Three 21-week-old sexually intact female domestic shorthair cats were brought to the after-hours emergency service of the Veterinary Medical Center, Western College of Veterinary Medicine, because of sudden respiratory distress. The cats were littermates and had no prior history of disease. They had been adopted at 8 weeks of age and were up-to-date on all vaccinations. All 3 cats had been left confined in a room for the day (approx 10 hours), with food and water. When the owner returned home in the evening, the cats appeared lethargic, with difficulty standing up, and were visibly tachypneic. The room in which the cats had been confined was approximately 50 square feet in area. An ozone-generating air purifier was present and operating as set for an 1,800- to 3,500-square-foot room. The 3 cats had never been left confined in this room prior to this event.

One cat (cat 1) appeared more severely affected than the others and was brought in first to the emergency center. Two hours later, the respiratory signs worsened in the other 2 cats (cats 2 and 3), so they were brought for evaluation as well.

On initial evaluation, cat 1 (body weight, 2.5 kg [5.5 lb]; body condition score, 3/5) was minimally responsive. Heart rate (150 beats/min; reference interval, 150 to 220 beats/min) and rectal temperature (38.4°C [101.1°F]; reference interval, 37.8° to 39.5°C [100.0° to 103.1°F]) were unremarkable, but respiratory rate was markedly high (80 breaths/min; reference interval, 16 to 40 breaths/min). Mucous membranes were pale, pink, and slightly tacky, and capillary refill time was < 2 seconds. No heart murmur, gallop sounds, or arrhythmias were detected on cardiac auscultation, and peripheral pulses were strong and synchronous. However, crackles were auscultated over both lung fields. Abdominal palpation revealed no abnormalities, and no lymphadenomegaly was evident.

Cats 2 and 3 were similar to cat 1 (respective body weights, 2.2 and 2.5 kg [4.8 and 5.5 lb]), with respective respiratory rates of 72 and 80 breaths/min and an unremarkable heart rate and rectal temperature. Mucous membranes were tacky, and pulmonary crackles were audible over both hemithoraces.

No burn marks consistent with electrocution from chewing on an electric cable were visible on
oral examination of any cat, and the owner reported finding no evidence of any damaged electrical cords in the room where the cats were confined. According to the owner, there were no other possible toxicants or hazards in that room, such as chemicals, medications, cosmetics, or other electric devices, that the cats could have been exposed to.

Following physical examination of cat 1, an IV catheter was placed, and a blood sample was collected for emergency assessment tests that included PCV, blood total protein concentration as measured via refractometer, blood glucose concentration as measured via glucometer, and BUN concentration as estimated via a test strip. Results for these tests were within reference intervals, except for BUN concentration, which was mildly high (16 to 25 mmol/L; reference interval, 5 to 15 mmol/L). Three-view (ventrodorsal and left and right lateral) thoracic radiographs were obtained and interpreted by a board-certified veterinary radiologist (GSS), revealing a marked, diffuse increase in pulmonary soft tissue opacity, characterized by a marked, peribronchial, unstructured interstitial pulmonary pattern that coalesced to a patchy alveolar pattern (Figure 1). Findings were deemed most suggestive of airway inflammation (eg, bronchitis or pneumonitis) with concurrent pulmonary edema of noncardiogenic origin. Because of the concern for CPE, the cat was treated with furosemide (2 mg/kg [0.9 mg/lb], IV) and placed in an oxygen cage providing 80% oxygen. Similarly, because of the concern for asthma crisis, terbutaline sulfate was also administered (0.01 mg/kg [0.005 mg/lb], IM).

The same procedures were performed for cats 2 and 3, and of the emergency assessment tests performed, only results for BUN concentration were abnormal (16 to 25 mmol/L). Three-view thoracic radiography revealed a moderate to marked unstructured interstitial pattern coalescing to a marked alveolar pulmonary pattern in the peripheral lung lobes, causing effacement of portions of the border of the cardiac silhouette, vascular margins (including the caudal vena cava), and diaphragm. Compared with findings for cat 1, the pulmonary pattern for cats 2 and 3 had a patchier appearance, with the more prominent changes located within the periphery of the caudal lung lobes. A milder bronchial pulmonary pattern was noted. Inflammatory airway disease with concurrent NCPE was considered the primary differential diagnosis. Cats 2 and 3 were provided the same treatments as cat 1 and were placed in the same oxygen cage with their littermate.

Over the next 8 hours in the oxygen cage, cats 2 and 3 had a return of respiratory rate to within the reference interval, whereas cat 1 had a decrease to 50 breaths/min. All 3 cats at this point had signs of considerable improvement in the respiratory effort. Pulmonary crackles were no longer audible in cats 2 and 3 and had substantially improved in cat 1. Radiography was repeated for cat 1, revealing no noticeable improvement (Figure 2).
After the cats had spent 24 hours in the oxygen cage at 80% oxygen saturation, respiratory rates and thoracic auscultation findings were unremarkable for all 3 cats. The oxygen concentration was then progressively decreased by increments of 10% every 2 hours until the cats were breathing room air. With room air, respiratory rates remained unremarkable, and all 3 cats appeared able to breathe normally. Pulse oximetry measurement was attempted multiple times, but none of the cats allowed this. Because of concerns for worsening of the respiratory distress during blood sample collection, no arterial blood gas analysis was attempted for any cat. No echocardiography was performed because of the unavailability of the veterinary cardiologist at the time, and no cardiac biomarker measurement was performed owing to financial concerns of the owner.

Three days after initial evaluation, the 3 cats continued to have unremarkable respiratory rates and no audible crackles or wheezes on thoracic auscultation. Three-view thoracic radiography was repeated for all 3 cats, revealing almost complete resolution of the previously noted abnormalities, with only a residual minimal ventral interstitial pattern persisting on the right lateral view (Figure 3). The cardiac silhouette and associated peripheral pulmonary vessels appeared unremarkable, as did the pleural space and mediastinum. All 3 cats were discharged from the hospital at this time. The high BUN concentrations at initial evaluation were believed to be likely attributable to dehydration, and because the 3 cats were in good clinical condition with noteworthy improvement of the radiographic lesions, this analyte was not reevaluated prior to discharge.

The owner stated that the 3 cats began to behave normally as soon as they returned home. On recheck examination 3 months after the episode, findings for all 3 cats were unremarkable. Follow-up thoracic radiography was performed, and findings were unremarkable as well.

**Discussion**

This case report describes the simultaneous development of severe dyspnea with ozone exposure in 3 kittens cohoused in a closed room. The observed clinical and radiographic signs were strongly suspected to be secondary to NCPE. The term NCPE is used for any instance of pulmonary edema that is not the direct result of cardiac disease. Noncardiogenic CPE can result either from an increase in vascular endothelial permeability caused by direct or indirect injury to the alveolar-capillary membranes or from a local increase in the pulmonary transcapillary hydrostatic pressure without an increase in left atrial pressure. The disruption of gap junctions between cells of the epithelial and endothelial membranes results in exudation of protein-rich fluid, causing pulmonary edema. Radiographically, NCPE is characterized by a pulmonary interstitial, alveolar, or interstitial to alveolar pulmonary pattern. The distribution of these lesions within the lungs varies; however, the caudal dorsal lung lobes are preferentially affected. Noncardiogenic CPE is generally associated with a symmetric lesion pattern, but lesions may be more prominent on the right side. An unremarkable size and shape of the cardiac silhouette (with an unremarkable or low vertebral heart score) are typical, as is a normally appearing or smaller than usual vasculature suggestive of normovolemia or hypovolemia. Other than NCPE, the main differential diagnoses given these findings would be CPE and primary inflammatory or infectious diseases.
Cardiogenic pulmonary edema could not be definitively ruled out for the cats of the present report for several reasons. No continuous ECG was performed, and therefore, intermittent arrhythmias could have been missed. In addition, radiographic signs of cardiac failure in kittens have not been well described, and cardiomyopathy without cardiomegaly could be missed. No echocardiography was performed to assess cardiac structures and function. Furthermore, no measurements of cardiac biomarkers were performed; however, the age of the cats and their concurrent disease would have made biomarker interpretation difficult. Nevertheless, CPE was deemed highly unlikely owing to the lack of suggestive clinical signs (e.g., tachycardia or audible heart murmur or gallop rhythm on auscultation), the simultaneous rapid development of the pulmonary signs in all 3 cats, and the rapid resolution of the pulmonary edema without the need for long-term diuretic administration or other cardiac treatments. Moreover, the unremarkable size of the heart, absence of pulmonary venous congestion, and distribution of the pulmonary edema on thoracic radiographs also supported a diagnosis of NCPE rather than CPE.

Collection of airway samples by tracheal wash, bronchoalveolar lavage, or lung biopsy would have been helpful to rule out infectious or primary inflammatory causes for the pulmonary lesions in the cats of the present report and to characterize findings associated with ozone toxicity. Such sample collection was deemed too risky in early management of these patients and in the end proved unnecessary because the cats were responding to treatment and ultimately made a full recovery. Because of financial concerns and the rapid clinical improvement observed, the cats’ owner declined more thorough diagnostic investigations, including a CBC, fecal parasite analysis, or serum testing for antibody against lung worms or Toxoplasma gondii. Without those results, we could not completely rule out primary inflammatory or infectious causes for the observed respiratory signs and radiographic changes. However, such causes appeared highly unlikely given the rapid and complete resolution of the respiratory signs without administration of anti-inflammatory or antimicrobial medications. As a result, NCPE was considered the most likely diagnosis. Most of the well-recognized causes of NCPE in veterinary patients, including head trauma, electric shock, smoke inhalation, near drowning, or upper airway obstruction,28 were also ruled out as a cause on the basis of history and lack of supportive physical findings.

Ozone (O₃) is a molecule consisting of 3 oxygen atoms. In the upper atmosphere, it plays a critical role in filtering out potentially damaging UV light; however, in the lower atmosphere, ozone is an air pollutant capable of causing harmful effects to the respiratory system of humans and other animals at concentrations as low as 0.12 mg/m³ (0.06 ppm).38 Ozone is a strong oxidizing agent that can induce direct and indirect damage to pulmonary alveolar and endothelial membranes, leading to an increase in vascular permeability, pulmonary inflammation, and airway hyperresponsiveness.30

The formation of ROS can permanently damage unsaturated fatty acids in cell membranes and surfactant fluid (lipid peroxidation) as well as cause damage to DNA and proteins, altering gene and protein expression and leading to activation or inactivation of specific enzymes and proteins. This ultimately may lead to cell death through triggering of apoptosis. Ozone-induced lipid peroxidation activates eicosanoid metabolism, giving rise to the formation of highly reactive peroxides, which further contribute to oxidative stress and damage. The ROS lead to inactivation of surfactant proteins, which reduces the ability of the surfactant film to reduce lung surface tension during breathing, which can further contribute to respiratory distress. Oxidative modification of surfactant proteins may also render the lungs more susceptible to lipid peroxidation, inflammation, and oxidative damage because these proteins have been reported to inhibit these processes. The resulting pulmonary damage from ozone leads to recruitment of inflammatory cells, mostly macrophages and polymorphonuclear leukocytes, into the lungs. These cells release proinflammatory mediators, such as tumor necrosis factor-α and interleukin-13 as well as their own ROS, including superoxide and hydrogen peroxide, which further enhance inflammation,11 contribute to tissue injury,12 and increase pulmonary epithelial and endothelial permeability.

Airway responsiveness has also been shown to increase markedly after acute exposure to ozone in dogs.13 Such hyperresponsiveness is a state characterized by easily triggered bronchospasm (contraction of the bronchioles or small airways), which is a characteristic feature of asthma in humans and can increase with ROS injury to the lungs.10 Ozone can also contribute to exacerbation of asthma in humans and animals with experimentally induced disease through the development of airway hyperresponsiveness,8 and humans with asthma have greater sensitivity to ozone than those without asthma.14 It was possible that airway hyperresponsiveness played a role in the respiratory distress in the 3 cats of the present report. Given the similarities between feline and human asthma, asthmatic cats could be predisposed to ozone sensitivity as suggested for humans. However, given the young age of the 3 cats, a preexisting asthmatic condition appeared unlikely.

Ozone toxicity in rats and dogs can result from acute or chronic ozone exposure. In rats, pulmonary inflammation can be induced as soon as 4 hours after exposure to ozone at 3.53 mg/m³ (1.8 ppm) and with acute exposure to concentrations as low as 0.2 mg/m³ (0.1 ppm).15,16 In dogs, exposure to ozone of lobar segments at 1.96 mg/m³ (1 ppm) for a brief period (5 minutes) produces a recognizable inflammatory response.17 It was impossible to know the exact concentration of ozone to which the 3 cats were exposed.
in the room where they were confined. However, an ozone-producing air purifier similar to the one used in this instance, when set to cover 2,500 square feet, is reportedly able to produce an ozone concentration up to 2.53 mg/m³ (1.287 ppm) 2 inches from the machine and 1.11 mg/m³ (0.567 ppm) 24 inches from the machine.18 When tested in an 88-square-foot room, the ozone concentration produced by that model reached 0.17 mg/m³ (0.089 ppm) at a setting of 1,000 square feet.18 The FDA room air standard indicates a maximum safe ozone concentration of 0.098 mg/m³ (0.05 ppm). The surface area of the room of the present report was approximately 50 square feet; hence, the ozone concentration likely exceeded the recognized toxic dose for dogs, rats, or humans, even though the air exchange rate was unknown.

Sensitivity to ozone toxicosis is known to differ greatly on the basis of several factors, including species, age, sex, genetics, and preexistence of pulmonary disease. Rats are more sensitive than rabbits, humans are more sensitive than rats, and young rats are more sensitive than adult rats.9,20 Ozone toxicosis can also be enhanced in humans and rats by exercise.21,22 Even though it would be logical to presume that kittens may be more susceptible to ozone toxicosis than adult cats, to the authors’ knowledge, no data have been reported on this subject. Mechanisms of ozone injury to lungs have been elucidated in other species, and one could reasonably presume that ozone has the potential to cause NCPE in cats as in other species. The combination of increased epithelial and endothelial permeability leading to pulmonary edema and inflammation induced by ozone is consistent with the radiographic lesions observed in the cats of the present report.

The long-term consequences to the cats from this acute ozone exposure remain unknown. However, in young Beagles with 6 weeks of exposure to ozone, no significant alterations in pulmonary function were identified.23 Given these findings and the rapid and complete resolution of the clinical and radiographic abnormalities in the cats, long-term consequences were deemed unlikely but could not be ruled out.

Treatment for NCPE is largely supportive in nature.2 Elimination of the initiating cause or causes and treatment of any comorbidities while maintaining hemodynamic stability are important. Oxygen supplementation, with the goal of maintaining oxygen saturation as measured by pulse oximetry > 93% and Pao₂ > 60 mm Hg, may be necessary for patient survival. Mechanical ventilation is indicated when prolonged refractory hypoxemia (Pao₂ ≤ 60 mm Hg) exists despite oxygen supplementation. Conservative IV fluid administration (providing a fluid intake equivalent to fluid output) and judicious furosemide administration (when indicated) are recommended but require intensive monitoring because overzealous IV fluid treatment can exacerbate NCPE. Diuretic treatment is typically not effective but can be used to promote bronchodilation in veterinary patients with NCPE.2 Oxygen supplementation, bronchodilator and diuretic treatment, and time appeared adequate to resolve the respiratory signs in the 3 cats of the present report.

Few inhalant intoxications have been reported for client-owned companion animals, and most reports7,24 involve dogs. For example, severe respiratory distress has been reported for 2 small dogs following inhalation of carbon waterproofing spray.24 Both of those dogs had a diffuse interstitial pattern on thoracic radiographs, similar to that identified in the cats of the present report. Both dogs required 1 week of hospitalization and supportive treatment but finally recovered fully. A similar situation has been reported for 2 cats exposed to a footwear-proofing aerosol.25 Respiratory signs in those 2 cats were first noted 12 hours after exposure and resolved after 5 days of supportive treatment. Thoracic radiographic findings were unremarkable in one cat, and the other had signs of pneumomediastinum. These previous findings25 differ from those for the 3 cats of the present report and might suggest different pathophysiological mechanisms between hydrocarbon and ozone toxicosis or could reflect differences among cats in the response to inhalant toxicants. Interestingly, all 3 cats eventually recovered fully, suggesting that the prognosis for certain inhalant intoxications can be good once the acute phase has passed. However, severe pulmonary hemorrhage has been reported for 2 cats after exposure to a black mold toxin,26 both of which died of the pulmonary injury (one 10 days after exposure).

To our knowledge, respiratory distress associated with acute ozone exposure has not been reported for cats, but such exposure reportedly causes airway hyperresponsiveness and pulmonary inflammation in animals in experimental settings.11-13,15,21,25 The combination of sudden, simultaneous onset of dyspnea in the 3 previously healthy cats of the present report, radiographic evidence suggestive of NCPE, and rapid resolution of clinical and radiographic signs with conservative supportive care provided a strong argument in favor of a diagnosis of ozone-induced pulmonary toxicosis. More importantly, the inappropriate settings of the ozone air purifier used in a small room suggested that a toxic ozone concentration could have been reached in this scenario. Therefore, we believe ozone toxicosis was the most likely cause of the observed respiratory lesions and that ozone exposure should be considered a risk factor for NCPE in companion animals, including cats.

Footnotes

a. Fresh Air LA-3500 v2.0 Living Lightning Alpine air purifier, Alpine Air Technologies, Santa Ana, Calif.
b. Azostick reagent strips, Siemens Health Care Diagnostics Inc, Tarrytown, NY.
c. Salix 5%, Merck Animal Health, Kirkland, QC, Canada.
d. Chiron, Guelph, ON, Canada.
e. Alpine Air XL-12/ LA Lightning Air RA 2500, Alpine Air Technologies, Santa Ana, Calif.
References


New Veterinary Biologic Products

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<tr>
<th>Product name</th>
<th>Species and indications for use</th>
<th>Route of administration</th>
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<tr>
<td>Staphylococcus Aureus Bacterin (HIPRA USA, LLC, Lincoln, Neb, US Vet Permit No. 449A)</td>
<td>This product has been shown to be effective for vaccination of healthy goats 28 weeks of age or older against mastitis caused by Staphylococcus aureus. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov</td>
<td>IM</td>
<td>USDA permit 9/14/18</td>
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