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Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis

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Summary

Background We have previously suggested that cryptogenic fibrosing alveolitis (CFA) may be caused by occupational exposures, particularly to metal or wood dust. We have specifically investigated this hypothesis in a case-control study of patients with CFA.

Methods We obtained lifetime occupational histories by postal questionnaire from 218 patients with CFA and 569 controls matched for age, sex, and community, living in the Trent region of the UK. Information was subsequently verified by telephone interview in 165 cases and 408 controls. Serum IgE, rheumatoid factor, and antinuclear antibodies and skin sensitivity to common allergens were measured in cases and in one matched control for each.

Findings The relative risk of CFA, after adjustment for smoking, was significantly increased in relation to questionnaire-reported exposure to metal dust (odds ratio 1·68 [95% CI 1·07–2·65], p=0·024) or to wood dust (1·71 [1·01–2·92], p=0·048). Similar results were obtained with the telephone interview data. Significant exposure-response effects were found for both metal-dust and wood-dust exposure. CFA was also associated with the presence of rheumatoid factor or antinuclear antibodies, but not with positive allergen skin tests or raised IgE concentrations. There was no evidence of interaction between the effects of rheumatoid factor, antinuclear antibodies, positive skin allergen tests, or IgE concentrations and exposure to metal or wood dust. The combined aetiological fraction attributable to exposure to metal or wood dust was of the order of 20%.

Interpretation Occupational exposures to metal or wood dust are independent risk factors for CFA. Avoidance or limitation of these exposures may provide an opportunity to prevent the disease.

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Introduction

Cryptogenic fibrosing alveolitis (CFA) is an interstitial lung disease that affects up to 20 adults per 100 000.[1] The disease is characterised by progressive dyspnoea, dry cough, inspiratory crackles on auscultation of the chest, and restrictive lung function. It is more common in men than in women and in older than in younger people.[1] The median survival time from diagnosis is about 5 years.[2] The causes are as yet unknown.

We have previously shown that mortality from CFA in the UK is increasing and tends to be higher in areas of the country that traditionally had high levels of employment in manufacturing industries.[3] We presented preliminary evidence that occupational exposure to metal or wood dust may be a cause,[4] and also suggested atopy as a risk factor for the disease.[4,5] We have tested these hypotheses in a case-control study specifically designed to investigate the role of occupational exposure to metal, wood, and other dusts as risk factors for CFA, and whether susceptibility to occupational causes of CFA is influenced by atopy, cigarette smoking, and autoimmune status.

Patients and methods

Cases and controls

We identified all potential cases of CFA seen in four teaching hospitals and five district general hospitals (total catchment

Data-set	Number reporting exposure		Unadjusted analysis		Adjusted* analysis	
	Cases	Controls	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Questionnaire	54 (24·8%)	95 (16·7%)	1·92 (1·25–2·94)	0·003	1·68 (1·07–2·65)	0·024
Interview	46 (27·9%)	53 (13·0%)	2·32 (1·36–3·94)	0·002	2·22 (1·26–3·91)	0·006
Combined†	32 (22·2%)	32 (8·9%)	2·93 (1·39–6·17)	0·005	2·59 (1·13–5·90)	0·024

*Adjusted for smoking status and exposure to wood dust. †Participants who reported exposure both on questionnaire and in interview *vs* those who reported exposure in neither.

Table 1: **Odds ratio for exposure to metal dust**

population about 3·5 million) in the Trent Region between October, 1992, and March, 1994, by regular inspection of lung function results, local diagnostic registers, and inpatient coding data. Clinical records for each potential case were inspected. A case of CFA was defined by a histological diagnosis from an open lung biopsy or by the following diagnostic criteria: basal inspiratory pulmonary crackles; bilateral interstitial lung shadowing on chest radiograph; no documented history of exposure to asbestos or other recognised fibrogens, including birds; no clinical evidence of coexisting collagen-vascular disease, no other coexisting cause of interstitial lung disease; restrictive lung function (forced expiratory volume in 1 s as a percentage of forced vital capacity [% FEV_1/FVC]>70% together with FVC or transfer factor for carbon monoxide [TLCO] <80% of predicted). In the absence of restrictive lung function patients were included if there were pathognomonic changes of CFA on a high-resolution computed tomography scan.

All patients alive at the start of the study (prevalent cases) and all new cases identified during the 18 months of the study period (incident cases) were eligible. Information on characteristics at presentation (date of diagnosis, duration of dyspnoea, presence of clubbing, and pulmonary function results) were extracted from the clinical records. Cases from our previous pilot study[4] and those diagnosed by the authors were not included.

Controls living in the same communities were identified from the local Family Health Service Authority (FHSA) lists of patients registered with the same general practitioner as the case; four same-sex individuals closest in age to the case were selected. If no controls responded, the next four closest in age to the case were selected from the list.

Occupational exposure

We asked the family practitioner for consent to approach each case and control. We sent each potential participant a questionnaire asking for details of lifetime occupational history, and in particular details of exposure to metal or wood dust and of the types of metal or wood involved. We included questions about other occupational dust exposures, lifetime history of smoking, and symptoms consistent with asthma, rhinitis, or conjunctivitis after exposure to pollen or household dust. Cases and controls were not told the hypothesis being tested. After return of the questionnaire we attempted to interview each case and control by telephone to verify data on occupational dust exposure. The initial part of the interview was structured and designed to produce a full occupational history with details of any dust exposure. After these structured questions, open questions were asked to elucidate further details about any dust exposures, however brief. At the outset of the interview the interviewer was unaware of the disease status of the subject, but it was not possible to maintain this unawareness throughout the interview. All telephone interviews were tape-recorded.

Cases and controls who did not return questionnaires were sent reminders. Since the accuracy of FHSA data lists has been reported to be limited,[6] 100 control non-respondents were randomly selected for checking. We checked the names and addresses against the local electoral register and then telephoned the individuals to confirm their address and to ask for details of dust exposure.

Autoimmunity status

Each case and the control closest in age were visited at home so that a venous blood sample could be taken and skin-prick tests for *Dermatophagoides pteronyssinus,* grass pollen, cat fur, and *Aspergillus fumigatus* (Bencard UK) could be done. Skin tests were taken to be positive if any allergen weal exceeded the saline response by 1 mm or more. Serum was separated and stored at −70°C until assay for rheumatoid factor and antinuclear, smooth-muscle, thyroid, and parietal-cell antibodies. Rheumatoid factor was assayed initially by latex agglutination and positive results were confirmed if the reciprocal titre was 40 or more, by gelatin agglutination. Autoimmune screening was by immunofluorescence with sections of rat liver, kidney, stomach, and oesophagus and human thyroid. IgE concentrations were measured by a kinetic ELISA technique (Melenia Immunoassay Systems, EURO/DPC Ltd, Llanberis, Wales).

Ethics approval for the study was granted by the Nottingham City Hospital Medical Ethics Commitee and by the local medical ethics committee for each participating centre.

Analysis

Data from the questionnaires and telephone interviews were coded and entered on a micro-computer by one research assistant who was unaware of disease status of participants or the hypothesis being tested. Lung function was expressed as mean percentage of predicted values from the summary equations according to the European Community for Steel and Coal.[7] For both the questionnaire and interview data-sets, dust exposures were defined from self-reported occupational histories as ever having been exposed to metal dust or wood dust, and agreement for dust exposures between the two data sources was assessed with the kappa statistic. The questionnaire and interview data-sets were then combined to produce a third data-set, made up of only individuals who reported dust exposure in both questionnaire and the telephone interview, and those who denied dust exposure in both. Similar analyses were carried out for asbestos and for other occupational dust exposures reported by more than 2% of cases or controls. We chose the 2% cut-off point since the study had insufficient statistical power to assess the effects of exposures with prevalence lower than this. Social class was assigned on the basis of occupation for the greatest number of years, according to the guidelines of the Registrar-General.[8] Smoking histories were defined from self-reported smoking histories as ever-smoker if the subject had smoked one or more cigarettes per day for a year and never-smoker if otherwise, and quantified into pack-years (1 pack-year is equivalent to smoking 20 cigarettes a day for a year). Symptoms consistent with allergy to household dust or pollen were defined as ever allergy if the subject responded positively to questions about symptoms consistent with asthma, rhinitis, or conjunctivitis after exposure to household dust or pollen.

Matched case-control analysis was carried out by conditional logistic regression. For each of the three data-sets, the effects of each occupational dust exposure, smoking, atopy, and autoimmunity variables on disease status were first assessed by univariate analysis. The effects of those exposures significantly associated with CFA were then analysed together in a multivariate model. Multiplicative terms were included to test for interactions between the effects of allergen skin sensitivity, IgE concentrations, autoantibodies, and occupational exposures. IgE data were not normally distributed and were log transformed before analysis. To look for exposure-response relations for occupational exposures significantly associated with CFA, total dust exposures were calculated from questionnaire responses as work-years of exposure (one work-year of exposure was equivalent to 8 h of dust exposure per day for a year). The time between the end of dust exposures and diagnosis of disease was also assessed, and the attributable risk for each dust exposure calculated.[9] Occupational exposures were then compared

Data-set	Number reporting exposure		Unadjusted analysis		Adjusted* analysis	
	Cases	Controls	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Questionnaire	30 (13·8%)	45 (7·9%)	1·92 (1·15–3·23)	0·013	1 71 (1·01–2·92)	0·048
Interview	24 (14·5%)	32 (7·8%)	2·55 (1·26–5·15)	0·009	2·58 (1·17–5·64)	0·018
Combined†	18 (11·9%)	16 (4·3%)	3·39 (1·30–8·83)	0·013	3·81 (1·11–13·1)	0·034

*Adjusted for smoking status and exposure to metal dust. †Participants who reported exposure both on questionnaire and in interview *vs* those who reported exposure in neither.

Table 2: **Odds ratio for exposure to wood dust**

between incident and prevalent cases by logistic regression with adjustment for age at diagnosis and sex.

The study was designed to include 225 cases of CFA and an average of four controls per case matched for age, sex, and community to provide more than 90% power to detect an odds ratio of 3·0, assuming an exposure prevalence in the control group of 3·0%.

Results

Participants

From the nine centres 244 cases of CFA that met the specified diagnostic criteria were identified. 225 (92%) returned completed questionnaires. 569 of a potential 1066 eligible controls returned completed questionnaires. From a random sample of 100 control non-respondents we established contact with 40, identified 21 who had either died or moved (not listed in the electoral register or their telephone numbers had been disconnected), and were unable to account for the remaining 39. Since at least 21% of potential cases identified in the FHSA lists were not available, our participating controls represented about 68% of those eligible. For seven cases (three male) we were unable to obtain a control response. Thus, 218 matched case-control sets provided questionnaire data for analysis, with an average of 2·6 controls per case. Telephone interviews were completed for 165 cases (76%); of the remainder 22 had died since returning the questionnaire, 11 reported themselves too unwell, four were deaf, seven had no telephone, one could not speak English, two refused, and six could not be contacted. Telephone interviews were completed for an average of 2·5 controls per case.

The mean age of the 218 cases was 66·6 (SD 11·3) years. 149 (68%) were men and 69 women (ratio 2·16/1). For 31 (14%) cases, a histological diagnosis from an open lung biopsy was available. All but one of the cases diagnosed histologically also met the clinical diagnostic criteria; the remaining case had obstructive lung function due to coexisting airways disease. There were 151 (69%) prevalent cases and 67 (31%) incident cases. Incident cases tended to be older than prevalent cases (mean age 69·8 [9·7] *vs* 65·2 [11·8] years, p=0·006) and included a higher proportion of men (78 *vs* 64%, p=0·072). There was no difference in mean age or sex distribution between the 218 cases who provided questionnaire data and the 165 cases interviewed or between either of these populations and the initial sample of 244 patients. The presence or absence of finger clubbing at presentation was recorded for 184 of the 218 cases; of these 93 (51%) had clubbing. This sign was more common in men than women (56 *vs* 39%, p=0·044). The mean percentage predicted FVC was 78·4% (21·0), total lung capacity (TLC) 69·6% (18·1), and TLCO 51·2% (18·0).

Smoking history

77% of cases and 71% of controls were ever smokers. Univariate analysis showed that a history of ever smoking was significantly associated with CFA (odds ratio 1·57 [95% CI 1·01–2·43], p=0·043). The odds of CFA increased with pack-years of smoking but this effect was not significant (odds ratio for each additional 10 pack-years of smoking 1·05 [0·99–1·12], p=0·117).

Metal and wood dust exposure

Exposure to metal dust (table 1) and wood dust (table 2) was reported by more cases than controls, both in the questionnaire and telephone interview. The kappa values for agreement between the two data sets for history of metal dust exposure were 0·67 for cases and 0·50 for controls and for history of wood dust exposure were 0·67 for cases and 0·46 for controls. Univariate analysis of questionnaire data revealed significant associations between CFA and a history of exposure to metal or wood dust. Analysis of data from telephone interviews produced slightly stronger estimates of such associations, and analysis of the combined data-set produced the highest odds ratios for metal or wood dust exposures. No association was found between social class and CFA. Analysis of work-years of exposure revealed evidence of exposure-response relations for both metal dust (odds ratios per work-year of exposure 1·11 [1·06–1·16], p<0·001) and wood dust (1·12 [1·02–1·24], p=0·020).

Metal-dust and wood-dust exposures were reported from a variety of occupations. For metal dust the commonest job among cases was machine operator, including lathe turners and metal polishers (n=31, 57%) and for wood dust the commonest job was woodworker, including carpenters and French polishers/cabinet makers (n=14, 47%). The particular types of metal and wood dust exposure involved and their relation with CFA are listed in table 3.

In all cases, dust exposures had started at least 5 years before diagnosis. The median time between the start of exposure and diagnosis of disease was 47·5 years for metal

	Number reporting exposure		Univariate odds ratio (95% CI)	p
	Cases	Controls		
Metal dusts				
Aluminium	14 (6·4%)	26 (4·6%)	1·61 (0·82–3·16)	0·167
Brass	21 (9·6%)	32 (5·6%)	1·97 (1·10–3·52)	0·022
Bronze	4 (1·8%)	6 (1·1%)	2·09 (0·57–7·61)	0·266
Cobalt	1 (0·5%)	0	. .	
Copper	15 (6·9%)	28 (4·9%)	1·56 (0·81–3·02)	0·185
Chrome	1 (0·5%)	4 (0·7%)	0·72 (0·08–6·52)	0·772
Gold	1 (0·5%)	0	. .	
Iron	17 (7·8%)	39 (6·9%)	1·22 (0·65–2·29)	0·537
Lead	8 (3·7%)	4 (0·7%)	5·54 (1·63–18·8)	0·006
Manganese	0	1 (0·2%)	. .	
Silver	0	3 (0·5%)	. .	
Steel	40 (18·3%)	75 (13·2%)	1·72 (1·09–2·70)	0·019
Tin	1 (0·5%)	3 (0·5%)	0·90 (0·09–8·68)	0·925
Tungsten carbide	2 (0·9%)	0	. .	
Zinc	3 (1·4%)	4 (0·7%)	2·02 (0·43–9·41)	0·372
Wood dusts				
Chipboard	2 (0·9%)	3 (0·5%)	1·89 (0·31–11·6)	0·491
Pine	8 (3·7%)	6 (1·1%)	3·37 (1·14–9·96)	0·028
Beech	1 (0·5%)	4 (0·7%)	0·79 (0·09–7 10)	0 834
Birch	1 (0·5%)	2 (0·4%)	1·00 (0·08–11·9)	1·000
Larch	1 (0·5%)	1 (0·2%)	2·45 (0·15–39·7)	0·529
Mahogany	6 (2·8%)	7 (1·2%)	2·07 (0·68–6·30)	0·202

Table 3: **Odds ratios for exposure to specific metal dust or wood dust**

	Cases (n=205)	Controls (n=192)	Odds ratio* (95% CI)	p
Rheumatoid factor	26 (12 6%)	10 (5·2%)	2·44 (1·13–5·31)	0·024
Antinuclear antibodies	77 (37·6%)	50 (26·0%)	1·70 (1·10–2·61)	0·016
Smooth-muscle antibodies	19 (9·2%)	13 (6·8%)	1·50 (0·72–3·11)	0·277
Parietal cell antibodies	5 (2·4%)	11 (5·7%)	0·30 (0·08–1·09)	0·067
Reticulum antibodies	3 (1·5%)	3 (1·6%)	1·00 (0·20–4·96)	1·000

*Based on analysis of 192 case control sets.

Table 4: **Presence of autoantibodies and rheumatoid factor in cases and controls**

dust and 45·5 years for wood dust. More prevalent cases than incident cases reported metal-dust exposure, though the difference was not significant (odds ratio adjusted for age, sex, and smoking 2·16 [0·97–4·81], p=0·059). There was little difference in reported wood-dust exposure between the prevalent and incident cases (1·04 [0·44–2·50], p=0·929).

The estimated attributable risks for metal-dust exposure from the questionnaire, interview, and combined data-sets, respectively, were 10·3%, 13·4%, and 12·5%; the corresponding risks for wood-dust exposure were 5·3%, 10·8%, and 7·1%.

We were able to assess occupational exposure by telephone interview in 32 of the sample of 100 control non-respondents. The proportions who reported metal-dust exposure (four, 13%) and wood-dust exposure (two, 6%) were similar to those for controls included in the study.

Other occupational dust exposures

No significant association was found between CFA and asbestos exposure (adjusted odds ratio 1·00 [0·41–2·40], p=0·997). Other occupational dusts reported by 2% or more of cases included dusts from textiles, coal, building sites, and tobacco, as well as sand. Questionnaire data suggested a significant association with exposure to textile dust (1·80 [1·10–2·96], p=0·019) and sand (1·76 [1·01–3·07], p=0·047) but not to other dusts. However, the effect of sand exposure was lost after adjustment for smoking, and neither effect of sand nor textile dust was significant in the telephone interview data-set.

Autoimmunity and atopy

Cases were significantly more likely than controls to report symptoms of allergy to household dust (1·51 [1·01–2·26], p=0·044) but there was no difference for symptoms of allergy to pollen (1·20 [0·75–1·91], p=0·440). 205 cases and 192 controls gave a venous blood sample and 194 cases and 187 controls had allergen skin tests. The frequency of positive tests was similar for cases and controls (15·5 *vs* 19·2%; odds ratio 0·81 [0·45–1·44], p=0·467). The geometric mean IgE concentration was also similar in cases and controls (29·6 *vs* 29·2 kU/L; 1·00 [0·89–1·14], p=0·917). Significantly more cases than controls had rheumatoid factor and antinuclear antibodies in their serum (table 4). There was no relation between presence of rheumatoid factor, antinuclear antibodies, positive skin-prick tests, or IgE concentration and a history of dust exposure, and no interaction or effect modification between these variables.

Discussion

This study has confirmed our earlier preliminary evidence that metal and wood dusts are independent risk factors for CFA, as well as the findings of Iwai et al,[10] which also suggested that CFA is more common among workers in some occupations believed to involve metal-dust exposure. We also found evidence of an exposure-response effect between dust exposure and disease. The estimates of attributable risk for metal and wood dust suggest that these dusts may be the cause of 10–13% and 5–10% of cases of CFA, respectively, in our local population. CFA was significantly associated with smoking, but adjustment for the effects of smoking did not greatly affect the associations with metal-dust or wood-dust exposure. By contrast with our previous study,[5] however, we found no evidence of an association between atopy and CFA, and although rheumatoid factor and antinuclear antibodies were more common among cases than controls, the presence of these antibodies was not associated with susceptibility to the effects of dust exposure.

We used a case-control design to test our hypothesis because CFA is not common and because the duration of any lead time from exposure to presentation is likely to be long.[9] We tried to minimise selection bias for the cases by attempting to identify and recruit all cases seen at each participating centre during the specified study period, and by setting clear diagnostic criteria relevant to usual diagnostic practice.[11] Since only about 10% of cases in the UK[11] undergo an open lung biopsy, this procedure was not required for eligibility, though the use of open lung biopsy in this series was commoner than expected. We did not include cases from our previous study,[4] or cases we diagnosed ourselves, to avoid any possible diagnostic bias resulting from our previous findings. The participation rate among potential cases was high, and this, together with the fact that our cases were similar to those described previously[1,2] in terms of age distribution, male/female ratio, presence of clubbing, results of lung function tests, and presence of autoantibodies, suggests that our cases were indeed generally representative.

We used individual matching of controls to avoid confounding by age and sex, and also by area of residence, since this factor will affect accessibility to particular occupations, and diagnostic and referral characteristics of the family practitioner. We cannot calculate our true control response rate precisely because of inaccuracies in the FHSA registers, but we estimated the rate to be at least 68%. The prevalence of reported dust exposures in the sample of control non-respondents whom we subsequently interviewed was similar to that for controls who responded to our questionnaire, so it is unlikely that there was much bias in control participation in relation to dust exposure. We also ensured that as far as possible our cases and controls remained unaware of the hypothesis being tested. The telephone interview to confirm the occupational histories was carried out after the questionnaires had been returned to assess possible recall bias in the questionnaire data, a particular objective being to provide controls with a further opportunity to recall dust exposures. In the event, agreement between the two data-sets was good; a smaller proportion of controls reported dust exposure during the telephone interview than on the questionnaire which suggests that controls may have tended to overestimate, rather than underestimate, dust exposure when completing the questionnaire.

Since smoking was associated with CFA, we adjusted for the effect of smoking in the analysis. This adjustment did not greatly affect the estimated effects of metal-dust or wood-dust exposure. Occupation-defined social class

was not associated with CFA and did not confound the effects of metal-dust or wood-dust exposure. No consistent associations were found with other reported occupational exposures, although the associations with textile dust and sand dust in the questionnaire data raise the possibility that other exposures are important and warrant further investigation. Our findings therefore indicate that the occupational dust exposure associations observed are specific to the exposures investigated and are unlikely to have arisen through bias or confounding in our study methods.

We found that exposure to steel, brass, and lead was specifically associated with CFA. However, we still do not know whether CFA results from exposure to these particular metals, or to other related exposures that occur in the industries involved. Exposure to certain metals can cause a wide range of respiratory diseases including asthma, bronchitis, emphysema, and acute or chronic interstitial lung diseases.[12,13] Case reports have suggested that several metals may cause an interstitial lung disease that clinically resembles CFA.[12,13] For example, diamond polishers exposed to cobalt dust[14] and workers who polish tungsten carbide (which contains cobalt as a binding agent) may develop fibrosing alveolitis,[15] and interstitial lung fibrosis has been reported in potroom workers exposed to aluminium dust[16] and in aluminium welders and polishers.[17,18] Other metals for which there are case reports of diffuse interstitial lung diseases or pulmonary fibrosis occurring as a long-term consequence of exposure include zinc,[19] cadmium,[20] and mercury.[21] We did not find evidence of association with these specific metal exposures, but low level exposure in the form of constituents of steel may have occurred for aluminium and cobalt.

Exposure to wood dust causes both airflow obstruction[22] and extrinsic allergic alveolitis due either to exposure to fungi and moulds contained within the wood[23] or to exposure to isocyanates during the processing of wood.[24] There has been one case report of an interstitial lung disease resembling CFA in an individual with heavy exposure to a wood-burning stove[25] and a report of acute extrinsic allergic alveolitis in two subjects resulting from penicillium species contained in wood fuel chips.[26] In our study only pine wood exposure was significantly associated with CFA. Although exposure to pine dust may be a cause of CFA, it is also possible that this exposure may be merely a marker for other exposures encountered while working with wood. For example, carpenters may also work with asbestos sheeting, and French polishers are exposed to many solvents. Although exposure to asbestos was specifically sought, residual effects of unreported exposures cannot be excluded.

The finding of a significant association between CFA and smoking contrasted with the results of our pilot study[4] but is supported by one previous report[10] and by the high incidence of smoking reported from clinical case series.[2,27] Smoking may cause alveolitis,[28] but it is possible that patients with CFA who smoke have worse lung function than those who do not and hence are more likely to present with symptoms of disease. One implication of the association of smoking with CFA is that in assessing the effects of an occuptional exposure it is important to consider potential confounding by smoking in the analysis; no such allowance was made in the two previous case-control studies of occupation in CFA.[4,10] In our study, however, adjustment for smoking did not influence the effect of dust exposures appreciably, so it is likely that smoking and metal-dust or wood-dust exposures are independent.

In our pilot study we found that patients with CFA were more likely to report symptoms consistent with atopy than controls and to have higher concentrations of IgE and a higher prevalence of positive skin-prick tests. However, this study did not confirm those findings. Our results confirmed that CFA is associated with autoantibodies and rheumatoid factor,[29] but there was no interaction between autoantibody or rheumatoid factor status and occupational dust exposure. The presence of autoantibodies and rheumatoid factor may represent a non-specific result of lung injury, as is believed to be the case in asbestosis.[30]

We conclude, therefore, that our findings represent new evidence that CFA occurs in association with exposure to metal or wood dust, and that these associations are independent and dose related. The combined attributable risk of these exposures in our population was about 20%, which indicates that a substantial proportion of cases of CFA, and of the approximately 1000 deaths from CFA in England and Wales each year,[3] are potentially preventable through measures to control these dust exposures. Although the cause of most cases of CFA remains unexplained our findings challenge the concept that this is a disease of unknown aetiology.

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Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty

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Summary

Background In-vitro studies indicate that platelet function and the coagulation cascade are impaired by hypothermia. However, the extent to which perioperative hypothermia influences bleeding during surgery remains unknown. Accordingly, we tested the hypothesis that mild hypothermia increases blood loss and allogeneic transfusion requirements during hip arthroplasty.

Methods Blood loss and transfusion requirements were evaluated in 60 patients undergoing primary, unilateral total hip arthroplasties who were randomly assigned to normothermia (final intraoperative core temperature 36·6 [0·4]°C) or mild hypothermia (35·0 [0·5]°C). Crystalloid, colloid, scavenged red cells, and allogeneic blood were administered by strict protocol.

Findings Intra- and postoperative blood loss was significantly greater in the hypothermic patients: 2·2 (0·5) L *vs* 1·7 (0·3) L, $p<0·001$). Eight units of allogeneic packed red cells were required in seven of the 30 hypothermic patients, whereas only one normothermic patient required a unit of allogeneic blood ($p<0·05$ for administered volume). A typical decrease in core temperature in patients undergoing hip arthroplasty will thus augment blood loss by approximately 500 mL.

Interpretation The maintenance of intraoperative normothermia reduces blood loss and allogeneic blood requirements in patients undergoing total hip arthroplasty.

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Introduction

Mild perioperative hypothermia (core temperature 34–36°C) results from intraoperative heat loss and anaesthetic-induced inhibition of normal thermoregulatory control.[1] Postoperative restoration of a normal core temperature typically requires several hours,[2] increasing the duration of hypothermia well beyond the time in surgery. Although intraoperative hypothermia can easily be prevented,[3] it remains common;[4] no prospective randomised study has shown adverse outcomes as a result of mild hypothermia.

In-vitro studies suggest that perioperative hypothermia may aggravate surgical bleeding by impairing platelet function and directly reducing clotting factor enzyme function.[5,6] Hypothermia increases the bleeding time, an inhibition apparently related to defective thromboxane A_2 release, upregulation of platelet surface protein GMP-140, and downregulation of platelet glycoprotein Ib-IX complex.[5] Furthermore, hypothermia prolongs both the prothrombin (PT) and partial thromboplastin (PTT) times—most likely via direct inhibition of clotting factor enzyme function.[6]

Despite in-vitro evidence that hypothermia impairs coagulation, the extent to which mild perioperative hypothermia increases bleeding during surgery remains unknown. Accordingly we tested the hypothesis that a policy of maintaining normothermia reduces blood loss and allogeneic transfusion requirements during hip arthroplasty. This is a relatively standardised operation associated with considerable microvascular blood loss.

Methods

We evaluated blood loss and transfusion requirements in patients undergoing initial, unilateral total hip arthroplasties at the Hospital of Amstetten, Austria. The study was approved by review boards at the Hospital of Amstetten, the University of Vienna, and the University of California at San Francisco; written informed consent was obtained from participating patients. We studied 60 patients because a preliminary study indicated that this number would provide about an 80% chance of identifying a significant hypothermia-induced increase in