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Acute Lung Injury after Instillation of Human Breast Milk into Rabbits' Lungs

Effects of pH and Gastric Juice

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Background: **The authors compared the lung injury in rabbits that occurred after tracheal instillation of human breast milk (HBM) acidified to pH 1.8 with hydrochloric acid (HCl), HBM at its native pH (7.0), and HBM acidified with gastric juice to pH 1.8 and 3.0.**

Methods: **The alveolar-to-arterial oxygen tension gradient and dynamic compliance were recorded before and hourly for 4 h after intratracheal instillation of 0.8 ml/kg HBM acidified with HCl (pH 1.8), HBM at its native pH (7.0), HBM acidified with gastric juice (pH 1.8 or 3.0), or 5% dextrose solution acidified with gastric juice (pH 1.8) as a control in 30 adult rabbits. The circulating neutrophil count and phagocyte oxidant activity were determined before and 1 and 4 h after instillation.**

Results: **The alveolar-to-arterial oxygen tension gradient increased and dynamic compliance decreased significantly in all groups after instillation of HBM compared with baseline values and those in the control group. The severity of the lung injury after instillation of HBM at all pH values (1.8, 3.0, and 7.0) and after acidification with gastric juice or HCl was similar. The circulating neutrophil count increased steadily for 4 h after instillation ($P < 0.013$), whereas spontaneous phagocyte oxidant burst activity peaked at 1 h ($P < 0.007$) and returned to baseline by 4 h after instillation.**

Conclusions: **The severity of the lung injury after tracheal instillation of 0.8 ml/kg HBM in rabbits is similar at pH values between 1.8 and 7.0 after acidification with HCl or gastric juice. Tracheal instillation of HBM increases the circulating neutrophil count and phagocyte oxidant burst activity. (Key words: Aspiration; blood; compliance; chemiluminescence; neutrophils; phagocyte.)**

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SEVERAL factors affect the severity of acute lung injury after acid and particulate instillation into the trachea, including the pH and volume of the instilled fluid and the particle size. Published studies have shown that in animals the severity of pneumonitis and the risk of death increase as the pH of the aspirated fluid decreases (< than 2.5) and the volume of the fluid increases.[1–6] This is not to suggest that aspiration of fluid at an alkaline pH is not injurious to the lungs; rather, in the range of gastric fluid pH, the more acidic the pH, the more severe the pneumonitis. The severity of the lung injury is also know to increase as the concentration of particles increases.[7] Furthermore, Knight *et al.*[7] found synergy between the level of acidity and particulate-induced lung injury in the rat. However, in most human infants, the pH of the gastric fluid is greater and the volume less than the corresponding variables that were associated with severe lung injury in the rat.[8] In a previous study, we showed that tracheal instillation of 0.8 ml/kg of either human breast milk (HBM) or infant formula, but not dextrose, acidified to a pH of 1.8 injures the lungs of adult rabbits.[9] Currently, the role of HBM in the genesis of an acute lung injury has not been addressed in the range of pH values that are encountered clinically. Therefore, we designed the following controlled, labo-

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ratory investigation to evaluate the physiologic and inflammatory responses to intratracheal instillation of HBM acidified with hydrochloric acid (HCl) or gastric juice to pH values between 1.8 and 7.0.

Materials and Methods

Surgical Preparation

With approval from the institutional animal care committee, 30 pathogen-free, adult New Zealand white rabbits (Charles River, St. Constant, Quebec, Canada) weighing 3.2 ± 0.3 kg were studied. The rabbits were fasted overnight for solids and allowed free access to clear fluids for as long as 4 h before anesthesia was induced. Each rabbit was premedicated with 10 mg/kg ketamine, 0.16 mg/kg atropine, and 0.2 mg/kg acepromazine given intramuscularly. After electrocardiographic monitors were applied to the rabbits, anesthesia was induced with halothane in a nitrous oxide–oxygen gas mixture. Lactated Ringer's solution was infused at a rate of 10 ml · kg^{-1} · h^{-1} through a 24-gauge cannula in a marginal ear vein. Systemic blood pressure was monitored continuously using a 24-gauge catheter that was inserted under direct vision into the common carotid artery. The internal jugular vein was fitted with a cannula using a 5-French umbilical catheter that was advanced into the right atrium. After bupivacaine (1 mg/kg) with epinephrine was injected subcutaneously into the anterior neck caudal to the cricoid cartilage, a surgical tracheostomy was created between the third and fourth tracheal rings. A 3.5-mm Portex uncuffed endotracheal tube was inserted through the stoma to a depth of 3 cm and sealed with a ligature. The lungs were ventilated mechanically after the rabbits were paralyzed with an intravenous bolus of 0.5 mg/kg pancuronium bromide and followed by a continuous infusion at 0.4 mg · kg^{-1} · h^{-1}. The adequacy of lung ventilation was confirmed by observation of symmetrical chest expansion, by auscultation of the thorax bilaterally, and by the arterial carbon dioxide tension. Intermittent positive-pressure ventilation was delivered *via* a pneumatically operated, time-cycled, and volume-controlled ventilator (Ventimeter Ventilator; Airshield, Hatboro, PA). Fresh gas flow was composed of 1% halothane in humidified oxygen. Rectal body temperature was maintained at 38 ± 1°C using a warming blanket and an overhead infrared radiant heater. Lactated Ringer's solution was titrated intravenously to maintain the central venous pressure and base deficit within normal limits. All rabbits were in the supine position during the study.

Experimental Protocol

After anesthesia was induced, the tidal volume was adjusted to deliver 10–12 ml/kg. The respiratory rate was adjusted to produce normocapnia (partial pressure of carbon dioxide in arterial blood [Pa_{CO_2}], 35–45 mmHg) before the instillation of the breast milk and was not adjusted subsequently. Positive end-expiratory pressure was not applied, and cardiotonic and vasoactive drugs were not used. Baseline (time zero) arterial blood–gas measurements and dynamic compliance were recorded 10 min after cardiorespiratory variables were shown to be stable. The rabbits were assigned to receive one of five study fluids: HBM at pH 1.8 with HCl, HBM at native pH (7.0), HBM at pH 1.8 or 3.0 with gastric juice, or 5% dextrose at pH 1.8 with gastric juice. Discarded and unfiltered gastric juice from children in the critical care unit who were free of gastrointestinal bleeding was used. The pH of the acidified study fluid was titrated to the assigned pH using a Radiometer PHM62b pH meter (Copenhagen, Denmark) that was calibrated using three commercial buffer solutions (pH 1, 4, and 7; Fisher Scientific, Nepean, Ontario, Canada) before each measurement. The accuracy range of this instrument is ± 0.01 pH units.

After baseline measurements were completed, 0.8 ml/kg of the study fluid was instilled into the trachea through the tracheotomy tube. Blood gas analysis, peak inspiratory pressure, and lung volumes were recorded hourly for 4 h after instillation. Mean arterial blood pressure greater than 40 mmHg and right atrial pressures of 2–5 mmHg were maintained during the study with intermittent fluid boluses of lactated Ringer's solution of 5–10 ml/kg as necessary. Venous blood (2 ml) was collected as soon as the intravenous catheter was inserted (before instillation) and 1 and 4 h after tracheal instillation to determine the peripheral neutrophil count and the chemiluminescence activity in the HBM, pH 1.8, with gastric juice and the HBM at its native pH groups only. When the final physiologic measurements were completed, the rabbits were killed rapidly by intravenous administration of 100 mg/kg pentobarbital followed by 6 mmol/kg potassium chloride into the central venous catheter.

Methods of Measurement

Arterial blood gas tensions (carbon dioxide and oxygen) and pH were measured using an ABL330 analyzer (Radiometer). The alveolar-to-arterial oxygen tension gradient ($AaDO_2$) was calculated as follows: $AaDO_2 = (FI_{O_2}[pB - pH_2O] - Pa_{CO_2} \div 0.8 - Pa_{O_2})$. The arterial

and central venous pressures were measured using a heparin-prepared, saline-filled transducer (Hewlett Packard 78342A, Mississauga, Ontario, Canada). The transducers were set to zero at the mid-thoracic level. Dynamic compliance calculations were based on pressure and volume measurements. Peak inspiratory pressure was measured at the distal inspiratory limb of the ventilator tubing using an airway pressure manometer. Expiratory tidal volume was measured at the endotracheal tube connector (Neonatal Volume Monitor-1; Bear Medical Systems Inc., Riverside, CA) using a calibrated pneumotachograph.

Changes in the oxidant activity of circulating phagocytes before and after tracheal instillation of milk were quantified using whole blood chemiluminescence. Chemiluminescence was measured in a computer-controlled Berthold AutoLuminat LB953 Chemiluminometer (Berthold, Germany) after incubating the samples for 30 min at 37°C. Whole blood samples (40 μl) were diluted in 3,960 μl Hank's balanced salt solution (without calcium or magnesium) at pH 7.4 (Gibco BRL, Grand Island, NY). A fraction of the diluted mixture (100 μl) was added to each tube of 600 μl Luminol (in a concentration of 13.3 mg/500 ml Hank's balanced salt solution–calcium and magnesium; Sigma Chemical Co., St. Louis, MO) that contained Hank's balanced salt solution with calcium (Gibco BRL) at 37°C. Chemiluminescence was measured in unprimed phagocytes (nil) and in phagocytes that were primed with 100 nM phorbol myristate acetate (PMA; Sigma Chemical Co. in dimethyl sulfoxide 0.1% by volume total reaction or 100 μl unopsonized zymosan (ExOxEmis Inc., San Antonio, TX). Each analysis was performed three times. The area under the chemiluminescence–time curve was integrated and expressed per neutrophil. Although neutrophils comprise most of the phagocytes in blood and account for the largest proportion of chemiluminescence measured, the contributions of monocytes and other granulocytes were also included.

Chemiluminescence or photon emission, a byproduct of microbicidal oxygenation activity, is used as an index of reaction oxygen production.[10] The use of sensitive chemiluminescent dyes, such as Luminol, which are easily oxidized by various reactive oxidant species, has overcome the difficulty in measuring the small photon yield of these reactions. Luminol is dioxygenated at physiologic pH, and, in the presence of hypophalous acid (the principal oxidant product of phagocytes), it decays to aminophthalate and a photon, the latter detectable by a luminometer. Luminol can react with hypophalous acid and hydrogen peroxide to yield light at physiologic pH. To measure the oxidative burst activity of naïve phagocytes, the chemiluminescence activity of unprimed phagocytes was measured. To measure the oxidative burst activity of primed phagocytes, the phagocytes were incubated with one of two activators: PMA or zymosan. Priming with PMA activates reduced nicotinamide adenine dinucleotide phosphate and haloperoxidase by releasing the granular contents from the phagocytes. In contrast, priming with zymosan activates phagocytes by direct contact with the cell surface and indirectly by a complement receptor type 3 mechanism.

Data Analysis

Data are presented as the mean ± SD. Demographic data were analyzed using one-way analysis of variance and the Student-Newman-Keuls test for intergroup differences. The $AaDO_2$, dynamic compliance, total peripheral neutrophil counts, and chemiluminescence activity were analyzed using multivariate analysis of covariance with repeated-measures (Statistica for the Macintosh Statsoft, Tulsa, OK). *Post hoc* testing was performed using the Student-Newman-Keuls test for significant main effects and interactions. $P < 0.05$ was considered significant.

Results

Baseline $AaDO_2$ measurements in the five groups were similar (fig. 1). Analysis of the posttreatment responses showed statistically significant effects for treatment and time, but no interaction between the variables. The $AaDO_2$ values in the four HBM groups were significantly greater than their respective baseline values at all four times after instillation ($P < 0.0002$), whereas the $AaDO_2$ in the 5% dextrose group did not change significantly at any time. Although the four HBM-treated groups did not differ from one another at any time after instillation, they were all significantly greater than that in the 5% dextrose group at each hourly measurement after instillation ($P < 0.0002$). To show that the $AaDO_2$ gradients in this study do not represent the maximum possible gradient after instillation of HBM into rabbits tracheas, we included in figure 1 the $AaDO_2$ responses to tracheal instillation of 2 ml/kg HBM, pH 1.8, from another study.[11]

Baseline dynamic compliance measurements for all treatments were similar (fig. 2). Analysis of the posttreatment responses revealed statistically significant effects for treatment, time, and interaction between the two variables. Dynamic compliance measurements in the

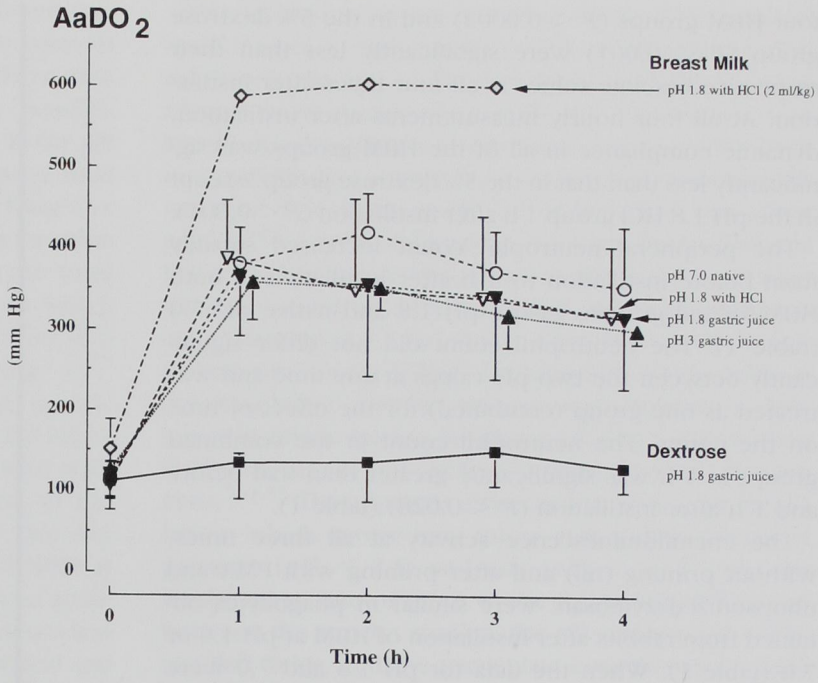

Fig. 1. The alveolar-to-arterial oxygen tension gradient ($AaDO_2$; mean ± SD) measurements for all treatments (0.8 ml/kg) were similar. The $AaDO_2$ measurements in the four human breast milk (HBM) groups were significantly greater than their respective baseline values at all four times after instillation ($P < 0.0002$), whereas the $AaDO_2$ in the 5% dextrose group did not change significantly at any time. Although the $AaDO_2$ in the four groups did not differ significantly from one another at any time after instillation, they were all significantly greater than the $AaDO_2$ in the 5% dextrose group at each respective hour ($P < 0.0002$). To show that this model could produce a worse injury than already shown, the $AaDO_2$ response to the tracheal instillation of 2 ml/kg HBM at pH 1.8 was included.[11]

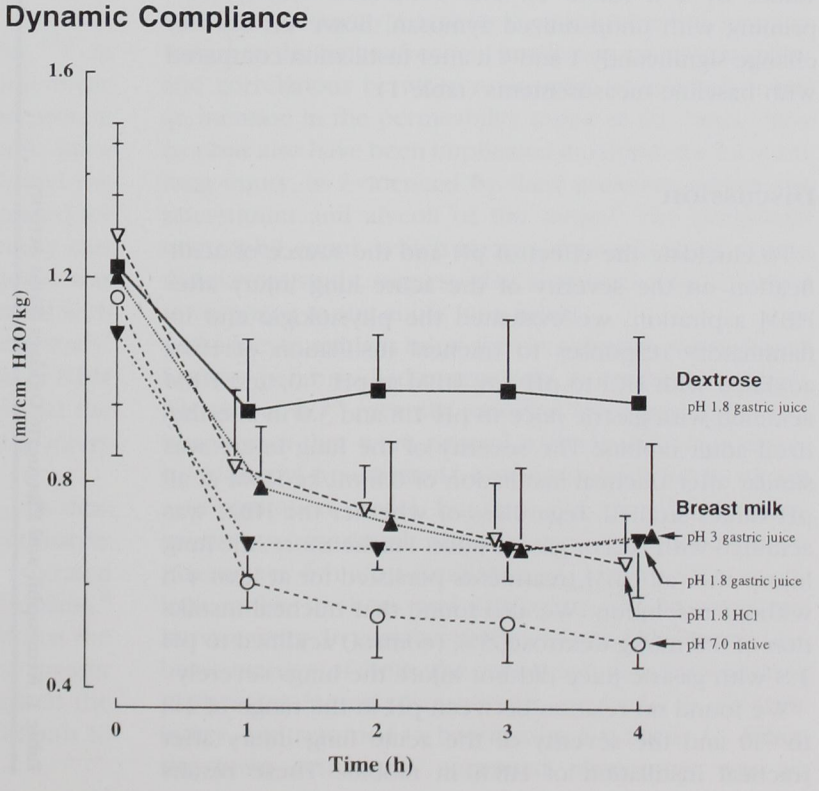

Fig. 2. Dynamic compliance (mean ± SD) was measured before and hourly for 4 h after instillation of human breast milk (HBM) acidified with hydrochloric acid (HCl) to pH 1.8, HBM at its native pH 7.0, HBM acidified with gastric juice to pH 1.8 or 3, or 5% dextrose at pH 1.8 in adult rabbits. Baseline compliance for all treatments were similar. Compliance in the four HBM groups ($P < 0.0002$) and in the 5% dextrose group ($P < 0.001$) were significantly less than their respective baseline values at all four times after instillation. Compliance in all of the HBM groups was significantly less than that in the 5% dextrose group at all four hourly measurements after instillation, except in the pH 1.8 HCl group 1 h after instillation ($P < 0.001$).

four HBM groups ($P < 0.0002$) and in the 5% dextrose group ($P < 0.001$) were significantly less than their respective baseline values at all four times after instillation. At all four hourly measurements after instillation, dynamic compliance in all of the HBM groups was significantly less than that in the 5% dextrose group, except in the pH 1.8 HCl group 1 h after instillation ($P < 0.001$).

The peripheral neutrophil count increased steadily from before instillation to 4 h after instillation in both HBM-treated groups, gastric pH 1.8 and native pH 7.0 (table 1). The neutrophil count did not differ significantly between the two pH values at any time and was treated as one group (combined) for the effect of time on the count. The neutrophil count in the combined groups at 4 h was significantly greater than that before and 1 h after instillation ($P < 0.028$) (table 1).

The chemiluminescence activity at all three times, without priming (nil) and after priming with PMA and unopsonized zymosan, were similar in phagocytes obtained from rabbits after instillation of HBM at pH 1.8 or 7.0 (table 1). When the data for pH 1.8 and 7.0 were combined, the activity without priming and after priming with PMA both peaked 1 h after instillation ($P < 0.015$ and $P < 0.01$, respectively, compared with preinstillation measurements) and decreased to preinstillation values by 4 h (table 1). The combined activity after priming with unopsonized zymosan, however, did not change significantly 1 and 4 h after instillation compared with baseline measurements (table 1).

Discussion

To elucidate the effect of pH and the source of acidification on the severity of the acute lung injury after HBM aspiration, we evaluated the physiologic and inflammatory responses to tracheal instillation of HBM acidified with HCl to pH 1.8, HBM at pH 7.0, and HBM acidified with gastric juice to pH 1.8 and 3.0 in anesthetized adult rabbits. The severity of the lung injury was similar after tracheal instillation of 0.8 ml/kg HBM at all pH values studied, regardless of whether the HBM was acidified with HCl or gastric juice. Furthermore, the lung injury after all HBM treatments persisted for at least 4 h without resolution. We also found that tracheal instillation of 0.8 ml/kg dextrose, 5%, (control) acidified to pH 1.8 with gastric juice did not injure the lungs severely.

We found no relation between pH in the range of 1.8 to 7.0 and the severity of the acute lung injury after tracheal instillation of HBM in rabbits. These results

Table 1. Neutrophil and Phagocyte Oxidant Burst Activity

	*p*H 1.8			*p*H 7.0			Combined*		
	Pre	1 h	4 h	Pre	1 h	4 h	Pre	1 h	4 h
Polymorphonuclear cells (PMN)	1.28 ± 1.22	1.63 ± 2.15	2.2 ± 2.72	0.77 ± 0.71	1.04 ± 1.57	2.33 ± 1.2	1.03 ± 0.99	1.33 ± 1.82	2.27 ± 2.01†
Chemiluminescence activity									
Nil	512 ± 619	1,743 ± 2,237	252 ± 220	381 ± 300	1,874 ± 2,532	103 ± 39	447 ± 499	1,809 ± 2,279‡	178 ± 170
PMA	591 ± 701	2,021 ± 2,488	408 ± 270	477 ± 300	1,964 ± 2,184	258 ± 98	534 ± 517	1,992 ± 2,232§	333 ± 209
Unopsonized zymosan	4,388 ± 4,828	5,202 ± 4,159	4,091 ± 3,676	4,287 ± 1,650	6,021 ± 4,140	2,814 ± 1,120	4,338 ± 3,440	5,612 ± 3,979	3,453 ± 2,676

Data are means ± SD. Preinstillation refers to steady-state conditions before instillation of HBM into the tracheal tube; 1 h and 4 h postinstillation are times after instillation of HBM into the endotracheal tube.

*Data for the six rabbits in each of the pH 1.8 and 7.0 groups were combined.

†$P < 0.028$ *versus* pre- and 1 h postinstillation.

‡$P < 0.015$.

§$P < 0.01$ *versus* preinstillation and 4 h postinstillation

contrast with those of Knight *et al.*,[7] who showed synergy between acid and particulate-induced lung injury in the rat. The difference in results between these two studies may be attributed, in part, to three possible factors: (1) the animal models were different, (2) the pH of the acidified fluid was greater and the volume of fluid was less in this study compared with that by Knight *et al.*, and (3) the current model could not reflect a more severe lung injury if it occurred. To address the third factor, we included data from a recent study in which we found that the $AaDO_2$ after tracheal instillation of 2 ml/kg HBM exceeded that after 0.8 ml/kg (fig. 1).[11] Therefore, if pH or any other condition (*i.e.*, gastric juice) had injured the lungs more severely than 0.8 ml/kg HBM at pH 1.8, this model could have responded with evidence of a more severe lung injury. Based on the limited range of data presented in this study, we can neither rule out a relation between the pH of HBM at volumes greater than 0.8 ml/kg and the severity of acute lung injury nor a relation between HBM at pH values less than 1.8 and lung injury. Whether the effects of acid and particulate-induced lung injury are synergistic after tracheal instillation of HBM during conditions similar to those used by Knight *et al.*[7] remains to be determined.

We speculated that gastric juice would injure the lungs more than HCl at the same pH because gastric juice contained particulate matter and lysozyme enzymes. However, published data do not support this.[1,12] In those studies, the response to tracheal instillation of the acid was assessed either histologically or by protein extravasation into the lung parenchyma. Gastric juice produced a lung injury similar to that by HCl, and the severity of the injury increased as the pH decreased for both sources of acid. Interestingly, the lung injury that occurred after instillation of filtered gastric juice was attenuated in severity and duration when compared with the response after unfiltered juice. In the current study, the similarity in the lung injury after acidification of HBM with HCl and gastric juice supports the notion that the source of acid does not affect the severity of lung injury after tracheal instillation of HBM.

We acidified HBM and our control solution, 5% dextrose, to a pH of 1.8 because this pH was approximately 1 SD below the pH of gastric fluid that was aspirated from the stomachs of infants 2 h after breast-feeding.[8] Based on these data from infants,[8] we estimated that the gastric fluid pH in 79% of breast-fed infants was greater than or equal to pH 1.8. Therefore, to strengthen the clinical relevance of this study, we acidified all fluids to a minimum pH of 1.8.

The lack of a substantive lung injury after tracheal instillation of a control solution (0.8 ml/kg dextrose, 5%, solution at pH 1.8) in this and previous studies[9,13] may appear to be inconsistent with the current body of knowledge regarding acid aspiration, but in reality this is not so. Published studies have shown that tracheal instillation of clear fluids at pH 1.8 in the rat[5,6] and rabbit models[9,13] causes minimal or no lung injury. The pH below which severe lung injury is likely to occur after tracheal instillation of a clear fluid in animal models is approximately 1.5,[6] and this is a pH that occurs in few infants who ingest HBM.[8] To maximize the severity of the lung injury and the inflammatory response to that injury in animal models, investigators have acidified clear fluids to pH 1–1.25 before instillation into the trachea.[7,14,15] The apparent difference in the threshold pH below which severe lung injury consistently occurs in primates ($pH < 2.5$) and rats ($pH < 1.5$)[5,6] may be attributed to one or more of the following: differences between the species studied, the pH and volume of the instilled fluids, and the particulate concentration of the instilled fluids.

Neutrophils have been implicated in the pathogenesis of the acute lung injury after acid aspiration.[16–18] Evidence in support of the role of neutrophils in the acute lung injury includes transient increases in circulating cytokines, phagocyte activity coupled with leukosequestration in the lungs after acid instillation into the trachea, and correlations between neutrophil sequestration and an increase in the permeability index of the lungs. Neutrophils also have been implicated in HBM-induced acute lung injury, as evidenced by their presence within the interstitium and alveoli of the lungs.[9] The peripheral neutrophil count, which increased progressively during the current study, suggests that leukoactivation occurred in response to the acute lung injury.

Phagocyte oxidant burst activity (chemiluminescence) has not been studied extensively in aspiration models. Nishina *et al.*[18] recently reported the burst activity of phagocytes that were primed with opsonized zymosan or N-formyl-L-methionyl-L-luecyl-L-phenylalanine in an acid aspiration model, but they did not report the response to unprimed phagocytes. They collected the phagocytes 6 h after instillation of 3 ml/kg HCl, 0.1 N, into rabbit tracheas and showed markedly increased burst activity. In contrast to the findings in our study, the burst activity of both the unprimed and PMA primed phagocytes increased transiently, peaked 1 h after the injury, and returned to baseline by 4 h (table 1). When the burst activity of unprimed phagocytes was ac-

counted for, priming with PMA did not augment the phagocyte oxidant burst activity. Without taking the burst activity of unprimed phagocytes into consideration, it is difficult to interpret the effects of priming on the oxidant activity (table 1). Our results suggest that phagocytes are maximally activated by virtue of the HBM-induced lung injury and that priming is unnecessary to assess the oxidant burst activity in this model.

The return of phagocyte oxidant burst activity to the pre-HBM levels by 4 h (table 1) may be attributed to either leukosequestration at the site of injury (*i.e.,* the lungs) and in other target organs or to a rapid diminution in burst activity (*i.e.,* phagocyte burnout). Previous studies have shown that leukocytes sequester in the lungs within 4 h of the lung injury and marginate in the vasculature of other organs.[12,16] In contrast, Nishina *et al.*[18] found burst activity 6 h after instillation of acid in neutrophils obtained from the pulmonary artery. The difference in burst activity between our study and that by Nishina *et al.* may be attributed to (1) a less severe lung injury in the current study, (2) differences in phagocytes from the peripheral circulation and those in the pulmonary circulation, and (3) an attenuated phagocyte response in milk-induced compared with acid-induced lung injury.

In conclusion, the acute lung injury that occurs after tracheal instillation of 0.8 ml/kg HBM at pH 1.8 in adult rabbits is similar in severity (based on physiologic and inflammatory responses) to that after HBM at pH 7.0, but both are significantly more severe than that induced by 5% dextrose at pH 1.8. Acidification of HBM with gastric juice or HCl yields an acute lung injury of similar severity. Tracheal instillation of HBM increases the concentration of circulating neutrophils and induces phagocyte burst activity.

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