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FUNCTIONAL RESPIRATORY CHANGES UPON CHRONIC EXPOSURE TO MONOMERIC AND POLYMERIC VINYL CHLORIDE

C. Mapp, L. Fabbri, A. Rossi, G. Moro and G. Cervi

A less investigated but nonetheless important aspect of the "vinyl chloride syndrome" is the field of respiratory function. LANGE (1974) found in 13 workers afflicted with vinyl chloride syndrome that 8 of them had restrictive type functional defects and attributed this clinical picture to a pulmonary localisation of the process of connective systemic scleroses. On the other hand already SZENDE et al. (1970) reported a case of pneumokoniosis in a patient exposed to PVC powders: upon histological examination the micronodules were found to consist of "foreign body" type granulomae. FRONGIA et al. (1974) have experimentally reproduced on rats exposed in working environment to PVC powders the lesions already demonstrated on humans by SZENDE, thus confirming the hypothesis of the foreign body pathogenetic mechanism. This created a divided way of looking at the problem: on the one hand the possibility of pulmonary fibrosis caused by exposure to the monomer, with the picture of functional restriction, and on the other hand the picture of true pneumokoniosis of "inert powders" caused by exposure to the polymer, very likely included within a mixed or obstructive functional picture. Although unable to consider the problem in ^{an}/analytical manner either at the experimental or at the histological level, it was considered important enough to report the results of a study carried out on workers exposed to monomeric and polymeric vinyl chloride, emphasising the functional and radiological aspects.

ENUMERATION OF CASES AND METHODS

The present study coincided with the national epidemiological investigation promoted by the Chemical Workers Union (FILC): 258 workers were examined, these were employed in the production of polyvinyl chloride in a factory situated in Ferrara. The field work was carried out in cooperation with Service of Industrial Medicine of the Public Health Association of Ferrara. The average age of the

subjects, all males, was 38.9 ± 9.3 years, with 10.8 ± 6.4 years of average length of service.

Each subject was tested in the following manner:

- Survey of respiratory symptoms by means of the CECA questionnaire.
- Complete clinical examination with anamnesis listed on the card proposed by FU
- Complete spirographic examination, the determination of the residual volume was carried out with the helium dilution technique. The Godart Expirograph was used. The theoretical reference values were obtained by means of the CECA formulae (1971). A spirometric picture characterised by $VEMS/CV \times 100$ lower than 65 % and/or residual volume higher than 130 % of the theoretical value was defined as obstructive; a picture characterised by a total lung capacity less than 80 % of the theoretical value was defined as restrictive.
- Measurement of CO transfer by the "single respiration" method using the Morgan Transfer Test apparatus, model C. The inhaled gas concentrations were 13 % helium and 0.28 % CO. In each case the air volume of the "wash-out" was higher than 900 cc and the sample volume was 900 cc. The period of apnea was always pre-programmed in 10". The inhaled volume was pre-programmed as 90 % of the vital capacity measured at the time of testing. This examination was always performed before the spirometric examination which followed after at least 10 minutes to permit complete wash-out of the inhaled helium needed for the transfer test. On the average the alveolar volumes determined by single respiration ($V_A = V_I \times \frac{\text{He inhaled}}{\text{He exhaled}}$) did not vary by values higher than ± 10 % from the lung capacities measured with the dilution under stable conditions. All the transfer test values were corrected by the alveolar volume, obtaining in this way the $DICO/V_A$ ratio expressed in ml CO/min/mm Hg Co alv/l V_A . This ratio (K) defined by COTES as "diffusion constant", was compared with the expected value obtained from the prediction formula established by the same COTES (1975). The significantly reduced values were considered to be those which were lower than 90 % of the expected values.
- The radiographs of the thorax were read according to the ILO UICC (1971) classification by a radiologist especially experienced in this field. The hands were also radiographed by the standard technique; in line with the instructions of the Epidemiological Commission on national scale, the X-rays were evaluated separately by two radiologists.
- Ophthalmological examination of the fundus oculi.

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- Digital photoplethysmography was carried out under basic conditions and after cold test (immersion of hands into 12 - 14°C water for 10 minutes, repeating the plethysmographic test after properly drying the hands without friction). The reflection technique was used here, the test consisted of graphic recording by photoelectric cell the variations of the fleshy portion of the fingertips in transparency to light, primarily in relation to variations of blood content, for the purpose of indirect examination of the anatomical-functional conditions of the arterial-capillary system of the fingers. The test result was considered pathological when the following conditions were indicated: flattening of the curve or reduction of the width to below 25 % of the basic graph after the cold test.

WORK ENVIRONMENT

The factory in which the examined subjects were employed produces vinyl polymer from monomer. The production cycle comprises in a first stage the storage of the monomer produced elsewhere, the polymerisation in kettles using two processes, i.e., suspension and emulsion polymerisations, the drying of the obtained polymer and its packaging. There is also a maintenance section and a section where the polymer is stabilised with lead salts. In accordance with the informations collected in the course of contacts with the workers and from the environmental data made available partly by the Works Management and partly by the local Health Authorities, we were able to assess the degree of exposure to monomeric vinyl chloride according to the following formula:

$$\text{Years of risk} = (\text{no. of high exposure years} \times 2) + (\text{no. of medium exposure years} \times 1.5) + (\text{no. of low exposure years} \times 1)$$

where "high exposure" was considered in the polymerisation phases, "medium" in the drying phases, packaging and internal maintenance, and "low" in the phases of external maintenance and stabilisation of polymer.

The correction factors (2, 1.5, 1) express the logarithm of vinyl chloride monomer concentration as function of time, thus 100 ppm for high exposure, 30 ppm for medium and 10 ppm for low exposure.

In this way, although with obvious approximation, we have overcome the problem of assessing the comprehensive exposure of a given subject during the time of employment in several locations with presumably different degrees of exposure. In line with this criterion we have obtained four classes of "risk years".

Years of risk	Number of cases	%
< 5	38	14.7
5 - 15	88	34.1
15 - 25	80	31.0
> 25	52	20.2
Total	258	100.0

Regarding the exposure to polymer in powder form we had to rely on very recent data which indicated the presence of powder up to 10 mg/m^3 in the drying stage and up to 5 mg/m^3 at the packaging of the final product. The investigation of the particle size distribution of the powders indicated a definite, but obviously a numerical prevalence of particles less than 5 microns in diameter.

Finally, in the assessment of the respiratory function we have taken into consideration the confusing factor of "tobacco consumption" by subdividing our population into three groups:

1 - non-smokers (who have never smoked or are now non-smokers for more than 5 years)	90 cases	34.9 %
2 - medium smokers (up to 20 cigarettes per day)	135 cases	52.3 %
3 - heavy smokers (more than 20 cigarettes per day)	33 cases	12.8 %

RESULTS AND DISCUSSION

Perusal of the results concerning the entire population (Table 1) immediately indicates the high prevalence of chronic bronchitis with previous history (88 cases, 34.1 %) and symptoms of chronic bronchial obstruction (sibilant respiration in 27 % of cases), while the prevalence of bronchial asthma is low in all cases. Another important feature is that the prevalence of chronic bronchitis increases with increasing years of risk, stabilising above 15 years of risk at a level of 37 - 40 %; also the correlation between the years of risk and dyspnea appears to be significant.

Regarding the functional respiratory picture (Table 2), the most important findings are the high prevalence of subjects with residual volume above the maximum expected limit, this prevalence not being in linear relationship with the work exposure, and the significant percentage of subjects with mutual reduction of vital capacity and of VEMS, progressing linearly with classes of exposure. The diffusion constant K is changed most in the first risk group and, at least in parts, it is not connected with the concurrent functional respiratory changes.

From the radiological point of view (Table 3) the most significant finding is the high occurrence of clinical pictures which may be classified as p/s 0/1 according to the ILO (1971) classification. Micronodulation, classifiable as p 1/0, was indicated in a single case. To ascertain any differences between the incidence of alterations found in subjects exposed mainly to the monomer (kettle attendants) or to the polymer (workers employed in the drying and packing of polymer powders), we have separated the two groups, adding a third group exposed to monomer as well as to powdered polymers (Table 4). More frequent occurrences of chronic bronchitis and increase of residual volume (obstructive) were found among the workers employed in processes dealing with powders, while the difference in the percentage reduction of the total lung capacity (restrictive) appeared less evident. This finding is based, on the one hand, on a bronchial obstruction caused by polymer powders (bearing in mind the particle size distribution mentioned in conjunction with the environmental data), and on the other hand it is based on a restrictive change which can be presumably related to exposure to the monomer. To some extent this finding is confirmed by the radiological result: the radiological pictures of initial micronodulation appear to be almost equally divided between the two groups in question, with a slight prevalence of micronodulation among the workers exposed to the monomer.

Table 1. Prevalence of syndromes and respiratory syndromes in the total population as a function of the risk index

Risk index	Chronic bronchitis	Dyspnea grades II-V	Sibilant respiration	Bronchial asthma
< 5	12 (31.6%)	11 (28.9%)	7 (18.4%)	1 (2.6%)
5 - 15	25 (28.4%)	27 (30.7%)	27 (30.7%)	6 (6.8%)
15 - 25	30 (37.5%)	30 (37.5%)	18 (22.3%)	2 (2.5%)
> 25	21 (40.4%)	28 (53.8%)	18 (34.6%)	4 (7.7%)
Total	88 (34.1%)	96 (37.2%)	70 (27.1%)	13 (5.0%)
	p n.s.	p < 0.01	p n.s.	p n.s.

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The expected spirometric results were obtained on 251 persons; 249 had full residual volume. The DICO was measured on 233 subjects.

In order to facilitate understanding of the nature and interpretation of these radiological pictures, in Table 5 we have presented the description of these. It can be seen that previous work risk is indicated in 9 cases which, by itself, can justify the radiological survey; among the remaining 21 cases only 5 subjects were exposed to polymer powders, 8 were exposed only to monomer and 8 (employed

in maintenance) were exposed to monomer as well as to polymer. The nine cases in which restrictive ventilatory change was observed were all exposed to monomer or to monomer and polymer, while those with increased residual volume were mainly found among the maintenance workers. Because of only three cases of non-smokers, stratification on the basis of this factor is obviously not feasible. The distinct majority of findings relates to subjects with more than five years of exposure, not considered in terms of risk index. An observation which certainly merits attention is that among these 30 subjects two indicated concurrent acroosteolytic lesion and three indicated concurrent suspected or initial osteolytic lesion in the region of the distal phalanxes of the fingers. This seems to suggest a common pathogenic mechanism which may be related to exposure to monomer.

Table 2. Prevalence of changes in spirometric indices and in the diffusion constant in the population classified into risk groups (o = observed; t = theoretical; CV = vital capacity; VR = residual volume; CPT = total lung capacity)

Risk index	CVo/CVt 0.8	VEMSo/VEMSt 0.8	VEMS/CV 0.65	VRo/VRt 130%	CPTo/CPTt 0.80	Ko/Kt 0.9
<5	3(7.9%)	1(2.6%)	0	10(26.3%)	1(2.6%)	9(26.4%)
5-15	8(9.4%)	7(8.2%)	5(6%)	34(40%)	7(8.2%)	15(18.5%)
15-25	19(25%)	9(11.8%)	1(0.7%)	24(31.6%)	11(14.5%)	12(16.9%)
>25	16(30.8%)	11(21.1%)	2(4%)	13(26%)	7(14%)	8(17.0%)
Total	46(18.3%)	28(11.2%)	8(3.2%)	81(32.5%)	26(10.4%)	44(18.9%)
	p < 0.001	p < 0.01	p n.s.	p n.s.	p n.s.	p n.s.

Table 3. Prevalence of radiological signs indicating interstitial fibrosis in the population grouped according to risk index

Exposure	Number of cases	0/1 form
< 5	37	3 (8.1 %)
5 - 15	86	12 (14.0 %)
15 - 25	80	7 (8.8 %)
> 25	52	8 (15.4 %)
Total	225	30 (11.8 %)

Considering now the response to the cold test, which was measured by the digital photoplethysmography, it is noted that 16 subjects (53.3 %) show alterations in this test; considering that changes were found in 15 % of the total population, further survey was indicated.

Table 4. Prevalence of pulmonary changes among the cases, subdivided into groups according to predominant exposure to monomer (A), to polymer powder (B) and to both (C) to varying extents

	Chronic bronchitis	Obstructive change	Restrictive change	Pulmonary fibrosis
A	26.9 %	20.0 %	15.4 %	13.4 %
B	39.6 %	45.1 %	5.9 %	11.3 %
C	35.5 %	33.8 %	9.8 %	11.1 %

χ^2 A-B per obstructive changes = 8,41063; $p < 0.005$

Finally, the findings of sclerosis in the fundus oculi in 15 out of 26 subjects examined among those afflicted with pulmonary fibrosis (57.7 % as against 33 % in the total population), confirm the common pathogenesis of the phenomena under consideration.

Arranged according to tobacco consumption, it is shown that all indices of bronchial irritation are influenced by this factor in determining manner. Only the restrictive changes fail to show any relationship with this parameter (Figs. 1, 2 and 3). When examining the prevalence of chronic bronchitis and of the obstructive and restrictive functional changes, a certain relationship with the risk index is indicated only in the case of chronic bronchitis and the restrictive changes, with pathological aspects mainly in the smokers, while this is not indicated for the obstructive changes which appear much more distinctly influenced by tobacco consumption.

The diffusion constant K was found to be changed in 44 subjects from which 41 were smokers, also this appears to be more influenced by this confusion factor.

Fig. 1: Prevalence of chronic bronchitis among the cases grouped according to years of exposure and tobacco consumption (f = smokers; nf = non-smokers; anni rischio = years of exposure)

Fig. 2: Prevalence of restrictive functional respiratory changes among the cases grouped according to years of exposure and tobacco consumption (f = smokers; nf = non-smokers; anni rischio = years of exposure; restrittivi = restrictive changes)

Fig. 3: Prevalence of obstructive functional respiratory changes among the cases grouped according to years of exposure and tobacco consumption (f = non-smokers; nf = smokers; anni rischio = years of exposure; ostruttivi = obstructive changes)

Table 5. Analytical description of individual cases (30) showing radiologic signs of the pulmonary fibrosis type characterised by micronodulation (form p/s 0/1)

No.	Age	Smo-ker	Section	Exposu- re, months	Previous exposure	Spiro- metry	Ko Kt	Chron. bronch.	Cold test	Acro- osteo- lysis	Scle- sis fund
1	43	+	polymer.	152	-	R	N	-	+	-	+
2	37	+	polymer.	38	-	R	-85%	-	-	-	+
3	45	-	polymer.	78	foundry (5 years)	N	N	-	+	-	-
4	35	+	polymer.	6	-	N	N	-	+	-	-
5	44	+	polymer.	156	-	N	-80%	-	-	-	+
6	28	+	drying	52	-	O	N	-	-	-	-
7	52	+	mainten.	246	welder (15 yrs)	R	N	pres.	-	-	-
8	44	+	mainten.	168	-	R	N	-	+	C	+
9	51	+	polymer.	264	-	R	N	pres.	-	S	+
10	51	+	packaging	168	-	-	N	-	-	-	+
11	36	+	packaging	24	welder (7 yrs)	N	-84%	-	-	S	-
12	28	+	packaging	28	welder (7 yrs)	N	N	-	-	-	-
13	45	+	polymer.	238	-	O	-86%	pres.	+	-	+
14	42	+	store	66	-	N	N	-	+	-	-
15	45	+	mainten.	128	-	O	N	-	+	-	+
16	49	-	grinding	160	-	N	N	-	+	-	-
17	29	+	polymer.	72	-	O	N	pres.	+	-	-
18	29	+	stabiliz.	82	welder (5 yrs)	N	N	-	-	-	-
19	54	+	packaging	178	kilnman (4 yrs)	R	N	-	+	S	+
20	43	+	mainten.	180	-	N	N	-	-	-	+
21*	28	+	stabiliz.	60	welder (10 yrs)	N	-90%	-	-	C	-
22	27	+	stabiliz.	36	welder (8 yrs)	N	N	pres.	+	-	+
23	44	+	mainten.	180	-	O	N	-	+	-	-
24	50	+	mainten.	204	-	O	N	pres.	-	-	+
25	51	+	mainten.	276	asbestos (15 yrs)	R	N	pres.	+	-	-
26	47	+	mainten.	12	-	N	N	-	+	-	+
27	41	+	mainten.	156	-	O	N	-	-	-	-
28	45	-	polymer.	72	-	R	N	pres.	+	-	+
29	53	+	store	122	-	O	N	-	+	-	+
30	46	+	mainten.	270	-	R	N	pres.	-	-	+

Spirometry: N = normal; R = restrictive; O = obstructive.

C = definite acroosteolysis.

S = suspected acroosteolysis.

* Radiological sign of chest X-ray incompatible with form p 1/0

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To ascertain whether our conclusions would be in line with the data obtained for homogeneous group, considered as predominantly exposed section (to this end the population was divided into three groups, the first of these comprising the workers employed in the polymerisation, the second group covering successive phases of the production cycle with predominant exposure to polymer dust, and the third group comprising the maintenance workers) in Table 6 and in Fig. 4 we have represented the average observed values of the individual functional indices on the basis of the prediction formula: the result being severe shortening of the vital capacity and especially that of the total lung capacity in the first group which is mainly exposed to monomer, both in terms of quantity and duration, while in the case of the remaining two groups, the first of these exposed mainly to powders and the second irregularly exposed to powder and to monomer in their capacity as the members of these two groups engaged in maintenance work or in polymer stabilisation, the significant feature is the increment of residual volume. While in the first case the severe shortening of the vital capacity is attributed to a reduction of compliance and thus of the inspiratory reserve volume possibly in direct relationship with pulmonary fibrosis, in the second case the severe reduction of vital capacity with concurrent increase in the residual volume is attributed to the impairment of the narrow air ducts; actually, in the course of the procedure used for determining the expiratory reserve volume a blockage of the narrow air ducts occurred and this, in turn, reduced the vital capacity in favour of the residual volume.

The superimposable distribution of the radiological signs of pulmonary fibrosis among those exposed to monomer and to monomer plus polymer, supports the hypothesis that the fibrosis could be related to the exposure to monomer.

Table 6. Mean values of observed and expected spirometric indices in prevalence of pulmonary fibrosis in the population subdivided according to homogenous groups (CV = vital capacity; VR = residual volume; CPT = total lung capacity)

	Employed (67) in polymerisation	Employed (53) in drying and packaging	Employed (138) in maintenance and PVC stabilisation
CV obs.	452 ± 63	463 ± 78	447 ± 70
CV theor.	510 ± 43	502 ± 60	500 ± 52
	p < 0.001	p < 0.005	p < 0.001
VEMS o.	374 ± 61	378 ± 71	368 ± 68
VEMS th.	393 ± 39	389 ± 50	384 ± 45
	p < 0.05	p n.s.	p < 0.05

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Table 6 (continued)

VR obs.	160 ± 48	191 ± 66	191 ± 60
VR theor.	156 ± 16	154 ± 21	157 ± 19
	<u>p</u> n.s.	<u>p</u> < 0.001	<u>p</u> < 0.001
CPT obs.	612 ± 89	654 ± 98	638 ± 97
CPT theor.	665 ± 52	656 ± 76	657 ± 67
	<u>p</u> < 0.001	<u>p</u> n.s.	<u>p</u> n.s.

Fig. 4: Theoretical (right column) and observed (left) values of total lung capacity (CPT) and residual volume (VR) in the three homogeneous groups with different degrees of exposure (volumi polmonari = lung capacities; (polimerizzazione = polymerisation; essiccazione, insacco = drying, packing; manutenzione, premix = maintenance, premix (stabilisation))

By comparing our values with those published in the literature, in the first place a contrast with the data found by MILLER et al. (1975) is indicated: this author, examining a population exposed to both monomer and polymer, and assuming nonconventional functional parameters with very low confidence limits, concluded in favour of an obstructive functional defect. The only comparable finding is the change in VEMS in all the population which is 45 % as against our 11.2 %, although with respect to the chronic bronchitis cases it is quite comparable with ours (30.5 % as against our 34.1 %).

SUCIU et al. (1975), finding a prevalence of the obstructive type changes, decided to identify the specific lesion caused by exposure to monomer as a systemic interstitial fibrosis which, therefore, also affects the lungs.

These aspects are well in line with the restrictive signs we have encountered in those exposed to vinyl chloride monomer; simultaneous exposure to other irritants (e.g. PVC powders) of similar particle size distribution to that we have found in the factory in question, will result, on the other hand, in a sign indicating impairment of the narrow air ducts.

The extent of the specific functional impairment may be considered as limited, in fact we have found significant reduction of total lung capacity in 10 % of the total population and in 15 % of those employed in polymerisation, i.e., exposed only to monomer. However, we must not neglect the finding of the concurrent irritative effect manifested in chronic symptomatic bronchitis enhanced by the consumption of tobacco and by the simultaneous presence of PVC powders, being responsible for 40 to 50 % of the pathological findings. Confirmation of the hypothesis of systemic fibrosis is provided by our findings of interstitial pulmonary fibrosis, acroosteolytic changes and functional peripheral circulatory changes

and changes in the fundus oculi in percentages higher than those found by RUTH LILIS (1975).

Finally, the presence of micronodulations in one subject exposed predominantly to polymer powders (case no. 21, Table 5), in p 1/0 concentration, also justifies the finding of possible pneumokoniosis caused by polymer, but this is an altogether negligible aspect in comparison with the fibroses caused by the monomer, as our investigations have indicated.

CONCLUSIONS

Basically our findings permit us to draw three conclusions:

- 1) The specific functional picture of exposure to vinyl chloride monomer is represented by a consensual reduction of lung capacities which is in agreement with the clinical picture of interstitial fibrosis involving reduced lung function. The CO transfer test does not appear to be appropriate for the detection of this first change, considering that it is significantly influenced by tobacco consumption.
- 2) In the radiological picture of the lung exposed to vinyl chloride monomer a non-evolutive interstitial fibrosis with micronodulations in very limited concentration can be determined. The homogeneous spectrum of the initial radiological signs found in the various exposure groups leads us to conclude that the vinyl chloride monomer has a predominantly systemic effect, in comparison with the "foreign body" type reaction due to the polymer.
- 3) The specific changes due to exposure to monomer are, generally, moderate, both in terms of prevalence and in terms of severity. Nevertheless, one must not disregard the significant potentiation of effects between monomer, polymer powders and tobacco consumption which leads to the obstructive type clinical picture of lung function and to the appearance of the symptoms of chronic bronchitis.