**Effect of Treatment on Maxillary Sinus and Nasal Nitric Oxide Concentrations in Patients With Nosocomial Maxillary Sinusitis***

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**Study objectives:** In maxillary nosocomial sinusitis (MNS) related to severe sepsis, nitric oxide (NO) concentration in the maxillary sinuses is drastically reduced secondarily to a downregulation of type-2 NO synthase. NO plays a major role in nonspecific immune defense of sinuses. We therefore aimed to study maxillary NO concentration during the treatment of MNS with drainage, daily lavage, and removal of any nasally introduced tube.

**Patients and methods:** Nine patients were studied during the first 4 days of treatment of MNS. We measured the concentration of NO gas in the maxillary sinus and in the nasal cavity, and the NO metabolite levels (nitrites/nitrates [NOx]) in the sinus lavages.

**Measurements and results:** Maxillary NO concentration (median [25 to 75 percentile]) increased from 70 parts per billion (ppb) [40 to 100 ppb] to 2,050 ppb (1,700 to 3,000 ppb) after 4 days of treatment of MNS (p < 0.0001). In the meantime, nasal NO increased from a median of 100 ppb (98 to 148 ppb) to 180 ppb (180 to 188 ppb) [p < 0.001]. At any time, there was a correlation between maxillary NO (logarithmic value) and nasal NO ($r^2 = 0.57$, p < 0.0001). NOx levels remained stable in the lavages.

**Conclusions:** We conclude that the treatment of the sinusitis with drainage, daily lavage, and removal of the gastric tube lead to a spectacular increase of maxillary and nasal NO concentrations. *(CHEST 2005; 128:1699–1705)*

**Key words:** nitric oxide; nosocomial maxillary sinusitis; sepsis

**Abbreviations:** CRP = C-reactive protein; MNS = maxillary nosocomial sinusitis; NO = nitric oxide; NOS = nitric oxide synthase; NOS2 = type-2 nitric oxide synthase; NOx = nitrites/nitrates; PCD = primary ciliary dyskinesia; ppb = parts per billion; SOFA = sepsis-related organ failure assessment

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Nitric oxide (NO) is implicated in a wide range of disease processes, exerting both detrimental and beneficial effects.¹ NO is a free-radical gas generated from L-arginine by a family of enzymes, the NO synthases (NOS).² NO generated by the type 2 NOS (NOS2) has a major role in nonspecific host defense in humans.³ In most organs, basal expression of NOS2 and thereby basal NO concentrations are very low, while in case of inflammation or infection, NOS2 expression is induced and NO acts as a second line of defense.⁴ In case of severe sepsis, induction of NOS2 results in sustained production of NO for a prolonged period of time, and this increased NO production plays a pivotal role in hypotension, leading to septic shock.⁵ The scenario for host defense in the paranasal sinuses appears to be exactly the reverse: the epithelium constitutively expresses NOS2, leading to NO concentrations of 5,000 to 20,000 parts per billion (ppb),⁶ whereas in case of maxillary sinusitis related to severe sepsis and septic shock, paranasal NO production is almost completely suppressed due to a downregulation of NOS2.⁷ **Maxillary nosocomial sinusitis (MNS) is a frequently unrecognized cause of fever in critically ill**
patients. Treatment classically consists in sinus drainage and lavages, nasal tracheal tube removal or tracheotomy, nasal gastric tube removal, and parenteral antibiotics. The underlying mechanisms for fluid retention and compromised immune defense in MNS are poorly understood. The sinuses communicate with the nasal cavity through a narrow ostium. Blockage of this ostium by nasal tubing has been considered to be a central event in the pathogenesis of sinusitis, but this is still controversial. Deja et al. have described a drastic reduction of maxillary NO concentration in patients with MNS. Simple inflammation of the sinus mucosa (without evidence of infection) was associated with dramatic inhibition of the expression of NOS2 within the epithelium. The resultant substantial decrease of intracavitary NO may account for marked impairments of nonspecific host defenses, thus promoting mucus accumulation and rapid superinfection.

The aim of the present study was to investigate the effect of treatment of MNS (drainage, daily lavage, and removal of nasally introduced tubes) on NO concentration in the maxillary sinus and in the nasal cavity. We also measured NO metabolite levels (nitrites/nitrates [NOx]) in the sinus lavages.

**Materials and Methods**

**Study Population**

This prospective study was conducted in a 16-bed ICU at the teaching hospital in Toulouse, France. The study protocol was approved by the local ethics committee. Patients enrolled in the study fulfilled all the following criteria: (1) age > 16 years, (2) endotracheal intubation, (3) mechanical ventilation for > 72 h, and (4) criteria of severe sepsis, according to the current definition. The worst simplified acute physiology score II during the first 24 h of intensive care stay was recorded. The sepsis-related organ failure assessment (SOFA) score was calculated retrospectively for the 4-day follow-up. For each patient, the worst value for each organ system (respiratory, cardiovascular, renal, coagulation, liver, and neurologic) in each 24-h period was considered. Patients were excluded from the study if they met at least one of the following criteria: (1) history of sinusitis, (2) transfer to the radiology department considered by the attending physician as a high risk of morbidity because of severe respiratory state, or (3) coagulation disorders contraindicating transnasal puncture. Patients underwent a routine fever workup that included a chest radiograph, urine analysis with culture, and blood cultures. When these studies failed to identify the source of the fever or if fever was persistent despite administration of antibiotics effective against isolated causative organisms of a diagnosed infection, CT of the paranasal sinuses (5-mm incremental thickness scans in the axial plane) was performed within 24 h. Maxillary sinusitis was defined as the presence of unilateral or bilateral opacification on a CT scan, reflecting air-fluid levels and/or opacification within the maxillary sinuses. Patients with radiographic maxillary sinusitis underwent transnasal puncture of the maxillary sinus involved and placement of an Albertini drain (Porges SAS; Le Plessis Robinson, France). The antibiotic regimen was not modified during the follow-up.

**Measurement of NOx**

Samples were assayed in duplicate for oxidation end-product of NO (NOx). Nitrate (NO3-) in the samples was first reduced to nitrite (NO2-) by incubating the samples for 1 h with Escherichia coli nitrate reductase enzyme prepared from bacteria grown under anaerobic conditions, in the presence of nicotinamide adenine dinucleotide phosphate and flavine adenine dinucleotide (Boehringer-Mannheim; Mannheim, Germany). NO2- levels were then determined by the Griess reaction by measuring the absorbance of each sample at 543 nm. The total amount of nitrite was expressed in micromoles per liter.

**Microbiological Examination**

Transnasal sinus puncture was performed by an otorhinolaryngologist using a standardized protocol; nostrils were disinfected with antiseptic solution (povidone-iodine solution). If necessary, a general anesthesia was induced, using a combination of sufentanil and midazolam. Transnasal puncture of the maxillary sinuses was performed using an Albertini trocar. Sinus contents were directly aspirated prior to lavage and immediately transported for bacteriologic examination. An Albertini drain was left in the sinus cavity.

**Gas Sampling and NO Measurements**

For gas sampling in the sinus, the Albertini drain was connected to a glass syringe. The atmospheric NO in the room was controlled to be inferior to 5 ppb. We collected 250 mL of gas in aliquots of 50 mL with a continuous aspiration rate of 0.1 L/min. The five syringes were pooled in an inert plastic bag (Tedlar bag; Hoffmann-Plastiques; Saint-Etienne, France), and NO concentration was measured immediately by a chemiluminescence NO analyzer (Cosma; Igny, France) sampling with a constant flow of 0.7 L/min.

To measure nasal NO, we used the same chemiluminescence NO analyzer (Cosma) sampling with a constant flow of 0.7 L/min. The probe was connected to a nasal olive and gently introduced into the vestibulum of one nostril. The contralateral nostril was left open. Measurements were performed in both nostrils.

**Lavages**

The sinuses were irrigated with 20 mL of sterile saline solution in order to remove pus from the surface of the sinuses so that a “true” lavage could be obtained with minimal effects from bacterial debris. Lavage was then performed with 5 mL saline solution and immediately reaspirated into a plastic syringe through the Albertini drain. The lavage was immediately placed on ice, removed from light, and subsequently stored at −80°C until assay for NOx was performed.

**Statistics**

The data were expressed as median (25 to 75 percentiles). Comparisons were made by the Friedman analysis of variance followed by posttests of Wilcoxon with a correction of Bonferroni. The correlation analysis was performed with the Pearson correlation test for n > 30 and with the Spearman correlation test for n < 30; p < 0.05 was considered significant. Analysis was performed using statistical software (SPSS version 11.0; SPSS; Chicago, IL).

**Results**

A total of nine patients fulfilling the inclusion criteria completed the whole procedure during a
1-year period. Patient characteristics are displayed in Table 1. At inclusion, intubation was performed through the oral route in all patients, and a gastric tube was placed through the nasal route in all patients.

The median (25 to 75 percentile) NO concentration measured in the maxillary sinuses within 6 h of drain placement was 70 ppb (40 to 100 ppb). In the meantime, nasal NO in the nostril homolateral to the drainage was 100 ppb (98 to 148 ppb), and NOx concentration in the lavage was 12.0 μmol/L (11.6 to 14.0 μmol/L).

Maxillary NO concentration and nasal NO increased significantly on measurements conducted during the 4 days following the onset of treatment (Fig 1, 2). We found a correlation between SOFA score and sinus NO at day 4 (Fig 3). There was a correlation between maxillary NO (logarithmic value) and nasal NO (Fig 4). In the meantime, NOx concentration in the lavage (Fig 5) did not change significantly.

**Discussion**

To study NO in paranasal sinuses of patients with severe sepsis treated for a MNS, we measured NO levels in the sinus and in the nose daily during the 4 days of drainage. Our data confirm that such patients present with very low NO concentration within the maxillary sinuses. We found that maxillary NO increased with the treatment of the sinuses with drainage, daily lavage, and removal of the gastric tube. We also found that nasal NO increased in the meantime, and that nasal NO (logarithmic value) was correlated with maxillary NO.

Deja et al.7 clearly demonstrated that the reduction of maxillary NO concentration in patients with MNS was secondary to a downregulation of NOS2 within the ciliated epithelial cells of the maxillary sinus mucosa; however, those authors did not study the two other isoforms of NOS (NOS type 1 and NOS type 3), and they did not investigate the mucosa during the recovery of the MNS for any isoforms of NOS. In our study, we did not investigate directly the sinus mucosa at any time. We therefore cannot conclude about which type of NOS is involved in the increase of NO within the sinus cavity during recovery. However, Lundberg et al.6 showed that NOS2 was the only isoform that displayed a positive staining in immunohistochemistry and in situ hybridization in normal sinus mucosa. We therefore believe that NOS2 is the major (if not the only) enzyme present in the ciliated epithelium either in normal or inflamed sinus mucosa, and that NOS2 also plays the major role in the restoration of NO gas with treatment of MNS.

The increase of NO concentration in the sinus air may be related not only to an increase of production by NOS but also to a decrease of catabolism. In order to approach the NO catabolism, we measured the levels of metabolic end products of NO (NOx) in the sinus lavage. We found that NOx was almost stable while NO gas increased. This stability of NOx may have several explanations. First, NOx is generated by the interaction between NO and superoxide anion (O2−). Sinusitis induces the recruitment of phagocytic cells in the sinus cavity (monocyte/macrophage and polymorphonuclear), which on activation generate large amounts of O2−. Because NO and O2− both contain an unpaired electron, they rapidly react together, leading to the secondarily production of nitrite and nitrate, which could explain the initial concentration of NOx (relatively low NO gas and low O2− gas, and relatively high O2−). Second, induction of NOS2 in the airway epithelium is expected to increase levels of NO gas in air and, in the meantime, to increase the metabolic end products NOx in respiratory tract fluids.17 Indeed, in aqueous aerobic

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**Table 1—Description of Patients***

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Main Diagnosis</th>
<th>Microorganisms Isolated in Sinus Puncture</th>
<th>SAPS II</th>
<th>SOFA Score (Day 0)</th>
<th>SOFA Score (Day 4)</th>
<th>CRP (Day 0), mg/L</th>
<th>CRP (Day 4), mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>COPD</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>33</td>
<td>5</td>
<td>5</td>
<td>230</td>
<td>185</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>Aspiration pneumonia</td>
<td><em>Staphylococcus epidermidis</em> anaerobe</td>
<td>39</td>
<td>10</td>
<td>9</td>
<td>302</td>
<td>324</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>ARDS</td>
<td><em>Acinetobacter baumannii</em> anaerobe</td>
<td>31</td>
<td>10</td>
<td>110</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>Thoracic trauma</td>
<td><em>Streptococcus spp</em></td>
<td>37</td>
<td>4</td>
<td>4</td>
<td>115</td>
<td>123</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Abdominal surgery</td>
<td><em>P aeruginosa</em></td>
<td>42</td>
<td>8</td>
<td>6</td>
<td>410</td>
<td>195</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>Abdominal surgery</td>
<td><em>Staphylococcus aureus</em> anaerobe</td>
<td>32</td>
<td>12</td>
<td>11</td>
<td>365</td>
<td>378</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>COPD</td>
<td><em>S epidermidis; E coli</em></td>
<td>38</td>
<td>6</td>
<td>7</td>
<td>105</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>COPD</td>
<td><em>P aeruginosa</em></td>
<td>35</td>
<td>5</td>
<td>4</td>
<td>157</td>
<td>102</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>Aspiration pneumonia</td>
<td><em>E coli</em></td>
<td>36</td>
<td>8</td>
<td>7</td>
<td>268</td>
<td>296</td>
</tr>
</tbody>
</table>

*SAPS II = simplified acute physiology score II (calculated during the first 24 h of intensive care stay).*
solution, NO autoxidizes and hydrolyzes to yield nitrite.\textsuperscript{18} Based on kinetic data and NO concentrations, this reaction of NO with O\textsubscript{2} is expected to be much slower than the reaction between NO and O\textsubscript{2}\textsuperscript{-}.\textsuperscript{19} This could account for the final concentration of NOx during the recovery of MNS (relatively high NO and high O\textsubscript{2}, and relatively low O\textsubscript{2}\textsuperscript{-}). Third, NOx concentration may be decreased by the presence of bacteria, especially during the initial phase of MNS treatment.\textsuperscript{3} Many bacteria we found in the sinus sputum, such as Pseudomonas and E coli, are denitrifying and consume NOx during protein synthesis and energy production.

A question arises to know whether the fall in sinus

**Figure 1.** Time course of maxillary sinus NO concentration in patient with MNS and severe sepsis (n = 9). Maxillary NO was measured within 6 h of drain placement (day 0), and then during the first 4 days of treatment. *p < 0.001 vs day 0. **p < 0.0001 vs day 0.

**Figure 2.** Time course of nasal NO concentration in patients. *p < 0.001 vs day 0. **p < 0.0001 vs day 0.
NO concentration is a cause or a consequence of MNS. Deja et al.\textsuperscript{7} clearly showed that the drops in NO concentration and in NO production in MNS were related to sepsis and not to sinus infection. According to this scenario, low NO concentration could impair ciliary motility and cytotoxic activity against microorganisms and thus increase the risk for secondary superinfection. We found a relationship between SOFA score and sinus NO at day 4, suggesting that the severity of illness was associated with low NO concentration and thus with impaired local defense. However, we also measured a spectacular increase of NO at day 4 compared to day 0, while the SOFA score and the inflammatory marker C-reactive protein (CRP) did not decrease significantly in the meantime. We therefore believe that the local treatment of MNS associating drainage, lavage, and removal of nasally introduced tubes contributes to the

**Figure 3.** NO concentration in the maxillary sinus and SOFA score at day 4. There was a correlation between SOFA score and sinus NO ($r^2 = 0.84$, $p = 0.01$).

**Figure 4.** Nasal and maxillary NO concentrations. There was a correlation between nasal and maxillary NO ($r^2 = 0.57$, $p < 0.0001$).
increase in sinus NO and thus to a restoration of the local defense of the paranasal sinuses.

An interesting finding of this study is that nasal NO increased during the treatment of MNS. Moreover, nasal NO was well correlated with maxillary NO. This is in agreement with a study conducted in children with acute sinusitis, whose concentration of nasal NO was initially very low and returned to normal after antibiotic therapy. Lindberg et al reported that patients with chronic sinusitis had a significantly lower nasal NO than healthy subjects. After sinus surgery, the nasal NO of the patients with successful outcome of surgery increased to the same level than subjects. Those results are most often believed to be a consequence of a restoration of the sinus ostium permeability rather than a restoration of maxillary NO concentration. As we found that the nasal NO concentration was well correlated with maxillary NO, our data strongly suggest that the increase of maxillary NO largely participate in the increase of nasal NO.

We found that maxillary NO increased as early as 2 days after the onset of treatment. This is not in accordance with the findings of Deja et al, who found an increase of sinusal NO that was delayed and lower than ours. There are at least two explanations for this discrepancy. First, Deja et al performed fenestration, while we performed drainage. It is possible that fenestration lead to a better ventilation of the sinus but also to a slower increase of NO gas concentration within the sinus. Second, we performed a daily lavage of the sinus cavity, which could lead to a better elimination of bacteria and mononuclear cells, and then to a better NO availability.

There are some limitations in our study. The main limitation is the uncontrolled design. We did not include a control group of untreated patients for ethical reasons. Indeed, Holzapfel et al clearly demonstrated that the treatment of nosocomial sinusitis decreased the occurrence rate of nosocomial pneumonia in patients undergoing prolonged mechanical ventilation. Another limitation is the small sample size. Despite the 1-year period of enrollment, only nine patients completed the study. Four were patients who were discarded because it was impossible to aspirate gas from the sinus through the Albertini drain; in these four patients, the evolution of nasal NO was, however, similar to the nine included patients (data not shown). We did not look for the diagnosis of primary ciliary dyskinesia (PCD) in our patients, although a dramatically low nasal NO was clearly described in such patients. It is, however, unlikely that one of our patients had PCD for at least three reasons. First, PCD is a very infrequent disease, with a prevalence of 1/16,000. Second, the patients in our study had no history of sinus disease, which is common in PCD. Third, all of our patients had a nasal NO > 150 ppb, which is higher than the concentration usually found in PCD.

In conclusion, we found that in patients with MNS the impaired concentration of maxillary NO spectacularly increased with the treatment of the sinusitis with antibiotics and daily lavages. We also found that nasal NO increased in the meantime. According to the important role of NO on ciliary function and nonspecific immune defense, the restoration of nasal and maxillary NO could contribute to prevent maxillary cavity superinfection and eliminate one of the

![Figure 5. Time course of NO metabolites concentration (NOx) within the maxillary sinus lavage in patient (n = 9). NOx concentration did not change significantly.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22030/ on 03/30/2017)
reasons why the lung is a target organ for nosocomial microorganisms in critically ill patients receiving mechanical ventilation.

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