

## Higher Urine Nitric Oxide Linked to Better Outcomes in Acute Lung Injury

In patients with acute respiratory distress syndrome (ARDS), higher urine nitric oxide was associated with improved survival, more ventilator-free days, and lower rates of organ failure, according to the results of a study reported in the February 1 issue of the *American Journal of Respiratory & Critical Care Medicine*.

"Nitrogen oxide (NO) species are markers for oxidative stress that may be pathogenic in acute lung injury (ALI)," write Dana E. McClintock, and colleagues from the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network. "We tested two hypotheses in patients with ALI: (1) higher levels of urine NO would be associated with worse clinical outcomes, and (2) ventilation with lower  $V_T$  would reduce urine NO as a result of less stretch injury."

The investigators measured urine NO levels by chemiluminescence in 566 patients enrolled in the NHLBI ARDS Network trial of 6 vs 12 mL/kg  $V_T$  ventilation. Findings were expressed both corrected and uncorrected for urine creatinine.

Multivariate analysis revealed that higher baseline levels of urine NO to creatinine were associated with lower death rate (odds ratio, 0.43 per  $\log_{10}$  increase in the ratio), more ventilator-free days (mean increase, 1.9 day), and more days free of organ failure (mean increase, 2.3 day;  $P < .05$  for all analyses). Using urine NO alone yielded similar findings. Compared with the 12 mL/kg  $V_T$  group, the 6-mL/kg group had higher NO to creatinine levels on day 3 ( $P = .04$ ).

"Contrary to our hypothesis, higher urine NO was associated with improved outcomes in ALI at baseline and after treatment with the 6 mL/kg  $V_T$  strategy," the authors write. "Higher endogenous NO may reflect less severe lung injury and better preservation of the pulmonary and systemic endothelium or may serve a protective function in patients with ALI."

Study limitations are inability to include all patients from the ARDS Network trial of lower  $V_T$  ventilation because urine samples were not collected in the last 235 of the 861 patients in the original trial; use of urine samples limits the ability to determine the source of measured NO; and possible effect of urinary tract infection on NO levels.

"Higher baseline urine NO levels are strongly associated with better clinical outcomes, including increased survival, more VFD [ventilator-free days, and more OFFD [days free of organ failure]," the authors conclude. "These associations remained significant even after controlling for potentially confounding factors.... Our findings suggest that (1) endogenous NO may be protective during ALI or (2) endogenous NO may serve as a marker of less severe organ injury or both."

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## Clinical Context

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ALI and the ARDS cause acute respiratory failure in critically ill patients. Markers of lung injury include nitrogen oxide species ( $\text{NO}_x$ ) and NO with animal studies showing higher  $\text{NO}_x$  levels in burns and smoke inhalation and other lung injuries with subsequent poorer clinical outcomes, while human studies have demonstrated worse outcomes in patients with higher levels of NO, suggesting greater oxidative injury in these patients.

This is a study of urinary NO and creatinine levels in patients included in the NHLBI ARDS Network study comparing outcomes of higher vs lower  $V_T$  ventilation (12 vs 6 mL/kg) and examine the ability of the urinary NO to predict clinical outcomes. The authors hypothesized based on previous studies that higher NO levels would be associated with poorer clinical outcomes in patients with ALI.

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## Study Highlights

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- 576 of 861 patients in the network had urine samples available for analysis and were included in this study.
- Risk factors predisposing to ALI (sepsis, pneumonia, aspiration, trauma, and other) were determined at study enrollment.
- Day 0 and day 3 urine samples were analyzed for creatinine and NO.
- The ratio of NO to creatinine was used in the analysis to control for urine dilution and analysis without correction was also performed.
- Mean age was 52 years, 60% were men, 75% were white, and 25% had sepsis as an ALI risk factor.
- 50% were in the 6-mL/kg ventilation group.
- For each  $\log_{10}$  increase in urine NO/creatinine, the risk for death on day 0 decreased by more than half (OR, 0.39; 95% CI, 0.27 - 0.57;  $P < .0001$ ).
- This effect persisted on day 3 when the OR was 0.47 for each  $\log_{10}$  increase in urine NO/creatinine (95% CI, 0.32 - 0.71;  $P = .0003$ ).
- Analysis of the NO value alone showed that the risk for death dropped to less than one third for each  $\log_{10}$  increase in urine NO.
- This association was significant on both day 0 and day 3 ( $P < .0001$  for both).
- Higher levels of urine NO/creatinine were associated with better outcomes, including more ventilator-free days and more organ-failure free days.
- On average for each  $\log_{10}$  increase in urine NO/creatinine at baseline, there were 3.6 fewer days of organ failure and 2.5 fewer days on the ventilator.
- This association was even stronger when only NO was considered.
- Higher urine NO/creatinine was associated with lower serum creatinine and younger age.

- Urine NO/creatinine levels showed no correlation with Acute Physiology and Chronic Health Evaluation III (APACHE III) score or baseline number of organ failures.
- Patients with sepsis as a primary risk factor for ALI had significantly higher levels of urine NO/creatinine ( $P = .0008$ ).
- When controlled for age, sex, glomerular filtration rate, APACHE III score, vasopressor use, and sepsis, higher urine NO was still independently predictive of lower mortality.
- For each  $\log_{10}$  increase in urine NO corrected or not corrected for urinary creatinine, the risk for death decreased by more than half.
- The OR for death when NO was corrected for creatinine was 0.43 per  $\log_{10}$  increase in urine NO/creatinine.
- The risk for death without correcting for creatinine was 0.33 per  $\log_{10}$  increase in urine NO.
- In the ARDS Network study, lower  $V_T$  reduced mortality.
- The NO/creatinine levels were higher in the 6-mL/kg than in the 12-mL/kg groups by day 3 ( $P = .05$ ) in this study.
- There was a significantly greater rise in urine NO/creatinine in the 6-mL/kg compared with the 12 mL/kg group from day 0 to day 3.
- Because these results contradict the authors' hypothesis that higher NO is associated with greater oxidative injury, the authors explained the current findings by postulating that endogenous NO has a beneficial effect on organs other than the lung during ALI or that higher NO levels are biologic markers of less severe injury.

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### Pearls for Practice

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- Higher urine NO with and without correction for creatinine is associated with better clinical outcomes in patients with ALI.
- The association between higher urine NO and better clinical outcomes is confirmed by analysis of patients on lower ventilation (6 vs 12 mL/kg) with better clinical outcomes.