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CASE STUDY

Weakness of respiratory and skeletal muscles after a short course of steroids in patients with acute lung rejection

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Weakness of respiratory and skeletal muscles after a short course of steroids in patients with acute lung rejection. S. Nava, C. Fracchia, G. Callegari, N. Ambrosino, N. Barbarito, G. Felicetti. ©ERS Journals Ltd 2002.

ABSTRACT: There have been occasional reports of acute respiratory and skeletal muscle weakness in intensive care unit patients treated with massive doses of corticosteroids. However, in this setting the concomitant use of other drugs may have influenced the finding.

In this study the effects of 5 days of treatment with high doses of steroids in consecutive patients with acute lung rejection after transplantation were systematically evaluated. Maximal inspiratory pressure during phrenic nerve stimulation and peak torque of isokinetic contraction of the quadriceps and hamstring muscles were measured objectively.

Compared to the pretreatment condition, ~45% of patients showed acute generalised muscle weakness that recovered after ~2 months.

This demonstrates muscle weakness induced by steroids within patients.

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Lung transplantation may be a life-saving procedure in patients affected by irreversible respiratory failure. Unfortunately, rejection of a lung allograft is a relatively common event that may profoundly influence prognosis. Rescue therapy for lung rejection is based mainly on a short course of high doses of corticosteroids (*e.g.* 1,000 mg of methylprednisolone for 5 consecutive days) [1]. Most of the patients are still recovering from the surgical intervention at this stage, so respiratory and skeletal muscle weakness is likely to be present [2]. Five days of treatment with massive doses of steroids have been shown, in rats, to induce severe respiratory and limb muscle wasting with alterations in muscle contractile properties [3]. The current authors systematically examined the potential deleterious effects of acute steroid administration on respiratory and limb muscle function in patients undergoing rejection of a lung transplant.

Methods

Over a 6-yr period (1992–1998) the inotropic properties of the respiratory and limb muscles in consecutive patients developing acute rejection after a single or double lung transplant were studied. Table 1 shows the main clinical and physiological characteristics of the 13 patients enrolled. The study was approved by the local Ethics Committee and informed consent to the study was given by each patient. When acute rejection was determined, both clinically and histologically, the patients followed a protocol consisting of 12 $mg \cdot kg^{-1}$ of methylprednisolone for 3 consecutive days and 10 $mg \cdot kg^{-1}$ for the next 2 days. Additional immunosuppressive drugs were started after this period only in the case of steroid-resistant acute rejection.

Diaphragmatic inotropic properties were assessed using the technique of electrical stimulation of the phrenic nerves [4]. Briefly, the phrenic nerves were simultaneously stimulated with 0.1 ms square-wave pulses, with an intensity >20% than the minimum required to achieve maximal stimulation. The diaphragm compound action potentials evoked from each hemidiaphragm were recorded *via* two pairs of surface electrodes placed over the sixth and seventh intercostal spaces. Phrenic nerve stimulations were superimposed upon voluntary contractions of the diaphragm, so that the amplitude of mouth pressure generated during the manoeuvre (P_{mt}) decreased progressively, indicating a progressive increase in diaphragm activation. This method provides objective information on the level of diaphragm activation and how this relates to the level of inspiratory efforts achieved by the patient.

Skeletal muscle function was assessed by the peak torque of isokinetic contraction at a test speed of 120 s^{-1} of the flexor (hamstring; IFX) and extensor (quadriceps; IEX) muscles of the leg, measured by an isokinetic dynamometer.

All the above mentioned measurements, together

Table 1. – Main clinical and physiological characteristics of the patients enrolled

Patients No.	Age yrs	Sex	BMI	Pathology	Time from transplant months	pH	P_{a,CO_2} mmHg	P_{a,O_2} mmHg	FEV1 mL	FVC mL
1	19	M	18.73	CVD	6	7.40	32.9	66.6	1440	2260
2	26	M	21.06	SPH	2	7.47	36.8	94.3	2450	2520
3	55	M	24.00	COPD	4	7.40	45.6	58.7	900	2530
4	49	M	34.16	IPF	5	7.45	32.5	40.7	2110	2810
5	21	F	18.96	CVD	25	7.46	29	69.8	1330	1560
6	49	M	27.65	COPD	1	7.44	41.3	68.8	1600	3200
7	53	M	30.56	COPD	12	7.41	37.9	79.3	1580	3980
8	23	F	21.77	CVD	1	7.47	36	70.9	1430	2100
9	52	M	24.96	COPD	8	7.40	52.2	48.9	1820	2760
10	59	M	22.22	IPF	7	7.45	34.2	70.4	3001	3670
11	47	M	19.47	SPH	3	7.38	48.9	58.3	2900	3500
12	61	F	16.64	COPD	2	7.40	52.1	53.5	1120	3560
13	25	M	21.13	CVD	2	7.39	34.9	63.8		
Mean	41.5		23.17		6.0	7.42	39.6	65.3	1800	2940
SD	15.9		5.03		6.5	0.02	7.8	14.6	670	740

BMI: body mass index; P_{a,CO_2}: carbon dioxide tension in arterial blood; P_{a,O_2}: oxygen tension in arterial blood; FEV1: forced expiratory volume in one second; M: male; F: female; CVD: congenital vascular disease; SPH: secondary pulmonary hypertension; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis.

with pulmonary function tests (PFT), were recorded immediately before the first bolus of methyprednisolone and 24 h after the last administration.

The individual relationships between the P_{mt} amplitude as a function of the voluntary inspiratory effort on which electrical stimulation was superimposed showed that in most cases (10 of 13) no twitch could be detected during maximal efforts indicating that all stimulated motor units were fully activated. The maximum pressures predicted (MIP_p) from the twitch occlusion were calculated using the following equation:

$$MIP_p = a + b \times \text{maximal voluntary } P_{mt} \quad (1)$$

where a and b are the intercept and the slope, respectively.

Results

At the time of rejection MIP_p was overall markedly reduced (43±13% of predicted). Figure 1a illustrates the individual changes in MIP_p before and after the 5-day course of steroids. Six of the 13 patients showed a clear decrease (>15%) in maximal inspiratory pressure after steroid treatment; these findings were not correlated with body mass index, age or type of surgery, but four of these six patients were affected by congenital or secondary pulmonary hypertension. Functional residual capacity, the main determinant in the assessment of the inotropic characteristic of the inspiratory muscle, was identical (3.56±0.54 *versus* 3.69±0.61 L) before and after the treatment, as were the other PFTs. At the time of rejection IFX and IEX were also overall markedly reduced (53±11 and 58±9 of predicted, respectively). Figure 1b showed that in four out of nine patients able to complete the peak torque test, IEX was decreased >15% after the treatment. In these patients (except one) changes in MIP_p closely paralleled those in IFX and IEX. Both skeletal and respiratory muscle strength fully recovered after 52±13 days. All the patients survived the episode of rejection. The mean time of survival from enrolment into the study in the patients not showing respiratory muscle weakness was

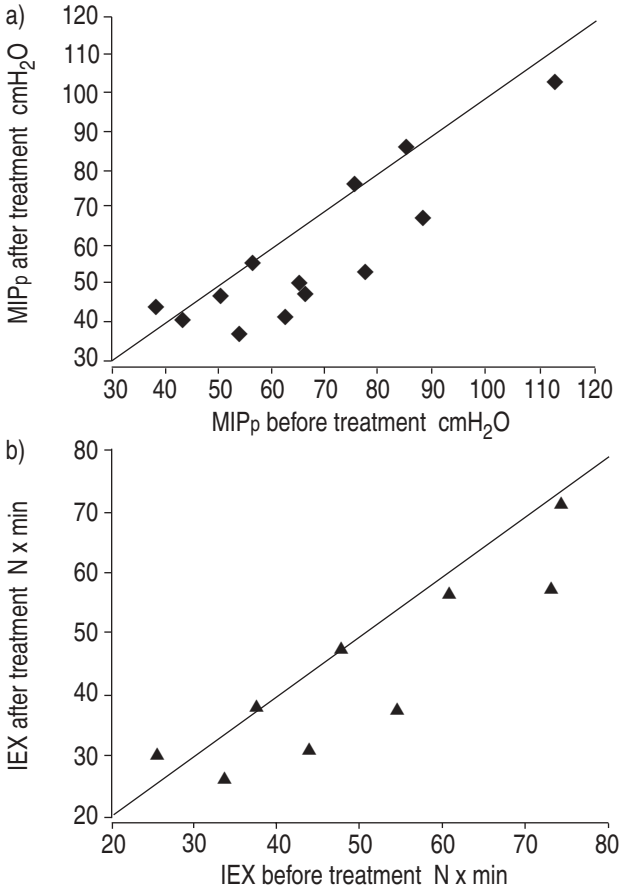

Fig. 1. – Identity plot detecting the effects of the short-term steroid administration on a) maximum inspiratory pressure predicted (MIP_p) and b) peak torque of isokinetic contraction of leg extensor (IEX).

63±18 months whereas it was 45±12 months for the remaining patients.

Discussion

There have been occasional reports of generalised weakness occurring in patients treated with massive doses of corticosteroids, sometimes interfering with the process of weaning from mechanical ventilation. However, intensive care unit patients are also likely to be treated with other drugs (antibiotics, muscle relaxants) which have been shown to produce massive neurogenic changes and rhabdomyolysis, so it is not possible to determine the significance of these findings [5]. The current authors′ observations give the first systematic clinical demonstration that a high dose of steroids for only 5 days, in the absence of other therapy, induces profound respiratory and limb muscle weakness, at least in some individuals. The large majority of these patients already manifested a marked reduction in MIP_P, IFX and IEX at the time of the acute rejection because they were still recovering from the surgical procedure and probably the effects of prolonged bed-rest and/or limited physical activity prior to the surgery. The occurrence of generalised muscle weakness is likely to be related to myopathy which, when it develops on a chronic basis, may also influence the survival of the patients [6], even though in most of the patients in this study full recovery was observed ~2 months after the treatment.

These data demonstrate that short-term treatment with high doses of steroids can lead to generalised muscle weakness, thus further hampering the patient′s prompt clinical recovery after rejection of an allograft.

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