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A Reduction in Pulmonary Capillary Blood Volume in Patients with Disseminated Testicular Carcinoma

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Abstract—*Pulmonary function tests, including the transfer factor for carbon monoxide of the lungs (T1CO) and pulmonary capillary blood volume (V_c), were measured in 43 patients with disseminated testicular carcinoma and in eight patients with disseminated malignant melanoma before the start of a bleomycin-containing cytostatic combination. Their relation to the development of bleomycin-induced pulmonary toxicity was evaluated. We found two subgroups of patients, one group with and one group without an abnormal pretreatment T1CO and V_c. In the latter group the risk of bleomycin-induced pulmonary toxicity is not increased. Reduction in bleomycin dose during treatment is not necessary. The hypothesis is formulated that tumor embolism could be the explanation for this phenomenon.*

INTRODUCTION

CYTOSTATIC drugs can cause pulmonary damage [1]. One of these drugs, bleomycin, is used as a single agent or in combination chemotherapy schedules in various malignancies [2]. The main side-effect of bleomycin is an interstitial pneumonitis [3]. In monitoring the effects of bleomycin on lung function it has been found that the single-breath carbon monoxide transfer factor (T1CO) was an indicator of pulmonary toxicity [4]. Recently Luursema *et al.* described the pulmonary capillary volume (V_c) as a more sensitive parameter for monitoring the changes in pulmonary function during the Einhorn regimen [5, 6].

In these and other studies it has been assumed that the pretreatment pulmonary function is normal and that any changes during therapy result from the toxic effect of the cytostatic agent. In a prospective study of the effect of bleomycin-containing cytostatic combinations we evaluated the initial pulmonary function and its relation to the development of bleomycin-induced pulmonary toxicity.

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MATERIALS AND METHODS

Two groups of patients were studied prospectively. The first group consisted of 43 patients with disseminated testicular carcinoma. The mean age in this group was 29.6 yr (range, 17–48 yr). Nineteen patients had pulmonary metastases; of these none had pre-existent pulmonary disease. None of the patients had previously received radiotherapy or cytostatic treatment. Serum levels of alpha fetoprotein (AFP) were measured with an enzyme-linked immunosorbent assay (ELISA) (AFP-EIA, Abott. Diagnostic Products GmbH, Wiesbaden, F.R.G.) with a sensitivity of 0.5 μg/l and an upper limit of normally of 20 μg/l. Serum levels of human chorionic gonadotropin (HCG) were estimated with a radio-immunoassay (Institut National des Radioéléments, Fleurus, Belgium) characterized by a cross-reactivity with the β-HCG subunit and with luteinizing hormone of 5 and 2% respectively. The upper limit of normal value was established at 2 μg/l. Circulating immune complexes were determined with a C_1q ELISA method [7]. These patients received four cycles of 21 days of chemotherapy with *cis*-diamminedichloro-

platinum, 20 mg/m³, infused in 4 hr for 5 consecutive days with adequate diuresis. On days 1 and 2 of each cycle vinblastine 0.15–0.20 mg/kg was given. On day 2 of the cycle and further at weekly intervals for 12 weeks 30 mg bleomycin was given in a 15-min infusion. Before the start of all therapy and at 3-week intervals during remission induction lung function tests were done. After completion of cytostatic treatment the same tests were performed at 6-week intervals. Slow vital capacity (VC) and forced expiratory volume in 1 sec (FEV_1) were measured with a water-sealed spirometer. Pretreatment values of VC and FEV_1 were expressed as body temperature pressure saturated (BTPS). The transfer factor for carbon monoxide (TlCO) was measured with the single-breath technique of Krogh [8], modified by Ogilvie *et al.* [9] and Cotes [10]. The TlCO values, breathing air, were corrected for abnormal hemoglobin concentrations according to Hilpert [11], to obtain TlCO under standard conditions. TlCO was expressed as mmol/kPa/min. The membrane factor (D_m) and the pulmonary capillary blood volume (V_c), the two components of TlCO, were determined from measurements of TlCO at high (88%) and low (18.4%) inspiratory oxygen concentrations. The calculation was performed according to the equation originally developed by Roughton and Forster [12]: $1/\text{TlCO} = 1/D_m + 1/\theta(\text{Hb})\ V_c$ [1]. In this equation, θ is the reaction rate of carbon monoxide with oxyhemoglobin at the average normal hemoglobin concentration of 14.6 g/100 ml and (Hb) is the hemoglobin concentration as a fraction of normal. Since the hemoglobin concentration appears explicitly in this equation, no correction for Hb is needed. A detailed description of the determination of D_m and V_c is given by Cotes [10]. The measurements were done in duplicate. V_c was expressed as a percentage of the predicted value (ml) according to Cotes [10]. The normal value of V_c was defined as a value greater than 75% of the predicted value as described by Cotes [10]. Alveolar volume (V_A) was calculated from the inspiratory and expiratory helium concentrations measured during the single-breath maneuvre, necessary for the determination of TlCO. V_A was expressed in liters.

The second group consisted of eight patients with disseminated malignant melanoma; five patients had pulmonary metastases. None of the patients had pre-existent pulmonary diseases, and none had received previous radiotherapy or chemotherapy. Due to the limited survival of these patients no extensive follow-up data on pulmonary function are available and only the initial values are presented.

Student's *t* test was used for statistical analysis.

RESULTS

It was unexpectedly found that in the group of patients with testicular cancer there were two subgroups. The V_c in untreated patients was significantly different in both groups. One subgroup showed patients with a normal initial V_c and the other subgroup showed patients with an abnormal pretreatment V_c, i.e. a V_c equal to or less than 75% of the predicted value [10]. Furthermore, it can be calculated from the equation that determines the TlCO that the difference in TlCO in these subgroups is caused by the difference in V_c and not by a difference in D_m. The other pulmonary function tests are not different in both groups (Table 1).

The two subgroups showed no significant differences in the number of patients with pulmonary metastases or with elevated HCG, or elevated AFP. Their mean age, smoking habits and body temperature also did not differ (Table 2). In the patients with a normal pretreatment V_c we found a significant decrease during the bleomycin-based combination chemotherapy ($P < 0.025$), and a significant increase starting from week 12 until week 42 ($P < 0.025$). In the second group of patients, those who had a low pretreatment V_c, we found a significant increase in V_c after 3 weeks ($P < 0.025$). Afterwards a

Table 1. *Distribution of the means of lung function parameters measured first before the start of remission induction chemotherapy in the group of patients with testicular cancer*

	Parameter					
	TlCO % of predicted value	D_m % of predicted value	V_c % of predicted value	VC % of predicted value	FEV^1 (% VC)	V_A (l)
V_c >75% predicted value ($n = 24$)	96.4	67.9	95.2	97.5	75	6.3
V_c ≤75% predicted value ($n = 19$)	88.4	69.8	59.4	90.6	74	6.4

Results are given as percentage of the predicted value. The group is divided into normal (>75% of the predicted value) and abnormal (≤75% of predicted value).

significant decrease in V_c during the rest of the remission induction occurred ($P<0.01$). After discontinuation of therapy a significant increase in V_c was seen ($P<0.01$) (Fig. 1).

The group of patients with malignant melanoma consists also of two subgroups, one with an initially normal V_c (V_c >75% of the predicted value) and one with an initially decreased V_c (V_c ≤75% of the predicted value). This difference results in comparable variation in TlCO, while other parameters are alike in both subgroups (Table 3).

Other parameters in this group of patients do not indicate significant differences (Table 4).

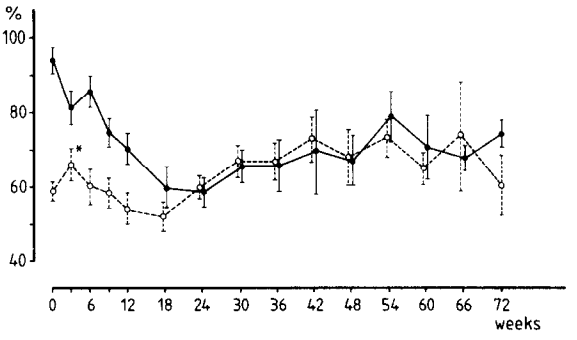

Fig. 1. The relation between time (in weeks) *and the percentual changes in* V_c *of patients with testicular cancer divided in two subgroups, one with normal and one with abnormal* (V_c ≤75%) *pretreatment values.*

DISCUSSION

In both groups of patients with disseminated malignancies 50% of the patients had an abnormally low pretreatment V_c. Theoretically this decrease can be explained in two ways. The first is an absolute decrease in the pulmonary

Table 2. Distribution of various characteristics in patients with testicular cancer with either normal or abnormal (≤75%) *pretreatment values*

	Parameter							
	Body temperature (°C)	No. of patients with pulmonary metastases	No. of patients with elevated βHCG	No. of patients with elevated α_1FP	Hb (g/l)	Mean age	BIP	No. of patients smoking
V_c >75% predicted value ($n=24$)	36.9	12	11	9	121	29.0	4	12
V_c ≤ predicted value ($n=19$)	37.6	7	12	10	124	30.6	4	15

Table 3. The distribution of the means of the pretreatment lung function parameters in patients with malignant melanoma

	Parameter					
	TlCO % of predicted value	D_m % of predicted value	V_c % of predicted value	VC % of predicted value	FEV_1 (% VC)	V_A (l)
V_c >75% predicted value ($n=4$)	90.0	68.7	99.0	97.0	74	6.0
V_c ≤75% predicted value ($n=4$)	72.5	71.0	58.8	91.5	76	6.1

Table 4. Distribution of various characteristics in patients (n = 8) *with malignant melanoma either with normal or abnormal* (V_c ≤75%) *pretreatment values*

	Parameter				
	Body temperature (°C)	C_1q	No. of patients with pulmonary metastases	No. of patients smoking	Mean age (yr)
V_c >75% predicted value ($n=4$)	37.1	3	2	2	49
V_c ≤75% predicted value ($n=4$)	36.8	1	3	1	44

capillary blood volume. The second is a change in the chemical reaction rate between CO and Hb resulting in the measurement of a low pretreatment V_c.

A number of causes of a compromised pulmonary capillary system can be present in malignant disease: the presence of pulmonary metastases, the existence of immune complexes in the lung, and tumor micro-embolism. Factors such as position, smoking habits or meals are not relevant because in all patients the measurement of the lung function parameters was done with the same standardized method, with a period of non-smoking before the start of the determination of diffusion.

The relevance of pulmonary metastases is unlikely, because they were present equally in all subgroups. Immune complexes could well play a role. Brentjens *et al.* demonstrated the pulmonary damage by immune complexes in the pulmonary circulation [13]. Heatly *et al.*, however, could not find any correlation between the occurrence of immune complexes and a decrease in TlCO in patients with inflammatory bowel disease [14]. Indeed, although in both patient groups immune complexes were sometimes present, their presence was not related to the capillary volume.

Tumor embolism remains a possible explanation. The significant increase of V_c after 3 weeks of treatment could be explained as a result of disappearance of these embolised tumor clots under the influence of polychemotherapy. The subsequent decrease in V_c in both subgroups of testicular cancer patients is probably caused by the toxic effects of bleomycin on endothelium. This hypothesis is supported by the experiments of Adamson and Bowden, who found that the first damage caused by bleomycin is localized in the endothelium of the pulmonary vascularity [15]. The increase in V_c in the group of patients with an initially low V_c has to be the net effect of the increase of V_c caused by the disappearance of tumor emboli and the decrease in V_c caused by the toxic effects of bleomycin.

The second explanation for the initially low V_c, the change in the reac tion of CO and Hb, can be caused by a change in body temperature, occurrence of an abnormal hemoglobin, such as HbF, or anemia. These possibilities are all unlikely. Holland measured the influence of temperature on the reaction rate of Hb and CO [16], and found that the effect of temperature on the cell reaction constant was very small. Thus the difference in pretreatment V_c cannot be explained by the small differences in body temperature in the subgroups of group I and II. Lee *et al.* showed a correlation between HCG and the levels of HbF in women with normal and with hydatiform molar pregnancy [17]. One could assume that a high level of HCG accompanied by a high abnormal hemoglobin (HbF) would lead to an abnormal V_c, but in our study the patients with elevated HCG are equally divided over the two subgroups of patients with testicular cancer, while HCG was absent in the melanoma patients. The concentration of hemoglobin in both groups and subgroups was equal, so a difference in hemoglobin concentration also cannot be the explanation for the pretreatment difference in V_c.

The consequence of a low pretreatment V_c remains unclear. However, the risk of occurrence of BIP in both subgroups of patients with testicular cancer is the same: in both subgroups four patients developed BIP.

In conclusion, an initial low pulmonary capillary blood volume can be caused by tumor embolism. The finding of an abnormally low initial TlCO and V_c should not lead to reduction in bleomycin dose or treatment period in these patients, because the ultimate bleomycin-induced toxicity is not different in both subgroups.

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