Effects of acid aspiration-induced acute lung injury on kidney function

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Hoag JB, Liu M, Easley RB, Britos-Bray MF, Kesari P, Hassoun H, Haas M, Tuder RM, Rabb H, Simon BA. Effects of acid aspiration-induced acute lung injury on kidney function. Am J Physiol Renal Physiol 294: F900–F908, 2008. First published February 6, 2008; doi:10.1152/ajprenal.00357.2007.—Acute lung injury (ALI) in combination with acute kidney injury carries a mortality approaching 80% in the intensive care unit. Recently, attention has focused on the interaction of the lung and kidney in the setting of ALI and mechanical ventilation (MV). Small animal models of ALI and MV have demonstrated changes in inflammatory mediators, water channels, apoptosis, and function in the kidney early in the course of injury. The purpose of this investigation was to test the hypothesis that ALI and injurious MV cause early, measurable changes in kidney structure and function in a canine HCl aspiration model of ALI when hemodynamics and arterial blood gas tensions are carefully controlled. Intratracheal HCl induced profound ALI as demonstrated by increased shunt fraction and airway pressures compared with sham injury. Sham-injured animals had similar mean arterial pressure and arterial Pco2 and HCO3 levels compared with injured animals. Measurements of renal function including renal blood flow, urine flow, serum creatinine, glomerular filtration rate, urine albumin-to-creatinine ratio, and kidney histology scores were not different between groups. With maintenance of hemodynamic parameters and alveolar ventilation, ALI and injurious MV do not alter kidney structure and function early in the course of injury in this acid aspiration canine model. Kidney injury in large animal models may be more similar to humans and may differ from results seen in small animal models.

Patients with combined acute lung injury (ALI) and acute kidney injury (AKI) have a mortality rate approaching 80% in the intensive care unit (17). Considerable clinical and experimental data support the existence of a direct pulmonary-renal interaction in the setting of ALI and the acute respiratory distress syndrome (ARDS). In the Acute Respiratory Distress Syndrome Network study (1) comparing low tidal volume to conventional tidal volume (Vt) ventilation, protective modes of ventilation not only improved mortality from ARDS, but led to improved function in other organ systems. Specifically, patients receiving 6 ml/kg Vt had a lower number of days with renal failure in the first 28 days compared with patients receiving 12 ml/kg Vt (1). Similarly, a smaller study (24) showed a decrease in the number of patients developing renal failure in the first 72 to 96 h when low tidal volume ventilation was used.

Likewise, animal models of ALI and mechanical ventilation have been used in an effort to determine mechanisms of organ cross talk in response to injury. Most well-described are the influences of mechanical ventilation in the setting of ALI on hemodynamics, thus modifying renal blood flow. Positive end-expiratory pressure (PEEP) has a negative correlation with renal blood flow (12, 22). Blood gas tensions and acid base status can alter renal blood flow and thus impair renal function (2, 8, 25). The idea of “lung biotrauma” has been postulated as a mechanism of distant organ injury (16, 27). In this case, inflammatory mediators such as cytokines and chemokines that are released in response to lung injury spill into the systemic circulation and exert deleterious effects on distant organs (16, 27).

Small animal models of ALI demonstrated alterations in distant organ function in response to lung injury and mechanical ventilation. Large tidal volume ventilation, alone or in conjunction with acid aspiration, has been shown to alter aquaporins (AQP-2) and water channel [epithelial sodium channel (ENaC)] expression (13), local cytokine, including IL-1β, IL-6, VEGF (9, 23), and chemokine, including monocyte chemotactic protein 1 (MCP-1), IL-8, growth-related oncogene (GRO), concentrations (11), adhesion molecules production (ICAM-1) (23), inflammatory cell distribution, and apoptosis (11) in the kidneys in small animal models. These changes are manifested early, usually within 2 to 4 h of lung injury and mechanical ventilation. Although small animal models have strengths, a major problem has been that many mechanisms and interventions elucidated in rodents have not been borne out in humans. In these models, careful control of hemodynamics and intravascular volume, arterial blood gas tensions, as well as serial biochemical measurements in the same animal are generally not feasible. There may also be differences in organ function between large and small animals. We hypothesized that ALI and injurious mechanical ventilation (large Vt) would have minimal effect on the kidney if there were optimal control of hemodynamics and arterial blood gases. We tested our hypothesis in a well-established canine model of ALI with tight control of hemodynamics and maintenance of alveolar ventilation.

Methods

Johns Hopkins University Institutional Animal Care and Use Committee approved all animal protocols, and they were consistent with National Institutes of Health Guide for the Care and Use of Laboratory Animals. All animals were housed in an animal facility with air-conditioning and light-dark cycle under pathogen-free condition and were provided free access to food and water during their housing. Animal preparation. Eleven male beagles (weight average 17.0 ± 1.0 kg) were anesthetized with pentobarbital sodium (10 mg/kg bolus then 1–3 mg·kg⁻¹·h⁻¹ iv) and relaxed with pancuronium (0.1 mg·kg⁻¹·h⁻¹ iv). Animals were orally intubated and mechanically

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ventilated (LifeCare PLV-102) using volume control with high V_T (25 mL/kg) and PEEP (5 cmH2O). Respiratory rate was set to achieve an end-tidal carbon dioxide pressure (PETCO2) of 30–35 mmHg and subsequently adjusted to maintain arterial pH between 7.20 and 7.45. Initial FiO2 of 0.40 was increased as required to maintain arterial oxygen saturation (SaO2) of more than 88% or PaO2 of more than 60 mmHg. Recruitment maneuvers (PEEP increase to 25 cmH2O) for 30 s were performed hourly during the study protocol. Animals were instrumented with femoral artery and vein catheters, a thermistor-tipped pulmonary artery catheter, and a Foley catheter. Airway pressure (Paw), mean arterial pressure (MAP), central venous (CVP) pressures, and central venous blood gases quantified gas exchange. Venous admixture (Qs/Qt) was calculated using standard equations (20). All previously mentioned parameters plus pulmonary artery occlusion pressure (PAOP) and cardiac output (CO) were recorded at baseline, 30 min after injury or sham, and then hourly throughout the study protocol. Subjects received an initial saline bolus (40 mL/kg) and maintenance saline (15 mL·kg⁻¹·h⁻¹) during the experimental protocol. Additional intravenous saline was administered as a bolus (10 mL/kg) as needed for hypotension (MAP <60 mmHg) or CO depression (>30% decrease). Animals were killed at the conclusion of the study with supplemental pentobarbital sodium followed by exsanguination.

Lung injury/intratracheal HCl administration. After instrumentation and baseline measurements, animals were randomized to lung injury (n = 6) or sham control (n = 5). Under fiberoptic bronchoscopic visualization, a custom-made small-diameter catheter was inserted into the airway to a level just above the carina. The catheter had tiny holes at the distal end designed to partially aerosolize the hydrochloric acid (HCl) solution (or saline in sham animals). Animals were placed in the left lateral decubitus position. HCl (0.5 N, 0.75 mL/kg) or saline was injected into the airway through the catheter. Animals remained in that position for 2 min, and then the procedure was repeated in the right lateral decubitus position. Animals were then returned to the supine position for the remaining 300 min of the study.

Measurement of glomerular filtration rate. After instrumentation, a bolus dose (16 mg/kg) of inulin (MW, 5000, Sigma, St. Louis, MO) was administered intravenously over 1 h followed by a continuous infusion (40 mg·kg⁻¹·h⁻¹) maintained throughout the experimental protocol. Glomerular filtration rate (GFR) was calculated by measuring the clearance of inulin ([urine inulin concentration × urine flow rate)/plasma inulin concentration] according to the method of Smith et al. (28).

Measurement of renal blood flow. Renal blood flow (RBF) was measured by calculation of para-aminohippurate (PAH; MW 804.87, Sigma) clearance by a previously described method (30). In another set of animals (n = 2), direct measurements of RBF were made by the placement of unilateral renal artery flow probes (Transonic Systems, model T106, Ithaca, NY) through a flank incision.

Measurement of serum and urine electrolytes. Serum and urine samples were assessed for creatinine, osmolality, and sodium concentration. Serum (Scr) and urine (Ucr) levels were measured using a 557A creatinine kit (Sigma Diagnostics, St. Louis, MO) and analyzed on a Cobas Mira S Plus automated analyzer (Roche Diagnostics, Indianapolis, IN). Urine albumin was measured using standard ELISA techniques (Bethyl Laboratories, Montgomery, TX). To correct for the effect of urine volume on albumin concentration, urine albumin-to-creatinine ratios were calculated (4).

Cytokine measurements. Serial serum samples were collected throughout the protocol and analyzed for cytokines (IL-6, IL-10, TNF-α, and INF-γ) using standardized ELISA assays (R&D Systems, Minneapolis, MN). Intravenous lipopolysaccharide (LPS; 20 μg/kg, n = 2) was administered to a separate group of animals, otherwise treated similar to the injury group, to serve as a positive control for serum cytokine assays. Also, serum cytokines were measured in animals (n = 2) that received surgical placement of renal flow probes (n = 2).

Caspase-3 activity assay. Caspase-3 activity was measured in kidney and lung tissue homogenates using a fluorescence-based assay (Apo-One, Promega) as previously described (21).

Renal histology. Kidney histology scores were calculated on hemotoxylin eosin (H&E)-stained sections of kidney tissue from each animal. Scoring was performed under light microscopy at ×200 power and confirmed at ×400 power by an independent renal pathologist who was blinded to the treatment group of each subject. Scoring was based on the presence of isometric vacuolization of proximal tubular epithelium, epithelial necrosis or cell sloughing, and the presence of leukocyte infiltration. Scores ranged from 0 to 4 based on the severity of the processes (0 = absent, 1 = <10% of cortex, 2 = 10–25% of cortex, 3 = 26–50% of cortex involved, 4 = >50% of cortex involved). Scoring was performed on sections from both left and right kidneys of all subjects. For electron microscopic (EM) examination, small (~1 cubic mm) portions of harvested kidneys were fixed overnight in 3% glutaraldehyde in phosphate buffer, and then washed and further fixed in 1% osmium tetroxide and embedded in Epon resin. Ultrathin sections of the tissues were cut and stained with uranyl acetate and lead citrate and were examined in a Philips CM12 transmission electron microscope.

Statistical analysis. Hemodynamic, pulmonary, and renal function and cytokine measurements were compared at each time point using Student’s t-test and Mann-Whitney Rank Sum for nonnormally distributed data. ANOVA was performed to compare trends through the protocol. Data are presented as means ± SE with statistical significance defined at P < 0.05.

Fig. 1. Pulmonary mechanics and gas exchange. Plateau pressure increased after injury. PaO2/FiO2 ratio decreased in the injury group over the course of the experiment. *P < 0.05 vs. baseline. **P < 0.05 vs. sham.
RESULTS

Gas exchange and pulmonary mechanics. Intratracheal HCl-induced ALI resulted in a significant decrease in the ratio of the partial pressure of arterial oxygen to fractional oxygen inspired (P/F ratio; 84 ± 8 vs. 403 ± 56, P < 0.005) and increase in shunt fraction (50 ± 6 vs. 11 ± 3%, P < 0.001) compared with sham injury animals (Fig. 1). Airway plateau pressures reflected the severity of injury (ALI 28 ± 2 vs. sham 13 ± 1 cmH2O, P < 0.001).

Lung histology. Grossly, lungs from injured canines demonstrated profound edema and hemorrhage with a predilection for dependent regions. Figure 2 shows representative histology (H&E staining) from injured (A, B, C) and control (D) animals. Microscopically, lungs from injured animals showed heterogeneous injury, with large patchy areas of extensive hemorrhage, edema, and neutrophil infiltration.

Hemodynamics. MAP, pulmonary artery occlusion (Paop), and CVP pressures did not change significantly over the course of the study protocol and were not significantly different between groups (Fig. 3). CO decreased from baseline in both groups, although was only statistically lower in the injury group beginning 60 min into the protocol. CO was significantly lower at 180 min in the injured animals compared with sham subjects. Fluid administration over the course of the experiments was similar between sham and lung injury animals (Fig. 4). Total fluid administration was not different between groups or over the course of the experiments (Fig. 5), and there was no difference from sham-treated animals.

Arterial blood gases and hemoglobin. Arterial pH and PCO2 were not different between groups or over the course of the experiments (Fig. 4). Arterial Po2 was similar at baseline (sham: 219 ± 24 vs. injury: 244 ± 23 mmHg, P = 0.43), but decreased in the injury group over the course of the experiment, and was significantly lower than the sham group within 60 min (sham: 190 ± 17 vs. injury: 103 ± 13 mmHg, P = 0.003) of injury and remained so for the 300-min study duration (sham: 176 ± 24 vs. injury: 64 ± 10 mmHg, P = 0.004). Hemoglobin levels increased in the injury group over the course of the experiment from 9.1 ± 0.6 to 12.7 ± 0.6 mg/dl (P < 0.05) and were significantly higher than sham animals at the end of the protocol, reflecting hemoconcentration related to the fluid accumulation in the injured lung.

Renal function. Measurements of renal function are shown in Fig. 6. Serum creatinine, urine sodium, and urine flow rate remained stable throughout the protocol and were not different between groups. Urine creatinine decreased from baseline in the sham group but was not different from the injury group. Urine osmolality in the sham group decreased significantly by 180 min and was significantly lower than the injury group. Urine albumin-to-creatinine ratio (Alb/Cr) increased significantly in the sham animals from baseline (0.5 ± 0.1) to 2.1 ± 0.9 at the end of the experiment (P < 0.008). Although a similar trend was observed in the injury group, it did not reach statistical significance. GFR remained stable throughout the protocol and was not different between groups. Moreover, loss of inulin into bronchoalveolar lavage (BAL) fluid as a potential confounder (as was seen with PAH) was not observed (data not shown).

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Fig. 2. Evidence of alveolar injury in dependent lung areas instilled with hydrochloric acid. A: extensive recent hemorrhage in peribronchial and perivascular connective tissue (arrows). B: alveolar edema, incipient hemorrhage, and early neutrophil influx (arrows). C: marked neutrophilic infiltration in alveolar spaces (arrows). D: tissue from control animal showing normal nondependent lung with preserved airway, pulmonary vessels, and alveolar tissue. Hemotoxylin and eosin, A: ×10 lens; B: ×20 lens.
Renal histology. Kidney histology scores reflected no injury and were the same between the injured and sham animals. Mean cumulative histology scores were baseline (0.3 ± 0.5), injury (1.1 ± 0.2), and sham (1.0 ± 0.1). We performed EM examination of the kidney (Fig. 7) to evaluate possible structural changes responsible for the observed increase in urine albumin-to-creatinine ratio from both control and acid aspiration dogs. Kidneys were collected at the end of mechanical ventilation upon death, and small portions of each were fixed in glutaraldehyde and processed for EM examination. We found
that while podocyte foot processes remained almost completely intact in the control animal, the foot processes in the kidney from the dog subjected to acid aspiration became partially effaced (Fig. 7). We also noted very segmental mesangial electron-dense deposits in the control kidney (not shown).

Serum cytokines. Serum cytokines were not different between sham and injury groups for any of the cytokines measured (TNF-α, IL-6, IL-10, and INF-γ) over the course of the experiment (Fig. 8). Overall, values tended to decrease over the experiments after an initial increase from baseline within groups, although without statistical significance. Both surgical manipulation for insertion of RBF probes (n = 2) and intravenous LPS (n = 2) transiently increased serum cytokines and thus served as positive controls to validate our assays. In addition, LPS-treated animals had a dramatically decreased GFR (data not shown) which served to demonstrate sensitivity of our inulin clearance assays.

Caspase-3 activity. Caspase-3 activity in kidney and lung tissue homogenates was not different between groups.

DISCUSSION

We established a canine model of severe ALI caused by acid aspiration and high tidal volume ventilation that leads to profound elevations in airway peak and plateau pressures and perturbation of gas exchange. Our degree of lung injury was more severe than described in the small animal models (9, 11, 13, 23). Hemodynamics and oxygenation were optimally controlled. Under these conditions, over a 5-h observation period, no alterations in inulin clearance, RBF, urine flow or electrolytes, or kidney histology were observed. However, both ALI and sham animals had increases in urine albumin excretion. Systemic cytokines did not increase in the face of profound lung injury.

Despite the severity of lung injury, alveolar ventilation and hemodynamic parameters were maintained within an acceptable range with aggressive management. Preservation of renal function is intimately tied to renal perfusion, thus maintenance of RBF is paramount. RBF is determined by complex interactions of driving pressure, autonomic nervous system tone, hormonal activation and inhibition. Although not entirely understood in the canine, autoregulatory RBF mechanisms are thought to function over a range of MAP between 70 and 170 mmHg (10, 14, 29). In our experiments, MAP remained stable and well within this range, compatible with preserved RBF. In one small animal study in which blood pressure was monitored continuously, MAP was maintained at 55–60 mmHg, a level much closer to the lower limit of intrinsic renal autoregulation (11), which may account for some of the alterations seen in renal function in that rabbit model of acid aspiration- and mechanical ventilation-associated lung injury.

Arterial Pco2 and pH have similarly been demonstrated to influence RBF through autonomic activation or direct vasoactive interactions (2, 8, 25). In our experiments, these influences remained stable and not different between groups. CO fell slightly in injury group compared with sham but was equal by the end of the 5 h. Heart rate was not different between groups and not different over the course of the experiments. Thus, the alterations in CO were likely related to stroke volume. Since filling pressures remained constant throughout (or trended upward), this reduced stroke volume suggests reduced contractility. Previous studies showed that IT-HCl induces cardiac depression (26), but the mechanisms are not entirely understood. We could postulate a direct influence of acid treatment on autonomic function, although we failed to observe a significant systemic acidosis. Another possible cause of the change in stroke volume could be related to alterations in end diastolic volume from stiffening of the myocardium related to edema formation. We did not assess the myocardium of the injured animals histologically, but if there is leak of fluid in other tissues, it is possible that the myocardium suffered a similar reaction with an accumulation of intercellular fluid and reduced compliance. There may also have been a direct cardio-depressant effect of the medications used for anesthesia on CO (5, 6), although the drugs and doses used were the same between groups. Finally, increased airway pressures from maintaining tidal volume to the injured lung would increase intrathoracic pressure, reducing effective preload and increasing afterload, although the transmission of increased alveolar pressure to the intrathoracic space is somewhat mitigated by the increased lung stiffness. Nevertheless, the fall in CO had no apparent effect on MAP and RBF.

Animals received fluid replacement by protocol with predefined criteria for supplementation for hypotension and drops

Fig. 5. A: measurements of para-aminohippurate (PAH) in bronchoalveolar lavage samples from injury and sham animals. There was significant leakage of PAH into the alveolar spaces in injury animals, thus altering measurements of renal blood flow by PAH clearance (*P < 0.01). B: comparison of renal blood flow measurements using PAH and direct measurement with renal artery flow probes. Note the stability of measurements with renal flow probe in injured animals compared with PAH measurements in sham-treated animals throughout the experimental protocol. PAH measurements in injured animals were widely variable and tended to overestimate direct measurements.
in CO, and fluid loading was withheld if cardiac filling pressures remained stable. In these experiments, no animal required fluid loading for hypotension. Animals did receive fluid boluses for drops in CO of greater than 30% from baseline; however, the magnitude of the fluid loading was similar between groups. As filling pressures remained within our predefined acceptable range, a strategy of continuing to fluid load the animals was not followed, and CO was allowed to decline. Moreover, with the severity of pulmonary edema in the injury group, persistent volume loading would likely have led to an increase in fluid extravasation into the lungs, thus worsening oxygenation, shunt fraction, and plateau pressures in the injured lungs. This compromise strategy led to a relative hypovolemia in the injured animals, evidenced by the progressive rise in hemoglobin, which did not compromise MAP or renal perfusion. If anything, one would expect this hypovolemia to have increased the risk of renal dysfunction.

RBF measurements through the clearance of PAH showed widely variable changes throughout the protocol. We suspected the cause of this variability arose from the assumption that all

**Fig. 6. Renal outcome measurements.** There was no difference in urine output, glomerular filtration rate (GFR), serum creatinine, or urine sodium between groups or over the course of the experiments. Urine osmolality decreased in the injury group in the later time points of the protocol, demonstrating preserved concentrating ability of the kidneys, and urine creatinine decreased in the control group in the setting of volume loading. Urine albumin-to-creatinine ratio increased over the experimental protocol but reached significance only in the sham group. *P < 0.05 vs. baseline. *P < 0.05 vs. sham.
of the PAH in the animal is cleared through the kidney without extrarenal losses. To test this, we measured the concentration of PAH from BAL samples and found that there was significant loss of PAH into the protein-rich alveolar edema fluid induced by the lung injury. We therefore concluded that PAH clearance is not an accurate reflection of actual RBF in this lung injury model. We directly measured RBF with surgically placed renal artery flow probes in a subset of animals. These measurements showed stable RBF throughout the protocol. As MAP was maintained in the autoregulatory range of the kidney, RBF should also remain stable unless there is a direct effect of the ALI or mechanical ventilation on these autoregulatory mechanisms.

Given that pilot studies failed to show changes in serum creatinine, a late and insensitive marker of AKI, we set up inulin clearance measurements, the gold standard for GFR. Importantly, measurement of GFR by inulin clearance should be unaffected by extrarenal losses (although no increase in BAL inulin was found). GFR was unchanged throughout the experiments in both groups. In addition, urine creatinine did not change, although urine osmolality increased in the injury group with comparable urine volumes, representing the preserved ability of the kidney to concentrate urine to maintain intravascular volume with volume loss into lungs. There was no evidence of histological injury to the kidneys by H&E staining. Finally, since kidney apoptosis has been demonstrated in a lung injury model in rabbits (11), we assessed the degree of apoptosis by caspase-3 assays, which were not different in injured and sham animals in lung and kidney tissue lysates.

Fig. 7. Electron microscopy of kidney. Electron micrographs of kidneys from dogs receiving saline (A) or HCl aspiration (B) and then undergoing 5-h mechanical ventilation. The podocyte foot processes remained intact in the control kidney (thin arrows) but became partially effaced (thick arrows) in the kidney of the dog subjected to acid aspiration. A total of 2–3 glomeruli from each animal were examined and findings were similar in all glomeruli from the same animal. Uranyl acetate and lead citrate stain; original magnification of both electron micrographs ×3,800.

Fig. 8. Serum cytokines in pg/ml measured at baseline and throughout the experiments. LPS induced significant increases compared with surgery and profound increases compared with both sham and injury groups in those measured.
There was a significant increase in urine albumin-to-creatinine ratio in control animals, and a trend for increase in the lung injury group. This finding suggests that there is a direct effect of either mechanical ventilation or anesthesia on permeability in the kidney. As protein-rich fluid accumulates in the alveolar space in response to ALI from acid aspiration, losses of albumin into the edema fluid in the lung may have reduced the concentration gradient for loss in the kidney. Previously, microalbuminuria has been proposed as a marker of a renal microvascular leak phenomenon in the setting of mechanical ventilation/lung injury (3, 7) possibly related to a renal hemodynamic and renal perfusion model of canine acid aspiration. However, there are a number of limitations to our study. One is related to the small number of animals in each of the study groups, given the significant cost of canine work. It is possible that small changes in renal function may be found with larger sample sizes. Also, this study was designed to determine the effects of ALI and mechanical ventilation early in the course of injury. In small animal models, changes can be seen early (<2 h in some cases) after induction of lung injury. It is possible that when followed longer, evidence of kidney dysfunction could be observed in this model. We did not perform mRNA studies or inflammatory markers in kidney, as performed in previous small animal studies.

In conclusion, although significant clinical and small animal data suggest a kidney-lung interaction in the setting of ALI and mechanical ventilation, we were not able to demonstrate in this canine aspiration model early in the course of injury when hemodynamic and alveolar ventilation influences were controlled. It is possible that transient hypotension that is readily apparent in patients as they develop ALI and are sedated and intubated for mechanical ventilatory assistance, or unmeasured hemodynamic influences in the small animal models, may propagate a lung-kidney interaction in this setting. As patients with ALI/ARDS continue to die from multisystem organ failure, finding mechanisms linking distant organs function and dysfunction is of paramount importance.

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