Decreased ventilatory function in hard metal workers

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Abstract

Objectives—To study individual effects on pulmonary function of exposure to hard metal including cobalt.

Methods—All of the workers in a hard metal company (583 men and 120 women) were examined for smoking, respiratory symptoms, ventilatory function, occupational history of exposure to hard metal, and present exposure to airborne cobalt. The ventilatory function indices (forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), forced expiratory volume in one second per cent (FEV₁%), peak expiratory flow (PEF), mid-maximal flow (MMF), forced expiratory flow at 50% vital capacity ($\dot{V}_{50}$), forced expiratory flow at 25% vital capacity ($\dot{V}_{25}$)) were standardised for height and age and expressed as a percentage of predicted values.

Results—Two way analysis of variance of indices of ventilatory function showed that an interaction of hard metal exposure and smoking decreased % $\dot{V}_{50}$ for both men and women. Among the currently exposed men, those with asthmatic symptoms (defined as reversible dyspnoea with wheeze) had significantly lower %FVC, %FEV₁%, %PEF, %MMF, % $\dot{V}_{50}$, and % $\dot{V}_{25}$ than did workers without asthma. The ventilatory dysfunction did not differ between exposed and non-exposed workers with asthmatic symptoms. Even among the men without asthmatic symptoms, % $\dot{V}_{50}$ was significantly lowered by the interaction of hard metal exposure and smoking. The multilinear regression analysis of indices of ventilatory function for all of the subjects on sex, smoking (Brinkman index), exposure to hard metal, and asthmatic symptoms showed that asthmatic symptoms and smoking had significant effects on all variables and that the decrease in % $\dot{V}_{25}$ was associated with hard metal exposure. In the currently exposed and non-exposed workers, multilinear regression analysis applying indices for cobalt exposure (mean cobalt concentration, duration of exposure, and cumulative dose) showed that not only asthmatic symptoms or smoking but also duration of exposure had significant decreasing effects on %FVC, %MMF, and % $\dot{V}_{25}$.

Conclusions—Occupational exposure to hard metal probably causes impairment

of ventilatory function in a dose dependent manner.

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Occupational exposure to hard metal including cobalt is known to cause interstitial pneumonitis, pulmonary fibrosis, and asthma among workers.¹⁻³ Cobalt has been suspected of provoking asthma in some people by hypersensitivity⁴ and has also been assumed to be responsible for pneumonitis and pulmonary fibrosis on the basis of the results of animal experiments.^{5,6} As well as case reports on these disorders, the ventilatory function of hard metal workers has also been reported with special reference to the concentrations of airborne cobalt in Swedish,⁷ American,⁸ French,⁹ and Japanese¹⁰ working environments. A field survey was also completed at a Finnish cobalt production plant as early as 1980, in which exposure to cobalt was found to cause asthma and bronchial irritation with increased bronchial reactivity.¹¹ There are also recent reports on the relation between level of cobalt exposure and pulmonary function in a cobalt refining industry,¹² a diamond-cobalt saw producing industry,¹³ and diamond polishing industries¹⁴ in Belgium. All of these studies showed some decrease in ventilatory function related to cobalt exposure.

The exposure limit for cobalt in many developed countries including Japan has been designated as 50 $\mu\text{g}/\text{m}^3$. According to the International Labour Office (ILO) statistics¹⁵, some countries still have a standard for cobalt of 100 $\mu\text{g}/\text{m}^3$. Adjustment of the exposure limit has been based on reports of the relation between the concentration of airborne cobalt and onset of interstitial pneumonitis or between the concentration of cobalt in the workplace atmosphere and impairment of ventilatory function sometimes associated with respiratory symptoms.

We previously studied an entire group of hard metal workers engaged in shaping pre-sintered hard metal products at a corporation,¹⁰ and we have continued to accumulate information on the health of hard metal workers at each of the various steps of hard metal production and exposures to airborne cobalt. The data for all the hard metal workers involved in the different manufacturing steps can be subjected to overall analysis of general

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Table 1 Characteristics of subjects

Sex	n (%)	Age mean (SD, range)	Smoking habit	n (%)	Exposure to hard metal (current cobalt exposure µg/m ³)	n (%)
Men	583(83)	38.4 (10.8, 18–69)	Non-smoker	107 (19)	None	263 (45)
			Ex	92 (16)	Former	75 (13)
			Current	374 (65)	Current	242 (42)
					0–50	151 (63)
					50–100	37 (15)
				>100	54 (22)	
Women	120 (17)	34.0 (11.7, 18–69)	Non-smoker	103 (87)	None	91 (76)
			Ex	4 (3)	Former	1 (1)
			Current	12 (10)	Current	27 (23)
					0–50	19 (70)
					50–100	3 (11)
					ND	5 (19)

*ND, not determined.

pulmonary function in relation to concentrations of airborne cobalt.

It is well known that asthma decreases pulmonary function, in some cases with permanent obstructive impairment. Our study³ on people with hard metal asthma suggested that continuing exposure to hard metal increases chronic obstructive pulmonary disease. This would indicate that the presence of asthma should be taken into consideration in the analysis of association of cobalt with impairment of pulmonary function.

The purpose of the present study, therefore, was to clarify the relation between the concentrations of airborne cobalt associated with hard metal and the ventilatory function of hard metal workers. Smoking and asthmatic symptoms were also considered as relevant factors in the analysis.

Subjects and methods

All of the workers (583 men and 120 women) at a hard metal corporation were studied. The factors evaluated included occupational history of exposure to hard metal, respiratory symptoms, smoking, concentrations of airborne cobalt, and ventilatory function. The history of respiratory symptoms was taken by trained interviewers with the Japanese version¹⁶ of the British Medical Research Council (MRC) questionnaire,¹⁷ and attacks of reversible dyspnoea with wheeze were defined as asthmatic symptoms. Smoking was determined according to the criteria recommended by the MRC, and the Brinkman smoking index,¹⁸ multiplication of numbers of cigarettes smoked daily by duration of smoking (years), was calculated. Individual concentrations of airborne cobalt were measured with personal sampling by atomic absorption spec-

trophotometry as described previously.¹⁰ Air samples were obtained on two or more different working days; from these samples the arithmetic means were calculated and used as representative of the present daily exposure.

Indices for ventilatory function (forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), forced expiratory volume in one second per cent (FEV₁%), peak expiratory flow (PEF), mid-maximal flow (MMF), forced expiratory flow at 50% vital capacity ($\dot{V}_{50}$), and forced expiratory flow at 25% vital capacity ($\dot{V}_{25}$)) were derived from the flow volume curve from maximum forced expiratory manoeuvres, as described previously.¹⁰ Variables were expressed as percentages of predicted values (%FVC, %FEV₁, %FEV₁%, %PEF, %MMF, % $\dot{V}_{50}$, and % $\dot{V}_{25}$) by dividing the measured values by the predicted values derived from the predictive equations for each sex and multiplying by 100. For calculation of %FVC, the equation developed by Baldwin *et al*¹⁹ was used. The equations by Berglund *et al*²⁰ were used for calculation of %FEV₁ and %FEV₁%. A preliminary study used the equation of Schmidt *et al*²¹ for calculation of %MMF and the equation of Chermiack and Raber²² for %PEF, % $\dot{V}_{50}$, and % $\dot{V}_{25}$. These generated low values, with means of less than 80% even in the non-smoking and non-exposed workers. Therefore, the equations developed from Japanese men and women by Fujimoto *et al*²³ were adopted for calculation of %PEF, %MMF, % $\dot{V}_{50}$, and % $\dot{V}_{25}$.

Differences in ventilatory indices between groups divided for various characteristics were examined by Student's *t* test and by one way or two way analysis of variance (ANOVA) with Bonferroni's multiple comparison. Stepwise multilinear regression analysis of indices on various independent factors was conducted. Differences were considered to be significant at *P* < 0.05. All of the statistical analyses were conducted with SAS procedures.²⁴

Results

CHARACTERISTICS OF SUBJECTS

Table 1 summarises the age, smoking habits, and occupational history of exposure to hard metal. The data on smoking for 10 men and one woman could not be obtained. Three men were exposed to steel dust alone. The

Table 2 Two way ANOVA of indices of ventilatory function and exposure to hard metal and smoking in men

Indices	Significance of model* (R ²)	Significant factor
%FVC	No	
%FEV ₁	No	
%FEV ₁ %,	Yes (0.03)	Hard metal exposure × smoking habit
%PEF	Yes (0.03)	Hard metal exposure × smoking habit
%MMF	Yes (0.03)	None
% $\dot{V}_{50}$	Yes (0.04)	Hard metal exposure × smoking habit
% $\dot{V}_{25}$	Yes (0.03)	None

*The model adopted was: ventilatory function index = exposure to hard metal + smoking habit + (exposure to hard metal × smoking habit).

Table 3 Two way ANOVA of indices of ventilatory function and exposure to hard metal and smoking in women

Indices	Significance of model* (R^2)	Significant factor
%FVC	No	
%FEV ₁	No	
%FEV ₁ %	No	
%PEF	No	
%MMF	No	
%V ₅₀	Yes (0.11)	Hard metal exposure
%V ₂₅	No	

Footnote as for table 2.

Figure 1 Ventilatory functions among the asthmatic and non-asthmatic currently exposed male workers. All of the indices except for %FVC were significantly lower in the asthmatic workers than in the non-asthmatic workers.

currently exposed workers were also stratified by whether the concentration of airborne cobalt was $\leq 50 \mu\text{g}/\text{m}^3$, $50\text{--}100 \mu\text{g}/\text{m}^3$, or $> 100 \mu\text{g}/\text{m}^3$.

VENTILATORY FUNCTION IN WORKERS BY EXPOSURE TO HARD METAL AND SMOKING HABIT

The ventilatory function in men was examined by two way ANOVA on exposure to hard metal (current, former, and no exposure), smoking habit (current, ex, and non-smoker), and interaction of the two factors. The model tested was:

indices of ventilatory function = exposure to hard metal + smoking habit + (exposure to hard metal $\times$ smoking habit).

Table 2 shows that for men the models were significant for the variables %MMF and %V₂₅. Interaction of hard metal exposure and smoking had significantly decreased %FEV₁%, %PEF, and %V₅₀.

Table 3 shows the results from the women: only for %V₅₀ was the model significant with

Table 4 Two way ANOVA of indices of ventilatory function on exposure to hard metal and smoking in men without asthmatic symptoms

Indices	Significance of model* (R^2)	Significant factor
%FVC	No	
%FEV ₁	No	
%FEV ₁ %	No	
%PEF	Yes (0.03)	Hard metal exposure $\times$ smoking habit
%MMF	No	
%V ₅₀	Yes (0.03)	Hard metal exposure $\times$ smoking habit
%V ₂₅	No	

Footnote as for table 2.

hard metal exposure alone being independently significant. Bonferroni's test clarified that the mean %V₅₀ in the woman formerly exposed to hard metals ($n = 1$) was significantly higher than that in the non-exposed or the currently exposed women. Interpretation of this was difficult because of small numbers.

VENTILATORY FUNCTION IN WORKERS WITH ASTHMATIC SYMPTOMS

Figure 1 shows that all indices of ventilatory function except for %FVC were significantly lower in the currently exposed men with asthmatic symptoms than in those without. On the other hand, there was no difference for any index (data not shown) between the currently exposed ($n = 33$) and non-exposed men ($n = 17$) with asthmatic symptoms, indicating that the decrease of impairment of ventilatory function was similar in these two groups.

When men with asthmatic symptoms were excluded from the analysis two way ANOVA of indices of ventilatory function showed that the interaction of hard metal exposure and smoking still affected %PEF and %V₅₀ (table 4).

The same analysis for women did not show similar findings probably because of the few asthmatic women (data not shown).

VENTILATORY FUNCTION IN CURRENTLY EXPOSED WORKERS WITH REFERENCE TO COBALT CONCENTRATION

The currently exposed men were stratified into three groups by their workplace concentration of airborne cobalt: $\leq 50 \mu\text{g}/\text{m}^3$, between 50 and $100 \mu\text{g}/\text{m}^3$, and $> 100 \mu\text{g}/\text{m}^3$. The indices of ventilatory function for these subgroups were then compared with those in the non-exposed controls by t test. There was a significantly lower %V₂₅ in those exposed to cobalt at a concentration of more than $100 \mu\text{g}/\text{m}^3$. Figure 2 shows that %V₂₅ tended to decrease with increasing concentration of airborne cobalt, whereas %FVC remained stable at all concentrations. One way ANOVA did not show a significant effect of cobalt exposures on any of the indices of ventilatory function (data not shown).

Figure 2 Dose dependent decrement in %V₂₅ by airborne cobalt concentration (exposure level).

Table 5 Multilinear regression analysis of indices of ventilatory function on independent variables in all subjects

Indices and related factors	Estimate correlation	R ²	P value
%FVC:			
Brinkman smoking index	-0.008	0.020	0.0002
Asthmatic symptoms	-3.736	0.006	0.0350
%FEV ₁ :			
Asthma	-6.916	0.021	0.0001
%FEV ₁ %:			
Asthmatic symptoms	-4.315	0.020	0.0002
Brinkman smoking index	0.004	0.020	0.0001
%PEF:			
Hard metal exposure	3.595	0.006	0.0407
%MMF:			
Asthmatic symptoms	-13.200	0.022	0.0001
Brinkman smoking index	-0.008	0.007	0.0221
%V ₅₀ :			
Asthmatic symptoms	-14.288	0.025	0.0001
%V ₂₅ :			
Brinkman smoking index	-0.014	0.018	0.0003
Asthmatic symptoms	-11.769	0.012	0.003
Hard metal exposure	-5.088	0.006	0.045

Table 6 Results of multilinear regression analysis of indices of ventilatory function among the non-exposed and the currently exposed groups and variables including both cobalt concentration and duration of exposure

Indices and independent variables	Estimate correlation	R ²	P value
%FVC:			
Brinkman smoking index	-0.010	0.031	0.0001
Sex	4.212	0.008	0.023
Duration of exposure	-0.217	0.008	0.023
%FEV ₁ :			
Asthmatic symptoms	-5.390	0.013	0.005
%FEV ₁ %:			
Brinkman smoking index	0.0047	0.024	0.0001
Asthmatic symptoms	-3.175	0.012	0.008
%PEF:			
None			
%MMF:			
Asthmatic symptoms	-9.850	0.014	0.004
Duration of exposure	-0.363	0.009	0.019
%V ₅₀ :			
Asthmatic symptoms	-11.134	0.017	0.002
%V ₂₅ :			
Duration of exposure	-0.768	0.027	0.0001
Brinkman smoking index	-0.011	0.010	0.011
Asthmatic symptoms	-9.080	0.044	0.046

In the currently exposed women, the % $\dot{V}_{50}$ of those exposed to cobalt at concentrations of 50–100 $\mu\text{g}/\text{m}^3$ was significantly lower than that in the non-exposed controls (*t* test). No indices were affected by the cobalt concentrations in one way ANOVA.

MULTILINEAR REGRESSION ANALYSIS OF INDICES OF VENTILATORY FUNCTION IN ALL HARD METAL WORKERS

The above univariate analyses and ANOVA showed that some indices of ventilatory func-

tion were clearly related to smoking, asthmatic symptoms, and exposure to hard metal in both men and women. Therefore, to elucidate the independent effects of these factors on indices of ventilatory function, we conducted multilinear regression analysis on these indices in all subjects. For analysis, exposure to hard metal was dichotomised into current or former exposure (1) and no exposure (0): the asthmatic symptoms were dichotomised into presence of (1) and absence (0). The Brinkman smoking index was used as an independent variable representative of smoking habit which quantitatively reflects consumption of tobacco not only in current smokers but also in exsmokers. Sex (men = 1, women = 0) was also included in the independent variables.

Table 5 shows that asthmatic symptoms and smoking significantly and independently decreased all of the variables except %FEV₁. Exposure to hard metal significantly decreased % $\dot{V}_{25}$. The effect of sex was not significant.

MULTILINEAR REGRESSION ANALYSIS OF INDICES OF VENTILATORY FUNCTION IN WORKERS CURRENTLY EXPOSED AND NOT EXPOSED TO HARD METAL

The associations between independent variables and indices of ventilatory function were examined in the currently exposed workers and the non-exposed workers with stepwise multilinear analysis. The independent factors included sex, Brinkman smoking index, asthmatic symptoms, and indicators for hard metal exposure. As measures of hard metal exposure, concentrations of airborne cobalt ($\mu\text{g}/\text{m}^3$), duration of exposure (years), and cumulative dose (multiplication of cobalt concentration by duration) were considered to be independent variables. As the cumulative exposure variable may confound duration of exposure, two analyses were performed. Firstly, the concentration and the duration were chosen as independent variables. Secondly, the cumulative dose alone was chosen as an independent variable for the exposure.

Table 6 shows that from the first regression analysis asthma and smoking had significantly decreased all of the indices except %PEF. Also, the duration of exposure had a significantly decreasing effect on %FVC, %MMF, and % $\dot{V}_{25}$. The cobalt concentration did not have a significant and independent effect on any indices. The increasing effect of being male was found only on %FVC.

Table 7 shows the results from the second analysis. Although asthmatic symptoms and smoking had significantly decreasing effects on all indices except %PEF, cumulative dose was not significant for any.

Discussion

The results of the present study differ from those in our previous report¹⁰ for ventilatory impairment related to exposure to hard metal. The association of decrease in FEV₁% of the 47 shaping workers with hard metal exposure found previously was not confirmed in the present study. Two way ANOVA in the current

Table 7 Results of multilinear regression analysis on indices of ventilatory function in the non-exposed and the currently exposed groups and variables including cumulative dose as an exposure indicator

Indices and independent variables	Estimate correlation	R ²	P value
%FVC:			
Brinkman smoking index	-0.010	0.031	0.0001
Sex	3.442	0.008	0.023
%FEV ₁ :			
Asthmatic symptoms	-5.390	0.013	0.005
%FEV ₁ %:			
Brinkman smoking index	0.0047	0.024	0.0001
Asthmatic symptoms	-3.175	0.012	0.008
%PEF:			
None			
%MMF:			
Asthmatic symptoms	-10.360	0.014	0.004
Brinkman smoking index	-0.008	0.008	0.030
%V ₅₀ :			
Asthmatic symptoms	-11.293	0.017	0.002
%V ₂₅ :			
Brinkman smoking index	-0.014	0.017	0.002
Asthmatic symptoms	-10.159	0.008	0.027

study showed that a decrease in %FEV₁ was associated with interaction of exposure to hard metal and smoking. Moreover, a decrease in %FEV₁ was shown in the multiple linear regression analysis to be associated only with smoking and asthmatic symptoms. This difference might be partly related to the differences in methods of statistical analysis between the two studies.

Another explanation for the discrepancy may be a difference in the degree of pulmonary disease. The subjects of the previous study (1984) were 47 workers including three asthmatic people with moderate to severe ventilatory impairment due to asthma, whereas the present study (1987) included workers with asthmatic symptoms who may not have had as heavily impaired function as those in the previous study.

Also, there may have been a difference in duration of exposure or in the earlier dose to which the subjects of the two studies were exposed. The subjects of the previous study had been exposed to a mean cobalt concentration of 120 µg/m³ for the mean duration of 10 years before the study, although exact data on exposures to cobalt in the past could not be collected for both studies. Thus, there remains a possibility that notably heavy and prolonged exposure to cobalt results in decreased FEV₁%, especially associated with asthma and heavy smoking.

The exposed workers with asthmatic symptoms were found to have greater impairment of ventilatory function than the exposed workers without asthmatic symptoms, and the severity of deterioration of ventilatory function was not as pronounced as that in the non-exposed controls with asthmatic symptoms. However, we found that the onset of asthma may speed up in association with exposure to hard metal, especially with cobalt concentrations of less than 50 µg/m³.²⁵ Therefore, the inclusion of asthmatic workers has a notable effect on the measured impairment of ventilatory function. Furthermore, when the workers with asthmatic symptoms were excluded from analysis of the currently exposed workers, this group still had significantly lower ventilatory function than the non-asthmatic controls.

The correlation (R^2) for each variable was small, which suggests that other independent factors such as working conditions, environmental pollution, and nutrition need to be explored in future studies. Irrespective of this, the present study leads to a hypothesis: that decreases of MMF, $\dot{V}_{50}$, and $\dot{V}_{25}$ in the workers, including those formerly exposed, are related to hard metal exposure. As shown from the multivariate analyses and partly from the ANOVA, hard metal exposure may cause persistent small airway disease with increasing duration of exposure. Except for people with asthmatic symptoms, workers currently exposed to hard metals did not seem to develop obstruction of the large bronchi as reflected by FEV₁ or FEV₁%. The multilinear regression analysis of %FVC also showed its positive association with the period of hard metal exposure, which may indicate progress

of restrictive ventilatory impairment possibly compatible with pulmonary fibrosis.

A definite relation between concentration of airborne cobalt and the size of decrease in indices of ventilatory function was not confirmed by the multiple regression analysis for currently exposed workers. This evidence should be taken into consideration to establish and amend the standard limit for cobalt.

Our findings are partly consistent with the Swedish report by Alexandersson and Swensson,⁷ that decreases in FEV₁, FEV₁%, and MMF were associated with exposure to cobalt at a mean concentration of 60 µg/m³. In that study the flow-volume curve which produces $\dot{V}_{50}$ and $\dot{V}_{25}$ was not measured. Again, it should be pointed out that the discrepancy between the studies may be the result of the ventilatory function tests being dependent upon the prevalences of asthma in the subjects.

On the other hand, in the study by Meyer-Bisch *et al.*,⁹ at French hard metal plants, FVC, FEV₁, or MMF did not show any significant relation with exposure to hard metal after controlling for age. Sprince *et al.*⁸ showed that with the same linear regression model as used by us, FVC and FEV₁ in hard metal workers in the United States were not correlated with exposure dose or duration. In neither of these studies did the flow volume curve follow the forced maximum manoeuvre used. In the American study, wheeze was not prevalent among the hard metal workers, whereas the French study showed a correlation between prevalence of work related wheeze and cobalt concentration. In the French study, unlike ours, no distinction was made between workers with wheeze (about 17% in the exposed subjects) and those without in the analysis of ventilatory function. These methodological discrepancies may have led to differences from our results.

The pulmonary function of Belgian employees at a cobalt refinery plant,¹² a diamond-cobalt saw production plant,¹³ and diamond polishing workshops¹⁴ have also been studied. Swennen *et al.*¹² found a positive association between decrease in FEV₁% and cobalt concentrations in biological samples (urine, blood) collected at the largest cobalt refinery in the world. All of the indices of ventilatory function (%FVC, %FEV₁, %FEV₁%, %PEF, %MMF, % $\dot{V}_{50}$, % $\dot{V}_{25}$) examined in a study by Gennart and Lauwerys¹³ conducted at a diamond-cobalt saw production plant showed a significant decrease in association with the duration of exposure, which is consistent with our results. Nemery *et al.*¹⁴ pointed out the presence of impairment of ventilatory function (%FVC and %FEV₁) among polishers exposed to cobalt even at concentrations of less than 50 µg/m³ and noted its significant relation to the cobalt concentration in urine in a linear regression model. At a Danish porcelain factory, Raffin *et al.*²⁶ found a decrease of $\dot{V}_{25}$ in workers exposed to cobalt in blue dye compared with controls. All of these reports suggest that occupational exposure to cobalt has an adverse effect on ventilatory function.

Smoking is a well known confounding factor for occupational respiratory diseases, as we have found. Smoking should be avoided by workers exposed to hard metal, although the exposure alone also disturbs the bronchi. Furthermore, the impairment of ventilatory function can be enhanced by asthma attacks, which are related to exposure to hard metal.

The functional impairment in the small airways found in the current study needs to be followed up, to find its possible association with chronic bronchial obstruction and respiratory failure. Thereafter, results from the present cross sectional study should be extended. Asthmatic workers with impairment in the large bronchi should also be followed up.

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