ORIGINAL ARTICLE

Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart

A Linna, P Oksa, K Groundstroem, M Halkosaari, P Palmroos, S Huikko, J Uitti

Occup Environ Med 2004;**61**:877–885. doi: 10.1136/oem.2003.009605

See end of article for authors' affiliations

Correspondence to: Dr A Linna, PO Box 26, 67101 Kokkola, Finland; asko.linna@boliden.com

Accepted 25 May 2004

Aims: To investigate whether exposure to cobalt in cobalt plants has any measurable effect on the cardiovascular system.

Methods: Occupational, cross sectional study, using a self administered questionnaire, blood pressure measurement, electrocardiography, and laboratory tests in which 203 male workers with at least one year of exposure to cobalt and 94 unexposed controls participated. Echocardiography was performed on a subset of 122 most highly exposed cobalt workers, of which 109 were analysed, and on 60 controls, of which 57 were analysed. Analysis of covariance and a multiple regression analysis were used to evaluate the data.

Results: Two of the echocardiography parameters measured were associated with cobalt exposure. In the higher exposure group the left ventricular isovolumic relaxation time (mean 53.3, 49.1, and 49.7 ms in the high exposure, low exposure, and control groups respectively) and the deceleration time of the velocity of the early rapid filling wave (mean 194.3, 180.5, and 171.7 ms for those in the high exposure, low exposure, and control groups respectively) were prolonged, indicating altered left ventricular relaxation and early filling.

Conclusion: Cumulative exposure to cobalt was found to be associated with the results of Doppler echocardiography measurements, indicating altered diastole. This finding supports the hypothesis that cobalt accumulation in the myocardium could affect myocardial function. Whether this finding has clinical implications remains to be evaluated.

An epidemic of cardiomyopathy occurred in the 1960s in Canada, the United States, and Belgium among persons who drank large amounts (that is, several litres per day) of beer containing cobalt.[1–3] The disease was severe, and almost half of the diseased persons died. According to postmortem analyses, the patients' hearts were dilated and the walls of the left chamber had thickened. It was assumed that heavy drinking and dietary deficiencies, in addition to exposure to cobalt, played a role in causing the disease.[4]

Single cardiomyopathy cases have been reported among persons exposed to cobalt at work.[5 6] Exposure levels have been high in these cases (that is, 0.1–5 mg Co/m^3). These workers have been diagnosed as having a cardiac condition similar to dilative cardiomyopathy.

In a study among hard metal workers, a weak but still significant inverse correlation was found between exposure time and the left ventricular ejection fraction, as measured by radionuclide ventriculography.[7] The study group consisted of 30 men, and the exposure levels were not mentioned. In a second echocardiogram and radionuclide study (31 men, exposure levels 0.09–13.6 mg Co/m^3), men who had been diagnosed with hard metal disease (n = 12) were found to have a significantly lower left ventricular ejection fraction during both rest and exercise than persons who had not been diagnosed with hard metal disease.[8] In the study group, the left ventricular peak filling rate at rest was lower than the average of the general population. The researchers assumed that this finding might have been due to increased diastolic pressure caused by increased wall stiffness and fibrosis due to cobalt deposits in the myocardium.

Alexandersson and Attehög discovered that persons who had been exposed to an average cobalt concentration of 0.01 mg Co/m^3 in hard metal work had more hypertension and reversible electrocardiographic (ECG) changes (depressed ST and T waves, arrhythmias) than persons in their control group.[9 10] In another study it was found that female porcelain workers who had been exposed to cobalt blue colour (average exposure level of 0.8 mg Co/m^3) had a higher heart rate than control subjects, but there were no differences in the ECG findings between the groups.[11]

The inhibition of cellular respiration due to the inhibition of mitochondrial dehydrogenase is considered to be one of the possible mechanisms of cobalt toxicity.[3] In the case of beer drinkers' cardiomyopathy, two or three factors may be responsible for the early fulminant cardiotoxic manifestation of cobalt. It is possible that hard metal workers develop heart failure more readily than other people when challenged with coronary heart disease, hypertension, valvular heart disease, viral infections, and alcohol.[7]

Since the 1960s cobalt exposure and cardiomyopathy has been a subject of discussion. Even though case reports have been published, a need still exists for epidemiological studies, especially in cobalt and cobalt chemical production, regarding possible changes in the heart and vascular system as a result of cobalt exposure. The purpose of our study was to determine whether any differences in echocardiographic, ECG, blood pressure, heart rate, and laboratory parameters of those exposed and those not exposed to cobalt and cobalt compound production could be ascribed to cobalt exposure.

SUBJECTS AND METHODS

Cobalt process and exposure

The cobalt plant of this study is located in Kokkola on the western coast of Finland. Between 1966 and 1987 cobalt

Abbreviations: DT, deceleration time; ECG, electrocardiography; EF, ejection fraction; FS, fractional shortening; IVRT, isovolumic relaxation time; IVSD, diastolic interventricular septum; LVEDD, left ventricular end diastolic diameter; LVPWD, left ventricular posterior wall; S-ANP-N, N-terminal atrial natriuretic peptide; S-CDT, carbohydrate deficient transferrin; S-GT, gamma-glutamyl transferase

Main messages

- Cumulative cobalt exposure was associated with echocardiographic changes indicating altered left ventricular relaxation and early filling.
- No clinically significant cardiac dysfunction due to cobalt exposure was found. In case studies involving cardiomyopathy exposure levels have been higher, and in epidemiological studies in which cobalt exposure has been associated with hypertension or ECG changes, exposure levels have been similar or higher than in our study (mean level approximately 0.05 mg Co/m^3.

Policy implications

- The current Finnish occupational exposure limit (OEL) of 0.05 mg Co/m^3 is not low enough to prevent echocardiographic changes. A lower OEL should be considered.
- The clinical significance of the findings needs further evaluation. A cause specific longitudinal study, including the retired workers, would give more information on effect of cobalt exposure on incidence of heart disease.

powder was produced from pyrite ore concentrate. Thereafter cobalt powder, inorganic cobalt, and nickel compounds have been produced using by-products of the metallurgic industry as raw material (fig 1).

Exposure to most dusts and gases in the process has been regularly monitored several times every year since 1966. Air samples have been collected by an authorised hygienist both at stationary points and with personal samplers in the workers' breathing zones. Exposure to cobalt has varied in large ranges according to job title even within same department. The range has been 0.02–1.0 mgCo/m^3 in the sulphatising roasting department, 0.01–0.05 mgCo/m^3 in the leaching and solution purification department, 0.05–0.25 mgCo/m^3 in the reduction and powder production department, and 0.01–0.20 mgCo/m^3 in the chemical department. The mean exposure levels to cobalt and its compounds were slightly over the current Finnish occupational exposure limit (0.05 mg/m^3) before 1987, and they have been slightly under the limit since the new process was initiated (fig 2). Substantial uptake of cobalt occurs through the lungs, although limited data are available on humans.[12]

Experiences from the biomonitoring of exposed workers have shown no notable differences in the bioavailability of the produced compounds. According to biological monitoring surveillance, exposure to cobalt has been highest in the reduction department. The highest urinary content of cobalt has been about 16 000 nmol/l (level of unexposed persons being <40 nmol/l). In the solution purification and the chemical departments the urinary cobalt levels have primarily been between 300 and 2000 nmol/l. In our present study, cumulative exposure to cobalt, presented as milligram-years (mg-y), was calculated for each worker using a job exposure matrix based on ambient air measurements. Workers in the cobalt plant are not exposed to zinc. In the control group (zinc plant workers) all the workers were exposed to zinc. For four fifths of the zinc workers the exposure level was 0.1–0.2 mg/m^3, and for one fifth it was around 1 mg/m^3.

Study population

The employees who were working at the end of 1999 in the cobalt plant and had been exposed to cobalt for at least one year were invited to participate in the study. The control group consisted of a stratified random sample of male workers in a zinc plant located in the same industrial area. Age group was taken as the stratum. The motivation for the stratified sampling was to control the confounding effect of age. The control group had not been exposed to cobalt, arsenic, or lead.

Questionnaire

Data on working history in the plant and earlier possible exposure to cobalt, lead, carbon disulphide, and arsenic were requested in the self administered questionnaire. The reasons for changing work tasks or jobs and workplaces were also

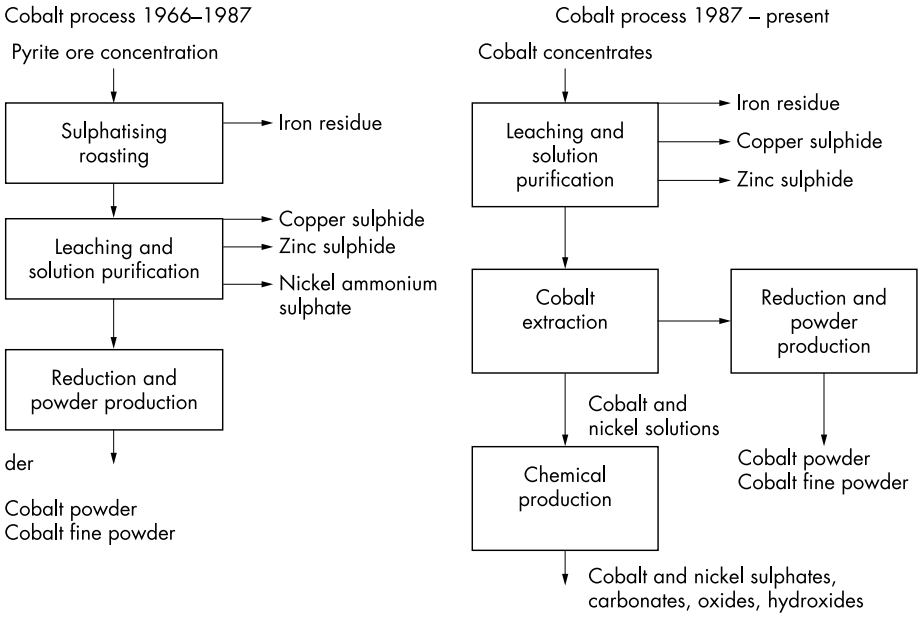

Figure 1 Cobalt production process in the Kokkola cobalt plant in 1966–87 and 1987–present.

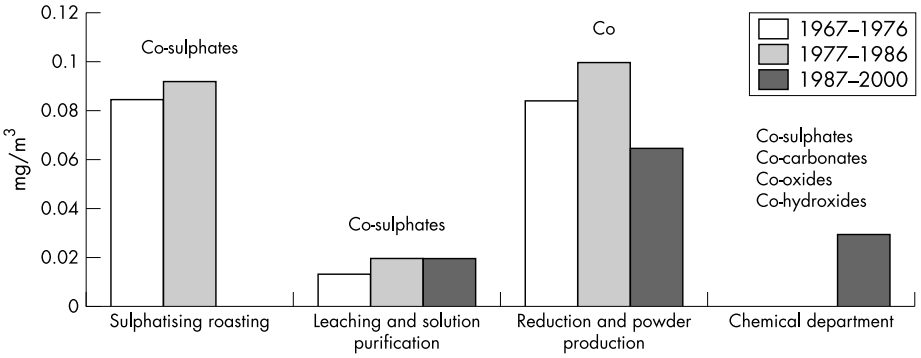

Figure 2 Mean exposure levels of the cobalt workers in the Kokkola cobalt plant in 1967–2000.

requested. There were also questions regarding physical exercise, smoking, alcohol consumption, cardiovascular and pulmonary diseases, and diabetes. There were 352 male workers who had been employed and exposed to cobalt for at least one year before leaving the factory. The 321 cobalt factory workers who were still living and the 318 ex-workers with a similar age distribution from the zinc plant were sent the same questionnaire with an additional question regarding reasons for leaving the plant.

Echocardiography

According to the assessment of the statistical power, 122 cumulatively most exposed cobalt workers and 60 controls with the same age distribution underwent echocardiography. Persons with congenital or acquired cardiac valvular disease and those with a history of myocardial infarction were excluded from the echocardiographic analysis. Transthoracic echocardiography was performed in the standard fashion,[13] using a Vingmed System Five Premium (Horten, Norway) with a 2.5 MHz or 3.5 MHz probe from the parasternal, apical, subcostal, and supracostal windows with the subject in the left lateral recumbent position. M-mode dimensions were normalised for body surface area. The mean of at least three consecutive beats was used. The left ventricular ejection fraction (EF) was calculated from the fractional shortening (FS) using the method of Pombo. Spectral Doppler measurements of blood flow were performed by aligning the interrogating beam with the direction of flow according to anatomical and colour Doppler information. Mitral and tricuspid flows were obtained with the pulsed Doppler sampler at the valve tips. Intraventricular relaxation time was measured using the technically better pulsed or continuous wave recording of mitral inflow and left ventricular outflow tract flow. No angle correction was used. Valvular regurgitation was quantified using colour Doppler information from multiple views. Images were stored on videotape in a Sony videocassette recorder (SVO-9500MDP), on optic disks in an Echopac Workstation, and on paper using a thermal printer UP-890CE.

The echocardiograms were analysed by two experienced clinicians without knowledge of the status of the examined persons (exposed/control). Abnormalities were agreed on by consensus. MH performed the measurements of cardiac size and function.

Blood pressure measurement and electrocardiography

Blood pressure was measured after 10 minutes of rest in the sitting position using an automatic Omron 705CP (Omron Matsusaka CO Ltd, Japan), which was tested and validated by the importer before and after the study. After two measurements the lower systolic and diastolic pressure and pulse were noted. A standard 12 lead electrocardiogram was obtained with 12 channels ECG equipment (Marquette Electronics Inc., Milwaukee WI, USA) at a paper speed of 50 mm/s. The recordings were analysed independently by two experienced clinicians, who both coded the recordings without knowing their origin (exposed/control). Coding was performed according to the Minnesota 1982 method.[14]

Laboratory tests

Gamma-glutamyl transferase (S-GT) and carbohydrate deficient transferrin (S-CDT) were analysed to study alcohol consumption. Thyroid gland function (serum free thyroxine, S-T_4-V, and thyroid-stimulating hormone, S-TSH), vitamin B1 deficiency (thiamin, B-B1-vit), and the serum lipid and glucose values were studied as possible confounding factors of cardiomyopathy and ischaemic cardiac disease.

N-terminal atrial natriuretic peptide (S-ANP-N) was determined to complement possible findings of cardiac failure.[15] It was analysed by radioimmunoassay with kits purchased from BIOTOP Oy, Oulu, Finland.

Statistical methods

The normality of the variables was checked, and logarithmic transformation was applied if the distribution of the variable was skewed. Crude means and standard deviations have been reported in the tables.

A regression analysis and an analysis of covariance (ANCOVA) were used to study the echocardiographic data. A forward stepwise regression analysis was performed on all echocardiographic parameters. The potential explanatory factors included exposure as mg-years, age, blood pressure, smoking status, overuse of alcohol, and physical activity. Body mass index was included if the outcome variable had not been divided by body surface area, and heart rate if the outcome variable was time related. ANCOVA was additionally used to study the differences in echocardiographic parameters between various designated exposure groups. The first categorisation of exposure to cobalt used a time related definition. The exposure was called recent if the person was working (or had worked during the last year) in conditions in which he could be regularly exposed to a cobalt concentration of 0.01 mg/m^3 or more; otherwise the exposure was called past. In another classification of exposure the grouping was determined according to the length of exposure time to cobalt. Exposure time was defined by the number of years worked with cobalt, with two groups being defined above and below the median length of time of 24 years. In the final analyses high and low exposure was determined on the basis of being above or below the median mg-years of cobalt exposure (0.47 years for the subset in the echocardiography analysis). The effect of age on several important echocardiographic parameters is known. It was included as a continuous variable in the regression analyses and categorised above and

below 50 years,[17] which allowed its interaction with exposure to be studied in the ANCOVA.

Blood pressure (as raised or as hypertension), overuse of alcohol (weekly consumption more than 20 drinks or S-GT >80 or S-CDT >20), smoking (never smokers versus ex or current smokers), physical activity, and, in some calculations (see above), body mass index and heart rate were included in the model as covariates because they were considered to be confounders.

Statistical power calculations (requiring the power of at least 0.8 at the significance level of 0.05) were performed to assess the number of echocardiographic analyses needed in the study. Calculations were carried out in relation to the deceleration time (DT) and the isovolumic relaxation time (IVRT), which were considered to be the most important outcome variables because of their ability to reflect the earliest changes in the cardiac function.[16] The power calculations were based on ANCOVA, the difference to be detected in outcome variables being 10%, with a standard deviation of 30.0 ms for DT and 10.0 ms for IVRT in each group. Calculations showed a need for 186 analyses altogether (62 in each group) when the differences between three groups in DT were studied, and a need for 180 analyses in IVRT respectively.

Simple statistics were used to describe the data. The 95% confidence intervals (95% CI) were calculated for the differences between two percentages. The level of significance in ANCOVA was set at equal to 0.05, but exact p values are reported. Computations were carried out using Statistica/Win (1998 edition) and SPSS/Win (version 12.0) software.

RESULTS

Table 1 presents the characteristics of the examined groups and calculated mg-year values. The cobalt exposure of 132 workers was considered recent, and that of 71 workers was recorded as past. All analyses were carried out on all measures of exposure. The results are presented in relation to the cumulative amount of exposure only, because it was the most reliable and accurate method of assessing the exposure, and the other measures did not show indication of association.

All the invited current workers were men, and all 203 participated. We used age groups of 4 years as a stratum when selecting the control group. Because the zinc plant employed fewer workers who had been born in the 1960s and 1970s than the cobalt plant, the number of controls remained small. From the control group (n = 96), two persons did not want to participate.

In the exposed group two persons had been exposed to arsenic, and two had had lead exposure when working outside the plant. Two workers in the control group had been exposed to carbon disulphide for a short time (six months and three months) during their working history. In the control group more workers were or had been competing athletes than in the exposed group. When leisure time sports activities were taken into account, there were no significant differences in the amount of physical exercise between the workers of the exposed and control groups.

Echocardiography

Persons with congenital or acquired cardiac valvular disease (n = 14) and those with a history of myocardial infarction (n = 2) were excluded from the echocardiographic analysis. Thirteen of these persons belonged to the exposed group, and three were controls. Only the results from the ANCOVA are presented. The results from the multiple regression analysis broadly concurred on the inclusion of the cobalt exposure variable in the explanation of the echocardiographic parameters.

Table 1 Characteristics of the study groups

Characteristic	Exposed group n = 203	Control group n = 94
Age (y)		
Mean (SD)	42.0 (10.5)	42.2 (10.6)
Median (range)	45 (23–62)	44 (24–60)
Height (cm)		
Mean (SD)	177.9 (5.8)	177.5 (6.6)
Median (range)	178 (165–193)	178 (164–196)
Weight (kg)		
Mean (SD)	83.6 (11.3)	83.7 (12.6)
Median (range)	82 (58–142)	82 (62–133)
Work history (y)		
Mean (SD)	17.0 (11.9)	19.1 (10.8)
Median (range)	20 (2–34)	25 (3–36)
Exposure time to cobalt, (y)*		
Mean (SD)	15.0 (11.6)	
Median (range)	9 (1–34)	
Exposure to cobalt, (mg-y)		
Mean (SD)	0.40 (0.47)	
Median (range)	0.18 (0.02–2.52)	
Smoking status (%)		
Non-smokers	33.5	32.6
Ex-smokers or smokers	66.5	67.4
Pack-y		
Mean (SD)	10.8 (13.6)	9.2 (11.1)
Median (range)	7 (0–76)	6 (0–51)
Consumption of alcohol Drinks/week		
Mean (SD)	4.8 (4.5)	5.6 (4.8)
Median (range)	3 (0–20)	4 (0–20)
Competing athlete status (%)		
No	84.7	75.0
Now or earlier	15.3	25.0
Leisure time sport activities (%)		
No, never	8.9	8.7
Yes, two times a week or less	52.0	46.7
Yes, at least three times a week	39.1	44.6

*Regularly >0.01 mg Co/m^3.

Table 2 gives the characteristics and calculated mg-year values of the groups who underwent echocardiography. Table 3 presents the echocardiographic results. Two exposed persons and one control had a left ventricular end diastolic diameter index (LVEDIDI) that was over 32 mm/m^2. The ratio between the wall thickness and the left ventricular diameter measured at end diastole [(IVSD+LVPWD)/LVEDD] was greater among the highly exposed workers than among the controls. The interaction of age and exposure was not significant (p = 0.06), but the effect seemed stronger for younger persons. Among the younger persons the highly exposed workers differed from the less exposed and the controls, but for older people there were no differences between the groups (fig 3).

In the highly exposed group the left ventricular isovolumic relaxation time (IVRT) was longer than in the less exposed and control groups. Both exposure level and age contributed to the explanation of the variation in the IVRT, the values being shorter for younger people. The ratio of the peak early rapid filling wave to peak filling wave due to atrial contraction (E/A ratio) did not differ between the exposure groups. The E/A ratio was lower for older people. The deceleration time of the velocity of the early rapid filling wave (DT) was longer among the highly exposed subjects than among the less exposed persons or the controls. The systolic parameters of the left ventricular function did not differ between the groups.

In order to be able to assess the reproducibility of the echocardiography measurements, two experienced clinicians (MH, KG) measured the same parameters in 20 echocardiograms.

The mean coefficients of variation were 1.42% for the left ventricular end diastolic diameter (LVEDD), 5.21% for the

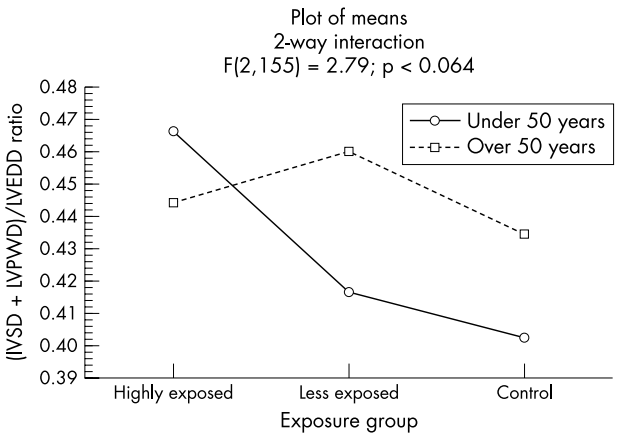

Figure 3 The ratio between wall thickness and left ventricular diameter measured at end diastole in different exposure and age groups

diastolic interventricular septum (IVSD), 4.16% for the diastolic left ventricular posterior wall (LVPWD), 3.7% for the ejection fraction (EF), 4.7% for the isovolumic relaxation time (IVRT), and 2.3% for the deceleration time (DT).

Electrocardiographic findings

There were no significant differences in the ECG findings or conduction parameters between the exposure group and the control group (table 4).

The readers coded 20 recordings from the same persons in order to test the reproducibility. In 17 cases the coding was identical. In three there were differences: in two recordings one reader had not noticed the ORS axis deviation of −30 to −90 in leads I, II, III, and in one recording an ST segment increase of 1 mm in the anterior leads had not been marked.

Blood pressure and laboratory tests

Table 5 shows the results of the blood pressure measurements and the laboratory tests. In an ANCOVA analysis the S-ANP-N values were the highest in the group with high exposure, 0.43 nmol/l (SD 0.3). The corresponding values of the low exposure and control groups were 0.36 (SD 0.11) and 0.37 (SD 0.08) respectively. The p value was 0.008 for exposure group effect and 0.017 for age. The p value for the interaction of age and group was not significant (p=0.485).

Table 2 Characteristics of cumulatively most exposed workers and age stratified controls participating in the echocardiographic examination

Characteristic	Exposed group (n = 122)	Control group (n = 60)
Age (y)		
Mean (SD)	46.8 (8.1)	47.2 (8.1)
Median (range)	49 (27–62)	49 (28–60)
Height (cm)		
Mean (SD)	177.6 (5.7)	176.2 (6.5)
Median (range)	178 (165–193)	175 (164–192)
Weight (kg)		
Mean (SD)	84.4 (12.2)	84.9 (11.5)
Median (range)	84 (59–142)	82 (67–118)
Work history (y)		
Mean (SD)	22.9 (9.7)	24.6 (7.7)
Median (range)	25 (2–34)	26 (3–36)
Exposure time to cobalt (y)*		
Mean (SD)	21.2 (9.9)	
Median (range)	24 (1–34)	
Exposure to cobalt (mg-y)		
Mean (SD)	0.58 (0.51)	
Median (range)	0.47 (0.03–2.52)	

*Regularly >0.01 mg Co/m^3.

Diseases

There were no significant differences between the exposure group and the control group in the prevalence of reported cardiovascular diseases, diabetes mellitus, or pulmonary diseases, except asthma, diagnosed by a physician (table 6).

Former workers

Of the former cobalt and zinc plant workers, altogether 404 persons responded to the questionnaire (that is, 76% of the former cobalt plant workers and 51% of the former zinc plant workers). Twelve workers (5%) had left their work in the cobalt plant due to some form of cardiovascular disease: 10 cases of coronary artery disease or myocardial infarction, one diagnosed case of heart failure, and one diagnosed case of cardiac arrhythmias. In four cases (2.5%) the reason for leaving the zinc plant had been some form of cardiovascular disease: three cases of coronary artery disease and one case of hypertension.

DISCUSSION

This study is the first to have a large occupationally exposed study population and to use modern methods to assess the possible effects of cobalt on the cardiovascular system. Cobalt exposure had been monitored with exceptional accuracy from the early days of the studied plant. The cobalt plant and the zinc plant, from which the controls were taken, have both been business units of the same corporation. Therefore the employees had been recruited using similar criteria, for example, by using the expertise of the company's occupational health professionals. Most of the workers who were invited to take part in the study, 98% of the controls, and all the workers in the exposed group participated. The characteristics of the groups, including the measured confounding factors of cardiomyopathy and ischaemic cardiac disease, were very similar. The health reasons for leaving the job were equally distributed in both groups of retired persons.

Because the minimum exposure requirement for cobalt was one year (ever), there were many workers in the exposed group who had changed job tasks and were not exposed to cobalt at the time of the study. Some of them had not been exposed to cobalt for many years, even decades. Therefore, we studied those with recent or past exposure and those with cumulatively high or low exposure separately. Since cumulative exposure becomes higher with age and several echocardiographic parameters are age related, we used age limits (that is, workers under and over 50 years) similar to those used by the European Study Group on Diastolic Heart Failure.[17]

The production processes in the cobalt and zinc plants have several phases, and, therefore, the plant workers had been exposed, for example, to several metals and gases. Workers exposed to lead or arsenic were excluded from the study, and, as far as we know, the two environments offered no exposure to agents that would have harmful effects on the cardiovascular system.

Cardiomyopathy has been reported (in case reports) in relation to industrial cobalt exposures, sometimes with alcohol consumption, after the inhalation of cobalt concentrations of 0.1 mg/m^3 or higher for varying periods of time.[18] The mean levels of cobalt in the ambient air in this plant have been generally at the level of the current occupational exposure limit in Finland (that is, 0.05 mg/m^3). During the first years of cobalt production the cobalt levels may have been considerably higher (that is, over 1 mg/m^3), especially in the roasting department. The Finnish occupational limits have often been exceeded also in the reduction and powder

Table 3 Echocardiographic results

Variable	Group: Exposure to cobalt >0.47 mg-y n=55		Exposure to cobalt <0.47 mg-y n=54		Control n=57		Age (p value)	Group (p value)	Age* group (p value)	Covariates (p value)
	Mean (SD)	Adjusted mean	Mean (SD)	Adjusted mean	Mean (SD)	Adjusted mean				
LA (mm/m^2)*	19.7 (2.6)	–	18.7 (2.0)	–	19.7 (2.6)	–	0.054	0.218	0.692	–
RVD (mm/m^2)	11.3 (2.3)	–	11.2 (2.3)	–	11.5 (2.1)	–	*0.012*	0.821	0.498	–
RVS (mm/m^2)	10.5 (1.6)	–	10.6 (1.9)	–	10.9 (1.8)	–	*0.036*	0.394	0.425	–
LVEDD=LVEDIDI (mm/m^2)	26.7 (2.5)	–	26.5 (2.5)	–	27.0 (2.3)	–	*0.679*	0.453	0.618	–
LVESD (mm/m^2)	16.7 (2.4)	–	16.7 (2.1)	–	17.0 (1.9)	–	0.626	0.368	0.224	–
IVSD (mm/m^2)	6.2 (1.0)	6.3	6.0 (0.8)	6.0	6.1 (0.7)	6.0	*0.075*	0.198	0.294	bp (0.012)
IVSS (mm/m^2)*	8.3 (1.1)	8.3	7.9 (1.0)	8.1	8.0 (0.9)	8.0	*0.026*	0.292	0.370	bp (0.009)
LVPWD (mm/m^2)*	5.7 (0.8)	–	5.3 (0.6)	–	5.25 (0.6)	–	*0.024*	*0.005*	0.058	–
LVPWS (mm/m^2)*	8.2 (1.0)	–	7.9 (1.0)	–	7.9 (1.1)	–	0.208	0.196	0.158	–
LVMASS (gr/m^2)	149.9 (28.1)	150.9	145.1 (24.0)	145.2	145.5 (29.3)	145.2	0.865	0.481	0.998	bp (0.009)
(IVSD+LVPWD)/LVEDD ratio	0.45 (0.09)	0.46	0.44 (0.06)	0.44	0.42 (0.05)	0.42	0.263	*0.011*	0.064	bp (0.016)
IVRT (ms)*	53.3 (7.9)	53.6	49.1 (7.2)	49.2	49.7 (10.0)	49.8	*0.022*	*0.010*	0.243	bmi (0.009) hr (0.034)
E/A ratio*	1.33 (0.33)	1.32	1.41 (0.36)	1.37	1.37 (0.34)	1.39	*0.041*	0.398	0.197	bp (0.002) hr (<0.001)
DT (ms)*	194.3 (32.1)	192.4	180.5 (28.2)	179.1	171.7 (28.5)	172.0	0.179	*0.001*	0.151	hr (<0.001)
EF (%)	75.2 (6.2)	–	74.9 (5.2)	–	74.5 (5.2)	–	0.060	0.527	0.138	–
FS (%)	37.6 (5.1)	–	37.3 (4.2)	–	36.9 (4.5)	–	0.124	0.522	0.161	–

*Logarithmic transformation was made for the outcome variable before the analysis.
LA, left atrium; RVD, right ventricle (diastolic); RVS, right ventricle (systolic); LVEDD, left ventricular end diastolic diameter; LVEDIDI, left ventricular end diastolic diameter index; LVESD, left ventricular end systolic diameter; IVSD, interventricular septum (diastolic); IVSS, interventricular septum (systolic); LVPWD, left ventricular posterior wall (diastolic); LVPWS, left ventricular posterior wall (systolic); LVMASS, left ventricular mass; IVRT, isovolumic relaxation time; E, early rapid filling wave; A, filling wave due to atrial contraction; DT, deceleration time; EF, ejection fraction; FS fractional shortening.
The diameters and LVMASS normalised for body surface area.

Table 4 Electrocardiographic findings and conduction parameters

Findings, classified according to the Minnesota method	Exposed group (n = 203) %	Control group (n = 94) %	Difference*	95% CI†
Q and QS patterns	0.5	3.3	−2.8	−6.6 to1.0
QRS axis deviation	2.5	1.1	1.4	−1.6 to 4.4
High amplitude R waves	21.2	23.9	−2.7	−13.1 to 7.7
T wave items	0.5	2.2	−1.7	−4.9 to 1.5
A-V conduction defect	3.9	1.1	2.8	−0.6 to 6.2
Ventricular conduction defect	1.5	6.5	−5.0	−10.3 to 0.3
Arrhythmias	8.4	9.8	−1.4	−8.6 to 5.8
S-T segment increase	3.9	2.2	1.7	−2.3 to 5.7
Conduction parameter				
PR time (ms)				
Mean (SD)	164 (24)	165 (23)		
QRS time (ms)				
Mean (SD)	98 (11)	99 (9)		
QTc time (ms)				
Mean (SD)	407 (19)	411 (17)		
QT time (ms)				
Mean (SD)	418 (39)	418 (34)		
Heart rate/minute				
Mean (SD)	59 (10)	60 (11)		

*Difference between the percentages.
†95% confidence interval for the differences between the percentages.

production departments. Results from the biological monitoring show that marked exposure still exists regardless of an intensified use of respirators. Since the workers have been exposed to many different cobalt compounds, it was not possible to study the differences in the toxicity of the compounds.

In most cardiac diseases the initial sign of dysfunction is impaired relaxation.[16] We found that higher cobalt exposure

Table 5 Blood pressure, heart rate, and laboratory test results

	Exposed group (n = 203)	Control group (n = 94)
Blood pressure, systolic (mm Hg)		
Mean (SD)	134 (15)	137 (15)
Median (range)	134 (102–188)	137 (102–179)
Blood pressure, diastolic (mm Hg)		
Mean (SD)	87 (10)	88 (11)
Median (range)	86 (64–121)	87 (68–124)
Heart rate/minute		
Mean (SD)	69 (11)	68 (12)
Median (range)	68 (44–113)	66 (45–102)
Serum gamma-glutamyl transferase, S-GT (U/l)		
Mean (SD)	50.0 (66.3)	41.2 (24.1)
Median (range)	32 (11–743)	35 (14–149)
Serum carbohydrate deficient transferrin, S-CDT (U/l)		
Mean (SD)	15.6 (4.8)	15.1 (4.3)
Median (range)	15 (8–38)	14 (8–30)
Blood vitamin B1, B-B_1-vit (nmol/l)		
Mean (SD)	148 (29)	153 (31)
Median (range)	145 (88–233)	149 (94–246)
Serum total cholesterol (mmol/l)		
Mean (SD)	5.5 (1.1)	5.4 (1.1)
Median (range)	5.4 (3.1–8.6)	5.3 (3.0–8.1)
Serum LDL cholesterol (mmol/l)		
Mean (SD)	3.6 (1.0)	3.5 (0.9)
Median (range)	3.5 (1.2–6.3)	3.5 (1.6–6.1)
Serum HDL cholesterol (mmol/l)		
Mean (SD)	1.3 (0.3)	1.3 (0.3)
Median (range)	1.2 (0.6–3.0)	1.2 (0.6–2.4)
Serum triglycerides (mmol/l)		
Mean (SD)	1.6 (0.9)	1.5 (0.9)
Median (range)	1.3 (0.3–6.3)	1.3 (0.5–5.5)
Serum glucose (mmol/l)		
Mean (SD)	5.4 (0.6)	5.4 (1.0)
Median (range)	5.3 (4.2–8.6)	5.3 (4.2–10.5)
Serum free thyroxine, S-T_4-V (pmol/l)		
Mean (SD)	12.8 (1.6)	13.6 (2.9)
Median (range)	12.7 (9.5–17.5)	13.3 (10.0–35.0)
Serum thyroid-stimulating hormone, S-TSH (mU/l)		
Mean (SD)	1.9 (1.2)	2.0 (0.9)
Median (range)	1.7 (0.3–13.7)	1.9 (0.6–4.8)

Table 6 Prevalence of reported diseases diagnosed by a physician

Disease	Exposed group (n = 203) %	Control group (n = 94) %	Difference†	95% CI‡
Ischaemic heart disease*	3.4	2.2	1.2	−2.7 to 5.1
Heart failure	0.5	0.0	0.5	−0.5 to 1.5
Heart arrhythmias	8.0	14.3	−6.3	−14.4 to 1.8
Cardiomyopathy	0.0	0.0		
Any other cardiac disease	2.5	2.2	0.3	−3.4 to 4.0
Hypertension	14.3	16.3	−2.0	−11.0 to 7.0
Stroke	0.5	0.0	0.5	−0.5 to 1.5
Claudicatio intermittens	0.5	1.0	−0.5	−2.8 to 1.8
Bronchial asthma	2.5	0.0	2.5	0.3 to 4.7
Chronic bronchitis	2.0	3.3	−1.3	−5.4 to 2.8
Emphysema	0.0	0.0		
Any other chronic lung disease	3.0	2.2	0.8	−3.0 to 4.6
Diabetes mellitus	1.0	3.2	−2.2	−6.0 to 1.6

*Coronary heart disease or myocardial infarction or both.
†Difference between the percentages.
‡95% confidence interval for the differences between the percentages.

was associated with altered left ventricular diastolic function, as measured by Doppler echocardiography. The isovolumic relaxation time (IVRT) was prolonged with higher exposure. This occurrence, as well as a prolonged deceleration time (DT) among the exposed persons, may support the theory of D'Adda and colleagues,[8] who reported that an accumulation of cobalt in the myocardium might result in increased myocardial stiffness. The fact that the level of cumulative exposure, rather than the time of the exposure, affected the results also supports this conclusion. The ratio between the wall thickness and left ventricular diameter measured at end diastole tended to increase as the exposure increased. Despite their limitations, these results concur with the findings on diastolic parameters. We contrasted the disease histories, including hypertension, between exposed and control workers, and concluded that they were sufficiently similar to have minimal effect on the outcome measures, but we did not obtain further information on risk factors such as stress and personality. In our earlier study of this cobalt plant, we found that cobalt exposure did not cause pulmonary fibrosis or hard metal disease.[19] Therefore, the echocardiographic changes described in our report, we believe, were not due to changes in pulmonary function, as some researchers have suggested.[7 8]

No signs of systolic cardiac dysfunction were found. The ejection fraction (EF), fractional shortening (FS), and left ventricular end diastolic diameter (LVEDD), were similar in the exposed and control groups.

In our study the same observer performed all the echocardiographic measurements. Because intra-observer errors are lower than those between two observers,[20 21] and because the inter-observer coefficients of variation in our reproducibility study were moderate, the results of the echocardiographic measurements can be considered reliable. Especially for LVEDD and DT, even the inter-observer coefficients of variation were low.

There were no differences in the ECG parameters, including heart rate, between the exposed and control workers. This finding contrasts with those reported by Alexandersson and colleagues[9 10] and Raffn and colleagues.[11] The cobalt exposure levels in these studies were similar or markedly higher than the levels of our study. This finding implies that cobalt exposure of this level in cobalt production does not cause ECG changes or the ECG may be too insensitive to register minor changes in the myocardium or the conduction system.

The S-ANP-N concentrations of the highly exposed group were greater than those of the other groups, but their dependency on parameters describing left ventricular size (the ratio IVSD+LVPWD/LVEDD) and left ventricular diastole (IVRT and DT) was poor.

In summary, we found no major cardiac dysfunction that could be directly attributed to cobalt exposure. Cumulative cobalt exposure was associated with echocardiographic changes that suggest altered left ventricular relaxation and early filling. Minor increases in left ventricular wall thickness concurred with these observations. A possible mechanism behind the findings in our study could be the accumulation of cobalt in the myocardium, the result being an increase in myocardial stiffness. The clinical significance of these changes, however, needs further evaluation.

ACKNOWLEDGEMENTS

This study was conducted with financial support from the Finnish Work Environment Fund.

Authors' affiliations

A Linna, Kokkola Zinc Oy, Kokkola, Finland
P Oksa, P Palmroos, S Huikko, J Uitti, Tampere Regional Institute of Occupational Health, Tampere, Finland and Clinic of Occupational Medicine, Tampere University Hospital, Tampere, Finland
K Groundstroem, Tampere School of Public Health, University of Tampere, and Department of Medicine, Tampere University Hospital, Tampere, Finland
M Halkosaari, Keski-Pohjanmaa Central Hospital, Kokkola, Finland

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ECHO

Exposure to fume emitting heaters in the first year of life found to be associated with asthma in later childhood

Please visit the *Occupational and Environmental Medicine* website [www.occenvmed.com] for a link to the full text of this article.

Primary school children exposed to fume emitting heaters during their first year of life have been found to have more airway hyperresponsiveness (AHR) and wheeze than those not so exposed, according to a case-control study from New South Wales, Australia.

A total of 627 children aged between 8 and 11 years (51% of the target population) were tested for AHR by a histamine challenge test, and also for atopy by skin prick tests to common allergens. Parents completed questionnaires which included questions about exposure at home to pets and tobacco smoke and the type of heating and cooking appliances used–both during the first year of life and currently.

The predominant types of fume emitting appliances were non-flued gas type heaters and wood stoves. There was a strong association between the use of these appliances during the child's first year of life and the presence between the ages of 8 and 11 of AHR (adjusted relative risk 1.47, 1.06 to 2.03), recent wheeze (1.44, 1.11 to 1.86), and current asthma (2.08, 1.31 to 3.31). There was no association with atopy or with current use of fume emitting heaters.

This study reflects the importance of different exposures in early life in the aetiology of asthma. Although limited by a low response rate, if the findings were to be confirmed in other settings, there would be implications for the type of heating suitable for houses in which young children live.

▲ Phoa LL, *et al*. *Thorax* 2004;**59**:741–745.