Cardiovascular risk profile in shift workers

cardiac control, biological and lifestyle risk factors

Ludovic G.P.M. van Amelsvoort

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Abstract

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PhD thesis by Ludovic G.P.M. van Amelsvoort, Division of Human Nutrition and Epidemiology, Wageningen University, Wageningen, The Netherlands, April 19, 2000

Background: Evidence available so far indicates a 40% excess cardiovascular disease risk among shift workers. As, in the Netherlands alone, about one million people are working in shifts, this might have a considerable public health impact. Factors responsible for this elevated risk have not yet been elucidated. Both changes in biological and lifestyle risk factors and disturbance of the cardiac control, as reflected by an increased frequency of premature ventricular complexes and decreased heart rate variability, might be involved in this excess risk. The purpose of this study was to investigate whether shift work related changes occur in these factors that might explain the elevated CVD risk among shift workers.

Methods: A cohort study was carried out in 1997 to 1999 among 227 shift workers and 150 controls working in daytime, all starting in a new job as nurse or industrial worker. One-year changes in cardiac control (premature ventricular complexes and heart rate variability), biological risk factors (blood pressure, body mass index, waist to hip ratio and blood cholesterol) and lifestyle risk factors (dietary habits, smoking, and decreased physical activity) were investigated.

Results: We observed a significantly greater one-year increase in the frequency of premature ventricular complexes in the shift workers compared with the day workers. In 48.9% of the shift workers versus 27.3% of the day workers the frequency of premature ventricular complexes increased ($p = 0.03$). Moreover, the number of worked nights was significantly associated with the change in frequency of premature ventricular complexes (Spearman correlation r: 0.33; $p = 0.004$).

The one-year change in the heart rate variability was similar between the shift and day workers. However, among the shift workers the low frequency component of the total heart rate variability (%LF) was stronger during sleep after a night shift than after a day shift (%LF increase 3.04, $p < 0.01$). This suggests an increased sympathetic activity during a sleep after night shift.

The magnitude of the reported effects was related to the shift schedule. In our study, type of shift schedule was associated with cardiac control. Backward rotating schedules (three to five shifts of night work, evening work, day work, respectively) appeared to be the most unfavourable. From the other risk factors, smoking was the only one that showed an unfavourable one-year change in the shift workers.

Conclusions & implications: An unfavourable change in cardiac control and in smoking behaviour, as observed, might explain a part of the elevated risk in shift workers. Unfavourable changes were greatest in the workers on certain backward rotating schedules so we would recommend adoption of the fast forward rotating schedule.

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1

Introduction

Shift and night work have become accepted consequences of the modern 24-hour economy. From the industrial revolution onwards, the number of people working outside normal office hours has been steadily increasing. Traditionally, shift work has been associated with the heavy industries. However, due to the increasing grade of automation and robotisation in the heavy industry, the number of people working outside the normal office hours is shifting more and more towards the service and transport sectors.

In the Netherlands in 1998 approximately 977.000 people were working on irregular work schedules, including nights[1]. This is 14.8 % of the working population (16.1 % of the male population and 12.7 of the female population). As can be seen in figure 1.1, after a slight decline during the early 1990's the number of shift workers has been increasing ever since. This increase is mainly due to the number of jobs in the service and transport sectors.

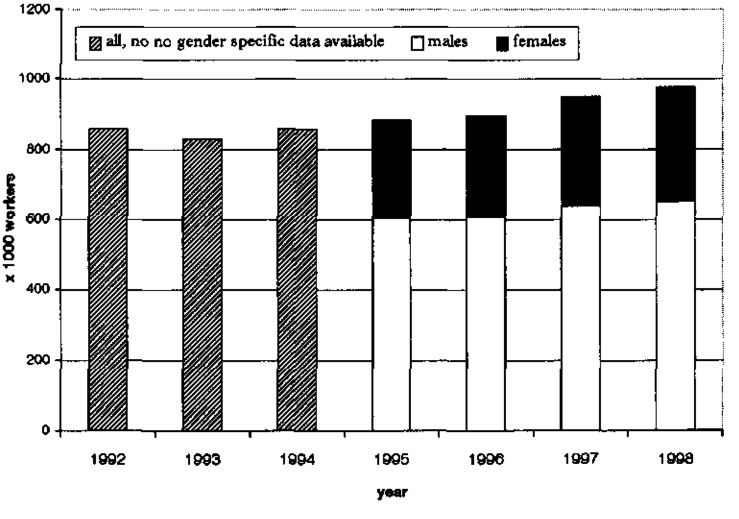

Figure 1.1. *Number of shift workers in the Netherlands, 1992 – 1998*[1-4].

There are many types of work hour schedules for people working outside the normal daytime hours. In this thesis the focus will be on people working in shifts. There is no general agreement on the definition of the term «shift work».

Table 1.1. *Studies on cardiovascular morbidity and mortality among shift workers.*

Reference	exposed population	control population	number of cases	years of follow up
cross-sectional/ case referent				
Thiis-Evensen, 1949[12]	463	941	388	
Pierach, 1955[77]	30 cases	1141 referents	141	
Aanonsen, 1964[78]	380	345	13	
Michel-Briand, 1980[70]	99 retired	93 retired	19	
Koller, 1983[79]	199 blue collar workers	68 blue collar workers	45	
Alfredsson, 1982[16]		882 referents	334 cases	
McNamee, 1996[80]		467 nested refs.	467 nested cases	42
Steenland, 1996[81]		781 nested refs.	163 nested cases	1
Knutsson, 1999[17]		1808 referents	1417 ca	2
Cohort studies				
Taylor, 1972[76]	4188	3860	540	12
Angersbach, 1980[8]	370	270	102	11
Alfredsson, 1985[82]	?	985096	1201	1
Knutsson, 1986[74]	394	110	43	15
Åkerstedt, 1987[83]. Data taken from[18]	?	?	1059 cases	1
Tüchsen, 1993[84]	22795	1293888	5966 cases	1
Kawachi, 1995[15]	46956	32153	292 cases	4
Tenkanen, 1997[75]	666	1140	Ca. 150	5.6
Bøggild, 1999[71]	1123	4084	1006 cases	22

Endpoints*	Controlled confounders†	Main results(95 % CI)	study quality ‡
cross-sectional/ case referent			
Total mortality	.	OR 1.55 (1.21 - 1.97)#	oo
MI morbidity	.	OR 2.29 (0.87 – 5.74)#	o
AP & AMI morbidity & mortality	Age	OR: 0.43 (0.11 – 1.59)#	oo
Mortality, AP Morbidity	.	OR 1.69 (0.64 – 4.51)#	o
ECD 390-459 Mortality	Age	OR: 2.97 (1.06 – 9.03)#	ooo
AMI Morbidity & mortality	Multivariate	OR 1.25 (0.97-1.62)	ooo
AMI morbidity & mortality	Multivariate	OR 0.9 (0.68-1.21)	ooo
CVD Mortality	Multivariate (not SES)	OR (log) 0.64 (0.28-1.47)	oo
AMI Morbidity & mortality	Multivariate	men OR 1.3 (1.1-1.6) women 1.3 (0.9-1.8),	ooo
Cohort studies			
AMI morbidity	Age	RR,unadj 1.00(0.84-1.18)#	oo
AMI morbidity, arrhythmia	.	RR 1.13 (0.79-1.63)*	oo
AMI morbidity	Age	SMR men 115 (104-126), women 152 (119-191)	ooo
AP & AMI Morbidity & mortality	Age	RR 1.4 (0.7-2.7), OR /y 1.08 (1.02 – 1.13)#	oooo
IHD & AMI morbidity	Multivariate	SMR AMI 148 (112-191) IHD 128 (103-158)	ooo
IHD morbidity	Age	SHR 168 (151.8-185.5)&	ooo
AMI Morbidity & mortality	Multivariate	< 6 y: 1.21 (0.92 –1.59) > 6 y: 1.51 (1.12-2.03)	ooo
CHD morbidity	Multivariate	RR 1.38 (1.01-1.89)	ooo
IHD Morbidity & mortality	Multivariate	IHD: 0.9 (0.7-1.1)	ooo

*AMI: Acute myocardial infarction; AP: Angina Pectoris; IHD: Ischemic Heart Disease; OR: Odds ratio; RR: Relative risk; SHR: Standardised Hospitalisation Ratio; SMR: Standardised Mortality Ratio; RR: Relative Risk; T: Mortality

† Multivariate adjusted for Age, socio-economic status and others.

SES: socio-economic status.

‡Score based provided by or based on Kristensen[13] (range from o (low) to oooo (high))

 # (re)calculated on basis of provided data.

& 90 % CI

The ILO{International Labour office, conditions of work digest (Geneva), 1986;5:390} defines it as "A method of work organisation under which groups or «crews» of workers succeed each other at the same workstation to perform the same operation. Each crew working a certain schedule or «shift» so that the undertaking can operate longer than the stipulated weekly hours for any worker." More often however the term «shift work» is used in the broader sense of describing work hours outside the normal office hours. We will use the term shift for a work schedule, which includes night work. A large number of rotation schedules are used. Two major groups are distinguished on the basis of the direction of rotation: backward rotation and forward rotation schedules. In the backward rotation schedules several night shifts are followed by several afternoon shifts, followed by several morning shifts. In the forward rotation schedule this order is reversed, i.e. several morning shifts are followed by several afternoon shifts, followed by several night shifts. The number of successive shifts of the same type determines the speed of rotation.

Working irregular hours or during the night has often been associated with health problems. The group of shift workers, with many hours outside normal office hours, is considered to be highly affected by their non-normal schedule. Shift work has been associated with acute health problems like insomnia, fatigue, gastrointestinal complaints and malaise[5-7]. Chronic exposure to working in shifts has been associated with sleep-wake disorders[8; 9], gastrointestinal[10] and cardiovascular disease[11]. In this thesis the main focus will be on the effects on risk factors for cardiovascular disease.

Coronary Heart Disease among shift workers

Already in 1949 a study on the relation between shift work and mortality was conducted by Thiis-Evensen[12]. Since 1949 another seventeen studies regarding cardiovascular mortality and morbidity risk among shift workers have been found in the literature. Table 1.1 gives a summary of the epidemiologic studies in relation to shift work and cardiovascular mortality and morbidity published so far. Thirteen of the eighteen studies show an elevated cardiovascular disease risk in the shift workers compared with workers in daytime. For nine of these thirteen studies this elevation was significant. Of the remaining studies, four reported a, non-significant, inverse association and one no difference at all. A major problem when comparing the different results is the large heterogeneity, not only in study design, but, maybe even more important, in exposure characterisation. Factors like type of shift or night work, rotation schedule, duration of exposure and changing from a shift to daytime job might all be regarded as determinants of a possible risk.

Nevertheless, taking all results together, there seems sufficient evidence to assume an elevated cardiovascular disease risk in shift workers. Kristensen and Olsen suggested[13; 14] an excess risk of 40 %, based on the methodologically most sound studies so far, as the most reasonable risk estimate. However the actual risk might be different among subjects. There might be considerable differences depending on, for example, rotation schedule, duration of exposure and personal characteristics. For gender, the studies conducted so far do not indicate a different risk between males and females[15-17].

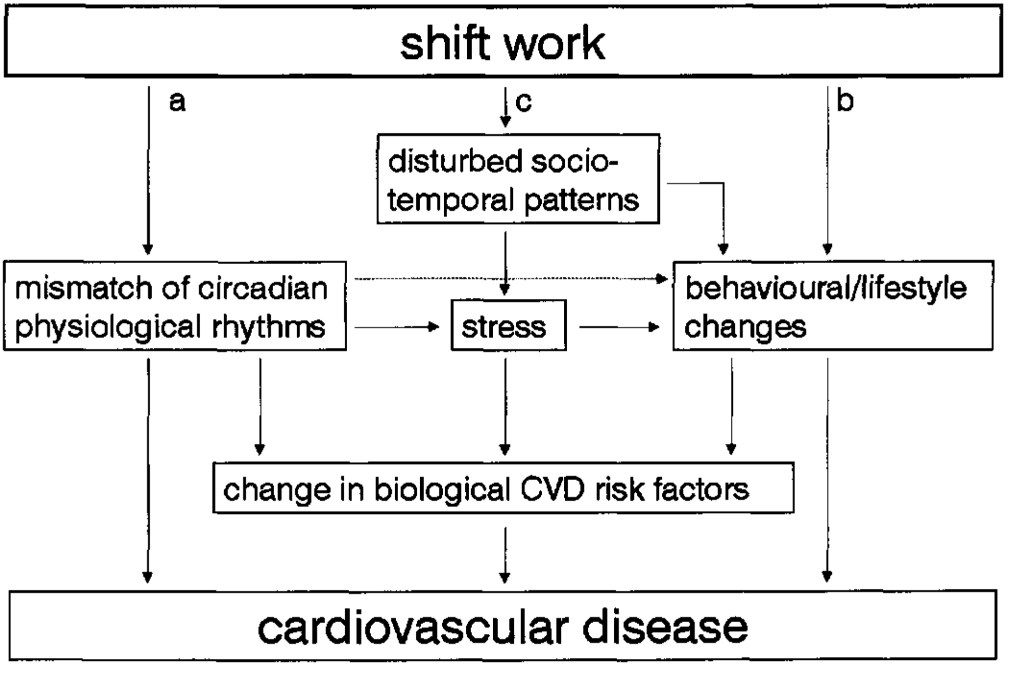

Figure 1.2. *Conceptual model of mechanisms for cardiovascular disease in shift workers [adapted from Knutsson[18]]. (a) disturbed physiological rhythms; (b) psycho-social and behavioural factors; (c) disturbed sociotemporal rhythms.*

Several mechanisms have been proposed as an explanation for the elevated cardiovascular disease risk among shift workers. A model incorporating possible pathways has been proposed by Knutsson[18]. This model introduces (a) disturbed physiological rhythms, (b) psycho-social and behavioural factors and (c) disturbed socio-temporal rhythms as interrelated pathways from shift work to disease. Changes in biological CVD risk factors have been proposed by Bøggild and Knutsson[11] as a fourth possible pathway. However, we regard changes in biological risk factors more as possible intermediary factors that might provide clues about the mechanisms behind the elevated CVD risk. In figure 1.2 a model is depicted , representing a conceptual model of mechanisms for CVD, adapted from Knutsson[18], incorporating the changes in biological CVD risk factors.

By studying the impact of shift work on lifestyle and biological risk factors, the contribution of different pathways or risk factors to the elevated cardiovascular disease risk might be elucidated. In the next paragraph we will summarise the results from studies investigating these factors among shift workers. Besides, possible factors, which might confound the correlation between shift work and CVD will be regarded.

Biological risk factors among shift workers

Cardiac control: premature ventricular complexes

A study conducted by Härenstam *et al.*[19] indicated the occurrence of an increased frequency of premature ventricular complexes (PVC) during days worked in night shift. The PVC frequency is an indicator of arrhythmogeneity[20]. In men without coronary heart disease who had frequent or complex arrhythmias the relative risk for fatal or nonfatal myocardial infarction was estimated to be 2.30 (95% CI: 1.33 to 3.38)[21]. Kannel *et al.*[22] reported an increased sudden death risk in both men and women free from CVD, with PVC's (RR sudden death in males with premature ventricular complexes versus none: 2.9, $p < 0.001$; in females: RR 1.6, not significant). So far the frequency of PVC's in relation with shift work has only been reported in one cross-sectional study. This study, by Härenstam *et al.*[19], showed an increased number of PVC's during work in a night shift compared with work in a day shift.

Two possible mechanisms might contribute to an increased frequency of PVC's among shift workers. Härenstam *et al.*[19] reported an increased urinary excretion of noradrenaline during night work and linked this finding with an increased frequency of PVC's. This indicates that working at night can be regarded as a potential stress factors. In rat experiments social stress has been linked to an increased incidence of arrhythmias and decreased heart rate variability, together with elevated plasma catecholamines[23]. Also in humans, exposure to stressful circumstances has been correlated to an increased incidence of PVC's[24]. A second mechanism might be via an increased prevalence of insomnia in shift workers. Shift work has frequently been connected with an increased prevalence of insomnia[9; 25]. And, so far only in the elderly, insomnia has been correlated with cardiac arrhythmia[26].

Considering the findings of Härenstam *et al.*[19] together with all possible mechanisms linking ventricular premature complexes with working in shifts, makes this factor an interesting candidate for further study.

Cardiac control: heart rate variability

Heart rate variability (HRV), a method to describe beat-to-beat fluctuations in heart rate, is mainly determined by activity of the cardiac sympathetic and parasympathetic systems. HRV is therefore regarded as a non-invasive marker of cardiac autonomic control[27]. Various stresses have been associated with changes in the HRV[28]. HRV might therefore provide a tool to assess stress related short and long-term effects of shift work on the cardiovascular regulation. So far, only one, small-scale study on HRV in shift workers has been published. This study, by Freitas *et al.*[100], did not find differences in HRV levels during sleep and work, between a night and morning shift in 12 shift workers.

Variations in heart rate can be evaluated in time and frequency domain. Spectral analysis in the frequency domain enables a crude separation between vagal and sympathetic cardiac control. Fluctuating efferent vagal activity is the major contributor to high frequency (HF) HRV power[29; 30]. About interpretation of the low frequency (LF) HRV component there is still some disagreement. Some authors consider it as a marker of sympathetic modulations[30; 31]; others adhere the view that it reflects fluctuations in both sympathetic and vagal activity[32; 33].

Acute changes in HRV parameters have been proposed as indicators of exposure to stressful conditions[28]. Sloan *et al.*[34] reported an elevated heart rate and decreased very low frequency, low frequency and high frequency power during exposure to mental stress. No influence was observed on the LF /HF ratio (ratio between low and high frequency power). Myrtek *et al.*[35] reported lower SDNNi (mean standard deviation of all 5-minute intervals, a measure of total HRV) during increased mental load but did not differentiate between low and high frequency power components.

As working in shifts or at night is often regarded as a potential stress factor, HRV analysis might provide a tool to evaluate the acute effect of night work on the cardiovascular regulation. Problems with family life and social relations, which might lead to social stress, have often been mentioned in relation to shift work. But also the requirement to work on hours when the circadian physiological rhythms are tuned to rest might lead to stress. Serum cortisol, a factor in the classical stress response has been linked to working at night. Fujiwara *et al.*[36] reported a significant increase of the mesor (mean of assumed 24-hour sinusoidal rhythm) of serum cortisol from 7.64 μg/dl during a day shift day to 8.77μg/dl on a day worked at night ($p < 0.05$). Comparable results were reported by Weibel *et al.*[37] who compared 11 day-active subjects with 11 night workers (mean plasma cortisol in day shift workers 8.53 μg/dl, in night workers: 9.10 μg/dl). Theorell and Åkerstedt[38] reported an increased excretion of catecholamine during the first week of night work compared with day work in 17 railway workers. After the return to day work (after three weeks of night work) the level of adrenaline went back to normal. The level of noradrenaline, however, remained elevated after the return to daytime work.

Analysis of HRV might also provide a tool to assess the more chronic effects of working at night. As mentioned before, an increased incidence of disturbed sleep and sleepiness have frequently been reported among shift workers[9; 25]. In a study among 12 insomniacs and matched normal sleepers, Bonnet and Arend[39] reported a decreased level of total HRV (SDNNi: Mean of the standard deviations of all 5-minute NN intervals). HRV was found to be decreased in all stages of sleep in insomniacs compared with the same stages of sleep in normal sleepers. In follow-up studies, a high frequency of PVC incidence and unfavourable HRV have been related with increased cardiovascular morbidity and mortality[21; 40-43]. Tsuji reported a hazard ratio of 1.47 for new cardiac events (95% CI 1.16 to 1.86) for a one-standard deviation decrement in SDNN (standard deviation of all RR-intervals within a certain period)[41]. One might hypothesise that the increased CVD mortality in shift workers might partly be mediated by a less favourable cardiovascular regulation due to increased sleep problems.

To summarise, acute and chronic changes in both PVC frequency and HRV might provide a useful tool to assess the potential effect of shift work on the arrhythmogeneity and cardiovascular regulation. Both factors might play an important role in the relation between shift work and CVD.

Blood pressure

Most of the studies regarding CVD risk factors among shift workers included blood pressure, or incidence of hypertension. One might assume that exposure to stress related to working in shifts, or a disturbance of the circadian blood-pressure rhythms in relation to shift work might affect blood pressure.

Bøggild and Knutsson[11] summarised 12 cross-sectional and 7 small-scale prospective studies (between 7 and 75 subjects) on blood pressure or hypertension. Eleven of the studies did not find differences in mean systolic or diastolic blood pressure between day and shift workers. Of the remaining studies four reported a lower and three a higher blood pressure for the shift workers, compared with the day workers. After the publication of this review, results from a larger cohort study were published. Morikawa *et al.*[44] reported an increased hypertension risk in 134 young (18-29 y) shift workers during a five year follow up period but not for the other age groups (adjusted for age, BMI, alcohol consumption). Unfortunately, no adjustment was carried out for smoking habits and socio-economic status, two potential confounders. Summarising, from the rather diverse results of the studies so far, blood pressure does not seem to be an important factor in relation between shift work and CVD.

Body mass index and waist to hip ratio

It has been suggested that working in shifts might be related to a decreased physical activity, changes in food intake or metabolic disturbances (such as insulin resistance). All these factors might lead to changes in body mass index (BMI) or waist to hip ratio (WHR). Study of BMI and WHR, both positively correlated with an increased CVD risk, might therefore provide more information regarding the elevated CVD risk among shift workers.

Most studies addressing the relationship between BMI or WHR and shift work have focused on current shift work status. The studies of Rosmond *et al.*[45] and Nakamura *et al.*[46] revealed a significantly higher WHR among shift workers compared with day workers. Rosmond *et al.*[45] also reported significantly elevated BMI values whereas Niedhammer *et al.*[47] reported a significantly elevated prevalence of overweight among nurses working nights compared with controls working in daytime. Other studies reported no significant elevation of BMI[48; 49] or prevalence of overweight[50] for shift workers. Since an effect of shift work on body composition may have a considerable time lag, current shift work may be less relevant in this respect than a history of shift work. Therefore, job rotation may explain the absence of an association in some of the studies mentioned. Five studies reporting the relationship between BMI and duration of shift work were found in the literature. The data from a study by Kawachi *et al.*[51] show a positive relationship between an increasing number of years worked in rotating night shift (no significance levels given) and BMI. Also the study of Romon-Rousseaux *et al.*[52]reported an increased weight gain per year of age for shift workers compared with day workers. Niedhammer *et al.*[47] reported an association between prevalence of overweight and weight gain and exposure to night- work. Two studies did not find a relationship between annual weight gain[49] or prevalence of overweight[50]. To summarise, the results from most studies conducted so far seem to support a positive correlation between shift work and an increased BMI and WHR.

As a possible explanation a circadian rhythmicity of diet-induced thermogenesis(DIT) might be considered. Romon *et al.*[53] evaluated the DIT in nine young subjects. They reported the highest DIT in the morning (15.9 % of energy content of meal), a lower DIT during the afternoon (13.5%), and the lowest DIT in the night (10.9 %). Because shift workers tend to have a higher energy intake during the night[54] a different DIT might explain a possible higher BMI in shift workers. Another mechanism involved might be the disturbance of the circadian rhythm of neuroendocrine secretion of hormones. For growth hormone secretion and cortisol levels, for example, modification of by night work has been reported[37; 55; 56].

Blood lipids

A comparison in cholesterol (total, HDL and LDL/HDL ratio) levels has been made in a number studies, most of which were of a cross-sectional design. One of the two largest cross-sectional studies, the study of Thelle *et al.*[57] reported a significantly elevated (not adjusted) total cholesterol level in 1291 shift workers compared with 5224 day workers (6.79 versus 6.58 mmol/l). In contrast, the study by Lasfargues *et al.*[58] reported a lower total cholesterol level in both 676 male (5.81 versus 5.91, p: 0.03) and in 524 female (5.24 versus 5.32, P: 0.15) shift workers compared with day workers, matched on age and socio-economic status. Of the other smaller-sized cross-sectional studies, one reported a significantly elevated cholesterol level[46], one a slightly elevated total cholesterol level[48], two reported no difference[59; 60], and two reported a (not significantly) lower[61; 62] cholesterol level in shift workers compared with day workers. The studies reporting HDL[48; 61] did not find significant differences between shift and day workers. Of the longitudinal studies, Theorell *et al.*[38] reported an 2% increase in cholesterol between the first and third week of continuous night work and a 4% decrease between one and three weeks after night work (working in day time). This difference (comparing a group of 16 and 17 subjects) was significant (P <

0.05). Knutsson[63] did not find a different 6 month change in cholesterol level after starting in a new job between 12 shift and 13 day workers. Lennernäs et al[64] reported a significant positive correlation between % of energy intake at night and LDL/HDL ratio. In conclusion there seems no evidence for the assumption that shift workers have a less favourable cholesterol profile. However there seems some evidence for a short-term effect towards a less favourable cholesterol profile when working and/or eating at night.

Three of the studies on triglycerides levels in shift workers reported significantly higher levels in shift workers[48; 58; 59; 65]. Other studies reported non-significantly elevated levels[46; 57; 61]. Of the longitudinal studies, Orth-Gomér et al[66] reported a higher triglyceride level in 46 subjects working in a counter clockwise rotating schedule compared with the same subjects working in a clockwise rotating schedule. Knutsson[63] found a significant increase in triglyceride level over 6 months after starting in a new job in 12 shift workers compared with 13 day workers. Summarising the results for triglycerides, the results seem to direct towards a higher triglyceride level in shift workers.

Lifestyle risk factors among shift workers

Changes in the agenda of social and leisure time activities are almost inevitable when people start working in shifts. Together with attempts to cope with the stresses related to working in shifts and other inconveniences such as a closed canteen during the night this might lead to changes in behaviour or lifestyle.

Dietary habits

Cross-sectional studies[48; 52; 58; 63; 67; 68] reported similar dietary intakes in shift and day workers. Most of these studies were restricted to energy intake but Lennernäs *et al.* did also not find significant different intakes in proteins, total fat, carbohydrates, vitamin A, ascorbic acid, vitamin B1, iron, zinc, selenium and coffee between 37 day workers, 34 two-shift and 25 three-shift workers. Only the intake of calcium was significantly higher in the three-shift workers compared with the day workers (1514 mg /day versus 1215 mg/day). Lasfargues *et al.*[58] did not find significant differences between 1200 shift workers and 1200 day workers (matched on gender, age and socio-economic status) in intake of proteins, calcium, sucrose, fat and cholesterol. Both Lennernäs *et al.* and Lasfargues *et al.* reported a change in the distribution of meal times over a day when working at night with more skipped meals[58], and a lower intake on days on night shift, compensated on other days[54]. Meal timing might have an impact on cortisol levels[69] or HDL cholesterol levels[64]. In a prospective study among 12 shift and 13 day workers, measured before their employment and after six months Knutsson *et al.*[63] reported a decreased intake of dietary fibre but not of energy, protein, fat, carbohydrates and vitamins in the shift workers compared with the day workers. Summarising the studies regarding dietary intake in shift workers, the results so far do not support a substantial involvement of diet in the excess CVD risk among shift workers. Differences in meal timing however might be a relevant factor with a possible link to elevated cortisol and cholesterol levels.

Most studies regarding the intake of alcohol intake did not find significant differences between day and shift workers[61; 65; 70]. One study reported less alcohol consumption among shift workers[48]. Lasfargues *et al.*[58] reported a lower alcohol consumption in the female shift workers and similar levels in the male shift workers, compared with day workers. One study reported a higher alcohol consumption among shift workers[71]. Summarising, so far there is inconclusive evidence to assume differences in dietary habits and alcohol consumption between shift and day workers.

Smoking

Most studies on smoking habits reported a higher prevalence of cigarette smoking among shift workers. In their review Bøggild and Knutsson[11] summarised fifteen cross-sectional studies on smoking habits among shift workers. Eight studies reported a significantly higher number, four a non-significantly higher, two reported no difference and one a significantly lower number of smokers among shift workers compared with day workers. None of three small-scale prospective studies found a significantly different change in the smoking habits of shift workers. Whether the increased number of smokers is related to the generally lower socio-economic status of shift work or a direct consequence of working in shifts is not clear. In one small-scale prospective cohort study (12 shift workers and 13 controls) no changes in smoking habits were found during a six-month period in new shift workers compared with day workers[63]. Orth-Gomér *et al.* did not find significant differences in smoking habits in 46 subjects changing from a counter clockwise (or backward) to a clockwise (or forward) rotation schedule[66]. From the findings so far one can conclude that smoking is more common among shift workers, which might lead to a higher CVD morbidity and mortality. However, most of the studies reporting an increased CVD risk in shift workers did adjust for smoking habits. It is therefore concluded that smoking could not fully explain the reported excess risk CVD risk among shift workers.

Leisure time physical activity

Decreased leisure time physical activity has been proposed as a possible factor in the elevated CVD risk in shift workers It is generally assumed that shift workers have more problems participating in team sports due to their irregular working times. However, so far, the results from the few studies investigating leisure time physical activity in shift workers are controversial and inconclusive. The study of Nakamura *et al.*[46] reported that 69.2 % of shift work reported no exercise versus 50.2 % of the controls working in daytime. Lasfargues *et al.*[58] found no differences in men but reported a significantly higher amount of physical activity in shift working women (exercise more than 1 hour a day: 50.7 versus 26.7). Bøggild[71] reported a higher VO_2 fitness value in shift workers, compared with day workers and a non-significantly lower proportion of low leisure time physical actives. One might conclude, that the results from studies so far are not sufficient to tell whether or not shift workers are less physically active during leisure time.

Confounding factors

Occupational risk factors

Differences in working conditions between shift workers and day workers, apart from shift work, might lead to a changed disease risk between both groups. Work place noise, job strain, social support at work, work place physical activity, and exposure to several chemical factors are all mentioned for their possible link with an elevated cardiovascular morbidity and mortality[13; 14; 72]. No studies were found exploring potential differences in these occupational factors between shift- and day workers but the assumption that shift workers encounter less favourable working conditions is a plausible one.

Socio-economic status

Several studies reported a lower socio-economic status of shift workers. Bøggild *et al.*[71] reported 93.5 % of the 1123 shift workers included in their study as social class III, IV or V versus 68.4 % of the 4084 day workers ($P < 0.001$). Socio-economic status has frequently been reported as an important determinant of cardiovascular disease risk[73] with a higher risk in the lower socio-economic groups. This factor, therefore, might explain, a least a part of, the elevated CVD risk in shift workers. On the other hand, shift work might just as well be regarded as a factor, which explains a part of the elevated CVD risk in the lower socio-economic groups. Besides, several studies on the cardiovascular disease risk among shift workers, which adjusted for socio-economic status, or were restricted to certain occupations, reported a significantly elevated risk[15; 74; 75]. We therefore conclude that socio-economic status might be regarded as an important factor when studying CVD among shift workers but that this factor alone is not sufficient to explain the elevated CVD risk.

Healthy shift worker effect

Pre job selection of healthy workers and a continuing outflow of less healthy shift workers moving from shift to daytime work might lead to a considerable underestimation of the effect of shift work. In the study of Taylor and Pockock for example[76] the highest CVD risk was found in the group of ex-shift workers. However, very little is known about the actual importance of this selection process.

Summarising

From the data available so far, it is not possible to decide which of the suggested pathways is responsible for the elevated risk. Most studies regarding cardiovascular risk factors among shift workers have been of cross-sectional design with a potential for bias. Due to processes like self-selection and pre-job selection by the employer, shift workers tend to be a selective group of workers. This type of selection might be an important source of bias when conducting cross sectional studies comparing shift workers with controls working in daytime. To avoid this bias we conducted a cohort study in which one-year changes in cardiovascular risk factors were assessed in shift workers and controls working in daytime.

Aim of the study

Monitoring changes in cardiovascular disease risk factors in shift workers could provide better evidence for a plausible explanation for the elevated cardiovascular disease risk. Such information might contribute to effective strategies for cardiovascular disease prevention in shift workers. Therefore, in the study, the influence of working in shifts on biological and lifestyle cardiovascular disease risk factors was explored.

The research questions addressed in this thesis are:

1) What is the effect of shift work on the cardiac control (frequency of ventricular premature complexes and heart rate variability)?
2) What is the effect on cardiovascular risk factors (blood pressure, body mass index, waist to hip ratio, total, HDL and LDL cholesterol, dietary habits, smoking, and leisure time physical activity?
3) Is there a difference in the effects under 1) and 2) for distinct shift systems?

Methods

A cohort study was conducted among shift workers and day workers, recruited from the same companies. Baseline characteristics and one-year changes in cardiovascular risk factors were compared between the shift workers and the day workers.

Study population

Potential participants were approached during an 18 month period starting in 1996 using three strategies in order to have different shift work schedules represented in the study: (1) persons undergoing a pre-employment medical examination in two occupational health services; (2) workers employed in a newly built waste incinerator plant; and (3) nurses, starting with their practical in hospital training. Initially, respondents who worked previously in shifts were to be excluded from the study population to prevent potential bias due to former shift work experience. However, due to a slow start of the recruitment this exclusion criterion was ignored. In stead, we decided to adjust the possible effect of former shift work experience in both day and shift workers during the statistical analysis of the results. In total 227 subjects starting in a shift work job and 150 subjects starting in a daytime job were included. A more detailed overview of the total number of approached subjects and the percentage of rejected and included subjects can be found in chapter 5. 24-hour ECG (Holter) recordings were conducted in a sample of the entire cohort.

Observed cardiovascular risk factors

On the basis of the previously discussed risk factors, and feasibility, a selection of biological, lifestyle and confounding factors to be incorporated in the study:

- Cardiac control: frequency of premature cardiac complexes and heart rate variability.
- Biological risk factors: blood pressure, body mass index, waist to hip ratio, total, HDL and LDL cholesterol, dietary habits, smoking, and leisure time physical activity.

- Life style risk factors: diet, alcohol use, smoking and leisure time physical activity.
- Confounding factors: Job strain, work place noise, physical activity at work, socio-economic status (educational level was used to determine differences in socio-economic status)

Outline of the thesis

In this thesis, the results of a longitudinal study on cardiovascular risk factors in shift workers and controls working in daytime will be addressed. *Chapter two, three and four* deal with the risk factors related to cardiac control: frequency of premature complexes and heart rate variability. *Chapter five and six* deal with the other biological and lifestyle risk factors, which were included in this study.

In chapter *two* the one-year changes in the frequency of premature atrial and ventricular complexes and heart rate variability will be discussed.

Chapter *three* concerns a separate study in the shift workers only. In this chapter the impact of working at night on heart rate variability was assessed by comparing a day on morning and night shift. This comparison enables an estimation of the effect of working at night on cardiac autonomic control and the impact of the rotation schedule.

In chapter *four* baseline differences in heart rate variability measures in relation to shift work and other occupational factors are considered. The focus of this chapter is on influence of shift work and other potential unfavourable work conditions on autonomic control of the heart.

Chapter *five* deals with the one-year changes in the biological and lifestyle cardiovascular risk factors. Chapter *six* concerns baseline differences in body mass index and waist to hip ratio, two important cardiovascular disease risk factors, in relation to previous shift work experience.

The main findings of the study will be summarised and placed in a broader perspective in chapter *seven*. Also, in this chapter the strengths and limitations of the study will be discussed, together with the implications of the results for occupational health and possible directions for further research.

2

Shift work related changes in frequency of premature complexes and heart rate variability*

L.G.P.M. van Amelsvoort[a], E.G. Schouten[a], A.C. Maan[b], C.A. Swenne[c], F.J. Kok[a]

Abstract

Objectives: Shift workers have an elevated cardiovascular risk. This might be caused by increased arrhythmogeneity and by unfavourable changes in autonomic cardiac control. The current study aims to investigate both factors, by studying changes in the occurrence of premature complexes (PVC's) and in heart rate variability (HRV) in subjects who start to work in shifts. ***Methods:*** One-year changes in frequency of PVC's and HRV were measured in 49 shift workers and 22 control subjects working in daytime. All respondents were starting in a new job in integrated circuit or waste incinerator plants. ***Results:*** The PVC incidence increased significantly in shift workers over the one-year follow up, compared with day workers. The frequency of ventricular extrasystoles increased in 48.9 % of the shift workers, and in 27.3 % of the day workers. The Spearman correlation coefficient between the number of worked nights and the change in PVC's was 0.33 ($P = 0.004$). HRV displayed a small, non-significant change in a non-favourable direction for both the shift and day workers (one-year change in SDNNi in shift workers: -2.0 msec; in day workers –7.0 msec). ***Conclusions:*** A change in arrhythmogeneity, but not in cardiac autonomic control, might explain the elevated cardiovascular risk in shift workers.

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*Submitted for publication

[a]Division of Human Nutrition and Epidemiology, Wageningen University,
[b]Foundation for ECG analysis, University Hospital, Leiden
[c]Department of Cardiology, University Hospital, Leiden

Introduction

The majority of the studies on cardiovascular disease in shift workers are supportive of the hypothesis that they are at increased cardiovascular risk[15; 17; 74]. In their review, Bøggild and Knutsson estimated the excess risk at 40 %[11]. Several explanations have been put forward, including disturbance of circadian rhythm, changes in behaviour and disturbed sociotemporal activities[18]. So far, approximately forty studies have been reported that investigated the lifestyle and biological risk factors in shift workers[11]. Although some of these studies report a significant relation between cardiovascular risk and shift work, it seems unlikely that these risk factors can fully explain the elevated disease risk in shift workers.

Research into other factors that may explain the elevated cardiovascular risk is scarce. Two of these factors are increased myocardial arrhythmogeneity and disturbed cardiac autonomic control. The frequency of ventricular premature complexes is an indicator of arrhythmogeneity[20]. In men without coronary heart disease who had frequent or complex arrhythmias the relative risk for myocardial infarction or cardiovascular death was estimated to be 2.30 (95% CI: 1.33 to 3.38)[21]. Kannel *et al.*[22]reported an increased sudden death risk in both men and woman with ventricular premature beats. Heart rate variability is a non-invasive marker of cardiac autonomic control[27]. In follow-up studies, a high frequency of PVC incidence and unfavourable HRV have been related with increased cardiovascular morbidity and mortality[21; 40-43]. Tsuji reported a hazard ratio of 1.47 for new cardiac events (95% CI 1.16 to 1.86) for a one-standard deviation decrement in SDNN (standard deviation of all RR-intervals within a certain period)[41]. The aim of the current study is to investigate whether working in shifts induces changes in heart rate variability and frequency of atrial and ventricular premature complexes. This might provide possible explanatory factors in the relation between CVD risk and shift work. One-year changes of these factors were compared between shift workers and daytime working controls, all recently starting in their jobs.

Methods

Population

The study population of the present study was a subset of participants from a cohort study in 396 shift workers and daytime controls. Main objective of the cohort study was to determine the influence of working in shifts for one year on cardiovascular risk factors. The subjects of the present study started new jobs in either the integrated circuit manufacturing industry or in waste incinerator plants in 1996 or 1997. The Ethical Committee of the Wageningen University approved the study; all respondents gave their written informed consent. Inclusion criteria were:

- Starting in a new job.
- Working at least 32 hours a week
- Expecting to work at least one year in the same job
- No use of medication or previous hospitalisation for cardiovascular disease.
- No insurmountable objections to shift work (see Measurements)
- Age between 18 and 55 years.

This study regards the 125 participants (42 day workers and 83 shift workers) of the cohort who were asked to undergo two 24 hour Holter recordings, one year apart. Shift workers had their Holter recording during a day worked in morning shift and day workers during a usual working day. Thirteen respondents refused (8 daytime, 5 shift workers); one was excluded because of a 2nd degree AV block; four had to be discarded because of technical problems like excessive noise. This left 107 participants (32 day workers and 75 shift workers) who had a Holter recording at the start.

Seventeen of them refused the second Holter because "it was to cumbersome" (13) or because of skin irritation due to the electrodes (4). Fourteen were excluded because they quit their job. Five second Holters could not be used because of technical problems. In total 71 complete pairs were used in the analysis (22 day workers and 49 shift workers).

Data collection

Initial data collection was performed between one week and two months after the start of a new job, follow up data was collected one year later.

24 hour Holter recordings

All subjects had a 24-hour Holter recording starting at the beginning of a morning shift (for the shift workers) or day shift (for the day workers). They were instructed to report start and end time of sleep, work, meals, leisure time, physical activities and other possibly relevant events or activities in a diary. These diaries were coded afterwards according to a list of standard activities. Sleep was defined as 1 hour after going to bed until 1 hour before getting up, as recorded in the diary.

Personal and work characteristics

All subjects completed a questionnaire addressing the personal and work characteristics.

Personal characteristics: In the questionnaire, educational level was coded in seven categories: from primary to university education. In the final analysis these levels were reduced to categories lower, intermediate and higher education. Physical activity indexes for work, sport and leisure time were assessed as described by Baecke, *et al.*[85]. Leisure time physical activity and sports scores were combined into an overall leisure time physical activity score. Though current (type, quantity) and past (type, years, and quantity) smoking habits were asked, in the final analysis only the smoking status (non-smoker, current smoker, or ex-smoker) was used.

Current job title and job history: The questionnaire asked for the current job, including company, department, and shift work schedule. If in doubt concerning the shift work schedule status in the questionnaire, we verified the data with the occupational health service or the human resources department of the employing firm. All jobs were coded for social status and job content. A total of nine different job titles were coded. In this study we defined shift work as working in an alternating work schedule including nights. Information on all previous jobs including job title, employer, starting and ending date and shift work status was asked.

Job strain: The amount of job strain was assessed using the Dutch version of the "job demands, decision latitude and social support" questionnaire[86]. The mean of the scores was taken as the cut-off point between high and low job strain.

Dietary assessment: A self-administered food frequency questionnaire that measured the intake of energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol was filled out by the respondents[87].

HRV Assessment

The 24-hour Holter recordings were analysed with a Marquette Series 8000 Holter Analyser by an experienced Holter analyst. The ventricular and atrial premature complexes were coded. The onset-Q instants of all beats were determined with the CCTOC Marquette Holter research software module. The resulting inter-beat interval series were down-loaded from the Holter analyser, and further analysed on a personal computer as described by Janssen *et al.*[88].

The complete recording was split into 5-minute segments. Only segments with 5% or less missing values (due to noise or failure) were used. Heart rate and HRV parameters were computed for each segment. The 24-hour values and the mean values during sleep and work were obtained by averaging over the respective periods. For the normal beats the average standard deviation (SDNNi) was calculated as mean standard deviation of all five-minute recordings.

The algorithm used for spectral analysis has been described elsewhere[89]. Briefly, intervals were normalised to the duration of the mean interval. Then, linear trend removal, and 10% left and right tapering was done. After padding the data with zeros to the nearest power of two, the power density spectrum was computed by means of a Fast Fourier algorithm. We computed the spectral powers within two frequency bands: low frequency power, LF (0.05-0.15 Hz; a marker of fluctuations in either sympathetic or sympathetic plus vagal activity) and high frequency power, HF (0.15-0.40 Hz; a marker of vagal activity[30].The spectral components were calculated both as absolute units and as normalised units (the latter by dividing LF and HF by their sum, and multiplying this by 100).

The frequency of ventricular and atrial premature complexes was calculated by dividing the number of premature complexes by the total analysed time. Day mean values were calculated as mean of the frequencies during sleep, work and leisure time to adjust for differences in duration of sleep, leisure and work.

Data analysis

Because of the skewed within and between subject distribution of the high and low frequency spectral HRV components, log-transformation of these parameters was performed. Standard methods were used for descriptive analysis. The distribution of the frequency of premature complexes, nor its one-year change, did approach a normal distribution, even after transformation. Differences were tested with the non-parametric Wilcoxon rank sum test. To evaluate the correlation with other continuous parameters the Spearman rank correlation statistic was calculated. Seven respondents reported poor sleep quality during their first Holter measurement due to wearing the recorder for the first time. This had a significant influence on the

HRV parameters (for SDNNi: p: 0.004). Therefore differences in the one-year change in HRV parameters were adjusted for reported poor sleep quality. Regression analysis was used to assess the effect of potential other confounders. All statistical analysis was done using the SAS program[90].

Results

In table 2.1 the population characteristics and baseline frequency of premature complexes and HRV levels are given.

Table 2.1. *Baseline population characteristics and baseline levels*

	Day workers	Shift workers	P-level
Population characteristics			
N	32	75	
age (years)	29.3 (5.3)	30.4 (6.7)	0.4
Gender (% female)	9 %	11 %	0.8$
Smoking habits (%)			
never smoker	48 %	41 %	0.4$
current smoker	26 %	40 %	
ex-smoker	26 %	19 %	
Education			
Lower	3 %	38 %	0.001$
Intermediate	35 %	44%	
Higher	61 %	18 %	
Baseline frequency of PAC (1/hour)@	0.54 (0.2; 2.0)	0.50 (0.2; 1.5)	
Baseline frequency of PVC (1/hour)@	0.04 (0; 0.11)	0.04 (0; 0.09)	
PAC (respondents with more than 1 per hour)&	30.9 %	38.7 %	0.4&
PVC (respondents with more than 0.1 hour)&	25.8 %	23.4 %	0.8&
Baseline HRV levels			
Heart rate (beats/min)	71.6 (8.4)	75.3 (8.4)	0.04
SDNNi (msec.)	89.1 (28.7)	74.6 (20.7)	0.01
Log(lf) (log msec.)	- 2.67 (0.18)	- 2.76 (0.21)	0.03
Log(hf) (log msec.)	-2.98 (0.35)	- 3.15 (0.30)	0.03
% lf	65.1 (10.8)	68.4 (8.1)	0.2

PAC *premature atrial complexes*
PVC *premature ventricular complexes*
Log(lf) *log of low frequency power*
Log(hf) *log of high frequency power*
@ *median (25% ; 75% quantile)*
$ *p value according to chi-square test.*
& *p value according to Wilcoxon 2-sample test.*

The only significant differences were found to be a significantly higher educational level and heart rate and a lower SDNNi and low and high frequency power in the shift workers compared with the day workers.

Table 2.2. *One-year change of HRV parameters and frequency of premature complexes between baseline and one year measurement.*

	Day workers	Shift workers	P value day /shift-worker difference
N	**22**	**49**	
Number of night shifts	**0**	**63**	
Frequency of premature complexes			
Decrease of PAC frequency&	54.6 %	43.7 %	0.6&
No change in PAC frequency	4.6 %	0.0 %	
Increase in PAC frequency	40.9 %	56.3 %	
Decrease of PVC frequency&	45.4 %	20.4 %	0.03&
No change in PVC frequency	27.3 %	30.6 %	
Increase in PVC frequency	27.3 %	48.9 %	
HRV parameters			
Heart rate (bpm)	1.83	-2.08*	0.08
SDNNi (msec.)	-7.0*	-2.0	0.2
Log(lf) (10^{-3} log msec.)	-36.9	-29.9	0.84
Log(hf) (10^{-3} log msec.)	-83.9*	-16.2	0.06
% lf	1.99	-0.72	0.16

Between brackets 1-3 quartile levels for PAC and PVC, standard deviation for the HRV parameters
PAC premature atrial complexes
PVC premature ventricular complexes
Log(lf) log of low frequency power
Log(hf) log of high frequency power
* *sign. change from baseline P < 0.05; ** P < 0.01; ***; P < 0.001*
& *Percentage of subjects. P value according to Wilcoxon 2-sample test.*

Premature complexes

The one-year changes in frequency of premature complexes and HRV levels are given in table 2.2. The change in frequency of atrial premature complexes was not significantly different between the shift and day workers. The change in frequency of premature ventricular complexes (PVC) was significantly different between the shift and day workers. The observed increase in shift workers was associated with the number of nights worked during the follow-up period (figure 2.1). The Spearman correlation coefficient was 0.33 (p: 0.004). Univariate adjustment for smoking, age, one-year weight gain, change in alcohol consumption, or poor sleep quality did not have a substantial effect. The increase in PVC frequency was found to be higher in the group of workers working in a medium backward rotating schedule compared with forward and irregular rotating shift schedules ($p < 0.1$).

Heart Rate Variability

For the HRV levels (SDNNi and frequency power levels) in day workers a significant decrease was observed. In shift workers a significant decrease of 24-hour mean heart rate was found. None of these changes were significantly different when compared with the shift, respectively day workers. Adjustment for changes in BMI, coffee consumption or job strain did not change the conclusions.

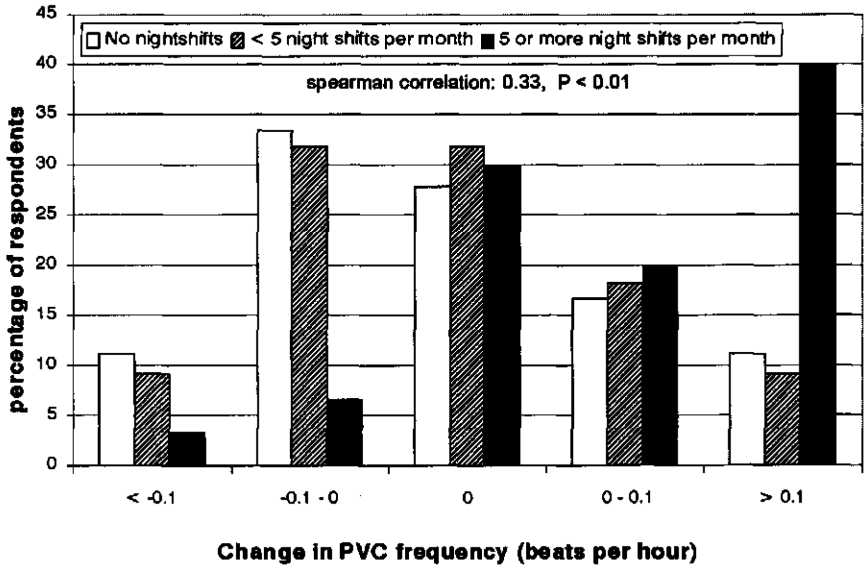

Figure 2.1. *Distribution of individual one-year changes in the number of premature ventricular beats in relation to the number of night shifts.*

Discussion

In summary, we found that the one-year change in frequency of ventricular premature complexes was greater in the shift workers, as compared with the day workers. The changes in heart rate variability parameters were not significantly different.

Given the cohort design, where each respondent serves as its own control, most potential sources of bias, related to selection of the study population, are considered to be insignificant. However, selective drop out after the first measurement might have been a potential source of bias when this drop out is correlated to the one-year changes. This form of selection biased could not be evaluated. However, considering the relatively small number of drop-outs, together with the similar baseline levels in the drop-outs and the follow-up population, selection bias is considered to be low. The choice of a control group remains problematic when investigating the effects of shift work. And, although the cohort design is less sensitive to the choice of the control group, differences in the potential effects of working in shifts between shift workers and day workers might have influenced the results. Also differences in work conditions between shift workers and day workers might have occurred. However, correction for job strain, the most likely work related confounder, did not yield different results. Furthermore the high correlation with the number of nights worked during follow up indicates that the increase in frequency of ventricular premature beats in the shift workers is due to working at night.

Although most of the change in heart rate variability seems to be caused by regression to the mean, the baseline differences remain puzzling. It might be that this baseline difference reflects a selection effect. Because the first measurement was conducted after the start of a new job these baseline differences might also be related to adaptation to working in shifts. An effect which might fade in due time. Within the current data set it is not possible to determine which factor is responsible for this difference.

One other study reported about the relationship between ventricular premature complexes and shift work. In this study by Härenstam *et al.*[19] working at night was related to an increased frequency of ventricular premature complexes, compared with working at daytime. Both the study of Härenstam and our study support the involvement of increased susceptibility of the myocardium to arrhythmia in the cardiovascular risk profile of shift workers. An increased frequency of ventricular premature complexes has been associated with an increased cardiovascular disease risk. Bikkina *et al.*[21] reported an adjusted relative MI and CHD risk of 2.12 (95% CI, 1.33 to 3.38) in men without CHD with complex or frequent ventricular arrhythmia (more than 30 PVC's per hour).

Coffee consumption[91], BMI[92] and smoking[93] have been associated with the occurrence of ventricular premature complexes. However, when analysing these potential confounding factors in our study, neither one was able to explain the reported increased frequency of premature ventricular complexes in shift workers. Speculating about a possible explanation for the increased frequency of ventricular premature complexes in shift workers, it might be that working at night acts as a chronic stressor. Theorell *et al.*[38] showed that a shift from day work to night work can induce acute sympatho-adrenal arousal. Similarly, in a cross-sectional analysis in shift workers we found evidence for a shift of the sympatho-vagal cardiac regulation towards sympathetic dominance during a day worked in night shift compared with day worked in morning shift (chapter 3). In animal experiments it has been shown that exposure to social or psychological stress is related to an increased frequency of premature complexes[23] and an increased vulnerability of the myocardium[94]. Also in humans stress and fatigue have been related to increased arrhythmia[24] and increased ventricular premature complex frequency[95]. Another possible mechanism might be via the disturbance of the circadian rhythm of noradrenaline excretion by working in shifts. Härenstam *et al.*[19] reported a relation between excretion of noradrenaline during daytime and frequency of ventricular extrasystoles. They also reported a higher excretion of noradrenaline during a night shift.

Decreased levels of SDNNi have been associated with an increased cardiovascular morbidity and mortality[41; 42]. We found the highest decrease of SDNNi in the day workers and not in the shift workers, although this difference was non-significant. We therefore do not consider chronic changes in heart rate variability as a plausible factor in the pathway from shift work to CVD. No other studies were found reporting long-term effects of shift work on the sympatho-vagel regulation. Short-term changes in the level of heart rate variability as reported in chapter 3, which might occur during days working at night, can not yet be dismissed as factor in the elevated cardiovascular risk.

Conclusions

An increase in frequency of ventricular premature complexes during the first year of shift work, as found in this study might explain the elevated cardiovascular disease risk in shift workers. A change in heart rate variability during days working in morning shift is probably not factor in the mechanism leading to an elevated cardiovascular disease risk in shift workers. Further study is needed to confirm the results and to elucidate the factors involved in the elevated frequency of ventricular premature complexes.

In our study only one of the shift workers reached the level of 30 PVC's per hour (the cut-off level used in the study of Bikkinia *et al.*). Nevertheless, we conclude that the increase in frequency of premature ventricular beats might be an important factor in the relationship between shift work and the elevated cardiovascular disease risk.

Acknowledgements

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3

24-Hour heart rate variability in shift workers: impact of shift schedule*

L.G.P.M. van Amelsvoort[a], E.G. Schouten[a], A.C. Maan[b], C.A. Swenne[c], F.J. Kok[a]

Abstract

Objective: Disturbance of the circadian pattern of cardiac autonomic control by working at night when the physiological system anticipates rest could possibly explain part of the elevated cardiovascular risk in shift workers. Analysis of Heart Rate Variability (HRV) is a non-invasive tool to estimate possible disturbances of the cardiac autonomic control. To assess the influence of working at night on cardiac autonomic control, HRV in shift workers during a day on morning shift and a day on night shift were compared. ***Methods:*** 24-hour ECG recordings were made in 65 shift workers during a day working on morning shift and during a day working on night shift. Within person differences between morning and night shift of 24-hour mean HRV measures and of the mean values during sleep and work were calculated. Possible modification of the reported effects by the shift schedule was determined. ***Results:*** Significantly elevated mean %LF during sleep was found on a day worked in night shift compared with a day worked in day shift (%LF + 3.04, $P < 0.01$). Type of Shift schedule was found to be a significant modifier of this effect. The age adjusted least square mean difference in % LF between the night and day shift for the different shift schedules apart were: + 0.88 % for the workers in the fast forward rotating shift, + 3.06 % for the fast backward rotating shift, + 6.15 % ($P < 0.001$) for the medium speed backward rotating shift and + 1.18 % for the shift workers without a regular shift schedule. ***Conclusions:*** The results suggest an increased sympathetic dominance during a night shift sleep indicating an inferior sleep quality. The magnitude of the reported effect was related to the shift schedule. Optimisation of this schedule could therefore provide a tool in diminishing the impact of working at night on cardiac autonomic control and may contribute to a reduction of the cardiovascular disease risk among shift workers.

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*Submitted for publication

[a]Division of Human Nutrition and Epidemiology, Wageningen University,
[b]Foundation for ECG analysis, University Hospital, Leiden
[c]Department of Cardiology, University Hospital, Leiden

Introduction

During the last decade the evidence for an elevated cardiovascular risk in people working in shifts has become more convincing[13; 15; 17; 75]. However, the mechanisms behind this elevated risk remain unclear. Suggested hypotheses include undesirable changes in eating habits, in physical activity, the involvement of metabolic factors and disturbances in the physiological circadian rhythm[17; 64]. Disturbance of the circadian cardiovascular autonomic control pattern could be a factor in the latter mechanism. A non-invasive technique used for investigating cardiovascular autonomic control is the analysis of heart rate variability. Heart rate variability and its spectral components reflect the dynamics of cardiac parasympathetic and sympathetic outflow[30; 89]. In post myocardial infarction patients as well as in the general population heart rate variability measures have been found to be inversely associated with cardiovascular morbidity and mortality[41-43].

Cardiac autonomic control as measured by heart rate variability displays a marked circadian rhythmicity[96; 97]. Circadian rhythmicity of cardiac control could explain part of the diurnal distribution of the reported diurnal distribution of myocardial ischemia and infarction[98]. Possibly, the disturbance of the circadian rhythm of autonomic nervous system activity is also a relevant factor in the elevated cardiovascular risk of shift working. Working at night when the physiological system anticipates rest and recuperation can be regarded as an extra burden to the cardiovascular system due to a mismatch of the work/rest cycle and the output of intrinsic circadian pacemakers. Optimisation of the shift schedule may be a way to relieve this burden. Barton and Folkard[99] reported a poorer physical and psychological health among workers with advancing (that is, rotated in a backward direction: nights-afternoons-mornings) compared with delaying shift system (that is, rotated in a forward direction: mornings-afternoon-nights).

So far only a small-scale study by Freitas *et al.*[100] reported about the influence of working at night on heart rate variability by working in shifts. In the twelve monitored subjects he found that the circadian pattern of HRV seemed to be predominantly related to the sleep-wake rhythm and was independent of the night-day cycle.

Our study aims at determining, in the 24-hour heart rate variability profile, the differential effects of forward and backward rotating shift schedules on circadian cardiac autonomic control. We focussed our study on the night shifts of 110 subjects.

Methods

Population

110 shift workers on rotating schedules participating in an ongoing cohort study comparing cardiovascular risk factors among shift workers with controls working in day time including nights were asked to undergo two 24 hour Holter recordings. In the cohort study changes in cardiovascular risk factors are monitored over a one year period in shift workers and in day time working controls to identify possible factors that might be responsible for the elevated cardiovascular disease risk among shift workers. The study was approved by the ethical committee of the Wageningen Agricultural University.

The following inclusion criteria were applied:

- Starting in a new job.
- Working at least 32 hours a week
- Expecting to work next year in the same job
- No use of medication or previous hospitalisation for cardiovascular disease.
- No insurmountable objections to shift work (see measurements)
- Aged between 18 and 55 years.

Holter recordings were performed on two 24-hour periods: a day with a morning shift and a day with night shift duty. In total 110 respondents were approached for two Holter recordings. Nineteen of the respondents refused to carry a Holter recorder. Seventeen shift workers refused to finish the first or measurement or to enrol for the second measurement because "it was to cumbersome" (10) or due to due to skin irritation (7).

Seven recordings could not be used due to a poor signal to noise ratio (4) or technical malfunction of the equipment (3). Two pairs of recordings were not used due to an excessive number of premature beats. This left 65 complete pairs of 24-hour Holter recordings for further analysis.

Measurements

Measurements were performed between one week and two months after the start of a new job.

24-hour Holter recordings:

The participants were had a 24 hour Holter recording starting at the beginning of a morning shift period and the beginning of a night shift period. All participants were instructed to note down start and end time of sleep, work, meals, leisure time, physical activities and other possibly relevant events or activities. These diaries were later coded into a choice out of a list of standard activities. Sleep was defined as 1 hour after going to sleep until 1 hour before getting up, as recorded in the diary.

Table 3.1. *Structure of the included shift schedules.*

Shift schedule	structure
fast forward	MMEENNNNxxMMEEENNxxMMMEENNxxx
fast backward	NNEEMMMMxxNNEEEMMxxNNNEEMMxxx
medium backward	EEEExxMMMxxNNNNxxxEEExxMMMMxxNNNxxxEEEExxxMMMxxNNNNxxx

M *morning shift*
E *evening shift*
N *night shift*
x *day off*

Personal and work characteristics:

All participants completed a questionnaire regarding:

Current job title: We asked for the current job, including company, department, and shift schedule. According to social status and job content all jobs were coded in one of nine different job titles. Shift schedules were coded as forward rotating (nights-afternoons-mornings, advancing schedule) or backward rotating (mornings-afternoon-nights, delaying schedule). We coded rotation as fast when at most three consecutive night shifts were worked. At most five consecutive night shifts on a row were coded as medium rotation. Irregular shift schedules, often made each month after consultation with all workers involved were coded as "irregular". In Table 3.1 the subsequent time schedules of the rotation schedules are represented.

Personal characteristics: Educational level was coded in seven levels from elementary school to university education (junior, senior, or higher education). The physical activity indexes for work, sport and leisure time were assessed as described by Baecke, Burema and Frijters[85]. The ranges of the indexes were 1.1 - 4.3, 1.0 - 5.2 and 1.3 - 4.5 respectively. Current and past smoking habits were asked.

HRV Assessment

The 24-hour Holter recordings were analysed with a Marquette Series 8000 Holter Analyser by an experienced Holter analyst. The onset-Q instants of all beats were determined with the CCTOC Marquette Holter research software module. The resulting inter-beat interval series were downloaded from the Holter analyser, and further analysed on a personal computer as described by Janssen *et al.*[88].

The complete recording was split into 5-minute segments. Only segments with 5% or less missing values (due to a noisy ECG) were used. Heart rate and HRV parameters were computed for each segment. The 24-hour values and the mean values during sleep and work were obtained by averaging. For the normal beats the standard deviation (SDNNi) was calculated as standard deviation during a five-minute reference period, with the exclusion of all segments with more than 5% missing values.

The algorithm used for spectral analysis has been described elsewhere[89]. Briefly, intervals were normalised to the duration of the mean interval. Then, linear trend removal, and 10% left and right tapering was done. After padding the data with zeros to the nearest power of two, the power density spectrum was computed by means of a Fast Fourier algorithm. We computed the spectral powers within two frequency bands: low frequency power, LF (0.05-0.15 Hz; a marker of fluctuations in either sympathetic or sympathetic plus vagal activity) and high frequency power, HF (0.15-0.40 Hz;, a marker of vagal activity[30]). The spectral components were calculated both as absolute units and as normalised units (the latter by dividing LF and HF by their sum, and multiplying this by 100).

Statistical analysis

Because of the skewed within and between person distribution of the high and low frequency spectral components of the heart rate variability, log-transformation of these parameters was performed before any averaging was done.

Comparisons of night shift day and morning shift day HRV measures were performed using the paired t-test. For the evaluation of effect modification of the night shift - morning shift differences, ANOVA modelling was used, with using the SAS program. Least square mean values are shown to enable comparison of mean values between subgroups, adjusted for a covariant. Least square means are the class or subclass means that one would expect for a balanced design involving the class variable with all covariates at their mean value[101]. For the evaluation of possible modification of the reported effects by the number of successive days worked in the same shift, mixed model analysis was used[102].

Results

Table 3.2. *Population characteristics.*

	Males	Females	Total
N	53	12	65
Age (years)	34.2(8.1)	25.3 (5.7)	32.5 (8.4)
Smoking (%)			
non smoker	49.0	41.7	47.6
smoker	33.3	33.3	33.3
ex smoker	17.7	25.0	19.0
Job strain categories (%)			
• High demands, low control	5.9	58.3	15.9
• High demands, high control	9.8	8.3	9.5
• Low demands, low control	31.4	25.0	30.2
• Low demands, high control	52.9	8.3	44.4
Shift schedule (%)			
• Fast forward	35.9	16.7	32.3
• Fast backward	20.8	0.0	16.9
• Medium backward	43.4	0.0	35.4
• irregular	0.0	83.3	15.4
Heart rate (beats/min)*	73.3 (7.0)	86.0 (9.1)	75.6 (8.8)
%LF*	69.6 (8.4)	66.2 (8.6)	68.9 (8.4)
SDNNi (10^{-3} sec.)*	76.0 (19.4)	60.2 (19.4)	73.1 (20.2)
Log(LF) (log sec.)*	-2.78 (0.21)	-2.85 (0.21)	-2.79 (0.21)
Log(HF) (log sec.)*	-3.19 (0.33)	-3.18 (0.31)	-3.19 (0.32)

Mean values with standard deviation in brackets or %.
**24 hour mean during day with morning shift.*

Table 3.2 lists general characteristics of the study group/ Most participants had industrial work sites with a predominantly male work force (this caused the large proportion of male subjects in our study). Almost all female subjects (except two) worked as a nurse. These nurses worked primarily without a fixed shift schedule with approximately 2-4 night shifts per month. All other workers worked an average of 5-7 nights per month.

In tables 3.3, 3.4 and 3.5 individual differences (night shift day minus morning shift day values) are presented. In table 3.3 the 24 hour means of the individual differences are shown. The most prominent difference between the night and morning shift heart rate values are present in the irregular shift schedule group where next to a lower heart rate during night shifts also higher SDNNi and %LF values can be observed. When correcting for the difference in 24 hour heart rate, the difference in SDNNi and %LF between the night and morning shift disappears (For heart rate corrected differences: δSDNNi: 0.5, SE: 2.3; δ%LF -1.0, SE: 1.4). In the three other groups a change towards dominance of low frequency heart rate variability was observed but only reached statistical significance in the fast forward rotating group.

Table 3.3. *Night and morning shift differences in 24 hour mean values.*

	All workers	**Shift schedule**			
		fast forward	**fast backward**	**Medium backward**	**Irregular shift schedule**
δHeart rate (beats/min)	-0.47 (0.66)	1.25 (0.98)	-1.15 (1.11)	-0.03 (1.19)	-4.50 (1.86)*
δSDNNi (10^{-3} sec.)	1.88 (1.33)	0.34 (1.45)	-1.47 (3.83)	2.68 (2.67)	7.0 (2.9)*
δLog(LF) (10^{-3}log sec.)	18.4 (13.6)	30.0 (12.4)*	-26.9 (35.7)	51.9 (27.5)	-33.1 (33.9)
δLog(HF) (10^{-3}log sec.)	-4.8 (17.9)	-21.7(23.6)	-65.0 (58.8)	24.5 (32.1)	29.3 (38.9)
δ%LF	0.96 (0.61)	2.18 (0.89)*	1.44 (1.69)	1.33 (1.07)	-2.97 (1.27)*

Mean values of difference between a night shift and morning shift day. Standard error of mean between brackets. P values according to the paired t-test: significant difference between night and morning shift values ($p < 0.05$; ** $p < 0.01$)*

In table 3.4 mean differences of night and morning shift HRV values measured during working hours are presented. Respondents working "irregular shift schedule", "fast forward shift schedule" or "fast backward shift schedule" exhibited a considerably lower heart rate during work in a night shift compared with a morning shift. The mean log(LF) values for all shift schedules are lower during night shifts but only significant for the irregular shift schedule group and for the data of all workers combined.

Twenty-four hour mean differences between night and morning shift days reflect differences in work and leisure time activities as well as differences due to disturbance of circadian physiological rhythms. Mean values during sleep are probably much less influenced by the differences in work and leisure time activities and therefore might be better indicators of disturbances of the circadian physiological rhythm. In table 3.5, the night and morning shift differences in mean values during sleep are presented. The most prominent differences in mean values during sleep can be observed in the workers working according to a medium backward rotating shift schedule. They show a considerable shift towards low frequency power dominance (elevated %LF and Log LF), and an increased SDNNi, during sleep on a day on night shift. A less pronounced effect in the same direction for %LF was present in workers on a fast backward rotating shift schedule.

Table 3.4. *Mean night and morning shift difference during work.*

	All Workers	Shift schedule			
		fast forward	fast backward	medium backward	Irregular shift schedule
δHeart rate (bpm)	-3.12 (0.89)**	-3.91 (1.45)*	-3.10 (0.97) **	0.25 (1.59)	-9.22 (2.15)**
δSDNNi (10^{-3} sec.)	1.48 (1.47)	5.44 (2.19)*	-1.46 (3.48)	-3.08 (2.66)	6.91 (3.01)*
δLog(LF) (10^{-3}log sec.)	-36.4 (13.1)**	-19.3 (19.4)	-78.4 (35.6)	-18.9 (25.6)	-66.2 (23.0)*
δLog(HF) (10^{-3}log sec.)	-36.4 (21.5)	-19.9 (29.8)	-97.2 (82.1)	-39.5 (30.5)	30.2 (55.4)
δ%LF	-0.29 (0.73)	-0.08 (1.04)	0.11 (2.51)	0.65 (1.07)	-2.97 (1.27)*

Mean values of difference between a night shift and morning shift day. Standard error of mean between brackets. P values according to the paired t-test: significant difference between night and morning shift values.($p < 0.05$; ** $p < 0.01$)*

Investigation of possible effect modification by other factors than shift schedule was done by including the possible effect modifiers age, job strain, sex and physical activity at work, one by one in an anova model. Only for age there was an indication for a small, but non-significant effect modification on several HRV parameters. The most prominent effect modification was found for %LF. With each five year increase of age the effect of working in a night shift on mean %LF during sleep increased with 0.9 % LF ($p = 0.18$).

Table 3.5. *Mean night and morning shift difference during sleep.*

	All Workers	Shift schedule			
		fast forward	fast backward	medium backward	Irregular shift schedule
δHeart rate(bpm)	0.70 (0.71)	0.90 (1.02)	0.43 (1.78)	1.36 (1.38)	-0.93 (1.78)
δSDNNi (10^{-3} sec.)	2.81 (2.73)	0.27 (3.00)	-1.56 (6.92)	5.24 (6.26)	7.39 (4.08)
δLog(LF) (10^{-3}log sec.)	51.9 (26.4)*	16.9 (35.1)	-10.0 (75.6)	131.3 (52.0)*	10.7 (40.4)
δLog(HF) (10^{-3}log sec.)	-10.1 (30.1)	-11.1 (43.7)	-106.0 (95.5)	15.7 (57.7)	38.3 (57.8)
δ%LF	3.04 (1.11)*	1.25 (1.68)	4.55 (2.93)	5.92 (2.02)*	-1.50 (2.18)

Mean values of difference between a night shift and morning shift day. Standard error of mean between brackets. P values according to the paired t-test: significant difference between night and morning shift values ($p < 0.05$; ** $p < 0.01$)*

Table 3.6. *Age adjusted mean night and morning shift difference during sleep.*

Shift schedule	**fast forward**	**fast backward**	**medium backward**	**Irregular shift schedule**
δHeart rate (bpm)	0.89 (1.29)	0.36 (2.08)	1.38 (1.28)	0.63 (5.67)
δSDNNi (10^{-3} sec.)	1.17 (3.52)	0.58 (5.67)	6.41 (3.50)	-1.59 (7.15)
δLog(LF) (10^{-3}log sec.)	20.1 (44.6)	-5.8 (71.7)	137.8 (44.3)**	-13.8 (71.6)
δLog(HF) (10^{-3}log sec.)	-0.91 (41.5)	-76.4 (66.7)	19.6 (41.2)	-38.4 (66.7)
δ%LF	0.88 (1.62)	3.06 (2.61)	6.15 (1.64)***	1.18 (2.61)

Least square mean of difference between a night shift and morning shift day corrected for age; SDNNi, Log(LF), Log(HF) and %LF also corrected for difference of heart rate during sleep. Standard error of mean between brackets. p: significant difference between night and morning shift values ($p < 0.05$; ** $p < 0.01$; *** $p < 0.001$)*

Because of the correlation between the various HRV measures with heart rate a separate analysis was performed on the mean values during sleep with correction for mean heart rate during sleep. Differences in age might explain the different effects of the shift schedules as presented in table 3.5. Therefore, to adjust for possible confounding of the effect of shift schedule by age, age was included in the model presented in table 3.6. Adjustment of the results resulted yielded only small differences, compared with the unadjusted results, as presented in table 4.5.

Discussion

Increased levels of 24-hour %LF were found during a night shift day compared with a day shift day, except for the participants working in an irregular shift schedule. Decreased 24-hour mean heart rate values during a night-shift day were found in most workers but most prominent in the nurses working in an irregular shift schedule. Next to other possible sources of bias, differences in tasks during work and leisure time are likely to have influenced the 24 hour heart rate and heart rate variability. Especially the respondents working in irregular shift schedules seem to have different work tasks at night compared with their daytime task. This is reflected in the considerable differences in heart rate and heart rate variability levels during work. Because the differences during sleep are much less prone to bias due to differences in work and leisure time activities[125] we will focus the discussion on these results.

Measurements during sleep on either night- or morning shift days are considered to be less susceptible to differences in leisure time or work activities. Elevated values of %LF during sleep were found on night shift days compared with morning shift days for all respondents together. When taking effect modification by shift schedule into account, the elevation was largest in the workers working in a medium backwards rotating shift schedule whereas the workers working in the irregular shift schedule did not show this elevation.

Because we compared night and morning shift differences within subjects, variation between individuals is not considered a major source of bias. Effect modification, due to differences in sensibility between individuals, however can not be ruled out. From the factors considered as possible effect modifiers, type of shift schedule was the most important and the only one to reach statistical significance. In our study, gender and number of nights worked per month was highly correlated (p chi-square: < 0.001) with type of shift schedule and both factors could therefore not be assessed separately as a possible effect modifier. One could argue that the deviant results in the group of workers working with "irregular shift schedule" are caused by a difference in gender, or a smaller number of nights worked per month, rather than a different shift schedule. Extrapolation of the presented results to female workers and to workers in irregular shift schedules needs further research.

Differences between days on night shift and morning shift within individuals are a likely source of bias of the presented results. Eating habits, coffee consumption, alcohol consumption, medication use and physical activity are all likely to differ on night shift compared with morning shift days. These factors could also influence heart rate variability, and might therefore be intermediary factors between shift and HRV. Nevertheless, we do not consider it likely that the difference between the shift schedules is explained by differences these factors.

Because the measurements during the different shifts were not all on the same day from the start of a new rotation cycle, bias or effect modification could be present due to differences between the number of the day in a row of days on the same shift. Mixed model analysis was used to evaluate possible effects of the number of days worked in the same shift. No significant influence of the number of consecutive shift in a row was found.

The effect of working at night is on average larger during sleep than measured during 24 hour. This indicates that a part of the elevated %LF values during sleep is compensated elsewhere during the day. Because the differences during work did not show considerable differences between a night and day shift day a change during leisure time is therefore considered the most likely explanation. Unfortunately, because of the large variation in leisure time mean values it was not possible to assess this in the current data.

Only one other study has been found reporting 24-hour heart rate variability differences during night- and morning-shift days was found[100]. No differences in HRV levels during sleep and work, between the night and morning shifts, were reported. However, in this study, only 12 observations were included and no shift rotation schedule was given.

When comparing the different shift schedules included in this study, the ordered levels of differences in %LF during sleep for the different shift systems coincides with the on the basis of theoretical health considerations ordered shift systems (i.e. forward rotation favoured above backward, fast rotation favoured above slow rotation). A forward rotation is considered more healthy because in the absence of external cues the sleep-wake and other circadian rhythms run with a period of approximately 25 hours so sleep occurs later and later[99; 103]. Sleeping when working in a forward rotation is considered to be less disruptive because the shift in relation to the internal circadian clock is smaller. The elevation of %LF during night could be an indication of less favourable sleep. This effect was largest in the group working in a medium speed backward rotating shift schedule so one might hypothesise that this shift schedule causes a larger disruption in the normal wake-sleep cycle and therefore leads to a decreased sleep quality.

In conclusion, our study provides empirical data that support the hypothesis that working nights causes a shift of the autonomic balance towards sympathetic dominance. This effect was most pronounced during sleep, but was also found in 24-hour averages. This is especially true for workers with an anti-clockwise (or backward) rotating shift schedule.

One might hypothesise hat the less favourable shift in the autonomic balance towards sympathetic predominance, as found in this study might lead to an increased cardiovascular burden. This could be a component in the elevated cardiovascular disease risk of shift workers. Because the type of shift was related to the reported effect, type of shift schedule has to be considered as a possible factor in the reduction of the adverse impact of shift work on cardiovascular health.

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4

Occupational Determinants of Heart Rate Variability*

L.G.P.M. van Amelsvoort[a], E.G. Schouten[a], A.C. Maan[b], C.A. Swenne[c], F.J. Kok[a]

Abstract

Objectives: Analysis of heart rate variability (HRV) has been suggested as a way to study effects of work related stresses on the cardiovascular autonomic regulation. The aim of this study was to evaluate the use of HRV in the investigation of work related stressors. ***Methods:*** Cross-sectional data from an ongoing cohort study were used to analyse the relation of the potential workplace stressors job strain, noise and shift work with HRV. Mean HRV values during sleep and work were calculated in 135 twenty-four-hour ECG recordings. ***Results:*** Shift workers displayed significantly decreased SDNNi (mean standard deviation of all 5 minute intervals) levels during sleep, compared with the day workers (adjusted least square mean values: 69.3 and 85.8 msec, respectively: $p < 0.05$). Compared with the control group reporting low demands and high control (mean: 73,2) significantly elevated %LF means (normalised low frequency power variability) during work adjusted for sleep in the low demands, low control group (77.9, $P < 0.01$), high demands, high control group (77.7, $p < 0.05$) and high demands, low control group (77.7, $p < 0.05$). Workers reporting a high noise level compared with a low work noise level also displayed an elevated adjusted mean %LF during work (78.0 and 75.3 respectively, $p < 0.06$). ***Conclusions:*** The finding of a decreased SDNNi level during sleep in shift workers compared with day workers indicates a less favourable cardiovascular autonomic regulation which may explain part of excess cardiovascular disease risk in shift workers. The elevated %LF during work in employees exposed to high job strain or high noise levels indicates a direct shift of the autonomic cardiac balance towards sympathetic dominance. We concluded that the analysis of HRV may provide an useful tool in the study of physiological effects of work related stresses.

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[a]Division of Human Nutrition and Epidemiology, Wageningen University,
[b]Foundation for ECG analysis, University Hospital, Leiden
[c]Department of Cardiology, University Hospital, Leiden

Introduction

Heart rate variability has become the accepted term to denote variations of both instantaneous heart rate and RR interval[27]. Since the publication of studies establishing heart rate variability as a strong and independent predictor of mortality after acute myocardial infarction[104-107], analysis of heart rate variability has frequently been used in a clinical setting [1]. However, outside the clinical setting, assessment of heart rate variability can be used as a non-invasive tool for predicting cardiovascular morbidity and mortality in healthy subjects[40-43]. Tsuji reported a hazard ratio of 1.47 for new cardiac events (95% confidence interval of 1.16 to 1.86) for a one-standard deviation decrement in a popular heart rate variability measure (SDNNi, the standard deviation of all RR-intervals within a certain period)[41].

Fluctuations in cardiac sympathetic and parasympathetic outflow cause significant part of the beat-to-beat fluctuations in heart rate. Analysis of heart rate variability could therefore be used as a tool to assess cardiac autonomic control. Variations in heart rate can be evaluated in time and frequency domain. Spectral analysis in the frequency domain enables a crude separation between vagal and sympathetic cardiac control. Fluctuating efferent vagal activity is the major contributor to high frequency (HF) HRV power[29; 30]. There is still some disagreement about the low frequency (LF) HRV component. Some authors consider it as a marker of sympathetic modulations[30; 31]; others adhere the view that it reflects fluctuations in both sympathetic and vagal activity[32; 33].

During the past decade, HRV analysis has been proposed as a non-invasive technique for the assessment of job related cardiovascular stressors[28]. Up till now, only a very limited number of studies in which the relationship between working conditions and HRV is described. Work by Pagani *et al.*[108] demonstrated a relationship between exposure to a psychological stressor (computer-controlled mental task, or stressful interview) and the LF component of HRV. So far no studies using more general scoring of overall workplace stressors were found. In this investigation we used the cross-sectional data of an ongoing cohort study designed to examine the effects of shift work on the cardiovascular risk profile. The influence of the workplace stressors noise, job strain, physical activity, and shift work on heart rate and heart rate variability (HRV) was investigated. We calculated 24-hour mean heart rate and HRV values, and mean values during sleep and work, from all 5-minute heart rate and HRV in the 24-hour recording. Means during sleep and work were analysed to differentiate between more acute and longer term effects. Mean values during work, corrected for values during sleep, were used as estimates of the direct effects of the indicated amount of workplace related stressors on heart rate and heart rate variability.

Methods

Population

All subjects participate in an ongoing cohort study of 396 shift workers and daytime controls and two of its pilot studies of similar design. The participants work in the integrated circuit manufacturing industry, waste incinerator plants, or in hospitals. Main objective of the cohort study was to determine the influence of working in shifts for one year on cardiovascular risk factors. The ethical committee of the Wageningen University approved the study, that implied that all respondents gave a written informed consent before being included. Inclusion criteria were:

- Starting in a new job.
- Working at least 32 hours a week
- Expecting to work next year in the same job
- No using medication or previous hospitalisation for cardiovascular disease.
- No insurmountable objections to shift work (see Measurements)
- Age between 18 and 55 years.

This study regards the 107 members of the cohort and 48 of two pilot studies who had an initial 24h Holter recording covering a standard daytime working day. Of these recordings, 20 could not be used for this study (incomplete recordings due to non-compliance, skin irritation, technical failure, unexpected changes in the work schedule; two persons had an excessive amount of premature beats. This left us with 135 complete and analysable recordings.

Data collection

Measurements were performed between one week and two months after the start of a new job.

24 hour Holter recordings

The participants were submitted to a 24-hour Holter recording starting at the beginning of a morning shift (for the shift workers) or day shift (for the day workers). A trained research nurse prepared the Holter recorder. All subjects were instructed to note down start and end time of sleep, work, meals, leisure, physical activities and other possibly relevant events or activities. These diaries were later coded into a choice out of a list of standard activities. Sleep was defined as 1 hour after going to sleep until 1 hour before getting up, as recorded in the diary.

Personal and work characteristics

All participants received a questionnaire and were asked to complete and return by mail. Unclear or missing answers were verified by telephone. Most questions were close-ended and came from standardised questionnaires.

Personal characteristics: In the questionnaire, educational level was coded in seven levels: from primary to university education. In the final analysis these levels were reduced to categories lower, intermediate and higher education. Physical activity indexes for work, sport and leisure time were assessed as described by Baecke, *et al.*[85]. Leisure time physical activity and sports scores were combined into an overall leisure time physical activity score. Though current (type, quantity) and past (type, years, and quantity) smoking habits were asked, in the final analysis only the smoking status (non-smoker, current smoker, or ex-smoker) was used.

Current job title and job history: The questionnaire asked for the current job, including company, department, and shift work schedule. If in doubt concerning the shift work schedule status on the employment form, we verified the data with the occupational health service or the human resources department of the employing firm. All jobs were coded for social status and job content. A total of nine different job titles were coded. In this study we defined shift work as working in an alternating work schedule including nights. Shift schedules were coded as forward rotating (nights-afternoons-mornings, advancing schedule) or backward rotating (mornings-afternoon-nights, delaying schedule). We coded rotation as fast when at most three consecutive night shifts were worked. At most five consecutive night shifts on a row were coded as medium rotation. Irregular shift schedules, often made each month after consultation with all workers involved were coded as "irregular". Information on all previous jobs including job title, employer, starting and ending date and shift work status was asked.

Workplace noise: Workplace noise was assessed using a question developed by Ising[109]:

Please indicate the level of noise, which matches best with the noise level at your workplace: 1) refrigerator; 2) typewriter; 3) electric lawnmower; 4) electric drill; 5) road drill.

Because of small numbers, especially in the higher categories, we collapsed the two lowest workplace noise categories (both estimated as 55 dB(A)) and the highest three noise level categories (estimated as 75, 90 and 100 dB(A)) to a low and high noise level category.

Job strain: The amount of job strain was assessed using the Dutch version of the "job demands, decision latitude and social support" questionnaire[86]. The mean of the highest and lowest scores was selected as the cut-off point between high and low job strain.

HRV Assessment

The 24-hour Holter recordings were analysed with a Marquette Series 8000 Holter Analyser by an experienced Holter analyst. The onset-Q instants of all beats were determined with the CCTOC Marquette Holter research software module. The resulting inter-beat interval series were down-loaded from the Holter analyser, and further analysed on a personal computer as described by Janssen *et al.*[88].

The complete recording was split into 5-minute segments. Only segments with 5% or less missing values (due to a noisy ECG) were used. Heart rate and HRV parameters were computed for each segment. The 24-hour values and the mean values during sleep and work were obtained by averaging.

For the normal beats the standard deviation (SDNNi) was calculated as standard deviation during a five-minute reference period, with the exclusion of all segments with more than 5% missing values.

We adopted the mean HRV values during sleep as individual reference values, because they are the least influenced by day to day differences in work and leisure time activities[110]. 24-hour mean values are included to differentiate between changes in overall mean levels or changes in mean value during sleep compensated during an other time of the day.

The algorithm used for spectral analysis has been described elsewhere[89]. Briefly, intervals were normalised to the duration of the mean interval. Then, linear trend removal, and 10% left and right tapering was done. After padding the data with zeros to the nearest power of two, the power density spectrum was computed by means of a Fast Fourier algorithm. We computed the spectral powers within two frequency bands: low frequency power, LF (0.05-0.15 Hz; a marker of fluctuations in either sympathetic or sympathetic plus vagal activity) and high frequency power, HF (0.15-0.40 Hz;, a marker of vagal activity[30]The spectral components were calculated both as absolute units and as normalised units (the latter by dividing LF and HF by their sum, and multiplying this by 100).

Data analysis

Because of the skewed within and between subject distribution of the high and low frequency spectral HRV components, we log-transformated these parameters before any averaging. Standard methods were used for descriptive analysis and linear regression. Least square mean values, calculated with SAS proc GLM, are shown to enable comparison of mean values between subgroups, adjusted for covariates. Least square means are the value of class or subclass means that are expected for a balanced design involving the class variable with all covariates at their mean value[101]. Differences between categories and significance levels are identical to the differences and p-values from analysis of covariance. Visual inspection of the residual values of the regression models was performed to affirm the linear model was appropriate.

Results

Our study group consists of 113 male and 22 female subjects with a mean age of 30.8 year (SD: 7.5). Table 4.1 summarises the main work related population characteristics, smoking habits and educational level.

In Table 4.2 the least square mean values and regression coefficients for heart rate and heart rate variability during sleep are presented, together with the least square mean values for potential confounders (gender, age, smoking status, leisure time physical activity). Very few of the occupational factors did show a relationship with heart rate or heart rate variability during sleep. Only for SDNNi decreased values were found shift workers (-19 %, p = 0.04) and for the high demands, high control group (-17 % compared with the low demands, high control group, p = 0.05).

Tabel 4.1. *Population characteristics.*

N	135
Age (years)	30.8 (7.5)
Leisure time physical activity (score)	5.45 (1.37)
Work time physical activity (score)	2.75 (0.54)
Smoking	
Never	41.7 %
Ex	22.0 %
Current	36.4 %
Educational level	
Lower	26.2 %
Intermediate	46.9 %
Higher	26.9 %
Work schedule	
Daytime only	23.7 %
Working in shifts	76.3 %
According to shift schedule:	
Fast forward	17.8 %
Fast backward	8.9 %
Medium backward	41.5 %
Irregular	8.1 %
Job strain categories	
Low demands, high control	39.3 %
Low demands, low control	28.9 %
High demands, high control	17.8 %
High demands, low control	14.1 %
Occupational noise level	
Low (Refrigerator/typewriter)	53 %
High (Lawnmower/Elec. Drill)	47 %

Mean (standard deviation between brackets) or percentage.

The adjusted least square mean values and regression coefficients of heart rate and heart rate variability during work are given in table 4.3. Compared with regression equations for the mean values during sleep, the relations for smoking and gender are similar. Significant differences were found for shift workers compared with day workers in heart rate (+ 6 %; p = 0.02), SDNNi (-15 %; P = 0.03) and %LF (+ 7 %; P = 0.03). Also a significantly elevated heart rate was found for the high demands, low control group (+ 6 %; P = 0.05) and increased levels of %LF for the low demands, low control (+ 6 %; P = 0.02) and high demands, high control group (+ 7 %; P = 0.01), all compared with the low demands, high control group.

Table 4.2. *Least square mean values and regression coefficients of mean heart rate variability parameters during sleep.*

	Heart rate beats/min	SDNNi millisec.	%LF	Log(LF) $\log(10^{3}sec^{2})$	Log (HF) $\log(10^{3}sec^{2})$
Gender					
female#	68.2 (1.8)	64.1 (6.4)	54.1(3.2)	-3095(62)	-3186 (90)
male	58.2 (1.0)***	91.0(3.6)***	52.2(1.8)	-2918(35)*	-2961(50)*
Smoking					
never-smoking#	60.4 (1.4)	91.2 (5.1)	53.1 (2.5)	-2889 (49)	-2959 (71)
ex-smoker	64.0 (1.6)*	77.4 (5.7)*	57.0 (2.8)	-2956 (55)	-3097 (80)
current smoking	65.3 (1.4)**	64.0 (5.2)***	49.3 (2.6)	-3174 (50)***	-3164 (73)*
Job strain categories					
Low demands, high control#	62.4 (1.4)	83.0 (5.2)	52.6 (2.6)	-2991 (51)	-3046 (73)
Low demands, low control	63.5 (1.6)	76.5 (6.0)	54.1 (3.0)	-3001 (58)	-3089 (84)
High demands, high control	65.4 (1.7)	68.7 (6.3)*	56.5 (3.1)	-3032 (61)	-3162 (88)
High demands, low control	61.6 (1.9)	82.0 (7.1)	49.5 (3.5)	-3000 (68)	-2997 (99)
Work schedule					
day shifts only#	62.7 (1.8)	85.8 (6.7)	51.9 (3.3)	-2959 (64)	-3002 (93)
working in rotating shifts	63.8 (1.1)	69.3 (4.0)*	54.4 (2.0)	-3053 (39)	-3145 (56)
Work place noise					
low level noise#	64.1 (1.2)	80.8 (4.2)	52.9 (2.1)	-2959 (41)	-3022 (59)
high level noise	62.4 (1.4)	74.3(5.2)	53.4 (2.6)	-3053 (50)	-3125 (73)
age (per 10 years)+	1.91 (0.95)*	-9.9 (3.5)**	8.2 (1.7)	-26 (34)	-203 (49)***
leisure time physical activity (per 1 SD increase)+	-1.24(0.67)	2.2 (2.5)	-0.4 (1.2)	-26 (24)	-19 (34)
physical activity during work (per 1 SD increase)	0.5 (0.9)	5.8 (3.3)	- 0.8 (1.6)	31(32)	48 (46)

Multiple linear regression analysis results. Class variables presented as least square mean values adjusted for the other factors in the table. Standard error of estimated between brackets.

%LF *normalised low frequency power variability*

SDNNi *mean standard deviation of all 5-minute intervals*

Log(HF) *Power in the High frequency range (0.15-0.40 Hz.). In logarithmised units.*

Log(LF) *Power in the Low frequency range (0.05-015 Hz.) In logarithmised units.*

\# *Reference category for P-values of categorical variables.* **P < 0.05;* ** *P < 0.01;* *** *P < 0.001*

The least square means and regression coefficients during work, adjusted for age, gender, smoking status, leisure time physical activity and for mean values during sleep are given in table 4.4. As expected due to a decrease of the between person variation lower standard errors of the estimates can be observed. The relationships between gender, and smoking with heart rate and heart rate variability which were present in the regression equation without adjustment for mean values during sleep disappeared. Elevated heart rate levels were present in the high demands, low control group (+ 7 %; P = 0.01). %LF was elevated for the low demands low control group (+ 6%; P = 0.005), the high demands, high control group (+ 6 %; P=0.01) and the high demands, low control group (+ 6 %; P = 0.03). The high workplace noise group displayed an elevated %LF (+ 4 %; P = 0.06) and increased LOG(LF) (+3 %; P=0.02). For the shift workers only the mean heart rate was elevated compared with the day workers. A significant negative correlation was found between physical activity during work and SDNNi and LOG(LF).

Table 4.3. *Least square mean values and regression coefficients of mean heart rate variability parameters during work.*

	Heart rate beats/min	**SDNNi** millisec.	**%LF**	**Log(LF)** $\log(10^{3}sec^{2})$	**Log (HF)** $\log(10^{3}sec^{2})$
Job strain categories					
Low demands, high control#	84.3 (1.6)	72.0(3.6)	73.3(1.5)	- 2668(37)	- 3159(57)
Low demands, low control	85.2 (1.8)	70.0(4.0)	77.8(1.7)*	- 2647(41)	- 3243(63)
High demands, high control	86.5(1.9)	64.3(4.2)	78.6(1.8)*	- 2665(44)	- 3267(67)
High demands, low control	89.2(2.1)*	73.0(4.7)	76.0(2.0)	- 2579(49)	- 3113(74)
Work schedule					
day shifts only#	83.6(2.0)	75.5(4.3)	74.0 (1.8)	- 2623(45)	- 3121(69)
working in rotating shifts	89.0(1.2)*	64.2(2.7)*	78.9 (2.0)*	- 2657(28)	- 3270 (43)
Work place noise					
low level noise#	86.9(1.3)	68.1(2.9)	75.4(1.2)	- 2665(30)	- 3194 (46)
high level noise	85.6(1.6)	71.6 (3.4)	77.5(1.5)	- 2614(36)	- 3196 (55)
physical activity during work (per 1 SD increase)	2.57 (1.0)	- 3.5 (2.2)	- 0.3 (0.9)	- 26 (23)	- 15 (35)

Multiple linear regression analysis results, adjusted for gender, age, smoking status and leisure time physical activity. Class variables presented as least square mean values. Standard error of estimated between brackets.
%LF normalised low frequency power variability
SDNNi mean standard deviation of all 5-minute intervals
Log(HF) Power in the High frequency range (0.15-0.40 Hz.). In logarithmised units.
Log(LF) Power in the Low frequency range (0.05-015 Hz.) In logarithmised units.
*# Reference category for P-values of categorical variables. * $P < 0.05$; ** $P < 0.01$*

No relationship was found between heart rate or heart rate variability and social support or education during sleep, work or 24- hour means, nor did the inclusion of these factors in the regression model lead to an appreciable change of any of the other coefficients.

Table 4.4. *Least square mean values and regression coefficients of mean heart rate variability parameters during work corrected for mean values during sleep.*

	Heart rate beats/min	SDNNi millisec.	%LF	Log(LF) log(10⁻³sec²)	Log (HF) log(10⁻³sec²)
Job strain categories					
Low demands, high control#	82.6 (1.4)	72.7 (3.1)	73.2 (1.3)	- 2657 (32)	- 3143 (43)
Low demands, low control	83.3 (1.6)	71.7 (3.6)	77.9 (1.5)**	- 2635 (37)	- 3224 (50)
High demands, high control	83.1 (1.8)	68.9 (3.8)	77.7 (1.6)*	- 2658 (38)	- 3224 (53)
High demands, low control	88.1 (1.9)*	72.5 (4.2)	77.7 (1.7)*	- 2562 (43)	- 3134 (59)
Work schedule					
Day shifts only#	82.0 (1.8)	72.9 (4.0)	75.1 (1.6)	- 2629 (41)	- 3155 (55)
Working in rotating shifts	86.6 (1.1)*	69.9 (2.5)	78.1 (1.0)	- 2627 (25)	- 3208 (34)
Work place noise					
Low level noise#	84.5 (1.2)	69.2 (2.5)	75.3 (1.0)	- 2669 (26)	- 3195 (35)
High level noise	84.1 (1.4)	73.6 (3.1)	78.0 (1.3)	- 2587 (32)*	- 3167 (44)
Physical activity during work (per 1 SD increase)	2.11 (0.89)*	- 6.2 (2.0)**	0.15 (0.81)	- 43 (20)*	- 50 (28)

Multiple linear regression analysis results, adjusted for gender, age, smoking status and leisure time physical activity. Class variables presented as least square mean values. Standard error of estimated between brackets.
%LF normalised low frequency power variability
SDNNi mean standard deviation of all 5-minute intervals
Log(HF) Power in the High frequency range (0.15-0.40 Hz.). In logarithmised units.
Log(LF) Power in the Low frequency range (0.05-015 Hz.) In logarithmised units.
 # Reference category for P-values of categorical variables. $^{*}P < 0.05$; $^{**}P < 0.01$

Discussion

In summary, in this study indications have been found for a decreased heart rate variability during sleep for people working in shifts but not for any of the other recorded workplace stressors. For the mean heart rate variability values during work, corrected for mean values during sleep, the results indicated a relation of specific indicators of heart rate variability with workplace noise, job strain and physical activity at work but not with shift work.

Error in the measurement of heart rate variability is expected to be small and non differential. The presented means were calculate from a recording over several hours. Since the data were based on average mean values over several hour recordings, the influence of a outlying 5-minute interval was small. Besides, the ECG's were coded by an experienced Holter analyst who was unaware of the condition of the respondent.

From other studies the within person day to day variation of heart rate variability measurements were low (intra-class correlation of SDNNi between two recordings between 18 and 65 day apart: 0.9)[111]. Error could arise if the Holter recorder had induced changes of behaviour in the respondents during the measurements, for example, a decline in physical activity because the respondents were not allowed to take a shower during the measurements or poorer sleep quality due to the annoyance of carrying the Holter recorder. Error in sleep time as coded in the diary could lead to bias of the mean values during sleep. The exclusion of data within a one hour time window from the coded start to end of sleep for the calculation of the mean values during sleep bias due to imprecision of the coded sleep time was not very likely.

Quantification of the amount of noise, job strain and physical activity at work was done by questionnaire. Systematic differences in reporting between different occupational groups could be present. We assume that this bias is most likely to have caused a reduction of the reported correlations, although we can not completely rule the possibility of inflation of the reported effects. Another source of bias could have been the selection of workers most fit for particular jobs, or selective drop out of workers not able to adapt to their working conditions. This selection of workers, often referred to as the healthy worker effect, could have reduced or eliminated possible adverse health effects of job related unhealthy work conditions.

We considered gender, age, smoking and leisure time physical activity to be confounding factors in this study. Inclusion in the regression model of other possible confounders was considered: educational level and social support, did not change the reported relationships.

Obviously heart rate and the level of heart rate variability are the result of interaction between the neurocardiac regulatory system and external and internal stimuli. The Calculation of mean heart rate and heart rate variability values during sleep was done to minimise bias due to differences between individuals in their response to external stimuli. Nevertheless, differences in sleep quality or lag effects of activities before sleep (alcohol consumption, smoking, strenuous physical activity) could have biased the sleep time mean values. Adjustment of the HRV values during work for the mean levels during sleep was performed to remove between person variation in baseline HRV levels. This should enable a less biased estimate of the direct effect of the occupational circumstances on HRV.

In the next section the different occupational factors reported in this paper will be considered in correlation with heart rate variability. In all sections we will first deal with the mean heart rate variability levels during sleep. Next the results regarding the mean values during work, adjusted for the mean values during sleep will be discussed.

Workplace noise

Ising *et al.*[109] reported a significantly elevated risk of myocardial infarction with increasing workplace noise category (electric lawnmower: RR 1.4; electric drill: RR 2.0; road drill: RR 3.8). A possible pathway of this increased risk could be via increased sympathetic stimulation due to the exposure to high levels of workplace noise. One might hypothesise that this might lead to a less favourable cardiac regulation after chronic exposure to workplace noise. In this study no changes on heart rate, or heart rate variability during sleep are found. Because of the relative short time between the measurements and the start of a new employment (between one week and two months) it is not clear from the current study if the absence of an effect is due to a lack of power in the study, a relative short exposure time, or the absence of a long-term effect of exposure to high workplace noise levels. When looking at the acute effects of workplace noise on heart rate variability, taking the sleep time mean corrected values during work, we found increased %LF and LOG(LF) in the high noise group. This might indicate that exposure to high levels of workplace noise causes a shift of the cardiovascular regulation toward sympathetic dominance.

Shift work

There is strong evidence of an elevated cardiovascular disease risk among shift workers[13; 15; 17; 74; 75]. Changes in the neural cardiovascular control could be in the causal pathway of this elevated cardiovascular risk. In this study only workers who started a new job within the last 2 months were included. Among the shift workers a significantly decreased SDNNi during sleep as well as during work time was found, compared with day workers. One might hypothesise that this was caused by a disturbance of the circadian rhythm of the cardiac neural regulation for example by increased sympathetic activity on a time the cardiovascular system anticipated rest. Another explanation could be a poorer sleep quality for shift workers compared with the day workers. There is some evidence of decreased heart rate variability in individuals with sleep problems[39].

However, due to the cross-sectional design, we cannot rule out that the reported results were caused by selection effects of the respondents or might be due to adaptation to irregular working hours. The analysis of the HRV levels during sleep, adjusted for the mean values during sleep did not show significant differences between the shift workers and day workers. This might indicate a similar level of job stress in the shift work and daytime jobs, when adjusted for the other workplace related stressors included in this study.

Job strain

The evidence available so far is equivocal regarding the presence of an elevated cardiovascular disease risk in high strain jobs (high job demands in combination with low work control)[112]. No studies regarding long term effects of working in a high strain job on heart rate variability were found. Analysing the mean heart rate variability levels during sleep, we found a decreased SDNNi for the high demands high control compared with the low demands high control group. This could indicate a less favourable cardiac regulation for the high demands high control group. However, because of the cross-sectional design of this study, it can not be ruled out that this effect was caused by self-selection of the workers enrolled in this group. Those who favour high strain jobs might react different to workplace stressors from workers favouring low strain jobs. However it could also be a reflection of a true effect of working in a high demands, high control job towards a less favourable cardiac control. One might hypothesise that workers in the high demands, high control group frequently found in managerial positions, could be more often occupied with their work outside the normal working hours. This might have led to a shift in the cardiovascular regulation toward more sympathetic dominance during sleep, possibly due to a poorer sleep quality. Because all workers started a new job within the previous 2 months, the reported effect might also be due to a more difficult adaptation to a new job with high, high control, an effect with might subside after several months.

When looking at the effects of job strain on heart rate variability during work, corrected for mean values during sleep, we observed decreased values of %LF for the low demands, high control group compared with the other groups. Thus indicating a shift in cardiovascular regulation toward more sympathetic dominance for the other groups. Due to the correction of the means at work for individual mean values during sleep, the probability of bias due selection of respondents is low, because most of the between person variation is removed. Therefore, the regression coefficients for the mean values during work are likely to reflect a rapid change due to the conditions during work suggestive of a direct relation between job strain and the neural cardiac regulation. In the literature only a few studies were found dealing with stress and heart rate variability. Of the investigations published so far which reported on the influences of short-term stressful situations, Sloan *et al.*[34], reported an elevated heart rate and decreased very low frequency, low frequency and high frequency power during exposure to mental stress. In this study no influence was found on the LF /HF ratio. Myrtek *et al.*[35] reported lower SDNNi during increased metal load but did not differentiate between low and high frequency power components. In contrast. Our data showed an increased level of %LF during work, and not on SDNNi, for workers reporting high job strain. Whether this was due to the different nature of the investigated stressors, the different time frame of exposure, or just a chance finding warrants further study. Further research is needed to investigate the contribution of specific frequency components although our data indicate an increase of the LF/HF ratio, which suggested a shift of the cardiovascular regulation towards sympathetic dominance. One might hypothesise that exposure to workplace conditions related with a sympathetic dominance in the cardiovascular regulation might lead adverse effects comparable to the effects caused by exposure to stress, as increased frequency of cardiac arrhythmias (Stamler *et al.* 1992; Sgoifo *et al.* 1997).

Physical activity at work

No relation was found between physical activity at work and heart rate and heart rate variability during sleep. No other studies were found reporting the relationship between physical activity at work and heart rate variability. This is in contrast with the study of Mølgaard, Sørensen, *et al.*[113] which reported a positive correlation between the level of leisure time physical activity and SDNNi, primarily due to increases in the high frequency power component. The relative short interval (from 1 week to 2 months) between the start of the current job and the measurements, or a rather low contrast between the high and low physical active jobs, could be possible explain the lack of a significant effect.

For the mean values during work, adjusted for the mean values during sleep an inverse relationship was observed between SDNNi and Log (LF) and physical activity during work. The assume that the increased heart rate during physical activity was the most probable cause of these correlations. This was confirmed by including the mean heart rate during work in the regression model. The reported regression coefficients decreased from -6.2 to -2.4 ($p = 0.12$) for SDNNi and from -0.043 to -0.33 ($p = 0.10$) when mean heart rate during work was included.

Conclusion

Despite the one week and two months time between the start of the current job and the measurements, we found significant lower heart rate variability levels in the shift workers compared with the day workers and for the high demands, high control group. These differences could be caused by the differences in the occupational factors themselves, but due to the cross sectional design of the study we can not rule out that the effect is caused by selection of the workers in the different groups. Nevertheless, the decreased SDNNi level in shift workers may be related to a less favourable cardiovascular regulation and could possibly explain a part of the increased cardiovascular morbidity and mortality among shift workers. Further study is needed to investigate long-term effects of chronic exposure to working conditions with less favourable effects on the cardiovascular regulation.

The %LF present in the variability of the heart rate, measured as mean values during work, corrected for the mean values during sleep shows a relationship with the work related stressors job strain and workplace noise. Therefore we conclude that analysis of heart rate variability can be used for measuring the effect of work related stressors. One might hypothesise that the chronic disturbance of the autonomic cardiac balance towards sympathetic dominance might be a factor contributing to an elevated cardiovascular disease risk due to exposure to workplace stressors. However, further research is needed to investigate the health effects of a long-term shift of the cardiovascular neural regulation towards sympathetic dominance.

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5

Impact of one year of shift work on cardiovascular disease risk factors*

L.G.P.M. van Amelsvoort, E.G. Schouten, F.J. Kok

Abstract

Objective: The purpose of the study was to investigate whether the reported increased cardiovascular disease risk in shift workers could be explained by unfavourable changes in risk factor levels. ***Methods:*** Cohorts of 227 shift workers and 150 day workers were recruited who started not longer than 2 months ago in their current jobs. At baseline and after one year, biological (Body Mass Index, Waist to Hip ratio, LDL, HDL cholesterol, blood pressure) and lifestyle (smoking, physical activity and energy, alcohol and fat intake) cardiovascular risk factors were measured. Changes in CVD risk factors in shift workers and day workers were compared. ***Findings:*** The number of cigarettes smoked per day increased significantly in shift workers compared with day workers (+ 12.1% and – 9.6% respectively, $p < 0.05$). Both body mass index (BMI) and LDL/HDL cholesterol ratio decreased significantly in shift workers compared with day workers (average change in BMI: -0.31 kg/m^2 and +0.13 kg/m^2 respectively, $p < 0.01$; change in LDL/HDL ratio: -0.33 and -0.13 respectively $p < 0.01$). No differences were found between the shift- and day workers for changes in the other major biological and lifestyle cardiovascular risk factors. ***Conclusion:*** Only for smoking the observed change was unfavourable. This may explain only a part of the excess CVD risk reported in shift workers.

*Submitted for publication

Introduction

Evidence available so far, seems to indicate an elevated cardiovascular disease risk in shift workers. In a recent review Bøggild and Knutsson[11] presented a relative risk of 1.4 as the most reasonable risk estimate. Because of the diversity in the 17 studies a proper meta-analysis on cardiovascular disease endpoints was not possible. Whereas most studies so far have been conducted in males, the four studies addressing females suggest that shift-working women have a relative risk similar to men. Several explanations for the elevated risk have been proposed including disturbance of physiological rhythms, changes in behaviour, and disturbed sociotemporal activities[18]. Up till now, information favouring the involvement of one or more of these mechanisms is not available. Monitoring changes in cardiovascular disease risk factors in shift workers could provide evidence confirming or refuting possible explanations for the elevated cardiovascular disease risk. This information might contribute to effective strategies for cardiovascular disease prevention in shift workers.

Most studies that addressed cardiovascular disease risk factors in shift workers have been cross sectional, with the potential for bias[11]. So far, only two longitudinal studies were performed. The study of Knutsson *et al.*[63] did not show significant different changes in cardiovascular disease risk factors between the 12 shift workers and 13 day workers, during a six month period. This might be a consequence of the relatively small sample size. The study of Morikawa *et al.*[44] displayed an increased 5 year hypertension risk in younger shift workers but not for the older shift workers. No other cardiovascular risk factors were included in this study. To summarise, involvement of unfavourable changes in one or more risk factors in the elevated cardiovascular disease risk in shift workers can be excluded nor confirmed.

We conducted a one-year cohort study among 227 shift workers and 150 controls working in daytime. The aim of this cohort study was to compare changes in cardiovascular risk factors over a one-year period between shift workers and daytime controls to identify factors that might explain the elevated cardiovascular disease risk among shift workers. To avoid selection bias, much effort was put in keeping track of dropouts and participants who changed jobs.

Subjects and methods

Study population

Potential participants were approached during an 18 month period using three strategies in order to have different shift work schedules represented in the study: (1) persons undergoing a pre-employment medical examination in two occupational health services; (2) workers employed in a newly built waste incinerator plant; and (3) nurses, starting with their practical in hospital training.

The following inclusion criteria were used:

- Starting in a new job.
- Working at least 32 hours a week.
- Expecting to work next year in the same job
- Not using medication or previous hospitalisation for a cardiovascular disease.
- No insurmountable objections to shift work (see measurements)
- Aged between 18 and 55 years.

A total of 707 people were approached for participation in the study, 98 were not eligible (13.8 %), 213 refused to participate (35%). Nineteen subjects were excluded for missing data during the baseline measurement. Leaving 377 persons for inclusion in the study. The major determinant of the non-response rate was the time involved in travelling to the research location. For the respondents who were measured close to their workplace (n=518) the response rate was 75 % whereas the response rate for workers who had to travel to participate in the study (n=91) was 8 %. The estimated response rates for shift workers and day workers were 65 and 63% respectively. In table 5.1 the status of all respondents during the second measurement is given.

The ethical committee of Wageningen University approved the study.

Data collection

Measurements were performed between one week and two months after the start of a new job or change in shift work schedule and were repeated after one year.

All participants received a questionnaire and were asked to return it by mail after completion. Unclear or missing answers where verified by telephone. Most questions were closed-ended and came from standardised questionnaires.

Table 5.1. *Number of subjects during follow up.*

	Baseline work schedule	
Status	Day work	Shift work
Included		
Remained in same job	105	159
Changed work schedule	32	34
Unemployed	2	4
Sick leave (W.A.O.)	1	5
Excluded		
Missing data	6	13
Became pregnant during follow up	0	3
Lost to follow up		
Discharged & refused further co-operation	9	20
Refused second measurement	1	2

W.A.O.: receiving a benefit according to the Dutch disablement insurance act.

Current job title and job history. We asked for the current job, including company, department, and shift work schedule. According to social status and job content all jobs were coded. In total nine different job titles were used. In this study we defined shift work as working in an alternating work schedule including nights. Information on all previous jobs including job title, employer, starting and ending date and shift work status was collected.

Objections to shift work. In order to improve comparability between shift workers and day workers only day workers with no insurmountable objections to working in shifts were included. The following question was used to assess this: "Would you keep working in your current job if the department would switch to shift work jobs? (1) Yes, without any objections; (2) Yes, but only if there is a financial reward; (3) Only if there are no other jobs available; (4) On no account". We excluded people who gave answer (4) to this question.

Personal characteristics. In the questionnaire educational level was divided in seven categories from elementary school to university education. In the final analysis these were categorised in junior education, senior education and higher education. The physical activity indexes for work, sport and leisure time were assessed as described by Baecke, Burema and Frijters[85]. The ranges of the indexes were 1.1 - 4.3, 1.0 - 5.2 and 1.3 - 4.5 respectively. Current (type, quantity) and past smoking habits (type, years, and quantity) were asked.

Anthropometric measurements. Measurements were carried out between one week and two months after the beginning of a new job. Only subjects without missing data were included in the data-analysis. Weight, height and waist and hip circumferences were measured in a standing position. The waist circumference was measured at the level of the umbilicus, and the hip circumference at the widest part over the buttocks. Body Mass Index (BMI): weight/height^2 (kg/m^2) and the waist-to-hip ratio (WHR): ratio between the waist and hip circumferences were calculated.

Plasma cholesterol measurements. Serum of non-fasting blood samples was obtained by centrifugation and stored at -80 °C. The sera were analysed enzymatically for high-density (HDL) and total cholesterol[114]. LDL cholesterol was calculated using the Friedewald formula.

Dietary assessment. A self-administered food frequency questionnaire that measured the intake of energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol was filled out by the respondents[87].

Blood pressure. Blood pressure measurements were performed using a tensoplus OSZ2 oscillometric sphygmomanometer. A trained technician read the blood pressure with a stethoscope placed on the brachial artery. All measurements were performed in triplo, all at least five minutes apart. An average of the three readings was used in the data analysis.

Data analysis

Data are presented as mean values or level of change between the first and second measurement. The Student t-test and Chi-square statistics were used for testing differences. Regression analysis was used to evaluate possible confounding factors. All analyses were performed using the Statistical Analysis System (SAS)[90].

Results

In table 5.2 the mean baseline values are presented. At baseline the shift workers had a slightly higher age and a significantly less favourable cardiovascular risk profile (smoking habits, BMI, WTHR and LDL/HDL ratio).

Table 5.2. *Baseline characteristics according to work schedule*

		Day workers	Shift workers	p value difference shift - day
Background and job related factors				
N		150	227	
Gender (% male)		41.0	55.4	0.005$
Age (years)		24.1	26.8	0.0001
Education	lower (%)	16.6	38.9	0.001$
	Intermediate (%)	54.9	52.3	
	Higher (%)	28.5	8.8	
Work time physical activity index		3.00	3.12	0.11
Demands		2.30	2.14	0.0003
Control		1.80	1.57	0.0001
Support		1.82	1.77	0.23
Diet				
Energy intake (kJ /day)		11,540	12,170	0.16
Energy from fat (% of total energy intake)		38.1	40.3	0.002
Alcohol intake (gram/day)		6.1	8.5	0.05
Cholesterol intake (mg/day)		281	306	0.09
Anthropometry				
Weight (kg)		71.5	73.8	0.09
BMI (kg/m^2)		23.1	24.0	0.006
Waist to hip ratio		0.836	0.863	0.0002
Diastolic blood pressure (mmHg)		76.5	76.4	0.9
Systolic blood pressure (mmHg)		127.7	126.1	0.3
Blood lipids				
Total serum cholesterol (mmol/l)		4.85	4.87	0.8
HDL cholesterol (mmol/l)		1.34	1.30	0.3
LDL cholesterol (mmol/l)		2.86	2.95	0.3
LDL/HDL ratio		2.28	2.44	0.2
Lifestyle				
Smoking	Never (%)	68.2	51.6	0.006$
	Former (%)	9.3	12.9	
	Current (%)	22.5	35.5	
Cigarettes smoked per day (in current smokers)		10.7	11.7	0.4
Physical activity during sport (score)		2.66	2.61	0.6
Leisure time physical activity (outside sport, score)		2.78	2.68	0.15

Difference between day workers and shift workers :

$ chi-square test, p value for all categories together.

n.a not applicable

In table 5.3 the changes in cardiovascular risk factors from baseline to one year follow up are presented. During follow up, the percentage of smokers and the number of cigarettes smoked per day (in smoker only) in shift workers increased significantly, compared with day workers. In shift workers Body mass index (BMI) and waist to hip ratio (WHR) decreased significantly compared with baseline. Only for body mass index this change was significantly different in the controls working in daytime. No different change was found between the shift- and day workers in diastolic and systolic blood pressure. Comparing the one-year change in energy intake between the shift- and day workers, both groups displayed a decrease but the decrease in the day workers was significantly higher. Also the amount of energy from fat and the cholesterol intake were reduced in both the daytime as well as shift workers but this decrease only reached statistical significance in the day workers, whereas the difference between the shift and day workers was not significant. Psychological job demands were significantly increased in both groups but the difference was not significant. Total and LDL cholesterol concentrations decreased and HDL increased significantly in both groups, but shift versus daytime differences were not significant. The LDL/HDL ratio was significantly decreased in both shift workers and controls but the decrease was almost 50% higher in the shift workers compared with the day workers ($P < 0.01$).

A separate analysis in males and females revealed similar results as presented before (data not shown). Only in males, a significantly decreased level of social support was found in shift workers compared with daytime (shift workers: -0.13, day workers: + 0.12, p value difference: 0.001).

Analysis of the respondents changing from a daytime job to a shift work job (n=32) revealed a significantly higher decrease in BMI compared with day workers (respectively - 0.36 kg/m^2 and +0.13 kg/m^2, p=0.05). They also displayed a higher increase in number of cigarettes smoked per day in smokers (respectively +2.54 and -1.03 cigarettes per day, p=0.02). No considerable differences were found for any of the other cardiovascular risk factors.

In respondents changing from a shift work to a daytime job (n=34) a higher decrease of physical activity during sport (-0.40 versus -0.09, p=0.04) was observed compared workers who remained working in shifts. They also displayed a higher increase in waist to hip ratio (+0.0051 versus -0.009, p = 0.04) and a higher decrease in amount of cigarettes smoked per day (-1.17 versus + 1.42 cigarettes per day, p=0.1) for the smokers. No significant changes in any of the other factors were found.

Table 5.3. *One year changes in CVD risk factors according to work schedule*

		Day workers	Shift workers	p-value difference shift - day
Job related factors				
Work time physical activity index		0.024	0.084*	0.3
Demands		0.11**	0.17***	0.2
Control		0.003	-0.016	0.6
Support		0.015	-0.071*	0.10
Diet				
Energy intake (kJ /day)		-1306***	-481	0.04
Energy from fat (% of total energy intake)		-0.78	-0.52	0.8
Alcohol intake (gram/day)		0.04	-0.03	0.4
Cholesterol intake (mg/day)		-22.4*	-13.8	0.5
Anthropometry				
Weight (kg)		0.43	-0.98**	0.003
BMI (kg/m^2)		0.13	-0.31**	0.004
Waist to hip ratio		-0.0052	-0.0093***	0.3
Diastolic blood pressure (mmHg)		1.07	0.16	0.3
Systolic blood pressure (mmHg)		-1.26	-1.33	0.9
Blood lipids				
Total serum cholesterol (mmol/l)		0.00	-0.04	0.6
HDL cholesterol (mmol/l)		0.080***	0.11***	0.2
LDL cholesterol (mmol/l)		-0.04	-0.15**	0.15
LDL/HDL ratio		-0.13*	-0.33***	0.004
Life style				
Smoking	Stopped last year (%)	2.9	2.5	0.5$
	No change (%)	93.2	89.9	0.5$
	Started last year (%)	3.9	7.5	0.5$
Cigarettes smoked per day (in current smokers)		-1.03	1.42	0.03
Physical activity during sport (score)		0.007	-0.09	0.3
Leisure time physical activity (outside sport, score)		-0.05	-0.06	0.9

Only the data from workers not changing work schedule is presented. (104 daytime and 161 shift workers)
$: Chi-square test, p value for all categories together.
*Significance level 1 year change not equal to 0: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.*

Discussion

At baseline significantly more shift workers were smoking and they had a higher BMI, WTHR and percentage energy intake from fat, compared with day workers. BMI and LDL/HDL ratio decreased, the number of cigarettes increased significantly in shift workers compared with day workers. The change in the other cardiovascular risk factors was not significant different between the groups. First the validity of the reported results will be discussed.

One of the most important sources of bias is the selection of people starting in shift work. People who assume that they are not capable of working in shifts are less likely to apply for a shift work job. Also, companies may use different criteria when selecting shift workers compared with day workers. By investigating longitudinal changes one might expect that the effect of existing pre-job differences between shift workers and controls due to selection, is removed. Moreover, day workers who indicated that they would never work in shifts for whatever reason were excluded from the study. Nevertheless, differences in sensitivity to the effects of shift work might still be present between the shift workers and controls and might bias the findings. The size of this bias is probably small is expected to have lead to underestimation of the difference between the groups.

Differential loss to follow up may be another source of bias. Analysis of the people moving out of their shift work job however, did not reveal unfavourable changes in any of the cardiovascular disease risk factors compared with the shift workers. Moreover, analysis of the one-year changes according to shift work status at baseline (in analogy to the analysis for intention to treat) did not reveal differences compared with the presented results. We therefor conclude that differential loss to follow up did not bias the results.

Risk factors in shift workers might have temporarily changed as a consequence of recent night shifts. Because for most respondents the baseline and repeated measurements were performed at the same time of the day and in the same phase of the shift rotation schedule, we assume that it ahs not affected the estimated changes. Differences in working condition may have biased the observed results. However adjustment for work place noise, job strain and physical activity at work did not yield different results. Therefore work conditions are not considered to be important confounders in this study. Because the shift workers had a higher BMI and smoked more regression to the mean might have been responsible for the reported change in BMI and smoking. Regression analysis including baseline values of BMI or smoking did not affect the reported results. Overall, although the total amount of bias can not be estimated precisely, the sources of error appear to have been mainly non-differential and may have lead to some underestimation of the relation between shift work and change in cardiovascular risk factors.

Only a few other longitudinal studies comparing changes in cardiovascular risk factors between shift and day workers were found. In the study of Morikawa *et al.*[44] a higher 5-year relative risk for hypertension in younger shift workers (18-29) but not for the older shift workers was reported. We did not find changes in blood pressure in a similar age group. This might be due to the shorter follow up or to the decrease in BMI that we observed.

Three studies reported a positive relationship between body mass index and duration of shift work[15; 47; 115]. This is at variance with the decrease of BMI in shift workers, as found in this study. One might hypothesise that this is explained by the change in smoking. As in other studies[116; 117], significantly lower BMI levels were found in smokers, but this was not sufficient to explain the total reported effect. A change in the basic metabolic rate, as a consequence of shift work, might be a different explanation. Indications for this disturbance can be found in a study by Lennernäs *et al.*[64] reporting a relation between serum low-density lipoprotein-cholesterol values and the percentage carbohydrates intake during the night. However the discrepancy between the reported increase of BMI with number of years worked in shifts found in several studies and the decrease of BMI found in this study remains puzzling. It is possible that an initial decrease in BMI is followed by an increase after several years, because of a compensatory increase in energy intake. A completely different explanation might be a change of behaviour of the participants, because of their participation in a study on cardiovascular. The decreased levels of energy intake as reported in the shift- as well as the day workers might be an indication for such an effect. Knutsson *et al.*[63] was the only other cohort study reporting changes in smoking habits and other lifestyle risk factors in shift workers. They did not observe different changes in smoking habits between the groups, however, this was only a small study.

Results from the cross sectional studies, reviewed as by Bøggild and Knutsson[11], revealed 12 studies that reported higher smoking rates among shift workers, compared with day workers (only one reported a significant difference), one study reported no difference, and one study reported more smokers in the daytime group. Most authors explained this by differences in socio-economic status between the shift workers and day workers. But the results from this study, with an increased change smoking rate in the shift workers, which remained significant even after correcting for educational level, might indicate that other factors might be important in the elevated smoking rate among shift workers. Using the data on the cardiovascular disease risk from the Framingham study[118] a crude estimate of the risk of the increased cigarette smoking in shift workers can be calculated. Assuming that the increase of 2.4 cigarettes per year remains constant over a 20 year working life in the 36 % of smoking shift workers, an average excess of 17 pack years can be calculated. The relative cardiovascular disease risk in the shift workers due to an increased smoking rate is than estimated to be 1.1.

The study of Knutsson *et al.*[63] is the only cohort study published so far, reporting on changes in blood lipids in shift workers. As in our study, Knutsson reported no significant different changes in cholesterol between thirteen-day workers and twelve shift workers, from the start of employment compared with 6 months at work. Also most of the cross sectional studies on biomarkers of cardiovascular disease among shift workers, reported no or small differences between shift workers and day workers[11].

To conclude, our results combined with the results from other studies, provide no evidence for the hypothesis that working in shifts does lead to a less favourable change in lifestyle or traditional cardiovascular risk factors. The only factor found in our study that could explain a part of the elevated cardiovascular disease risk for shift workers is smoking. One may speculate that shift workers increase their smoking to compensate for a decreased social support or due to the stress related to working in a shift schedule.

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6

Duration of shift work related to body mass index and waist to hip ratio*

L.G.P.M. van Amelsvoort, E.G. Schouten, F.J. Kok

Abstract

Objective: An elevated cardiovascular disease risk for shift workers has frequently been reported, however, the mechanism is still unknown. Changes in eating habits, in physical activity or metabolic factors could be involved. In this study we assessed the relationship between body mass index (BMI) as a possible indicator of changed eating habits or metabolic involvement and duration of shift work ***Design***: Data from an ongoing cohort study among 377 shift workers and non-shift working controls, all starting in a new job were used. Anthropometric measurements were carried out at the start of the assignment. Job history was obtained by a questionnaire. ***Results:*** A positive relationship was observed between BMI and waist to hip ratio (WHR) and duration of shift work experience, with an adjustment for age. The linear regression coefficients, with additional adjustments for sex, smoking status, physical activity and educational level were 0.12 kg/m^2 per y in shift work for BMI ($P < 0.05$) and 0.0016 per y in shift work for WHR ($P < 0.05$). ***Conclusions:*** These results suggest a relationship between years worked in shifts with BMI and WHR for both males and females. Whether this might reflect an effect of changed dietary habits or a metabolic effect is not yet clear.

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Introduction

During the last decade convincing evidence for an elevated cardiovascular risk in people working in shifts has been reported.[13; 15; 75] However, the mechanisms behind this elevated risk remain unclear. Suggested hypotheses include changes in eating habits, in physical activity or the involvement of metabolic factors.[64] Elevated body mass index (BM1) and waist to hip ratio (WHR) as observed in shift workers may be possible intermediary factors in the relationship between shift work and cardiovascular disease.

Most studies addressing the relationship between BMI or WHR and shift work have focused on current shift work status. The studies of Rosmond *et al.*[45] and Nakamura *et al.*[46] revealed a significantly higher WHR for shift workers compared with day workers. Rosmond *et al.*[45] also reported significantly elevated BMI values whereas Niedhammer *et al.*[47] reported a significantly elevated prevalence of overweight among nurses working nights compared with controls working in daytime. Other studies reported no significant elevation of BMI[48; 49] or prevalence of overweight[50] for shift workers. Since an effect of shift work on body composition may have a considerable time lag, current shift work may be less relevant in this respect than a history of shift work. Therefore, job rotation may explain the absence of an association in some of the studies mentioned.

Only two studies reporting the relationship between BMI and duration of shift work were found in the English literature. The data from a study by Kawachi *et al.*[51] show a positive relationship between an increasing number of years worked in rotating night shift (no significance levels given) and BMI. Niedhammer *et al.*[47] reported an association between prevalence of overweight and weight gain and exposure to night- work. In the French literature three other studies were found regarding BMI and shift work. Two of the studies did not find a relationship between annual weight gain[49] or prevalence of overweight[50] and working in shifts whereas the study of Romon-Rousseaux *et al.*[52]reported an increased weight gain per year of age for shift workers compared with day workers.

In the current study, baseline measurements from an ongoing cohort study were used to investigate the relationship between the duration of shift work and BMI and WHR. Knowledge of this relationship could throw some light on the possible role of body composition in the elevated cardiovascular disease risk in shift workers.

Subjects and methods

Study population

In the present study, baseline data from an ongoing cohort study among shift workers and non-shift working controls, all starting in a new job were used. In the cohort study, changes in cardiovascular risk factors are monitored over a 1-y period in shift workers and daytime controls to elaborate possible factors in the elevated cardiovascular disease risk among shift- workers. The study was approved by the ethical committee of the Wageningen Agricultural University. The following inclusion criteria were used:

- Working at least 32 h a week.
- Expecting to work next year in the same job.
- No use of medication or previous hospitalisation for a cardiovascular disease.
- No insurmountable objections to shift work (see measurements).
- Aged between 18 and 55 y.

Potential participants were approached during an 18 month period using three strategies in order to sample from different shift work schedules: (1) persons undergoing a pre-employment medical examination in two occupational health services; (2) all workers in a newly built waste incinerator plant; and (3) nurses in training, starting their practical work in hospital training. A total of 707 people were approached for participation in the study, 98 were not eligible (13.8%) because they did not match the inclusion criteria mentioned above. Thirty because they worked less than 32 h a week, 32 because they expected to quit the new job within one year, 11 because they had a history of cardiovascular disease, 18 because they had 'insurmountable objections to shift work' and seven because they did not match the age criteria. Of the 609 eligible respondents, 213 refused to participate (35.0%). The major determinant of the non-response rate was the time involved in travelling to the research location. For the respondents who were measured close to their workplace (n = 518) the response rate was 75.2% whereas the response rate for workers who had to travel to participate in the study (n = 91) was 7.7%. The approximate response rates for shift workers and day- time workers were 65.4% and 63.4% respectively (only approximate numbers can be given because the shift work status of 18 non responders is not known). In total, 396 people participated but 19 observations were excluded from the analysis due to incomplete data.

Measurements

Measurements were performed between one week and two months after the start of a new job. All participants received a questionnaire and were asked to return it by mail after completion in a 'confidential' envelope to the research staff. Unclear or missing answers were verified over the telephone. Nevertheless, some participants refused to answer all questions. Most questions were close-ended and came from standardised questionnaires.

Current job title and job history.

We asked for the current job, including company, department, and shift work schedule. According to social status and job content all jobs were coded. In total, nine different job titles were used. In this study, we defined shift work as working an alternating work schedule including nights. Information on all previous jobs including job title, employer, starting and ending dates and shift work status was asked retrospectively. Respondents were asked to fill the job title, type of company, starting and end dates of the job and whether or not the job was in shifts, including night shifts for all their previous jobs, starting from their most recent job and finishing with the first job. Duration of shift work was calculated from these data.

Objections to shift work.

In order to improve comparability, to minimise confounding caused by differences between shift workers and day workers before starting a job (healthy worker effect), only day workers with no insurmountable objections to working in shifts were included. The following question was used to assess this. Would you keep working in your current job if the department were to switch to shift work jobs? (1) Yes, without any objections; (2) Yes, but only if there is a financial reward; (3) Only if there are no other jobs available; (4) On no account. We excluded people who gave answer (4) to this question.

Personal characteristics.

In the questionnaire educational level was coded in seven levels from elementary school to university education. In the final analysis these were categorised into junior education (elementary school only, junior secondary vocational education, and junior general secondary education), senior education (senior secondary vocational education and senior general secondary education or pre- university education) and higher education (higher vocational education and university). The physical activity indexes for work, sport during leisure time and physical activity during leisure time excluding sports, were assessed as described by Baecke et al[85] using a self-administered questionnaire. The range of the indexes were 1.1 – 4.3, 1.0 – 5.2 and 1.3 – 4.5 respectively. Current (type and quantity) and past smoking habits (type, years, and quantity) were asked. Only in the preset analysis was smoking status: non-smoker, current smoker or smoker, used.

Anthropometric measurements.

Measurements were done between one week and two months after the start of a new job. Only subjects without missing data were included for data analysis. Weight, height and waist and hip circumferences were measured unclothed in a standing position by one of two research nurses. The waist circumference was measured at the level of the umbilicus, and the hip circumference at the widest part over the buttocks. Circumferences were rounded to the nearest 0.5cm. Weight was rounded to the nearest 500-g value. Height was rounded to the nearest 0.5 cm. BMI: weight/height (kg/m^2) and the WHR: ratio between the waist and hip circumferences were calculated. Obesity was defined as having a BMI greater than or equal to 25 kg/m^2 according to the WHO criteria.[119] For woman, abdominal obesity was defined as having a WHR greater than or equal to 0.85 and for man as having a WHR greater than or equal to 1.0.[119]

Statistical analysis

Standard methods were used for descriptive analysis and linear regression. Least square mean values, calculated with SAS proc GLM, were used to enable comparison of mean values between subgroups, adjusted for a covariant. Least square means are the expected value of class or subclass means that would be expected for a balanced design involving the class variable with all covariates at their mean value.[101] Differences between categories and significance levels are identical to the differences and P-values obtained from analysis of covariance. Age adjusted odds ratios (OR) were calculated using logistic regression.[101] Linear regression analysis was performed using proc REG of the Statistical Analysis System (SAS).[101] Visual inspection of the residual values of the regression models was performed to affirm the appropriateness of the linear model.

Results

Table 6.1 shows the population characteristics. Differences between male and female participants in age, education and shift work duration are probably due to the large proportion of female nurses. Most nurses in the study reported finishing their senior education. Differences in the distribution of duration of shift work experience (see Table 2.2) between males and females can largely be contributed to the lower mean age of female shift workers. Of the 225 shift workers 121 worked in a schedule with backward rotation of shifts (anti-clockwise rotation), 32 with forward rotation of shifts (phase delay, clockwise rotation) and 72 worked in shifts without a fixed schedule.

Table 6.1. *Population characteristics*

	Female	Male	Total
N	196	181	377
Education			
Junior (%)	26.8	32.6	29.6
Senior (%)	67.0	39.8	53.9
Higher (%)	6.2	27.6	16.5
Smoking			
non-smoker (%)	64.3	50.8	57.8
current-smoker (%)	29.6	32.6	31.0
ex-smoker (%)	6.1	16.6	11.1
age (years)	22.6 (4.3)	29.2 (6.5)	25.8 (6.5)
Duration of work in shifts (y)	0.32 (0.85)	2.5 (4.7)	1.4 (3.5)
Height (cm)	169.5 (6.9)	181.5 (6.6)	175.2 (9.0)
Weight (kg)	66.8 (10.8)	79.4 (12.0)	72.9 (13.0)
BMI (kg/m^2)	23.2 (3.4)	24.1 (3.4)	23.6 (3.4)
WHR	0.80 (0.04)	0.91 (0.04)	0.85 (0.07)

Mean values. Figures within parentheses are standard deviations.
BMI = Body mass Index; WHR = waist to hip ratio.

A positive relationship was found between BMI and WHR and duration of shift work experience, with an adjustment for age. For males working between 2 and 5 y and more than 5 y in shifts the difference in WHR compared with persons without shift work experience was statistically significant (see Table 6.2 and 6.3) whereas for BMI the difference was only significant between the more than 5 y worked in shifts and never worked in shifts groups. When combining the >0 – 2 y, the >2 – 5 y and the >5 y to one always worked in shift group, the difference in BMI between this group and the never worked in shift group was (borderline) statistical significant in both the males and females (difference: 1.19kg/m^2 P=0.05 for females and 0.92 for males, P = 0.08).

In order to see whether the prevalence of obesity and abdominal obesity is associated with shift work history, age corrected OR's were calculated using logistic regression models. The age corrected OR for always working in shifts compared with never working in shifts were 1.71 (95%

CI = 1.03 – 2.83) for obesity and 3.38 (95% CI = 1.30 – 8.77) for abdominal obesity. Next to age we assessed the possible confounding factors smoking status, physical activity at work, physical activity during sport, educational level and last shift work more than 1 y ago by including them one by one in the logistic regression model together with shift work history and age. Only the model corrected for age and smoking status is presented here because smoking appeared to be only factor to have a considerable influence on the estimated OR and thus is a likely confounding factor. The results from this analysis, as presented in Table 2.4 and 2.5, show a similar trend as in Table 6.2 and 6.3, when comparing the different 'years of shift work ' groups, but with more pronounced effects for abdominal obesity.

Table 6.2. *Least square mean BMI according to the duration of shift work*

	Females			males		
Years of shift work	*n*	BMI kg/m²	P	*n*	BMI kg/m²	P
None	159	23.0		113	23.7	
> 0 - 2 y	27	24.1	0.10	17	23.7	0.9
> 2 - 5 y	9	24.3	0.25	18	24.1	0.7
> 5 y	1			33	25.6	<0.01

Age adjusted least square mean values, P values: difference with no years worked in shift.
BMI = body mass index.

Table 6.3. *Least square mean WHR according to the duration of shift work*

	Females			males		
Years of shift work	*N*	WHR	P	*n*	WHR	P
None	159	0.80		113	0.90	
> 0 - 2 y	27	0.80	0.5	17	0.91	0.7
> 2 - 5 y	9	0.81	0.2	18	0.93	0.02
> 5 y	1			33	0.93	<0.01

Age adjusted least square mean values, P values: difference with no years worked in shift.
WHR = waist to hip ratio.

Tables 6.6 and 6.7 give the crude and adjusted regression coefficients for duration of shift work on BMI and WHR. In the extended model, adjustment was made for possible confounders. To adjust for possible heterogeneity of the effect of age on BMI or WHR between males and females we included the interaction term age x sex in the linear regression model. We included the possible confounding factor 'last shift work more than 1 y ago' to adjust for a possible fading of the effect of working in shifts after return to a normal daytime job. Because of the high correlation between current job title and educational level, job title was omitted. Adjustment for current job title instead of educational level, however, did not importantly influence the reported regression coefficients. A separate analysis, performed with exclusion of respondents using medication with a possible influence on weight and metabolism (use of corticosteroids (n = 2), laxatives (n = 1), psychoactive drugs (n = 3) or anti- diabetics (n = 1)) did not yield different results. Both the multivariate adjusted linear regression coefficients for BMI and WHR show a significant positive correlation with years worked in shift system.

Table 6.4. *Multivariate odds ratios for obesity, according to the duration of shift work with correction for smoking habits*

Years of shift work	Females odds ratio	Males odds ratio
Age (per 5 years)	1.53 (1.07 - 2.20)	1.12 (0.85 - 1.46)
> 0 - 2 years[a]	1.95 (0.79 - 4.80)	1.19 (0.38 - 3.70)
> 2 - 5 years[a]	2.50 (0.59 – 10.6)	1.19 (0.40 - 3.55)
> 5 years[a]	NSO	2.35 (0.98 - 5.62)
Current smoking[b]	1.11 (0.53 – 2.36)	1.22 (0.58 - 2.55)
Past smoking[b]	0.66 (0.13 – 3.26)	2.17 (0.89 – 5.27)

Odds ratios with 95 confidence intervals (between brackets) calculated with logistic regression for moderate obesity (BMI ≥ 25 kg/m²).
[a] compared with never worked in shifts.
[b] compared with non-smokers.
NSO = Not sufficient observations.

Table 6.5. *Multivariate odds ratios for abdominal, according to the duration of shift work with correction for smoking habits*

Years of shift work	Females Odds ratio	Males odds ratio
age (per 5 years)	1.45 (0.84 - 2.51)	1.95 (0.85 - 1.46)
> 0 - 2 years[a]	4.12 (1.06 – 16.4)	5.09 (0.36 – 72.8)
> 2 - 5 years[a]	5.89 (0.86 – 40.4)	NSO
> 5 years[a]	NSO	5.43 (0.89 – 33.2)
current smoking[b]	1.70 (0.43 – 6.78)	2.30 (0.33 – 16.0)
past smoking[b]	4.60 (0.74 – 28.7)	3.31 (0.43 – 25.3)

Odds ratios with 95 confidence intervals (between brackets) calculated with logistic regression for abdominal obesity (females: WHR ≥ 0.85; males WHR ≥ 1.0). WHR = waist to hip ratio.
[a] compared with never worked in shifts.
[b] compared with non-smokers.
NSO = Not sufficient observations.

Table 6.6. *Linear regression of shift work duration on BMI*

	BMI (kg/m²)	Standard error	p value
Crude	0.20[a]	0.049	0.0001
age and sex adjusted	0.13[a]	0.054	0.012
Multivariate adjusted[b]	0.12[a]	0.057	0.036

BMI = body mass index.

[a]*increase in kg/m² per year of shift work.*

[b]*adjusted for sex, age, age × sex, smoking status, physical activity at work, physical activity during sport, educational level, last shift work more then 1 year ago.*

Table 6.7. *Linear regression of shift work duration on WHR*

	WHR	Standard error	p value
crude	0.0033[a]	0.00061	0.0001
age and sex adjusted	0.0019[a]	0.00062	0.0025
Multivariate adjusted[b]	0.0016[a]	0.00064	0.016

WHR = waist to hip ratio; BMI = body mass index.

[a]*increase in kg/m² per year of shift work .*

[b]*adjusted for sex, age, age × sex, BMI, smoking status, physical activity at work, physical activity during sport, educational level, last shift work more then 1 year ago.*

Discussion

We found a positive correlation between duration of shift work with BMI and WHR. This relation remained significant after adjustment for age and other possible confounding factors. The most pronounced effects were found for WHR and prevalence of abdominal obesity. Whether this reflects an effect of changed food habits, a change in physical activity (at work or at home) or a metabolic effect is not yet clear. However, we did not find evidence for a role of a change in physical activity.

Questions involving the work history could be biased due to errors in the recall or reporting of the information. The most probable recall errors are likely to be the start and end dates of different jobs, especially when involving several jobs or jobs further back in the past. We assume that if bias due to errors in the reporting is present it will mainly cause a shift of some observations to adjacent categories and, therefore, may have had some diluting effects but will not have influenced the reported final results significantly. No misclassification of always shift workers to never shift workers or *vice versa* is expected. Differential error in the conducted measurements of weight, height and circumferences is not anticipated because the research nurses were unaware of the duration of shift work of the participants.

In studies of the effects of shift work the pre-job selection and non-differential drop-out of workers could constitute a source of bias. Because we found a positive trend between BMI and increasing duration of shift work, the influence of differences between shift workers and day workers at the moment of their recruitment is not likely to have influenced the results. Drop out of workers could be related to their shift working status. If the drop out is related both to BMI and to shift work status, differential bias will arise. We assume this bias, if present, would tend to be small and would cause a dilution of the reported effects.

Another source of selection bias could arise from selective non-response. Unfortunately, no anthropometric data could be obtained from the non-responders. However, taking the response rate of 65%, the similar response rates in shift workers and the daytime controls, and the fact that a major part of the non response can be attributed to the long travel time to the research location, we assume that bias due to selective non response is likely.

When investigating the influence of the duration of shift work, age is likely to be an important confounding factor. It is strongly associated with duration of shift work and could be associated with body composition. Adjustment for age, therefore, is crucial in the analysis. In our study the total number of observations was insufficient to perform an age-stratified analysis that would enable a more rigorous way of dealing with age confounding in comparison to linear modelling. We regard the adjustment using general linear modelling performed in this study, as an appropriate alternative assuming a linear relation between age and BMI and WHR. Inclusion of second-order age adjustments were far from significant and did not yield different results nor did visual inspection of the data suggest anything other than a linear adjustment for age.

All day-working controls came from the same companies as the shift workers. Nevertheless, with a possible exception of the nurses, differences in working conditions like job strain, physical activity at work, payment, amount of spare time, between shift work jobs and day work jobs are inevitable. Separating effects caused by different conditions from the effects of shift work is not feasible and was not the purpose of the current study. Perhaps the ongoing cohort study could unravel some of the influence of different shift work characteristics.

Because we only included people starting with a new job, differences between day workers and shift workers in body composition only reflect a distinction that was present before recruitment. In our data a small difference in BMI and WHR between current daytime and shift workers was present. This difference, however, was not significant. We do not know if the difference is caused by personal differences or because the proportion of former shift workers is larger in people starting a new shift work job compared with starters in a daytime job or is just an artefact. In the studies conducted so far, comparing BMI between current shift- and day workers, differences already present before employment as found in our data could be responsible for, at least a part of, the reported differences. Analysing current shift work status in relation to body composition is also susceptible to the earlier transfer of workers from shift work to daytime work and *vice versa.*

Only two other studies have been found in the English literature, reporting data on the relationship between BMI and years worked in shift.[15; 47] As in this study, a similar positive trend was present between duration of work in rotating night shifts and BMI. From Niedhammer[47] an excess weight gain due to night work has been calculated of 0.9 kg per 5 y period. From these data we estimated the annual gain of BMI due to shift work to be 0.07kg/m^2 (using the average height of respondents of 161 m). From the data given by Kawachi *et al.*[15]we estimated an annual gain in BMI of 0.098 kg/m^2. These data are in line with our calculated annual excess weight gain due to shift work of 0.12 kg/m^2 per y.

When considering the information from previous studies together with our data, the hypothesis that shift work is related to an increase in body weight and WHR seems justified. WHR and body weight could be a mediating factor between shift work and cardiovascular disease risk. Difference in eating habits between day workers and shift workers is the first factor that comes to mind as an explanatory factor for an increase of WHR and BMI during shift work. However, according to the literature it seems reasonable to conclude that the type of work schedule does not affect the total intake of energy or nutrients.[68] Physical activity at work and during sports could also be responsible for the reported relationship. Although no studies were found reporting differences in free time physical activity between shift workers and day workers, one might argue that, due to the shifting work hours, participation in team sports is impracticable. In our study, adjustment for current physical activity at work or during sport did not influence the results, providing no evidence for an important role of physical activity. A third explanation, metabolic consequences of working during day and night time, has not been well investigated. A study by Lennernäs *et al*[64] revealed a relation between serum low-density lipoprotein-cholesterol (LDL-C) values and the percentage carbohydrates intake during the night. They speculated about the involvement of circadian rhythmicity of digestive processes or the involvement of the circadian rhythm of insulin secretion.[120] Indications for the involvement of circadian rhythmicity of metabolic processes can be found in a small number of studies: Romon *et al.*[53] reported a decreased diet-induced thermogenesis when a meal was given at night compared with a meal given in the afternoon or morning was reported; Romon et al[121] reported an elevated VLDL-C (very low-density lipoprotein-cholesterol) and a decreased LDL-C (low-density lipoprotein-cholesterol) and HDL-C (high-density lipoprotein-cholesterol) response after a night-time meal compared with a daytime meal. Another mechanism involved might be the disturbance of the circadian rhythm of neuroendocrine secretion of hormones. Growth hormone secretion and cortisol, for example, are modified by night work.[37; 55; 56] Forthcoming data from our cohort study may provide evidence with respect to the way that shift work might influence BMI and WHR.

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7
General Discussion

The study presented in this thesis was designed to investigate the impact of one year working in shifts on cardiovascular risk factors. So far, it is one of the largest longitudinal studies regarding the CVD risk factors among shift workers and the first to evaluate changes in the frequency of premature ventricular complexes (PVC's) and heart rate variability (HRV). In addition, cross-sectional analyses were conducted to evaluate baseline differences between shift and day workers participating in the study. In this chapter, first the main findings of the longitudinal and cross-sectional data analysis will be presented and discussed. Subsequently, the implications of the findings for CVD prevention among shift workers and suggestions for further research will be addressed.

Main findings

We will continue the general discussion with a brief summary of the main findings of the study as described in this thesis. In table 7.1 the main findings have been summarised in a more schematic way. In this paragraph, first the results concerning the PVC frequency and HRV will be addressed. Subsequently, the findings on biological and lifestyle risk factors will be dealt with.

During one year of follow-up, the increase in frequency of PVC's was found to be significantly greater in the shift workers, compared with the controls working in daytime (chapter 2). This increase in frequency of PVC's was found to be greatest in shift workers who had a medium speed backward rotating schedule (working three to five night shifts, followed by three to five evening shifts and three to five morning shifts). This suggests an increased susceptibility to arrhythmia as a consequence of shift work. For the HRV levels, the one-year change was similar between the shift and day workers (chapter 2). Analysis of the cross-sectional HRV data, assessed between one week to two months after the start of a new job, during a day or morning shift revealed a significantly lower SDNNi (mean of 5-minute standard deviations, a general measure of heart rate variability) during sleep and work in the shift workers, compared with the day workers (chapter 4). To evaluate the short-term effects of working at night, a separate analysis was performed in shift workers only, comparing HRV levels during morning and night shift days at baseline. A significantly elevated mean %LF (relative contribution of low frequency power to the total HRV) during sleep was found on a day worked in night shift compared with a day worked in day shift. High levels of % LF indicate an increased sympathetic activity relative to the parasympathetic activity. Type of shift schedule was found to be a significant modifier of this effect with the strongest effects in the backward rotating shift schedule (chapter 3). This suggests an increased sympathetic activity during sleep following a night shift, which might be a sign of an inferior sleep quality.

Table 7.1. *Summary of results of the relation between shift work and CVD risk factors, as described in this thesis.*

CVD Risk factors		One year change		Baseline
PVC	↑↑	PVC frequency (chapter 2)	-	(chapter 2)
HRV	-	(chapter 2)	↑↑	% LF during sleep (chapter 3)
			↓↓	SDNNi during work & sleep (chapter 4)
Biological	-	Blood pressure (chapter 5)	-	Blood pressure Serum cholesterol (chapter 5)
	↓	Serum LDL cholesterol (chapter 5)	↑↑	Body mass index Waist to hip ratio (chapter 5),(chapter 6)
	↓↓	Body mass index LDL/HDL cholesterol ratio (chapter 5)		
Lifestyle	↑↑	Cigarettes smoked per day (in smokers) Energy intake (chapter 5)	↑↑	% smokers Energy intake from fat Alcohol intake (chapter 5)
	-	Leisure time physical activity (chapter 5)	↑	Cholesterol intake (chapter 5)
			-	Leisure time physical activity (chapter 5)

Shift workers compared with day workers.
↑↑, ↓↓ *Significantly ($p < 0.05$) higher resp. lower;*
↑, ↓ *Not significantly higher resp. lower;*
- *No difference*
PVC: premature ventricular complex
HRV: Heart rate variability
%LF : percentage low frequency power.
SDNNi: mean of five minute standard deviations of normal intervals

The analysis of the one-year change in biological risk factors revealed a significant decrease in body mass index (BMI) and LDL/HDL cholesterol ratio in the shift workers compared with day workers (chapter 5). The decrease in LDL/HDL ratio was associated with the decrease in BMI. For the other investigated risk factors, blood pressure, total cholesterol and waist to hip ratio (WHR), a similar change was found in the day and shift workers. Cross-sectional analysis of the baseline data revealed a significant positive correlation between the number of years previously worked in shifts and BMI and WHR, adjusted for age, gender, smoking status, physical activity at work and educational level (chapter 6) but not for any of the other CVD risk factors.

Regarding the one-year change in lifestyle cardiovascular risk factors, the number of cigarettes smoked per day (in smokers), increased significantly during follow up in the shift workers, compared with the day workers. The number of smokers also increased more in the group of shift workers, but this increase was significantly different between the shift and day workers. Furthermore, energy intake in day workers was significantly decreased, compared with the shift workers. For the other lifestyle cardiovascular risk factors the changes were small and similar for the two groups. At baseline the prevalence of smoking, energy intake from fat, and alcohol intake were found to be significantly higher in the shift compared with the day workers (chapter 5).

Comparison with results from other studies

So far, no other long-term longitudinal studies have been published reporting a change in frequency of PVC's or HRV in shift workers. One short-term study, by Härenstam *et al.*[19] reported an increased frequency of PVC's during a day worked in night shift compared with a day on morning shift. In our data we did not find evidence for such an effect. This difference might be due to the younger age, or shorter period of shift work experience of our population as it has been suggested that the impact of working at night increases with ageing[6]. A different explanation might be that we had smaller numbers and insufficient power to detect a similar effect. The measurement of PVC frequency displays a large within person variation. Moreover, due to its non-normal distribution, it requires the use of less sensitive distribution-free statistical techniques for its analysis. In conclusion we were not able to confirm the short-term shift work related increase in PVC frequency as reported by Härenstam *et al.* but we did find evidence for a long-term shift work related increase in PVC frequency, which has not been reported in other studies before.

We observed an increase of %LF, indicating a higher sympathetic activity, during sleep following a night shift. This night shift related increase in sympathetic activity seems to be consistent with the findings of Härenstam *et al.*[19]. They reported an increased urinary excretion of noradrenaline in connection with night shift work, which also indicates sympathetic arousal. The only other study which reported heart rate variability levels among shift workers was conducted by Freitas *et al.*[100]. In contrast to our findings they reported no differences in HRV levels during sleep and work, between a night and morning shift. However, in this study, only 12 observations were included. This small number of observations was probably insufficient to detect results in the same order of magnitude as our findings. The detection of a significant difference during sleep but not during the rest of the day might be due to the assumed lower level of interference in the measurements during rest but might also indicate that the main effects of night work on HRV mainly occur during sleep.

Our finding that the type of rotating schedule is correlated with sympathetic activity during sleep after a night shift has not been reported before. We found the backward rotating shift schedule to be the most unfavourable, i.e. with the highest sympathetic activity during sleep. Several other studies[66; 99; 122; 123] reported the greatest unfavourable health effects in a backward compared with a forward rotating schedule. It has been suggested that forward rotation is the least disturbing for the biological circadian rhythm[66]. Especially the results from Orth-Gomér[66] correspond with our findings. They reported that after a forward rotating shift, systolic blood pressure and urinary excretion of catecholamines were significantly lower than after a backward rotation shift.

For most biological CVD risk factors, the results from studies published so far support the conclusion that shift workers do not differ from other working populations, as discussed in chapter 1, especially when differences in socio-economic status have been taken into account. Only for BMI a majority of studies reported a higher level among shift workers. This corresponds with our results showing a correlation between shift work history with an increased BMI and WHR (chapter 6). However, the one-year individual change in BMI displayed the opposite, with a significant decrease in the shift workers as compared with the day workers (chapter 5). This discrepancy remains puzzling. The increased cigarette smoking among the shift workers might be partly responsible. One could also speculate that after starting in shift work an initial decrease in BMI is followed by an increase after several years. Shift work related disturbances of the digestion or energy metabolism might lead to a short-term decrease in BMI. In the long term this could be compensated by a higher energy intake leading to an increased BMI. The increase in energy in the shift workers relative to the day workers seems to support this hypothesis. However, so far no further evidence is available.

We found a significant one-year increase in the cigarette consumption in shift workers compared with day workers. No other longitudinal studies found this increased cigarette consumption among shift workers, probably due to a lack of power. Most cross-sectional studies however, did report a higher number of smokers among the shift workers. This has been attributed to differences in socio-economic class between the shift and day workers. As the observed one-year increase was independent of educational level, there might be another explanation. Possibly increased stress, related to working in shifts, is involved. The energy intake was found to be decreased in both the shift and day workers, with the highest decrease in the day workers, as compared with the shift workers. So far, we do not have a sound explanation for this difference, which was not supported by results from other studies. For the other lifestyle risk factors, in agreement with the results from other studies as summarised in chapter 1, we did not find considerable different changes between the shift and day workers.

External validity

Insufficient data is available so far, to rule out between job differences in the impact of shift work. Traditionally, most shift work studies were carried out in the industrial sector, since shift workers are most numerous there. In our study we tried to include subjects from all sectors with a considerable amount of shift workers. However, we missed the fast growing groups of security guards and computer helpdesk workers, due to the low grade of organisation and high turnover rates in these sectors. Therefore, extrapolation of our results to all shift workers has to be done with some reservation. However, so far, there is no reason to suspect important differences in the effect of shift work between different job titles.

Methodological considerations

An intervention study, assigning subjects at random to a shift work or daytime job, would probably have been the best way to meet the aims of the current study. However, such a study is not feasible. In the current observational design, factors like pre-job selection of shift workers and information bias might have lead to considerable bias in the reported results. In the next paragraph we will discuss possible threats to the internal validity of the study.

Healthy worker effect

Originally the term healthy worker effect was used to describe the finding that the working population is, in general, healthier in comparison with a population comprising unemployed persons. In this study, similarly, the shift workers might be healthier compared with the day workers. Pre-job selection processes (due to self-selection as well as the pre-job medical examination) might have lead to differences between the shift and day workers. Less healthy subjects might have a greater chance to be rejected or might be less willing to start in a shift work job. Furthermore, subjects suffering from the possible negative effects of shift work on their health might quit working in shifts. All these selective forces would result in a healthier group of shift workers. The healthy worker effect has been discussed in detail in the preceding chapters where appropriate. To recapitulate, we did not find evidence for the shift workers to have more favourable CVD risk factors at baseline, as one might possibly expect due to pre-job selection processes. This might partly be due to the exclusion of day workers who indicated that they would never consider working in shifts, which was done to minimise potential bias due to pre-job selection. Also, we did not find differences in CVD risk factors between workers who left or changed job and workers who remained in the same job. Hypothetically, a last source of bias related to the healthy worker effect might be that the people who start as a shift worker have a higher resistance against the ill effects of shift work. This bias could not be investigated in the current data, but we do not consider the presence of such a different resistance between starting shift and day workers to be very likely. If present, it would probably have led to an underestimation of the true effect of shift work. Concluding, bias due to the healthy worker effect is considered to be small and would probably have lead to a moderate underestimation of the true effects of shift work.

Information bias

The subject of information bias has been discussed for the different cardiovascular risk factors in the respective chapters. In short, differential measurement errors might be present, as our study was not blinded and both the observers and the subjects were aware of job status. By conducting the measurements according to a strict protocol, and using pre-coded answer categories in the questionnaire we tried to minimise this potential bias. Moreover, the main outcomes of the study were individual one-year changes. Only when systematic differences in the reported one-year changes between the shift and day workers are present, differential bias might have occurred. We expect this inaccuracies in the calculated changes to be similar between the shift and day workers and therefore non-differential.

As we conducted the baseline measurements on average 2 weeks after the start of a new job there is the possibility of early shift work related changes already occurring during this period. Such changes would remain unnoticed and might bias the reported one-year changes. For most of the CVD risk factors however, we assume that the duration of this period, on average two weeks between the start of exposure and the baseline measurement, was too small to have a noticeable effect. Most lifestyle risk factors were assessed using a questionnaire concerning the preceding 3-month period. So the two weeks of exposure to shift work would probably not had a large impact on the questionnaire scores. Also for BMI and WHR a short-term effect within two weeks is not very likely. For HRV, blood lipids and blood pressure a short-term effect of shift work can not be excluded. This might even explain a part of the baseline differences in SDNNi and cholesterol levels between the shift and day workers. To conclude, we can not exclude that the reported changes in SDNNi and cholesterol levels are lower than the true shift work related changes. For the other reported findings information bias is considered to be low and would probably have lead to a small underestimation of the true effects of shift work.

Socio-economic status as confounding factor

As Bøggild *et al.*[71] stated, social class or socio-economic status might be an important confounder in the relation between shift work and CVD risk. Also in our data we found evidence for a relation between CVD risk factors, shift work and socio-economic class. Most of the baseline differences in CVD risk factors between the shift and day workers in our study disappeared when adjusting for educational level, an indicator of socio-economic status. One might therefore conclude that, at least a part of, the excess CVD risk among shift workers can be attributed to the less favourable CVD risk profile due to their lower socio-economic status. Nevertheless, as stated in chapter 1, several studies reporting an excess CVD risk among shift workers did control for socio-economic status, or were restricted to one job title, ensuring equal socio-economic status levels among the shift and day workers.

We do not consider a change in socio-economic status of the subjects in our study during the one-year of follow up to be very likely. Therefore, only if socio-economic status is related to a different change in CVD risk factors this factor can be regarded as a confounder of the reported one-year changes. Socio-economic status might also have been an effect modifier of these changes. We used educational level as indicator of socio-economic status. Stratified analysis by educational level, or multivariate adjustment for educational level, generated only minor differences in the reported one-year changes. We therefore concluded that socio-economic status in no important confounder or effect modifier for these changes. Some residual confounding, due to differences in socio-economic status between the shift and day workers, might still be present after adjustment, as educational level does not provide an exact estimate of socio-economic status. However, we believe that the amount of residual confounding is small and can not explain the reported findings.

Confounding due to different work conditions

Differences in work conditions between the shift and day workers, other than their work schedule, might have confounded the reported shift work related effects. Besides as confounding factors, differences in working conditions might also act as intermediate factors in the relation between shift work and cardiovascular disease. To minimise confounding due to different work conditions, we strove for similar working conditions between the shift and day workers. This was done by recruiting day and shift workers with similar work tasks and from the same departments. Nevertheless differences between the two groups were inevitable. Even in the groups of participating nurses, which we considered as the most homogeneous group, shift and day workers scored differently on the job strain questionnaire between the shift and day workers. Potential confounding due to different working conditions between the shift and day workers was evaluated using questionnaire data. The shift workers, in general, reported a higher job strain (especially a lower work control). Multivariate adjustment for job strain or stratified analysis for subjects reporting high or low job strain, however, did not yield different results. Therefore, we do not consider job strain to have been an important confounder nor effect modifier. Shift workers were found to have a higher work related physical activity score, compared with the day workers. This was found to explain a part of the one-year decrease of BMI in the shift workers compared with the day workers. However, even after adjustment for workplace physical activity, the one-year change in BMI remained significantly different between the shift and day workers. Other workplace conditions which might be different between shift and day workers and which have been suggested as CVD risk factors, workplace noise and exposure to chemicals, were not found to be significantly different between the shift workers and the day workers and therefore not regarded as potential confounders. To conclude, we found indications for the one-year change in BMI to be confounded by workplace physical activity but not by other work conditions.

Duration of exposure

Two different time windows are important when considering the excess CVD risk among shift workers: 1) Short-term effects of working at night, quickly subsiding when working days again; 2) Long-term effects of being a shift worker, also present when working in a day (or morning) shift. These long-term changes might be a consequence of prolonged exposure to short term effects. For example, eating at night might decrease the diet induced thermogenesis (DIT). A frequently occurring decrease of DIT during a night shift meal, might in the long-term lead to an increased BMI, an acknowledged CVD risk factor (chapter 1). For both short and long-term effects adaptation might occur after prolonged working in shifts. But it might also be that for the short-term effects as well as the long-term effects to occur, a minimal duration of exposure to shift work is needed.

So far most of the cross-sectional and even most of the longitudinal studies avoided the subject of the time window of shift work related effects. Our study was mainly designed to detect long-term shift work related changes. Nevertheless, in separate analyses we also regarded short-term night shift related effects on PVC and HRV. We did find evidence for short-term shift work related changes in HRV during sleep. Several studies have reported on short-term effects of exposure to stressful circumstances on PVC's and HRV[19; 24; 34]. These stress-related effects quickly disappeared after removal of the exposure. However, we assume that long-term changes in these parameters would be much better indicators of an increased CVD risk. In our data we found evidence for a long-term change of the frequency of PVC's due to shift work. The PVC frequency was found to be increased after one year of shift work, but was not different between a day worked in morning and a day worked in night shift. Unfortunately, no other longitudinal studies were found regarding long-term changes in PVC frequency. One might hypothesise that prolonged exposure to the stress of working at night, as reflected in changes in heart rate variability, brings about long term unfavourable changes in arrhythmogeneity of the heart, reflected in the PVC frequency.

A duration of follow up, not long enough to show significant changes in CVD risk factors is another concern regarding the time frame of the effects. It might be that our one-year period of follow up was to short. However, the results from studies conducted so far do not support such a long time-window without effects. The study of Knutsson *et al.*[74] for example, already showed a relative risk of 1.5 in subjects working two to five years in shifts.

Power of the study

For a study regarding a broad range of risk factors it is difficult to summarise the power calculations performed when designing the study. The original power calculations were based on an excess CVD risk of 40 %. We based the power calculations on the assumption that the mean individual changes in any of the major included CVD risk factors had to be sufficient to explain at least 50 % of this excess risk. Furthermore, we wanted to be able to detect different changes between three rotation schedules, in any of the major included CVD risk factors. This corresponded with a study size of 600 subjects. However, due to a less successful start of the recruitment, only 377 subjects were included. Nevertheless, the power of the study is considered to be sufficient to detect relevant changes between the shift and day workers, but might not be sufficient to detect different changes between different shift schedules for all included CVD risk factors. In spite of that we did find differences between different shift work schedules for some factors. The power of the study would also be insufficient if the increased CVD risk in shift workers is caused by small changes in a broad range of biological and lifestyle CVD risk factors.

Conclusions

We found evidence for a positive correlation between the number of nights worked during the year of follow up and the increase in premature ventricular complexes. This indicates that shift work might cause unfavourable changes in the myocardial system leading to increased arrhythmogeneity. We regard the increased PVC frequency in shift workers, more as an indicator of unfavourable changes in the cardiac control than as a precursor of cardiovascular disease. No different one-year change in HRV measures was found between the shift and day workers. Within the shift workers a significantly increased %LF during sleep after a night shift compared with day shift was found at baseline. This suggests that night work caused a short-term increase in sympathetic activity, especially during sleep. In addition, in a cross-sectional analysis, we did find a decreased level of SDNNi during sleep and work in the shift compared with the day workers indicating a less favourable cardiac autonomic control among the shift workers. However, this latter finding might have resulted from different selection processes, or existing differences, between the shift and day workers, but it might also be an indication of a poorer autonomic regulation of the heart. The reported one-year increase in PVC frequency might result from a repeated exposure to excess stress, as indicated by increased sympathetic activity, related to working at night. These findings demonstrate that independent from changes in lifestyle and other biological cardiovascular risk factors, working at night may have unfavourable effects on the cardiovascular system. We also found indications that these unfavourable effects might be lower in a fast forward rotating shift schedule compared with a medium backward rotating schedule.

Regarding the one-year changes in biological and lifestyle risk factors, only for smoking an unfavourable change was found in the shift workers compared with the day workers. A decrease was found for BMI and, in connection to the decrease in BMI, a decrease in the LDL/HDL cholesterol ratio was found in the shift workers compared with the day workers. Both a decreased BMI and LDL/HDL ratio have been correlated to a lower CVD risk. These reported changes are therefore not likely candidates for an explanation of the assumed increased CVD risk among shift workers. Together with the information from other studies so far, as summarised in chapter 1, only the increase in smoking might explain, a part of, the elevated CVD risk among shift workers. In addition we found conflicting results concerning the relation between BMI and shift work. A positive correlation between past shift work experience and baseline BMI seems contradictory to the one-year decrease in BMI in the shift compared with the day workers. Whether this is only a chance finding or reflects a true effect warrants further study.

Baseline differences do exist between subjects who start working in shifts and those who start in a daytime job. In general the starting shift workers exhibit a less favourable cardiovascular risk profile. This difference could be explained largely in terms of the educational level, a variable used as indication of the socio-economic status. We therefore conclude that social class may be an important confounder in the relation between shift work and CVD risk. However, we do not consider the reported changes in CVD risk factors to be confounded by socio-economic status.

In conclusion, we found indications that the elevated CVD risk among shift workers is, at least partly, due to unfavourable changes in the cardiovascular system. We regard the increased PVC frequency in shift workers, as found in this study, more as an indicator of unfavourable changes than as a precursor of cardiovascular disease. Smoking was found to be the only other risk factor that displayed an unfavourable change in the shift, compared with the day workers, and therefore may also explain, a part of, the elevated CVD risk among shift workers.

Implications for occupational health

The evidence indicating negative consequences of shift work on cardiovascular health has increased during the last decade, but there will always remain uncertainty. This uncertainty, however, must not become an excuse to refrain from preventive measures. As stated by the European Heart Network[124]: "Not acting is also, by default, an act with possible (negative) consequences. The goal should not be to act without ever making mistakes, but to make as few mistakes as possible. By not acting until there is 100% certain scientific evidence will certainly produce a very poor ratio between right and wrong decisions." So, even though the need fore more scientific evidence remains, one needs to consider improvement of shift work conditions to reduce its adverse health effects.

Our results imply that the reported elevated CVD risk among shift workers is directly related to working in shifts, and, except for smoking, not so much a result of changes in lifestyle. The negative health consequences of shift work therefore call for a careful consideration of the need for shift work. However, as shift work is regarded a necessary and unavoidable part of the modern society and it's "24-hour economy", strategies for disease prevention are needed to reduce its negative consequences. One of the more easily achievable measures is an optimisation of the rotation schedule. Only a limited number of studies regarded possible differences in health impact between different shift schedules. Most studies so far, have suggested that fast forward rotating shift schedules have less negative health consequences compared with other schedules currently in use[66; 103]. Our findings do support these previous findings. So, we would advise a change to a fast forward rotating shift schedule for all those departments still operating under other shift schedules. Furthermore, arrangements for an easy transfer to a daytime job for shift workers with shift related health complaints or older shift workers would be recommended. It might be worthwhile to advise shift workers about possible health effects of their work. One could think of information about healthy eating habits, meal timing during the different shifts (which might be a possible factor for reducing the CVD risk, although its scientific foundation is not yet very strong). And, last but not least, considering the increased cigarette consumption among shift workers, there might be sufficient cause for occupational health services to start a persuasive no smoking campaign, especially aimed at shift workers.

Future research

Although the evidence is sufficient for certain preventive measures, there is still a great need for more research in to health consequences of shift work. So far, only a very limited number of studies have been conducted looking at ways to decrease the negative health impact of working in shifts by adjusting the work schedule. More information from intervention studies, evaluating the effectiveness of preventive strategies improving the (CVD) health of shift workers is therefore needed. The interventions to consider would be on the rotation schedule, meal timing, and improvement of the availability and quality of canteen foods during the night.

We would also suggest studies with a long-term follow up (several years). This might provide additional information regarding the course of the change in CVD risk factors on the longer (> 1 year) term. It is important to discover if, and after what time lag, the reported shift work related changes will develop. Furthermore the conflicting findings of the one-year decrease in BMI in shift workers versus the reported positive correlation between shift work experience and BMI, warrants further study. This might be done by investigating the impact of shift and night work on the digestive process, lipid metabolism and thermogenesis. A detailed profile of blood lipids during one or more shift schedules in a group of shift workers might provide more insight of the effects of meal timing and disturbance of circadian metabolic processes. Another way to further investigate this conflicting finding, might be the conduct of an intervention study, aimed at the effects of changed meal timing on the lipid profile and metabolism. This study might provide valuable information whether or not meal timing is an important factor in the relation between shift work, BMI and CVD.

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Summary

In The Netherlands, about one million people are working in a diversity of shift work jobs that include working at night. Evidence of an elevated cardiovascular disease (CVD) risk in people working in shifts has grown over the last two decades. An excess risk of 40 % has been given as the most reasonable risk estimate. So far, the factors responsible for this elevated risk are not elucidated. One of the factors involved might be an unfavourable impact of shift work on cardiac control, reflected by an increased frequency of premature ventricular complexes (PVC's) or changes in heart rate variability (HRV). The frequency of PVC's is regarded as an indicator of arrhythmogeneity and has been associated with an elevated CVD risk and. HRV can be regarded as a marker of autonomic regulation of the heart, which has been inversely correlated to an increased CVD morbidity and mortality. Also shift work related changes in other biological (e.g. blood pressure, body mass index, waist to hip ratio, and blood cholesterol) or lifestyle CVD risk factors (e.g. dietary habits, smoking, and decreased leisure time physical activity) might contribute to the elevated CVD risk among shift workers.

Most studies which investigated the relation between shift work and biological or lifestyle risk factors were small scale and of a cross-sectional design. Furthermore, due to different selection processes between the shift workers and control groups working in daytime most of these studies were susceptible to bias. This might have resulted in the considerable discrepancies between the studies conducted so far. Insight into the factors involved in the elevated CVD risk among shift workers, however, might provide clues for prevention.

In our study, the influence of working in shifts on cardiac control and other biological and lifestyle cardiovascular disease risk factors was investigated, taking into account the methodological limitations of previous studies. The main study comprised of a longitudinal study among 227 subjects starting with a shift work job and 150 controls starting in a new daytime job. In all subjects biological and lifestyle risk factors were measured just after the start of a new job. These measurements were repeated after one year. The level of PVC frequency and HRV and their one-year changes were assessed in a sample of the total research population. For these factors, not only the one-year changes but also short-term influences of working nights and other work conditions were studied. In addition, using the cross-sectional data from the entire study population the relation between shift work history, shift work status and baseline cardiovascular risk factor levels was investigated.

Chapter 2 describes the analysis of one-year changes in cardiac control (arrhythmogeneity and autonomic regulation of the heart). On average two weeks after the start of a new job the frequency of PVC's and HRV were measured in 49 shift workers and 22 control subjects working in daytime. These measurements were repeated after one year. The frequency of PVC's increased significantly in shift workers over the one-year follow up, compared with day workers. The frequency of ventricular extrasystoles increased in 48.9 % of the shift workers, and in 27.3 % of the day workers. The Spearman correlation coefficient between the number of worked nights and the change in frequency of PVC's was 0.33 ($P = 0.004$). HRV displayed a small, non-significant change in a non-favourable direction for both the shift and day workers (one-year change in SDNNi, the mean of five-minute standard deviations of normal beat to beat intervals, an indicator of the overall level of HRV, in shift workers: -2.0 msec; in day workers –7.0 msec). These findings indicate that long term-changes in arrhythmogeneity, but not in cardiac autonomic control, might be related to the elevated cardiovascular risk in shift workers.

To assess the influence of working at night on cardiac autonomic control, HRV levels were compared between a day on morning shift and a day on night shift within a group of shift workers (chapter 3). Within person differences between morning and night shift of 24-hour mean HRV measures and of the mean values during sleep and work were calculated. Also, possible modification of the reported effects by the shift schedule was determined. We found a significantly elevated mean level of %LF (relative contribution of low frequency power component to the total heart rate variability) during sleep following a night shift compared with sleep following a day shift (%LF + 3.04, $P < 0.01$). This difference was not compensated during another time of the day. These results suggest an increased sympathetic activity during a sleep after night shift. This might be caused by a poorer sleep quality. The magnitude of the reported effects was related to the shift schedule with the most unfavourable difference in subjects on a medium speed backward rotating schedule.

Analysis of heart rate variability (HRV) has been suggested as a way to study effects of work related stresses on the cardiovascular autonomic regulation. In chapter 4 we studied the influence of stress related work conditions on HRV. Cross-sectional data from subjects who underwent a 24-hour ECG (Holter) recording was used to analyse the relation between the potential workplace stressors job strain, workplace noise and shift work with HRV. Mean HRV values during sleep and work were calculated in 135 twenty-four-hour ECG recordings. Shift workers displayed significantly decreased levels of SDNNi (the mean of five-minute standard deviations of normal beat to beat intervals, an indicator of the overall level of HRV) levels during sleep, compared with the day workers (multivariate adjusted least square mean values: 69.3 and 85.8 msec, respectively: $p < 0.05$). This finding indicates a less active cardiovascular autonomic regulation among shift workers during sleep. We also found evidence for a moderate influence of job strain and workplace noise on the % LF during work, adjusted for the %LF during sleep. This might indicate that exposure to these work related stresses is related to a short-term increase in sympathetic activity. It was therefore concluded that the analysis of HRV might provide a useful tool in the study of short-term physiological effects of work related stresses on the cardiovascular system.

The analyses of the one-year changes, compared between the day- and shift workers are described in chapter 5. At baseline and after one year, biological (Body Mass Index, Waist to Hip ratio, LDL, HDL cholesterol, blood pressure) and lifestyle (smoking, physical activity and energy, alcohol and fat intake) cardiovascular risk factors were measured. The number of cigarettes smoked per day was found to be significantly increased in shift workers compared with day workers (+ 12.1% and - 9.6% respectively, a difference of 2.5 cigarettes per day; $p < 0.05$). Also the number of smokers increased more among the shift workers compared with the day workers, but this difference was not significant. Contrary to our expectation, both body mass index (BMI) and LDL/HDL cholesterol ratio decreased significantly in shift workers compared with day workers (average change in BMI: -0.31 kg/m^2 or 1.3 % and +0.13 kg/m^2 or 0.6 % respectively, $p < 0.01$; change in LDL/HDL ratio: -0.33 and -0.13 respectively $p < 0.01$). No different changes between the shift- and day workers were found in any of the other included biological and lifestyle cardiovascular risk factors.

In chapter 6 the relation between BMI and WHR and shift work history was described, analysed in a cross-sectional analysis. A significant positive relationship was observed between BMI and waist to hip ratio (WHR) and duration of shift work experience, adjusted for age. The linear regression coefficients, with additional adjustments for sex, smoking status, physical activity and educational level were 0.12 kg/m^2, or 5 ‰, per year in shift work for BMI ($P < 0.05$) and 0.0016, or 1.9 ‰ per year in shift work for WHR ($P < 0.05$). These results suggest a relationship between years worked in shifts with BMI and WHR for both males and females.

The main findings of the preceding chapters were discussed in chapter 7. The major advantage of the longitudinal study design, as used in our study, is a minimisation of bias. Nevertheless, bias might still be present due to selective drop out, measurement errors or confounding factors as socio-economic status or differences in working conditions. However, due to strict measurement protocols, and a thorough evaluation of possible confounding, we consider the amount of bias to be small and have lead to a non-differential underestimation of the true effects. Nevertheless, we consider the power of the study to be sufficient to detect relevant changes. For cross-sectional analysis baseline differences between shift and day workers before employment have to be regarded as an important source of selection bias for the comparisons between both groups. These differences might be caused by differences in socio-economic class between the shift and day workers, or might be caused by pre-job selection processes.

In conclusion, we found indications that the elevated CVD risk among shift workers is, at least partly, due to unfavourable changes in the cardiovascular system. We regard the reported increase in PVC frequency in shift workers as found in this study, more as an indicator of these unfavourable changes than as an true precursor of cardiovascular disease. It might be that long-term exposure to the reported night shift related short-term increases in sympathetic activity are related to this increased PVC frequency among shift workers. These findings demonstrated that independent from changes in lifestyle and other biological cardiovascular risk factors, working at night has unfavourable influences on the cardiovascular system. We also found indications that the unfavourable effect differed between distinct rotation schedules, with the highest effect in subjects in the medium speed backward rotation schedule. For smoking, a higher increase in the shift workers as compared with the day workers was found. Smoking might therefore also be regarded as a possible factor in the relation between shift work and CVD. We did not find evidence for an unfavourable change in any of the other biological or lifestyle risk factors during a year of shift work. Only for BMI a positive correlation between shift work experience and baseline BMI was found, but this finding seems to be in conflict with to the one-year decrease in BMI in the shift compared with the day workers. Whether this is only a chance finding or reflects a true effect indicating a one-year decrease followed by an increase, warrants further study.

As we found that greatest unfavourable effects in the workers on a medium speed backward rotating shift schedule we would recommend an adaptation of these work schedules towards the fast forward rotating shift schedule design (working 1-3 morning shifts, followed by 1-3 evening shifts and 1-3 night shifts in a row). Assessment of the effectiveness of work schedule optimisation in reducing the potential negative health impact of shift work is an important topic for future research. Furthermore, elucidation of mechanisms responsible for the reported increases in PVC frequency and reported changes in BMI should be considered.

Samenvatting

In Nederland werken ongeveer een miljoen mensen regelmatig 's nachts. In het merendeel van de gevallen gaat het om werk in ploegendienst. Er zijn aanwijzingen dat werk in ploegendienst gepaard gaat met een verhoogd risico op hart- en vaatziekten. Het extra risico als gevolg van werken in ploegendienst wordt geschat op 40 %. Welke factoren dit verhoogde risico veroorzaken is nog niet bekend. Mogelijk speelt een verstoorde hartregulatie hierbij een rol. Hiervan kan een indruk worden verkregen via de frequentie van het aantal extrasystolen en via de hartritmevariabiliteit (HRV). Het frequent optreden van ventriculaire extrasystolen duidt op een toegenomen gevoeligheid van het hart voor ritmestoornissen en gaat gepaard met een verhoogd risico voor het krijgen van hart- en vaatziekten. HRV is een non-invasieve indicator voor het functioneren van de autonome hartregulatie. Een geringe HRV is geassocieerd met een verhoogde cardiovasculaire morbiditeit en mortaliteit. Naast een verstoorde hartregulatie worden ook met ploegendienst samenhangende veranderingen in andere biologische risicofactoren of veranderingen in leefgewoonten genoemd als mogelijke oorzaak voor het verhoogde risico.

De meeste studies naar ploegendienst en risicofactoren zijn dwarsdoorsnedenonderzoeken en betreffen slechts een relatief klein aantal personen. Bij de meeste van deze studies is bias door een mogelijk hogere uitval van werknemers met aan ploegendienst gerelateerde gezondheidsklachten, waarschijnlijk. Een beter inzicht in de factoren die verantwoordelijk zijn voor het verhoogde risico op hart- en vaatziekten onder ploegendienstwerkers, kan belangrijk zijn voor het nemen van effectieve preventieve maatregelen. Daarom hebben wij in deze studie onderzocht welke risicofactoren voor hart- en vaatziekten mogelijk veranderen na aanstelling in ploegendienst. Het gaat hier om de hartregulatie, biologische risicofactoren voor hart- en vaatziekten (overgewicht, bloeddruk, en cholesterolspiegel) en ongezonde leefgewoonten (rook- en eetgewoonten en lichamelijke activiteit). De studie is uitgevoerd onder 227 mensen die begonnen aan een nieuwe baan in ploegendienst en 150 controles die begonnen aan een nieuwe baan in dagdienst. Bij alle deelnemers is, gemiddeld na twee weken en een jaar later het niveau van de genoemde factoren vastgesteld. In een subpopulatie zijn tevens met behulp van 24-uur Holter registraties de frequentie van ventriculaire extrasystolen, de HRV gemeten. Bij de ploegendienstwerkers is bovendien het korte-termijn effect van een nachtdienst op de HRV bepaald.

In hoofdstuk 2 worden de veranderingen gedurende een jaar in de frequentie van het aantal extrasystolen en de hartritme variabiliteit beschreven bij 49 personen in ploegendienst en 22 controles van mensen in dagdienst. De frequentie van het aantal ventriculaire extrasystolen is significant meer (48,5%) gestegen bij de personen die een jaar in ploegendienst hebben gewerkt in vergelijking met de personen die een jaar in dagdienst hebben gewerkt (27,3%). De correlatie tussen het aantal gewerkte nachtdiensten en de verandering in de frequentie van ventriculaire extrasystolen was 0.33 (P = 0.004). De verandering van de HRV in dat jaar was weliswaar in een gunstige richting , maar klein, en niet significant voor zowel de dag- als ploegendienstwerkers. De verandering tussen de voor en an meting in 24-uurs SDNNi, een maat voor de totale hoeveelheid HRV, berekend als een gemiddelde van alle vijf minuten standaarddeviaties van de tijdsintervallen tussen normale hartslagen, was voor de ploegendienstwerkers –2,0 msec en voor de dagdienstwerkers –7,0 msec. Hieruit kan worden geconcludeerd dat veranderingen in de gevoeligheid voor ritmestoringen mogelijk een rol spelen in het ontstaan van het verhoogde risico op hart- en vaatziekten bij ploegendienstwerkers. Er zijn geen aanwijzingen gevonden voor het feit dat lange-termijn-veranderingen in de autonome hartregulatie hierbij een rol van betekenis spelen.

Individuele verschillen tussen dag- en nachtdienst in de 24-uurs gemiddelde HRV en in de gemiddelde niveaus tijdens slaap en werk zijn berekend in 135 24-uurs ECG opnames (hoofdstuk 3). Er zijn significant hogere niveaus van het %LF (een maat voor de relatieve bijdrage van de laag frequent power component aan de totale HRV) gevonden tijdens slaap na een nachtdienst in vergelijking met het niveau tijdens slaap na een dagdienst. Dit verschil wordt niet gecompenseerd op een ander tijdstip van de dag. Dit duidt op een verhoogde sympathische activiteit tijdens de slaap na een nachtdienst. Dit zou veroorzaakt kunnen worden door minder diepe slaap na deze dienst. De grootte van de gevonden effecten verschilt significant bij de verschillende ploegendienstroosters. Het minst gunstige effect is gevonden bij de personen die werken volgens een rooster waarin eerst drie tot vijf dagen in nachtdienst, dan drie tot vijf dagen middagdienst en vervolgens drie tot vijf dagen in dagdienst wordt gewerkt.

Verschillende studies hebben een effect van acute bloostelling aan stressvolle omstandigheden op de hartritmevariabiliteit (HRV) beschreven. Mogelijk kan analyse van HRV ook worden gebruikt voor het bepalen van het effect van werkgebonden stress op de autonome regulatie van het hart. In hoofdstuk 4 worden de resultaten beschreven van het effect van verschillende mogelijk stressvolle werkomstandigheden op de HRV. Hiervoor is gebruik gemaakt van de HRV-niveaus die gemiddeld twee weken na het begin in een nieuwe baan zijn bepaald. Voor werknemers met hoge "Job strain" en werknemers met veel lawaai op de werkvloer is een matig verhoogd %LF tijdens het werk, gecorrigeerd voor het %LF tijdens de slaap gevonden. Dit houdt waarschijnlijk verband met een korte-termijn verhoging van de sympathische activiteit tijdens de blootstelling aan deze factoren

In hoofdstuk 5 wordt de verandering in risicofactoren voor hart- en vaatziekten vanaf de aanstelling tot een jaar later vergeleken tussen de dag- en ploegendienstwerkers. Na het begin van een nieuwe baan en na een jaar zijn het niveau van biologische risicofactoren (Quetelet-index, heup-taille-ratio, LDL-, HDL-cholesterol, bloeddruk) en het gedrag (rookgewoonten, lichamelijke activiteit, energie, vet- en alcoholinname) bepaald en is de verandering na een jaar berekend. Het aantal sigaretten dat door rokers per dag is gerookt, stijgt significant meer bij de ploegendienstwerkers in vergelijking met de dagdienstwerkers (respectievelijke veranderingen van +12,1 % en –9.6 %, een verschil van 2,5 sigaret per dag; $p < 0.05$). Ook is het aantal rokers bij de ploegendienstgroep meer gestegen dan bij de dagdienstgroep, maar dit verschil is niet significant. Tegen onze verwachting in is bij de werknemers in ploegendienst een significant grotere daling van de Quetelet-index en daarmee gerelateerd de LDL/HDL-cholesterol-ratio gevonden vergeleken met de werknemers in dagdienst (verandering in Quetelet-index respectievelijk: -0.31 kg/m^2 of 1.3 % en +0.13 kg/m^2 of 0.6 %, $p < 0.01$; verandering in LDL/HDL-cholesterol-ratio: -0.33 and -0.13, $p < 0.01$). Tussen de dag- en ploegendienstwerkers is geen verschillende verandering gevonden voor een van de andere biologische of aan leefwijze gerelateerde risicofactoren.

In hoofdstuk 6 wordt de relatie tussen het aantal jaren dat er voor de baseline-meting in ploegendienst is gewerkt gerelateerd aan overgewicht. Er is een positieve correlatie gevonden tussen het aantal jaren dat een deelnemer in ploegendienst heeft gewerkt en zijn of haar Quetelet-index en heup-taille-ratio. De lineaire regressiecoëfficiënten, gecorrigeerd voor leeftijd, geslacht, rookgewoonten, lichamelijke activiteit en opleiding zijn 0,12 kg kg/m^2, oftewel 5 ‰, per in ploegendienst gewerkt jaar voor de Quetelet-index ($P < 0.05$) en 0,0016, oftewel 1.9 ‰ per in ploegendienst gewerkt jaar voor de heup-taille ratio ($P < 0.05$). Deze resultaten duiden op een samenhang van het werken in ploegendienst met een toename van het lichaamsgewicht en een minder gunstige verandering van de verdeling van het lichaamsvet.

In hoofdstuk 7 worden de belangrijkste resultaten uit de voorafgaande hoofdstukken samengevat en bediscussieerd. Het belangrijkste voordeel van de gekozen longitudinale opzet van dit onderzoek is dat bias door verschillen die voortkomen uit een verschil in het selectieproces tussen ploegendienst- en dagdienstwerkers, wordt geminimaliseerd. Meetfouten, selectieve uitval of de invloed van verstorende variabelen, zoals sociaal-economische status, kunnen echter nog steeds de gevonden resultaten hebben beïnvloed. Door het uitvoeren van de metingen volgens een strikt protocol en een nauwgezette evaluatie van mogelijke confounding verwachten wij dat invloed van bias heeft geleid tot een kleine non-differentiële onderschatting van de gerapporteerde resultaten. De resultaten, die gebaseerd zijn op de analyse van de gegevens uit dwarsdoorsnedenonderdeel, kunnen verstoord zijn door verschillen tussen dag- en ploegendienstwerkers die reeds aanwezig zijn vóór zij met hun baan beginnen. Deze verschillen zouden kunnen komen door verschillen in sociaal-economische status tussen de dag- en ploegendienstwerkers maar ook door mogelijke verschillen in (zelf)selectie van dag- en ploegendienstwerkers.

Samenvattend kunnen wij constateren dat wij een aanwijzing hebben gevonden voor het feit dat een verstoring van de hartregulatie een rol speelt bij het verhoogde risico op hart- en vaatziekten onder werknemers in ploegendienst. De gevonden verhoging van de frequentie van ventriculaire extrasystolen bij de ploegendienstwerkers zien wij meer als een indicator voor deze verstoring dan als een voorstadium van een mogelijke aandoening. Langdurige blootstelling aan de op korte termijn met nachtdienst samenhangende verhoging van de sympathische activiteit zou één van de mogelijke oorzaken kunnen zijn van de verhoging van het aantal ventriculaire extrasystolen. Deze bevindingen laten zien dat, onafhankelijk van verandering in andere cardiovasculaire risicofactoren of leefwijze, ploegendienst een ongunstig effect kan hebben op het hart. Daarnaast is geconstateerd dat de mate van het effect af kan hangen van het roostertype. De sterkste effecten zijn gevonden bij het achterwaarts met matige snelheid roterende schema. Ook de gevonden toegenomen consumptie van sigaretten onder de ploegendienstwerkers zou een deel van het verhoogde risico op hart- en vaatziekten kunnen verklaren. De andere onderzochte risicofactoren lijken dit verhoogde risico niet te kunnen verklaren. De enige uitzondering vormt mogelijk de Quetelet-index. Hiervoor is weliswaar een (als gunstig geziene) verlaging geconstateerd tijdens het jaar in ploegendienst maar in een analyse van de dwarsdoorsnedenresultaten is een positieve correlatie gevonden tussen het aantal in ploegendienst gewerkte jaren en de Quetelet-index. Of dit slechts een toevallige bevinding is of dat het een afspiegeling is van een daling tijdens het eerste jaar in ploegendienst, gevolgd door een toename, zal nader moeten worden onderzocht.

Omdat wij de meest ongunstige effecten hebben gevonden in werknemers bij een achterwaarts roterend rooster adviseren wij een aanpassing van deze roostertypes naar een snelle voorwaartse rotatie (een tot drie dagdiensten, gevolgd door een tot drie avonddiensten en daarna een tot drie nachtdiensten).

Onderzoek naar de effectiviteit van het optimaliseren van ploegendienstrotatieschema's op een mogelijke reductie van de negatieve gevolgen voor de gezondheid van het werken in ploegendienst zien wij als een belangrijk onderwerp voor toekomstig onderzoek. Daarnaast zal er aandacht moeten worden geschonken aan het uitzoeken van mechanismen die ten grondslag liggen aan de gevonden ploegendienst-gerelateerde-stijging in de frequentie van het optreden van ventriculaire extrasystolen en de mogelijke veranderingen in overgewicht.

Nawoord

Ruim zes jaar nadat de eerste ideeën over een onderzoek naar hart- en vaatziekten bij ploegendienstwerkers het daglicht zagen, schrijf ik nu de laatste regels van dit proefschrift. Dat was nooit gelukt zonder de hulp en steun van een groot aantal mensen. Op deze plaats wil ik dan ook iedereen bedanken die een bijdrage geleverd heeft aan de uitvoering van dit onderzoek en het schrijven van dit proefschrift. In de eerste plaats komen hierbij alle deelnemers. Zonder jullie geheel belangeloze medewerking was dit onderzoek in het geheel niet mogelijk geweest. Dit geldt vanzelfsprekend ook voor de contactpersonen in de verschillende bedrijven en instellingen die hebben bijgedragen aan het groot aantal deelnemers. Met name Marja Vos van Hilten, Drs. J.W.M. van Rooyen, Drs. W.J.A.M. Elshof, Dr. Ir. J.R. Durinck, Marc Razoux Schultz, mw. C Veldhuizen, Ans Pals, mw. van Oosterhout, Marja van Ingen, Theo van der Molen en Dhr. Gerritsen, wil ik bij deze hartelijk bedanken voor alle hulp bij het werven van de deelnemers en de hulp bij de uitvoering van het veldwerk.

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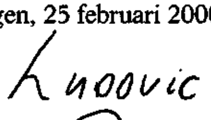

About the author

Ludovic Gertrudis Paulus Maria van Amelsvoort was born on January 5, 1967, in Heesch, The Netherlands. In 1985 he completed secondary school, VWO, at the Titus Brandsma College, Oss. He started in 1985 with the study "Environmental Sciences" at the Wageningen Agricultural University. He graduated in 1991 with majors in Epidemiology and Public Health, Occupational Hygiene and Air Pollution. From 1991 until 1994 he worked as a research associate at the Departments of Epidemiology and Public Health and Air Pollution of the Wageningen Agricultural University. During this time he was engaged in research and education on the field of occupational hygiene and epidemiology. In 1994 he was involved in the design and writing of the project proposal which resulted in the conduct of the study as described in this thesis. Before he was appointed as a PhD student on this project in July 1995 he worked as a free lance writer for the NIA (Netherlands Institute on Working Conditions) and organised an EU workshop on "Coronary heart disease among truckdrivers". Currently, he is employed as a postdoctoral fellow at the department of epidemiology of the Maastricht Health Research Institute for Prevention and Care (HEALTH).