Nitric Oxide Levels in Patients with Acute Allergic Reactions

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Citation

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Abstract

Background: Nitric oxide(NO) has been considered as a marker of inflammatory and allergic conditions in humans, but its role in human anaphylaxis has not been examined. The hypothesis that NO release is associated with clinical and laboratory aspects of anaphylaxis was examined in this study.

Methods: Serum from patients who had acute allergic reactions was assayed for nitric oxide levels. The NO assay utilized a measurement of NO conversion products(nitrite and nitrate). NO levels were examined for correlations with previously determined levels of tryptase, histamine, IL-6, and C-reactive protein levels. NO levels were also examined for clinical correlations, including urticaria, erythema, angioedema, wheezing, respiratory rate, and blood pressure.

Results: There was no correlation between NO levels and any of the other mediators/molecules. NO levels also did not correlate with the extent or presence of urticaria or erythema, or with the presence of wheezing, hypotension, or tachycardia. A positive correlation was observed between NO levels and respiratory rate. This was not related to the presence of wheezing, gender, or history of asthma.

Conclusion: Unlike histamine, serum NO levels do not correlate with the cardinal features of anaphylaxis but did correlate with respiratory rate in patients with acute allergic reactions. It is possible that in this clinical context, NO levels may be involved in a nonspecific stress response.

ABBREVIATIONS

NO nitric oxide
IL-6 interleukin 6

INTRODUCTION

Nitric oxide (NO) is of interest as a marker of inflammatory and allergic conditions in humans, but its role in human anaphylaxis has not been examined. The known effects of nitric oxide on vasculature are potentially relevant in anaphylaxis, since hypotension and edema may be promoted through vasodilator effects.

METHODS

Serum from a subset of 77 patients out of 91 patients, recruited from the Saint Vincent's Hospital Emergency Department between May 1998 and April 1999, who had acute allergic reactions in a study previously described ($_3$) was assayed for nitric oxide levels. In brief, recruitment criteria included adults with acute urticaria, acute angioedema, acute unexplained stridor, and acute pruritic rash (after ingested food or ingested, inhaled, or injected drug or after contact with latex). The study targeted patients whose symptoms had been present for no greater than 12 hours from the time of alleged allergen exposure. Fourteen of the original 91 patients were not included in this study due to inadequate serum availability. Historical features, symptoms, physical findings (including heart rate, blood pressure and respiratory rates), and treatments were recorded on a study specific data input form. The extent of involvement with urticaria and erythema was assessed using

a check off illustration of body areas (similar to that used to assess burn area extent) printed on the data input sheet.

Serum samples stored at –70C were assessed for nitric oxide levels using the Total Nitric Oxide Kit™ (R&D Systems Minneapolis MN). IL-6 and histamine levels were assessed on plasma as previously reported ([3,4]), using commercial immunoassays (QuantiGlo™ Human IL-6, R&D Systems Minneapolis MN, Histamine Test Kit, Immunotech, Marseille, France). Serum total tryptase levels, also previously reported, were performed on these samples using the B12mAb for capture and the G4 mAb for detection (UniCAP, Pharmacia Upjohn).

NO levels were examined for relationships with IL-6, histamine and tryptase levels using correlation coefficients. NO levels were examined for relationships with clinical variables including the presence and extent of urticaria and erythema, the presence or absence of angioedema, blood pressure (systolic, diastolic, mean arterial and pulse pressures), wheezing, heart rate, the duration of acute symptoms, and certain historical variables. In secondary analysis, stepwise regression was performed to examine for multivariate effects, including interaction effects. Variables including nitric oxide levels were normalized if necessary by logarithmic transformation for multivariate analyses. Analyses were performed using the JMP™ software package (Version 4.01)(SAS Institute, Cary NC).

RESULTS

The 77 patients with acute allergic reactions whose serum was assayed for nitric oxide levels had a median age 36 years (range, 19-74 years). Thirty-two (41.6%) of the patients were male; the other 45 (58.4%) were female. As shown previously in a larger group of patients from which this subset was derived, histamine levels correlated with heart rate (=.27, p=0.0154), erythema extent (=.29, p=0.008), and urticaria extent (=.41, p<0.001). Tryptase levels correlated with urticaria extent (=.30, p=0.009). NO levels were not significantly different in patients stratified by the presence or absence of urticaria, angioedema, or erythema. Patients with hypotension, wheezing, upper airway involvement, or tachycardia (HR>100) did not have different NO levels compared to those without these manifestations in separate analyses. There was no correlation between NO levels and the extent of urticaria or erythema. There were no correlations between NO levels and heart rate, mean arterial blood pressure, or age. In this study, NO levels did correlate with respiratory rates (=.30, p=0.0076). Pulse pressure also showed a trend towards being positively correlated with NO levels (=.21, p=0.07). There were no correlations between NO levels and histamine, IL-6, or tryptase levels. Respiratory rates showed no correlation between other parameters except for heart rate (=.33, p=0.0033) and there was no correlation between respiratory rates and either histamine or tryptase levels.

In multivariate analyses, adjustment for the presence of wheezing, asthma history, gender, histamine levels, and heart rates did not abrogate the significant correlation between NO levels and respiratory rates. Including both pulse pressure and respiratory rate as predictor effects for NO levels resulted in significant effects for both variables (p<0.01).

DISCUSSION

Systemic levels of nitric oxide have been correlated with illness severity in sepsis ([5,6]). However the utility of measuring systemic levels of nitric oxide have not been studied in allergic disease. Indeed, the present interest of studies on nitric oxide relates more to its role as a non-invasive marker in lower airway disease ([1]). Through inflammatory stimuli, nitric oxide synthase 2 is induced in pulmonary tissues and results in the generation of NO. Measurement of exhaled NO has been held as a possible way to measure airway-associated inflammation in a non-invasive manner ([1]). Because vasodilation and decreased peripheral vascular resistance is a significant component of anaphylaxis, there is a possibility that the vascular smooth muscle tone modulation known to be associated with induced NO production could have a contributory role. In the present study, however, NO levels had no correlation with manifestations that relate to cutaneous vasodilation, i.e. cutaneous erythema extent, and blood pressure. On the other hand, histamine, a known vasodilator had a significant correlation with erythema extent, as previously reported ([3]), which is again shown in the subgroup of patients studied for NO levels. Heart rate was also not correlated with NO levels, despite the fact that histamine levels and heart rates had a significant positive correlation. NO levels did not correlate with histamine levels either.

The finding of a significant correlation between NO levels and respiratory rate that was independent of wheezing or asthma suggests that NO levels may be involved in some aspect of the pathophysiology in acute allergic reactions. Possible mechanisms could relate to central and peripheral stimulation of ventilation. In an experimental model, NO

was shown to be involved in hypoxia induced tachypnea ([7]). Thus there may be some theoretical role of NO on ventilatory changes associated with acute allergic reactions.

Whether tissue production of nitric oxide is reflected in peripheral circulation is not known. Mast cells have been shown to be capable of expressing inducible nitric oxide synthase when stimulated ([8]). Mast cells are known to be activated in acute allergic reactions (as evidenced by tryptase elevations). While it may difficult to imagine that protein synthesis (e.g. NO synthase) can be induced in a time frame as short as that observed in anaphylaxis, it is well known that various tissues from vertebrates and invertebrates respond to external signal molecules by rapid release of nitric oxide (NO) mediated by constitutive nitric oxide synthase ([2,9]). Thus, it is conceivable that during systemic allergic cellular stimulation, nitric oxide generation may occur.

There is variation of measured serum NO levels seen in patients due to dietary nitrate intake. Nitrate is one of the conversion products measured in the assays of NO. Since a convalescent NO level was not performed and a dietary history focusing on nitrate intake was not taken, the potential presence of an “elevated” NO level for any given patient cannot be determined with certainty. Despite these sources of variation in measured NO levels, a significant positive correlation between NO levels and respiratory rates was still observed. In secondary analysis, NO levels were also correlated with pulse pressure after taking into account respiratory rates. Since pulse pressure increases are noted with epinephrine administration ([10]), it is conceivable that levels of NO and endogenous epinephrine increase concordantly in response to acute allergic stimuli. Furthermore, if increases in respiratory rates and pulse pressure relate to NO levels, NO related pathophysiology may be analogous to non-specific autonomic stress responses in acute allergic reactions. Clearly NO levels did not relate either to the classical allergic mediator histamine or to the classical signs of systemic allergic reactions such as urticaria, wheezing, tachycardia or hypotension. In short, more research is required to further investigate the role of NO in anaphylaxis.

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