

Application of exogenous NO_x and air plasma in the treatment of the trophic ulcers of the vascular etiology

Clinical experiments showed the high efficiency of NO_x- therapy during the treatment of the following widely widespread diseases of peripheral vessels: 1) the chronic venous insufficiency of lower extremities (CVILE), complicated by the formation of trophic defects (the so-called "venous" trophic ulcers); 2) chronic critical ischemia of the lower extremities (CCILE) against the background of the chronic occlusion diseases of the arteries of lower extremities.

The varicose expansion of the hypodermic veins of lower extremities is encountered according to numerous data of the different authors in 15-19,5% of adult population, moreover in 50% of these patients are developed the trophic disorders of the skin of the shins in the form of hyper-pigmentation, paratrophic eczema and paratrophic scleroderma, trophic ulcers. Surgical interventions (removal of the varicose changed hypodermic veins and the bandaging of communication veins) are connected with the high risk of festering operating wounds. By patients with the associated thrombosis of deep veins and with the edematic form of postthrombophlebitis syndrome operational interference apropos of the varicose expansion of hypodermic veins is contraindicated. From what was stated above is obvious the topical character of the problem of the conservative treatment of the trophic disorders of the skin against the background of CVILE. Not less immediate is the problem of the treatment of the trophic ulcers against the background of CCILE, which according to the data of WHO (World Health Organization) is encountered in 2% of population older than 60 years. Among the patients with CCILE the trophic defects of soft tissues are encountered in 20-22%; however, against the background of associated diabetes mellitus the frequency of the appearance of trophic defects comprises not less than 45%.

In the department of the faculty surgery of the 2nd therapeutic department MMA of I.M.Sechenov on the base CMH №61 the clinical experiment is carried out in 119 patients with the venous trophic ulcers of shin in the age from 41 to 82 years. On the basis a clinical and ultrasonic dopplerographic study was revealed, that 46 patients (39%) had the trophic ulcer against the background of the primary varicose expansion of the veins of lower extremities, in 73 (61%) - against the background of postthrombotic disease. Area of trophic ulcers - from 6 to 150 cm².

Conservative treatment was either the stage of preoperation preparation or the basic version of the treatment in patients, by which the surgical treatment was counter-indicative. For the judgment about the effectiveness of the conservative stage of treatment the clinical and planimetric indices of the course of the process of sanitation and epithelization of ulcer, a bacteriological study of discharge from the ulcer, the cytological study of exudate, a histopathological study of biopstat from boundary trophic ulcer, the indices of microcirculation (according to the data of laser Doppler floumetri - LDF) and of transcutaneous tension of oxygen (TTO), the periods of the readiness of patient for the surgical and phlebosclerotic treatment are used.

The basic group of observations (NO_x- therapy) composed of 82 patients, distributed into two subgroups: in the I basic subgroup (54 patients) trophic ulcers processed APF (air plasma flow) in the regime of NO_x- therapy; in the II basic subgroup (28 patients) prior to the beginning of NO_x- therapy the ulcerous surface finished APF in the regime of coagulation before the evaporation of necrotic detritus and formation of coagulation scab. Further during 15 days the surface of scab was finished in the regime of NO_x- therapy. Into the group of comparison (proteolytic and antimicrobial preparations - in the phase of exudation and necrosis and stimulators - in the phase of regeneration and epithelization) entered 37 patients.

For the substantiation of the time of the action of the NO_x- containing gas flow (NO_x - CGF) per unit of the area of ulcer are used the results of processing trophic ulcer by an area of 12 cm² for the concentration of NO_x in the zone of contact of 500 ppm. Each minute of action were taken reading of microcirculation changes by the method LDF. As a result conducted investigation was established that the duration of action on one zone with an area of 2 cm² must compose 8-10 flogged, and the total time of action - with respect to the area of ulcerous defect.

A quantity of sessions of the therapy by the oxide of nitrogen is determined by the appearance of bright granulations and expressed boundary epithelization.

Optimum time of action by the oxide of nitrogen depending on the area of the trophic ulcers

Area of ulcer, cm²	6-30	35-55	56-80	81-105	106-130	131-155
Time of working, min	0,5-2,0	2,0-3,5	3,5-5,0	5,0-6,5	6,5-8,	8,0-9,5

Planimetric observation of the dynamics of the reduction in area of trophic ulcers showed that in the group of comparison the area of ulcer decreased on the average by 0,7% in a 24 hour period, and in the basic group by 1,7% in a 24 hour period. The comparative estimation of the clinical indices of the healing of trophic ulcers in the different groups is represented in the following table.

Comparative estimation of the dynamics of the flow of wound process in the trophic ulcers

Evaluation criteria	Group comparison, of N-37	The basic group	
		I subgroup N-54	II subgroup N-28
Purification from the pathologic exudate, days	12,3±3,5	8,3±3,0	-
Regress of the phenomena of perifocal inflammation, days	11,5±2,1	8,4±2,2	5,5±1,8
Appearance of granulations, days	15,1±3,6	7,6±2,5	7,2±2,8
Appearance of epithelization, days	16,7±2,9	8,3±1,9	8,2±2,3
Reduction in area of ulcers, % in 24 hrs	0,7	1,6	1,7
Allergic dermatitis, %	29,7	22,2	25
Recurrent festering, %	0	0	0

In 2,5 months the complete healing of trophic ulcers in the group of comparison is noted in 43% of patients (the reference area of ulcers not more than 30 cm²), in the I subgroup of basic group - in 92% of patients, in the II subgroup of basic group - in 85% of patients, the reference area of trophic ulcers in the patients of these subgroups exceeding 50 cm² (Fig. 1).

Comparative estimation of the dynamics of the healing of the trophic ulcers

Group of the patients	Area (S) of trophic ulcers, cm²	Complete healing of trophic ulcers, %	
		21 days	76 days
Group of comparison, N-37	S<50;	0	43,2
The basic group, I subgroup N-54	S>50	22,2	92
The basic group, II subgroup N-28	S>50	21,4	85,7

Dynamics of the healing of trophic ulcer in the process of therapy



Fig. 1

A bacteriological study of wound treatment separable from the trophic ulcers prior to the beginning revealed the poly-microbial nature of flora, been microbial associations with the very weak sensitivity to the antibiotics of the wide spectrum of action. The qualitative and quantitative analysis of the bacterial flora, isolated from the trophic ulcers, showed that in the basic group against the background of NOx- therapy, especially in combination with the preliminary coagulation of ulcerous surface, is reduced the degree of bacterial seeding and already to 7-14 days it becomes below the critical level, necessary for maintaining the infectious process in the wound. In the control group an analogous decrease is noted not earlier than 21 days from the beginning of treatment (Fig. 2).

The executed by the method LDF **study of microcirculation** in the cloths of trophic ulcers prior to the beginning of treatment revealed in all patients its expressed disturbances according to the hyperemic type, that are accompanied by the paretic expansion of micro-vessels, by the stasis of the blood, by the disturbance of venous draining and mechanisms of modulation of woven blood flow (myogenic, neurogenic and respiratory), change in the blood pressure and its regulation, significant reduction in the vasomotor activity of vessels. A simultaneous study of the transcutaneous tension of oxygen on the edges of ulcer of up to the beginning of treatment revealed in all patients significant reduction in this index. The disorders of microcirculation, caused by intravascular and extravascular changes, served as the reason for local circulatory hypoxia prior to the beginning of treatment.

The normalization of the pathologically changed amplitude-frequency characteristics of microcirculation and the activating of regulator mechanisms was observed after the course of NOx- therapy. To 14-18 days the average index of microcirculation (IM), the value of the root-mean-square deviation (RSD), the coefficient of variation (CV) and index of flaksmot microcirculation (IFM) approached in the value indices of the symmetrical sections of healthy shin. In the group the comparisons of the disturbance of microcirculation remained.

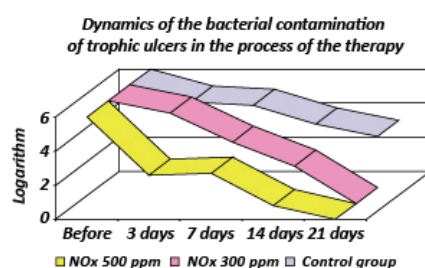


Fig. 2

Dynamics of the average index of microcirculation (IM) of LDF- grams in the process of the treatment

Groups of the patients	Index of the standard	Before the treatment	3 days	7 days	14 days	21 days
Group of the comparison	5,33±0,64	25,9±1,5	25,1±0,8	23,6±1,3	19,7±1,1	15,8±1,3
Basic group - I subgroup	5,33±0,64	25,9±1,5	20,3±0,9	21,9±1,4	14,7±1,2	6,14±1,1
Basic group - II subgroup	5,33±0,64	25,9±1,5	21,1±1,2	22,3±1,1	11,9±1,3	5,54±0,9

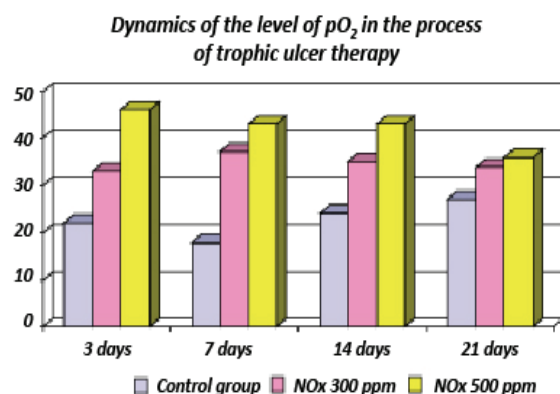


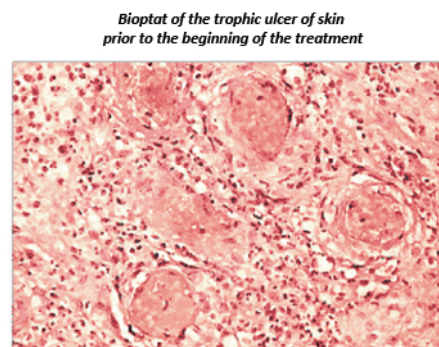
Fig. 3

Against the background treatment the normalization of the level of the transcutaneous tension of oxygen (T_aO_2) in the basic group, especially in the II subgroup, passed more intensively than to the group of comparison (Fig. 3).

Histological and histochemical studies of biopstat from boundary ulcer show, that before treatment cloth characterize presence express disorder microcirculation (stasis, sludge and micro-thrombosis), edema, plasmatic impregnation and lymphostasis, suppression phagocytosis, weakness macrophage reaction, chronic inflammatory infiltration, vasculit and pyonecrotic imposition on ulcerous surface (Fig. 4).

The weak proliferating potential and the dystrophia of fibroblasts prevented ripening granulating cloth, which under the conditions of chronic inflammation acquired the features of the defective persisting granulating cloth with the special cellular structure and the tendency toward the second necroses and the hyperergic reactions, braking of epithelization.

IN the I subgroup of basic group with the NOx- therapy already in 7 days, in contrast to the group of comparison, occurred the normalization of microcirculatory disturbances, decreased and disappeared the stasis of the blood, sludge of erythrocytes, micro-thrombosis, increased permeability of vessels. The purification of ulcerous surface from the necrotic detrite, the destroyed leukocytes and the bacterial colonies intensively occurred. The stimulation of wound process realized to a considerable degree because of the activation of macrophage reaction and strengthening of an increase in the fibroblasts. Active proliferation and differentiation of the latter from 7 days from the beginning of treatment was stimulated by the straight delivery of the exogenous nitrogen oxide. The proliferation of fibroblasts occurred simultaneously with angiogenesis, which created conditions for an increase in the granulating cloth (Fig. 5).



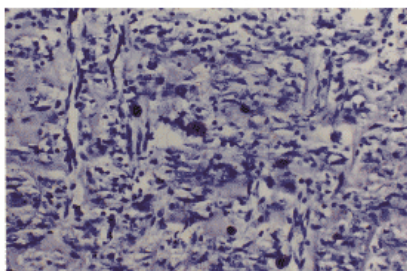
Sludge of erythrocytes and thrombocytes in the opening of vessels, edema and neutrophilic infiltration. Painting with hematoxylin and with eosin. Incr. x200.

Fig. 4

Biosynthetic activity of fibroblasts was strengthened, which was confirmed by histochemical reactions, increased the synthesis of glycosaminoglycans and collagen, fibrillogenesis and fibrogenesis of collagenic fibers, ripening granulating cloth and subsequent regeneration of the epithelium is synchronous with the purification of the surface of ulcer and the fibrous transformation of cloth. Valuable granulating cloth with the vertical vessels to 14 days already filled ulcerous defect, displacing pathologic granulating cloth and fibrocicatricial tissue "old" ulcers due to the production of collagenasis by macrophages and by fibroblasts. To 21 days on the edges of large ulcers and on the large part of the area of small ulcers occurred the fibrous transformation of granulating cloth and the regeneration of epidermis (Fig. 6).

In the II subgroup with the NOx- therapy after the preliminary coagulation of ulcerous surface by high-temperature air- plasma flow the stimulation of the process of wound healing occurred even more intensive. Inflammatory processes were diluted more rapidly under the thin scab because of the destruction of necrotic masses and sterilization of ulcerous surface, and the signs of the disturbance of microcirculation decreased because of the therapy by the nitrogen oxide. The proliferation of fibroblasts and angiogenesis to 7 days they already conducted to shaping of granulating cloth with the vertical vessels, which ripened to 14 and was fibrosed to 21 days. Boundary epithelization was accelerated and in the majority of the cases to 21 days the scars were shut.

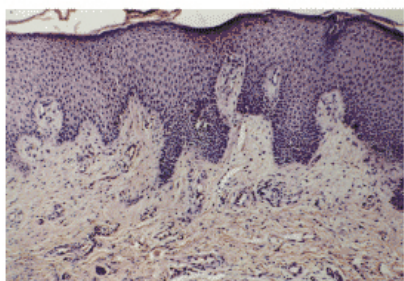
*Biostat of trophic ulcer to 7 days
from the beginning of the therapy*



Developed granulating cloth, the appearance of vertical capillaries, synthesis GAG, the proliferation of fibroblasts, macrophage and fat-cellular reaction, the disappearance of the disturbances of microcirculation. Painting with toluidine dark-blue. Incr. x200.

Fig. 5

*Biostat of trophic ulcer to 21 days
from the beginning of the therapy*



Cicatrization and the epithelization of ulcerous defect. Painting with hematoxylin and with eosin. Incr. x100.

Fig. 6

The clinical experiments of the effectiveness of the NOx- therapy of the trophic ulcers of the shin of venous and arterial genesis was carried out also in the division of surgery of vessels and angiosexology NIT MMA i.n. I.M.Sechenov on the base CMH №7. NOx- therapy was used for the treatment “venous” ulcers in 154 patients in the age from 46 to 62 years. In all patients it took place of CVILE which was complicated by the formation of trophic ulcers, of them in 15 were the edematic form of posttromboflebotic syndrome (PTFS) with reduction in the passability over the deep veins. The duration of existence of trophic ulcers up to the moment of hospitalization variable from 1 to 36 months. The size of ulcers was from 2 to 7 cm in the diameter. During the duplex scanning of veins was evaluated the passability of deep veins, the presence or the absence of the insufficiency of the valve apparatus of the deep and communication veins of lower extremities.

To the patients of basic group was conducted NOx- therapy with the use of an apparatus “PLASON”. Treatment consisted of the daily working of the region of ulcer NOx -CGF during the 2nd minutes. They moved away mechanically when there is dry scab at the ulcer present. Dry sterile bandage was superimposed at the end of procedure on the ulcer. The duration of the course of NOx- therapy amounted on the average to on 15 days.

For the objectivization of a study the group of comparison of 54 patients with the analogous trophic ulcers, which obtained the usual treatment (bandages with antiseptics and stimulators of woven increase, physiotherapy, elastic compression the like), was formed. The general state of patients, the duration of basic disease, and also gravity of trophic defects were similar. The effectiveness evaluation criteria for action exogenous NOx were: the dynamics of inflammatory process, the forming of granulating cloth and the epithelization of trophic defects.

The granulations in the trophic defects were absent prior to the beginning of treatment in 79,5% of patients or they were very sluggish. The presence of fibrinonecrotic impositions is noted in the overwhelming majority of patients (85,5%) in the trophic ulcers. In 81,8% of patients against the background of NOx- therapy occurred the complete healing of trophic defects, in 13,6% of patients - their decrease and the regress of periulcerous dermatitis, in 4,5% of patients trophic defects proved to be resistance to the NOx- therapy. In this case in 100% of cases the purification of the surface of ulcerous defects from the fibrinonecrotic detrite is noted. The absence of an increase in the microflora was noted during the control bacteriological sowings from the ulcers onto 5-7 days after the beginning NOx-therapy in 93,2% of patients. The time of purification and healing of trophic defects in the basic group was reliably lower than in the group of comparison - $15,2 \pm 3,0$ of the day in the basic group and of $21,6 \pm 2,0$ in the group of comparison. The periods of observation of the patients, who transferred NOx- therapy, were from 1 months of hospital period to year.

Any side effects from the application of a new procedure in the distant period (to the year) was not noted.

In parallel with these studies was conducted the study of the effectiveness of the NOx- therapy of trophic ulcers with chronic critical ischemia of the lower extremities (CCILE) against the background of the chronic occlusion diseases of arteries (“arterial” ulcers).

The basic group of observations they composed 68 patients at the age from 56 to 72 years, which suffer CCILE, which was complicated by the formation of trophic ulcers with the preferred localization on the foot. In 39,3% vascular pathology was combined with uncompensated diabetes mellitus. The period of the chronic occlusion disease of arteries composed from 1 year to 8 years, period of CCILE -

from the 2nd weeks to 2,5 months. Period of the appearance of trophic ulcers on the skin of shin to the moment of the hospitalization varies from 1 to 2 months. The size of ulcers was from 1 to 5 cm in the diameter. During the duplex scanning of arteries their passability, extent of the occlusion- stenotic defeat of arterial bed was evaluated.

The procedure of NOx- therapy is analogous to that described above. Duration of application - 15-25 days. Clinical effect was evaluated at the end the course of therapy.

In 35,7% of patients against the background NOx-therapy occurred the complete healing of trophic defects, in 33,6% - their decrease, but final healing it did not begin. In remaining patients, as a rule with associated heavy diabetes mellitus, trophic defects proved to be resistance to the NOx- therapy.

Thus, the NOx- therapy of trophic ulcers both in the patients with the chronic venous insufficiency of lower extremities and with the occlusion diseases of arteries gives the expressed effect in the overwhelming majority of the cases: (more than 80% "venous" and more than 65% "arterial" ulcers), it is considerable (doubly) accelerating their healing and drawing near the periods of the fulfillment of operational interference. The preliminary coagulation of ulcerous surface by air plasma with the subsequent NOx- therapy even more improves the results of treatment, making it possible from 3 days to already carry out flebectomy or flebosclerosation.

Biopstat – material from biopsy