The Journal of Emergency Medicine, Vol. 57, No. 2, pp. 177–180, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.03.028

Selected Topics: Toxicology

DOSE-DEPENDENT PULMONARY INJURY FOLLOWING NITROGEN DIOXIDE INHALATION FROM KINEPAK™ DETONATION

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☐ **Abstract—Background: Nitrogen dioxide (NO_2) is a pulmonary irritant produced as a byproduct of bacterial anaerobic metabolism of organic materials, and is also produced as a byproduct of explosive detonations. Significant NO_2 exposure results in free-radical–induced pulmonary injury that may be delayed up to 3–30 h after exposure and can progress to acute respiratory distress syndrome (ARDS) and death. Here we present a case series of 3 patients with dose-dependent pulmonary injury consistent with NO_2 inhalation following exposure to fumes from detonation of an ammonium nitrate/nitromethane (ANNM) explosive device. Case Reports: Three individuals presented to the emergency department over the course of 16 h, beginning approximately 16 h after exposure to fumes from an ANNM explosive device. Patient 1, with the most significant exposure, developed ARDS necessitating intubation and mechanical ventilation. Patient 2 exhibited hypoxia and findings concerning for diffuse airway inflammation, but ultimately required only supplemental oxygen. Patient 3, with the least exposure, had imaging abnormalities but required no intervention. Why Should an Emergency Physician Be Aware of This?: Respiratory distress is a common presenting complaint to the emergency department. Because of the delayed presentation and the potential for progressive worsening of symptoms associated with NO_2 exposure, it is important that emergency physicians be aware of the multiple potential means of exposure and consider this diagnosis in the proper clinical context. Patients with suspicion of NO_2-related lung injury should undergo more extended observation than their initial clinical presentation may suggest.** © 2019 Elsevier Inc. All rights reserved.

☐ **Keywords—nitrogen dioxide; silo filler's disease; NO_2; ammonium nitrate nitromethane; ANNM; ARDS; lung injury**

This case was presented as an abstract in poster form and as a lightning oral presentation at the North American Congress of Clinical Toxicology conference in October 2018 in Chicago, IL.

INTRODUCTION

Ammonium nitrate is a chemical compound commonly used as a fertilizer, and is also the major component of the most commonly used industrial explosives. Ammonium nitrate/fuel oil (ANFO) accounts for approximately 80% of industrial explosives in the United States (1). A similar compound, ammonium nitrate/nitromethane (ANNM), is a more powerful explosive used in demolition, such as the commercially available KinePak™, and has also been used in terrorist attacks, including the Oklahoma City bombing (2,3).

Nitrogen oxides, including nitrogen dioxide (NO_2), are produced in bacterial anaerobic metabolism of organic materials and are known byproducts of ANFO explosions (4–11). Commonly referred to as silo-filler's

RECEIVED: 31 December 2018; FINAL SUBMISSION RECEIVED: 6 March 2019;
ACCEPTED: 16 March 2019

disease, significant NO_2 exposure results in pulmonary injury by the production of free radicals and nitric acid, with resultant pulmonary edema and respiratory distress (4,6,12–14). Here, we present a case series of 3 patients with dose-dependent pulmonary injury following exposure to fumes from an ANNM explosive device used for demolition within a cave.

CASE REPORTS

Three patients who participated in the same spelunking expedition presented to the same urban, Level I trauma tertiary care emergency department (ED) over the course of 16 h. Approximately 16 h prior to arrival of the first patient, the trio descended into the cave and traveled 1.5 miles, partially submerged in water, to a planned excavation site. On arrival at the site, a KinePak™ binary explosive device was detonated as planned in order to open a new area of the cave to exploration. The spelunkers had permits for excavation and had performed similar excavations previously. Approximately 900 g net explosive quantity was used, comprising two full sticks of KinePak™, with 9 inches of 200 grain per foot detonating cord and a blasting cap, held together with duct tape. This was packed into a crack in the wall, with mud packed over it. A 100-foot electrical cord was used to provide adequate distance from the explosion. Following detonation of the device, the patients reported no "shockwave" or ear popping; however, they noted production of a cloud of heavy smoke and dust. Patient 1 was the closest to the explosion, became somewhat panicked in the presence of the dust cloud, and attempted to rapidly exit through the area of the explosion. Patient 2 was more distant from the explosion, but was able to sequester himself away from the dust cloud after a brief exposure, along with patient 3, who was the farthest away from the cloud. Patients 2 and 3 then waited for dissipation of the cloud prior to exiting the cave. Patient 3 did report some coughing with post-tussive emesis immediately after the exposure.

Patient 1

Patient 1 was an otherwise healthy 47-year-old male, with a medical history of hypertension who presented to the ED 12 h after the spelunking incident with progressively worsening dyspnea. On presentation, his vital signs were: blood pressure (BP) 112/52 mm Hg, heart rate 91 beats/min, respiratory rate (RR) 31 breaths/min, SpO_2 71% on room air (RA). On examination, he was in moderate respiratory distress with accessory muscle use. Crackles were heard in all lung fields bilaterally. He had no external signs of trauma. His chest x-ray (CXR) study showed diffuse bilateral nodular infiltrates (Figure 1A). A computed tomography (CT) of the chest was significant for extensive bilateral ground-glass infiltrates, consistent with acute respiratory distress syndrome (ARDS) (Figure 1B). Laboratory studies were notable for a white blood cell count of 16,000/mm^3, sodium of 128 mEq/L, and a lactate of 3 mmol/L. A venous blood gas on an FiO_2 of 1.0 demonstrated a pH of 7.32, pCO_2 of 42 and pO_2 of 30. The case was discussed with toxicology, and blood methemoglobin and carboxyhemoglobin concentrations were obtained; these were 0.6% (reference range 0.4–1.5%) and 4%, respectively.

Despite bilevel positive pressure ventilation, the patient continued to be hypoxic and thus was intubated in the ED. Shortly after intubation and sedation with propofol, the patient became hypotensive, requiring a norepinephrine infusion at 0.025 μg/kg/min to maintain a mean arterial pressure of 65 mm Hg. Intravenous methylprednisolone 125 mg and levofloxacin 750 mg were administered for inhalational lung injury and possible infection. On hospital day (HD) 4, he became febrile (maximum temperature 102.2°F) with diarrhea, and

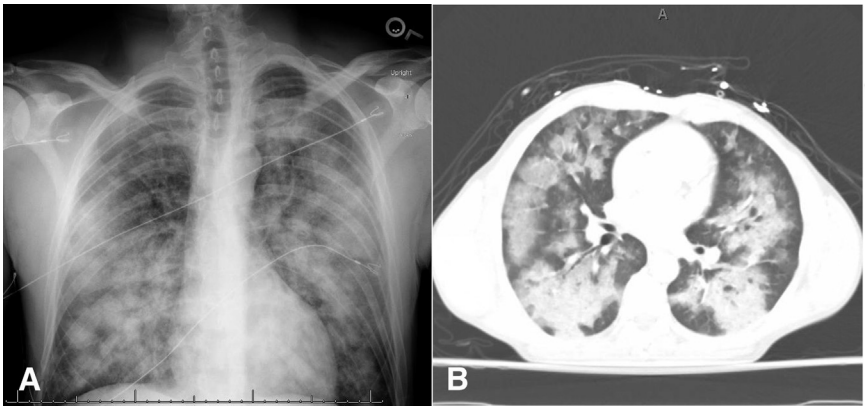

Figure 1. (A) Chest x-ray study with diffuse bilateral nodular infiltrates and (B) axial computed tomography image with extensive bilateral ground-glass opacities, consistent with acute respiratory distress syndrome.

tested positive for *Clostridium difficile*. He was successfully extubated on HD5, norepinephrine was weaned on HD5, and he was discharged on HD6. Urine *Histoplasma* antigen was negative.

Patient 2

Patient 2 was a previously healthy, 30-year-old, nonsmoking male who presented to the ED with shortness of breath approximately 14 h after the same incident noted above. He explained that he was initially feeling well, and came to visit patient 1 in the intensive care unit (ICU). ICU staff noted the patient appeared dyspneic, and the patient was encouraged to go to the ED.

On arrival to the ED, the patient's vital signs were BP 141/74 mm Hg, HR 104 beats/min, RR 18 breaths/min, and SpO_2 83%. He was placed on 100% oxygen by nonrebreather mask at 10 L/min with improvement in his oxygen saturation to 96%. On examination, he had clear breath sounds bilaterally and showed no external signs of trauma.

A brief cardiac ultrasound demonstrated numerous B-lines in bilateral lung apices (Figure 2A), suggestive of pulmonary edema. A CXR study showed diffuse bilateral infiltrates (Figure 2B), and CT chest (Figure 2C) showed extensive mixed opacities with a centrilobular and basilar predominance concerning for ARDS. Laboratory studies were notable for an arterial blood gas with PaO_2 79 mm Hg. Methemoglobin level was 1.5%; carboxyhemoglobin was not obtained.

The patient was admitted to the ICU and was weaned down to 3 L of supplemental oxygen over the next 24 h. The following day he became febrile (T_{max} 39.0°C), and was treated empirically with levofloxacin, though his fever was thought to be more likely secondary to a systemic inflammatory response than from infection. Blood and sputum cultures, including fungal sputum culture, returned negative and a urine *Histoplasma* antigen was negative. He was discharged home on HD3.

Patient 3

Patient 3 was an otherwise healthy 22-year-old female, who presented to the ED approximately 28 h after the spelunking incident with symptoms of dizziness and mild dyspnea. Her initial vital signs were BP 127/67 mm Hg, HR 110 beats/min, RR 20 breaths/min, SpO_2 100% on RA. On examination, she was noted to be tearful and anxious but in no acute respiratory distress. Her respiratory and cardiac examinations were normal and she had no external signs of trauma. Her CXR study showed subtle ground glass opacities bilaterally (left greater than right), concerning for early ARDS (Figure 3). Methemoglobin was 1.8% and carboxyhemoglobin was 2%. Given the clinical condition of her companions, she was admitted for observation. She remained stable without further complications. By the following afternoon her symptoms were resolved, and she was discharged home.

DISCUSSION

Nitrogen dioxide is a rust-brown, heavier-than-air gas with a "chlorine-like" odor (9,12,15). It has been most well described in silo-filler's disease, where anaerobic metabolism of fresh silage produces nitrogen oxides, including NO_2 (4–6). It is also a known explosive byproduct of commercially available explosives, such as ANNM (7–11). The mechanism of nitrogen oxide production in ANNM is likely similar to other high-energy events. Oxygen and nitrogen react in the presence of a sufficiently exothermic reaction. At the same time, oxygen in the air is used as an oxidant when an ANNM device is detonated, resulting in incomplete combustion of materials and production of nitrogen oxides, including NO_2 (7).

Because it is minimally soluble in water, NO_2 primarily distributes into the distal airways, though upper airway irritation may be evident in significant exposures

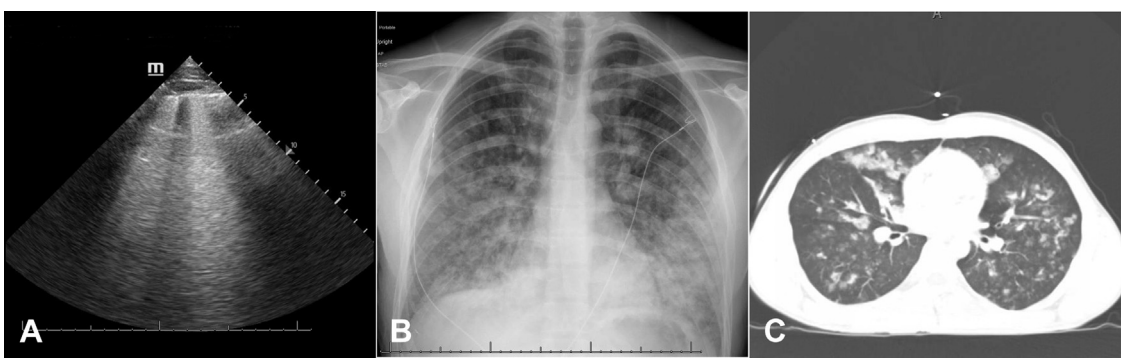

Figure 2. (A) Thoracic ultrasound image demonstrating copious B lines consistent with pulmonary edema. (B) Chest x-ray study with diffuse infiltrates and (C) computed tomography axial image with extensive mixed opacities with centrilobular predominance concerning for acute respiratory distress syndrome.

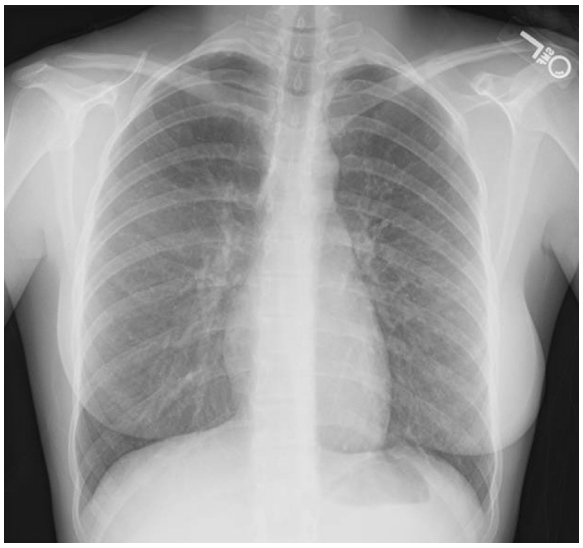

Figure 3. Chest x-ray study with subtle ground glass opacities bilaterally, concerning for early acute respiratory distress syndrome.

(12). In the lungs, NO_2 slowly reacts with water to form nitric and nitrous acid, with resultant alveolar inflammation (12,13,16,17). It also acts as a direct oxidant with resultant free-radical injury (13,18). Distal airway and alveolar inflammation may be delayed 3–30 h after exposure, producing pulmonary edema and ARDS (15). In surviving patients, bronchiolitis obliterans organizing pneumonia can be a late complication of NO_2 exposure, presenting more than 28 days later (6,19).

While clinical effects of NO_2 exposure after ANNM explosive detonation have not been described previously, our patients all had symptoms typical of NO_2 exposure, including delayed development of diffuse, distal airway inflammation. Patients 1 and 2, who had the most extensive exposure, went on to develop ARDS as a result of their exposure. In our patients, other etiologies for lung injury, including blast injury and infection, were considered and determined to be unlikely. Primary blast injury was felt to be unlikely due to the lack of pressure wave sensation from the patients, delayed onset of symptoms, lack of typical imaging findings, and hemoptysis. Infection, including fungal exposure, was less likely given the rapidity of symptom onset and lack of systemic symptoms. Histoplasmosis was considered in patients 1 and 2, however, *Histoplasma* antigen was negative in both.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Respiratory distress is a common presenting complaint to the ED with a broad differential diagnosis. NO_2 exposure can have an atypical presentation with delayed development of respiratory failure in otherwise healthy individuals, and therefore require extended monitoring even in the setting of initial stability. It is therefore important for emergency physicians to be aware of the different means of NO_2 exposure and to consider it as a cause of respiratory distress in the proper clinical context.

REFERENCES

1. Green EM. Explosives regulation in the USA. Ind Mater 2006;465:78–9.
2. KINEPAK. KINEPAK Liquid Component A (Nitromethane). Lewisville, TX: KINEPAK, Inc; 1986.
3. U.S. v. McVeigh, 153 F.3d 1166 (10th Cir. 1998).
4. Lowry T, Schuman L. "Silo-filler's disease"—a syndrome cause by nitrogen dioxide. J Am Med Assoc 1956;162:153–60.
5. Gailitis J, Burns L, Nally J. Silo-fillers disease. N Engl J Med 1958;258:543–4.
6. Cornelius EA, Betlach EH. Silo-filler's disease. Radiology 1960;74:232–8.
7. Mainiero RJ, Rowland JH III, Harris ML, Sapko MJ. Behavior of nitrogen oxides in the product gases from explosive detonations. Available at: https://www.cdc.gov/niosh/mining/UserFiles/works/pdfs/bonoi.pdf. Accessed: 27 March 2018.
8. Sapko M, Rowland J, Mainiero R, Zlochower I. Chemical and physical factors that influence NOx production during blasting—exploratory study. Proc Annu Conf Explos Blasting Tech 2002;2:317–30. Available at: http://www.cdc.gov/niosh/mining/UserFiles/works/pdfs/capft.pdf. Accessed: 27 March 2018.
9. Mainiero RJ, Harris ML, Rowland JH. Dangers of toxic fumes from blasting. Proc Annu Conf Explos Blasting Tech 2007;33:73.
10. Mainiero R. A technique for measuring toxic gases produced by blasting agents. Proc Annu Conf Explos 1997;23:1–10. Available at: https://www.cdc.gov/niosh/mining/UserFiles/works/pdfs/tfmt.pdf. Accessed: 27 March 2018.
11. Department of Employment, Economic Development, Innovation (DEEDI). Queensland Guidance Note—Management of Oxides of Nitrogen in open Cut Blasting. Queensland, Australia: DEEDI; 2011:95.
12. Sullivan J, Krieger G. Oxides of nitrogen and sulfur, Clinical Environmental Health and Toxic Exposures. 2nd ed. Lippincott Williams & Wilkins; 2001:818–32.
13. Mirowsky JE, Dailey LA, Devlin RB. Differential expression of pro-inflammatory and oxidative stress mediators induced by nitrogen dioxide and ozone in primary human bronchial epithelial cells. Inhal Toxicol 2016;28:374–82.
14. Elsayed NM. Toxicity of nitrogen dioxide: an introduction. Toxicology 1994;89:161–74.
15. Robinson DM, Yu ML, Prakash UBS. 60-Year-old man with respiratory distress and confusion. Mayo Clin Proc 1996;71:813–6.
16. Murphy CM, Akbarnia H, Rose SR. Fatal pulmonary edema after acute occupational exposure to nitric acid. J Emerg Med 2010;39:39–43.
17. Ayyagari VN, Januszkiewicz A, Nath J. Pro-inflammatory responses of human bronchial epithelial cells to acute nitrogen dioxide exposure. Toxicology 2004;197:149–64.
18. O'Donnell VB, Eiserich JP, Chumley PH, et al. Nitration of unsaturated fatty acids by nitric oxide-derived reactive nitrogen species peroxynitrite, nitrous acid, nitrogen dioxide, and nitronium ion. Chem Res Toxicol 1999;12:83–92.
19. Lee LT, Ho CHB, Putti TC. Bronchiolitis obliterans organizing pneumonia following nitric acid fume exposure. Occup Med (Lond) 2014;64:136–8.