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Impact of shift work on cardiovascular functions in a 10-year follow-up study

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Objectives The purpose of this study was to determine whether shift work affects the heart-rate-adjusted QT interval (QTc) in electorcardiography (ECG) and the blood pressure of workers without overt cardiovascular dysfunction.

Methods At a copper smelter, 158 shift workers and 75 day workers who underwent an ECG examination and blood pressure measurements in 1986 were followed for 10 years. In 1996, biochemical indicators such as high-density lipoprotein cholesterol and triglycerides were measured, together with the QTc.

Results In 1986 and 1996, the QTc was significantly longer in the shift workers than in the day workers. Of 180 workers with a normal QTc (<420 $ms^{1/2}$) in 1986, 15% had developed a prolonged QTc (420 $ms^{1/2}$) in 1996 (18% of the 117 shift workers and 11% of the 63 day workers). Among the workers with a normal QTc in 1986, the shift workers had a significantly longer QTc than the day workers when the QTc was examined in 1996. In addition, shift-day work in the group with a normal QTc was significantly related to the QTc in 1996 after control for age, work duration, biochemical indicators, smoking, and drinking habits. However, the blood pressures of the shift and day workers did not differ significantly, and in 1996 the values of both groups were significantly elevated.

Conclusions These data suggest that shift work is associated with QTc prolongation. This evidence may explain the increased risk for cardiovascular diseases due to shift work.

Key terms blood pressure, cardiovascular effect, heart rate-adjusted QT interval, shift work.

The causal relation between shift work and cardiovascular dysfunction remains unclear, although there is some evidence that shift work contributes to excess cardiovascular morbidity or mortality (1—7). The most reasonable estimate of the relative risk for cardiovascular diseases (CVD) induced by shift work has been suggested to be around 1.4 (3, 7), and other authors have also considered the link between shift work and CVD as causal (1, 2, 6). A few researchers, on the contrary, have reported that shift work does not increase the risk of death from ischemic heart disease (8—11). Much less information has been developed concerning a pathophysiological mechanism of the association between shift work and CVD (2).

In a study on the short-term effect of shift work on hospital nurses, blood pressure and heart rate tended to be higher on night shifts than on evening shifts (12). An elevation in plasma adrenaline was also found after work on night shifts. Likewise, the 24-hour blood pressure and heart rate of white-collar workers have been shown to increase with overtime work (13). The parasympathetic component of heart rate variability in white-collar workers with longer commuting time (≥90 min) has also been reported to be significantly depressed when compared with that in workers with shorter commuting times (<90 min) (14). These findings, taken together, would suggest that cardiovascular functions, especially autonomic nervous functions, can be influenced by shift work.

The purpose of this study was to clarify whether shift work causes cardiovascular changes, especially in workers without overt cardiovascular dysfunction. For this purpose, the heart-rate-adjusted QT interval (QTc) in electrocardiography (ECG) and blood pressure, both of which have been reported to have a close relationship to CVD (15—22), were followed among shift and day workers employed at a copper smelter.

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Subjects and methods

Subjects

The research cohort consisted of 280 workers who underwent a cardiovascular examination in 1986; female workers were not included because the shift workers were all men. In this study, general exclusion criteria such as disorders affecting cardiovascular and nervous functions, retirement from the company, and change of occupation between shift work and day work were applied. For this reason, 40 workers were excluded during the 10-year period: 8 workers suffered from diabetes mellitus; 19 left at retirement age; and 13 transferred from shift work to day work because of occupational unfitness or physical reasons. Furthermore, 7 workers could not undertake the ECG examination by chance in 1996. Finally, 233 workers had been followed for 10 years. Of these, 158 had worked as shift workers (ie, blue-collar workers) in divisions of the roaster, smelter, converter, anode casting, and fire and electrolytic refining. Shift work was predominantly a 4-shift schedule including a day-off shift, 1 week, and a forward rotation system. Seventy-five day workers (ie, white-collar workers) were engaged in administrative and clerical work. There was no significant difference in age between the shift workers (20—48 years, mean 36) and day workers (20—47 years, mean 36). In the early spring of 1996, they underwent the biochemical and physical examinations together with the ECG measurement and filled out a self-rating questionnaire. In spite of the nature of the industry, this plant has employed the latest automated production system with a high standard of industrial hygienic control in which regular monitoring indicated that no heavy exposure to hazardous substances such as lead, arsenic, cadmium, or sulfides had existed.

Methods

The examinations used in this study were among the mandatory health-checkup items under the Industrial Safety and Health Law in Japan. The workers were encouraged not to take drugs, alcohol, or beverages containing caffeine for 12 hours prior to each examination. At the time of the health examinations in 1986 and 1996, systolic and diastolic blood pressure was measured in a quiet setting with the subject in a seated position; thereafter the subject lay quietly supine for 5 minutes, a electrocardiogram (ECG) was recorded using an Autocardina FCP-221 electrocardiograph (Fukuda Denshi Co, Japan) to assess the cardiovascular function in the morning of the day or day-off shift. The electrocardiograph automatically calculated the QTc from the RR and QT intervals of the obtained ECG according to Bazett's formula (23) (ie, QTc = (QT interval)/(RR interval)$^{1/2}$. High-density lipoprotein cholesterol, triglycerides, alanine aminotransferase activity (ALT), fasting blood glucose, and hemoglobin, together with height and body weight to calculate the body mass index, were determined after fasting blood was taken from each worker in the morning of the day, day-off, or night shift. The subjects also completed a questionnaire regarding their past and present histories of illness, smoking, and drinking habits, which were confirmed by an occupational health nurse.

According to the criteria for hypertension published by the World Health Organization (24), the subjects with a systolic blood pressure of <140 mm Hg (<18.62 kPa) and a diastolic blood pressure of <90 mm Hg (<11.97 kPa) were diagnosed as normotensive, those with either a systolic pressure of ≥160 mm Hg (≥21.28 kPa) or a diastolic blood pressure of ≥95 mm Hg (≥12.64 kPa) were diagnosed as hypertensive, and values of 140 to <160 mm Hg(18.62—<21.28 kPa) and 90 to <95 mm Hg (11.97—<21.28 kPa], respectively, were considered to be borderline hypertensive. In addition, a QTc of ≥420 ms$^{1/2}$ was defined as prolonged and a QTc of ≥440 ms$^{1/2}$ was defined as abnormal (16).

Data analysis

The comparison between the cardiovascular data of 1986 and 1996 was made by the paired-sample t-test. The triglyceride and ALT values were transformed into common logarithmic values in the analyses because these data were highly skewed to the left. The differences between the workers with and those without prolonged QTc and between workers with and without hypertension were tested by a 2-way analysis of variance with repeated measurements (SS model of type II). The significance level of the differences between the day and shift workers without prolonged QTc and between the workers from these 2 groups without hypertension was determined using the Student's t-test and an analysis of covariance to control for age, or Fisher exact test.

For the workers without a prolonged QTc (or without hypertension) at the start of the study, the proportion of those with a prolonged QTc (or hypertension) after 10 years was calculated, and a multiple regression analysis was performed to examine the relations of work status (ie, day or shift work), work duration, body mass index, high-density lipoprotein cholesterol, triglycerides, ALT, fasting blood glucose, hemoglobin, age, smoking and drinking habits (15, 25) to the cardiovascular function measured in this study (QTc, systolic and diastolic blood pressure and heart rate). All the analyses were performed using the Statistical Package for the Biosciences (Winesteem Institute of Community Medicine, Japan).

Results

The QTc of the 158 shift workers was significantly longer than that of the 75 day workers in 1986 and 1996 (table

Table 1. Changes in the heart-rate-adjusted QT interval, systolic and diastolic pressure, and heart rate among 75 day workers and 158 shift workers between 1986 and 1996.

	1986		1996		Matched difference		Probability[a]
	Mean	SD	Mean	SD	Mean	SD	
Heart rate-adjusted QT interval ($ms^{1/2}$)							
Day workers	402	17*	397	19**	5	16	0.008
Shift workers	408	19*	409	21**	-1	17	0.573
Systolic blood pressure (mm Hg[b])							
Day workers	127	12	136	15	-9	14	<0.001
Shift workers	124	12	139	17	-15	15	<0.001
Diastolic blood pressure (mm Hg[b])							
Day workers	78	11	86	11	-8	10	<0.001
Shift workers	78	12	88	12	-9	11	<0.001
Heart rates (beats/min)							
Day workers	69	11	72	14	-3	14	0.050
Shift workers	70	10	74	12	-5	11	<0.001

[a] Paired-sample t-test.
[b] 1mm Hg≈0.133 kPa.
* P=0.036, ** P=0.0001 (Student's t test).

1). By contrast, the systolic and diastolic blood pressures and heart rate of both the day workers and the shift workers were significantly elevated after 10 years, but there were no significant differences between the 2 work groups.

Table 2 shows the data of the workers according to the QTc and blood pressures in 1986. The proportion of smokers and the mean values for the QTc and heart rate in 1996 were significantly higher in the cohort with a prolonged QTc than in the cohort with a normal QTc (<420 $ms^{1/2}$). In addition, there was a significant interaction between the QTc and hypertension only in relation to body mass index (table 2).

In 1996, the proportion of prolonged QTc values among the workers who had normal QTc (<420 $ms^{1/2}$) values in 1986 was 15.6% (18% of the shift workers and 11% of the day workers), and the proportion of hypertension in the cohort without hypertension in 1986 was 21.8% (24% of the shift workers and 17% of the day workers). In the group with normal QTc values, the QTc was significantly longer among the shift workers than among the day workers (table 3), although the QTc did not differ between the shift and day workers in 1986.

Table 2. Data obtained from workers when grouped according to the heart-rate-adjusted QT interval (QTc) and blood pressures in 1986. (HDL = high-density lipoprotein, ALT = alanine aminotransferase)

	Without prolonged Qtc (420 $ms^{1/2}$) or hypertension[a] (N=151)				Without prolonged QTc and with hypertension[a] (N=29)				With prolonged QTc and without hypertension[a] (N=37)				With prolonged QTc and hypertension[a] (N=16)				P values by ANOVA[b]	
	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	N	%	Mean	SD	QTc[c]	Hypertension[d,e]
Cardiovascular data in 1986																		
QTc ($ms^{1/2}$)	.	.	398	13	.	.	405	11	.	.	428	9	.	.	437	17	0.000	0.000
Systolic blood pressure (mm Hg[f])	.	.	121	9	.	.	139	10	.	.	122	9	.	.	141	10	0.634	0.000
Diastolic blood pressure (mm Hg[f])	.	.	75	9	.	.	94	12	.	.	77	10	.	.	94	7	0.212	0.000
Heart rate (beats/min)	.	.	68	10	.	.	65	7	.	.	74	10	.	.	78	10	0.000	0.702
Cardiovascular data in 1996																		
QTc ($ms^{1/2}$)	.	.	399	18	.	.	408	22	.	.	419	17	.	.	428	20	0.000	0.004
Systolic blood pressure (mm Hg[f])	.	.	135	15	.	.	150	13	.	.	136	15	.	.	150	19	0.872	0.000
Diastolic blood pressure (mm Hg[f])	.	.	85	10	.	.	96	11	.	.	86	12	.	.	97	11	0.587	0.000
Heart rate (beats/min)	.	.	72	12	.	.	72	15	.	.	76	11	.	.	83	16	0.005	0.328
Basic data in 1996																		
Age (years)	.	.	46	7	.	.	48	7	.	.	47	7	.	.	49	5	0.122	0.054
Working duration (years)	.	.	25	5	.	.	26	5	.	.	25	5	.	.	27	4	0.605	0.047
Body mass index (kg/m^2)	.	.	23.7	2.4	.	.	25.7	2.3	.	.	24.3	2.6	.	.	24.2	2.8	0.938	0.002
HDL cholesterol (mg/100 ml)	.	.	52	13	.	.	50	9	.	.	48	11	.	.	54	9	0.362	0.778
Triglycerides (mg/100 ml)[g]	.	.	158	106	.	.	173	80	.	.	190	223	.	.	135	59	0.944	0.653
Liver enzyme, ALT (KU)[e]	.	.	30	28	.	.	36	18	.	.	28	12	.	.	27	11	0.205	0.080
Fasting blood glucose (mg/100 ml)	.	.	98	11	.	.	101	14	.	.	98	14	.	.	97	10	0.929	0.409
Hemoglobin (g/dl)	.	.	15.1	1.1	.	.	15.4	1.0	.	.	15.0	0.8	.	.	15.1	1.5	0.364	0.281
Shift workers	99	66	.	.	18	62	.	.	31	84	.	.	10	63	.	.	0.065	0.246
Smokers	92	61	.	.	13	45	.	.	27	73	.	.	13	81	.	.	0.017	0.297
Drinkers	128	85	.	.	27	93	.	.	26	70	.	.	13	81	.	.	0.019	0.142

[a] Hypertension included the workers with borderline hypertension. See the Methods section.
[b] Two-way analysis of variance with repeated measurements.
[c] Comparison between the workers with and those without a prolonged QTc.
[d] Comparison between the workers with and those without hypertension.
[e] A significant interaction between QTc and hypertension was observed for body mass index (P=0.021).
[f] 1 mm Hg≈0.133 kPa.
[g] These data were transformed into common logarithmic values.

The results of the multiple regression analysis for the group with a normal QTc (table 4) showed that work status (shift or day work), age, and fasting blood glucose were significantly related to the length of the QTc (P=0.010, 0.037 and 0.044, respectively); this result was also identified by the stepwise regression analysis. In the cohort without hypertension, age and drinking were significantly related to the systolic blood pressure (P=0.018 and 0.001, respectively) and diastolic blood pressure (P=0.044 and 0.024, respectively), while work status was not significantly related to either of them (P>0.05). Apart from the results presented in table 4, only age was significantly related to the QTc among the 117 shift workers with a normal QTc (the standardized partial regression coefficient between the QTc and age was 0.417, P=0.018), when the relations of work duration, body mass index, high-density lipoprotein cholesterol, triglycerides, ALT, fasting blood glucose, hemoglobin, age, smoking,

Table 3. Data obtained from workers who had normal heart-rate-adjusted QT intervals (QTc <420 $ms^{1/2}$) or were normotensive in 1986. (HDL = high-density lipoprotein, ALT = alamine aminotransferase)

	Cohort with normal QTc									Cohort without hypertension									
	Day workers (N=63)				Shift workers (N=117)				Probability[a]	Day workers (N=58)				Shift workers (N=130)				Probability[a]
	N	%	Mean	Sd	N	%	Mean	Sd		N	%	Mean	Sd	N	%	Mean	Sd	
Cardiovascular data in 1986																		
QTc ($ms^{1/2}$)	.	.	397	18	.	.	400	13	0.226	.	.	399	15	.	.	406	18	0.024
Systolic blood pressure (mm Hg[b])	.	.	125	11	.	.	124	12	0.419	.	.	122	9	.	.	121	9	0.381
Diastolic blood pressure (mm Hg[b])	.	.	77	11	.	.	78	12	0.811	.	.	75	8	.	.	75	9	0.886
Heart rate (beats/min)	.	.	67	10	.	.	68	10	0.506	.	.	68	11	.	.	70	10	0.315
Cardiovascular data in 1996																		
QTc ($ms^{1/2}$)	.	.	394	18	.	.	403	19	0.002	.	.	393	17	.	.	407	19	0.000
Systolic blood pressure (mm Hg[b])	.	.	135	14	.	.	138	16	0.152	.	.	133	14	.	.	136	15	0.260
Diastolic blood pressure (mm Hg[b])	.	.	86	10	.	.	88	11	0.211	.	.	84	10	.	.	86	11	0.325
Heart rate (beats/min)	.	.	70	13	.	.	73	12	0.079	.	.	70	11	.	.	74	12	0.015
Basic data in 1996																		
Age (years)	.	.	46	7	.	.	46	7	0.958	.	.	45	6	.	.	46	7	0.382
Working duration (years)	.	.	26	5	.	.	24	5	0.026	.	.	25	5	.	.	24	5	0.092
Body mass index (kg/m^2)	.	.	23.8	2.1	.	.	24.2	2.7	0.269	.	.	23.5	2.1	.	.	24.0	2.6	0.187
HDL cholesterol (mg/100 ml)	.	.	51	12	.	.	52	13	0.832	.	.	51	12	.	.	51	13	0.650
Triglycerides (mg/100 ml)	.	.	149	85	.	.	167	110	0.212[b]	.	.	154	103	.	.	169	150	0.444[c]
Liver enzyme, ALT (KU)	.	.	31	13	.	.	31	32	0.220[b]	.	.	29	12	.	.	30	30	0.504[c]
Fasting blood glucose (mg/100 ml)	.	.	99	12	.	.	98	11	0.409	.	.	98	12	.	.	98	12	0.986
Hemoglobin (g/100 ml)	.	.	15.0	1.2	.	.	15.3	1.1	0.087	.	.	14.9	1.2	.	.	15.2	1.0	0.140
Smokers	31	49	.	.	74	63	.	.	0.082[c]	33	57	.	.	86	66	.	.	0.253[d]
Drinkers	55	87	.	.	100	85	.	.	0.824[c]	50	86	.	.	104	80	.	.	0.412[d]

[a] Analyses of covariance to control for age were used for all the calculations except those for age and work duration (these two were analyzed by Student's t-test).
[b] 1 mm Hg≈0.133 kPa.
[c] These data were transformed into common logarithmic values.
[d] Fisher's exact test.

Table 4. Results of the multiple regression analysis of data for the group without cardiovascular dysfunction in 1996. Values in italics were significant at P=0.05 in the stepwise regression analysis. (BMI = body mass index, HDLC= high-density lipoprotein cholesterol, TG = triglycerides, ALT = alanine aminotransferase, FBG = fasting blood glucose, Hb= hemoglobin, QTc = heart-rate-adjusted QT intervals, SBP= systolic blood pressure, DBP= diastolic blood pressure)

	Multiple correlation coefficient[a]	Standardized regression coefficients										
		Work[b]	Duration	BMI	HDLC	TG[c]	ALT[c]	FBG	Hb	Age	Smoking[d]	Drinking[d]
With normal QTc (N=180)												
Heart rate	0.353	0.117	-0.084	-0.104	-0.076	-0.019	0.144	0.133	*0.186*	0.182	0.063	0.005
QTc	0.367	*0.204*	-0.140	-0.085	0.031	0.105	0.074	*0.152*	0.038	*0.285*	0.012	-0.025
Without hypertension (N=188)												
SBP	0.448	0.064	-0.104	0.076	0.057	*0.121*	0.066	*0.149*	0.080	*0.296*	-0.073	*0.239*
DBP	0.377	0.067	-0.068	0.063	-0.015	0.063	*0.129*	0.017	0.108	*0.260*	-0.124	*0.166*

[a] Probabilities of these multiple correlation coefficients were 0.018, 0.009, 0.000, and 0.004, respectively.
[b] Work status was scored as "day work"=0 and "shift work"=1.
[c] These data were used after transformation into common logarithmic values.
[d] Smoking (or drinking) habit at the time of the examination was scored as "nonsmoker (nondrinker)"=0 and "smoker (drinker)"=1.

and drinking to the QTc were examined in the multiple regression analysis.

Discussion

So far, there have been no reports evaluating the influence of shift work on cardiovascular function. In our study, the QTc of the shift workers was significantly prolonged in comparison with that of the day workers in both 1986 and 1996. In the groups with normal QTc values or without hypertension, the QTc in 1996 was significantly longer among the shift workers, whereas, since these workers were not clinical patients with CVD, the difference in the QTc between the 2 groups was small (table 3). In addition, shift work was significantly related to an increased QTc in the group with normal QTc values (table 4). These results were internally consistent and, therefore, suggest that shift work is associated with prolongation of the QTc.

The comparability of this study was preserved because all the subjects were male, they worked in the same company, and age was comparable between the shift and day workers. The effects of other confounding factors, such as smoking and drinking, were controlled for in the process of the data analyses. (Moreover, the residuals in the multiple regression analysis were normally distributed.) A prospective design beginning with its measure at preemployment would be desirable as an approach to address the issue of interpersonal and intrapersonal differences (26); we selected day and shift workers with a normal QTc at the start of this study instead of the absence of data at preemployment. Nevertheless, there may have been selection bias (ie, healthy worker effect) for the subjects inasmuch as the workers who moved from shift work to day work, those who suffered from diabetes mellitus, and those who could not undertake the ECG examination in 1996 were excluded. [The average values of the QTc, systolic and diastolic blood pressures, and heart rate of the 13 dropouts in 1986 were not significantly different from those in table 1, being 405 $ms^{1/2}$, 130 mm Hg (17.29 kPa), 79 mm Hg (10.51 kPa), and 68 beats/min, respectively.] And such a bias would have weakened the outcome (27), in that, without the bias, the true association between shift work and QTc prolongation could have been stronger.

Shift work is known to disrupt biological rhythms and disturb social and family life, and therefore negatively affect performance efficiency, health, and social relations (28). Especially regarding mortality from CVD, 2 review articles (3, 6) indicated that shift work increases the risk for CVD, whereas one did not. In the case of the negative result, the reduced risk of death from CVD among the shift workers was explained as a healthy worker effect (10). The QTc is also prognostic of sudden death in patients with myocardial infarction, and an abnormal QTc contributes to an increased risk of cardiac death (16—22). Accordingly, our results may provide indirect evidence for the pathophysiological mechanism between shift work and CVD morbidity or mortality. Further research with many shift workers is necessary to determine which of the combined factors, such as a disturbance in circadian rhythm, sleep or work stress, affects QTc prolongation.

In our study, neither the systolic nor diastolic blood pressure differed between the shift and day workers although the blood pressures of both groups was significantly elevated after a 10-year period. The normotensive cohort showed no significant relationship between shift work and blood pressure either (table 3). This negative finding is concordant with the results of studies conducted by Japanese and European researchers. According to 2 Japanese studies (12, 29), there was no significant difference in heart rate or blood pressure between the day or evening shift workers and night workers despite the presence of an increasing trend for the night shift. Similarly, European shift workers were unlikely to have higher blood pressure (10, 25). On the other hand, Hayashi et al (13) used 24-hour monitoring of systolic and diastolic blood pressure and observed higher blood pressure among white-collar workers with overtime work as compared with workers without overtime work. One possible explanation for this paradox is that intermittent measurements of blood pressure may be less sensitive to work state than 24-hour measurements of blood pressure, because Hayashi et al (13) failed to find a significant difference in intermittently measured blood pressure between the 2 groups. Additional study with the concurrent measurements of QTc and 24-hour blood pressure, if possible, would be highly suggestive. Such a study would help clarify whether the QTc reflects the average 24-hour blood pressure.

For the cohort without hypertension in our study, drinking habit was selected as a significant independent variable of systolic and diastolic blood pressure (table 4), but smoking habit or ALT did not enter into the regression model. Heavy drinking has been shown to increase mortality from coronary artery disease in different studies (15). Acute and chronic alcohol intake has been reported to attenuate heart-rate variability (30, 31). Therefore, our findings suggest that drinking habit may influence cardiovascular function independently of shift work.

It has been suggested that shift work including night shifts results in QTc prolongation; the study in question pointed at the importance of sympathetic arousal in the association between shift work and cardiovascular risk (32). There are many shift workers in developed and developing countries, and the work conditions and such shift patterns as permanent night work versus alternating night and day work, rosters versus regular shift work, long versus short shifts (33) differ in culture, task (eg, overtime or monotonous, stressful or noisy work), and gender. Studies should be carried out on the specific effects of shift conditions in which objective and convenient methods are used. At least, the QTc appears to be one of the most applicable methods to such a field study.

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