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Tantalum inhalation and airway responses[1]

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ABSTRACT We studied the effects of tantalum inhalation bronchography on pulmonary function in 14 normal volunteers. Based on the radiographic type of deposition, the subjects were divided into three groups: (1) subjects who deposited tantalum mainly in the trachea, (2) subjects who deposited tantalum in segmental bronchi without radiographic evidence of bronchospasm, and (3) subjects who deposited tantalum in segmental bronchi with radiographic evidence of bronchospasm. Unlike the first two groups, the third group developed a significant but small decrease in the FEV_1. Airway reactivity as assessed by methacholine challenge did not explain the difference in response to tantalum in the third group. There were no consistent changes in total lung capacity, residual volume, or closing volume in any of the groups. Even though there were falls in FEV_1 and specific conductance in individuals in groups 2 and 3, these changes did not pose any significant clinical risk.

Since its introduction by Nadel *et al* in 1968, tantalum powder has been used in man to evaluate the pathology of the trachea, larynx, and airways (Nadel *et al*, 1970; Stitik and Proctor, 1973), to detect occult carcinoma (Stitik and Proctor, 1975), and to study regional clearance times in patients with chronic obstructive pulmonary disease (Gamsu *et al*, 1973). In all of these studies a selective catheter has been used to insufflate the tantalum into the desired area under examination. Whole lung inhalational bronchography has been performed in dogs demonstrating techniques that might accomplish more uniform deposition of tantalum throughout the lung area (Smith *et al*, 1976). Physiological measurements in dogs undergoing whole lung bronchography (Nadel *et al*, 1968) and man undergoing selective bronchography (Gamsu *et al*, 1973) have not shown significant changes in pulmonary function. We have noticed that normal subjects and patients undergoing whole lung bronchography have occasional radiographic evidence of bronchoconstriction though remaining free of symptoms. Although random pulmonary function tests performed on some of these subjects suggested that changes were occurring, no systematic evaluation was done. The present study was undertaken firstly to correlate the anatomical changes seen on radiography with changes observed in pulmonary function and, secondly, to determine if the deposition of, and physiological responses to, inhaled tantalum would correlate with airways reactivity as assessed by methacholine challenge.

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Methods

Fourteen volunteers (seven men) with no history of asthma or lung disease were selected. Their ages ranged from 22 to 28. Three had past histories of hay fever, one requiring desensitisation treatment until 1974 at which time her symptoms ceased. At the time of the study eight subjects had smoked more than one pack of cigarettes daily for more than three years.

Premedication included codeine 30–45 mg intramuscularly and topical anaesthesia performed in the following manner. Four per cent topical lidocaine was sprayed in the oropharynx with the patient seated. The pyriform sinuses were then selectively anaesthetised with cotton swabs; and finally, lidocaine was injected into the trachea by indirect laryngoscopy. Two subjects with excessive secretions during premedication with topical anaesthesia were given 0·6 mg atropine subcutaneously. All subjects were asked not to smoke cigarettes for three days before the study. The heart and lungs of each subject were auscultated before and after the inhalation.

The generation of a tantalum aerosol has been

previously described in detail (Smith *et al,* 1976). Briefly, tantalum powder was placed in a cylindrical polypropylene chamber fitted with rotational blades that rotated at 1200 rpm. A design of the apparatus is shown in fig 1B in the 1976 article by Smith *et al.* A 30 cm plastic tube connected to the generator was then placed in the oropharynx of the subject at the base of the tongue. Subjects were encouraged to position the tube as far back as possible to bypass most of the oropharynx. While in the prone position, they were then instructed to take short, shallow, as well as long, deep inspirations to deposit tantalum in the airways. Each tantalum study was terminated when distal airways became visible or when coughing prevented further inhalation of tantalum.

Pulmonary function tests were performed before the inhalation. Repeat tests were begun within 15 minutes of the inhalation and took a maximum of 30 minutes to complete. These included in order of performance: measurement of airways resistance, forced expiration, and the distribution of ventilation with a single breath nitrogen test. Airways resistance and thoracic gas volume were measured in triplicate (Dubois *et al,* 1956a and b) by using a body plethysmograph and photographic recorder (Electronics for Medicine, White Plains, New York).

Four forced expiratory manoeuvers were performed with a Stead Wells spirometer (Warren E Collins, Inc, Braintree, Massachusetts), and the best FEV_1 and forced vital capacity were chosen.

Closing volume and slope of the alveolar plateau (phase III) were obtained by the single-breath nitrogen washout technique (Anthonisen *et al,* 1969). Three determinations were made and averaged. The slope of phase III was determined by the best fit line drawn by eye through the latter half of phase III.

In 11 of 14 subjects a methacholine challenge was administered within one month of the inhalation bronchography according to the protocol of Fish *et al* (1976). Briefly, a dosimeter dispersed increasing doses of methacholine with five- to ten-minute rest periods between doses. Measurements of specific airways conductance (sGaw) and FEV_1 were made between each dose until a maximum of 250 units of methacholine had been given.

All the radiographs of the subjects were taken on a remote control fluoroscopic table where a supine posterioranterior radiograph of the chest was taken at the end of quiet expiration. The X-ray tube film distance was fixed at 100 cm (40 inches). The exposure was made with a nominal 1·3 focal spot. Medium speed intensifying screens (Dupont Par-Speed) and medium speed film (Kodak RP) were used. The exposure was made at 140 kVp and 300 mA with automatic exposure termination. The film was made with a stationary grid with 12 : 1 ratio, 40 lines per centimetre.

Results

Tantalum deposition varied widely in the subjects. Based on the chest radiographs, the subjects were arbitrarily divided into three groups: group 1 consisted of six people with tantalum deposition confined mainly in the trachea or in the trachea and right and left main stem bronchi; group 2 consisted of five people with tantalum deposition in segmental and subsegmental bronchi but with no radiographic evidence of bronchospasm; and group 3 consisted of three people with peripheral deposition similar to group 2 but with radiographic evidence of bronchospasm. Representative radiographs from each group with magnification are shown (figs 1–5). The presence of bronchospasm was most easily seen on fluoroscopy since the airways were seen to constrict while they were being outlined during inhalation of tantalum. Characteristics of the three groups are shown in tables 1 and 2.

Baseline pulmonary function (table 2) did not

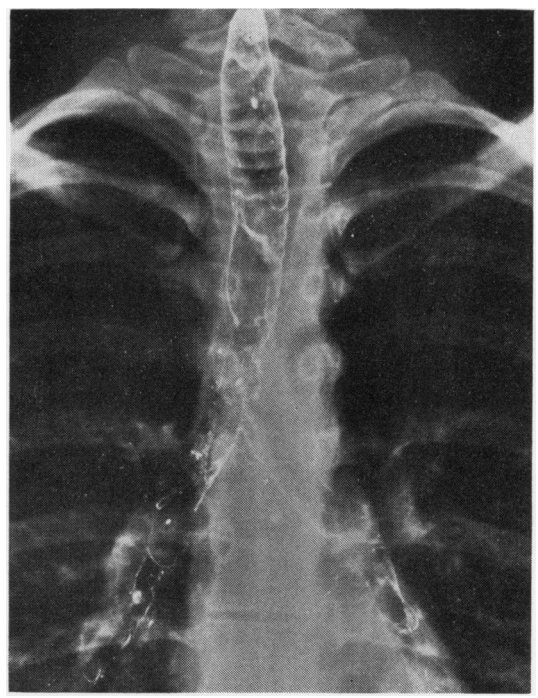

Fig 1 *Group 1. Representative chest film. Tantalum is primarily confined to trachea.*

differ between the three groups. Physiological responses varied between groups, but the following tests did not show any consistent pattern: closing volume, closing capacity, slope of phase III, residual volume, functional residual capacity, and total lung capacity. The individual values for sGaw before and after tantalum inhalation are shown in fig 6. In group 3 there was a significant decrease in sGaw after tantalum. None of the individuals in group 1 had falls of greater than 15%. SGaw fell more than 30% in two individuals from group 2, but changes in the group as a whole were not statistically significant.

After tantalum inhalation, FEV_1 fell in all three subjects in group 3 (fig 7). Isoprenaline aerosol was administered to the group 3 subjects and reversed the pulmonary function changes seen above. No wheezes or crackles were heard except in one subject in group 3 who had wheezing on auscultation after the bronchogram. He also had a history of rhinorrhea about one week before the study. The only symptoms reported during inhalation of tantalum were coughing and a choking sensation primarily in the group 1 subjects. In the subjects from this group coughing and the lack of tantalum

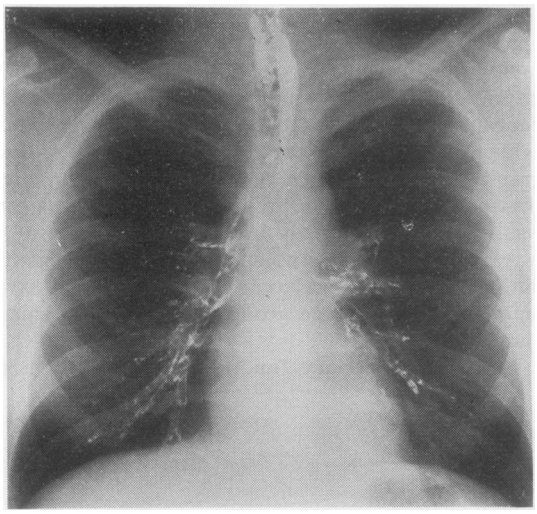

Fig 2 *Group 2. Representative chest film. Tantalum is deposited on trachea and large subsegmental airways.*

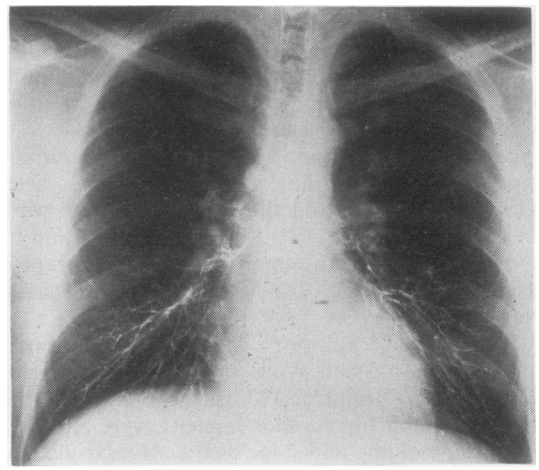

Fig 4 *Group 3. Representative chest film. More distal airways are constricted.*

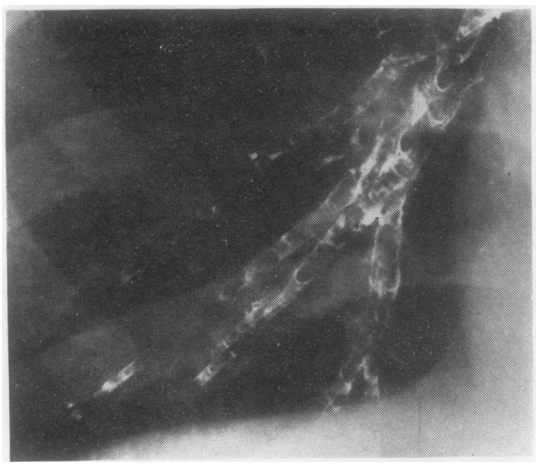

Fig 3 *Close-up of right lower lobe in fig 2 shows no bronchospasm.*

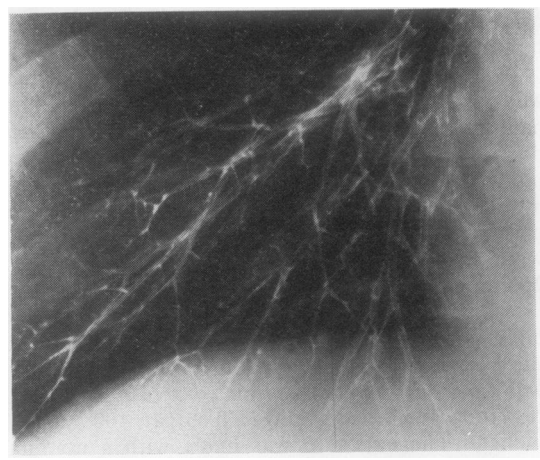

Fig 5 *Close up of right lower lobe in fig 4 shows bronchoconstriction (see text).*

Table 1 *Characteristics of subjects studied.*

	No. of subjects	*Age*	*Sex*	*Mean height (in)*	*Mean weight (lbs)*	*Smokers*
Group 1	6	24·1	2 M 4 F	66·5	133·3	2
Group 2	5	24·8	3 M 2 F	69·2	161·2	4
Group 3	3	24·6	2 M 1 F	69·2	143·3	2

deposition in distal airways necessitated termination of the procedure. All subjects coughed after the study was completed and as the anaesthesia wore off.

Eleven of the original 14 subjects had a methacholine challenge within one month after the tantalum bronchogram. All subjects tolerated doses up to 250 units, and the response to this

Table 2 *Mean lung function before and after tantalum bronchography*

	FEV_1 (l)	*FEV_1%*	*Specific conductance ($s^{-1}kPa^{-1}$)*	*Total lung capacity (l)*	*Functional residual capacity (l)*	*Residual volume (l)*	*Phase III (%N_2/l)*	*Closing volume (l)*	*Closing capacity (l)*
Group 1									
Before	3·74±0·29	84·7±3·3	2·78±0·54	5·682±0·51	3·120±0·28	1·45±0·16	0·60±0·05	0·22±0·08	1·67±0·22
After	3·69±0·27	86·0±2·8	2·62±0·55	5·568±0·46	2·888±0·30	1·22±0·17	0·82±0·15	0·24±0·08	1·46±0·19
Group 2									
Before	3·99±0·14	84·3±2·5	2·80±0·44	6·635±0·52	3·245±0·32	1·92±0·19	0·98±0·20	0·17±0·06	2·05±0·29
After	3·98±0·16	85·8±2·0	2·33±0·30	6·330±0·50	3·086±0·34	1·79±0·44	1·06±0·11	0·16±0·05	1·86±0·36
Group 3									
Before	3·99±0·45	84·2±5·4	2·67±0·12	6·303±0·42	3·253±0·20	1·68±0·21	0·83±0·07	0·35±0·21	2·02±0·10
After	3·45±0·32*	76·1±4·3*	1·84±0·18†	6·201±0·26	3·284±0·22	1·72±0·25	0·65±0·33	0·18±0·10	1·89±0·23

*P < 0·05.
†P < 0·01.

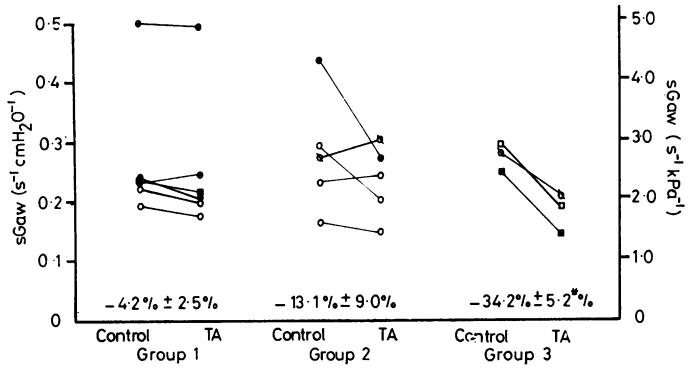

Fig 6 *Specific airway conductance before and after tantalum inhalation. Open figures represent smokers, closed figures represent non-smokers, and squares represent subjects with history of hay fever. A diagonal line through a figure indicates atropine was given. *Paired data differ significantly (P<0·01). Group percent mean fall±SE is recorded for each group.*

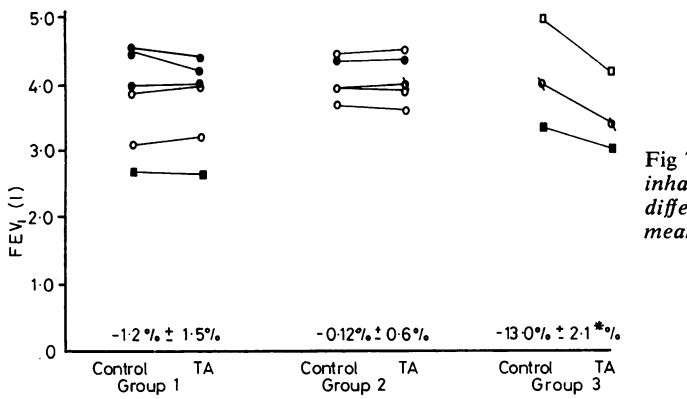

Fig 7 *FEV_1 before and after tantalum inhalation. Symbols as for fig 6. *Paired data differ significantly (P<0·05). Group percent mean fall ± SE is recorded for each group.*

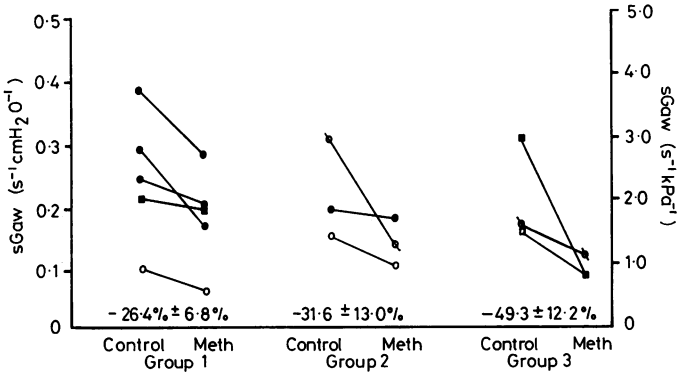

Fig 8 *Specific airway conductance before and after 250 units of methacholine. Symbols as in figs 6 and 7. Group percent mean fall ±SE is recorded for each group. Analysis by covariance showed no difference in response between the three groups.*

dose is shown in fig 8. There were no statistical differences in responses between groups. Not shown is the FEV_1 response that also showed no significant differences between the groups. In fact, only two people (one each from groups 1 and 3) had any changes in FEV_1, both falling 13%.

Discussion

Two previous tantalum studies, one in man (Nadel *et al,* 1970) and the other in dogs (Nadel *et al,* 1968), have not recorded changes in pulmonary function. In the human study (Nadel *et al,* 1970) a selective catheter technique was used resulting in deposition of small amounts of tantalum in specific areas of the lung. On the other hand, with whole lung bronchography there is a greater amount of material deposited; in our experience this has been associated with radiographic evidence of bronchospasm in some normal individuals. Furthermore, several investigators have shown that dust and inert particles may cause a significant fall in sGaw in man (Dubois and Dautrebande, 1958; Nadel and Comroe, 1961; Widdicombe *et al,* 1962; Sellick and Widdicombe, 1971). Because of the above observations, we anticipated an anatomical-physiological correlation between tantalum radiographs and pulmonary function. We expected to see evidence of bronchospasm with concomitant changes in pulmonary function recording the bronchoconstriction. Indeed, in the group 3 subjects this relationship was seen.

Based on previous human and animal experimentation, it might be anticipated that any tantalum striking the airways would produce changes in airway tone. However, except for the one subject with 6% fall in FEV_1, group 1 subjects had minimal evidence of airways constriction. Possibly we saw no significant changes in pulmonary function in this group because only a small amount of tantalum was deposited and remained in their airways. This was in part due to incessant coughing. This aspect of the study was disappointing since we had anticipated peripheral deposition in all subjects. It is also possible that the topical anaesthesia played a part in the deposition pattern and the airways response. The effects of local anaesthesia on irritant and cough receptors as it relates to airway tone is not fully understood. In animals, bupivicaine blocks both vagally induced bronchoconstriction and the cough reflex (Dain *et al,* 1975), while in human asthmatics, lidocaine may actually cause bronchoconstriction (Miller and Awe, 1975; Weiss and Patwardhan, 1977). Normal subjects in one study had no change in baseline resistance after the administration of lidocaine (Loehning *et al,* 1976). Since our subjects were not asthmatic, presumably the lidocaine did not affect the baseline airway tone. Whether it partially blocked responses induced by tantalum cannot be answered. Nevertheless, it is unlikely that lidocaine blocked the tantalum-induced bronchoconstriction in subjects from groups 1 and 2 and not in those from group 3.

Although individuals in groups 2 and 3 had similar patterns of tantalum deposition, our results indicate that the airways in group 3 reacted with more bronchoconstriction. It is unclear why airways in group 3 subjects exhibited more pronounced radiological and physiological changes than those in group 2. Several explanations are possible including differences in airway reactivity, anaesthesia, and depth of penetration. Since we had no evidence suggesting differences in anaesthesia or depth of inhalation in the groups, we investigated the possibility that subjects in group 3

had hyperreactive airways. Asthmatic and hay fever patients are known to have hyperreactive airways as defined by a fall in sGaw or FEV_1 after challenge with methacholine (Tiffeneau, 1955; Parker *et al*, 1965; Fish *et al*, 1976). In fact, two subjects in group 3 had histories of hay fever. In addition the third subject in group 3 reported a recent upper respiratory infection. This is noteworthy since normal individuals exhibit airways hyperreactivity after acute upper respiratory infection (Empey *et al*, 1976). Unfortunately, the methacholine challenge was not performed immediately after the tantalum inhalation in this subject so that it is not possible to say whether he was transiently hyperreactive. This would not, however, explain responses in the other two subjects of group 3. Statistically, there was no difference in the response to methacholine between the three groups, suggesting that hyperreactivity of airways cannot explain the difference in response to tantalum. Since our population is small, however, we cannot ignore the possibility that reactive airways may be contributory.

Changes in FEV_1 have not been reported in previous inert particle inhalation studies. The fall in FEV_1 reported in this study is less than that which occurs in patients with acute asthmatic attacks associated with dyspnoea and wheezing (McFadden *et al*, 1973). Certainly, tantalum produces far less change in pulmonary function than propyliodone (Dionsil). The latter is associated with as much as a 23% fall in FEV_1 and a 40% decrease in vital capacity (Christoforidis *et al*, 1962). Therefore, the inhalation technique appears to be relatively safe in normal individuals.

All three individuals in group 3 with radiographic bronchospasm had decreases in FEV_1. It is unresolved whether decreases in FEV_1 in these subjects reflected small or large airway changes, but most of the constriction seen was in airways larger than 2 mm. Despite this, bronchi less than 2 mm were definitely outlined and often appeared to be in spasm. Yet, there were no changes in "small airways" function as measured by changes in closing capacity, closing volume, or residual volume. In a previous study (Dubois and Dautrebande, 1958) there were also no consistent changes in residual volume or lung compliance with inert dust inhalation. Since small airways were seen to constrict in our study, the lack of measurable changes in small airway function may be due to the insensitivity of the tests. In other words, probably more small airways need to be affected before changes in their function can be appreciated.

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