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Study of plasma-chemical NO-containing gas flow for treatment of wounds and inflammatory processes

Alexander V. Pekshev [a], Anatoly B. Shekhter [b], Andrey B. Vagapov [a], Nikolay A. Sharapov [a], Anatoly F. Vanin [b, c, *]

[a] Bauman Moscow State Technical University, Moscow, Russia
[b] I.M. Sechenov First Moscow State Medical University, Moscow, Russia
[c] N.N. Semenov Institute of Chemical Physics, Moscow, Russia

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ABSTRACT

This work is aimed at exhaustive and detailed study of chemical, physical and physico-chemical characteristics of NO-containing gas flow (NO-CGF) generated by a plasma-chemical generator of Plason device, which has been used in medical practice for more than 15 years for effectively healing wound and inflammatory conditions with exogenous nitric oxide (NO-therapy). Data was obtained on spatial structure of the gas flow, and values of its local parameters in axial and radial directions, such as nitric oxide content, velocity, temperature and mass flow density of nitric oxide, providing altogether the effectiveness of treatment by the exogenous NO-therapy method, were determined experimentally and by computations. It was demonstrated that plasma-chemical synthesis of NO from atmospheric air in a low direct current (DC) arc provides a high mass flow of nitric oxide at the level of 1.6–1.8 mg/s, while in the area of impact of NO-CGF on the biological tissue, on its axis, NO content is 400–600 ppm, flow velocity about 5 m/s, nitric oxide mass flow density 0.25–0.40 mg/(s·cm^2), temperature 40-60 °C. Tendencies were determined for designing new devices for further experimental biological and medical research in the field of NO-therapy: lowering the temperature of NO-CGF to ambient temperature will enable variation, in experiments, of the affecting flow parameters in a wide range up to their maximum values: NO content up to 2000 ppm, velocity up to 20 m/s, nitric oxide mass flow density up to 2.5 mg/(s·cm^2).

1. Introduction

In 1997 Dr. R.K. Kabisov (P. Hertsen Moscow Oncology Research Institute, Moscow, Russia) discovered an unknown phenomenon of pronounced stimulation of healing of skin wounds by the atmospheric air flow containing nitric oxide (NO) produced by a plasma-chemical method. This discovery laid the foundation of a principally new method, named as exogenous NO-therapy [1], for treatment of wound pathologies, acute and chronic inflammatory processes.

Experimental clinical studies carried out under the guidance of Prof. A.B. Shekhter and Prof. A.F. Vanin, as well as analysis of literature data on the role of endogenous NO in the wound process, provided the justification of the NO-therapy method and identification of the following main mechanisms or pathways of effect of exogenous NO on disease processes [2–5]:

(i) direct or indirect (through formation of peroxynitrite) bactericidal effect;
(ii) induction of the phagocytosis of bacteria and necrotic detrite by neutrophils and by macrophages;
(iii) inhibition of the free oxygen radicals, which exert pathogenic influence, and also possible activation of the antioxidant protection;
(iv) normalization of microcirculation due to the vasodilatation, the anti-aggregation, and anti-coagulant properties of NO, that improves vascular trophicity and nutrient exchange;

Abbreviations: BMSTU, Bauman Moscow State Technical University; NO, nitric oxide; NO_2, nitrogen dioxide; NO-CGF, NO-containing gas flow; DC, direct current; exNO, exogenous nitric oxide; PCG, plasma-chemical generator; gNO, gaseous nitric oxide; CL, cooling liquid.

* Corresponding author. N.N. Semenov Institute of Chemical Physics, Kosygin str 4, 119991 Moscow, Russia. Tel.: +7 495 939 75 35; fax: +7 495 651 21 91.
E-mail address: vanin@polymer.chph.ras.ru (A.F. Vanin).

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(v) improvement of nerve conductance;
(vi) regulation of immune deficiencies which are common in wound pathology;
(vii) secretion of cytokines by the activated macrophages;
(viii) direct induction of proliferation of fibroblasts and synthesis of collagen by them;
(ix) regulation of apoptosis in remodeling of granular and fibrous tissues;
(x) effect on proliferation of keratinocytes and, therefore, epithelization of the wound defect.

The diversity of mechanisms of action of exogenous nitric oxide (exNO) determines its effect on all phases of general inflammatory and regenerative process (Scheme 1), which provides the pathogenetic validity and high efficiency of NO-therapy.

NO-therapy of wounds is accomplished by supplying to the place of pathology of NO-containing gas flow (NO-CGF), which is a flow of atmospheric air having a plasma background and comprising nitric oxide as a specific component. The flow is formed by a plasma-chemical generator (PCG) of Plason device (Fig. 1), which was developed by the staff of Bauman Moscow State Technical University (BMSTU) under the guidance of Dr. A.V. Pekshev, and manufactured since 2000 by Center BMSTU, LLC, Moscow, Russia; more than 400 devices were manufactured to date. Structure of the Plason device and method of NO-therapy were described in sufficient details earlier [6–10]; the device was certified for application in medical practice in Russia, Ukraine and the European Union as a medical device of Class IIb (EC Certificate No. 09 0637 QS/NB) [11–13]; and it is the first and, for the moment, the only commercial device for healing wound and inflammatory conditions with exogenous nitric oxide.

The Plason device has been used in medical practice for more than 15 years and demonstrated highly effective treatment of persistent and septic wounds, trophic venous and diabetic skin ulcers, thermal and chemical burns, sports injuries, chronic arthritis, and also reduces the risk of postoperative complications [14–21].

Analysis of operation modes of the device, which are used by most of the users, showed that at the typical flow rate of NO-CGF of 3 l/min the nitric oxide content on its axis in the area of effect on the tissue commonly varies in the range of 400–600 ppm, i.e. about 500 ppm in average, which we thought to be the determining parameter of NO-CGF, which provided the effectiveness of NO-therapy.

The assumption that the content of nitric oxide in the flow near the surface of tissue to be treated is not the only factor determining the effectiveness of NO-therapy came to us after the announcement by Nitric BioTherapeutics Inc. Brictol, PA, USA (later NB Therapeutics Inc.), company formed in 2006, on the beginning of works on development of the equipment for treatment of chronic wounds with gaseous nitric oxide (gNO); it was suggested, instead of directly blowing over the wound with NO-CGF (as in the Plason method), to supply it into a closed volume (bathing unit) completely covering the area of pathology and the healthy tissues around it. Fig. 2 [22] illustrates the essence of the suggested method: NO-CGF is injected into a bathing unit (boot) via a flexible tube from a tank at room temperature at the flow rate of 1 l/min and nitric oxide content of up to 400 ppm [23].

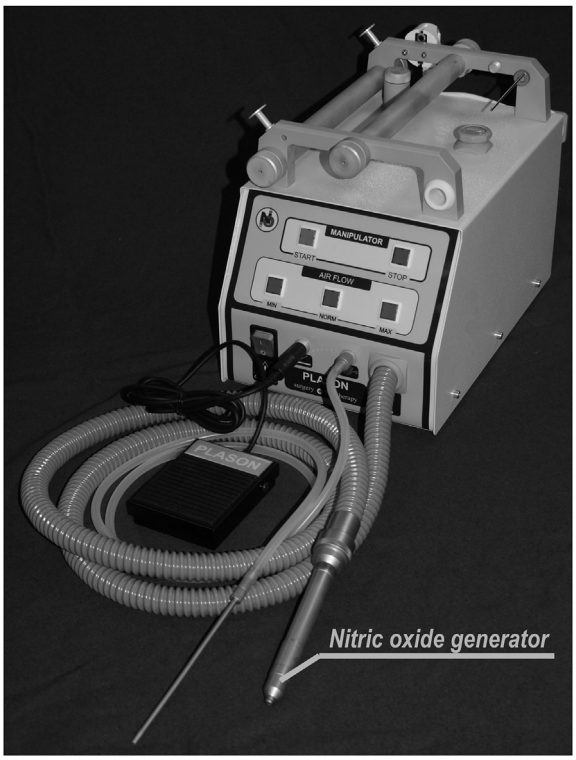
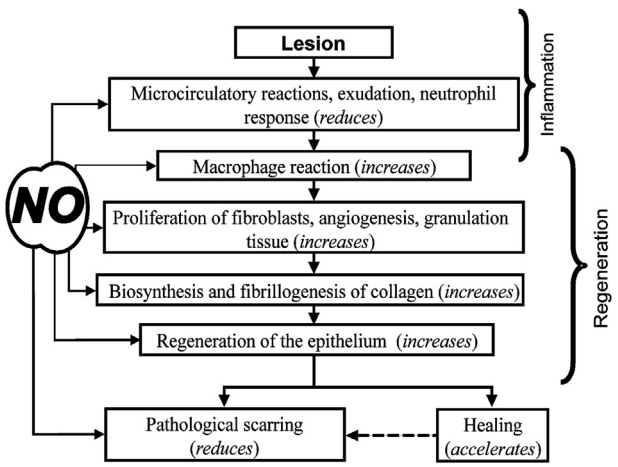


Fig. 1. Plason device for NO therapy of Center BMSTU.



Scheme 1. Effect of NO on various segments of wound process.

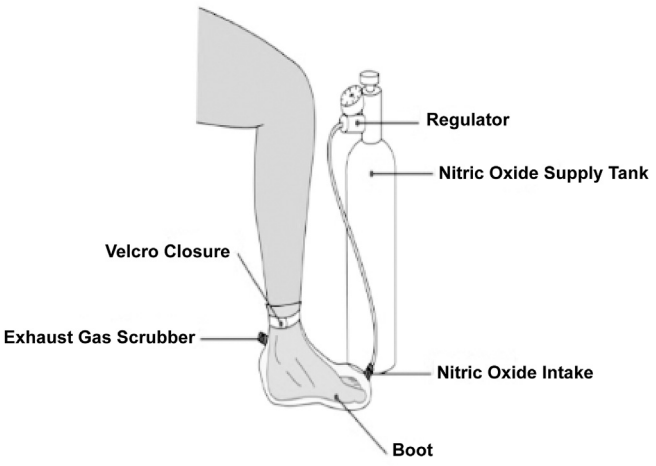


Fig. 2. Technology of NO therapy of Nitric BioTherapeutics.

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