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Retrospective evaluation of the prevalence, risk factors, management, outcome, and necropsy findings of acute lung injury and acute respiratory distress syndrome in dogs and cats: 29 cases (2011–2013)

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Abstract

Objective – To determine the prevalence and risk factors for veterinary acute lung injury (VetALI) and veterinary acute respiratory distress syndrome (VetARDS), assess mechanical ventilation settings and patient outcomes, and to evaluate the relationship of clinical diagnoses with necropsy findings.
Design – Retrospective study.
Setting – University teaching hospital.
Animals – Twenty-four dogs and 5 cats with a clinical diagnosis of VetALI or VetARDS. Control population includes 24 dogs and 5 cats with a clinical diagnosis of respiratory disease other than VetALI or VetARDS.
Interventions – None.
Measurements and Main Results – VetALI and VetARDS were diagnosed in 3.2% of dogs and 1.3% of cats presenting to the ICU. Systemic inflammatory response syndrome was the most common inciting condition (16/24 dogs, 2/5 cats), followed by vomiting and subsequent aspiration of gastric contents (9/24 dogs), sepsis (5/24 dogs, 3/5 cats), multiple transfusions (4/24 dogs), trauma (3/24 dogs), and adverse drug reactions (1/24 dogs, 1/5 cats). None of these conditions were found to be significantly associated with a risk of development of VetALI or VetARDS when compared to controls. Twelve dogs (50%) and 4 cats (80%) underwent mechanical ventilation for a median duration of 18 hours in dogs (range: 6–174 h) and 15.5 hours in cats (range: 6–91 h). Overall, 3/29 patients survived to discharge including 2/24 dogs and 1/5 cats. Necropsy results were available for 8/22 dogs and 3/4 cats. A total of 6/8 dogs (75%) dogs and 3/3 (100%) cats met the histopathologic criteria for diagnosis of VetALI or VetARDS.
Conclusions – VetALI and VetARDS can cause life-threatening respiratory distress in dogs and cats necessitating mechanical ventilation in 50% of dogs and 80% of cats in this study. These diseases are associated with a poor clinical outcome and a high rate of humane euthanasia.

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Keywords: ALI, ARDS, feline, mechanical ventilation, VetALI, VetARDS

Abbreviations

A-a gradient	gradient between alveolar and arterial partial pressure of oxygen
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
CT	computed tomography
I:E ratio	ratio of inspiratory time to expiratory time
OI	oxygenation index
OR	odds ratio
PaO_2/FiO_2	ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
PrCV	pressure-controlled ventilation
PEEP	positive end-expiratory pressure
PIP	peak inspiratory pressure

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The authors declare no conflicts of interest.

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SIRS	systemic inflammatory response syndrome
Vd/Vt	ratio of dead space ventilation to total tidal volume
VetALI	veterinary acute lung injury
VetARDS	veterinary acute respiratory distress syndrome
Vt	tidal volume

Introduction

Acute respiratory distress syndrome (ARDS) is a devastating clinical condition associated with peracute onset of respiratory distress that is characterized by severe hypoxemia and bilateral diffuse alveolar infiltrates seen on thoracic radiographs, and is not caused by left atrial hypertension or hydrostatic pulmonary edema.[1–4] Improved understanding of the pathophysiology of ARDS in recent decades has shown that ARDS is typically triggered by systemic inflammation and can progress to multiple organ dysfunction syndrome. Several inciting conditions for ARDS in people have been reported, including sepsis, pneumonia, burn injury, pancreatitis, transfusions, and trauma.[1,2] Mortality rates in people remain at approximately 35–40% despite improved management and changes in mechanical ventilation practices.[1,3–7]

The definition of ARDS in human medicine has changed in recent years. The American-European Consensus Conference led to the first broad consensus of definitions in 1994, where ARDS was defined as acute onset of hypoxemia with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) $\leq$ 200 mm Hg, with bilateral infiltrates on thoracic radiographs in the absence of left atrial hypertension.[8] The term acute lung injury (ALI) was used to define a condition with the same variables but less severe hypoxemia (PaO_2/FiO_2 ratio $\leq$ 300 mm Hg).[8] In an effort to improve the reliability and validity of definitions and diagnostic criteria of this disease, the Berlin Definition of ARDS was proposed in 2012.[9] Major changes introduced in this definition included the addition of a definitive timeframe for onset of clinical signs, removal of the criterion for pulmonary artery wedge pressure, and addition of a minimum level of positive end-expiratory pressure (PEEP) as well as mutually exclusive thresholds of PaO_2/FiO_2 to stratify patients based on the severity of ARDS (mild, moderate, and severe). Several therapeutic strategies for ARDS in recent years have been evaluated, including pharmacologic interventions and mechanical ventilation techniques. Of these, the concept of low tidal volume (Vt) ventilation (also known as lung protective ventilation) has received the most attention and has been shown repeatedly to improve outcomes in people with ARDS.[5–7]

There is limited veterinary literature on ARDS in small animals and the overall prevalence of ARDS in dogs and cats is largely unknown. A series of 2 retrospective studies on 19 dogs with ARDS[10,11] evaluated clinicopathologic features and the respiratory function of dogs diagnosed with ARDS based on necropsy findings. A study evaluating the use of positive pressure ventilation in cats showed that 2/36 cats ventilated for respiratory failure were diagnosed with ARDS, and neither cat survived to discharge.[12] A study of severe blunt trauma in dogs showed that ARDS was associated with nonsurvival to discharge.[13] A 2007 study evaluating positive pressure ventilation in dogs and cats reported ARDS in 16% of patients ventilated for hypoxemia unresponsive to oxygen supplementation. In that study, patients with ARDS had the lowest survival rates of all pulmonary disease processes (8.33%).[14] A case report published in 2013 documented the successful treatment of a French Bulldog with ARDS using airway pressure release ventilation.[15]

In 2007, the first clinically based veterinary consensus definitions on the syndromes of acute lung injury (VetALI) and acute respiratory distress syndrome (VetARDS) were published. Five diagnostic criteria were published, with 4 required, and a fifth highly recommended criterion (Table 1).[16] To the authors' knowledge, no veterinary studies have evaluated the clinical diagnosis of ARDS using these criteria and evaluated the diagnostic criteria in conjunction with necropsy findings.

The goals of the present study were to determine the prevalence of VetALI and VetARDS in a busy, urban university setting in a 3-year period and to evaluate outcomes in these patients. This study also aimed to evaluate mechanical ventilation settings where applicable, and to evaluate various risk factors implicated in the development of VetALI or VetARDS. Lastly, this study aimed to determine whether patients diagnosed with VetALI or VetARDS had histopathologic evidence of the same on necropsy findings, when available.

Materials and Methods

The medical records of the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania were searched to identify dogs that were diagnosed with VetALI or VetARDS between January 1, 2011, and December 31, 2013. Patients were included if they were admitted to the ICU, and if they fulfilled the diagnostic criteria for VetALI or VetARDS previously published.[16] Patients were excluded if they were euthanized within 24 hours after a diagnosis of VetALI or VetARDS was made in the Emergency Service based on clinical signs without additional supportive diagnostic testing.

Table 1: Diagnostic criteria for VetALI/VetARDS[16]

First 4 criteria required, fifth is optional but highly recommended

1. Acute onset (≤72 h) of tachypnea and labored breathing at rest.
2. Known risk factors (SIRS, sepsis, trauma, aspiration of gastric contents, multiple transfusions, adverse drug reactions, smoke inhalation, and drowning).
3. Evidence of pulmonary capillary leak without increased pulmonary capillary pressure (any ≥1 of the following):
   (a) Bilateral/diffuse infiltrates on thoracic radiographs (>1 quadrant/lobe)
   (b) Bilateral dependent density gradient on CT
   (c) Proteinaceous fluid within the conducting airways
   (d) Increased extravascular lung water
4. Evidence of inefficient gas exchange (any ≥1 of the following):
   (a) Hypoxemia without PEEP or CPAP and known FiO_2
      i. PaO_2/FiO_2 ratio
         1. ≤300 mm Hg for VetALI
         2. ≤200 mm Hg for VetARDS
      ii. Increased alveolar-arterial oxygen gradient
      iii. Venous admixture (noncardiac shunt)
   (b) Increased "dead-space" ventilation
5. Evidence of diffuse pulmonary inflammation
   (a) Transtracheal wash/bronchoalveolar lavage sample with neutrophilia
   (b) Transtracheal wash/bronchoalveolar lavage with biomarkers of inflammation
   (c) Molecular imaging such as positron emission tomography

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; CT, computed tomography; PEEP, positive end-expiratory pressure; SIRS, systemic inflammatory response syndrome.

Patients were also excluded if cardiogenic causes of respiratory distress were not definitively ruled out with thoracic radiographs or echocardiography, based on the medical record available. Patients with incomplete medical records were excluded.

Data collected for all study patients included signalment, presenting complaint, final diagnosis, duration of clinical signs, and presence or absence of the following risk factors for VetALI and VetARDS based on the veterinary consensus definitions: systemic inflammatory response syndrome (SIRS; diagnosed based on previously published criteria),[17] sepsis confirmed cytologically or with culture, trauma, multiple transfusions, smoke inhalation, drowning, aspiration of stomach contents, and adverse reactions to drugs and toxins.[16] The presence of hypoxemia due to poor lung function was determined by evaluating either PaO_2/FiO_2 ratio, the pulse oximetry (SpO_2) based SpO_2/FiO_2 ratio, or alveolar-arterial oxygen gradients (A-a gradient). An A-a gradient > 10 mm Hg on room air (FiO_2 of 0.21) was considered abnormal.[18] The A-a gradient was not calculated for dogs receiving oxygen supplementation at the time arterial blood gas samples were drawn. For the SpO_2/FiO_2 ratio, a cutoff of 315 was considered equivalent to a PaO_2/FiO_2 ratio of 300, and a cutoff of 235 was considered equivalent to a PaO_2/FiO_2 ratio of 200, based on previous findings in people.[19] The presence of pulmonary capillary leak in the absence of increased hydrostatic pressure was assessed by evaluation of either thoracic radiographs, thoracic computed tomography (CT) scan, echocardiography, or the presence of neutrophilic, proteinaceous airway fluid. Cardiogenic pulmonary edema was ruled out using thoracic radiographs by evaluation of cardiac and pulmonary vessel size, and distribution of pulmonary infiltrates. All thoracic radiographs and CT scans were evaluated by a board-certified radiologist, and all echocardiograms were reviewed by a board-certified cardiologist. The presence of airway inflammation was evaluated by recording results of endotracheal or trans-tracheal washes collected upon admission or the initiation of mechanical ventilation. All the airway samples were reviewed by a board-certified pathologist for cytologic evaluation. All samples were submitted for aerobic culture and sensitivity analysis.

Mechanical ventilation

The initiation of mechanical ventilation was recorded, if applicable, and the following settings and values were recorded:

1. Mode of ventilation (pressure or volume assist-control or synchronized intermittent mandatory ventilation)
2. Initial set respiratory rate (breaths/min)
3. Initial and final ratio of inspiratory to expiratory time (I:E ratio)
4. Initial and average Vt (mL/kg)
5. Initial and average PEEP, cm H_2O
6. Initial and average peak inspiratory pressure (PIP) (cm H_2O)
7. Initial and average dead space ventilation (Vd/Vt) calculated as $[PaCO_2 - ETCO_2]/PaCO_2$. For patients where an arterial PCO_2 was unavailable, this was not calculated.
8. Initial and final (prior to weaning, death, or euthanasia) oxygenation index (OI) calculated as $[FiO_2 \times MAP \times 100]/PaO_2$
9. Final PaO_2/FiO_2 ratio recorded prior to weaning, death, or euthanasia

The duration of mechanical ventilation (h), duration of hospitalization (d), and outcome (survived to discharge, died, or euthanized) were recorded for all patients. The presence of co-morbidities was recorded, when known, and necropsy findings were recorded, if available.

Control population for risk factor analysis

To evaluate the effects of various risk factors on the prevalence of VetALI or VetARDS, age-matched controls were identified from the same time period. These were patients that were hospitalized in the ICU for respiratory disease other than VetALI or VetARDS. Information recorded for these patients included signalment, presenting complaints, co-morbidities, duration of hospitalization, and final outcome. The presence or absence of the following known risk factors for VetALI and VetARDS[16] (SIRS, sepsis, trauma, multiple transfusions, smoke inhalation, drowning, aspiration of stomach contents, and adverse reactions to drugs and toxins) was recorded in each of these patients.

Statistical Analysis

Continuous variables were evaluated for normality using the Shapiro–Wilk test. Normally distributed data are reported as mean (±SD), while nonparametric data are reported as median (range). Risk factor analysis was performed using univariate logistic regression and the results are reported as odds ratios (ORs) with 95% confidence intervals calculated using the Woolf method. In the instances of 0 cell counts, ORs could not be calculated and the *P*-value was determined by Fisher's exact test. For all comparisons, a P-value < 0.05 was considered significant. Data were analyzed using commercially available software.[a]

Results

A total of 1,000 dogs and 395 cats were admitted to the ICU during the 3-year study period. Of these patients, 32 dogs and 5 cats were diagnosed with VetALI or VetARDS, resulting in a period prevalence of 3.2% in dogs and 1.3% in cats, respectively, in the 3 years studied. Eight dogs were excluded because of incomplete medical records. A total of 29 patients (24 dogs and 5 cats) were included in this study.

The mean age was 9.4 ± 3.9 years for dogs, and 9.4 ± 2.3 years for cats. The median weight was 10.4 kg for dogs (range: 2–63 kg), and 3.6 kg (range: 3.1–6 kg) for cats. Various dog breeds were represented, with Yorkshire Terriers being the most common ($n = 5$), followed by mixed breed dogs ($n = 3$), and 1 of each: French Bulldog, English Setter, Miniature Poodle, Standard Poodle, Toy Poodle, English Bulldog, Siberian Husky, Miniature Schnauzer, Labrador Retriever, Pomeranian, Rhodesian Ridgeback, Maltese, Dachshund, Pug, Great Dane, and Jack Russell Terrier. Of the 5 cats, 4 were domestic shorthairs and 1 was a domestic longhair.

All 29 patients had acute onset of clinical signs within 72 hours of presentation. The presenting complaints varied widely, and included most commonly respiratory distress (14/29), vomiting and/or regurgitation (8/29), lethargy (6/29), cough (5/29), witnessed trauma (3/29), and anorexia (3/29). One dog presented for an infusion of cystosine arabinoside following a previous diagnosis of granulomatous meningoencephalitis, and developed signs of VetARDS immediately following the drug infusion. One cat presented for chemotherapy administration following a previous diagnosis of gastrointestinal lymphoma, and was accidentally administered an overdose of vincristine, subsequent to which it developed signs of VetARDS. On physical examination at the time of diagnosis of VetALI or VetARDS, all patients had evidence of labored breathing at rest. The median initial respiratory rate at rest at the time of diagnosis was 46 breaths/minute (range: 23–80 breaths/min).

All patients had ≥1 risk factor for VetALI or VetARDS, with 12/24 dogs and 1/5 cats having multiple risk factors present (Table 2). The most common risk factor present was SIRS (16/24 dogs; 2/5 cats), followed by vomiting and aspiration of gastric contents (9/24 dogs), sepsis (5/24 dogs; 2/5 cats), multiple transfusions (4/24 dogs), trauma (3/24 dogs), and adverse drug reactions (1/24 dogs; 1/5 cats). None of the patients in this study had smoke inhalation or drowning as risk factors for

Table 2: Risk factors in dogs and cats for VetALI/VetARDS

	Dogs (*n*)		Cats (*n*)	
Risk factor	**Cases**	**Controls**	**Cases**	**Controls**
SIRS	16/24	12/24	2/5	3/5
Pancreatitis	4/16	1/12	–	–
Tracheal collapse	4/16	–	–	–
Neoplasia	3/16	3/12	1/2	1/3
Hemoabdomen following adrenalectomy	1/16	–	–	–
Acute kidney injury	1/16	–	–	–
Other	3/16	8/12	1/2	2/3
Aspiration of gastric contents (witnessed or suspected)	9/24	7/24	0/5	0/5
Multiple transfusions	4/24	0/24	0/5	0/5
Trauma	3/24	0/24	0/5	0/5
Multiple bite wounds	3/3	–	–	–
Pulmonary contusions	3/3	–	–	–
Rib fractures	2/3	–	–	–
Long bone fractures	1/3	–	–	-
Sepsis	5/24	11/24	3/5	2/5
Pyothorax	–	–	1/3	1/2
Pyelonephritis	1/5	–	1/3	–
Cervical abscess	–	–	1/3	–
Bacterial pneumonia	4/5	11/11	–	1/2
Adverse drug reactions	1/24	0/24	1/5	0/5
Smoke inhalation	0/24	0/24	0/5	0/5
Near drowning	0/24	0/24	0/5	0/5

n, number; SIRS, systemic inflammatory response syndrome.

VetALI or VetARDS. For patients with SIRS, causes of systemic inflammation included pancreatitis (4/9 dogs; 1/2 cats), tracheal collapse (4/9 dogs), neoplasia (3/9 dogs), hemoabdomen (1/9 dogs), acute kidney injury (1/9 dogs), and others (1/2 cats). A majority of the patients had multiple co-morbidities including tracheal collapse (4/29), pancreatitis (4/29), protein-losing nephropathy (1/29), brachycephalic airway syndrome (1/29), megaesophagus (1/29), inflammatory bowel disease (1/29), Well's-like syndrome (1/29), severe otitis interna (1/29), and necrotizing encephalitis (1/29). One dog and 1 cat experienced cardiopulmonary arrest and respiratory arrest, respectively, and were resuscitated successfully prior to development of VetARDS.

Thoracic radiographs were performed in 23/24 (96%) dogs and 5/5 (100%) cats in the patient group. Multilobar patchy alveolar infiltrates were seen in all 28 patients, tracheal collapse was evident in 2 patients, tracheal stents were seen in place in 2 patients, and mild pleural effusion was noted in 1 patient. Thoracic CT was performed in 2 dogs and in each case, bilateral dependent density gradients in multiple lung lobes were evident. Fluoroscopy was performed in 4 patients (all 4 were dogs with evidence of tracheal collapse). Cardiogenic pulmonary edema was ruled out through thoracic radiographs in 24/28 (86%) patients. Four patients (14%) including 2 dogs and 2 cats had an echocardiographic examination to definitively rule out cardiogenic pulmonary edema. The 1 dog that did not have thoracic radiographs performed was deemed too unstable for imaging, and was diagnosed with pulmonary capillary leak on the basis of the presence of proteinaceous, neutrophilic airway fluid.

Initial arterial blood gas values were available for 19/24 (79%) dogs in the patient group. The PaO_2/FiO_2 ratio was ≤ 200 in 14/19 (74%) dogs, supportive of a diagnosis of VetARDS (median, 120; range: 48.3–193). The PaO_2/FiO_2 ratio was > 200 but ≤ 300 in the remaining 5 dogs (26%), supportive of a diagnosis of VetALI (median, 246; range: 233–300). An A-a gradient with a FiO_2 of 0.21 was calculated for 8 dogs and was increased in all dogs with a mean of 64.5 ± 9.3 mm Hg. For 5/24 dogs, initial arterial blood gas values were not available. All these dogs had hypoxemia evidenced by a decreased SpO_2/FiO_2 ratio with a mean ratio of 168 ± 27.7. None of the 5 cats had arterial blood gas values available; however, all of them had evidence of hypoxemia with decreased SpO_2/FiO_2 ratios with a mean ratio of 130.3 ± 43.3.

Endotracheal wash findings were reported in 12/24 (50%) dogs and 3/5 (60%) cats and were consistent with severe neutrophilic pulmonary inflammation. Three dogs had evidence of septic suppurative inflammation with intracellular bacteria seen on cytology. All 3 patients had a positive bacterial culture. One additional dog had a positive bacterial culture from the endotracheal wash but no bacteria noted on cytology.

Risk factor analysis

The control population included 24 dogs and 5 cats. In the dog population, there were 4 mixed breed dogs, 2 each of West Highland White Terriers and Miniature Poodles, and 1 dog each of other breeds. The control cats included 4 domestic shorthairs and 1 Siamese. The median weight of the control dogs was 10.7 kg (range: 1.4–56 kg); the median weight of the control cats was 4.5 kg (range: 3.1–5.9 kg). No significant differences were found between the cases and control population with respect to weight ($P = 0.8286$). The most common disease processes diagnosed in the control dog population included aspiration pneumonia (9/24), pulmonary thromboembolism (6/24), neoplasia (5/24), infectious pneumonia (3/24), and neurogenic pulmonary edema (2/24). Pulmonary thromboembolism was diagnosed definitively in 2 dogs based on necropsy findings and suspected in the remaining 4 dogs based on a combination of a hypercoagulable state, acute onset of dyspnea, and echocardiographic evidence of acute pulmonary hypertension. The disease processes diagnosed in the control cat population included asthma (2/5), pyothorax with a pulmonary abscess (1/5), neoplasia (1/5), and pneumonia (1/5). The following risk factors were examined in the study population and compared to the age-matched controls in both dogs and cats: vomiting and aspiration of gastric contents (OR, 1.4; $P = 0.556$), sepsis (OR, 0.41; $P = 0.104$), SIRS (OR, 1.5; $P = 0.426$), multiple transfusions (OR, 4.5; $P = 0.16$), adverse drug reactions (Fisher's exact test, $P = 0.491$), and trauma (Fisher's exact test, $P = 0.112$). None of these were found to have a statistically significant effect on the development of VetALI and VetARDS. None of the control animals required mechanical ventilation.

Mechanical ventilation settings and patient parameters

A total of 12/24 (50%) dogs and 4/5 (80%) cats were mechanically ventilated using the same type of machine.[b] The average duration of mechanical ventilation was 18 hours in dogs (range: 6–174 h) and 15.5 hours in cats (range: 6–91 h). All patients underwent pressure-controlled ventilation (PrCV) with either assist-control mode in 7/12 dogs and 2/4 cats, or synchronized intermittent mandatory ventilation in 5/12 dogs and 2/4 cats. The initial median set respiratory rate was 27.5 breaths/minute in dogs (range: 20–65) and 22.5 breaths/minute in cats (range: 18–30). The initial I:E ratio was 1:2 in 4/12 dogs and all 4 cats, 1:1.4 in 1/12

Table 3: Mechanical ventilation parameters in dogs and cats with VetALI or VetARDS

Parameter	Dogs	Cats
Number of patients mechanically ventilated	12/24 (50%)	4/5 (80%)
Median duration of mechanical ventilation (h)	18 (range: 6–174)	15.5 (range: 6–91)
Mode: PrCV-SIMV	5/12 (41.7%)	2/4 (50%)
PrCV-A/C	7/12 (58.3%)	2/4 (50%)
Median initial RR (breaths/min)	27.5 (range: 20–65)	22.5 (range: 18–30)
Initial I:E ratio	1:3	1/12 (8.3%)
1:2.5	1/12 (8.3%)	–
1:2	4/12 (33.3%)	4/4 (100%)
1:1.4	1/12 (8.3%)	–
1:1.2	2/12 (16.7%)	–
1:1	2/12 (16.7%)	–
3.8:1	1/12 (8.3%)	–
Final I:E ratio	1:2.5	3/12 (25%)
1:2	6/12 (50%)	4/4 (100%)
1:1	2/12 (16.7%)	–
2.8:1	1/12 (8.3%)	–
Median Vt initial (mL/kg)	9.35 (range: 7.5–26.7)	9.4 (range: 7.3–11.6)
Average	12.4 (range: 6.8–25.8)	10.2 (range: 8.3–13.6)
Mean PEEP (cm H_2O)		
Initial	6.1 ± 1.3	5.5 ± 1.9
Average	7 ± 3.1	3.5 ± 1.2
Mean PIP (cm H_2O)		
Initial	25.1 ± 8.1	14.8 ± 4.4
Average	25.5 ± 7.8	18.3 ± 5.7
Mean Vd/Vt initial	0.63 ± 0.26	Not calculated
Average	0.69 ± 0.25	
Median OI initial	10.7 (range: 2.8–47.6)	Not calculated
Final	11.4 (range: 1.8–28.3)	
Median PaO_2/FiO_2 prior to weaning, death, or euthanasia	120.4 (range: 74–388)	Not calculated

A/C, assist control; OI, oxygenation index; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PrCV, pressure-controlled ventilation; RR, respiratory rate; SIMV, synchronized intermittent mandatory ventilation; Vd/Vt: dead space ventilation; Vt: tidal volume.

dogs, 1:1.2 in 2/12 dogs, 1:1 in 2/12 dogs, 1:3 in 1/12 dogs, 1:2.5 in 1/12 dogs, and 3.8:1 in 1/12 dogs. The final I:E ratio prior to weaning, death, or euthanasia was 1:2 in 6/12 dogs and all 4 cats, 1:2.5 in 3/12 dogs, 1:1 in 2/12 dogs, and 2.8:1 in 1/12 dogs. The initial Vt was 9.35 mL/kg in dogs (range: 7.5–26.7) and 9.4 mL/kg in cats (range: 7.3–11.6). The average Vt throughout the duration of mechanical ventilation was 12.4 mL/kg in dogs (6.8–25.8) and 10.2 mL/kg in cats (8.3–13.6). The initial PEEP was 6.1 ± 1.3 cm H_2O in dogs and 5.5 ± 1.9 cm H_2O in cats. The average PEEP throughout the duration of mechanical ventilation was 7 ± 3.1 cm H_2O in dogs and 3.5 ± 1.2 cm H_2O in cats. The initial PIP was 25.1 ± 8.1 cm H_2O in dogs and 14.8 ± 4.4 cm H_2O in cats. The average PIP throughout the duration of mechanical ventilation was 25.5 ± 7.8 cm H_2O in dogs and 18.3 ± 5.7 cm H_2O in cats. The initial and average Vd/Vt values in dogs were 0.63 ± 0.26 and 0.69 ± 0.25, respectively. The median initial and final values for OI in dogs were 10.7 (range: 2.8–47.6) and 11.4 (range: 1.8–28.3), respectively. The ventilator settings and patient parameters are summarized in Table 3.

Duration of hospitalization and outcome data – patient group

The median duration of hospitalization was 3.5 days (range: 1–13 d) for dogs and 2 days for cats (range: 2–14 d). Overall, 3/29 (10.3%) patients survived to discharge including 2/24 dogs, and 1/5 cats. Thus, an overall mortality rate of 90% was found in this study with 92% of dogs and 80% of cats succumbing to the disease. Of the 2 dogs that survived, 1 dog was weaned successfully from the ventilator. The other dog that survived to discharge did not require mechanical ventilation and recovered with supportive care. Both dogs were diagnosed with VetARDS secondary to aspiration pneumonia. The cat that survived was diagnosed with sepsis secondary to pyelonephritis, and was weaned successfully from the ventilator. This patient was still alive 1 year after discharge.

Of the patients that did not survive to discharge, 4/22 (18%) dogs died and 18/22 (82%) dogs were euthanized. Three of the 4 nonsurviving (75%) cats died, and 1 (25%) cat was euthanized. A combination of grave prognosis and financial constraints was cited as the reason for

Table 4: Necropsy findings in dogs and cats with a clinical diagnosis of VetALI or VetARDS

Histopathologic finding	Dogs, *n* (%)	Cats, *n* (%)
Neutrophilic interstitial pneumonia	7/8 (87.5)	2/3 (66.7)
Alveolar edema	3/8 (37.5)	1/3 (33.3)
Alveolar hemorrhage	1/8 (12.5)	1/3 (33.3)
Alveolar necrosis	0/8 (0)	1/3 (33.3)
Type II pneumocyte hyperplasia	3/8 (37.5)	1/3 (33.3)
Hyaline membranes	1/8 (12.5)	1/3 (33.3)
Intralesional ingesta	1/8 (12.5)	0/3 (0)
Pulmonary thrombi	1/8 (12.5)	0/3 (0)

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

euthanasia in all patients. Because of the small number of patients that survived to discharge, no meaningful statistical analysis could be performed to evaluate prognostic indicators.

Necropsy findings

Necropsy results were available for 8/24 (33%) dogs and 3/5 (60%) cats. The clinical diagnosis in the patients that underwent a necropsy examination included aspiration pneumonia (2/8 dogs); 1 dog each with airway obstruction secondary to tracheal collapse, necrotizing pancreatitis, necrotizing encephalitis, pulmonary contusions, pulmonary thromboembolism, and multiple myeloma; and 1 cat each with bronchopneumonia, pyothorax, and an adverse drug reaction. The most common histopathologic finding was neutrophilic interstitial pneumonia (7/8 dogs, 2/3 cats) followed by alveolar edema (3/8 dogs, 1/3 cats), type II pneumocyte hyperplasia (3/8 dogs, 1/3 cats), alveolar hemorrhage (1/8 dogs, 1/3 cats), hyaline membranes (1/8 dogs, 1/3 cats), alveolar necrosis (1/3 cats), intralesional ingesta (1/8 dogs), and pulmonary thrombi (1/8 dogs; Table 4).

Discussion

This study found that the prevalence of VetALI or VetARDS was 3.2% in dogs and 1.3% in cats that were hospitalized in the ICU during the study period. To the authors' knowledge, the period prevalence rate for VetALI and VetARDS has not been previously reported in small animals. Incidence rates reported in people in ICUs in the United States vary between 7.2 and 22.4 cases per 100,000 persons per year[2,20] with lower incidence rates being reported in more recent studies. The prevalence reported in this study, however, could have been affected by a number of factors. Cases presenting to the Emergency Service that were diagnosed with VetALI or VetARDS based upon clinical signs and were euthanized shortly after, prior to transfer to the ICU, were excluded from this study. It is also possible that some cases were missed while searching through medical records with the diagnosis codes of "acute lung injury," or "ALI," or "ARDS," or "acute respiratory distress syndrome." Thus, the number reported in this study may be lower than the actual prevalence of VetALI or VetARDS at this institution.

The average age of patients in this study was approximately 9.4 years at the time of diagnosis in both dogs and cats. This finding is different from a previous veterinary study of ARDS where the median age at the time of diagnosis was 3.5 years.[10] Another previously published veterinary case report documented ARDS in an 18-month old French Bulldog.[15] ARDS in people has been reported in both adults and children; however, the epidemiology of various risk factors is different between these populations.[21] Thus, the overall older age of patients reported in this study is likely reflective of the various risk factors observed. Since age-matched controls were selected for risk-factor analysis in this study, unfortunately, the influence of patient age as a risk factor in itself for developing VetALI or VetARDS could not be evaluated in this study.

A large number of these patients (48%) presented to the hospital in acute respiratory distress with a median initial respiratory rate of 46 breaths/minute. This is consistent with the findings reported in a previous veterinary study of ARDS patients.[10] The signs of respiratory distress observed upon diagnosis likely correlate with the rapidly progressive pulmonary inflammation and subsequent deleterious effects on gas exchange in the lungs that typify VetALI and VetARDS. Other presenting complaints observed in these patients included vomiting, regurgitation, lethargy, and anorexia. These signs were likely related to the patients' various underlying co-morbidities, including pancreatitis, megaesophagus, and inflammatory bowel disease.

Clinical signs were noticed within a 72-hour period prior to diagnosis in all patients, and all of them had labored breathing at rest. Known risk factors were also observed in all patients, with some patients having multiple risk factors. VetALI and VetARDS are characterized by noncardiogenic pulmonary edema, or a "high-permeability edema" resulting from an increase in extravascular lung water due to primary pulmonary vascular endothelial injury or primary alveolar epithelial injury.[22] The presence of pulmonary capillary leak was suspected based on thoracic radiographs that showed bilateral patchy alveolar infiltrates without left atrial enlargement and pulmonary venous congestion in 96% of the dogs and 100% of the cats in the current study. In the 1 dog that did not have imaging performed, neutrophilic, proteinaceous airway fluid was used to confirm the presence of pulmonary capillary leak. The utility of thoracic radiographs in distinguishing hydrostatic pulmonary

edema from high-permeability pulmonary edema has been evaluated in several studies, and the accuracy of this imaging modality is variable. This is especially true in cats, as they commonly display high variability in radiographic signs of congestive heart failure.[23–25] Echocardiography is currently the gold standard to rule out hydrostatic pulmonary edema in veterinary medicine. However, thoracic radiography remains one of the most widely used tools in veterinary medicine to diagnose pulmonary edema. Given this, the 2007 veterinary guidelines for the diagnosis of VetALI and VetARDS[16] allow for the use of thoracic imaging (radiographs or CT), or the presence of proteinaceous airway fluid to detect pulmonary capillary leak not related to increased hydrostatic pressure. Pulmonary neutrophil accumulation is seen in the early stages of VetALI and VetARDS histologically in dogs and cats.[22] Loss of capillary integrity, alveolar damage, accumulation of proteinaceous airway fluid, and development of pulmonary edema characterize the early exudative stages of VetALI and VetARDS.[16,22]

All patients had evidence of varying degrees of hypoxemia upon diagnosis. PaO_2/FiO_2 ratios were used to confirm hypoxemia in 79% dogs. An initial PaO_2/FiO_2 ratio of ≤300, consistent with VetALI, was found in 26% of these dogs, while a ratio of ≤ 200, consistent with VetARDS was found in 74% of dogs that had arterial blood gas values available. Arterial blood gas values were not available for 21% of the dogs or any of the cats. Arterial catheters are especially challenging to place in cats and are prone to complications such as dislodgement and thrombosis; arterial puncture is also difficult in dyspneic cats. Pulse oximetry is therefore often used as a surrogate for arterial blood gas analysis in these patients when an arterial catheter cannot be successfully placed. In these patients, the SpO_2/FiO_2 ratio was used as a surrogate marker to diagnose hypoxemia. The SpO_2/FiO_2 ratio is a noninvasive way to evaluate oxygenation and has been shown to have diagnostic utility in people, particularly in children with ARDS, in whom arterial blood sampling can be challenging.[19,26–28] Preliminary evaluation of the SpO_2/FiO_2 ratio in dogs found that this ratio correlated well with the PaO_2/FiO_2 ratio in a population of dogs requiring assessment of oxygenation.[29] To the authors' knowledge, the utility of the SpO_2/FiO_2 ratio has not been evaluated in dogs with VetALI or VetARDS, nor has it been evaluated in cats. The mean SpO_2/FiO_2 ratio in dogs in this study was 168, and was lower in the cat population with a mean ratio of 130. In people with ARDS, SpO_2/FiO_2 ratios of 235 and 315 were found to correlate with PaO_2/FiO_2 ratios of 200 and 300, respectively.[19] Thus, the values reported in this study were well below the equivalent values for a PaO_2/FiO_2 ratio of ≤200 corresponding to a diagnosis of VetARDS. However, future studies will be necessary to validate the routine use of the SpO_2/FiO_2 ratio in dogs and cats with VetALI and VetARDS as a noninvasive marker of hypoxemia.

VetALI and VetARDS have been known to occur in a wide variety of clinical settings, and can be triggered by several risk factors. Proposed risk factors in veterinary patients include SIRS, sepsis, multiple transfusions causing a syndrome of transfusion-related lung injury, drowning, smoke inhalation, trauma, pancreatitis, and aspiration of gastric contents.[16] All 29 patients in this study had ≥1 risk factor present, with systemic inflammation being the most common. Of the patients diagnosed with SIRS, pancreatitis and severe tracheal collapse causing airway obstruction and respiratory distress accounted for 25% each. Pancreatitis triggers a profound systemic inflammatory response that results in increased endothelial and epithelial permeability. This causes leakage of protein-rich exudates into the pulmonary interstitium and alveoli, resulting in hypoxemia. The development of ARDS secondary to necrotizing pancreatitis has been previously reported in a dog.[30] In people, ARDS secondary to severe acute pancreatitis is responsible for up to 60% of deaths within the first week.[31] Tracheal collapse is a condition that commonly affects small breed dogs (all 4 dogs with tracheal collapse in this study were Yorkshire Terriers). While there is evidence that certain canine upper airway disorders such as brachycephalic airway syndrome are intrinsically associated with systemic inflammation,[32] there is currently no literature documenting this in dogs with tracheal collapse. However, all 4 of the dogs in the current study developed acute respiratory crises secondary to upper airway obstruction: 2 of the dogs at initial presentation and 2 following general anesthesia for tracheal stent placement. Tracheal collapse has been known to cause airway inflammation in dogs,[33] and general anesthesia can trigger respiratory decompensation in these dogs secondary to decreased respiratory drive as well as stress and agitation upon recovery. Acute upper airway obstruction can also trigger the development of noncardiogenic pulmonary edema, which has been reported in people with dynamic tracheal collapse,[34] and has also been reported as an inciting cause of ARDS in a previous veterinary study.[10]

None of the risk factors that were studied in this population had a statistically significant effect on the development of VetALI or VetARDS when compared with age-matched control patients that had respiratory disease other than VetALI or VetARDS. In people, the common risk factors described for ARDS include SIRS, sepsis, trauma, pancreatitis, aspiration, and multiple transfusions.[1,2] Sepsis, along with liver cirrhosis, has been implicated with increased risk of development of ARDS, as well as an increased risk of mortality

when ARDS develops.[35–37] The lack of association found between the various risk factors evaluated in this study with the development of VetALI and VetARDS may be a consequence of the small number of patients in this study resulting in a type II statistical error.

Mechanical ventilation is an important intervention that is often used in the management of patients with VetALI and VetARDS. Indications for positive-pressure ventilation classically include inadequate oxygenation because of pulmonary disease, ventilatory failure leading to inability to eliminate carbon dioxide, or increased work of breathing with impending respiratory fatigue.[38] Fifty percent of the dogs and 80% of the cats in this study underwent mechanical ventilation for severe, persistent hypoxemia unresponsive to oxygen supplementation. Unfortunately, it was not evident from the records whether mechanical ventilation was not considered indicated because of lower severity of hypoxemia and respiratory effort in the remaining 50% of dogs and 20% of cats, or if it was recommended and offered to clients and subsequently declined. The median duration of mechanical ventilation in dogs was 18 hours and 15.5 hours in cats. This is shorter than the median duration of ventilation of 48 hours reported in a previous study in dogs and cats with inadequate oxygenation, although the duration of ventilation for patients with VetARDS specifically could not be discerned from this study.[14] A median duration of ventilation of approximately 8.8 days has been reported in people with ARDS, reflecting that this is a disease process that resolves slowly, while requiring extremely aggressive and intensive care for the duration of its course.[39] The overall shorter duration observed in this study can be attributed to the high rate of humane euthanasia for both prognostic and financial reasons, since unfortunately, long-term mechanical ventilation can be cost prohibitive.

PrCV was used in all patients that underwent positive pressure ventilation. PrCV is a time-cycled ventilation mode in which a set pressure is applied and released, typically in a decelerating flow pattern. However, flow patterns vary depending on the resistance and compliance of the lungs.[40] In theory, PrCV can lead to more laminar flow toward the end of inspiration, which allows for better distribution of the gas flow between heterogeneous areas of diseased and healthy lungs.[41] A 2015 meta-analysis comparing PrCV and volume-controlled ventilation in ARDS found no difference between the 2 modes.[42] The ratio of inspiratory time to expiratory time (I:E ratio) is an important ventilation setting to consider. A majority of patients in this study had a starting I:E ratio of 1:2, which is consistent with ratios suggested for use in small animals.[43] However, 50% of the dogs had longer set inspiratory times, and this was likely initiated to increase arterial oxygenation. One dog had a set inspiratory time that was higher than the expiratory time (inverse ratio ventilation) in an effort to increase mean airway pressure and improve severe, refractory hypoxemia. Inverse ratio ventilation can maintain the mean airway pressure and Vt at lower levels of PEEP and peak alveolar pressure. However, patients must be carefully monitored to ensure that end-expiratory gas-trapping does not occur since this can lead to the development of "auto-PEEP" which is end-expiratory pressure over the set level of PEEP, increased peak pressures, and potentially barotrauma, and pneumothorax.[44] The median initial Vt reported in this study was 12.4 mL/kg in dogs and 10.2 mL/kg in cats, which is higher than recommended values for patients with diseased lungs.[43] The normal Vt in healthy dogs is reported to be 10–15 mL/kg.[45] Low Vt (lung protective) ventilation has emerged as one of the single most important strategies in the management of people with ARDS since the ARDS Network reported a lower mortality in people ventilated with a Vt of 6 mL/kg versus 12 mL/kg.[6] Low Vt ventilation has since been supported by several studies and meta-analyses.[2–5] However, this approach may result in CO_2 retention with subsequent respiratory acidosis. A lower Vt may also increase relative dead space, which results in a decreased proportion of each breath being available for gas exchange.[46] A recent study found that low Vt ventilation was well tolerated in healthy dogs; however, 1 dog in the study developed mild hypoxemia with a Vt of 6 mL/kg that resolved when the Vt was increased to 8 mL/kg.[47] To the authors' knowledge, there are no clinical veterinary studies evaluating lung protective ventilation in dogs and cats with VetALI and VetARDS. Animals in the current study were ventilated using a pressure-controlled mode of ventilation where Vt is a dependent variable based on the set inspiratory pressure, flow rate, and the mechanics of the patient's respiratory system and the ventilator circuit. It is plausible that this subset of critically ill patients differs markedly from healthy dogs in the ability to tolerate low Vt ventilation without a significant deleterious effect on already compromised oxygenation. Such respiratory system compromise may have necessitated the use of higher inspiratory pressures and subsequently, higher Vts were achieved. Arterial CO_2 values were not recorded in this study. Therefore, the effect of the higher Vt on CO_2 levels cannot be determined, which is a significant shortcoming of this study. It is also possible, however, that the high Vt employed in this study caused volutrauma, which may have exacerbated lung injury. Future veterinary studies comparing ventilation with low Vt to conventional Vt would be beneficial.

PEEP is often used to increase oxygenation in diseased lungs by recruiting collapsed alveoli, splinting open already recruited alveoli, and reducing ventilator-associated lung injury. Employing PEEP is one of the

strategies set forth in the ARDS Network guidelines.[6] However, determining optimal levels of PEEP can be challenging. Excessive application of PEEP can cause significant cardiovascular compromise by increasing intrathoracic pressure and right ventricular afterload, and can cause lung overinflation.[45] The average PEEP reported in this study was 7.1 cm H_2O in dogs and 3.5 cm H_2O in cats. These values are lower than suggested values in small animals; PEEP levels of 10–15 cm H_2O have been proposed.[43] However, it is difficult to determine retrospectively the reason for the relatively lower values in this study and it is possible that the cardiovascular status of the patients precluded the application of higher levels of PEEP.

PIP is the highest pressure measured in the proximal airway during inspiration. The plateau pressure, which is the pressure across the respiratory system at the end of an inspiratory "hold" or plateau, represents the alveolar pressure. Since the plateau pressures are not automatically displayed on most ventilators with each breath, an inspiratory hold maneuver is necessary to calculate it. This value was not available for most patients in this study. Hence, the PIP was used as a surrogate marker of airway pressures, given that with lung disease, PIP and plateau pressures tend to rise proportionately.[48] The ARDS Network protocol targets a plateau pressure of $\leq$30 cm H_2O to prevent overdistension of, and barotrauma to, the lungs.[6] The mean initial PIP values reported in this study were 25.1 cm H_2O in dogs, with some dogs achieving a PIP as high as 35.9 cm H_2O, and 14.8 cm H_2O in cats. The values in dogs are similar to those reported in a 2007 study[14]; however, the values in cats were significantly lower than those reported previously.[12] The relatively higher PIP in some dogs in this study may reflect decreased lung compliance and greater airway resistance due to more severe lung disease.

The physiologic dead space fraction (Vd/Vt), which is the ratio of dead-space to Vt, reflects the proportion of the delivered Vt that does not participate in gas exchange and comprises exhaled gas without CO_2. In people with ARDS, a sustained increase in Vd/Vt is significantly associated with nonsurvival, with an initial Vd/Vt $\geq$ 0.6 associated with higher mortality.[49,50] The mean initial Vd/Vt in dogs in this study was 0.61, with some dogs having values as high as 0.89, which reflects the marked severity of lung disease in this patient population. The OI is a calculated value that was originally devised as a marker of disease severity in neonatal respiratory failure and takes into account the mean airway pressure while evaluating oxygenation abnormalities.[51] OI has since been validated as a prognostic indicator in both pediatric and adult respiratory failure.[52–54] Although no cut-off values have been established in dogs, an OI > 8.1 is consistent with ARDS and >5.3 with ALI in people.[54] The median OI in dogs in this study was 10.7 which would fall into the category consistent with ARDS, if cut-off values were extrapolated from the studied human population. No Vd/Vt or OI values were calculated in cats, given the lack of available arterial blood gas samples in this group. To the authors' knowledge, there are no clinical studies evaluating the utility of Vd/Vt or OI in small animals with pulmonary disease, and future studies in this area would be valuable.

The histopathologic changes that classically accompany ARDS include diffuse alveolar damage characterized by evidence of intra-alveolar inflammation, edema, hemorrhage, or necrosis with hyaline membranes, vascular congestion, interstitial edema and fibrosis, and type II pneumocyte hyperplasia.[11,55,56] However, a 2013 study[56] showed that only 45% of people that met the clinical criteria for ARDS diagnosed using the Berlin definition[9] had evidence of diffuse alveolar damage on autopsy, with some patients having no pulmonary lesions detected at all. Necropsy findings in the patients in our study varied widely, with neutrophilic interstitial pneumonia being the most common finding (88% of dogs and 67% of cats). This finding is consistent with the aforementioned human study[56] in which histopathologic evidence of interstitial pneumonia was found in half of the patients that met clinical criteria of ARDS but did not have evidence of diffuse alveolar damage or hyaline membranes. Opinion is divided among experts in human medicine as to whether patients with severe pneumonia are compatible with a diagnosis of ARDS as long as clinical criteria are met, even if histopathologic criteria are not.[56,57] Evidences of diffuse alveolar damage (edema, necrosis, hemorrhage, and type II pneumocyte hyperplasia) were reported in a total of 6/8 (75%) dogs and all 3 cats that had a necropsy, even though all patients met the clinical criteria[16] for diagnosis of VetALI/VetARDS. Hyaline membranes, which are considered a histopathologic hallmark of the syndrome, were reported in only 1 dog and 1 cat. Hyaline membrane formation may take up to 2–3 days[55] and the absence of this histopathologic finding in the remaining patients in this study could reflect earlier stages of the syndrome. ALI and ARDS represent a clinical continuum of disease processes, and classic histopathologic changes are more likely to be observed in the more severely affected patients,[56] which may be true of patients in this study as well. Further studies in veterinary patients will hopefully provide more information.

The mortality rate of patients in this study was high, with 91.7% of dogs and 80% of cats not surviving to discharge. These mortality rates are similar to those previously reported in veterinary medicine.[14] Humane

euthanasia was a major reason for nonsurvival in this study and 82% of nonsurviving dogs and 25% of nonsurviving cats were euthanized. Both a grave prognosis and financial constraints were cited as reasons for euthanasia in all the patients. The need for prolonged aggressive care including mechanical ventilation is quite expensive and frequently not possible for pet owners. Patients with VetALI and VetARDS are also likely to have multiple other disease processes, as is reflected by the large number of co-morbidities noted in this study. These co-morbidities likely contribute to worse patient outcomes, whether through euthanasia or death. The mortality rate of ARDS in people has been reported to be 35–40%, and has not improved significantly in recent years despite improved ventilation practices and management strategies.[1,3–7] As more potential therapeutic targets and interventions are studied in people with ARDS, the hope is that some of these interventions will translate into strategies that can be employed in veterinary medicine to help improve outcome.

This study has several limitations, many due to its retrospective nature. First, the number of cases included is small, which therefore resulted in a low power to detect significant differences between various risk factors evaluated. The cases included were based on a computerized medical record search for specific diagnostic terms, which may have underestimated the number of cases. Also, for the patients that did not undergo mechanical ventilation, it is difficult to determine what factors influenced that decision given the multiple confounding variables of patient care and owner wishes. Thus, the number of patients ventilated may not truly reflect the overall need for mechanical ventilation in this group of patients. Finally, the impact of humane euthanasia in this study population was significant, and may have resulted in overestimation of the true mortality rate of VetALI and VetARDS in small animals.

Conclusion

VetALI and VetARDS can cause life-threatening respiratory distress in dogs and cats, and required mechanical ventilation in 50% of dogs and 80% of cats in this study. These conditions are associated with a poor clinical outcome and a high rate of humane euthanasia. Further prospective and possibly multicenter studies of these syndromes in dogs and cats would be valuable to improve management strategies in these critically ill patients.

Footnotes

[a] Stata 12.1 for Mac, Stata Corporation, College Station, TX.
[b] Esprit Ventilator, Respironics Inc, Murrysville, PA.

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