Acid aspiration increases sensitivity to increased ambient oxygen concentrations

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Knight, Paul R., Carlos Kurek, Bruce A. Davidson, Nader D. Nader, Alka Patel, June Sokolowski, R. H. Notter, and Bruce A. Holm. Acid aspiration increases sensitivity to increased ambient oxygen concentrations. Am J Physiol Lung Cell Mol Physiol 278: L1240–L1247, 2000.—Previously we have demonstrated that prolonged exposure to 100% ambient oxygen leads to a marked loss in functional lung volume and lung compliance, hypoxemia, and surfactant system abnormalities similar to acute respiratory distress syndrome (ARDS). However, 50% oxygen administration is believed to be safe in most clinical settings. In the present study, we have evaluated the effects of a 24-h exposure to 50% oxygen in rabbits immediately following experimental gastric acid aspiration. Mild hypoxemia, but no changes in mortality, lung volume, lung compliance, surfactant metabolism, or edema formation occurred after 24 h of normoxia postacid aspiration. Conversely, a relatively short (24-h) exposure to 50% oxygen after acid aspiration results in increased pulmonary edema, physical signs of respiratory distress, and mortality, as well as decreased arterial oxygenation, lung volume, lung compliance, and type II alveolar cell surfactant synthesis. These results suggest that acid aspiration alters the “set point” for oxygen toxicity, possibly by “priming” cells through activation of inflammatory pathways. This pathogenic mechanism may contribute to the progression of aspiration pneumonia and ARDS.

Acid aspiration pneumonia; acute respiratory distress syndrome; oxidant stress

Acute respiratory distress syndrome (ARDS) is a severe progressive inflammatory disease that is associated with several distinct pathophysiological insults (risk factors) that by themselves may only produce mild to moderate acute pulmonary dysfunction. Mechanisms by which these acute processes develop into a more severe sustained progressive inflammatory lung injury, such as ARDS, have not been well defined, although the presence of more than one major risk factor facilitates this process. In this regard, the role of increased ambient oxygen in the pathogenesis of ARDS is controversial. However, it is currently accepted practice to keep inspired concentrations as low as possible when providing oxygen therapy in order to avoid any possible toxicity.

Aspiration of gastric contents is a frequent occurrence in the unconscious patient, occurring in approximately 1 of 2,131–3,216 anesthetized patients (29, 41). Additionally, “silent” aspiration can be indicted in the etiology of a number of unexplained cases of postoperative pulmonary dysfunction. Aspiration of gastric contents may result in a range of lung injuries, from a very mild, subclinical pneumonitis to a more severe, progressive disease with associated morbidity and high mortality. Oxygen therapy is the mainstay of therapy, and development of severe refractory hypoxemia can lead to treatment with high inspired concentrations. Gastric aspiration is a major risk factor in the development of ARDS. Approximately one-third of the patients with acute aspiration pneumonitis will develop a more severe, protracted course with complications (11, 30, 38). The progression of aspiration pneumonitis into ARDS carries a very high mortality and accounts for up to 20% of all deaths attributable to anesthesia (1, 3, 12, 18). Therefore, the development of strategies to decrease the severity of this form of lung injury once it has occurred is important in lessening the morbidity and mortality associated with this perioperative event.

Work from our laboratory has demonstrated that a mild, acid-induced lung injury can be greatly enhanced by secondary iatrogenic and/or phlogistic insults. For example, the additional presence of gastric particulate material and/or exposure to ~100% ambient oxygen for as little as 2 h can lead to large increases in protein leakage across the alveolar capillary border (17, 25). These studies also suggested that there may be a dose response between ambient oxygen concentrations and the extent of pulmonary damage.

Previous studies with models without any underlying inflammatory lung injury demonstrated that animals must be exposed to 100% oxygen for ~64 h to show acute respiratory distress. The respiratory distress caused by long-term hyperoxia is characterized by loss of lung volume, decreased lung compliance, edema formation, and acute hypoxemia (19). These changes appear to be related in part to surfactant abnormalities secondary to type II pneumocyte dysfunction (14). Conversely, exposure to 60% oxygen for as long as 3 wk results in only minimal respiratory distress and a stimulation of the surfactant system (15).

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In the current study, we have evaluated the effects of a 24-h exposure to 50% oxygen on adult rabbits following intrapulmonary instillation of low pH saline-HCl (pH 1.25) to simulate acid aspiration. Administration of this oxygen concentration is generally believed to be safe in most clinical situations. However, based on previous findings, we have hypothesized that acid aspiration-induced priming changes the set point for oxygen toxicity, thereby converting exposure to a normally benign oxygen concentration (50%) to a toxic insult. The findings from this study have important implications in the clinical management of patients following gastric aspiration.

**METHODS**

The Institutional Review Committee of Laboratory Animal Use and Care at the State University of New York at Buffalo approved the experimental protocols used in this study.

Animal model. Adult New Zealand White rabbits weighing ~2 kg were utilized for these studies. Food and water were provided ad libitum. Animals were divided into four groups. Animals from the first group (control) received no interventions and were exposed to air and observed for 24 h. The second group of rabbits (hyperoxia) received no interventions and was exposed to an ambient oxygen concentration of 50% for 24 h. The remaining two groups underwent intrapulmonary administration of a low pH insult. One group (acid) was left in air for 24 h, and the final group (acid/hyperoxia) was exposed to an environment of 50% oxygen for 24 h.

To simulate acid aspiration, rabbits were induced with 30 mg/kg ketamine intramuscularly, and anesthesia was supported with 2% isoflurane in air via a nose cone. The animals maintained spontaneous ventilation throughout the procedure. With the rabbit in a 60% upright position, 2.4 ml/kg of HCl-saline, pH 1.25, was injected directly into the lungs (intratraehally) through a percutaneously placed 18-gauge catheter. Previously, we demonstrated that instillation of normal saline at this volume causes minimal lung injury and does not sensitize the lung to short-term hyperoxic injury (25). After instillation of the aspirate into the lungs, the trachea and skin were repaired with 6-0 nylon and 4-0 silk, respectively. Animals were then exposed to air or to a 50% oxygen mixture and remained in that environment for a total of 24 h.

Exposures to room air or 50% oxygen in air were performed in a Plexiglas chamber, as previously described by Holm et al. (15). Oxygen levels were verified using a Rascal II Raman light-scattering spectrophotometer (Ohmeda; Salt Lake City, UT). Pilot studies (data not shown) demonstrated that respiratory status of the animals predictably deteriorated rapidly at ~23–24 h of hyperoxia. During the 24-h gas exposure period, the rabbits were observed repeatedly for the severity of physical signs of respiratory distress (tachypnea, ruffled fur, nasal cyanosis, decreased grooming behavior, and decreased appetite). If any animal was judged to be in extremis, it was immediately euthanized to relieve pain. These rabbits were considered a mortality. Although we assessed the lung injury in these animals, only rabbits that survived 24 h were considered for detailed analysis.

Assessment of lung injury. After 24 h of observation, the rabbits were placed in 100% oxygen for 15 min and blood samples (1 ml) were obtained from an auricular artery using a 1-ml heparinized syringe with a 22-gauge needle. The arterial sample was assessed for partial pressure of arterial oxygen with a blood gas analyzer (ABL4, Radiometer America; Westlake, OH). The oxygen extraction ratio, arterial oxygen partial pressure to inspired oxygen fraction (Pao2/Fio2), was calculated as a measure of alveolar gas-exchange efficiency. The animals were then killed using an overdose of pentobarbital sodium (0.8 ml of 390 mg/ml), and closed-chest pulmonary pressure-volume (static lung compliance) was measured by inflating and deflating the lungs. A catheter (3-mm OD, 4.3-mm OD) was inserted into the trachea in situ through a midline incision and secured with a suture. The tracheal catheter was attached to an air-filled syringe on a syringe pump (Harvard Apparatus, Holliston, MA) with an in-line pressure transducer. The timing of the injection and the pressure in the system were continually recorded by a Macintosh 650 Quadra Computer (Apple Computer; Cupertino, CA) equipped with a data-acquisition board (National Instruments; Austin, TX). Data were assessed using software written by the laboratory in LabVIEW 5.0 (National Instrument) as the syringe injected air into the lungs at ~28 ml/min (precise injection rates were determined before each experiment). When the pressure reached 50 cmH2O or when the pressure began to increase dramatically, the syringe pump was reversed. Volumes were calculated based on timing and the predetermined rate of injection or withdrawal of the pump. Compliance of the inspiratory limb of the hysteresis plot was assessed by measuring change in volume over change in pressure between 25 and 75% [dV/dP(25-75%)] of the maximum volume attained and normalizing to body weight, as previously described (16). Finally, the lungs were removed and wet weight was determined.

Isolation of alveolar type II cells. After removal, the lungs were processed for isolation of type II pneumocytes. These respiratory epithelial cells were isolated by enzymatic digestion and density gradient centrifugation, as previously described (14). Alveolar type II cell surfactant biosynthesis was evaluated by the rate of incorporation of [3H]choline into phosphatidylcholine in freshly isolated pneumocytes. Alveolar type II cells were obtained by perfusing the isolated lungs with normal saline until the tissue was blanched followed by bronchoalveolar lavage with 50 ml of normal saline five times. Lungs were then filled with 50 ml of normal saline containing 0.1 mg/ml of barium sulfate and incubated at 37°C to increase the density of alveolar macrophages after phagocytosis, thereby facilitating removal of these cells. The lung lavage procedure was repeated. After the second lavage, the lungs were fully inflated with Joklik modified minimum essential medium (Life Technologies; Grand Island, NY) containing 10 µg/ml DNase I (Sigma Chemical; St. Louis, MO), 20 mg/ml trypsin (Sigma Chemical), and 1.3 U/ml elastase (Worthington Biochemical; Freehold, NJ), and incubated at 37°C for 30 min. The digestion was stopped by the addition of cold (4°C) Joklik modified minimum essential medium with 50 µg/ml DNase I, 2.5 mg/ml trypsin inhibitor (Sigma Chemical), and 10% fetal bovine serum (Life Technologies). After enzymatic digestion, major bronchi were removed with microdissecting forceps, and the tissue was minced with dissecting scissors. The tissue mince was then filtered sequentially through three (160, 41, and 15 µm) Nitex nylon gauze filters (Tetko; Lancaster, NY) and washed free of proteinase. Alveolar type II cells were isolated from the crude cell preparation by centrifugation on a discontinuous Percoll gradient. Cell number and viability were determined on a hemocytometer and by trypan blue exclusion, respectively. This technique resulted in a cell suspension that was greater than 90% type II cells (5–20 million cells per isolation), with macrophages being the major cellular contaminant. Type II
cell viability was greater than 95% for all experimental groups and did not change over the course of the in vitro measurements.

Assay of surfactant synthesis by isolated alveolar type II cells. Studies of surfactant synthesis were performed in freshly isolated cells. Bronchoalveolar lavage fluid analysis demonstrated normal surfactant phospholipid composition as assessed by the ratio of dipalmitoylphosphatidylcholine to phosphatidylcholine. Therefore, choline incorporation into phosphatidylcholine was used as a surfactant biosynthesis marker, as described previously (14). In studies of fresh isolates, 2 × 10^6 type II cells/ml were incubated at 37°C for 2 h with [methyl-3H]choline chloride, 2 µCi/ml (Amersham; Arlington Heights, IL). The first hour of the incubation period allowed for substrate equilibration. Subsequently, reactions were stopped at 0, 30, and 60 min by the addition of cold saline. The cells were washed to remove unincorporated label and resuspended in 0.8 ml of normal saline. To this suspension, 3 ml of chloroform-methanol (1:2 vol/vol) were added, and phospholipids were extracted by the method of Bligh and Dyer (2). Phosphatidylcholine was isolated from the extract by thin-layer chromatography with the solvent system of Touchstone et al. (37) and compared with known standards after rhodamine visualization. The radioactivity of each spot was determined using an LS-6500 scintillation counter (Beckman Instruments; Palo Alto, CA).

Assessment of bronchoalveolar lavage fluid phosphorus content. To assess surfactant levels, the phospholipid fraction of the first bronchoalveolar lavage fluid of the type II cell isolation was assayed for phosphorus levels using the microphosphorus technique of Chen et al. (6). After extraction, the phospholipids were dried and resuspended in seven drops of 10% magnesium nitrate. The samples were then dried again in a 150°C oven and passed over a flame until the residue turned white. After cooling, 1 ml of 0.5 N HCl was added to each sample and the samples were incubated for 20 min at room temperature. The samples were incubated at 45°C for 35 min after 2 ml of a 6:1 solution of ammonium molybdate (0.42%) and ascorbic acid (10%) were added and read at 820 nm (Nova Spec II, Pharmacia; Piscataway, NJ). Phosphorus levels were determined by interpolation of the samples absorbancies on a standard curve.

Bronchoalveolar lavage fluid analysis. Dynamic surface activity measurements were carried out using a bubble apparatus as previously described by Enhorning (10). The pressure drop of a small air bubble formed in the surfactant-forming subphase was assessed. The bubble was pulsed at a rate of 20 cycles/min between maximum and minimum radii of 0.55 and 0.4 mm, respectively. Surface tension was calculated from the law of Young and Laplace: ΔP = 2γ/r, where ΔP is the pressure drop across the bubble interface, γ is surface tension, and r is the bubble radius. Subphase volume for the bubble experiments was 20 µl. All measurements were made at 37°C and 100% humidity, with a surface area compression of 100 to 95%. All bronchoalveolar lavage samples were concentrated to a standard lipid concentration (based on phospholipid analysis) of 1.0 µmol/ml for surfactant activity studies.

Statistics. Data were analyzed by Fisher’s protected least significant difference factor ANOVA for intergroup comparisons. Values presented are expressed as means ± SE. The null hypothesis was rejected at P < 0.05.

RESULTS

Characterization of physical signs and mortality of rabbits undergoing acid aspiration and exposed to air or 50% oxygen. There was no detectable difference in physical signs of respiratory adequacy between unjured rabbits that received air or 50% oxygen for 24 h. Predictably, there was also no mortality in these groups. Similarly, there was no mortality during the observation period in animals that received intratracheal acid instillation followed immediately by exposure to air. The intratracheally administered volume and pH of the HCl-saline that was employed in these experiments was chosen to produce maximal nonlethal (<10% mortality within 5 h postaspiration) lung injury (data not shown). Furthermore, although tachypnea was present immediately after administration of the acidified saline, after 24 h this group of animals did not demonstrate any physical signs of respiratory distress. A blinded observer could not distinguish these animals from controls that received just air or animals exposed to 50% oxygen with or without intratracheal instillation of nonacidic normal saline. Conversely, those rabbits that received intrapulmonary low pH saline and were exposed to 50% oxygen were moribund and displayed distinct evidence of respiratory distress, including tachypnea, ruffled fur, nasal cyanosis, decreased grooming behavior, and decreased appetite. Because of the obvious pulmonary dysfunction, these rabbits could be clearly differentiated from the other groups by a blinded observer. Two of the animals in the acid/hyperoxia group did not survive the 24-h oxygen exposure (died shortly before they were to have been killed), and one of the rabbits died at the time of euthanization before the pentobarbital sodium could be injected.

Effects of acid aspiration and exposure to air or 50% oxygen on indexes of lung injury. There was no difference in PaO2/FIO2 between uninjured rabbits exposed to air or to an environment of 50% oxygen for 24 h. Conversely, both groups of animals that underwent intratracheal acid instillation demonstrated hypoxemia 24 h postaspiration (Fig. 1). The hypoxemia after acid aspiration was much more severe in animals

Fig. 1. Ratio of arterial oxygen partial pressure to inspired oxygen fraction (PaO2/FIO2; oxygen extraction ratio) in rabbits breathing 100% oxygen (FIO2 = 1) for 15 min before sampling. Values are means ± SE. Treatment groups included control (n = 5), acid (n = 5), hyperoxia (n = 5), or acid/hyperoxia (n = 5). See METHODS for description of treatment groups. *P < 0.01 compared with control.
exposed to 50% oxygen compared with the air-exposed animals, 100 ± 50 and 260 ± 30 mmHg, respectively (P < 0.01). The acid/hyperoxia group also demonstrated a large, almost twofold increase in wet lung weight (Fig. 2) compared with the other three groups (from 7.5 ± 1.5 to 13 ± 2.5 g/kg, P < 0.01). Consistent with these changes, the pulmonary compliance of the acid/hyperoxia group of animals was dramatically decreased compared with that of the other groups (Figs. 3 and 4A). Additionally, there was a greater than threefold decrease in total lung volume (Figs. 3 and 4B) compared with the other three groups (from 36 ± 2.6 to 10 ± 3 ml/kg, P < 0.01). There was no difference in lung compliance between air or hyperoxic groups and those animals that received intratracheal HCl-saline and were exposed to air for 24 h, dV/dP(25–75%) = 1.511 ± 0.124 and 1.418 ± 0.099 ml·kg⁻¹·cmH₂O⁻¹, respectively (P > 0.5). Conversely, those animals that underwent acid aspiration and were exposed to 50% oxygen for 24 h demonstrated a striking decrease in pulmonary compliance, dV/dP(25–75%) = 0.564 ± 0.054 ml·kg⁻¹·cmH₂O⁻¹ (P < 0.005).

Effects of acid aspiration and exposure to air or 50% oxygen on the pulmonary surfactant system. Pulmonary surfactant biosynthesis was also evaluated in alveolar type II pneumocytes isolated from the lungs of rabbits following the different interventions. Similar to the parameters of lung injury described above, alveolar surfactant levels, as assessed by total bronchoalveolar lavage phosphate levels, decreased significantly in the acid/hyperoxia group compared with the control, acid-only, and 50% oxygen groups (Fig. 5). There was no difference in the incorporation of [³H]choline into phosphatidylcholine in freshly isolated pneumocytes from animals exposed to air alone or the group receiving intratracheal HCl-saline, 0.450 ± 0.050 and 0.451 ± 0.057 nmol·10⁶ cells⁻¹·h⁻¹, respectively. Similarly, rabbits exposed to 50% oxygen for 24 h demonstrated a normal rate of incorporation of the radiolabel into phosphatidylcholine (0.500 ± 0.029 nmol·10⁶ cells⁻¹·h⁻¹). Conversely, alveolar type II cells isolated from the lungs of rabbits received intratracheal HCl-saline and that were then exposed to a 50% oxygen environment for 24 h demonstrated a dramatic decrease in the rate of [³H]choline uptake into phosphatidylcholine, 0.250 ± 0.069 nmol·10⁶ cells⁻¹·h⁻¹ (Fig. 6) compared with the other groups (P < 0.01).

Surface tension of the bronchoalveolar lavage fluid was analyzed (Table 1). Predictably, this measurement was dramatically increased in the acid/hyperoxia group (28 ± 2 mN/m, P < 0.01) compared with control or rabbits exposed to hyperoxia only (2 ± 1 and 2 ± 2 mN/m, respectively). Surface tension was only slightly increased in rabbits maintained in room air for 24 h postaspiration (4 ± 2 mN/m).

**DISCUSSION**

These findings demonstrate that in a nonlethal rabbit model of acid aspiration untreated with oxygen therapy, a mild acute hypoxemia results but without associated changes in lung volume, lung compliance, surfactant metabolism, or evidence of edema formation 24 h after the pulmonary insult. Furthermore, a decrease in lung oxygen extraction capacity of this magnitude does not appear to cause obvious physical signs of respiratory distress or increase mortality. Conversely, in rabbits receiving intrapulmonary instillation of HCl-saline, a relatively short exposure to 50% oxygen results in severe respiratory distress with increased mortality. Additionally, lung oxygen extraction is further reduced in the animals that survive compared with rabbits similarly injured but exposed to air. There are also large decreases in lung volume, lung compliance, and respiratory epithelial type II cell surfactant synthesis following 24 h of 50% oxygen administration to these rabbits after acid aspiration. The changes in lung injury parameters are highly indicative of in-
creases in pulmonary edema fluid formation as a result of the oxygen exposure. Because a 24-h exposure to 50% oxygen alone causes no change in gas exchange, these results strongly suggest that acid aspiration primes the lungs to oxygen toxicity.

In patients, a severe, protracted course is seen in approximately one-third of gastric aspiration cases (11, 30, 38). Interestingly, patients are more likely to develop ARDS following acute aspiration when additional insults, such as gastric particulate matter, are present (11, 30, 38). Other investigators have demonstrated similar findings with acidified milk products (28). Thus we have postulated that additional pulmonary insults must occur for acid aspiration to progress to a severe lung injury.

In the original article by Mendelson (21) on aspiration pneumonia, all patients with documented acid aspiration survived. Interestingly, it appears as though these patients did not receive supplemental oxygen, although the author in the discussion section recommended its use in the treatment of patients with this respiratory complication. In contrast, today, if there is any indication of aspiration, supplemental oxygen with or without mechanical ventilation is liberally provided. The findings from the current study strongly suggest that acid aspiration may change the set point for pulmonary oxygen toxicity, the concentration and the duration of exposure. These results raise the specula-
that providing an increase in substrate (oxygen) during neutrophil activation could increase the production of more oxidants. Nonacidified food particle aspiration causes a similar level of acute lung injury as acid aspiration, with generation of large amounts of proinflammatory cytokines [tumor necrosis factor-α (TNF-α), IL-4, IL-10, interferon-γ, macrophage inflammatory protein-2 (MIP-2)] and recruitment of even larger numbers of neutrophils (7, 36). However, this injury does not increase after exposure to 100% oxygen. The findings from this study demonstrate that only acidified gastric aspirates, but not nonacidified gastric particulate aspirates, predispose the lungs to oxidant-mediated changes. Thus mechanisms other than direct generation of neutrophil-derived reactive species are likely to have a role in increasing the vulnerability of the lungs to hyperoxic injury following acid aspiration.

Another mechanism by which acid aspiration could increase the vulnerability of injured lungs to increased ambient oxygen exposure is by inhibiting the compensatory mechanisms that are upregulated after exposure to hyperoxia. Exposure to 100% oxygen causes an increase in the generation of oxidants, the deleterious effects of which are at least partially opposed by an increased production of antioxidants in the uninjured lung. Inhibiting resident lung cells from upregulating this compensatory mechanism may increase the sensitivity of the organ to injury by oxygen stress. Previously, we have demonstrated that lungs from rats exposed to low pH insults have a decrease in antioxidant reserve caused in part by increased proteinase activity from inflammatory cells (24, 26). The low pH exposure appears to be primarily responsible for this change in that nonacidified gastric particulate aspiration did not demonstrate this phenomenon. The combination of increased generation of reactive species from primed leukocytes coupled with decreased lung antioxidant capacity could be predicted to exacerbate lung injury if animals are also exposed to increased ambient oxygen (25).

In addition to direct tissue injury, an increase in the production of these toxic chemical effectors (e.g., reactive species and proteinases) can also augment the release of inflammatory regulators, promoting and accelerating the progression of the lung injury. For example, leukocyte-derived oxidants and nitric oxide are also capable of acting as second messengers. In vitro upregulation of proinflammatory cytokines by changes in the redox status of the cell appears to be mediated by the transcription factor nuclear factor-κB (33, 34). Studies performed both in vivo and in vitro demonstrate that increases in ambient oxygen can enhance production of interleukin-1β (IL-1β), TNF-α, MIP-1α, monocyte chemotactant protein-1 (MCP-1), and IL-8 in several different cell types (8, 22, 32, 39). MCP-1 and IL-8 increases occur after direct exposure of cells to hydrogen peroxide in vitro (8, 32). Nitric oxide is also reported to modulate expression of TNF-α, IL-1β, IL-4, IL-10, IL-12, interferon-γ, MCP-1, and MIP-1α, as well as to interact with superoxide to produce other reactive nitrogen species (4, 5, 13, 20, 40). Finally,

### Table 1. Surfactant activity

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<tr>
<th>Group</th>
<th>n</th>
<th>Surface Tension, mN/m</th>
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<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>5</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>Acid</td>
<td>3</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>Acid/hyperoxia</td>
<td>4</td>
<td>28 ± 2</td>
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Values are means ± SE; n, no. of animals. Lung surfactant activity was determined by assessing surface tension of fluid recovered from bronchoalveolar lavage from rabbits that received no treatment (Control), intratracheal administration of 2.4 ml/kg of HCl-saline, pH 1.25, followed by exposure to normoxia (air) for 24 h (Acid), exposure to 50% oxygen for 24 h (Hyperoxia), or intratracheal administration of 2.4 ml/kg of HCl-saline, pH 1.25, followed by exposure to 50% oxygen for 24 h (Acid/hyperoxia).
oxidants can also regulate proteinase activities by inactivating proteinase inhibitors and activating leukocyte-derived metalloproteinases (9, 31, 35, 42). Proteinases are capable of degrading antioxidants and can induce the production of neutrophil chemotactic cytokines (24, 27). We believe that the mechanisms by which acid primes the lung and changes the set point for oxygen toxicity. This mechanism may have an important role in the pathogenesis of inflammation (e.g., reactive species and proteinases).

In summary, we have demonstrated that in a rabbit model of acid aspiration the lungs are primed for increased sensitivity to normally safe levels of increased ambient oxygen. Exposure of animals to 50% oxygen after intratracheal instillation of HCl-saline, pH 1.25, causes severe hypoxemia, edema formation, and a rabbit model of hyperoxic lung injury, we speculated that the increased sensitivity to oxygen toxicity is due to enhanced generation of chemical effectors of inflammation (e.g., reactive species and proteinases). These results strongly indicate that acid aspiration changes the set point for oxygen toxicity. This mechanism may have an important role in the pathogenesis of ARDS, and understanding the mechanisms involved may offer opportunities for therapeutic strategies to prevent the development of this severe progressive pulmonary syndrome.

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