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Case-Control Study on Cardiovascular Function in Females with a History of Heavy Exposure to Cadmium

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It has been demonstrated that cadmium (Cd) causes various disorders of the cardiovascular system. However some of them are still open to question. With regard to blood pressure, there are contradictory views supporting the effect of Cd as a factor in hypertension (Baranski et al 1983; Perry et al 1979) or denying the possibility (Hammer et al 1972; Fingerle et al 1982). Furthermore, low blood pressure rather than high blood pressure was recently found in monkeys and humans exposed to Cd (Akabori et al 1984; Shinoda and Yuri 1981). In addition, the authors demonstrated that low blood pressure in females with heavy exposure to Cd correlated significantly with specific disorders; mainly kidney malfunction due to Cd exposure. In the present study, the effects of Cd on the heart in females exposed to Cd were investigated. Effects of Cd on the myocardium and contraction system have already been demonstrated in animal experiments (Dhalla et al 1978; Kopp and Hawley 1978). The results from the present study should promote a better understanding of the role of Cd in relation to the human cardiovascular system.

MATERIALS AND METHODS

All cases were selected from females receiving treatment at a general hospital (Hagino hospital) which specializes in Itai-Itai disease (Friberg et al 1974). Two cases with complete right bundle branch block and 1 case of Wenkebach syndrome diagnosed by electrocardiogram were excluded from the study. The remaining cases were divided into two groups. One (group I) consisted of 26 females with chronic Cd-induced disorders of Itai-Itai disease accompanied with typical osteomalacia findings on the X-ray film. Another (group i) consisted of 26 females who satisfied the criteria for the disease except for X-ray film findings. These definitions have been already described by Shiroishi et al (1979). Their mean ages were 75.3 years (SD = 7.4) and 76.2 years (SD = 7.4), respectively. It is assumed that they had experienced heavy exposure to Cd through ingesting polluted drinking water, rice, and fish around the World War I and II (Watanabe et al 1981). Afterwards, they continued to experience low-grade exposure from agricultural produce harvested from the Cd-polluted area (Kubota et al 1984). Since the present authors selected all cases from

patients of Hagino hospital, 104 controls matched by sex and age (10 year intervals) with the cases were also selected from patients with ischias and/or osteoarthritis. The cases and control patients were treated with analgesics such as ibuprofen and diclofenac sodium in the hospital. All controls lived out side the Cd-polluted area and did not show the combination of specific findings for Itai-Itai disease. The medical examination consisted of hemoglobin (Cyanmethemoglobin method), blood pressure, and electrocardiogram (Recording at a paper speed of 50 mm/sec). For various measurements of the heart conduction system, three beats of the IInd lead were used. According to the Minnesota code (Blackburn et al 1960), ischemic changes (IV : 1-3 and/or V : 1-3) and arrythmia (VIII : 1-9) were defined. The examinations were carried out in autumn and winter mornings, 1983 - 1984.

For observing the variation in electrocardiogram readings, the cases received the same examination in early summer of the next year. Furthermore, since electrocardiograms of group I females examined during a stay in Kanazawa Medical University for precise medical examination were available, a case-control study (The supplementary case-control study) was also carried out. At that time, the cases in the hospital had been free of drugs for a couple of weeks and controls were selected from volunteers living near the hospital. Their electrocardiograms were recordered at a paper speed of 25 mm/sec in the usual way. Most group I females examined in 1983 - 84 were included in the supplementary case-control study.

RESULTS AND DISCUSSION

Anemia and high blood pressure are disorders of the cardiovascular system which cause an aggravation of ischemic changes in the heart. As shown in Table 1, female cases in the present study had a significantly lower erythrocyte count ($p < 0.01$) and hemoglobin level ($p < 0.01$) compared to controls as has already been demonstrated (Nogawa et al 1979). With regard to blood pressure, this was significantly lower than the controls and this has also been demonstrated previously (Kagamimori et al 1985).
These two disorders are thought to have contradictory effects on ischemic changes in the heart. That is, anemia could aggravate

Table 1. Comparison of erythrocyte examination and blood pressure between case and control groups (Mean±SD)

	Erythrocyte ($10^{-4}/mm^3$)	Hemoglobin (g/dl)	Blood pressure (mmHg) Systolic	Diastolic
Cases (n=52)	276 (76)**	8.3 (2.7)**	138 (11)**	75 (12)**
Controls (n=104)	328 (61)	10.1 (3.2)	154 (35)	90 (17)

** : Significant compared to controls at $p < 0.01$

the changes but low blood pressure could prevent them.
Results of electrocardiogram readings for individual cases in group I and i are shown in Table 2 and Table 3. In addition, the results of ischemic changes are summarised in Table 4. The frequencies of the changes for whole cases in the respective examination (7.7 % and 13.5 %) were significantly lower than for the controls ($p < 0.01$ and $p < 0.05$). The frequency for the controls almost corresponded to the value estimated from the national survey on circulatory system diseases in Japan carried out in November, 1980 (Ministry of the Health and Welfare 1983). Therefore, despite significant anemia, females with chronic Cd disease were found to be more often free from ischemic changes of the heart than the general population. Since the changes are significantly correlated with high blood pressure in elderly Japanese (Kagamimori 1973), the low frequency may be explained by their lower blood pressure.

Table 2. Electrocardiogram data relating to group I

	Autumn and Winter 1983-84				Summer 1984		
No.	Age (years)	PR (sec)	PR/RR	Minnesota code	PR (sec)	PR/RR	Minnesota code
1	56	0.22	0.23		0.22	0.22	
2	63	0.23	0.29		0.22	0.19	
3	66	0.22	0.27	IV-2, V-2	0.24	0.24	IV-2, V-2
4	67	0.19	0.26		0.18	0.23	
5	67	0.18	0.16		0.20	0.23	
6	69	0.23	0.28		0.25	0.29	IV-3, V-3
7	70	0.19	0.24	V-2	0.19	0.27	V-2
8	73	0.24	0.24	IV-2, V-2	0.22	0.27	IV-2, V-2
9	73	0.20	0.26		0.22	0.22	
10	73	0.20	0.26		0.21	0.26	
11	74	0.20	0.24		0.20	0.15	
12	75	0.22	0.29		0.24	0.27	
13	75	0.21	0.19		0.21	0.20	
14	76	0.18	0.28		0.17	0.21	
15	78	0.18	0.22		0.17	0.19	VIII-9
16	80	0.20	0.26		0.22	0.28	
17	80	0.15	0.15		0.16	0.15	V-2
18	81	0.23	0.29	VIII-9	0.24	0.23	V-3
19	81	0.16	0.24		0.18	0.20	
20	82	0.21	0.25		0.22	0.27	
21	82	0.18	0.27	VIII-9	0.15	0.17	VIII-9
22	83	0.15	0.12		0.18	0.16	
23	83	0.22	0.25		0.22	0.25	
24	83	0.19	0.18		0.20	0.18	
25	83	0.16	0.22		0.14	0.21	
26	85	0.18	0.18		0.18	0.21	
Mean (SD)	75.3 (7.4)	0.197 (0.025)	0.235 (0.046)		0.201 (0.029)	0.221 (0.041)	

An increase in the PR interval of the electrocardiogram has been demonstrated in animals exposed to Cd regardless of the mode of administration (Dotta and Fruscella 1963; Kopp et al 1982). The specificity observed in the prolongation of the PR interval suggests that the mode of action of Cd involves a strong affinity for the AV node and/or common bundle of His, in order to cause a depression of this portion of the heart's conduction system (Samarawickrama 1979). The PR interval for individual cases of the respective groups is also included in Table 2 and Table 3. The correlationship of the interval between the two examinations was significant for whole cases ($r = 0.78$, $p < 0.001$). Therefore, the interval was found to be fairly consistent for each individual. The results described in Table 4 show that although the means of the PR interval for whole cases were not significantly different from control values in the two examinations, its prolongation ($\geqq 0.23$ sec) was significantly frequent compared to control values ($p < 0.05$ for the respective

Table 3. Electrocardiogram data relating to group i

	Autumn and winter 1983-84				Summer 1984		
No.	Age (years)	PR (sec)	PR/RR	Minnesota code	PR (sec)	PR/RR	Minnesota code
1	60	0.22	0.24		0.22	0.22	
2	63	0.21	0.17	VIII-9	0.18	0.17	VIII-9
3	67	0.18	0.17		0.20	0.16	
4	67	0.17	0.18		0.17	0.19	
5	67	0.19	0.18		0.20	0.18	
6	70	0.28	0.32		0.24	0.29	
7	71	0.17	0.23		0.18	0.27	
8	71	0.20	0.28		0.17	0.23	
9	73	0.22	0.26	VIII-9	0.24	0.21	
10	75	0.19	0.22		0.19	0.23	
11	75	0.21	0.26		0.18	0.22	
12	75	0.21	0.20		0.22	0.22	
13	78	0.24	0.34		0.22	0.33	
14	79	0.20	0.21		0.19	0.16	
15	79	0.20	0.15		0.21	0.25	
16	79	0.22	0.10		0.25	0.24	
17	80	0.22	0.20		0.23	0.25	
18	81	0.18	0.30	VIII-9	0.18	0.22	
19	82	0.18	0.26		0.18	0.24	
20	83	0.23	0.25		0.22	0.28	
21	83	0.18	0.20	V-3	0.20	0.17	V-3
22	83	0.17	0.23	VIII-9	0.16	0.18	
23	84	0.19	0.20		0.19	0.22	
24	84	0.24	0.27		0.22	0.33	
25	85	0.18	0.18		0.20	0.29	
26	88	0.18	0.30		0.19	0.28	
Mean (SD)	76.2 (7.4)	0.202 (0.027)	0.227 (0.056)		0.200 (0.024)	0.224 (0.064)	

examination). Since, in general, bradycardia is associated with prolongation of the PR interval, its ratio to the RR interval (PR/RR) was also investigated. The ratio for whole cases was significantly greater than for controls in the case-control study in autumn and winter, 1983 - 84 ($p < 0.05$). In another case-control study, however the difference between cases and controls was not significant, although the mean PR/RR was greater in cases than in controls. Cases therefore showed the tendency of a relatively prolonged PR interval.
As shown in Table 4, the mean of heart beats per minute was almost the same for whole cases and controls as has already been demonstrated in animals exposed to Cd (Kopp et al 1980), it was concluded therefore that the PR interval of cases was prolonged independently from the RR interval. Due to the fact that the frequency of arrythmia, the different type of heart disorders, was almost the same between the cases and controls, ischemic changes and the prolongation of the PR interval were thought to be specific cardiovascular abnormalities in females with chronic Cd disease.

In the supplementary case-control study, almost the same results were obtained with regard to the PR interval. As shown in detail in Table 5, the mean of the PR interval for each age group of cases was not significantly different from controls, although all the means of cases were greater than the controls. In addition, the mean PR/RR for whole cases was significantly greater than control values ($p < 0.05$). These results therefore provide

Table 4. Comparison of electrocardiogram data for case and control groups (Mean±SD)

	Cases		Controls
	Autumn and summer, 1983-84	Summer, 1984	
Age (years)	75.8 (7.4)	76.5 (7.5)	77.2 (8.1)
PR (sec)	0.200 (0.026)	0.201 (0.027)	0.195 (0.029)
Prolongation of PR (%)	15.4 (2.6)*	15.4 (2.6)*	4.8 (2.2)
PR/RR	0.231 (0.051)*	0.223 (0.054)	0.211 (0.060)
Heart beats per min.	70.6 (12.4)	68.5 (11.4)	67.9 (14.1)
Ishemic changes (%)	7.7 (1.9)**	13.5 (2.5)*	31.7 (4.7)
Arrythmia (%)	11.5 (2.3)	5.8 (1.7)	7.7 (2.7)

*:Significant compared to controls at $p < 0.05$, ** : at $p < 0.01$

Table 5. Comparison of PR time (sec) and PR/RR ratio in the supplementary case-control study (Mean±SD)

Age (years)	Group I females n	PR	PR/RR	Controls n	PR	PR/RR
40-59	3	0.175(0.028)	0.180(0.022)	6	0.163(0.013)	0.170(0.013)
60-69	8	0.174(0.027)	0.186(0.030)	24	0.163(0.024)	0.176(0.029)
70+	29	0.174(0.019)	0.201(0.043)	20	0.171(0.025)	0.188(0.034)
Total	40	0.174(0.021)	0.196(0.039)*	50	0.166(0.023)	0.180(0.030)

* : Significant compared to controls at $p < 0.05$

further confirmation that prolongation of the PR interval develops in females with chronic Cd disease.

In conclusion, females who have experienced heavy Cd exposure and subsequent continuous low-grade exposure have a tendency to develop disorders of the conduction system of the heart accompanied by less frequent ischemic changes due to lower blood pressure.

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