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CLINICAL PRACTICE REVIEW

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Noncardiogenic pulmonary edema in small animals

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Abstract

Objective: To review various types of noncardiogenic pulmonary edema (NCPE) in cats and dogs.

Etiology: NCPE is an abnormal fluid accumulation in the lung interstitium or alveoli that is not caused by cardiogenic causes or fluid overload. It can be due to changes in vascular permeability, hydrostatic pressure in the pulmonary vasculature, or a combination thereof. Possible causes include inflammatory states within the lung or in remote tissues (acute respiratory distress syndrome [ARDS]), airway obstruction (postobstructive pulmonary edema), neurologic disease such as head trauma or seizures (neurogenic pulmonary edema), electrocution, after re-expansion of a collapsed lung or after drowning.

Diagnosis: Diagnosis of NCPE is generally based on history, physical examination, and diagnostic imaging. Radiographic findings suggestive of NCPE are interstitial to alveolar pulmonary opacities in the absence of signs of left-sided congestive heart failure or fluid overload such as cardiomegaly or congested pulmonary veins. Computed tomography and edema fluid analysis may aid in the diagnosis, while some forms of NCPE require additional findings to reach a diagnosis.

Therapy: The goal of therapy for all types of NCPE is to preserve tissue oxygenation and reduce the work of breathing. This may be achieved by removing the inciting cause (eg, airway obstruction) and cage rest in mild cases and supplemental oxygen in moderate cases and may require mechanical ventilation in severe cases.

Prognosis: Prognosis is generally good for most causes of veterinary NCPE except for ARDS, although data are scarce for some etiologies of NCPE.

KEYWORDS
acute respiratory distress syndrome, neurogenic pulmonary edema, postobstructive pulmonary edema, re-expansion pulmonary edema, smoke inhalation

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CT, computed tomography; HFOT, high-flow oxygen therapy; NCPE, noncardiogenic pulmonary edema; NPE, neurogenic pulmonary edema; P/F, arterial partial pressure of oxygen to inspired fraction of oxygen ratio; PEEP, positive end-expiratory pressure; POPE, postobstructive pulmonary edema; RPE, re-expansion pulmonary edema; S/F, arterial hemoglobin oxygen saturation to inspired fraction of oxygen ratio; SIRS, systemic inflammatory response syndrome; Spo_2, arterial hemoglobin oxygen saturation measured by pulse oximetry; TRALI, transfusion-related acute lung injury; VetALI, veterinary acute lung injury; VetARDS, veterinary acute respiratory distress syndrome.

1 | INTRODUCTION

Edema is a state of abnormal fluid accumulation in tissues and can be caused by changes in the forces that normally control fluid flow across capillaries in the body. Ernest Starling described the forces that govern fluid balance, which include capillary hydrostatic pressure (P_c), capillary oncotic pressure (π_c), interstitial hydrostatic pressure (P_t), and interstitial oncotic pressure (π_t).[1] The relationship between these factors was later described as the following: net filtration pressure = $P_c - P_t - (\pi_c - \pi)$.[2] Pressures are not the only factors that influence fluid filtration, and the formula can be re-written as: $J_v = K_{fc}[(P_c - P_t) - \sigma_d(\pi_c - \pi_t)]$, with J_v being the volume of flow, K_{fc} being the filtration coefficient, and σ_d being the osmotic reflection coefficent for plasma proteins.[1] The filtration coefficient is determined by the size and number of the pores, the surface area of the capillary network, the thickness of the capillary wall, and the viscosity of the fluid being filtered, and represents the permeability for water. The osmotic reflection coefficient is a measure of capillary permeability for protein, with a reflection coefficient of 1 indicating impermeability of the capillary wall to plasma proteins and a reflection coefficient of 0 indicating that plasma proteins can freely cross the capillary membrane.[1] The reflection coefficient is a representation of endothelial integrity.[3] According to this model of transcapillary fluid movement, fluid filtration is determined by the transcapillary hydrostatic pressure gradient and the colloid osmotic pressure gradient between plasma and the interstitium, and the endothelial cells constitute the microvascular barrier.[4,5] In recent years, this paradigm has been called into question, as new insights into the structure of vascular beds were gained.[4] The luminal side of the endothelium is covered by the so-called glycocalyx, which consists of membrane-bound proteoglycans and glycoproteins associated with mucopolysaccharides.[4] Due to the hydrostatic pressure that is exerted on the vascular wall, proteins such as albumin accumulate in this glycocalyx layer in high concentrations; however, a small area adjacent to the endothelial surface (subglycocalyx space) is spared from this effect and remains virtually protein free. There is a colloid osmotic gradient between the glycocalyx layer and the subglycocalyx space and it is this gradient that is now believed to oppose the transcapillary hydrostatic pressure rather than the colloid gradient between plasma and the interstitium as was believed previously.[4] A consequence of this paradigm is that the integrity of the glycocalyx layer, not just the endothelium, is integral in maintaining normal fluid flux across the microvascular barrier.[4,5]

The last factor that plays an important role in the development of edema is the lymphatic system. In most tissues and circumstances, the Starling forces cause a net filtration from the plasma into the tissues, which is then removed via the lymphatics.[6] If the filtered fluid becomes too much for the lymphatics to clear, interstitial edema ensues. In the case of the lungs, to avoid excessive tissue swelling, the edema fluid will eventually spill over from the interstitium into the alveoli.[1] Resolution of pulmonary interstitial edema depends on lymphatic drainage and occurs faster than resolution of alveolar edema, which is dependent on the activity of the sodium–potassium ATPase pump located at the basolateral membrane of type 1 and 2 pneumocytes. This pump creates a favorable sodium gradient supporting sodium and water absorption from the alveoli to the pneumocytes and from the pneumocytes into the interstitium, where it is reabsorbed by the lymphatics.[7]

In the lung, the reflection coefficient for plasma protein is 0.7–0.95, which is lower than in other tissues and decreases the colloid osmotic gradient across the capillary membrane.[1] Decreases in capillary oncotic pressure play a minor role in the development of pulmonary edema, with the capillary hydrostatic pressure and vascular permeability being the main determinants for the development of edema.[8]

Noncardiogenic pulmonary edema (NCPE) is a subtype of pulmonary edema that does not directly result from cardiogenic causes or fluid overload.[8] It can be due to increased vascular permeability, increased pulmonary transcapillary pressure without increased left atrial pressure, or a combination.[8] An overview of the veterinary medical literature, the pathophysiology of certain types of NCPE, as well as diagnostic and therapeutic options will be discussed in the following sections.

2 | ACUTE RESPIRATORY DISTRESS SYNDROME

2.1 | Summary of veterinary clinical data

Acute respiratory distress syndrome (ARDS) is an inflammatory disease of the lung, characterized by a deranged immune response to an insult that can originate from pulmonary or nonpulmonary disease.[9] It is associated with high morbidity and mortality in both human and veterinary medicine.[10–12]

Two recent retrospective investigations describe the course and outcome of a series of dogs and cats with ARDS, with a prevalence among ICU patients of 3.2% in dogs and 1.3% in cats.[11,12] A variety of underlying causes were identified, and ARDS in dogs was more common secondary to pulmonary than nonpulmonary disease, with aspiration pneumonia being the leading cause.[11,12] In cats, ARDS was equally common due to pulmonary and nonpulmonary disease in cats, and sepsis/systemic inflammatory response syndrome (SIRS) was the most common cause in both studies.[11,12]

In a retrospective study of 19 dogs, postmortem histopathologic findings were compatible with those found in humans with a diagnosis of ARDS.[13,14] Predisposing factors included microbial and aspiration pneumonia, sepsis, and shock among others.[13] It was not uncommon to find more than 1 inciting cause for ARDS in dogs and cats.[11,13] Although not specifically investigating ARDS, cats with sepsis were found to have histopathologic findings of the lung that included edema, thrombi, hemorrhage, pneumocyte type II hyperplasia, and hyaline membranes, all of which can be found in the exudative phase of human ARDS.[15–17]

There are numerous case reports in dogs with ARDS, documenting a wide variety of inciting causes.[18–29] In cats, only 2 case reports on ARDS were identified: 1 described a cat that developed ARDS after a systemic toxoplasma infection,[30] while the other described a 12-year-old cat that had multiple thoracic and abdominal surgical procedures

TABLE 1 Diseases and conditions associated with the acute respiratory distress syndrome reported in humans, dogs, and cats.[11–13,16,18–32]

Disease or condition	Humans	Dogs	Cats
Pneumonia	×	×	×
(Nonpulmonary) sepsis or SIRS	×	×	×
Aspiration of gastric contents	×	×	
(Major) trauma, including surgical	×	×	×
Pulmonary contusion	×	×	
Pancreatitis	×	×	×
Inhalation injury/smoke inhalation or inhalant toxin	×	×	
Severe burns	×		
(Noncardiogenic) shock	×	×	
Drugs	×	×	
Transfusions	×	×	
Pulmonary vasculitis	×		
Drowning	×	×	
Lung lobe torsion		×	
Strangulation		×	
Hyperoxia		×	
Babesiosis		×	
Gastric and splenic torsion		×	
Apis spp. envenomation		×	
Parvoviral enteritis		×	
Systemic toxoplasmosis	×		×
Mechanical ventilation		×	×
Pulmonary neoplasia		×	×
Acute kidney injury		×	×

Abbreviation: SIRS, systemic inflammatory response syndrome.

performed and developed respiratory distress.[31] Diseases and conditions that have been associated with the development of ARDS in companion animals are presented in Table 1.[11–13,18–32]

2.2 | Pathophysiology

In human medicine, ARDS is divided into different pathophysiologic stages based on changes seen on histopathology, although they do not always correlate with clinical signs.[16] The first phase (exudative phase) is characterized by pulmonary vascular leakage, hemorrhage, thrombosis, and inflammatory cell infiltration (initially macrophages, followed by neutrophils) resulting in protein-rich edema accumulation in the alveoli and the formation of what is seen as hyaline membranes.[9,10] There is evidence of damage both to the vascular endothelium and the alveolar epithelium (type I pneumocytes). Damage of type I pneumocytes leads to alveolar edema, which dilutes surfactant and causes alveolar collapse. To make up for the loss of type I pneumocytes, type II pneumocytes proliferate and lose their surfactant-producing capabilities, further contributing to alveolar collapse. The early stages of this proliferation can be seen in the exudative phase. The combination of hyaline membranes, neutrophil migration, hemorrhage, and alveolar collapse is termed diffuse alveolar damage and is considered a hallmark sign of this phase of ARDS.[9,16,17] During the second phase of ARDS, the proliferative phase, type II pneumocytes continue to proliferate, and fibrosis occurs in the interstitium and the alveoli. Hyaline membranes can still be seen.[9] During the fibrotic phase, collagen is deposited in alveoli, the interstitium, and the vasculature. Since the latter 2 phases blend together, they are often referred to as "fibroproliferative phase."[9] Based on dog and cat models of ARDS, the pathophysiology in these species is similar to that in people.

Physiologically, the described changes translate into ventilation–perfusion mismatch, decreased compliance, increased functional dead space, increased pulmonary vascular resistance, and a decrease in functional residual capacity in people and dogs.[9,10,17,33]

2.3 | Diagnosis

2.3.1 | Consensus statements

ARDS is considered a clinical syndrome associated with an underlying cause and in both human and veterinary medicine, certain criteria are required for a diagnosis.[16,34,35] In human medicine, the oldest consensus statement for ARDS dates back to 1967, with several updates being published since then.[16] Originally, this clinical entity was termed acute lung injury (ALI), with ARDS referring only to the more severe forms of the syndrome. In 2012, the terminology was changed, with the term ALI being eliminated and ARDS being stratified according to severity.[16]

The current guidelines for diagnosis of ARDS in people are summarized in Table 2.[34] In comparison to previous definitions, the requirement for measurement of pulmonary artery occlusion pressure to exclude cardiac causes for edema was removed. In the absence of a risk factor for ARDS, hydrostatic causes need to be ruled out objectively (eg, performing an echocardiogram). Although not explicitly stated in the consensus criteria, requirement of an inciting cause is still implied.[16]

In veterinary medicine, a consensus statement on the definitions of veterinary acute lung injury (VetALI) and veterinary acute respiratory distress syndrome (VetARDS) was published in 2007.[35] For this review, the terms ALI and ARDS will be used to indicate VetALI/VetARDS. The criteria for VetARDS are summarized in Table 2.

At the time of publication of these guidelines, the list of risk factors for the development of VetALI/VetARDS included inflammation, infection, sepsis, SIRS, severe trauma (long bone fracture, head injury, pulmonary contusion), multiple transfusions, smoke inhalation, near-drowning, aspiration of stomach contents, drugs, and toxins.[35] Likely, this list can be expanded (Table 1).[11–13,18–32] To meet the second criteria (evidence of pulmonary capillary leak without increased pulmonary capillary pressure), absence of clinical signs of left-sided

TABLE 2 Consensus definitions for ARDS, VetALI/VetARDS, and TRALI.[34,35,52]

	ARDS (people)	VetALI/VetARDS	TRALI (people)	
			TRALI type I	TRALI type II
Timing of onset	1 week	72 hours	During or within 6 hours of a transfusion	
Risk factor	When none identified, need to objectively rule out hydrostatic edema	Required	No temporal association to an alternative risk factor for ARDS	Risk factor can be present or patients may have existing mild ARDS (P/F ratio between 200 and 300), but respiratory status deterioration is due to transfusion based on stable respiratory status in the 12 hours prior to transfusion
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules on thoracic radiographs/CT	Bilateral/diffuse infiltrates in more than 1 quadrant or lobe on thoracic radiographs or bilateral-dependent density gradient on CT	Clear evidence of bilateral pulmonary edema on imaging (eg, chest radiograph, chest CT, or ultrasound)	
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload	Evidence of pulmonary capillary leak without increased pulmonary capillary pressure	No evidence of left atrial hypertension, or if present, it is judged to not be the main contributor to the hypoxemia	
Oxygenation	a. Mild ARDS: P/F ratio of ≤300 but >200, while being ventilated with a minimum of 5 cm H_2O of PEEP/continuous positive airway pressure b. Moderate ARDS: P/F ratio of ≤200 but >100, while being ventilated with a minimum of 5 cm H_2O of PEEP c. Severe ARDS: P/F ratio of ≤100, while being ventilated with a minimum of 5 cm H_2O of PEEP	Hypoxemia 1. P/F ratio ≤300 for VetALI≤200 for VetARDS 1. Increased alveolar-arterial oxygen gradient 2. Venous admixture (noncardiac shunt) or Increased dead-space ventilation	P/F ratio of ≤300 or SpO_2 of <90% on room air	
Optional criteria		Evidence of diffuse pulmonary inflammation: Transtracheal wash/BAL sample neutrophilia or Transtracheal wash/BAL sample biomarkers of inflammation or Molecular imaging (positron emission tomography)		

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CT, computed tomography; P/F ratio, arterial oxygen partial pressure to fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure; SpO_2, arterial hemoglobin oxygen saturation measurement via pulse oximetry; TRALI, transfusion associated acute lung injury.

heart failure is generally considered sufficient, but additional means such as echocardiography to document normal cardiac function are encouraged.[35]

To meet the criteria for VetARDS, the arterial hemoglobin oxygen saturation to inspired fraction of oxygen (P/F) ratio as a marker of impaired gas exchange is needed; however, it may not be obtainable due to patient size or severe clinical compromise. Other requirements such as thoracic imaging may not be completed as well.[29] As such, it is common in the literature to utilize necropsy findings for a diagnosis.[12,25,29] Although certain histopathologic findings are considered hallmark signs of ARDS in people, clinical signs both in people and dogs do not always correlate with histopathologic findings.[12,16,27]

In 1 study, only 47% of dogs that met clinical criteria for ARDS had histopathologic criteria consistent with a diagnosis of ARDS, and 3 of 11 dogs that had findings consistent with ARDS on necropsy did not meet clinical criteria.[12]

For situations in which a P/F ratio cannot be obtained, use of the arterial hemoglobin oxygen saturation measurement via pulse oximetry (Spo_2) to inspired fraction of oxygen (S/F) ratio as a surrogate marker for the P/F ratio has become increasingly more utilized both in dogs and cats.[11,12,21,30] Although this approach is currently not reflected in the definition of VetALI/VetARDS, there is evidence that suggests that the use of the S/F ratio may be a promising tool to substitute for the P/F ratio in people and small animals.[36–40]

In a human adult ARDS trial, an S/F ratio <315 corresponded with a P/F ratio of <300, and an S/F ratio of <235 corresponded with a P/F ratio of <200.[36] In children, an S/F ratio of <263 corresponded to a P/F ratio of <300, and an S/F ratio of <201 corresponded to a P/F ratio of <200.[37] In 1 study in human ARDS, using a P/F ratio of <300 compared to an S/F ratio of <315 to diagnose ARDS when the other criteria were met as well showed that clinical characteristics and outcomes were not different between the groups, suggesting that the S/F ratio may be a reasonable surrogate to diagnose ARDS in cases where an arterial blood gas sample cannot be obtained.[38]

In 38 dogs spontaneously breathing room air at sea level, the S/F ratio and P/F ratio showed moderate correlation when the arterial hemoglobin oxygen saturation measured by pulse oximetry (Spo_2) was between 80% and 97%.[39] Due to the low number of patients enrolled, it was not possible to determine surrogate S/F ratio cutoffs for ARDS in this population.[39] In a similar study, a moderate correlation between Spo_2 and Pao_2 in awake dogs on room air was found. A much stronger correlation was found between the 2 parameters in dogs that were mechanically ventilated and P/F ratios of 200 and 300 correspond to S/F ratios of 188 and 223, respectively.[40]

2.3.2 | Thoracic imaging

Most case reports of cats and dogs with ARDS report diffuse interstitial or multilobar patchy alveolar infiltrates on thoracic radiographs[11,21,22,27] with 1 report of severe diffuse alveolar pattern in all lung lobes with the caudodorsal area more severely affected in a dog.[24] In a cat with ARDS secondary to systemic toxoplasmosis, a diffuse nodular interstitial pattern with areas of patchy alveolar infiltration was found.[30]

In human medicine, computed tomography (CT) scans are commonly used to aid in the diagnosis of ARDS. Typical changes are described as bilateral, diffuse ground-glass opacities, which are not entirely uniformly distributed and often gravity dependent.[41] ARDS after pulmonary insult can show both consolidated and ground-glass areas, whereas ARDS as a complication from systemic disease usually is associated with a higher degree of ground-glass areas.[17] In dogs and cats with ARDS, similar findings have been reported.[11,21,31] In 1 report of ARDS in a dog after inhalation of an airway irritant, the soft tissue attenuation spared the most peripheral areas of the lung.[28]

A study in people investigated lung ultrasound in 40 patients with cardiogenic pulmonary edema compared to lung ultrasound in 18 patients who met clinical criteria for ARDS.[41] All patients who met ARDS criteria had pleural line abnormalities, reduction or absence of the sliding sign, and spared areas, while none of the heart failure patients had reduced or absent lung sliding, spared areas, consolidations, and lung pulse. Although there are studies evaluating ultrasound appearance of cardiogenic versus noncardiogenic causes of respiratory distress in dogs and cats, to the authors' knowledge the ultrasonographic appearance of NCPE specifically has not been characterized in a significant number of dogs or cats.[42,43]

2.3.3 | Edema fluid to plasma protein ratio

Analysis of the pulmonary edema fluid may help in the diagnosis of high-permeability edema versus hydrostatic edema. A pulmonary edema fluid protein to plasma protein ratio of ≥0.65 was shown to have good diagnostic discrimination between high-permeability and hydrostatic pressure pulmonary edema in 390 mechanically ventilated human patients.[44] Ratios of 0.65 or higher identified patients with ARDS with a sensitivity and specificity of 81% each. Not only did this ratio differentiate between etiologies, but a higher ratio was also significantly associated with higher mortality rates and fewer ventilator-free days. Determination of the protein concentration in the edema fluid alone and not the ratio showed poorer diagnostic discrimination. To the authors' knowledge, a similar comparative investigation has not been performed in dogs or cats. However, the edema fluid protein to plasma protein ratio was 0.77 in a cat and 0.76 in a dog with suspected ARDS.[29,30]

2.4 | Prognosis

The prognosis for ARDS is more guarded than other types of NCPE. In people, mortality is reported to be 27% for mild, 32% for moderate, and 45% for severe ARDS.[34] In 2 retrospective studies on ARDS in cats and dogs, the mortality rates were 84% and 92% for dogs and 80% and 100% for cats. The overall mortality rate for both species was 86% and 89.7%, respectively.[11,12] Factors that were associated with survival could not be determined due to low case numbers. Another study reported a similar survival rate of 8.3% for dogs and cats that suffered from ARDS and were mechanically ventilated.[24]

For human ARDS survivors, the median duration of mechanical ventilation is 5 days in mild, 7 days in moderate, and 9 days in severe ARDS.[16] Dogs that were successfully treated for ARDS underwent mechanical ventilation between 17 hours and 17 days in several case reports,[22–24,26,28] while dogs underwent mechanical ventilation for a median of 18 hours and cats for a median of 15.5 hours, with ranges of 6–174 hours and 6–91 hours, respectively, in a retrospective study.[11] In another study, median duration of mechanical ventilation for dogs and cats with ARDS was 44 hours with a range of 3–936 hours.[12] By differentiating more clearly between median ventilation times for

survivors and nonsurvivors, future studies may be able to help the clinician to better guide client expectations.

3 | TRANSFUSION-RELATED ACUTE LUNG INJURY

3.1 | Summary of veterinary clinical data

While in human medicine transfusion-related acute lung injury (TRALI) is a recognized clinical entity and one of the most common causes of transfusion-associated morbidity and mortality, TRALI has not definitely been diagnosed in companion animals. There is a paucity of data in veterinary medicine regarding ALI temporally associated with the transfusion of blood products.[46–49] In 1 prospective study, 2 out of 54 dogs receiving blood products were diagnosed with ALI based on a P/F ratio of <300 and newly developed bilateral infiltrates on chest radiographs. Both of these dogs received fresh frozen plasma, and 1 dog showed respiratory distress 3 days after transfusion as well as histopathologic findings compatible with ARDS, while the other dog did not develop respiratory signs within 48 hours.[48] In a retrospective study investigating complications after transfusion of packed red blood cells, 10 of 211 dogs developed VetALI after initiation of the transfusion; some or all of them may have received other blood products in addition to red cells.[49] Two retrospective reports mention transfusions as a risk factor in a total of 11 dogs with ARDS, but it is not known if these dogs had other known risk factors for ARDS or what blood products were transfused.[11,12] To the authors' knowledge, no reports on ALI in association with transfusions in cats have been published. Whether or not the described cases of ALI in dogs receiving transfusions represent the clinical entity that is called TRALI in people is currently undetermined.

3.2 | Pathophysiology

In people, TRALI is a condition of acute respiratory distress that is associated with the transfusion of blood products. Two different pathophysiologic mechanism are recognized in the medical literature.[46,47] Immune TRALI is caused by granulocyte antibodies in donor blood that react with neutrophils in the recipient's blood after transfusion. These neutrophils become activated and are sequestered in the lung, where they initiate inflammation. This syndrome can be accompanied by additional systemic signs, such as hypotension, and is associated with more severe respiratory symptoms compared to nonimmune TRALI.[46,47] It can be seen in healthy patients, as well as those with underlying diseases associated with inflammatory states such as sepsis, cancer, or heart disease. Immune TRALI is seen after transfusions of plasma-containing products including platelet transfusions, especially with blood from multiparous women.[46,47]

Non-immune TRALI on the other hand is believed to be caused by bioactive mediators, such as lipids, that accumulate in blood products during storage. To cause pulmonary neutrophil sequestration and severe inflammation, the recipient's neutrophils must already be in an activated state due to another underlying disease.[46] This form of TRALI is seen with administration of stored packed red blood cells and platelets, but not fresh blood products or plasma, and typically takes a milder course than immune TRALI.[46,47]

Additionally, IV immunoglobulin infusion has been reported as a cause for TRALI in people in recent years. Whether these instances are better categorized as immune TRALI or nonimmune TRALI is currently unknown. Although it would be plausible to assume they represent immune TRALI due to the nature of the transfused product, some data suggest that they are antibody independent, consistent with nonimmune TRALI.[50]

3.3 | Diagnosis

3.3.1 | Consensus statement

While in previous years, TRALI was characterized as a condition resulting from a transfusion in the absence of a known risk factor for ARDS, this definition was recently revised to reflect new insights into the pathophysiology and epidemiology of TRALI.[51,52] Currently, 2 different types of TRALI are acknowledged, depending on whether the patient has underlying diseases that might constitute an ARDS risk factor or not.[52] The criteria that need to be met for each type are presented in Table 2.[52]

Patients who do not meet the TRALI type I or type II criteria should be categorized as having ARDS rather than TRALI if the onset of signs consistent with ARDS is within 6 hours of the transfusion, but the patient's respiratory status was deteriorating in the 12 hours before the transfusion, or the patient was diagnosed with ARDS of any severity before transfusion and the respiratory status was declining in the 12 hours before transfusion and further deteriorates within 6 hours of the transfusion.

3.3.2 | Thoracic imaging

Radiographic features of TRALI in people include bilateral, generalized pulmonary infiltrates that can be interstitial to alveolar with a patchy distribution.[46,47] A bilateral irregular reticulonodular pattern[53] or pleural effusion can also be seen.[54] In people, TRALI can manifest as heterogenous parenchymal consolidations with air bronchograms, and ground-glass appearance of the lungs is sometimes seen on CT.[54]

Thoracic ultrasound detected bilateral coalescent B-lines, pleural thickening, and subpleural consolidations in case reports in people with TRALI,[55,56] consistent with findings in people with ARDS.[41] In some cases, lung ultrasonographic changes can be present before significant changes can be detected on thoracic radiographs.[55]

3.4 | Prognosis

In human medicine, immune TRALI carries a mortality rate of 6%–23%,[46,57] while in 1 study, none of the 9 patients with nonimmune

TRALI died.[57] Mechanical ventilation was performed in 91% of immune TRALI and 89% on nonimmune TRALI patients.[57]

4 | NEUROGENIC PULMONARY EDEMA

4.1 | Summary of veterinary clinical data

Neurogenic pulmonary edema (NPE) is a type of NCPE that has been described after traumatic brain injury and seizures in dogs and after a variety of cerebral insults in people.[58–62] In a report of dogs with NPE, they suffered cranial trauma due to falls or after being stepped on, suffered trauma of unknown origin, or had seizures resulting from intracranial masses, idiopathic epilepsy, or hypoglycemia. In animals suffering traumatic brain injury, young dogs were overrepresented (6 were less than 6 months old), while 75% of patients with seizures were over 10 years old.[58]

Other cases of NPE reported in the literature include 3 dogs with seizures due to various reasons that developed respiratory distress and pulmonary edema immediately after the seizure event. Two of these dogs additionally showed hemoptysis, which has also been reported in people with NPE.[59,63]

Another type of NCPE can be seen in hunting dogs without any other known inciting factor for edema. The pathogenesis is not clear, but it is believed that this type of edema is due to 1 of 2 mechanisms. Either the severe sympathetic drive from excitement and exercise during hunting leads to a pulmonary edema similar to the neurogenic type or hunting dogs may pant or bark excessively and the edema is due to a postobstructive type mechanism, with the former theory more firmly supported.[8,64] Physical exertion with resultant hypoglycemic effects on the brain has also been suggested.[59,65] In 33% of dogs with a history of hunting-associated dyspnea, lung edema was evident on necropsy and 44% showed subendocardial necrosis, which was interpreted as an indicator that NPE after hunting is due to catecholamine release.[64]

4.2 | Pathophysiology

The exact pathophysiological mechanism of NPE is still not entirely elucidated. In order to investigate the pathophysiology of NPE, experimental models of cerebral insult in dogs by injection of veratrine or thrombin into the cisterna magna or by exposing the brain to hypoxemia while maintaining whole body normoxemia have been performed.[a,66–70]

Brain injury, especially if it affects the nucleus tractus solitarius and the dorsomedial nucleus of the vagus, can lead to fulminant sympathetic stimulation.[60] Controversies exist in terms of by which mechanism and mediator this sympathetic surge causes NPE. One theory states that sympathetic stimulation causes NPE by increasing systemic arterial and venous pressures (with the increase in venous pressure more pronounced than the increase in arterial pressure) as well as by increasing pulmonary arterial, capillary, and venous pressures, left ventricular end-diastolic pressure, and left atrial pressure.[67,68,70]

The arterial vasoconstriction is believed to lead to an increased left ventricular afterload, which overwhelms the left ventricular function and causes congestion of fluid into the lungs. Additionally, venous vasoconstriction likely shifts blood volume from the systemic to the pulmonary circulation, increasing the pulmonary capillary hydrostatic pressure even higher.[66] The severe increase in pulmonary capillary pressure induces stress-related endothelial damage and exudation of protein-rich fluid.[71] Contrary to this theory, some studies suggest that sympathetic stimulation causes an increase in capillary permeability and subsequent NPE, independent of pulmonary capillary pressure changes.[66,72] It is controversial whether this vasoconstriction or increase in permeability is mediated via direct neuronal pathways (innervation of vasculature) or circulating catecholamines.[66–70,72,73] Production of reactive oxygen species may also play a role[a] and it is likely that the formation of NPE is multifactorial.

4.3 | Diagnosis

In a systematic review of radiographic findings in dogs and cats with NCPE, patients with NPE most commonly showed a bilateral, symmetric, multifocal, mixed alveolar to interstitial lung pattern, focused in the caudal lung lobes or distributed throughout all lung fields. For the few animals with unilateral distribution, the changes were found on the right side of the lung.[74] In another study, dogs and cats with NCPE mostly showed an alveolar or alveolar to interstitial lung pattern on chest radiographs, and distribution pattern was mostly caudodorsal with or without another affected lung lobe (>75% of animals). The right lung lobes were more often affected than the left lobes, and the right lung lobes were more often affected than a combination of the right and left lung lobes.[58]

Other authors also report a diffuse, bilateral symmetrical interstitial to alveolar lung pattern mainly in the caudodorsal lung fields of dogs with NPE, which is sometimes described as patchy in appearance.[59,63] In a report on dogs with hunting-associated pulmonary edema, lung infiltrates were found exclusively in the caudal lung lobes in 75% of cases, only cranioventrally in 6.3% of cases, and both caudodorsally and cranioventrally in 18.7% of cases, with all dogs showing bilateral distribution.[64]

CT of the chest revealed an increased interstitial pattern with some areas of alveolar consolidation in the caudal lung lobes as well as the accessory lobe in 1 dog with seizures and hemoptysis.[63]

4.4 | Prognosis

Prognosis of NPE is generally good, as most cases in dogs resolve within a few days with minimal support.[59,63] In 1 study, 36.4% of dogs with NPE due to traumatic brain injury or seizures died or were euthanized. For patients with seizures, unfavorable outcome was attributed to the underlying disease rather than the effects of the pulmonary edema, whereas in patients with traumatic brain injury the severity of the NPE played a decisive role. Most patients that survived were discharged

within 48 hours.[58] One study reports a 33.3% mortality rate in dogs and cats with NPE, including those with electrocution, although details on the cause of death were not available.[74]

5 | NPE SECONDARY TO ELECTROCUTION

5.1 | Summary of veterinary clinical data

NCPE after electrocution is considered a subcategory of NPE. Due to its specific patient population, it will be discussed separately. The majority of dogs and cats described in the veterinary literature sustained an electric shock while chewing on a household electric cord.[58,75] Electrical injury secondary to higher voltages such as electric wires and lightning strikes are uncommon and no report of lightning accidents leading to NPE are available in dogs or cats.[58,76] In contrast to other causes of neurogenic edema, respiratory signs after electrocution were only observed in about 30% of cases in 1 report, even in the face of radiographic changes.[58] There seems to be an age predisposition in younger animals; in 1 study, over 85% of patients were younger than 5 months, and in another, the mean age was 3.5 months. Another source states similar findings, with 70% of dogs and 46% of cats that chewed on electrical cords being no older than a year.[77] This is likely a consequence of younger animals having a higher propensity to chew on objects such as electrical cords. Dogs seemed to be more predisposed than cats.[58,75]

In a retrospective study of 29 dogs and 7 cats sustaining electrocution, almost 80% of dogs and 57% of cats developed respiratory distress, most of them within 1 hour of the incident. In another study, only about 30% of dogs and cats developed respiratory distress after electrocution.[58,75] Dogs that died after electrocution and had a necropsy performed showed pulmonary edema with pink frothy sputum and subendocardial and subepicardial ecchymoses, which is commonly recognized as a consequence of severe sympathetic activation.[64,75]

5.2 | Pathophysiology

Pulmonary edema as a consequence of electrocution is generally accepted to be a result of the same pathophysiologic mechanism as NPE.[75,77] Nervous tissue has a high tendency to conduct electricity, predisposing the CNS to damage by electrical current, which then is believed to cause a sympathetic discharge similar to other types of NPE.[78] Direct electric stimulation of nervous fibers innervating the cardiovascular system is also possible.[79] Sympathetic discharge as the cause of pulmonary edema due to electrocution is further supported by the fact that necropsy findings of dogs with pulmonary edema due to electrocution showed subendocardial and subepicardial ecchymoses, which is commonly recognized as a consequence of severe sympathetic activation.[64,75] NPE is not a common feature of electrical accidents or lightning strikes in people.[80–84]

Electric injury and lightning injury can have a multitude of other effects on the mammalian body. Alternative causes for respiratory distress, such as edema in the upper respiratory tract or lung injury via other mechanisms (transmission of electric energy to heat, cellular necrosis), should be considered in electric or lightning injury victims.

5.3 | Diagnosis

Radiographs performed in dogs after electrical injury showed a diffuse alveolar or mixed interstitial and alveolar pattern with a concentration in the caudodorsal fields.[75] In another study, cats and dogs with electrical injuries had a similar pattern, but a lower percentage of lung involvement than patients with NPE due to traumatic brain injury or seizures.[58] Similar to veterinary species that developed NPE after electrical or lightning injury, thoracic radiographs of people showed bilateral, diffuse, heterogenous alveolar opacities.[81,82]

5.4 | Prognosis

In 1 report on electrocution in dogs and cats, 38.5% of hospitalized dogs did not survive, and it was presumed that this was a consequence of pulmonary edema, while all of the hospitalized cats survived.[75] In 1 report, 1 of 6 dogs that experienced electrocution died, whereas the only cat survived. The cause of death in this dog was associated with complication from the electrocution, not the NPE itself.[58]

Prognosis of NPE after electrical or lightning injuries in people is not known due to infrequent reporting of this complication. However, individual case reports often document survival of the patients.[81,82]

6 | POSTOBSTRUCTIVE PULMONARY EDEMA

6.1 | Summary of veterinary clinical data

There is a paucity of literature on postobstructive pulmonary edema (POPE) in dogs and cats; however, reported causes of this type of pulmonary edema include tracheal collapse, strangulation including excessive pulling on a leash, brachycephalic airway syndrome, pharyngeal obstruction by a foreign body, laryngeal edema or paralysis, laryngeal polyp, pharyngeal fibrosarcoma, and excitement while being manually restrained.[58,85,86] While in 1 study, 75% of dogs and cats with POPE were less than 1 year old, in another, dogs presented with an average age of 8.4 years. This age distribution reflects the underlying cause of the airway obstruction—younger dogs more commonly developed POPE after strangulation on a leash or due to brachycephalic airway syndrome, while older dogs suffered from neoplasia or degenerative disease such as laryngeal paralysis.[58,86] There is no confirmed association between duration of airway obstruction and development of clinical signs, as in many of these cases airway obstruction lasted for a very short time, but all animals developed respiratory distress.[58]

6.2 | Pathophysiology

POPE occurs in people secondary to laryngospasm, foreign body inhalation, croup, epiglottitis, strangulation, and goiter.[7,87–89] The proposed pathophysiologic mechanism by which upper airway obstruction can lead to pulmonary edema is based on forcible inspiration against a closed epiglottis, which decreases intrathoracic pressure dramatically. In young healthy adults, these pressures can get as low as −140 cm H_2O.[7] The consequence of increased negative intrathoracic pressure is twofold: it decreases the pulmonary interstitial hydrostatic pressure and increases venous return to the right side of the heart and to the lungs. Both mechanisms are believed to contribute to fluid leaking from the capillaries into the interstitium due to an increased pressure gradient between these 2 compartments.[87] The negative intrathoracic pressure may also impede left-sided cardiac function via decreasing left ventricular filling and increasing left ventricular afterload, both of which in turn can result in increased pulmonary capillary pressure as well.[85] Additionally, some researchers suggest that the dyspnea associated with airway obstruction causes an increased sympathetic surge similar to that seen in NPE.[7,88,90]

Type I POPE occurs during an acute obstruction of the airways, as described above. Type II POPE occurs after relief of a chronic airway obstruction. Likely, exhalation against a chronic airway obstruction causes a degree of intrinsic positive end-expiratory pressure (PEEP), with physiologic effects opposite to the ones described for type I POPE. Once the obstruction is relieved and the positive pressure abates, intrathoracic pressures become relatively more negative, and pulmonary edema develops in response to mechanisms similar to those of type I POPE.[89–91]

6.3 | Diagnosis

In a retrospective study, the most common radiographic finding in dogs and cats with POPE was a symmetric, alveolar–interstitial focal to multifocal pulmonary pattern with a bilateral distribution usually in the caudodorsal lung fields. In animals with a unilateral distribution (39%), the pulmonary edema was found almost exclusively on the right side.[74] Although bilateral distribution was more common than unilateral in this cohort of patients, unilateral right distribution was more common in animals with POPE compared to any other cause of NCPE investigated in this study.[74] Mixed interstitial to alveolar pulmonary infiltrates with a dorsocaudal distribution also were the dominant finding in a case series of 9 dogs with POPE. For patients with asymmetric degree of involvement, the right lung was usually more affected than the left.[86]

Similarly to CT findings of ARDS, POPE is also characterized by a ground-glass appearance in people, but the distribution is more central and nondependent, which is believed to be due to the more negative pressures in these areas compared to other parts of the thorax during forced inhalation.[92] CT findings after POPE in animals have not been described to the authors' knowledge.

6.4 | Prognosis

In 1 veterinary study, 50% of patients with POPE died or were euthanized due to the severity of the pulmonary edema, while in another study, no dogs succumbed to the consequences of POPE.[58,86] Mortality in a third report on dogs and cats with POPE was 34.8%, although it is not clear if euthanasia was due to severity of pulmonary edema or other circumstances.[74]

7 | RE-EXPANSION PULMONARY EDEMA

7.1 | Summary of veterinary clinical data

Re-expansion pulmonary edema (RPE) is uncommonly reported in veterinary medicine. It has mostly been described after correction of a traumatic diaphragmatic hernia in both dogs and cats, occurring more frequently in cats than dogs, and being implicated in 45% of postoperative deaths in cats in 1 study.[93–95] RPE was also mentioned as the suspected cause of death after surgery in 1 cat in a retrospective analysis of peritoneopericardial diaphragmatic hernias.[96] Other reports include a kitten with fatal pulmonary edema after surgical correction of severe pectus excavatum, which developed immediately after surgery, and a dog with pneumothorax.[97,98] This dog developed RPE after removal of 25 ml/kg of air over a time frame of 5 minutes and made a full recovery with supportive care.[98]

To prevent the development of RPE after correction of diaphragmatic hernias, some authors suggest avoiding aggressive lung reinflation attempts before closing the thoracotomy site.[93]

7.2 | Pathophysiology

RPE is a rare but potentially fatal complication in people seen after iatrogenic re-inflation of a previously collapsed lung, for example, due to pleural effusion, pneumothorax, 1-lung ventilation, or atelectasis due to complete bronchial obstruction.[99–105] It usually develops within 24 hours after atelectasis is relieved but can occur as instantly as within 1 minute.[100,105]

Although the pathophysiological mechanism of RPE is not completely clear, several theories exist, which may not be mutually exclusive. One theory states that during re-expansion, the lung may develop significant negative interstitial pressures, favoring fluid shifts from the pulmonary capillaries into the interstitium.[102] Capillary endothelial damage secondary to pressure changes may occur.[93] This is a pathophysiology similar to that proposed in POPE.

Another theory states that inflammatory mediators and reactive oxygen species secondary to ischemia–reperfusion injury are involved.[99,103,106] This theory is supported by a case series in people, in which pleural effusion leading to only partial atelectasis of the ipsilateral lung resulted in RPE formation only in the previously atelectatic lung areas, but not in the previously ventilated lung portion of the ipsi-

lateral lung. The authors of this study postulated that this is indicative of ischemia–reperfusion injury.[103] Additionally, RPE in an experimental study in dogs was associated with a 12% decrease in systolic arterial pressure and a 35% decrease in pulmonary artery pressure, which the authors contributed to the presence of vasoactive substances mediating inflammation in the lung as well as hemodynamic changes.[106] Other theories that have been postulated include surfactant abnormalities, changes in pulmonary artery pressure, and direct hypoxic damage to capillaries.[93]

Due to its low incidence, it is difficult to determine risk factors for RPE. Historically, chronicity of lung collapse, large volumes of removed fluid or air, and use of excessively negative pressures during thoracocentesis were implicated as major contributing factors.[93,105] However, there is evidence that short durations of atelectasis, even as brief as a few hours, can lead to RPE, and the rate of fluid or air removal may be a more important factor than the total volume removed.[99–101,105,106] It is also controversial if the degree of negative pressure applied during thoracocentesis plays a role.[93]

7.3 | Diagnosis

Thoracic radiographs in dogs and cats with RPE usually reveal diffuse alveolar opacities, sometimes with a focus in the caudodorsal regions.[93,94,98] Similarly, reports in people describe diffuse infiltrates, which most commonly affect the lung that was previously collapsed, although 1 case report describes RPE in the contralateral lung.[99–103] This was suspected to be due to atelectasis of the contralateral lung as a result of mediastinal shift from large-volume pleural effusion on the contralateral hemithorax. Thoracocentesis resulted in incomplete re-expansion of the ipsilateral and more pronounced expansion on the contralateral lung that most likely explained the distribution of RPE.[101]

On CT, RPE in people is associated with patchy ground-glass opacities with a vascular distribution.[101] In a retrospective study in 43 people with RPE after evacuation of spontaneous pneumothorax, thoracic CT additionally showed lung consolidation, interlobular septal thickening, and intralobular interstitial thickening within 1–24 hours after thoracocentesis. The lung changes were ipsilateral and located in the periphery in most cases.[107] CT findings after RPE in animals have not been described to the authors' knowledge.

7.4 | Prognosis

Mortality rates for RPE are difficult to estimate both in people and small animals as most reports describe single cases or case series.[93,94,98–100,102–104] Similarly, the severity of clinical signs and need for interventions such as oxygen support or mechanical ventilation varies widely.[99,101–104] It appears that in companion animals, RPE is more frequently encountered and takes a more dramatic course after thoracic surgeries than thoracocenteses, but definitive conclusions cannot be made due to lack of data.[93–95,97,98]

8 | DRUG INDUCED NCPE

8.1 | Summary of veterinary clinical data

Drug-induced NCPE in veterinary medicine has been reported rarely, and in most of these cases, the condition was characterized as ARDS rather than a separate entity of NCPE. This has been described because of cytarabine in a dog and after a vincristine overdose in a cat.[11] In another dog that ingested tetrahydrocannabinol, treatment with IV lipid emulsion resulted in acute respiratory distress. Based on histologic rather than clinical findings, the authors suspected ARDS.[29] In people, synthetic cannabinoids have been implicated in the development of NCPE, although the pathophysiology of this is suspected to be more compatible with NPE.[108] One dog that developed respiratory failure after repeated cytarabine infusions met clinical criteria for ARDS, but histopathologic findings were suggestive of an alternative pathogenesis of pulmonary edema.[27]

In people, many drugs have been implicated in the development of NCPE, and the suspected pathophysiologic mechanisms are variable. The clinician should be cognizant that pathophysiologic mechanisms other than ARDS could also play a role in dogs and cats with drug-induced NCPE.

8.2 | Pathophysiology

In the human medical literature, both pharmaceutical and illicit drugs are associated with the development of NCPE. The pathophysiological mechanism of how drugs induce NCPE in people is not uniform, and often not fully elucidated. For example, methadone is believed to cause NCPE via histamine release and subsequent increase in capillary permeability.[b] Neostigmine may cause NCPE by stimulating nicotinic receptors in autonomic ganglions and thus upregulating the sympathetic system. This would be a pathophysiological mechanism comparable to that of NPE.[109] Acetazolamide and hydrochlorothiazide are both diuretics containing sulfur groups and both compounds have been implicated in causing NCPE. It is suspected that the sulfur groups increase pulmonary vascular permeability, potentially via immunoglobulin G deposition in the lung.[110–112] Similarly, protamine seems to cause NCPE in an immunoglobulin G-mediated manner.[113] NCPE secondary to nonionic low-osmolar-radiocontrast material may be due to viscosity-induced erythrocyte damage, leading to capillary stasis and fluid extravasation. Alternatively, the agent may directly irritate lung endothelium and increase permeability.[114,115] The calcium channel blockers verapamil and diltiazem are speculated to cause NCPE by causing precapillary vasodilation causing increased capillary hydrostatic pressures, as well as inhibition of prostacyclin release, leading to increased pulmonary vascular permeability.[116,117]

Illicit drug use has also been associated with NCPE. In the case of heroin, it is not entirely clear if the overdose of the drug or the administration of naloxone as a rescue drug causes the NCPE. Naloxone may cause a type of withdrawal syndrome, which is known to cause a sympa-

thetic surge similar to that seen in NPE, and this may explain the development of NCPE. Alternatively, heroin-induced respiratory depression and the subsequent hypoxia-induced increased vascular permeability, morphine-induced anaphylactoid reactions, or attempted inspiration against a closed glottis may also be possible causes.[118,119] This may be more apparent after the patient starts breathing again after reversal with naloxone.[119] Methylenedioxymethamphetamine is a synthetic amphetamine derivative, which releases endogenous catecholamines, which can cause a sympathetic surge and NCPE development similar to NPE.[120] Synthetic cannabinoids may cause NCPE through seizures or respiratory depression.[108]

8.3 | Diagnosis

Thoracic radiographs in people with drug-induced NCPE may show bilateral or unilateral alveolar edema with air bronchograms, ranging from mild to complete opacification of all lung fields.[b,109–111,115,119] The distribution can be perihilar or diffuse.[112,117,119,120] The 1 dog with cytarabine-associated pulmonary edema showed a multilobar patchy alveolar pattern.[27]

Thoracic CT findings in humans with drug-related NCPE have been described as diffuse, bilateral alveolar and interstitial infiltrates.[111,114] No reports on CT findings in dogs or cats are available.

8.4 | Prognosis

Prognosis for drug-induced NCPE in people and small animals is not known, as most reports describe individual cases. Additionally, in many drug reactions complications other than pulmonary edema may contribute to the prognosis.[b,11,27,29,108–120] However, most reported cases in people seem to have a favorable outcome with short hospitalization times.[b,109–115,117,119,120]

9 | PULMONARY EDEMA SECONDARY TO DROWNING

The terminology for drowning incidents is still used inconsistently in the human medical literature, although an international consensus conference defined it as follows in 2002: Drowning is "a process resulting in primary respiratory impairment from submersion/immersion in a liquid medium." This term is to be used for both survivors and nonsurvivors and terms like near-drowning, wet-drowning, or dry-drowning should not be used any longer.[121] For the purpose of this review, the term drowning will be used in accordance with these recommendations.

9.1 | Summary of veterinary clinical data

There are only a small number of veterinary reports on drowning injuries in small animals. To the authors' knowledge, only 1 retrospective study has been published that describes the clinical course and outcome in a small group of dogs and cats. These included dogs that fell into bodies of fresh water such as rivers, lakes, and ponds or swimming pools. For some, a precipitating event or condition (seizure disorder, electric shock, permanent tracheostomy) or intentional submersion led to the drowning event, and for others (including the cats) the exact circumstances that led to the incident were not known. Mild to moderate respiratory distress was described in most animals, and respiratory failure was believed to be due to the development of pneumonia and ALI in 15 animals.[122]

In addition, 3 case reports describe drowning events in dogs. A 2-year-old Labrador Retriever that was submerged in fresh water for about 2 minutes developed respiratory distress a day after the incident; thoracic radiographs indicated NCPE. The dog was treated with supportive care and was able to be discharged within 5 days.[123] A 7-year-old Golden Retriever that was submerged in salt water for 30 seconds after having a seizure and whose clinical course was complicated by ARDS was mechanically ventilated for 4 days and survived to discharge.[22] Another dog succumbed to granulomatous bronchopneumonia after drowning in a drainage ditch as a consequence of a seizure.[124] Drowning has also been mentioned as a mechanism of injury in reports on animal abuse, but the clinical course was not described.[125]

9.2 | Pathophysiology

The pathophysiology of drowning is complex. Most of our scientific understanding is derived from experiments in dogs and this has recently been thoroughly reviewed by others.[126] When a victim's airways are covered by water or other liquid, the victim usually will voluntarily hold their breath for as long as possible. With submersion in cold water (less than 10°C or 50°F), this protective mechanism usually fails, and the victim gasps and hyperventilates.[121] Once breathing can no longer be suppressed, water will enter the oropharynx and larynx, likely leading to a vagally mediated laryngospasm, although this is controversial.[127,128] Although respiratory movements may be present and pronounced during the time of breath holding and laryngospasm, no gas exchange occurs due to a closed glottis, leading to hypoxemia and hypercapnia. With progressive hypoxemia, laryngospasm ceases either due to loss of consciousness or hypoxia-associated dysfunction of the laryngeal nerves and the patient starts gasping, both of which allows the victim to aspirate liquid.[121,126,127] Fresh water entering the lungs leads to alterations in the composition of surfactant and renders it unable to decrease alveolar surface tension; salt water on the other hand washes out surfactant. Both events will lead to alveolar collapse, ventilation–perfusion mismatch, and pulmonary hypertension.[121,126,129] Additionally, both fresh and salt water damage the alveolocapillary barrier and pneumocytes, which causes compromise of surfactant production and accumulation of fluid in the interstitium and the alveoli.[126,127,129]

While this is the main mechanism by which NCPE occurs after drowning, the destruction of the alveolocapillary membrane also leads

to infiltration with inflammatory cells, which can later progress to the development of ARDS.[129] Drowning has been reported as the precipitating factor for ARDS both in people and dogs.[16,22] Furthermore, other mechanisms of pulmonary edema due to drowning have been suggested by some. Severe sympathetic surge as a response to stress and hypoxia may lead to a neurogenic-type edema, and inspiration against a closed glottis during the phase of breath holding and laryngospasm may cause edema in a manner similar to POPE.[127,130]

In addition to pulmonary complications, other mechanisms can cause morbidity or mortality during or after the drowning event in people and animals, including cardiac arrythmias and hypoxic cerebral damage.[126-128]

9.3 | Diagnosis

Radiographic descriptions of pulmonary changes after drowning incidents in dogs are scarce, and include severe pulmonary edema with air bronchograms and mixed bronchial and interstitial infiltrates.[123,124] One report describes a focus of the changes in the dorsal lung lobes.[123] The distribution pattern can be bilateral, but in 1 case the right caudal lung lobe was more affected than the left.[22,123] In humans, radiographic changes are usually described as bilateral and diffuse in distribution and alveolar in nature.[130–134] In less severe cases, the distribution usually is perihilar with sparing of the peripheral lung areas, and it becomes more diffuse with progressive severity.[134]

Thoracic CT findings in human survivors of drowning incidents are described as bilateral patchy or diffuse ground-glass opacities with a mostly perihilar distribution. Additional findings can include interlobular septal thickening, and aspirated fluid is often visualized in the trachea or bronchi.[134] No information is available in small animal patients.

9.4 | Prognosis

The prognosis after drowning in animals is currently unknown. However, in 1 report overall mortality in canine and feline drowning victims was 36%; none of the cats survived, and 18 of 25 dogs survived (72%). Median hospitalization time for survivors was 2 days. For 9 out of the 10 dogs and cats that were not discharged, respiratory failure was the cause of death or euthanasia.[122] In people, experts estimate that about 375,000–500,000 patients die from drowning indicents each year, but this number likely underestimates the true incidents due to underreporting.[127] Death occurred in 18.4% of admitted patients in 1 study.[135] Cause of death in people may differ from what is observed in animals, with hypoxic encephalopathy being considered the most common cause of nonsurvival.[121]

10 | TREATMENT

The mainstay of treatment of all types of NCPE is supportive care with oxygen supplementation, including mechanical ventilation if needed, as well as removal of the inciting cause if possible (eg, treating the neurologic disease in NPE, removal of obstruction in POPE).[7,8] Likely, most causes of NCPE other than ARDS will not require mechanical ventilation, and oxygen can be supplied via a variety of methods.

Traditional methods of oxygen supplementation such as flow-by oxygen, oxygen masks, oxygen cages, and insufflation via nasal cannulas have been reviewed elsewhere and will not be discussed.[136]

10.1 | High-flow oxygen therapy

High-flow oxygen therapy (HFOT) has gained increasing interest in people who develop mild to moderate ARDS.[137,138] It has also been used in hypoxemic respiratory failure due to other causes in people.[139,140] High-flow nasal oxygen therapy is characterized by an air/oxygen gas mixture that is delivered to the patient in a humidified and warmed state, which allows much higher flow rates (up to 60 L/min) than conventional nasal cannulas without the anticipated side effects such as mucosal drying and nasal discomfort. The inspired oxygen concentration can furthermore be adjusted more precisely, as the high flow rates make delivery of the prescribed inspired oxygen fraction to the patient's airways more reliable than conventional cannulas.[141] In 1 veterinary study, an Fio_2 of 95% was achieved at flow rates of 1 L/kg/min when the machine was set to deliver an Fio_2 of 100%.[141] Data on HFOT in veterinary medicine are limited; however, several reports in dogs showed significantly improved arterial oxygenation and decreased respiratory rates and effort compared to conventional nasal cannulas. A flow-dependent increase in expiratory airway pressures and good tolerance, both in healthy dogs and dogs with hypoxemic respiratory failure, while awake or mildly sedated, has been documented. Clinically significant complications such as gastric distension or hypercapnia were rare.[141–145] Although further prospective trials in companion animals are certainly necessary to determine its use in different disease states, this treatment modality appears promising and should be considered as an alternative when mechanical ventilation is not available or affordable.

High flow nasal cannulas are available in a variety of sizes; a general recommendation is to choose a cannula size that does not occlude more than 50% of the nostril diameter in order to avoid excessive pressure build-up and re-breathing of carbon dioxide.[141,143,144,145] The cannulas can be sutured to the face for a more secure fit and modelling clay may be useful to improve alignment with the patient's nose.[141,144,145] Due to size limitations, HFOT may not be a viable option for all cats with respiratory distress. For small dogs in which an HFOT cannula that occludes no more than 50% of the nares is not available, some authors choose to insert only 1 prong of the cannula into a nostril and leaving the other prong unattached from the patient.[145] This may be a suitable solution for cats as well.

As flow rates of 0.4–1 L/kg/min were well tolerated and rates of 2 L/kg/min were acceptably well tolerated in 1 study, a starting flow rate of 0.4–2 L/kg/min has been recommended.[141] Alternatively, the flow rate can be based on the patient's minute ventilation, which is calculated by multiplying the respiratory rate by a set tidal volume of

10 ml/kg.[144] The Fio_2 should initially be set to 100% with the goal of decreasing it to the lowest concentration that will maintain an Spo_2 of 95% or higher.[144,145] No investigation has evaluated tolerance of high-flow nasal cannulas with different gas temperature settings, but a setting of 37–38°C (98.6–100.4°F) appears well tolerated.[143,144]

10.2 | Mechanical ventilation

Mechanical ventilation may become indicated in people and small animals with a wide range of NCPE types.[11,12,16,58,80,100,135] However, most details on mechanical ventilation have been published on the treatment of ARDS in these species. The cornerstone of mechanical ventilation in human ARDS patients is lung-protective ventilation. This consists of ventilation with lower tidal volumes and higher end-expiratory pressures in order to avoid lung overdistension and cyclic collapse and re-opening of alveoli, both of which can exacerbate inflammation in the lung.[17,146,147] The use of small tidal volumes (6 vs 12 ml/kg) resulted in significantly more ventilator- and organ failure-free days and a 22% reduction in mortality in people with ARDS in 1 landmark study, and ventilation with a higher PEEP (15 vs 10 cm H_2O) reduced oxygen requirements in another.[146,147] For a detailed discussion of ventilation strategies that have been investigated in people, the reader is referred elsewhere.[10]

In veterinary medicine, mechanical ventilation is also a mainstay of treatment of ARDS, with 42%–50% of dogs and 80%–100% of cats diagnosed with this condition receiving mechanical ventilation in 2 recent reports.[11,12] For dogs and cats, it is not always feasible to attain settings consistent with lung-protective ventilation per the human definition, although lung protective ventilatory strategies have been documented in a cat with ARDS, a dog with ARDS, and healthy Beagles, with tidal volumes between 6 and 9.5 ml/kg.[24,30,148] Some authors speculate that the variable chest conformations across different dog breeds makes it difficult to extrapolate from human medicine to a general dog population.[149] In fact, reports of dogs with ARDS showed that lower tidal volume ventilation (6.7–12.4 ml/kg) was poorly tolerated and caused severe hypercapnia ($Paco_2$ values between 70 and 106 mm Hg) and respiratory acidosis.[22,28] This seems unacceptable and indeed, in a recent human trial on almost 2000 patients, a $Paco_2$ at or above 50 cm H_2O was independently associated with increased ICU mortality.[150] Most reports in dogs and cats use tidal volumes between 10 and 15.9 ml/kg (up to 20 ml/kg) with PEEP between 1 and 13 cm H_2O.[11,14,22,23,27,28,31] Peak inspiratory pressures have been reported between 12 and 60 cm H_2O.[14,22,24,27,30] Airway pressure release ventilation as a method of ventilation has been reported in 1 dog, and experimentally this modality led to significantly increased P/F ratios in dogs with oleic acid-induced ARDS compared to volume-controlled ventilation.[26,151] No prospective trials have been performed to determine the optimal ventilatory strategy in dogs and cats with ARDS. A study on experimentally induced ARDS in dogs demonstrated that, when instituted early, using a PEEP of 5 cm H_2O improved oxygenation without affecting blood pH compared to using no PEEP.[152] Suggested initial ventilator settings for dogs and cats with NCPE are summarized from the veterinary literature in Table 3. These settings will need to be adjusted to meet patient needs based on arterial blood gas evaluation or pulse oximetry and capnography, with a target Pao_2 of 80–120 mm Hg and a target $Paco_2$ of 35–50 mm Hg.[153] For a more thorough review on concepts of mechanical ventilation in dogs and cats, the reader is referred to the relevant literature.[153,154]

TABLE 3 Suggested initial ventilator settings for dogs and cats with noncardiogenic pulmonary edema.[11,14,22–24,27,28,30,152,153]

Ventilator parameter	Suggested initial setting
Fraction of inspired oxygen (%)	100
Tidal volume (ml/kg)	7–12
Respiratory rate (breaths per min)	15–30
Minute ventilation (ml/kg/min)	100–250
Peak inspiratory pressure (cm H_2O)	15–25
Positive end-expiratory pressure (cm H_2O)	5–10
Inspiratory time (s)	0.8–1
Inspiratory-to-expiratory ratio	1:1–1:2

10.3 | Pharmacologic interventions for NCPE

Several pharmacologic interventions have been investigated in animal models and people with NCPE, but most do not show consistent benefits. The only 2 drugs for which recommendations have been generated in people with ARDS are neuromuscular blocking agents and glucocorticoids. Neuromuscular blocking agents may be beneficial in patients with severe ARDS to facilitate ventilation, but not in those with mild and moderate ARDS, where they might even be detrimental.[17] Methylprednisolone at a dose of 1 mg/kg/day may be used in people with moderate to severe ARDS within 1 week of onset or at a dose of 2 mg/kg/day after day 6 after onset of clinical signs, followed by a slow taper over 13 days.[155] Another, nonventilatory treatment strategy that has received much attention in people with ARDS is conservative fluid treatment. A negative fluid balance within the first week of treatment was associated with improved oxygenation indices and more ventilator-free days compared to a positive fluid balance.[156]

No consensus statements exist regarding the use of drugs for NCPE in dogs and cats. The use of furosemide, glucocorticoids, and bronchodilators has been reported in animals with ARDS and has also been described in other types of NCPE.[19–25,27,30,58,93,98] In a dog model of ARDS, a continuous rate infusion of furosemide at a rate of 0.2 mg/kg/h was associated with a significant improvement in lung injury score, P/F ratio, and shunt fraction, compared to control animals. The mechanism behind this is speculated to be a direct pulmonary vasodilatory property of furosemide that then improves ventilation–perfusion mismatch, or a positive influence on pulmonary capillary permeability.[157] However, systematic evaluations of the effects of these medications are lacking in clinical patients and recommendations for their use cannot be made at this time. Notwithstanding, using parenteral fluids

judiciously in dogs and cats with respiratory disease of all kinds seems prudent.

11 | SUMMARY

The term NCPE includes many different types of pulmonary edema not associated with heart disease or fluid overload. The pathophysiological mechanism can include hydrostatic changes, alterations in capillary permeability, or a combination thereof. These types of pulmonary edema are described both in humans and companion animals. ARDS is the best described and most serious form of NCPE. Diagnosis of all types of NCPE will depend on the clinical context (history and physical exam findings), as well as diagnostic imaging (thoracic radiography or CT) and blood gas analysis. Treatment is typically supportive in nature (oxygen supplementation, including mechanical ventilation in severe cases), with no medical therapies proven to be of benefit. Prognosis is fairly good for most types of NCPE; however, data are scarce in some instances. ARDS in companion animals currently carries a poor prognosis, with less than 10% of patients surviving to discharge.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

OFFPRINTS

No offprints will be available from the authors.

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ENDNOTES

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