Shift Work and the Risk of Coronary Artery Disease: A Cardiac Computed Tomography Angiography Study

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Keywords

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Abstract

Aims: Shift work disrupts the normal circadian rhythm and is associated with risk factors for coronary artery disease (CAD) and a higher incidence of CAD morbidity and mortality. Cardiac computed tomography angiography (CCTA) is a robust noninvasive modality for assessing the presence, extent, and severity of CAD. We sought to investigate whether shift workers are prone to a higher burden of CAD compared to non-shift workers. **Methods:** We conducted a historically prospective study in consecutive patients who underwent CCTA and answered a telephonic questionnaire. Due to significant differences in age and gender, we compared 89 well-matched pairs of shift workers and non-shift workers with the use of propensity scores. **Results:** Our cohort consisted of 349 participants, of whom 94 (26.9%) were shift workers. The mean age was 50.7 years, and 62.5% were males. After pairing, we showed that shift workers had a higher prevalence of CAD than non-shift workers (74.2 vs. 53.9%, respectively, $p = 0.01$), and a lower prevalence of coronary calcium

scores of zero (46.8 vs. 63.4%, respectively, $p = 0.034$). Stenosis $>50\%$ was more prevalent in shift workers than in non-shift workers (20.2 vs. 11.2%, respectively, $p = 0.006$), and the extent of CAD (defined as the presence of ≥ 1 -vessel disease) tended to be higher in shift workers than in non-shift workers (25.8 vs. 13.5%, respectively, $p = 0.06$). **Conclusions:** In this CCTA study, we showed in a well-matched cohort of consecutive patients that shift workers had a higher prevalence and extent of CAD than non-shift workers.

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Introduction

Based on previous reports, shift work can be defined as working hours extending beyond conventional daytime working hours (approximately from 8 a.m. to 5 p.m.) [1, 2]. The full spectrum of shift work comprises regular evening or night shifts, rotating, split, on-call, or 24-h shifts, irregular schedules, and other non-day schedules. Shift work is known to disrupt the circadian rhythm, wakefulness, eating patterns, and social activities [3]. Previous reports have shown that shift workers have a higher prevalence of CAD risk factors, including increased ciga-

rette smoking, increased blood pressure, increased serum cholesterol and glucose levels, and higher urinary adrenaline excretion [4, 5]. Data regarding the association between shift work and cardiovascular events (such as myocardial infarction and cardiovascular mortality) are scarce and were mainly drawn from the Nurses' Health Studies [1, 2]. Cardiac computed tomography angiography (CCTA) is a reliable and robust method for estimating the presence, severity, and extent of CAD [6]. In this study, we sought to assess the prevalence and the degree of CAD among shift workers, as detected by CCTA, compared with non-shift workers.

Patients and Methods

Definition of Shift Work

In accordance with previous large-scale studies [1, 2], we defined shift work occupation as working hours between 11 p.m. and 7 a.m. at least 3 times per month.

Participants

The trial was conducted as a historical cohort, single center study. Consecutive patients who underwent CCTA in our facility between February 2011 and February 2015 were telephonically addressed and asked if they agree to participate in this study. After obtaining their nonwritten informed consent, and using a specially designed telephonic questionnaire (Appendix 1), they were interviewed regarding their routine working schedules prior to the CCTA test. Medical history including weight, height, physical activity, and CAD risk factors (i.e., positive family history, hypertension, diabetes mellitus, hyperlipidemia, and smoking) was retrieved from past medical records and confirmed during the telephonic questionnaire. Additionally, medical records were reviewed for any hospitalizations and coronary interventions following the CCTA scan, and the results were confirmed during the telephonic questionnaire. The study was approved by the local institutional ethics committee.

CCTA Method

All patients underwent CCTA (Philips 256 iCT Brilliance; Philips Medical Systems, Cleveland, OH, USA). The CCTA protocol was described previously [7]. Shortly, a bolus of 50–70 mL of iodinated contrast medium (Iomeron; Schering, Berlin, Germany) was injected according to body weight, and a gated prospective scan was performed during breath hold, obtaining images from mid-diastole (at 73, 78, and 83% of the cardiac cycle). Then, CCTA specialists (H.S. and G.A.) analyzed the presence, extent, and severity of coronary artery plaques in a dedicated work station, as well as the degree of coronary calcium score (CCS), both manually and with the use of a unique software, and consensus measurements were obtained.

Statistical Analysis

Continuous variables were evaluated for normal distribution using a histogram and a Q-Q plot. Normally distributed variables were described using means and standard deviations, and nonnor-

mally distributed variables were described as medians and interquartile ranges. Categorical variables were expressed as frequency and percentage.

Continuous variables were compared using the independent sample *t* test, analysis of variance, Mann-Whitney test, or Kruskal-Wallis test as appropriate. Categorical variables were compared using the χ^2 test as appropriate.

Multivariate logistic regression was used to evaluate the association between outcome and prior shift work while controlling for confounders. Logistic regression included 2 blocks: the first one included prior shift work, age, and gender, and the second one included all other risk factors. Logistic regression was applied using the Hosmer-Lemeshow test for goodness of fit.

A propensity score was used to match exposed (shift workers) and unexposed (non-shift workers) participants in a 1:1 ratio and calculated using logistic regression. Variables included in the logistic regression were age, sex, hypertension, hyperlipidemia, diabetes mellitus, family history of CAD, history of smoking, body mass index (BMI), physical activity, and the clinical status of the patient (ambulatory vs. hospitalized).

An exposed participant was eligible to match an unexposed one if the absolute value of the difference in the propensity scores was $\leq 5\%$.

Matched samples were compared using the McNemar test and the Wilcoxon test. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

SPSS (released 2016: IBM SPSS Statistics for Windows, version 24.0; IBM, Armonk, NY, USA) was used for statistical analysis.

Results

Between February 2011 and February 2015, 743 patients underwent CCTA in our facility. Twenty-four patients were excluded due to known prior CAD, and 31 cases were excluded due to low-quality test results. We could not establish telephone contact with 129 patients, and 181 refused to participate in the study. According to medical records, 29 died. Finally, the study cohort included 349 patients. The mean age was 50.7 ± 11 years, with male predominance (62.5%). Most (64%) participants underwent the examination as outpatients, and the remainder (36%) as hospitalized patients. The indication for CCTA was atypical chest pain with low-to-intermediate pretest probability for obstructive CAD. The outpatients had < 2 risk factors, and the inpatients had ≥ 2 risk factors or borderline ECG changes. None of the participants had elevated cardiac biomarkers.

Ninety-four participants (26.9%) reported previous ($n = 72$, 20.6%) or current ($n = 22$, 6.3%) occupation in a shift work pattern. The mean duration of occupation in a shift work pattern was 10.3 ± 6.1 years, and the number of shifts done per month was 8.4 ± 6.4 . Shift workers tended to be males (76.6% shift workers vs. 57.3% non-shift

Table 1. Baseline characteristics

	Shift workers (<i>n</i> = 94)	Non-shift workers (<i>n</i> = 255)	<i>p</i> value
Age, years	47.8±11.1	51.7±9.8	0.024
Males, <i>n</i>	72 (76.6%)	146 (57.7%)	0.004
Occupation, years	10.3±6.1	–	–
Family history of CAD, <i>n</i>	31 (33%)	80 (31.4%)	0.79
Diabetes mellitus, <i>n</i>	13 (13.8%)	29 (11.4%)	0.58
Hypertension, <i>n</i>	36 (38.3%)	87 (34.1%)	0.52
Hyperlipidemia, <i>n</i>	45 (47.9%)	129 (50.6%)	0.71
Ever smoker, <i>n</i>	59 (62.8%)	138 (54.1%)	0.18
BMI	27±3.3	27.5±3	0.41
Physically active, <i>n</i>	31 (32.9%)	111 (43.5%)	0.08
Hospitalized, <i>n</i>	30 (32%)	97 (37.5%)	0.11

BMI, body mass index; CAD, coronary artery disease; occupation, duration of occupation in a shift work pattern; physically active, >30 min of physical exercise ≥3 times a week.

Table 2. Baseline characteristics: paired data

	Shift workers (<i>n</i> = 89)	Non-shift workers (<i>n</i> = 89)	<i>p</i> value
Mean age, years	49	48	0.53
Interquartile range	39.5–57	41–55.5	
Males, <i>n</i>	69 (77.5%)	75 (84.3%)	0.26
Family history of CAD, <i>n</i>	29 (32.6%)	25 (28.1%)	0.61
Diabetes mellitus, <i>n</i>	12 (13.5%)	6 (6.7%)	0.14
Hypertension, <i>n</i>	34 (38.2%)	29 (32.6%)	0.52
Hyperlipidemia, <i>n</i>	42 (47.2%)	36 (40.4%)	0.44
Ever smoker, <i>n</i>	55 (61.8%)	50 (56.2%)	0.56
BMI	27±2.5	27.5±2.5	0.48
Physically active, <i>n</i>	26 (29.2%)	29 (32.5%)	0.32
Hospitalized, <i>n</i>	24 (27%)	26 (29.2%)	0.38

BMI, body mass index; CAD, coronary artery disease; physically active, >30 min of physical exercise ≥3 times a week.

workers; *p* = 0.004) and were younger than non-shift workers (47.8 ± 11.1 vs. 51.7 ± 9.8 years, respectively; *p* = 0.024). The prevalence of CAD risk factors, BMI values, and the degree of physical activity did not differ between the two groups (Table 1). As described above, in order to eliminate statistically significant differences in age and gender between the two groups, we conducted paired matching and compared 89 well-matched pairs of shift workers and non-shift workers (Table 2).

Table 3. Cardiac CT angiography: paired data

	Shift workers (<i>n</i> = 89)	Non-shift workers (<i>n</i> = 89)	<i>p</i> value
Presence of atherosclerosis			0.01
No	23 (25.8%)	41 (46.1%)	
Yes	66 (74.2%)	48 (53.9%)	
Number of vessels involved			0.006
0	23 (25.8%)	41 (46.1%)	
1	28 (31.5%)	21 (23.6%)	
2	15 (19.9%)	15 (16.9%)	
3	23 (25.8%)	12 (13.5%)	
CCS			0.011
0	36 (46.8%)	52 (63.4%)	
>0	41 (53.2%)	30 (36.6%)	0.034
1–10	8 (10.4%)	9 (11%)	
11–99	16 (20.8%)	10 (12.2%)	
>100	17 (22.1%)	11 (13.4%)	
Severity of stenosis			0.006
0	23 (25.8%)	41 (46.1%)	
1–50%	48 (53.9%)	38 (42.7%)	
>50%	18 (20.2%)	10 (11.2%)	

CCS, coronary calcium score.

CCTA Results

CCTA results showed presence of CAD in 69.7% of the participants. Overall, and prior to pairing, shift workers had a numerically higher prevalence of coronary artery findings in most parameters. The presence of CAD was demonstrated in 74.5% of shift workers and in 67.9% of non-shift workers (*p* = 0.29). Coronary artery stenosis >50% (20.2 vs. 15.5%, respectively; *p* = 0.3) and 3-vessel CAD were found in a greater extent in shift workers than in non-shift workers (25.5 vs. 19.8%, respectively; *p* = 0.21). A CCS of zero was found in 45.7% of shift workers and 54.6% of non-shift workers (*p* = 0.13), and a CCS >100 Agatston units was found in 23.5% of shift workers and 15.5% of non-shift workers (*p* = 0.12).

As described above, in order to eliminate statistically significant differences in age and gender between groups, we conducted a propensity match score in a 1:1 ratio. Examining the results after pairing showed that shift workers had a statistically significantly higher extent of CAD (Table 3). CAD was present in 74.2% of shift workers and 53.9% of non-shift workers (OR 2.38, CI 1.21–4.96, *p* = 0.01), >1-vessel disease was shown in 25.8% of shift workers and 13.5% of non-shift workers (*p* = 0.06) (Fig. 1), stenosis >50% was more prevalent in shift work-

Fig. 1. Number of coronary arteries involved.

Fig. 2. Degree of coronary artery stenosis.

Fig. 3. Calcium coronary score.

ers (20.2 vs. 11.2%, respectively; $p = 0.006$) (Fig. 2), and a CCS of zero was shown in 46.8% of shift workers and 63.4% non-shift workers ($p = 0.034$) (Fig. 3).

Follow-Up

The mean elapsed time between the CCTA scan and the telephonic questionnaire was 18 ± 10 months. During this period, 13 (13.8%) of the shift workers and 33 (12.9%) of the non-shift workers were hospitalized ($p = 0.52$), most of them due to cardiovascular reasons (11 and 9.8%, respectively; $p = 0.7$), and 8.5% of the participants under-

went a coronary intervention (9.6 and 7.8% of the shift workers and non-shift workers, respectively; $p = 0.12$). Pairing did not change the results (Table 4).

Discussion

In this CCTA study, we demonstrated that in well-matched participants who had similar background risk factors, shift work was shown to be associated with the presence and degree of CAD and CCS.

Table 4. Outcomes during follow-up

Outcome	Shift workers (<i>n</i> = 89)	Non-shift workers (<i>n</i> = 89)	<i>p</i> value
Hospitalization	13 (14.6%)	9 (10.1%)	0.13
Due to CV cause	10 (11.2%)	6 (6.7%)	0.11
Coronary intervention	9 (10.1%)	6 (6.7%)	0.17
CV, cardiovascular.			

The circadian rhythm has a significant impact on human well-being [8, 9]. Shift work impairs the circadian rhythm [10], causing an elevation in stress-related neurohormones [11] and abnormal inflammatory responses [12], and even has a direct effect on the normal pattern of blood pressure with an observed loss of sleep-related blood pressure dipping [13]. In addition, shift workers were found to suffer from a higher burden of cardiovascular risk factors and harmful behavior, including alcohol abuse, cigarette smoking, overweight, and lack of physical activity [3]. Accordingly, shift work has been shown to be related to higher rates of cardiovascular morbidity and mortality [1]. Nevertheless, this pattern of results was found to be inconsistent [14].

In the present study, we sought to investigate the suggested correlation between shift work and cardiovascular morbidity in a unique way: the direct measurement of the extent of CAD with the use of a sensitive tool – CCTA. The results of our study showed that CAD is more prevalent and severe in shift workers. In addition, another measure of the presence of CAD, positive CCS, was also more prevalent in shift workers. These results were demonstrated in well-matched individuals who had similar baseline risk factors and were not shown to be influenced by the clinical status of the participants. To our knowledge, the only study attempting to examine the effect of shift work on CAD with the use of CCTA was recently done in 110 factory workers [15]. The results of this study showed that night shift workers suffered from a more extensive CAD burden than day shift workers. We believe that our study adds to these data in a number of aspects; first, our study included a larger number of participants,

second, both males and females were represented, and third, since both in our study and in the discussed trial, a statistically significant age difference was demonstrated between both study groups, we believe that our use of propensity matching assisted in improving the accuracy of the results.

Major limitations to our trial are its retrospective nature and its small sample size, which might have also prevented us from showing a statistically significant difference in the rate of outcomes during the follow-up period (Table 4).

In conclusion, this study shows that with the use of CCTA, shift workers were found to have a higher prevalence and extent of CAD.

Conflict of Interest

None of the authors has a conflict of interest.

Funding Source

There was no funding for this research.

Appendix

Questionnaire

- 1 Prior to your coronary CT scan:
 - a Did you ever smoke cigarettes regularly?
 - b Were you diagnosed with hypertension?
 - c Were you diagnosed with elevated blood lipid levels?
 - d Were you diagnosed with type 1 or 2 diabetes mellitus?
 - e Did you suffer from myocardial infarction or cerebrovascular event?
 - f Were you regularly treated with antihypertensives, glucose- or lipid-lowering drugs, aspirin, or anticoagulants, for example?
- 2 Do any of your first-degree relatives (men <55 years of age or women <60 years of age) suffer from a cardiovascular disease?
- 3 Do you regularly exercise? How often?
- 4 Were you ever employed in a shift work schedule?
 - a When?
 - b For how long?
 - c How many times per month?
 - d Do you still work in this pattern?

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