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Original papers

The "ECG modifications induced by the disturbance of the circadian rhythm in night-shift workers (ECGNoct)" study protocol

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Abstract

In many large cohort studies, the night shift constitutes a risk factor for developing cardiovascular disease and diabetes in workers. Current screening tests for people working in night shift include fasting glycaemia and electrocardiography. In fact, there are few studies focused on the description of the electrocardiographic changes after the night shift. This article describes the protocol of the "ECG modifications induced by the disturbance of the circadian rhythm in night-shift workers (ECGNoct)" study, which was initiated by the National Institute for Infectious Diseases "Prof. Dr. Matei Balș". Nurses represent the target population.

The protocol includes a full medical and occupational history, lifestyle habits (smoking, alcohol, nutrition), anthropometric and blood pressure measurements, blood tests (fasting glycemia, total cholesterol, triglycerides and high density lipoprotein cholesterol) and electrocardiogram recording. For nurses working in (night) shifts, we will record the electrocardiogram before and soon after the night shift. A cross sectional study will analyze the incidence of the metabolic syndrome criteria, the cardio-metabolic diseases and the electrocardiographic modifications and will compare the results between the group of nurses working and the group of nurse who do not. Based on these results, a longitudinal study will test the hypothesis that night shift increases the risk for cardio-metabolic diseases and that the electrocardiographic modifications precede the clinical symptoms. The results of the study will provide data on the association of night shifts and other non-occupational risk factors with the cardio-metabolic diseases in this specific population of healthcare workers that potentially will integrate into the occupational medicine policies.

Keywords: *night shift, electrocardiogram, metabolic syndrome, cardiovascular diseases, diabetes*

Introduction

Several cohort studies documented the relation between working in night shifts and metabolic and cardio-vascular disorders. The type of shift rotating, the length of time of working in shifts, environmental (mainly nutrition and exercise, but also exposure to persistent organic pollutants, arsenic or cadmium)

and genetic factors contribute in various proportions to the increased risk. Working in night shift affects nearly 20% of men and 17% of women in Europe. Romania distinguishes itself by the second highest number of weekly working hours in Europe (42.3 vs the average of 38.8) and as one of the few countries in which more women work in night shifts than men (almost 27% of women and 25% of men in the working force)[1].

The healthcare system accounts for a significant ratio of night shift workforce within its employee pool. The chronic nurses' shortage in Romanians directly affecting the efficacy of the health system, and constitutes a major public concern. Therefore, maintaining a healthy professionally satisfied nurse workforce to ensure a high quality of care is much needed. A national study is required to provide the scientific body of knowledge needed to support legislative modifications and improvement of health surveillance for healthcare staff by implementing evidence based public health strategies with possible relevance to other categories of the workforce that do shift work.

Concerning the metabolic syndrome and related diseases, the current legislation only recommends screening investigations such as fasting glycemia and ECG, but there is no published review of the data recorded by the occupational physicians' surveillance of this population in Romania. ECG screening in adults has been challenged by the US Preventive Services Task Force (USPSTF)[2]; the current recommendation of the USPSTF is not to perform screening (neither resting, nor exercise ECG) in adults with low risk of cardiovascular disease. Even for intermediate and high risk of cardiovascular disease, USPSTF did not find sufficient evidence to balance the benefits versus harms.

The increase in cardiovascular risk is generally associated with older age, gender (male), high blood pressure and by the presence of the smoking habit, abnormal lipid and glucose levels, obesity and physical inactivity. For people over 40 years old, SCORE risk is available. For younger adults, smoking, increase in BMI, inflammation, adipokine profile3 altered lipid metabolism [4,5,6] have been associated with an increase in the incidence of coronary heart disease and stroke.

There are few studies describing the effect of sleep deprivation on the ECG characteristics in night shift workers. However, independent reports mentioned a longer QT and T peak to T end interval (TpTe) [7,8] or an increased TpTe/QT [8]. Both studies concluded that a larger pool of data is needed because there is no standardization and validation of certain duration of the Tp interval for clinical use. To summarize, although night shift workers are considered to have a higher risk than the average population, they are not included in the risk assessment. Whether ECG screening has real value or not for this category of workers is not known. In the attempt to cover this gap, a study covering the already accepted risk factors, and the acute and chronic influence of night shift on the ECG modifications "ECG modifications induced by the disturbance of the circadian rhythm in night-shift workers (ECGNoct)" was initiated in the National Institute for Infectious Diseases "Prof. Dr. Matei Balș".

This article is the description of the research protocol. The ECGNoct study has a two-step approach: an initial, cross sectional, pilot study followed by a cohort study. The pilot study aims to compare the prevalence of metabolic syndrome and related diseases in nurses working in night shift with nurses that do not work in night shift. For the purpose of this study, the term "cardio-metabolic diseases" includes: coronary heart disease, blood hypertension, acute vascular events (cardiac, brain or peripheral) and type 2 diabetes.

The pilot study will test the following hypothesis:

1. Working in the night shift is positively associated with anthropometric characteristics predictive of the metabolic syndrome (a higher BMI, WC and body roundness index).
2. Working in the night shift is positively associated with the prevalence of cardio-metabolic diseases.
3. Working in the night shift is positively associated with abnormal ST and T wave ECG findings.

The longitudinal study will test the following hypothesis:

1. Working in night shift increases the risk of cardio-metabolic diseases
2. Working in night shift increases the risk of abnormal ST and T wave ECG findings
3. Abnormal ST and T wave ECG findings precede the cardio-metabolic diseases in night shift workers

Material and Methods

The study protocol that is presented below was approved by the Ethical Committee of this Institute. The pilot study will allow to obtain accurate data on the prevalence of the metabolic syndrome criteria, cardio-metabolic diseases and ECG modifications in

Table 1. Overview of the data recorded and of the measuring schedule

Measurement method	Data recorded and rationale	Measurement periodicity
Medical history	Pre-existing medical conditions for the risk assessment; presence or absence of cardio-metabolic diseases	At enrollment, reviewed annually
Occupational history	Duration of nightshift, type of rotation, intensity (number of shifts/months) for the occupational component in the risk assessment	At enrollment, reviewed annually
Questionnaire	Lifestyle habits for the risk assessment	At enrollment, reviewed annually
Anthropometry	BMI, WC for the risk assessment	At enrollment, reviewed annually
Blood pressure (BP)	Diagnosis of blood hypertension, component of the SCORE risk and of the general risk assessment	At enrollment, reviewed annually
ECG	ECG modifications	At enrollment, reviewed annually
Lab tests		
Fasting glycaemia	Diabetes	Annually
Triglycerides	Component of the metabolic syndrome	At enrollment
HDL cholesterol	Component of the metabolic syndrome	At enrollment
Total cholesterol	Component of the SCORE risk (with BP and smoking habit)	At enrollment

BMI = body mass index; BP = blood pressure; WC = waist circumference.

this population and to establish the relation with the occupational exposure. The longitudinal study aims as being a prospective five years cohort research of nurses working night shift and nurses that do not work in night shift. Should the necessary resources be available, the protocol can be prolonged to ensure follow up for a longer time, potentially even for the whole duration of the nurses' working contracts. The baseline evaluation includes questionnaires, anthropometry metrics, blood pressure measurements, blood samples and ECG recordings. For nurses working in night shift we will record the ECG before and after the nightshift. During the initial examination, the research investigator will explain the purpose of the study and will record data and blood test values that will be considered the reference for the enrolled person. During the annual evaluation, the researcher will register the acute or chronic diseases that have been documented between the examinations, the anthropometry metrics, the blood pressure, and the ECG. The schedule of the project is presented in Table 1. For each subject, we will code and anonymize personal data to be included in a database respecting the current personal data protection recommendations. From this database, data will be extracted for the analysis. Independent variables considered for the hypothesis that are tested in the pilot study are presented in Table 2.

A. Study population

The pilot study is conducted in the National Institute for Infectious Diseases "Prof. Dr. Matei Balș" and includes nurses aged 18-65 years old. All 406 nurses are invited to participate. No selection criteria will be applied for the pilot study. For the longitudinal one,

Table 2. Variable included in the analysis of the pilot study

Hypothesis	Dependent variables	Independent variables
Working in night shift is positively associated with anthropometric characteristics predictive of the metabolic syndrome (a higher BMI, WC and body roundness)	Body mass index Waist circumference Body roundness	Night shift Age, smoking, night shift working, change in nutrition habits
Working in night shift is positively associated with the prevalence of the cardio-metabolic diseases	Hypertension Ischemic heart disease Stroke Diabetes Periphery arterial disease	Night shift and morningness-eveningness preferences Age, body roundness roundiness index, smoking, lipid profile, fasting glycemia, change in nutrition habits
Working in night shift is positively associated with abnormal ST and T wave ECG findings	ST depression/elevation T wave amplitude QT duration TpTe	Night shift, morningness-eveningness preferences Age, body roundness index, smoking, lipid profile, fasting glycaemia, change in nutrition habits

we will exclude nurses with metabolic syndrome or with an already diagnosed cardio-metabolic disease. In the pilot study, we will conduct stratification by age by the number of years of shift timework and we will implement any necessary adjustments of the study design in the longitudinal research. The participants are allocated in the night shift working group if they have worked for at least 1 night shift (defined as working between midnight and 6.00 a.m.) in the last 5 years [9]. A physician aware of the study and protocol will perform a full medical examination.

B. Sample size calculation

We do not have reliable data on the incidence of the metabolic syndrome and of its complications in this specific population. We can estimate the number starting from the 38.5% prevalence of the metabolic syndrome in the general Romanian population [10] and assuming that the metabolic syndrome is around 17% in the female active population, based on data published in other countries [11,12]. We also do not have an estimation of the frequency of ECG abnormalities in the Romanian general population.

Data from a large, representative sample of the Belgian population showed [13] an age standardization prevalence of the ST segment depression of 2.7% and of the abnormal T wave of 9.6%. To obtain the accuracy of 0.05 and a 95% confidence interval, in the cross sectional study a number of 141 nurses have to be included in the analysis.

The sample size of the longitudinal study will be defined based on the pilot findings.

C. Study parameters

a) Night-shift work

Night shift is the occupational risk factor considered in the analysis. Therefore, we will record a full occupational history. This will include seniority in the job, duration in the current job and in night shift rotation in general, and the frequency of night shifts per month. A comparison between exposed - non-exposed subjects will be performed for all outcomes.

To search if the intensity of the risk factor influences the outcomes, exposure in number of years worked in night shift multiplied by the average number of nights per month. Special questions will assess if night work is perceived as difficult and if the person is more of a morning or an evening person, as this is a significant influencer for the subjective sleep quality [14] and for the neuro-humoral modifications [15]. The preference will be assessed using a Likert scale of 1-5.

b) Anthropometry

Either the researcher or the research assistant will measure body height, body weight and waist circumference. The waist circumference will be measured at the middle line between the superior border of the iliac crest and the lowest ribs. Body mass index will be calculated by dividing weight (in kilograms) to the square of height (in meters). The visceral adipose tissue has been recognized from long ago as one of the main influencers of the metabolic

functions. This was the basis for the inclusion of waist circumference instead of the BMI in the metabolic syndrome criteria. Recently, formula that aggregates BMI and WC data, such as body roundness index, was described as a more reliable marker of the metabolic risk. The body roundness index will be calculated with the formula described by Krakauer NY and Krakauer JC [16], as follows:

$$BRI = 364.2 - 365.5 \times \sqrt{1 - \left(\frac{(WC/(2\pi))^2}{(0.5 height)^2}\right)}$$

The change in body weight during the period of working in shifts will be recorded, as gaining weight is one of the earlier clinical signs related to night shift work, and obesity is closely linked to the cardio-metabolic risk.

c) Lifestyle habits

The questionnaire was constructed to cover the known influencers of the cardio-vascular risk; it was also designed to be short enough in order to become, if validated by the study, a practical instrument during the occupational health examination. Smoking habits are categorized as never smoker, current smokers, and former smokers. Former smokers are defined as having quit smoking for at least 12 months. The amount a person has smoked over a long time will be expressed in number of pack years and calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. The alcohol intake will be expressed in the number of drinks/week.

Concerning nutrition, reports of the change to unhealthy eating habits after beginning work in night shift occurred [17]. The questionnaire evaluates this change in the nutrition section; the predominant food intake habit (cooked versus snacks and types of snacks) during the night shift was graded on a 5-point Likert scale indicating the frequency of the consumption of each of these items. Based on these answers, the participants will receive a score of compliance with the basic healthy diet recommendations.

d) Medical history and symptoms

The investigator will take a detailed anamnesis. From family history, the researcher will take into account cardio-vascular disease (hypertension, cardiac disease, stroke) and diabetes. The personal medical history will focus on chronic disease related to the metabolic syndrome. To exclude the influence of medication on the ECG waves or segments, researchers will record the current medication. Nurses receiving medication that potentially influence the ECG will be analyzed in a separate group. Data about the dosage, duration of the prescription, time between drug administration and the ECG recording will also be documented. There is a special section in the questionnaire meant to identify if cardiac symptoms (chest pain, dyspnea, palpitations) were ever-present. This study was not designed to evaluate sleep, but to assess if chronic disruption of the sleep relates to cardio-metabolic effects. For the purpose of this study, from the variety of questionnaires available to quantify the effect of night shift on the sleep pattern (amount of sleep, difficulties in falling asleep or in waking up, sleepiness during daytime, etc.) [18] only the persistence of low quality of the sleep during vacation was selected as significant indicator of chronic sleep-wake cycle disturbance.

e) SCORE risk calculation

The SCORE risk is calculated as recommended by the European Society of Cardiology for persons above 40 years old (European Society of Cardiology. SCORE Risk Chart. The European cardiovascular disease risk assessment model [19]. For younger persons, the model is not validated and therefore the SCORE risk will be included only in the analysis of the subpopulation of nurses older than 40 years old.

f) ECG findings

All participants will have the ECG recorded during their day shift and comparison of the following ECG findings will be performed: rhythm, ST segment depression or elevation, T wave amplitude, QT interval duration, time interval from T wave peak to T wave end (TpTe). ST and T wave amplitude will be coded according to the Minnesota code [20]. TpTe, defined as the time interval from T-wave peak to T-wave end, will be manually assessed. The TpTe/QT ratio will be calculated. Comparison between actual QT and normal QT will be also performed. For this calculation, the normal QT duration will be defined based on the formula of correction derived from the Framingham study [21]:

QTc = QT x 0.156 x (1-RR), considered as the most accurate for the general population [22,23].

Two readers will independently evaluate the ECG. Major and minor modifications assessed with the Minnesota? Code will be classified following the methodology from other studies [13] to ensure data comparability (Table 3). Two indicators will be added to the major findings (the TpTe and the long QTc). As

Table 3. Classification of the ECG findings

	Minnesota code	TpTe interval	QTc
Major ECG findings	IV1-2, or V1-2 or VII1-2 or VIII1-3, IX2 **or** Arrhythmias (any from 8.1-1 to 8-9)	Longer than >75% percentile TpTe/QT ratio	Longer than normal
Minor ECG findings	I3 or II1-2 or IV3 or V3 or IX-1		

there is no clear cutoff for the normal population of the TpTe duration, the inclusion in the major criteria will be based on the upper values recorded in this population. A longer than the calculated normal value of QT, as a global marker of impaired repolarization, is also considered a major ECG finding.

Coronary heart disease develops in years. We do not know if the acute repolarization effects described after the night shift predict a susceptible population. Therefore, in nurses working in night shifts, a supplementary ECG will be recorded in the morning after one of the night shifts. This will allow, in time, to test the hypothesis that these modifications have a predictive value. The same ECG modifications will be noted, as previously described.

g) Blood tests

The standard screening tests: fasting glycaemia, total cholesterol, HDL cholesterol, and triglycerides will assess glucose and lipid metabolism. (VITROS 5,1 FS Chemistry System, Ortho Clinical Diagnostics, Raritan, NJ, USA). The lab test results will provide input for the metabolic syndrome definition and for the SCORE risk.

Results

In the first step, analysis will be performed separately per outcome and per mediating variable. As mentioned, independent variables considered in this study are: night shift, smoking, alcohol intake, compliance to healthy diet recommendations and a family history of cardio-metabolic diseases. Outcomes are represented by: high BMI and high roundness index, the presence of the cardio-metabolic diseases or of the ECG modifications. For multiple regression analysis having as independent value the night shift, the BMI, smoking, alcohol intake, compliance to healthy diet recommendations and SCORE risk value will be considered as mediating variables for the outcomes. One-way ANOVA analysis will test the difference between the ECG modifications before and after the night shift at enrollment for all continuous variables (segment or interval duration, amplitude, Tp/Te, QTc). The differences between the prevalence of one of the categories of ECG modifications (major or minor) will be assessed by the $\chi 2$ test. The type and frequency of these modifications will be used to calculate the odds ratio for the diagnosis of cardio-metabolic diseases and the sample size of the longitudinal study.

Discussion

Misalignment of sleep with the circadian rhythms is more and more frequent in the modern society. Research conducted in the last decade in night shift workers has noticed consequences such as poor quality (difficulty in falling asleep, impaired sleep architecture, nocturnal awakenings) and shorter sleep duration [24-25]. A direct effect of the misalignment of sleep is the impairment of the body's physiological functions that depend on the sleep cycle. Therefore, working night shifts was called a "physiological de-synchronization of body functions". It affects progression of many chronic diseases, such as: sleep disorders?, gastrointestinal, and cardio-vascular disorders, diabetes, asthma, epilepsy. Psychiatric conditions aggravation [26] and unhealthy behaviors (unhealthy nutrition, smoking, addictions) [27,28,29,30] were also reported. The circadian oscillations of the central clock are reflected in the peripheral cells and influence metabolism.

Experimental data and studies performed on healthy adults showed that sleep disruption is able to impair both glucose and lipid metabolism [31], ultimately affecting the endothelial function, creating a pro-inflammatory milieu and oxidative stress. The

medium and the long-term clinical effects of these pathological mechanisms are associated with a high incidence of metabolic syndrome, cardio-vascular disease and diabetes in employees working night shifts, for which epidemiological evidence continues to accumulate. For example, a meta-analysis of 12 studies showed that short sleep duration increases the risk of metabolic syndrome [32]. Cohort or cross-sectional studies on night shift employees from different countries evidenced statistically significant coronary heart disease or diabetes risk [9,33,34]. It is also well documented that metabolic syndrome, type 2 diabetes and cardio-vascular disease have a direct association with age.

Therefore, age is a significant factor taken into account as possible confounder. The study protocol and analysis will include other possible confounders such as smoking alcohol consumption and change in nutrition habits. There is also evidence that the intensity of exposure (number of years of working in night shift) has a significant influence on the incidence of these diseases [9]. For this reason we will estimate the total night shift work.

Recently published data on large cohort studies has shown that night shift and lifestyle factors have an additive effect on the excess in cardio-metabolic risk [35]. Change in nutrition habits after the employee starts working in night shifts was given to explain this interaction [17].

Our study integrates these findings in a protocol to detect major non-occupational influencers and the occupational exposure. It also aims to evaluate if one of the current screening methods is reliable for this risk assessment. In animal misalignment experiments, recording of ECG showed prolongation of the PR and QT intervals [36], but there are few data on ECG modifications from research conducted in night shift workers or experiments imposing forced sleep disruption in healthy individuals. Basically, the ECG modifications reflect the vascular stress [37], the imbalance between the sympathetic and the parasympathetic activity during the recovery sleep [38], and/or the impairment of the ventricular function [8]. Post night shift effects, such as higher systolic and diastolic blood pressure (reduction in blood pressure dipping), high inflammatory and prothrombotic markers expression during the sleep recovery period were noticed [39].

We do not have a prospective study focused on the demonstration of the ECG changes induced after working in night shift. Since ECG is challenging as a screening method, only a prospective study can properly characterize and validate the use of the ECG in the annual medical evaluation of workers in the night shift.The ECGnoct aims to find what are the significant ECG changes present in night shift workers and whether they are related to this particular occupational exposure.

Conclusion

In conclusion, the study we are proposing will be the first of its kind performed in Romania, assessing the association between night shift work and certain cardio-metabolic diseases and ECG changes in nurses. The study's results will potentially provide important insight into the association of risk factors for cardio-metabolic diseases in this specific population of healthcare workers, and inform occupational medicine policies.

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