
Case report

Level of exhaled nitric oxide during human anaphylaxis

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Background: Nitric oxide (NO) seems to play an important pathophysiologic role in modulating the systemic changes associated with anaphylaxis. Even if some effects of NO may be protective, animal models of anaphylaxis have shown that the summation effects of NO are deleterious, resulting in hypotension and loss of intravascular volume. There are no studies of NO production during anaphylaxis in humans.

Objective: To measure the level of exhaled NO during anaphylaxis induced by bee venom cluster immunotherapy in a 34-year-old beekeeper.

Methods: Exhaled NO was measured using a chemiluminescence analyzer at different flow rates, and alveolar NO concentration and airway NO production were calculated.

Results: We measured a high level of exhaled NO (78 ppb at 50 mL/s, with increased alveolar concentration and airway production) during anaphylaxis induced by bee venom immunotherapy in this patient. Normal values of exhaled NO were measured in the same patient 1 week later before and after a modified regimen of desensitization.

Conclusions: Nitric oxide production was increased in the respiratory tract during anaphylaxis. Having excluded all the common causes of increased exhaled NO levels, these results support the hypothesis that NO plays an important role in anaphylaxis.

Ann Allergy Asthma Immunol. 2006;97:264–265.

INTRODUCTION

Anaphylaxis is an unexpected, sudden, and sometimes lethal event caused by IgE-mediated immunologic release of mediators from mast cells and basophils. It has long been known that histamine and other mediators of anaphylaxis can act indirectly in an endothelium-dependent manner to produce vascular permeability and smooth muscle relaxation.¹ A potential secondary mediator of anaphylaxis is nitric oxide (NO), which is synthesized from L-arginine through the activity of NO synthase (NOS). There are 3 isoforms of NOS. Two of these exist constitutively (cNOS) and the third is inducible (iNOS). The cNOS is found in endothelium, myocardium, endocardium, skeletal muscle, platelets, and neural tissue, and iNOS is found in macrophages, fibroblasts, neutrophils, and smooth muscle. Mediators known to enhance the activity of cNOS are capable of acting very rapidly, with increased levels of NO occurring within seconds of exposure.² These mediators are the same as those seen in anaphylactic and anaphylactoid episodes, including histamine, platelet-activating factor, several of the leukotrienes, and

bradykinin. Synthesis of NO via iNOS requires gene transcription and can take minutes to hours; however, once initiated in this manner, the synthesis can continue in a protracted way for several hours, and the amount of NO produced exceeds that made through the activity of cNOS. The effects of NO are protean,³ and its effects in anaphylaxis have the potential to be both protective and damaging. Nitric oxide can relax bronchial smooth muscle while dilating vascular smooth muscle and enhancing vascular permeability. From animal models of anaphylaxis it seems that the summation effects of NO are deleterious, resulting in hypotension and loss of intravascular volume,⁴ and that methylene blue, an inhibitor of NO effects, exerts a beneficial effect in anaphylactoid shock in rabbits.⁵ To our knowledge, there are no studies of NO production during anaphylaxis in humans.

CASE REPORT

A 34-year-old beekeeper was referred to the Allergy and Immunology Clinic of the University of Torino for specific immunotherapy after she experienced anaphylactic shock after a bee sting 3 months previously. The patient, a nonsmoking, nonatopic healthy woman, was receiving a cluster regimen of desensitization on a weekly basis.⁶ Ten minutes after receiving the 50- μ g dose, she developed hypotension (systolic blood pressure, 80 mm Hg) associated with generalized pruritus, erythema, cough, rhinorrhea, and chest tightness. After intramuscular injection of epinephrine (0.3 mg), intra-

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This study was supported by a grant from Ministero Italiano dell'Università e della Ricerca.

Received for publication December 11, 2005.

Accepted for publication in revised form February 26, 2006.

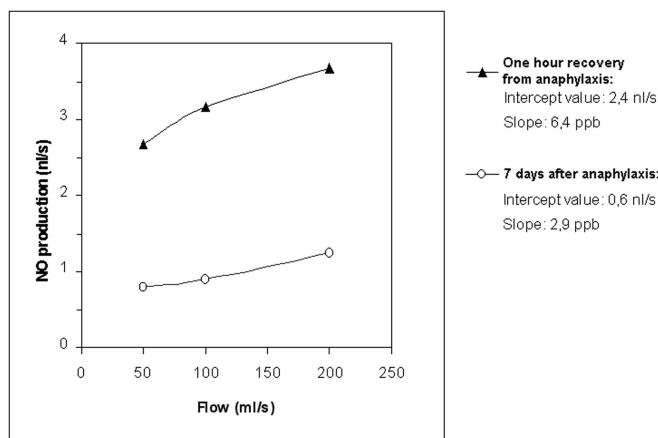


Figure 1. Airway nitric oxide (NO) production (intercept) and alveolar NO concentration (slope) were significantly higher within 1 hour of recovery from anaphylaxis compared with 1 week later.

venous saline infusion, and intravenous chlorpheniramine administration (10 mg), her clinical condition rapidly improved, and she fully recovered within 1 hour, when she gave her consent to have exhaled NO levels measured. Exhaled NO, measured at 50 mL/s⁷ using a chemiluminescence analyzer (NiOX; Aerocrine AB, Solna, Sweden), was 78 ppb (reference value, <20 ppb), similar to levels commonly observed in asthmatic patients. The patient never complained of asthma or allergic rhinitis, and skin test results to common allergens were negative. Using the multiple flows technique,⁸ we ascertained an increased production of airway NO (intercept value, 2.4 nL/s; mean $\pm$ SD reference value, 0.55 $\pm$ 0.1 nL/s) and an increased alveolar NO concentration (6.4 ppb; mean $\pm$ SD reference value; 4.6 $\pm$ 0.5 ppb) (Fig 1). Three hours later, when the patient was still asymptomatic, the exhaled NO level, measured only at 50 mL/s, was still elevated (68 ppb), whereas the serum tryptase level (UniCAP; Pharmacia Upjohn, Uppsala, Sweden) was more than halved compared with the value measured after 1 hour (4.5 vs 14 ng/mL). One week later, the patient tolerated well a modified regimen of desensitization, and exhaled NO values at baseline and 1 hour after immunotherapy were normal (15 and 13 ppb, respectively). The possibility that part of the increase in the exhaled NO level could be due to epinephrine itself cannot be excluded, as a mild increase in the exhaled NO level has been reported after β_2 -agonist use in asthmatic patients.⁹

CONCLUSION

This patient demonstrated increased NO production in the respiratory tract during anaphylaxis, having excluded the other common causes of increased exhaled NO levels, including respiratory tract infection during the past 4 weeks. We

suggest that the increased production of NO in the respiratory tract in anaphylaxis may also mirror similar increases in NO production by the systemic circulatory system, as suggested by the relationship between exhaled NO and dialysis-induced hypotension.¹⁰ This observation supports the hypothesis that NO plays an important role in anaphylaxis and that NO-inhibiting drugs could theoretically be useful in the most severe cases, refractory to epinephrine treatment.¹¹

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