV), elevation of blood pressure (BP), dysrhythmias, altered catecholamine excretion, elevations of serum cholesterol, uric acid and potassium during and after night shift have been

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reported.<sup>5,6</sup> In addition, there is some evidence for a 'dose-response' relationship between shift work and CVD.<sup>7</sup>

Similar to classical shift work, physicians doing night shifts are considered to be at risk for CVD and impaired mental well-being.<sup>8</sup> In contrast to classical shift work, OCD are irregular, include longer working hours (usually 24 h) and are associated with frequent induction of arousals or partial arousals during the night interfering with the cyclicality between different sleep stages. Non-physiological timing of physical activity and nutritional intake influence circadian rhythms, balanced functions of the circulatory system [e.g. BP, heart rate (HR), catecholamine excretion] and may represent one possible explanation for the negative impact on cardiovascular homeostasis in this group.<sup>3</sup>

Studies on the effect of OCD on the cardio-endocrine axis are sparse and partly suffered from low subject numbers or restriction to the determination of either electrophysiological [electrocardiogram (ECG) BP] or biochemical variables.

The aim of this study was to evaluate the effects of a 24 h OCD on 24 h ECG, HRV, BP, and various biochemical serum and urinary 'stress markers' compared with a 'regular' day at work.

## Methods

### Participants

This study was conducted at the Departments of Internal Medicine, Neurology, and Otorhinolaryngology at the Medical University Innsbruck, Austria from 2005 to 2006. Selection of the disciplines was based on comparable characteristics of night shifts and 44 residents/senior physicians were recruited for the study. Demographic data were collected by using a standardized questionnaire (Table 1). Informed consent was obtained from all participants. The study protocol was approved by the local Ethics Committee.

### Study design

The study was designed as a prospective randomized controlled cross-over trial. Before initiation, the participants were randomized by a

statistician (H.U.) to start with either the day not on-call (NOC) (i.e. control) or the 24 h OCD.

The OCD comprised routine work from 8 a.m. to 4.30 p.m. followed by OCD for about 16 h. The day NOC comprised a non-OCD from 8 a.m. to 4.30 p.m. followed by staying and sleeping at home for the rest of the day until next morning.

In between 8.00 and 9.00 a.m. before OCD and NOC, respectively, a 24 h ECG and a 24 h BP measurement were applied and blood samples were drawn at standardized conditions. Furthermore, subjects were instructed to perform a 24 h urine collection. In between 8.00 and 9.00 a.m. after OCD and NOC, respectively, the 24 h ECG and the 24 h BP monitor were removed and blood samples were drawn again at standardized conditions.

### Inclusion and exclusion criteria

Healthy colleagues (25–60 years old) from the Departments of General Internal Medicine, Neurology, and Otorhinolaryngology, University Hospital Innsbruck were eligible for this study.

Physicians who attended OCD within 72 h prior to participation, or found to suffer from narcolepsy, obstructive sleep apnoea syndrome (OSAS) as well as cardiac, neuromuscular, psychiatric, endocrine or infectious diseases were excluded from the study.

### Event diary

Participants were instructed to fill out an event diary during OCD and NOC. Beside all exceptional events (high rate of psychological strain, increased physical activity, etc.), the main area of interest was the sleeping period (bedtime, awakenings by a phone call, wake time during sleeping period, and time of getting up in the morning).

Following variables were calculated: number of awakenings during sleeping period (A), time in bed (TIB, time from going to bed until waking up in the morning in minutes), total wake time (TWT, total amount of time awake during TIB in minutes), total sleep time (TST, total amount of time sleeping during TIB in minutes).

### Biochemical parameters, 24 h electrocardiogram and blood pressure measurement

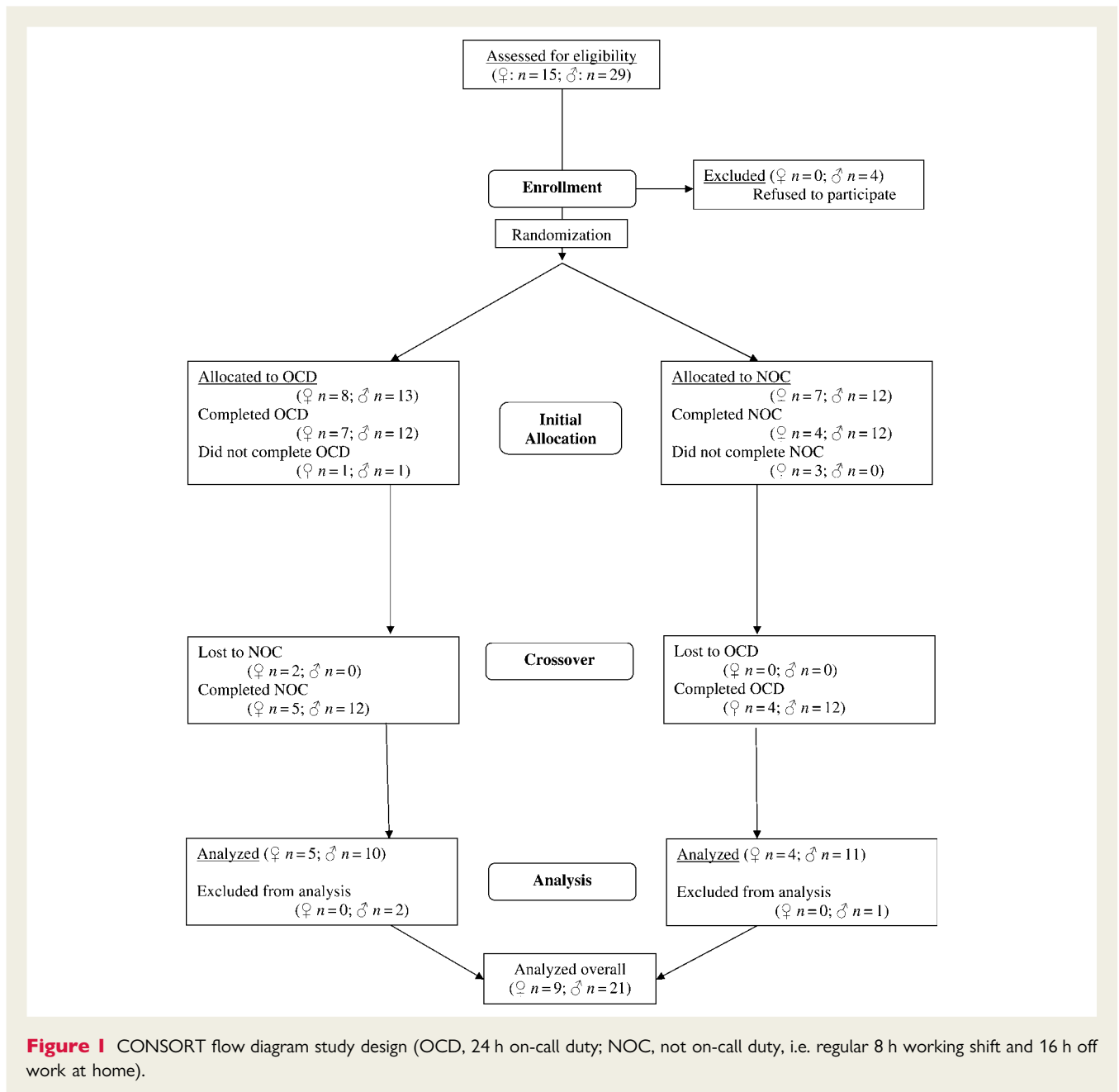
Plasma glucose concentration was measured using a standard enzymatic method (Roche Diagnostic Systems, Basel, Switzerland). Urea and creatinine were determined with standard methods. Total Cholesterol (TC) was measured with CHOL (Cholesterin CHOD-PAP, Roche), triglycerides (TG) with TG (Triglyceride GPO-PAP, Roche), and high-density lipoprotein cholesterol (HDL-C) was determined with HDL-C plus 2nd generation (Roche). High-sensitive C-reactive protein was measured using C-reactive protein (Latex) HS (Tinaquant<sup>®</sup>, C-reaktives Protein (Latex) hoch sensitiv). Interleukin 6 (IL-6) was determined with IL-6 EASIA (Biosource, Belgium) and tumour necrosis factor-alpha (TNF-α) with TNF-α EASIA (Biosource). Urine parameters for adrenalin and noradrenalin were measured with fluorimetric method. Twenty-four hours BP were measured with Tonoport V<sup>®</sup> (GE Medical Systems IT Inc., Milwaukee WI, USA) using the software CardioSoft<sup>®</sup> V4.2 bzw. V6.01 Software (GE Medical Systems IT Inc.).

Twenty-four hours ECG were performed using a CardioMem<sup>®</sup> CM3000 (getemed Medizin- und Informationstechnik AG, Teltow, Germany). Variables were calculated using the software available on the analyser and as described previously<sup>9,10</sup> (CardioDay<sup>®</sup> PC-Software, Medizin- und Informationstechnik AG). Detailed analysis of rhythm, HRV, and BP was performed both for the entire 24 h and separately for the early morning hours (0–6 h a.m.) which were

**Table 1** Baseline characteristics of the study participants

|                            | Participants (n = 30) |
|----------------------------|-----------------------|
| Age (years)                | 33.5 (31.0–36.0)      |
| Sex                        |                       |
| Male                       | 21 (70%)              |
| Female                     | 9 (30%)               |
| First night shift (months) | 76.0 (58.0–106.0)     |
| Night shifts per month (n) | 4.0 (4.0–4.4)         |
| Height (m)                 | 1.80 (1.58–1.89)      |
| Weight (kg)                | 72 (49–86)            |
| BMI                        | 21.83 (17.78–25.76)   |
| Smokers (n)                | 4                     |

Values are absolute numbers and percentage or median (interquartile range); BMI, body mass index; n, number of subjects.



considered to be specifically different in terms stress between OCD and NOC.

## Statistics

Sample size of this randomized, cross-over trial was pre-calculated aiming to show clinical relevant differences for HR and systolic BP. A sample size of  $n = 30$  will have 80% power to detect a difference in means of approximately five beats of HR, (assuming a standard deviation of differences of 9.3 beats) as well as  $\sim 10$  mmHg of systolic BP (assuming a standard deviation of differences of 19.7 mmHg) using a 0.05 two-sided significance level. Normal distribution of the data was assessed using the Kolmogorov–Smirnov test with Lilliefors correction. Since most variables were not normally distributed, all variables were presented as median (interquartile range) and non-parametric methods for paired data were used. All pairwise comparisons were

performed utilizing Wilcoxon's signed rank test. Spearman's correlation coefficient was calculated to analyse associations between A, TIB, TWT, TST, number of night shifts per months, age, and biochemical (including urine) or electrophysiological (ECG, BP) variables. A  $P$ -value less than 0.05 was considered significant.

## Results

### Demographics

Forty-four physicians were assessed for eligibility and 40 colleagues agreed to participate in the study. Thereof, seven study participants were lost to follow-up [cancelled consent of participation ( $n = 4$ ), aborted night shift ( $n = 1$ ), refused to participate ( $n = 1$ ), moved away from Innsbruck ( $n = 1$ )]. Since three colleagues had to be

**Table 2** Results of the event diary during night shift and control day

|                | OCD (n = 30)        | NOC (n = 30)        | P-value |
|----------------|---------------------|---------------------|---------|
| Awakenings (n) | 1.00 (0.00–2.25)    | 0.00 (0.00–00.0)    | <0.001  |
| TIB (min)      | 330.0 (292.5–390.0) | 420.0 (413.3–457.5) | <0.001  |
| TWT (min)      | 15.0 (0.0–45.0)     | 0.0 (0.0–20.0)      | 0.047   |
| TST (min)      | 315.0 (263.8–362.5) | 396.0 (378.8–420.0) | <0.001  |

Values are median (interquartile range); min, minutes; n, number of subjects; OCD, 24 h on-call duty; NOC, not on-call duty (i.e. regular 8 h working shift and 16 h off work at home); TIB, time in bed; TWT, total wake time; TST, total sleep time.

excluded from analysis due to manifest cardiac abnormality ( $n = 1$ ) or alcohol consumption on control day ( $n = 2$ ), 9 female and 21 male physicians remained for data analysis (Figure 1). Median age was 33.5 years (interquartile range 31.0–36.0), median frequency of night shifts per months during 3 months prior to the study was four (4.0–4.4). First OCD was dated back 76 months (58.0–106.0) (Table 1).

### Event diary

As expected, participants showed a higher rate of A ( $P < 0.001$ ) and TWT ( $P = 0.047$ ) as well as a lower TIB and TST (each  $P < 0.001$ ) during OCD compared with NOC (Table 2).

### Biochemical variables

A significant increase in HDL-C ( $P = 0.010$ ) and TNF- $\alpha$  ( $P = 0.045$ ) concentrations as well as a significant decrease in TG ( $P = 0.001$ ) and uric acid ( $P = 0.017$ ) levels was observed during OCD (Table 3). During NOC only an increase of white blood cells was seen ( $P = 0.043$ ). Furthermore, HDL-C ( $P = 0.043$ ) and uric acid concentrations ( $P = 0.019$ ) were higher and TG were lower ( $P = 0.021$ ) after ODC when compared with NOC (Table 3). Glucose, TC, low-density lipoprotein cholesterol (LDL-C), procalcitonin, C-reactive protein, and IL-6 did not differ between groups.

Twenty-four hours urine analyses showed higher noradrenaline ( $P = 0.007$ ) and a tendency for higher adrenaline ( $P = 0.061$ ) concentrations during OCD (Table 4).

### Twenty-four hours electrocardiogram, blood pressure monitoring

Twenty-four hours ECG showed a higher rate of ventricular premature beats (VPB) (0–6 h,  $P = 0.047$ ) and of low-frequency normalized units (LFnu) ( $P = 0.050$ ) during night shift when compared with control day (Table 4). Blood pressure monitoring revealed greater 24 h diastolic BP values ( $P = 0.025$ ) and a greater diastolic BP during night-time ( $P = 0.028$ ) as well as a higher rate of systolic BP values more than 125 mmHg during sleep time ( $P = 0.031$ ) while on duty (Table 4).

### Correlation analyses

During OCD, correlation analyses revealed positive correlations of A with TWT ( $r = 0.548$ ,  $P = 0.002$ ), VPB 0–6 h ( $r = 0.418$ ,  $P = 0.042$ ), and supraventricular premature beats 8–24 h (SVPB,  $r = 0.499$ ,  $P = 0.013$ ). Furthermore, positive correlations were seen

between months since first OCD and diastolic BP ( $r = 0.452$ ,  $P = 0.034$  and  $r = 0.459$ ,  $P = 0.032$ , respectively) and percentage of diastolic BP more than 85 mmHg during wake time ( $r = 0.432$ ,  $P = 0.045$  and  $r = 0.521$ ,  $P = 0.013$ , respectively) for both OCD and NOC. Finally, a significant positive correlation of number of OCDs per month and TNF- $\alpha$  concentrations before OCD ( $r = 0.401$ ,  $P = 0.028$ ) as well as before NOC ( $r = 0.501$ ,  $P = 0.015$ ) was seen. No correlation was detected between age, sex, or smoking and any other variables.

### Sex-specific analyses

Comparisons of age, first night shift (months), number of OCDs per month (Supplementary material online, Table S1.) as well as A, TWT, TIB, and TST during OCD and NOC between males and females showed no significant differences.

In women, LDL-C concentrations showed lower concentrations before OCD when compared with before NOC ( $P = 0.035$ ). Furthermore, a decrease of TC was seen during NOC ( $P = 0.025$ ) (Supplementary material online, Table S2).

In men, an increase in HDL-C concentrations ( $P = 0.020$ ) as well as a decrease in TG ( $P = 0.007$ ) and uric acid ( $P = 0.040$ ) levels was observed during OCD (Supplementary material online, Table S3). During NOC, only an increase of white blood cells was seen ( $P = 0.045$ ). Furthermore, HDL-C was higher ( $P = 0.027$ ) and uric acid concentrations were lower ( $P = 0.020$ ) after OCD when compared with NOC (Supplementary material online, Table S3). Tumour necrosis factor-alpha concentrations showed lower concentrations before OCD when compared with before NOC ( $P = 0.028$ ). Twenty-four hours urine analyses revealed greater noradrenaline ( $P = 0.001$ ) and adrenaline ( $P = 0.022$ ) excretion during OCD (Supplementary material online, Table S5).

Twenty-four hours ECG showed a higher rate of VPB (0–6 h,  $P = 0.033$ ) and of LFnu ( $P = 0.006$ ) during OCD when compared with NOC (Supplementary material online, Table S5). Blood pressure monitoring revealed a greater diastolic BP during night-time ( $P = 0.006$ ) as well as a higher rate of systolic BP values more than 125 mmHg during sleep time ( $P = 0.039$ ) and a higher rate of diastolic BP more than 80 mmHg during sleep time ( $P = 0.041$ ) for OCD (Supplementary material online, Table S5).

### Discussion

This is the first study evaluating the effect of 24 h OCD on 24 h ECG, HRV, BP, and various biochemical stress markers compared with a regular day at work in a carefully selected cohort of healthy

**Table 3** Biochemical data of the study participants

|                            | OCD                 |                     | P-value | NOC                 |                     | P-value | P-value <sup>a</sup> | P-value <sup>b</sup> |
|----------------------------|---------------------|---------------------|---------|---------------------|---------------------|---------|----------------------|----------------------|
|                            | Pre                 | Post                |         | Pre                 | Post                |         |                      |                      |
| Glucose (mg/dL)            | 94.0 (83.0–102.5)   | 99.0 (88.3–109.3)   | 0.300   | 90.0 (86.0–111.0)   | 93.0 (84.5–100.5)   | 0.968   | 0.767                | 0.277                |
| TC (mg/dL)                 | 184.0 (165.0–204.5) | 187.0 (160.8–207.5) | 0.525   | 194.0 (163.5–213.0) | 182.5 (160.3–211.5) | 0.076   | 0.089                | 0.761                |
| HDL-C (mg/dL)              | 62.0 (51.5–71.5)    | 63.5 (56.3–75.8)    | 0.010   | 60.0 (51.5–72.8)    | 59.0 (53.0–73.0)    | 0.755   | 0.808                | 0.043                |
| LDL-C (mg/dL)              | 117.0 (95.5–134.0)  | 120.0 (94.0–133.5)  | 0.954   | 116.0 (95.0–132.0)  | 119.5 (97.3–134.3)  | 0.936   | 0.137                | 0.345                |
| TG (mg/dL)                 | 94.0 (60.5–127.5)   | 72.0 (54.0–105.0)   | 0.001   | 82.5 (62.8–141.3)   | 87.0 (87.0–142.0)   | 0.627   | 0.797                | 0.021                |
| White blood cells (mg/dL)  | 5.2 (4.4–6.1)       | 5.2 (4.6–6.6)       | 0.396   | 5.0 (4.0–6.1)       | 5.2 (4.0–6.1)       | 0.043   | 0.455                | 0.807                |
| Procalcitonin (µg/L)       | 0.08 (0.07–0.11)    | 0.08 (0.06–0.10)    | 0.246   | 0.09 (0.06–0.12)    | 0.09 (0.07–0.12)    | 0.855   | 0.769                | 0.053                |
| C-reactive protein (mg/dL) | 0.10 (0.10–0.16)    | 0.10 (0.10–0.13)    | 0.119   | 0.10 (0.10–0.13)    | 0.10 (0.10–0.13)    | 0.832   | 0.530                | 0.475                |
| TNF-α (pg/mL)              | 0.05 (0.00–2.79)    | 0.76 (0.00–6.63)    | 0.045   | 5.43 (0.30–6.89)    | 5.43 (0.00–9.30)    | 0.463   | 0.006                | 0.435                |
| IL-6 (pg/mL)               | 0.26 (0.00–1.69)    | 0.00 (0.00–1.12)    | 0.297   | 1.03 (0.00–2.05)    | 0.56 (0.00–7.18)    | 0.861   | 0.233                | 0.052                |
| Uric acid (mg/dL)          | 5.02 (3.95–6.08)    | 4.86 (3.83–5.70)    | 0.017   | 5.21 (3.98–6.29)    | 4.85 (3.88–6.40)    | 0.108   | 0.438                | 0.019                |

Values are median (interquartile range); TG, triglycerides; OCD, 24 h on-call duty; NOC, not on-call duty (i.e. regular 8 h working shift and 16 h off work at home); TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TNF-α, Tumour necrosis factor-alpha; IL-6, Interleukin-6.

<sup>a</sup>P-values are given for the comparison of Pre-OCD and Pre-NOC.

<sup>b</sup>P-values are given for the comparison of Post-OCD and Post-NOC.

**Table 4** Twenty-four hours ECG monitoring, blood pressure measurement, and urine analyses of the study population

|  | OCD (n = 30)        | NOC (n = 30)        | P-value |
|--|---------------------|---------------------|---------|
| 24 h ECG                                   |                     |                     |         |
| Frequency (1/min)                          | 75.0 (71.0–80.0)    | 75.0 (70.5–79.0)    | 0.247   |
| Minimum frequency (1/min)                  | 52.0 (50.0–55.8)    | 52.0 (48.0–56.0)    | 0.455   |
| Maximum frequency (1/min)                  | 129.0 (122.0–144.0) | 131.0 (124.3–155.5) | 0.187   |
| Arrhythmias 8–24 h                         | 17.0 (4.8–55.5)     | 26.0 (2.0–50.0)     | 0.396   |
| Arrhythmias 0–6 h                          | 16.0 (6.0–37.3)     | 21.0 (6.0–38.0)     | 0.780   |
| SVPB 8–24 h                                | 1.0 (0.0–4.0)       | 1.0 (0.0–4.0)       | 0.636   |
| SVPB 0–6 h                                 | 1.0 (0.0–2.8)       | 0.0 (0.0–2.0)       | 0.178   |
| VPB 8–24 h                                 | 0.5 (0.0–3.0)       | 0.0 (0.0–3.0)       | 0.341   |
| VPB 0–6 h                                  | 0.0 (0.0–1.8)       | 0.0 (0.0–1.0)       | 0.047   |
| LFnu                                       | 29.31 (24.39–35.19) | 25.45 (20.11–33.52) | 0.050   |
| HFnu                                       | 62.14 (55.39–65.23) | 61.61 (51.67–69.34) | 0.480   |
| LF/HF                                      | 0.50 (0.36–0.67)    | 0.48 (0.30–0.60)    | 0.060   |
| 24 h Blood pressure measurement            |                     |                     |         |
| 24 h Systolic BP (mmHg)                    | 131.2 (120.2–142.6) | 130.2 (117.7–134.3) | 0.163   |
| 24 h Diastolic BP (mmHg)                   | 83.5 (77.5–91.2)    | 80.2 (75.6–88.4)    | 0.025   |
| Systolic BP >135 mmHg during wake time (%) | 35.2 (9.5–79.9)     | 35.2 (9.8–52.6)     | 0.227   |
| Diastolic BP >85 mmHg during wake time (%) | 50.0 (22.5–81.1)    | 34.4 (19.2–76.3)    | 0.573   |
| Systolic BP >125 mmHg during sleep (%)     | 35.7 (12.2–77.1)    | 27.7 (7.1–46.6)     | 0.031   |
| Diastolic BP >80 mmHg during sleep (%)     | 33.3 (6.5–44.4)     | 14.2 (0.0–33.3)     | 0.066   |
| Systolic BP during daytime (mmHg)          | 134.2 (118.9–145.1) | 134.2 (122.1–136.3) | 0.246   |
| Diastolic BP during daytime (mmHg)         | 86.1 (79.4–95.1)    | 83.9 (78.4–93.2)    | 0.163   |
| Systolic BP during night-time (mmHg)       | 124.0 (112.4–132.5) | 121.3 (109.4–128.1) | 0.084   |
| Diastolic BP during night-time (mmHg)      | 75.4 (68.5–79.0)    | 73.0 (64.5–75.6)    | 0.028   |
| 24 h Urine analyses                        |                     |                     |         |
| Noradrenaline (µg/24 h)                    | 46.0 (37.5–51.3)    | 36.0 (30.8–44.3)    | 0.007   |
| Adrenaline (µg/24 h)                       | 20.0 (15.8–25.0)    | 17.0 (12.8–20.3)    | 0.061   |

Values are median (interquartile range); n, number of subjects; SVPB, supraventricular premature beats; VPB, ventricular premature beats; LFnu, low-frequency normalized units; HFnu, high-frequency normalized units; LF/HF, low frequency/high frequency; BP, blood pressure; OCD, 24h on-call duty, NOC, not on-call duty (i.e. regular 8 h working shift and 16 h off work at home).

middle-aged physicians. Irregular working hours have been reported to be associated with higher incidence of CVD and myocardial infarction not simply explainable by job strain or pre-existing risk factors.<sup>1,11</sup> Knutsson et al.<sup>3,11</sup> found an excess risk for shift work reaching ~30% for both sexes with some kind of time–response relationship even after adjustment for smoking and various other cardiovascular risk factors. Nevertheless, there are several important aspects of OCD that warrant further discussion. In healthy subjects, fundamental changes in respiratory and cardiovascular functions are among the hallmarks of sleep. As a general consensus, cardiac autonomic function is largely under the influence of a sleep–wake cycle with a relative dominance of the sympathetic system during daytime and of the parasympathetic system during night-time, leading to a reduction in BP and HR paralleled by increased baroreflex sensitivity during night time.<sup>12</sup> Measurement of HRV is a useful and non-invasive method for the evaluation of cardiac autonomic function.<sup>9,13</sup> Correspondingly, normalized values of high frequency component are markers for vagal activity, whereas the LFnu or LF/HF reflect the sympathetic activity or sympatho-vagal balance.

As previously described, night shift work dissociates physical activity from circadian rhythms, particularly of BP, HR, HRV, and catecholamine secretion.<sup>14</sup> Analyses of HRV and 24 h ECG in our study revealed a higher rate of LFnu as well as more VPB (0–6 h) during OCD compared with NOC, indicating a sympathetic predominance. Correlation analyses revealed a significant positive correlation of awakenings with VPB (0–6 h) and SVPB (8–24 h) during OCD. Interestingly, no correlation of number of night shifts per month and HF was seen. This is in line with prior studies that did not observe significant effects of shift work on mean HR. Reported changes in heart rhythm during shift work comprise sinus tachycardia or bradycardia, sinus arrest, SVPB, couplets and triplets, supraventricular tachycardia, and VPB.<sup>5</sup> Furthermore, sympathetic activity during sleep was higher and parasympathetic activity was lower during shift work, possibly resulting in unfavourable effects on cardiac autonomic activity and the risk of CVD.<sup>15,16</sup> We hypothesize that night shift as part of OCD and job strain possibly induce short-term activations of the sympathetic-adrenomedullary system and the pituitary-adrenocortical axis, leading to a significant shift towards sympathetic dominance frequently associated with the occurrence of

ventricular and supraventricular tachyarrhythmias or premature beats.

There is still controversy whether night shift work has deleterious effects on sleeping BP. Some studies reported higher sleeping BP in night shift work than in day shift work.<sup>17</sup> In the present study, BP monitoring revealed higher 24 h diastolic BP, a higher diastolic BP during night-time as well as a higher rate of systolic BP more than 125 mmHg during sleep time associated with OCD. Furthermore, time since first OCD was associated with increased diastolic BP and a greater number of measurements showing diastolic BP more than 85 mmHg during wake time both for OCD and NOC. Since only healthy middle-aged physicians participated in this study and the changes observed for BP did correlate with age, we assume that BP behaviour suggests a long-term effect of OCD in this cohort.

As first described by Theorell *et al.*<sup>6</sup> in the mid-1970s, catecholamine excretion is affected during and after night work. Furthermore, night shift leads to higher urinary norepinephrine levels during night work in pregnant women<sup>18</sup> and 6 or more years of shift work may increase the risk of chronic heart disease (CHD) in women.<sup>19</sup> Increased urine catecholamine secretion in our study supports the hypothesis of an influence of OCD on sympathetic activity.

Inflammatory cytokines and mediators (e.g. TNF- $\alpha$ , IL-6) induce the expression of cellular adhesion molecules known to be involved in atherosclerotic processes.<sup>20,21</sup> Cytokines have been implicated in the development as well as in the progression of CHD and seem to be linked with catecholamine secretion.<sup>22</sup> In our study, TNF- $\alpha$  concentrations increased significantly during OCD. The positive correlation of the number of OCDs per months and TNF- $\alpha$  concentrations measured at the beginning of OCD and NOC may indicate a chronic effect of OCD. However, a final conclusion cannot be drawn due to different baseline TNF- $\alpha$  levels prior to OCD and NOC.

## Strengths and limitations

The strengths of the study are the strict selection criteria and the investigation of a wide range of cardiovascular parameters during standardized conditions.

The main limitation of the current study is the ambiguous definition of shift work. Therefore, the results obtained in our study are characteristic for this specific setting of 24 h OCD only and have to be interpreted with caution. Differences in type of shift work, duration of shift work, number of working hours per week, and the degree of psychological stress or physical work load may also affect the parameters investigated and possibly explain differences to previous studies. Finally, sex-specific analyses revealed similar tendencies for both sexes with significant findings restricted to males. However, owing to the unequal number of female and male participants, the application of statistical tests naturally leads to non-comparable results (larger type II error in females).

## Conclusion

Our results highlight the association of OCD with an increased risk profile for CVD. In addition to the acute effects observed, frequent

OCD over a longer period possibly elicit sustained alterations in cardiovascular homeostasis. The current study supports the hypothesis of a multi-factorial process involving diverse mechanisms including over-activity of the sympathetic system, disruption of circadian BP, and selective activation of inflammatory pathways. Longitudinal studies would be necessary to clarify the effect of on-call night shift on chronic diseases in advanced age.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## References

- Fujino Y, Iso H, Tamakoshi A, Inaba Y, Koizumi A, Kubo T, Yoshimura T. A prospective cohort study of shift work and risk of ischemic heart disease in Japanese male workers. *Am J Epidemiol* 2006;**164**:128–135.
- Furlan R, Barbic F, Piazza S, Tinelli M, Seghizzi P, Malliani A. Modifications of cardiac autonomic profile associated with a shift schedule of work. *Circulation* 2000;**102**:1912–1916.
- Knutsson A, Boggild H. Shiftwork and cardiovascular disease: review of disease mechanisms. *Rev Environ Health* 2000;**15**:359–372.
- Takeyama H, Itani T, Tachi N, Sakamura O, Murata K, Inoue T, Takanishi T, Suzumura H, Niwa S. Effects of shift schedules on fatigue and physiological functions among firefighters during night duty. *Ergonomics* 2005;**48**:1–11.
- Adams SL, Roxe DM, Weiss J, Zhang F, Rosenthal JE. Ambulatory blood pressure and Holter monitoring of emergency physicians before, during, and after a night shift. *Acad Emerg Med* 1998;**5**:871–877.
- Theorell T, Akerstedt T. Day and night work: changes in cholesterol, uric acid, glucose and potassium in serum and in circadian patterns of urinary catecholamine excretion. A longitudinal cross-over study of railway workers. *Acta Med Scand* 1976;**200**:47–53.
- Boggild H, Knutsson A. Shift work, risk factors and cardiovascular disease. *Scand J Work Environ Health* 1999;**25**:85–99.
- Malmberg B, Persson R, Jonsson BA, Erfurth EM, Flisberg P, Ranklev E, Orbaek P. Physiological restitution after night-call duty in anaesthesiologists: impact on metabolic factors. *Acta Anaesthesiol Scand* 2007;**51**:823–830.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;**17**:354–381.
- Stein PK, Kleiger RE. Insights from the study of heart rate variability. *Annu Rev Med* 1999;**50**:249–261.
- Knutsson A, Hallquist J, Reuterwall C, Theorell T, Akerstedt T. Shiftwork and myocardial infarction: a case-control study. *Occup Environ Med* 1999;**56**:46–50.
- Parati G, Lombardi C, Narkiewicz K. Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk. *Am J Physiol Regul Integr Comp Physiol* 2007;**293**:R1671–R1683.
- Berntson GG, Bigger JT Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997;**34**:623–648.
- Matsumoto K, Sasagawa N, Kawamori M. Studies of fatigue of hospital nurses due to shift work—with special reference to night shifts and short off-duty (author's transl). *Sangyo Igaku* 1978;**20**:81–93.
- Boggild H, Jeppesen HJ. Intervention in shift scheduling and changes in biomarkers of heart disease in hospital wards. *Scand J Work Environ Health* 2001;**27**:87–96.
- Holmes AL, Burgess HJ, McCulloch K, Lamond N, Fletcher A, Dorrian J, Roach G, Dawson D. Daytime cardiac autonomic activity during one week of continuous night shift. *J Hum Ergol (Tokyo)* 2001;**30**:223–228.
- Munakata M, Ichi S, Nunokawa T, Saito Y, Ito N, Fukudo S, Yoshinaga K. Influence of night shift work on psychologic state and cardiovascular and neuroendocrine responses in healthy nurses. *Hypertens Res* 2001;**24**:25–31.

18. Yamauchi H. Effects of night work on urinary excretion rates of 6-sulfatoxymelatonin, norepinephrine and estriol in pregnant women. *Ind Health* 2004;**42**:268–276.
19. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE, Hennekens CH. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;**92**:3178–3182.
20. Kritchevsky SB, Cesari M, Pahor M. Inflammatory markers and cardiovascular health in older adults. *Cardiovasc Res* 2005;**66**:265–275.
21. Pober JS. Effects of tumour necrosis factor and related cytokines on vascular endothelial cells. *Ciba Found Symp* 1987;**131**:170–184.
22. von Haehling S, Jankowska EA, Anker SD. Tumour necrosis factor-alpha and the failing heart—pathophysiology and therapeutic implications. *Basic Res Cardiol* 2004;**99**:18–28.