Nitric oxide synthesis in patients with infective gastroenteritis

P Forte, R S Dykhuizen, E Milne, A McKenzie, C C Smith, N Benjamin

Abstract
Background—There is evidence that endogenous nitrate synthesis is notably increased in patients with infective gastroenteritis.
Aims—To determine whether this is due to nitric oxide (NO) production via the L-arginine/NO pathway.
Methods—Seven male patients with community-acquired bacterial gastroenteritis and 15 healthy male volunteers participated in this study. All patients had stool culture positive infective gastroenteritis. A bolus of 200 mg L-[15N]2-arginine was administered intravenously after an overnight fast. Urine was collected for the next 36 hours. Urinary [15N]:[14N]nitrate ratio was assessed by dry combustion in an isotope ratio mass spectrometer.

Results—Mean 36 hour total urinary nitrate excretion in the gastroenteritis group was 5157 (577) µmol compared with 2594 (234) µmol in the control group (p<0.001). Thirty six hour urinary [15N]nitrate excretion was considerably higher in the gastroenteritis group compared with the control group (13782 (1665) versus 1698 (98) µmol; p<0.001). These values represent 1.129 (0.139)% and 0.138 (0.007)% of [15N]nitrogen administered (p<0.001), respectively. Corrected 36 hour urinary [15N]nitrate excretion for urinary creatinine was also significantly higher in the patient compared with the control group (1934 (221) versus 303 (35) µmol/ mmol; p<0.001).

Conclusion—Results show notably enhanced nitrate synthesis due to increased activity of the L-arginine/NO pathway in patients with infective gastroenteritis. (Gut 1999;45:355–361)

Keywords: endothelium derived relaxing factor; L-[15N]2-arginine; nitrites; infection; diarrhoea

Nitric oxide (NO) is synthesised from the guanidino nitrogen atoms of L-arginine by NO synthase (NOS).1 Three isoforms of NOS have been identified: an endothelial type (eNOS), a neuronal type (nNOS), and a macrophage (inducible, iNOS) type. Both nNOS and eNOS tend to be expressed constitutively; however, iNOS expression generally requires induction under the influence of various cytokines and/or lipopolysaccharide (LPS).2 Several studies have shown the existence of a cytokine inducible high output L-arginine/NO pathway in humans. Ochoa et al reported a ninefold increase in plasma nitrate concentrations in patients with cancer receiving interleukin 2.3 Furthermore, Hibbs et al, using L-[15N]2-guanidino arginine as a metabolic tracer, showed that this increase in nitrate synthesis is by activation of the L-arginine/NO pathway.4 Moreover, Sherman et al showed the expression and the isolation of cDNA for a cytokine induced NOS in a transformed human intestinal epithelial cell line,5 a finding which has been confirmed by other independent investigators.6,7

Increasing data indicate that NO exerts important antimicrobial activity against a wide range of pathogenic microorganisms.8 For instance, inhibitors of NOS exacerbatate infection in vitro and in vivo against enterobacteria such as Escherichia coli and Salmonella sp.,9 and iNOS deficient mice are highly susceptible to infections with Leishmania major and Listeria monocytogenes.10 Conversely, accumulating evidence also suggests that reactive species derived from NOS play a significant role in acute and chronic inflammation. Recently, several reports have suggested that overproduction of NO could play an important role in the pathogenesis of inflammatory bowel disease (IBD). Indeed, increased levels of NO and iNOS activity have been shown in the colonic lumen and mucosa of patients with ulcerative colitis.11–13 Furthermore, inhibitors of NOS have been shown to exert a protective role in ileitis induced by trinitrobenzene sulphonic acid in guinea pigs14 and rats.15 In addition, iNOS deficient mice generate significantly less footpad swelling after injection with carrageenin and are also more resistant to LPS induced death than wild type.16

Nitric oxide in blood is rapidly oxidised to nitrate by oxygenated haemoglobin, molecular oxygen, and superoxide anions and is excreted as such into the urine.17 Hegesh and Shiloah17 showed in 1982 that infants with acute gastroenteritis had a notable increase in plasma nitrate concentration. Our group18 and Wagner and colleagues19 have previously reported a similar increase in plasma nitrate concentration and urinary nitrate excretion in adults with infective gastroenteritis. This increase in nitrate production was also much greater in patients with infective gastroenteritis than that seen with more severe inflammation caused by IBD.20 The main problem with the use of total nitrate production rate as a measure of NO synthesis is, however, that nitrate may arise from sources other than that generated from the metabolism of NO and dietary intake of

Abbreviations used in this paper: LPS, lipopolysaccharide; IBD, inflammatory bowel disease; NO, nitric oxide; NOS, nitric oxide synthase.
nitrates may exceed endogenous production.\textsuperscript{21} Based on the calculated half life for nitrate in plasma (about eight hours),\textsuperscript{22,23} diet restriction must be maintained for at least 40 hours (five half lives) in order to eliminate the confounding influence of exogenous nitrate/nitrite. It is not yet clear, however, whether all endogenous nitrate production results from NO oxidation. In previous studies, our group\textsuperscript{24} and Rhodes and colleagues\textsuperscript{25} reported that enrichment of \(^{15}\text{N}\) in urinary and plasma nitrate was lower than that seen in steady state plasma L-\(^{15}\text{N}\)-arginine, suggesting that endogenous production of nitrate may occur in humans.

To overcome these limitations, we have developed a sensitive and specific method of measuring the conversion of L-arginine into NO.\textsuperscript{26} The method is based on the measurement of \(^{15}\text{N}\)nitrate excretion in urine after the intravenous administration of the stable isotope L-\(^{15}\text{N}\)-guanidino arginine. The aim of this study was to compare the activity of the L-arginine/NO system more directly in patients with infective gastroenteritis and matched healthy controls.

Materials and methods

Subjects

The study was carried out in the Infection Unit at Aberdeen Royal Infirmary. Permission was obtained from the local Ethics Committee and all subjects gave their written, informed consent before participating. Seven consecutive male patients (age 22–40 years) referred to the Unit with community acquired bacterial gastroenteritis were entered into the study. All patients had stool culture positive for infectious gastroenteritis: five with \textit{Campylobacter jejuni}, one with \textit{Cryptosporidium}, and one with \textit{Salmonella enteritidis}. The control group consisted of 15 healthy male volunteers (age 21–41 years) from hospital and laboratory staff. All subjects were normotensive, non-diabetic, non-smokers, and were receiving no medication. Table 1 presents the clinical characteristics of all subjects who took part in each protocol.

Tracer Infusion Study

Healthy volunteers received a limited nitrate diet (the diet excluded food items which contain a high concentration of nitrate—that is, cured meat, fruit, and particularly, green leafy vegetables\textsuperscript{27}) 24 hours before and for 36 hours after the administration of L-\(^{15}\text{N}\)-guanidino arginine. Patients were given only intravenous nitrate free fluid replacement solutions (a combination of 5% dextrose and 0.9% sodium chloride) throughout the first 24 hours of admission. Healthy volunteers were studied in the hospital ward under similar conditions to the patients. After an overnight fast, an 18 gauge catheter was inserted into a left antecubital vein and 200 mg (1.13 µmol) sterile pyrogen free L-\(^{15}\text{N}\)-guanidino arginine (99 mol % \(^{15}\text{N}\); Tracer Technologies, Massachusetts, USA) dissolved in 20 ml 0.9% sodium chloride was administered over 10 minutes by means of a constant rate infusion pump (Braun Per fusor ED 2, Germany). Baseline urine samples (before administration of the iso top e) were collected to determine the natural enrichment of \(^{15}\text{N}\)nitrate. Complete urine collections were made in prewashed (distilled water) two litre polypolyethylene bottles containing 5 ml of 5 mol/l sodium hydroxide to prevent reduction of nitrate for the periods 0–12, 12–24, and 24–36 hours after dosing. Healthy volunteers did not exercise during the study period, but usual ambulatory activity was permitted. The urine volume was measured, and samples from each collection were frozen at –80°C until analysis.

Table 1 Baseline subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=15)</th>
<th>Patients (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.6 (1.8)</td>
<td>32.4 (1.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.5 (2.2)</td>
<td>77.1 (3.1)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.78 (0.03)</td>
<td>1.81 (0.06)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>23.9 (1.1)</td>
<td>23.7 (1.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>126 (1.21)</td>
<td>122 (5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>68.5 (1.4)</td>
<td>70 (4.5)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>87.1 (1.13)</td>
<td>87.3 (4.1)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.7 (0.15)</td>
<td>4.8 (0.4)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>103.5 (4.6)</td>
<td>106.9 (3.3)</td>
</tr>
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Results expressed as mean (SEM).

Analysis of total urinary nitrate

Total urinary nitrate was measured as previously described.\textsuperscript{28} Briefly, nitrate was reduced to nitrite in a copper/cadmium reduction column and subsequent Griess reaction, modified by replacing carrier fluid with 1.5% glycine, pH 9.4. The detection limit of this method is 1 µM and interday coefficient of variation over the measured concentration range (20–1000 µM) was less than 3%.

Measurement of \(^{15}\text{N}/^{14}\text{N}\)nitrate ratio

In order to determine \(^{15}\text{N}\) enrichment of nitrate in urine, a modification of the procedure described by Brooks and colleagues\textsuperscript{27} was followed.\textsuperscript{29} Briefly, urinary nitrate was extracted using a selective ion exchange resin (IMAC HP555; Merck Laboratories, Domsstadt, Germany), and converted to ammonia using 0.4 g Devarda's alloy (BDH, UK) in the presence of 0.2 g magnesium oxide (Sigma, St Louis, Missouri, USA) with subsequent conversion to nitrogen gas by combustion at 1000°C, and analysis by continuous flow gas isotope ratio mass spectrometry (20–20, Europa Scientific, UK). The precision of \(^{15}\text{N}/^{14}\text{N}\) ratio measurement of this mass spectrometer was ±0.0004%. The linearity of the measurements was shown across the range of the expected enrichments (0.368–1 atom %) with a correlation coefficient of 0.999 by linear regression analysis. The interday coefficient of variation ranged from 0.41% to 0.78%.

Calculation and statistical analysis

Total urinary nitrate excretion was calculated from the volume of urine excreted and duplicate measurement of urinary nitrate concentration. The \(^{15}\text{N}\)isotope enrichment of nitrate was calculated according to Hauck and colleagues\textsuperscript{30}:

\[ \text{Atom per cent } ^{15}\text{N} = 100/(2R + 1) \]
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*p<0.001.

[15N]nitrate excretion was significantly higher in the gastroenteritis group compared with the control group (p<0.001). Mean 36 hour urinary nitrate excretion in the gastroenteritis group was 5157 (577) μmol; whereas the control group excreted 2594 (234) μmol. The detention of the urinary excretion of [15N]nitrate following intravenous administration of L-[15N]arginine was determined by measuring the total urinary nitrate excretion multiplied by the measured atom per cent excess of urinary [15N]nitrate. A one compartment pharmacokinetic model was used to analyse the urinary data obtained in this study. The total elimination rate was determined by a single pool kinetic equation.29 All values are presented as mean (SEM). Statistical analysis was performed using the unpaired Student’s t test on log transformed measurements of urinary [15N]nitrate excretion in the two study populations. A value of p<0.05 was considered significant.

**Results**

Mean 36 hour total urinary nitrate excretion in the gastroenteritis group was 5157 (577) μmol compared with 2594 (234) μmol in the control group (p<0.001). Mean 36 hour urinary [15N]nitrate excretion was significantly higher in the gastroenteritis group than in the control group (13782 (1665) versus 1698 (98) μmol; p<0.001). These values represent 1.29 (0.139)% and 0.138 (0.007)% of [15N]nitrogen administered (p<0.001), respectively, assuming one labelled guanidino nitrogen per arginine molecule is incorporated to nitrate. Corrected 36 hour urinary [15N]nitrate excretion for urinary creatinine was also significantly higher in the patient than in the control group (1934 (221) versus 303 (35) μmol/mmol; p<0.001). Table 2 shows the urinary excretion of [15N]nitrate in each 12 hour period after the administration of L-[15N]-arginine. Figure 1 shows the cumulative recovery of [15N]nitrate in urine. The total elimination rates of nitrate in patients and healthy volunteers were similar (~0.083/h and ~0.082/h). Likewise, the urinary creatinine clearance was similar in both groups (106.1 (2.5) versus 103.2 (2.4) ml/min, respectively).

**Discussion**

The results of this study show, for the first time, that the considerable increase in endogenous nitrate production in patients with infective gastroenteritis is due to oxidation of L-arginine via NOS. The tissue location of the sevenfold increase in NO synthesis in this study cannot, however, be determined.

Direct measurement of NO production is difficult because of its short half life in vivo.49 In mammalian cells, NO is enzymatically synthesised from the guanidino nitrogen atoms of L-arginine, and this is the only known enzymatic biochemical route by which these nitrogen atoms may be incorporated into nitrate.1 Determination of the urinary excretion of [15N] labelled nitrate following intravenous administration of L-[15N]-guanidino arginine is therefore independent of nitrate excretion from dietary or other unknown endogenous sources. The notable finding in this study was that the mean 36 hour urinary [15N]nitrate excretion was significantly higher in patients with infective gastroenteritis than in healthy volunteers after systemic administration of L-[15N]-guanidino arginine. We considered that an alteration in the renal clearance of nitrate in the study groups may explain the observed difference. However, urinary [15N]nitrate excretion was assessed over 36 hours (more than 90% of generated nitrate was excreted). In addition, the mean elimination constants of nitrate were similar in both groups, as was the creatinine clearance. Therefore, differences in renal handling of nitrate are unlikely to explain the difference in [15N]nitrate excretion.

We also contemplated the possibility that the [15N]nitrate synthesised came from metabolism of L-[15N]-arginine by intestinal microflora (i.e. the NOS present in these organisms). This is, however, unlikely to explain the large differ-

![Figure 1: Cumulative urinary excretion of [15N]nitrate after intravenous administration of L-[15N]2-guanidino arginine in patients and controls. Values are mean (SEM) for seven patients and 15 healthy volunteers. *Significant difference between healthy volunteers and patients (p<0.001).](image-url)
ence observed between the two groups, as L-[¹⁵N]arginine was administered intravenously. In addition, Smith and MacFarlane recently reported that the metabolism of L-arginine by human intestinal bacteria involves the arginine deaminase pathway as the exclusive pathway of catabolism. This pathway includes the combined activity of the enzymes, arginine deaminase, ornithine transcarbamylase, and carbamate kinase, which catalyses the conversion of L-arginine to ornithine, ammonia, and carbon dioxide with the concurrent formation of ATP. This indicates that the guanidino amino groups of L-arginine are primarily metabolised to ammonia, which may subsequently be used as a cellular nitrogen source during bacterial growth. Moreover, as the enzymatic synthesis of NO requires consumption of molecular oxygen, this hypothetical L-arginine/NO pathway in intestinal bacteria would not be favoured under the anaerobic conditions present in the intestinal lumen.

However, there are reports suggesting that enteric bacteria could generate nitrate. Ioanidis et al and Crawford and Goldberg have reported in enterobacteria such as E coli and Salmonella sp. the presence of an inducible flavohaemoglobin that metabolises NO to nitrate. Nitric oxide reacts with the haem group of this protein and is metabolised to nitrate by an oxidoreductase reaction. Although the role of this bacterial haemoglobin is still unknown, it may represent a cellular protective mechanism against nitrosative stress exerted by NO and nitrosothiols. This pathway could, therefore, constitute a novel enzymatic pathway of nitrate generation by enterobacteria in the intestinal lumen. However, this source of nitrate would not affect the results obtained in the present study, as [¹⁵N]nitrate generated from L-[¹⁵N]arginine is independent of other pathways of nitrate generation. As the healthy volunteers were ambulant while the patients were in the hospital ward and in bed, it is possible that ambulatory related vasodilatation might have affected the results obtained. Nevertheless, this difference would tend to underestimate the whole body conversion of L-[¹⁵N]arginine to [¹⁵N]nitrate in the patient group, as they were confined to bed and exercise is known to increase NO synthesis. As the subjects were of similar age and body mass index, and were normotensive, non-smokers, and non-diabetic, the most likely explanation of our findings is that the production of [¹⁵N]nitrate after the intravenous administration of L-[¹⁵N]arginine is higher in infective gastroenteritis than in healthy controls under basal conditions.

In this study, the site from which [¹⁵N]nitrate derives cannot be determined, nor can we establish whether the source of nitrate is from a constitutive or inducible NOS. The sevenfold increase in urinary [¹⁵N]nitrate excretion observed in patients with gastroenteritis does, however, suggest that the high output iNOS could be the major source of NO production in this condition. Intestinal epithelial cells are known to respond to bacterial invasion with the production of a range of proinflammatory cytokines. It is likely, therefore, that the increase in NO production could have derived from infiltrating inflammatory cells (macrophages and neutrophils), epithelial cells, endothelial or vascular smooth muscle cells, or other mucosal cells. Indeed, studies in vitro have shown that infection of human colonic epithelial cells with enteroinvasive bacteria activates epithelial cell iNOS expression and NO production. Moreover, Islam et al and Kolios et al showed in biopsy specimens of patients with acute shigella and salmonella colitis, increased expression of iNOS in intestinal epithelial cells. There is also a growing body of experimental evidence suggesting that the expression of iNOS is upregulated in the colon of patients with IBD. Lundberg et al found NO concentrations in luminal gas sampled from the colon 100 times higher in patients with active ulcerative colitis than in controls. Middleton et al showed high concentrations of L-citrulline, coproduct of the conversion of L-arginine to NO, in rectal biopsy specimens from patients with active ulcerative colitis. Furthermore, several groups have reported a significant increase in calcium independent NOS activity in colonic mucosa of patients with active ulcerative colitis and Crohn’s disease. Other investigators have also shown increased expression of iNOS in the surface epithelium of colonic mucosa from patients with ulcerative colitis. Moreover, recent data have confirmed that iNOS mRNA is upregulated in adults and children with IBD. Taken together, these data suggest that the increased levels of NO in the colon of patients with infective gastroenteritis and IBD could result from high expression of iNOS.

However, there are also reports of increased NO production by calcium dependent NOS in the colon of patients with Crohn’s disease and megacolon due to ulcerative colitis, suggesting the possibility that activation of cNOS may also contribute to the overproduction of NO in infective gastroenteritis. Further studies are necessary to determine whether the increased NO production in infective gastroenteritis is from an inducible and/or constitutive NOS. In a previous study we observed that the whole body NO synthesis did not increase after typhoid vaccination in humans, even when there was clear evidence for an inflammatory response in terms of fever, peripheral blood white cell count, and plasma C-reactive protein. We suggest that acute infective gastroenteritis is a strong inflammatory stimulus to increase NO production mediated by either luminal bacterial products or intramucosal release of cytokines such as tumour necrosis factor α, interleukin 1, interleukin 2, and interferon γ. Further studies are required to determine the role of this overproduction of NO in infective gastroenteritis. However, we consider that this increase in NO production could represent a mechanism for limiting tissue injury from infection. In line with this proposition, we have reported in patients with infective gastroenteritis...
that plasma nitrate concentrations correlated positively with the clinical severity of the infection, and the levels of plasma nitrate decreased as the patients recovered from illness. Likewise, Islam et al and Kolios et al reported that iNOS expression in colonic surface epithelium was significantly reduced at convalescence, when all patients’ stool cultures were negative for infecting agents. It is not clear how NO exerts intracellular inhibition of bacteria, but NO has been shown to inhibit mitochondrial respiration by inactivation of complex I and complex II of the electron transport chain and the aconitase of the Krebs cycle. In addition, there is increasing evidence to suggest that bactericidal activity against a number of targets is mediated by the reaction of NO and reactive oxygen intermediates. Nitric oxide may also contribute to host defence in infective gastroenteritis by securing blood flow to tissues with increased metabolic needs and by modulating intestinal epithelial permeability.

Another possible mechanism by which increased NO synthesis could protect against bacterial invasion is by increasing the entero-salivary circulation of nitrate. Indeed, we have shown that salivary nitrate is rapidly reduced to nitrite by lingual bacteria, and subsequently high concentrations of NO are generated by chemical reduction of nitrite in the stomach. Our group has also shown in vitro the bactericidal effect of acidified nitrite (in concentrations similar to those found in saliva) on the different microorganisms involved in the aetiology of infective gastroenteritis. Therefore, this pathway may protect the host against faecal–oral reinfecion, transmission of infection, and the development of a chronic carrier state. However, there is also evidence suggesting that gut mucosal injury and bacterial translocation across the intestinal tract may be mediated through increased NO production by activated iNOS. For instance, Mishima et al and Sorrels et al have shown in rats that LPS induced mucosal injury and bacterial translocation could be prevented by the administration of L-NMMA and aminoguanidine (a selective inhibitor for iNOS). Furthermore, Mishima et al recently showed that endotoxin induced gut injury and bacterial translocation was significantly higher in the wild type NOS +/+ mice than in the iNOS deficient mice. However, they did not find any difference in the degree of bacterial translocation, and the extent of mucosal injury between these strains in a model of intestinal bacterial overgrowth. Likewise, Laubach et al did not observe any difference in survival between iNOS +/+ and iNOS deficient mice treated with LPS.

However, McCafferty et al reported that iNOS deficient mice were more susceptible to a mild colonic insult than their wild type controls, and also lacked the capacity to heal. Furthermore, Horton et al showed that parenteral supplementation of L-arginine reduced bacterial translocation through an NO dependent mechanism. The reasons for the discrepancies observed in these studies are not apparent, but possible explanations include the use of different models of bacterial translocation, differences in genetic backgrounds, and use of different endotoxin concentrations. Regardless of the exact nature of these disparities, the extrapolation of these results to humans should be considered with caution, as the reported data in those murine models may not reflect bacterial translocation in the acute setting of human infective gastroenteritis.

It is also unclear whether the increased NO production in IBD is beneficial or harmful. NO may protect the intestinal mucosa and microvasculature against the multiple damaging factors involved in inflammation. For instance, NO prevents leucocyte–endothelial cell adhesion in postcapillary venules and emigration to the intestinal mucosa, thereby limiting an important source of toxic reactive oxygen metabolites. In addition, NO could play an important role in host defence against bacterial invasion and intramural penetration of the colonic wall. The idea of a protective role of NO in IBD has been sustained by a recent study which showed that iNOS deficient mice developed more severe inflammation than wild type controls in an experimental model of colitis.

Conversely, there are growing experimental and clinical indications suggesting that enhanced production of NO is related to microvascular damage and occurrence of tissue injury observed in IBD. Kimura et al showed a positive correlation between iNOS activity and disease severity, based on histological evidence in the colonic mucosa of patients with active ulcerative colitis. Furthermore, it was also found that the rate of nitrotyrosine (reaction product between NO derived oxidants and protein tyrosines) staining in the colonic mucosa increased proportionally with disease severity. Ouderk Pool et al reported that serum nitrate concentrations correlated with inflammatory variables and disease activity indexes. McLaughlan et al reported a moderate correlation between polymorphonuclear cell infiltration and interleukin 8 and iNOS mRNA levels in colonic mucosal biopsy specimens from untreated patients with ulcerative colitis and Crohn’s disease. Mechanisms by which excess production of NO may promote tissue injury and inflammation in IBD include inhibition of DNA synthesis and mitochondrial function, release of intracellular iron, relaxation of smooth muscle, and generation of carcinogenic nitrosamines. Taken together, it does seem that the acute and increased NO synthesis observed in infective gastroenteritis may mainly to control the infectious process, whereas the chronic and sustained overproduction of NO in IBD may contribute to cellular toxicity by overflowing the intestinal mucosa’s antioxidant buffer capacity, and rendering the mucosa more susceptible to microvascular damage and tissue injury.

In summary, the results reported here suggest that infective gastroenteritis is a potent inflammatory stimulus of intestinal production of NO in humans. Further studies are needed to determine the role of this NO overproduction, and whether this source is from a constitutive and/or inducible NO.
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