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PLETHYSMOGRAPHICAL AND CLINICAL OBSERVATIONS ON BRICANYL THERAPY IN RAYNAUD'S PHENOMENO

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Abstract. A beta-stimulating agent, Bricanyl (terbutaline) has been used for the treatment of Raynaud's phenomenon. A clinical improvement occurred in 4/8 patients (2 with Raynaud's disease and 2 with scleroderma). An increase in skin temperature and pulse amplitude was demonstrated in 6 patients whereas the same parameters decreased in 2 patients with scleroderma. Further studies might be rewarding.

Recently a beneficial effect on Raynaud's phenomenon has been mentioned as a side effect in one case following treatment with a beta-stimulating agent Bricanyl (terbutaline sulphate), for asthma bronchiale (5). It was also mentioned in the same report that two patients who were given beta-blocking agents for high blood pressure, developed symptoms of vasospasm with a tendency to have cold fingers and hyperhidrosis.

Treatment with beta-stimulating agents in Raynaud's phenomenon has to the authors' knowledge not been reported previously. Since conflicting results are obtained with sympathectomy and with the use of several vasodilating drugs (3), it seemed justified to investigate more closely the effect of the named beta-stimulating agent on this disorder. In this paper some preliminary results are reported.

MATERIAL AND METHODS

The study comprised 8 patients with episodes of Raynaud's phenomenon (Table I). Three patients (2 males and 1 female) in the age range 46 to 63 years, had a history of Raynaud's disease for 1 24 years. One of them (no. 2) had, however, worked as a typist for 40 years, while another (no. 3) had played the violin for several years. Otherwise no apparent reason for the vascular abnormality could be detected in these patients by clinical, roentgenological or haematological examination.

Five patients (2 females and 3 males) aged 42 to 70 years suffered from scleroderma with Raynaud's phenomenon. The duration of vascular symptoms was from 1 to 13 years and of the scleroderma about 1 to 10 years. The fingers of all patients in this group showed a hardening of the skin. Patients 4, 6 and 7 had calcinosis cutis; patients 4 and 7 had periungual teleangiectasiae (CRST syndrome). Table I shows the patients' ages and duration of the clinical symptoms.

Temperature measurements

The skin temperature was measured with an Electric Universal Thermometer (Ellab) type TE_3. The skin applicator (Type H_1) was placed on the pulpa region on the first and third finger of both hands. Recordings were taken while the patients were sitting comfortably in a chair at a room temperature of 22°–23° and after an accommodation period of at least half an hour. Right and left hand were successively examined; (*a*) at room temperature, (*b*) after immersion of the contralateral hand in cold water (15° C, 10 min) and (*c*) in warm water (32° C, 10 min).

Plethysmography

This was performed immediately after the skin temperature measurements under the same circumstances as described above. The plethysmograms were recorded by means of a piezoelectric pulse meter and directly photographed on an oscilloscope. The measuring head of the pulse meter was gently fixed on the pulpa region of the first and third finger and the amplitude expressed in mV (1 mV ≈ 3 mmHg). The technique has been described elsewhere (7).

Table I. *Age of patients and duration of clinical symptoms*

Patient number	Sex	Age	Duration (years)	
			Raynaud's phenomenon	Scleroderma
1	♂	46	10	—
2	♀	49	24	—
3	♂	63	1	
4	♀	42	13	10
5	♂	63	2	3
6	♂	70	1	1
7	♀	64	4	2
8	♂	61	3	3

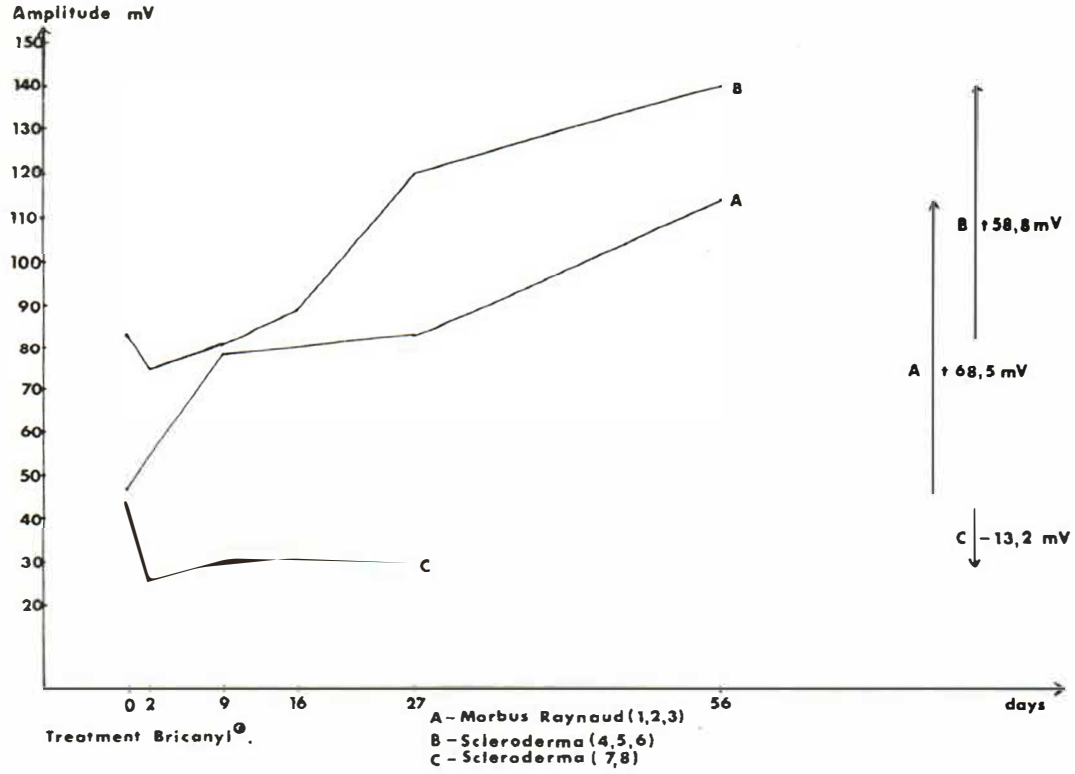

Fig. 1. Effect of terbutaline (Bricanyl) on the pulse amplitude in Raynaud's phenomenon. (A) Raynaud's disease (3 patients). (B) Scleroderma (3 patients). (C) Scleroderma (2 patients). For explanation see text.

Each patient was examined once before the therapy started and three to five times at different intervals during the therapy for about 1 or 2 months. Each investigation took place under identical circumstances. The given dose of terbutaline was 2.5 mg three times daily for the first 2 days, later 5 mg three times daily. Objective or subjective changes were noted during the whole period.

RESULTS

Plethysmography

Fig. 1 shows the results obtained by plethysmography. To get an overall impression of the effect of the therapy, the measured pulse amplitudes of the first and third fingers of each hand were summarized and divided by the number of patients in each group. The given values are thus the means of four fingers in each patient, obtained at the different temperatures as mentioned above. Group (A) with Raynaud's disease (patients 1, 2 and 3) showed a continuous increase in pulse amplitude amounting to 68.5 mV (from 46 to 115 mV) after 56 days. The increase was most marked during the first 9 days. Fig. 2 shows the changes in pulse amplitude and form typical after treatment with terbutaline in patient 3.

The group with scleroderma showed a different pattern as a decrease in pulse amplitude was observed during the first 2 days. However, in 3 patients (4, 5 and 6) the pattern changed to an increase for the rest of the observation period. After 56 days a total increase of 58.8 mV was noted (group B in Fig. 1). A contrary effect occurred in the 2 other

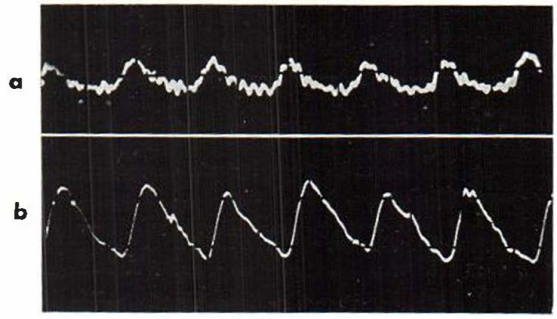

Fig. 2. Effect of terbutaline (Bricanyl) on the pulse form in Raynaud's disease (patient 3). (*a*) Before treatment. (*b*) After 58 days of treatment.

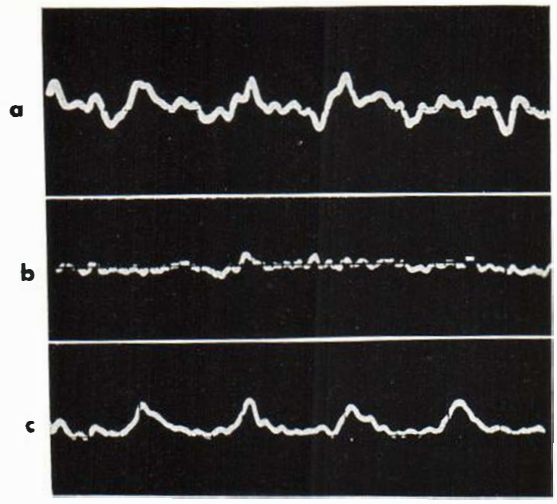

Fig. 3. Pulse curves obtained after 16 days of treatment with terbutaline (Bricanyl) in scleroderma (patient 7). (*a*) At room temperature. (*b*) After cold water immersion. (*c*) After warm water immersion.

patients (7 and 8) with scleroderma (group C). In these there was no increase, but a decrease of 13.2 mV also after 27 days of treatment. Fig. 3 shows the pulse curves in patient 7 after 16 days of treatment.

Skin temperature

Fig. 4 shows the results obtained by temperature measurements. The values given represent the skin temperature of one finger as measured at room temperature before and during the therapy. Group A (patients 1, 2 and 3) showed an overall increase. This was especially marked on the first 2 days when it increased from 24.4° to 29.9°. The increase was less on the 9th and 27th day but amounted to a total of 4.9°c after 56 days of therapy.

In the scleroderma group, 3 patients (4, 5 and 6) also showed an increase in skin temperature, amounting to 2.2°C after 56 days. These were the same patients who also reacted with an increase in pulse amplitude (group B in Figs. 1 and 4). A decrease in skin temperature of 2°C occurred in 2 patients with scleroderma (7 and 8). This also corresponded to the decrease in pulse amplitude noted in these patients (group C in Figs. 1 and 4).

Clinical evaluation

Table II shows a correlation between the clinical response to therapy, plethysmography, and skin temperature. In group A with Raynaud's disease, patients 1 and 2 showed subjective improvement. The skin felt warmer and was less sensitive to cold. The tendency to whiteness, acrocyanosis and hyperhidrosis was objectively diminished. Patient 2 who had suffered from symptoms for 24 years, described the changes as dramatic. The clinical condition deteriorated when the treatment was stopped for a short while but improved markedly after reinstitution. Patient 3 experienced no clear clinical improvement despite the increase in skin temperature and pulse amplitude.

In the group of scleroderma, patients 4 and 5 felt a subjective improvement and also the episodes of whiteness and cyanosis decreased in intensity. There was an improvement in the calcinosis in one patient (no. 4). Patients 6, 7 and 8 showed no clinical improvement.

The only side effects observed were tremor of hands and palpitations. These occurred in 2 patients only, and were of more transient character. In no case was it necessary to discontinue the treatment.

DISCUSSION

In total 4/8 patients showed clinical improvement whereas the finger temperature and pulse amplitude increased in 6/8 patients. The pulse amplitude, i.e. the pulse pressure, is no quantitative measure of the blood flow and may in this situation represent a more central than a real peripheral vascular action. According to Carlström & Westling (1) terbutaline has a preferential action on the beta$_2$-stimulators. In an investigation on anaesthetized cats and dogs Persson & Olsson (6) found that the hemodynamic effect of terbutaline could be characterized as follows: A reduction of arterial mean pressure due to peripheral vasodilation, increase in heart rate and increase in pulse pressure; in man the dominant vascular effects were increased heart rate and stroke volume, as well as muscular and subcutaneous vasodilation.

The results obtained in the present study confirm that terbutaline induces an increase in the peripheral pulse pressure. In addition the peripheral temperature is also raised; presumably this is a consequence of improved peripheral circulation.

The observed effect on Raynaud's phenomenon might thus be due to beta-stimulation of the cardiovascular system proximal to the skin vessels since, according to current opinion, beta-receptors are not present in the skin. This effect is quite different

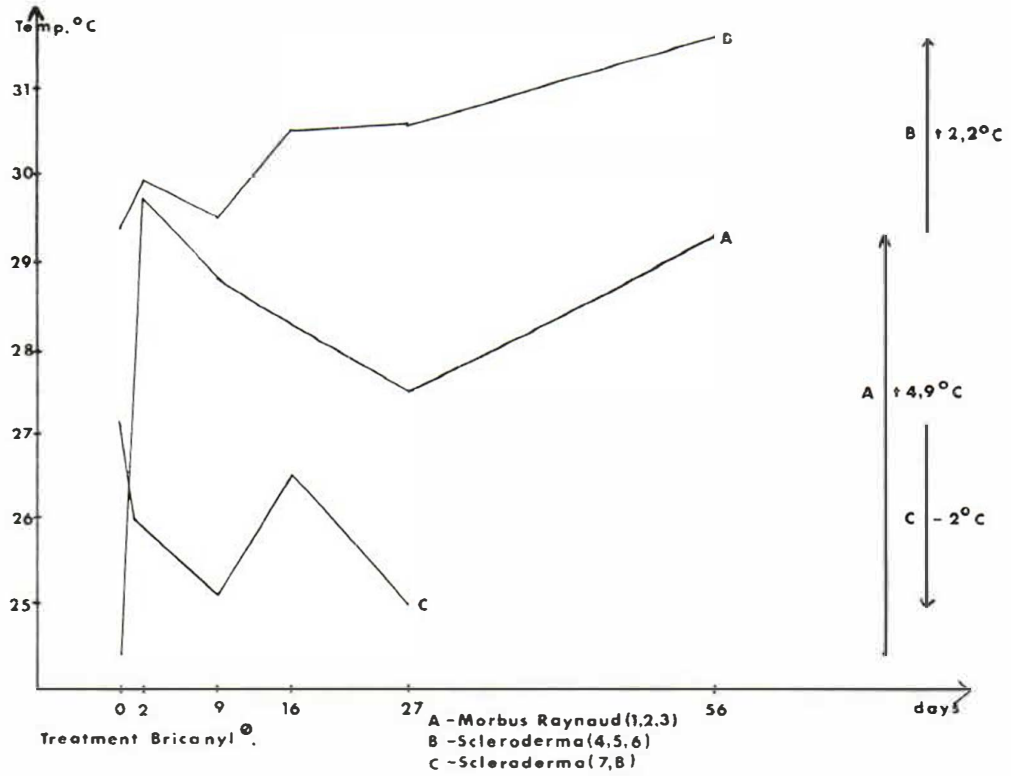

Fig. 4. Effect of terbutaline (Bricanyl) on skin temperature measured at room temperature (22°–23°C).

from the sympathicolytic one effectuated by the alpha-blocking agents which are commonly tried in this disorder. In this connection one should not forget the occurrence of sympathetic underactivity which has been demonstrated by Jablonska (4) and others (2) in scleroderma. This underactivity has, however, not been found in Raynaud's disease.

Table II. *Results after treatment with terbutaline sulphate (Bricanyl)*

Group	Patient no.	Clinically	Plethysmography	Skin temp.
A	1	+	+	+
	2	+	+	+
	3	−(+)	+	+
5	4	+	+	+
	5	+	+	+
	6	−	+	+
C	7	−	−	−
	8	−	−	−

+ = improvement, − = no improvement.

The decrease in pulse pressure and skin temperature observed in 2 patients with scleroderma, indicates that the cardiovascular effect may sometimes be reversed.

The present preliminary study is too small for the drawing of conclusions as to the protracted therapeutic effect of terbutaline on Raynaud's phenomenon. Further studies might, however, be promising.

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