Negative-pressure pulmonary edema in 35 dogs

Abstract

Objective: To describe the clinical characteristics and outcomes in a population of dogs with negative-pressure pulmonary edema (NPPE) and to identify the main causes of the disease. To evaluate any associations with morbidity and mortality.

Design: Retrospective study.

Setting: Three university teaching hospitals and two private referral centers.

Animals: Thirty-five client-owned dogs presented with NPPE.

Interventions: None

Measurements and Main Results: Data collected included patient characteristics, clinical history, clinicopathological abnormalities, radiographic features, treatments and outcome. Median age was 4 months (range 2-90) and median weight was 7.1 kg (range 1.7-37.2). There were many causes of NPPE including leash tugs, near hanging, accidental choking, anatomical obstruction to airflow and purposeful airway obstruction by people. The most common cause of NPPE was accidental choking (40% of cases). Dogs with an anatomical obstruction were older than 24 months. Hypoxemia with an increased alveolar-arterial gradient was common on presentation. The majority of thoracic radiographs (65.7%) showed an alveolar or interstitial pattern in the caudodorsal area as previously described in the literature. Oxygen therapy was administered to 33 (94.3%) dogs. Furosemide was administered to 18 (51.4%) dogs. Median length of hospitalization was 2 days (range 0-14). Twenty-eight (80%) dogs survived to discharge. Seven dogs were mechanically ventilated and only 2 of them (28.6%)

26 survived to discharge. Requirement for mechanical ventilation ($p<0.001$) was the
27 only parameter associated with mortality.
28 Conclusions: Most cases of NPPE occur in juvenile dogs. Different incidents
29 associated with upper airway obstruction can produce an episode of NPPE.
30 Choking on food or toys and near hanging have not been previously described in
31 the veterinary literature as inciting causes of NPPE. The overall prognosis is
32 good.
33

Abbreviation List

ARDS: acute respiratory distress syndrome

A-a: alveolar-arterial (gradient)

BAL: bronchoalveolar lavage

BP: blood pressure

BOAS: brachycephalic obstructive airway syndrome

CT: computed tomography

NPPE: negative-pressure pulmonary edema

PBF: pulmonary blood flow

PE: pulmonary edema

SpO_2: blood oxygen saturation measured with pulse oximetry

TP: total protein

Introduction

Pulmonary edema (PE) is the accumulation of serous or serohemorrhagic fluid in the pulmonary interstitial space and alveoli. Patients with PE have been traditionally classified as having cardiogenic PE or non-cardiogenic PE .[1] The pathophysiological classification of PE based on changes of the pulmonary parenchyma and pulmonary vasculature differentiates 3 groups of PE: high-pressure PE, increased-permeability PE and mixed-cause PE.[2] High-pressure PE is due to an increase in pulmonary hydrostatic pressure and is associated with left-sided congestive heart failure and/or overzealous fluid therapy. Increased-permeability PE occurs secondary to damage of the respiratory membrane as seen in acute respiratory distress syndrome (ARDS), pulmonary thromboembolism, ventilator-associated lung injury or inhalation of toxins. Mixed-cause PE is

produced by concurrent changes in pulmonary vascular pressures and permeability of the vascular beds. Mixed-cause PE include neurogenic PE (produced by seizures, traumatic brain injury or electrocution), re-expansion PE and negative-pressure PE (NPPE).[2]

NPPE, also called "post-obstructive PE", occurs due to vigorous inspiratory efforts against an obstructed airway. In human medicine this is known as the Müller maneuver and is used diagnostically in certain settings.[3] These efforts produce large negative pleural pressures that increase transvascular fluid filtration and precipitate interstitial and alveolar edema. The pathophysiology of NPPE could be explained by a rise in pulmonary capillary pressure associated with the transient drop in intrathoracic pressure and subsequent increase in venous return to the right side of the heart. In addition, the negative pleural pressure transmits to the pericardium increasing cardiac afterload. The increase in afterload elevates left ventricular, left atrial and hence pulmonary capillary pressures. This upsurge in pressure promotes fluid movement from the pulmonary capillaries towards the pulmonary interstitial space and alveoli. Moreover, nervousness associated with airway obstruction and hypoxemia may produce sympathetic activation contributing towards further increases in cardiac afterload. [4-6] In the majority of human patients these mechanisms produce a low-protein edema fluid, demonstrated by a low edema fluid-to-plasma protein ratio (<0.65), although a small subset of patients present with values above this cutoff suggesting an additional increased permeability mechanism. This may be due to pressure-induced rupture of pulmonary capillaries as some patients present with blood-tinged pulmonary secretions.[5,7]

There is a lack of veterinary information relating to this condition and no information from multiple centers. Two veterinary publications have described NPPE in companion animals. One described 9 adult dogs with PE due to anatomical upper airway obstruction including laryngeal paralysis, laryngeal edema, laryngeal polyps and laryngeal fibrosarcoma. All dogs survived to discharge.[8] The second publication described a population of 26 dogs and cats with non-cardiogenic PE of which 6 dogs and 2 cats had presumed NPPE secondary to airway obstruction. Six of these animals with NPPE were less than 1 year old and causes included leash tugs, human physical restraint and brachycephalic obstructive airway syndrome (BOAS). Amongst the cats and dogs with NPPE there was a 50% mortality rate. Six out of 26 patients with non-cardiogenic PE required mechanical ventilation and only 1 of these survived to discharge.[9]

The objective of our study is to describe a population of dogs presenting with NPPE to 5 clinics in XXXX. A secondary objective was to evaluate any associations with morbidity and mortality.

Materials and Methods

This study was approved by the primary author's institution's Ethics and Welfare committee (ethics reference number M2016 0080). The databases of 3 teaching hospitals and 2 private practices in XXXX were retrospectively searched for dogs with a clinical diagnosis of NPPE presenting between 2006 and 2018. Dogs were included in the study if they had acute signs of tachypnea and/or dyspnea and a clinical history compatible with NPPE. The clinical history was

suggestive of NPPE when there was a witnessed or suspected episode of upper respiratory tract obstruction.

Data collected included patient demographics, clinical history, admission physical examination findings, blood test results [arterial and venous blood gases, PCV and refractometric total protein (TP), WBC, platelet count, serum biochemistry], blood pressure (systolic Doppler blood pressure or mean oscillometric blood pressure), blood oxygen saturation (SpO_2) with pulse oximetry, thoracic radiographs and computed tomography (CT) scans, echocardiograms, cytological and microbiological results of bronchoalveolar lavage, treatments performed including medications and type of oxygen administration, length of hospitalization and outcome. A board-certified radiologist (XX) reviewed all available radiographs. In patients where arterial blood gas analysis was performed on room air, these results are reported as PaO_2 and alveolar-arterial (A-a) gradient. In patients where arterial blood gas analysis was performed on supplemental oxygen, these results are reported as PaO_2/FiO_2 ratio. A-a gradients were calculated in patients breathing room air at sea level using the following formula: (A-a) gradient= $P_AO_2 - P_aO_2 = [150 - P_aCO_2/0.8] - P_aO_2$

To further classify the type of upper airway obstruction causing NPPE 5 categories were created. Category 1 was injury produced by pulling hard on the dog´s leash either by the dog or the dog owner/care giver. Category 2 was an episode of near hanging. Category 3 was choking on foodstuffs or toys. Category 4 had an anatomical obstruction to airflow. Category 5 had purposeful airway obstruction by the owner/care giver.

Patients that did not survive were categorized into natural death or euthanasia.

Statistical methods

Statistics were performed using a commercial statistical software.[a] Normality of the data was assessed using the Shapiro-Wilk test. Continuous parametric data was described as mean and SD and non-parametric data as median and range. A Chi-square test or Fisher´s exact test was performed to evaluate the relationship between categorical variables. A Student's t-test was performed to evaluate continuous, normally distributed data and a Mann-Whitney U test for continuous, not normally distributed data. In order to control family-wise error from performing multiple comparisons the Bonferroni correction was applied. After applying the Bonferroni correction, the significance threshold was set at $p<0.002$.

Results

Thirty-five cases met the inclusion criteria. There were 19 different breeds represented in the study. Most dogs were crossbreed (6), followed by English Bulldog (4), Cocker Spaniel (3), Labrador Retriever (3) and Staffordshire Bull Terrier (3). Fourteen dogs (40%) were brachycephalic including English bulldog, French bulldog, Staffordshire bull terrier, Chihuahua, pug, Pomeranian, Lhasa Apso and shih tzu. The median age was 4 months (range 2-90) and the median weight was 7.1 kg (range 1.7-37.2). There were 19 entire males (54.3%), 2 castrated males (5.7%), 13 entire females (37.1%) and 1 neutered female (2.9%). The majority of cases were referred from a primary care veterinarian (85.7%) and the rest (14.3%) presented as primary care emergencies.

There were 10 dogs (28.6%) with NPPE caused by a leash pull (category 1). Six dogs (17.1%) had an episode of near hanging (category 2); two were hanged

by their leashes on becoming trapped outside an ascending elevator, one got his head stuck between fencing panels and 3 had a near hanging episode at the groomers´ table. Fourteen dogs (40%) had accidental choking (category 3). Nine choked on foodstuffs and 5 choked on toys or balls. There were 3 dogs (8.6%) with an anatomical obstruction to airflow (category 4); one each of laryngeal paralysis, laryngeal collapse and presumed BOAS. All dogs in category 4 were older than 24 months of age. Two dogs (5.7%) had purposeful airway obstruction by the owner/care giver (category 5). One dog was restrained round the neck by a dog trainer during a puppy class and the other dog bit its owner whilst playing and in response the owner clamped the muzzle shut while pinning the dog on its back for several seconds.

On physical examination 15 (42.9%) dogs were reported as alert, 10 (25.7%) were obtunded and one arrived anesthetized to the hospital (2.9%). Mucous membranes were pale in 5 (14.3%), pink in 20 (57.1%), cyanotic in 4 (11.4%) and white in 2 (5.7%). The median heart rate was 142 beats per minute (range 56-180), the median respiratory rate 80 breaths per minute (range 20-180) and the median rectal temperature 38.1ºC (range 34.9-38.8). Eight dogs were hypothermic on presentation (rectal temperature < 37.9ºC) and there were no hyperthermic dogs.

Blood pressure (BP) was measured on presentation using the Doppler method in 7 dogs and oscillometric method in 4 dogs. The median Doppler BP was 110 mmHg (range 80-120) and the median mean arterial pressure with the oscillometric method was 90 mmHg (range 72-130). Only 2 dogs were classified as hypotensive on presentation (Doppler BP < 100).

Pulse oximetry was performed in 15 dogs (42%). Median SpO_2 was 90% (range 56-99). FiO_2 could only be obtained from the medical records from 5 dogs who had pulse oximetry performed; 3 of them were breathing room air and 2 of them were on mechanical ventilation with various FiO_2. One dog had a FiO_2 of 0.6 with a SpO_2 of 99% and another dog had a FiO_2 of 1 with a SpO_2 of 91%. Arterial blood gas analysis was performed on 9 patients, 6 of them breathing room air and 3 on supplemental oxygen. Patients breathing room air had a low mean PaO_2 [7.5 ± 2.5 KPa, RI 10.6-14 (56 ± 19 mmHg, RI 80-105)] with an increased mean (A-a) gradient [6.9 ± 2.4 KPa, RI<2 (52 ± 18 mmHg, RI <15)]. Patients on supplemental oxygen had a low median PaO_2/FiO_2 ratio {10 (10-61) kPa, RI 50.5-66.5 [75 (75-458)]. Two of these patients had a PaO_2 of 75mmHg with a FiO_2 of 1 and the remaining patient had a PaO_2 of 275mmHg with an FiO_2 of 0.6. The rest of blood test results are displayed in Table 1.

Bronchoalveolar lavage (BAL) was performed in 7 (20%) dogs. In 5 dogs BAL was performed soon after commencing mechanical ventilation and one dog after a thoracic CT scan. Cytology in these dogs was consistent with neutrophilic inflammation and microbiological culture was negative. In the remaining dog it was performed 48 hours after commencing mechanical ventilation and cultured *Escherichia coli*, *Enterococcus* spp. and a multi-drug resistant *Pseudomonas aeruginosa* due to presumed ventilator-associated pneumonia.

Echocardiography was performed in 3 (8.6%) dogs. One dog had reduced systolic function which had resolved 8 days later.

Thoracic radiographs were obtained in 32 (91.4%) dogs. One dog had a CT scan only, 3 had CT scan and radiographs and the remaining 2 did not have thoracic imaging due to severe respiratory compromise. Thirty-one radiographic

studies were retrieved for review. The pattern of infiltration was defined as alveolar in 26 (74.3%) cases, interstitial to alveolar in 4 (11.4%) cases and purely interstitial in 1 (2.9%) case. The pattern of infiltration was predominantly caudodorsal in 23 (65.7%) cases. All lung lobes were affected in 13 cases (37.1%). The 3 thoracic CT scans documented alveolar patterns in various lung lobes compatible with pulmonary edema.

Oxygen therapy was administered to 33 (94.3%) dogs. Two (5.7%) dogs received nasal oxygen through cannulae and 24 (68.6%) dogs via oxygen cages. Seven (20%) dogs had endotracheal intubation and mechanical ventilation. Two (5.7%) dogs had tachypnea and radiographic features of NPPE but improved soon after presentation and did not require oxygen therapy. Antibiotics were administered to 12 (34.2%) dogs. Eight dogs received amoxicillin-clavulanic acid[b] and 4 dogs received cefuroxime[c]. Eighteen (51.4%) dogs received furosemide[d] at any time point. In 10 (28.5%) dogs this was prior to referral and 8 (22.9%) dogs at the referral hospital. Median dose of furosemide was 2 mg/kg (range 0.5-6.5).

Nine (25.7%) dogs received corticosteroid at any time point. Dexamethasone[e] was administered to 5 (14.3%) dogs prior to referral and to 4 (11.4%) dogs at the referral hospitals. Median dose of dexamethasone was 0.2 mg/kg (range 0.13-0.37).

Twenty-eight (80%) dogs survived to discharge. Of the 7 (20%) dogs that did not survive, 4 were euthanized and 3 died naturally. It was not possible to tell from the medical records if euthanasia was financially driven or if it was due to a perceived poor prognosis. Dogs that were mechanically ventilated had a survival rate of 28.6%. Necropsy was performed in 1 non-survivor and identified

231 congested and collapsed lungs consistent with pulmonary edema. The median
232 length of hospitalization was 2 days (range 0-14).

233 Univariate statistical analysis was performed to identify factors that were
234 associated with survival. These results are displayed in tables 2 and 3. PaO_2, A-a
235 gradient, PaO_2/FiO_2 ratio, bicarbonate, BE, total and ionized calcium, albumin,
236 ALT, ALP, total bilirubin, urea and the number of brachycephalic dogs were not
237 included in the analysis as these parameters were only measured in one non-
238 survivor each. Requirement for mechanical ventilation ($p<0.001$) was the only
239 parameter associated with mortality.

240 Discussion

241 To the authors' knowledge, this is the largest study of dogs with NPPE.
242 The most common incident causing NPPE was choking on foodstuffs or toys
243 (40% of cases). Choking and near hanging had not been previously described as
244 causes of non-cardiogenic PE in veterinary medicine but are well known causes
245 in human medicine, both in infants and adults.[10-12] In order to avoid choking or
246 neck leash injuries in puppies veterinarians may choose to advise their clients to
247 avoid large chews that could block the airway or recommend the use of a body
248 harness instead of a neck collar or neck leash. Although there are a variety of
249 causes producing NPPE we did not find significant differences as regards
250 mortality amongst the different groups.

251 In our study 85% of the cases were less than 1 year old. It is reported that
252 young, healthy people can achieve up to -140 cmH_2O of negative intrathoracic
253 pressure.[13] It is possible that juvenile dogs, as seen in young humans, can
254 produce larger negative intra-thoracic pressures than adults. Other age-related
255 factors such as the tendency to chew and eat voraciously, tug on the leash and

undergo training, may also be a factor. The 3 dogs with an anatomical obstruction to airflow were older than 24 months of age. This is probably because the majority of anatomical obstructions to airflow happen in older dogs, as it is the case of laryngeal paralysis, or develop slowly over the course of months or years, as is the case in BOAS.

The majority of thoracic radiographs (65.7% of cases) showed an alveolar or interstitial pattern in the caudodorsal area as previously described in the literature (Figure 1).[8,9,14] A recent radiographic study found that NPPE produces caudodorsal lung patterns more frequently than the other causes of non-cardiogenic PE.[14] It is unknown why NPPE has this predilection for the caudodorsal area, but it could be that because dogs have increased pulmonary blood volume and flow in the caudal lung lobes[15] they are more likely to have transvascular fluid filtration associated with NPPE in this region. This increase of pulmonary blood flow (PBF) in the dorsocaudal area against gravity is also seen in other standing quadrupeds like horses.[16] Studies of canine PBF under anesthesia and mechanical ventilation show a gravitational effect on PBF[17,18] as is the case of conscious human subjects[19] but this may not represent what happens in non-anesthetized dogs. Another factor that may play a role in the development of caudodorsal PE is the normal presence of pleural pressure gradients. Dogs have more negative pleural pressures in the dorsal regions of the lung in comparison with the ventral regions.[20] In situations of airway obstruction in dogs, pleural pressures may be more negative in the dorsal area hence favouring the development of a caudorsal pattern.

Thoracic CT scan was performed in 3 dogs that had thoracic radiography performed. We could not tell from the medical records the indication for this

study but one dog had laryngeal paralysis and one dog had laryngeal collapse so a CT might have been performed to rule out concurrent underlying diseases.

In human medicine it is common to measure protein concentration of the edema fluid to then calculate the edema fluid-to-plasma protein ratio.[21] A ratio of <0.65 suggests a low-protein edema as seen in cases of cardiogenic PE but also in the majority of humans with NPPE.[5] Higher ratios are consistent with increased-permeability PE and mixed-cause PE.[21] This is uncommonly performed in veterinary medicine and the majority of clinicians perform BAL infusing sterile saline solution into the airway, which would affect the fluid-to-plasma protein ration. The bronchoalveolar fluid obtained in our cases revealed neutrophilic inflammation. This inflammatory response may be due to rupture of pulmonary capillaries resulting from large negative pulmonary pressures.

The recommended treatment for NPPE in human medicine is oxygen supplementation and, if necessary, endotracheal intubation and mechanical ventilation with protective ventilation strategies.[5] Antimicrobials are not indicated, unless there is evidence of additional diseases such as ventilator-associated pneumonia. Furosemide can be considered given that the edema is a low-protein fluid in most cases but there is not strong evidence suggesting its efficacy.[5] Edema fluid-to-plasma protein ratios have not been measured in veterinary medicine so it is not known whether dogs might benefit from furosemide. Since most events that cause NPPE are transient and there is no persistence of increased pulmonary capillary pressures, furosemide is unlikely to be helpful. The use of furosemide could potentially be deleterious as it may lead to hypovolemia and decreased tissue perfusion. Judicious use of fluid therapy with isotonic crystalloids should be considered to avoid dehydration.

306 Glucocorticoids are not indicated.[5] They may predispose the patient to
307 gastrointestinal ulceration or increase predisposition to infection among other
308 adverse effects. The administration of corticosteroids or furosemide were not
309 associated with survival in our study, but because of the retrospective
310 observational nature of the study and the small number of dogs that received
311 these drugs, their role in the resolution of the disease cannot be completely
312 excluded.

313 Statistical analysis found that mechanical ventilation requirement was the
314 only parameter associated with mortality. Our study demonstrated an overall
315 survival rate of 80% which is between previous reported values of dogs with
316 NPPE (50% and 100%).[8,9] The survival rate of dogs requiring mechanical
317 ventilation due to NPPE of our study (28.6%) is lower than the reported survival
318 rates of mechanically ventilated dogs with cardiogenic PE (77%)[22] but is higher
319 than the overall canine ARDS population requiring mechanical ventilation (8.3%
320 and 16%).[23,24] The higher survival rate of ventilated patients with cardiogenic PE
321 compared to NPPE ventilated patients may be related to the effectiveness of
322 diuretic therapy in reducing pulmonary hydrostatic pressure and rapid
323 correction of the underlying mechanism of edema formation in these patients. As
324 patients severely affected by NPPE likely have microvascular permeability
325 alterations and capillary rupture, the edema fluid may be richer in protein and
326 less likely to be eliminated by diuretics.

327

328 Our study has several limitations. Due to its retrospective nature there
329 were some missing data that may have affected our results. Another limitation is
330 the small number of cases. Despite being a multi-institutional study NPPE

remains an uncommon cause of PE. Also, because it is an observational study, we cannot draw valid conclusions regarding influence of treatment strategies such as type of oxygen supplementation and use of diuretics. Additionally, we could not ascertain from the medical records whether euthanasia was performed due to a perceived poor prognosis or financial motives and this could have impacted outcome. Another limitation is that by applying the Bonferroni correction a type II statistical error could be committed reducing statistical power.

In conclusion, most cases of NPPE occur in juvenile dogs. NPPE can happen due to choking on foodstuffs or toys, leash tugs, near hanging, purposeful obstruction by humans or anatomical obstructions. Choking and near hanging have not been previously described in the veterinary literature as inciting causes of NPPE. The overall prognosis is good with a short hospitalization period, unless severe respiratory distress that requires mechanical ventilation ensues.

Acknowledgments

Footnotes

a. IBM SPSS Statistics version 23. IBM United Kingdom Limited, PO Box 41, North Harbour , Portsmouth, Hampshire, PO6 3AU.
b. Augmentin® 500mg/100mg powder for solution for injection. GlaxoSmithKline UK, Stockley Park West, Uxbridge Middlesex UB11 1BT. United Kingdom.
c. Zinacef® 1.5g powder for solution for injection. GlaxoSmithKline UK, Stockley Park West, Uxbridge Middlesex UB11 1BT. United Kingdom.
d. Dimazon® 50 mg/ml solution for injection. NOAH, MSD Animal Health. Walton Manor, Walton, Milton Keynes MK7 7AJ, United Kingdom
e. Dexafort® 4 mg/ml suspension for injection. NOAH, MSD Animal Health. Walton Manor, Walton, Milton Keynes MK7 7AJ, United Kingdom

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423 outcomes of acute respiratory distress syndrome in dogs and cats: 54
424 cases. J Vet Emerg Crit Care 2019;29(2):173-179.

425 Figure 1: Dorsoventral and right lateral thoracic radiographs of a 4 month-old
426 dog with negative-pressure pulmonary edema.

427 There is a diffuse alveolar pattern with indistinct margins more marked in the
428 left caudal, left cranial and right caudal lung lobes on the dorsoventral view and
429 in the dorsocaudal region in the lateral view.

430

431 Table 1: Summary of blood tests results obtained on admission from dogs with
432 NPPE. TP: total protein.
433

Parameter	Number of cases where test was performed	SI units Mean ± SD Median (range)	Reference interval	Conventional units Mean ± SD Median (range)	Reference interval
PCV	25	0.39 ± 0.06	0.37-0.55	39.7 ± 5.8 %	37-55

TP	23	60 (44-85) g/L	60-75	6 (4.4-8.5) g/dL	6-7.5
pH	18	7.381 (7.083-7.453)	7.35-7.46	7.381 (7.083-7.453)	7.35-7.46
PCO_2	18	4.9 (3.7-12) KPa	4.3-5.7	37 (27.6-89.5) mmHg	32-43
HCO_3^-	11	21.8 ± 1.9 mmol/L	18-26	21.8 ± 1.9 mEq/L	18-26
BE	10	-3.0 ± 1.8 mmol/L	-5-1	-3.0 ± 1.8 mEq/L	-5-1
Lactate	14	1.6 ± 1.0 mmol/L	0.5-2	14.4 ± 9 mg/dL	4.5-18
Na	19	144.5 ± 4.8 mmol/L	140-150	144.5 ± 4.8 mEq/L	140-150
K	19	4.1 ± 0.7 mmol/L	3.9-4.9	4.1 ± 0.7 mEq/L	3.9-4.9
Cl	12	112.7 ± 4.5 mmol/L	109-120	112.7 ± 4.5 mEq/L	109-120
Ionised calcium	15	1.32 ± 0.15 mmol/L	1.25-1.5	5.28 ± 0.6 mg/dL	5-6

Total calcium	11	2.6 ± 0.3 mmol/L	2.1 – 2.6	10.4 ± 1.2 mg/dL	8.4 – 10.4
Blood glucose	19	6.7 (5.6-11) mmol/L	3.6-6.2	120.7 (100.9-198.2) mg/dL	64.9-111.7
Urea	14	6.7 ± 2.3 mmol/L	1.8-10.7	18.8 ± 6.4 mg/dL	5-30
Creatinine	17	58.9 ± 18.5 umol/L	61.9-159.1	0.67 ± 0.21 mg/dL	0.7 – 1.8
Albumin	11	30.9 ± 2.3 g/L	25-37	3.1 ± 0.2 g/dL	2.5-3.7
Total bilirubin	11	0.35 (0-4.0) umol/L	0-15.9	0.02 (0-0.23) mg/dL	0-0.93
ALT	11	27 (18-1192) U/L	16-91	27 (18-1192) U/L	16-91
ALP	11	134 ± 44 U/L	20-155	134 ± 44 U/L	20-155
WBC	14	17.6 ± 5.4 10^9/L	5.3-19.8	17.6 ± 5.4 10^3/uL	5.3-19.8

Platelet count	14	360 ± 127 10^9/L	177-398	360 ± 127 10^3/uL	177-398

434

435 Table 2: Comparison between survivors and non-survivors of patients´

436 characteristics, type of injury and physical examination findings in dogs with

437 NPPE.

438

Parameter		Survivors	Non-survivors	p value
Sex	Male	16	5	0.676
	Female	12	2	
Sexually intact		26	6	0.499
Age (months)		4 (2-90)	4 (2.5-60)	0.732
Weight (kg)		6.4(1.7-37.2)	9(2.7-19.2)	0.466
Type of injury	Category 1	9	1	0.376
	Category 2	6	0	
	Category 3	10	4	
	Category 4	2	1	
	Category 5	1	1	
Mentation	Alert	15	0	0.022
	Obtunded	5	5	

	Anesthetized	1	0	
Heart rate		140(80-180)	160(56-180)	0.247
Respiratory rate		80(32-180)	90(20-200)	0.960
Mucous membranes color	Pale	3	2	0.010
	Pink	20	0	
	Cyanotic	2	2	
	White	2	0	
Temperature (ºC)		38.2(35.9-38.8)	37.7 (34.9-39.7)	0.358

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440

441 Table 3: Comparison between survivors and non-survivors of diagnostic test
442 results and treatments in dogs with NPPE. The number of times each test was
443 performed can be found on table 1. SpO_2: blood oxygen saturation measured
444 with pulse oximetry, TP: total protein.
445

Parameter	Survivors	Non-survivors	p value
PCO_2	4.9 (3.7-6.7) KPa 37.2(27.6-50.4) mmHg	7.7 (4.6-11.9) KPa 58(34.4-89.5) mmHg	0.203
pH	7.379 (7.240--7.490)	7.261 (7.083-7.440)	0.641
SpO_2	91(81-99) %	87(56-91) %	0.365
Lactate	2.2 ± 1.5 mmol/L 19.8 ± 13.5 mg/dL	1.4 ± 0.1 mmol/L 12.6 ± 0.9 mg/dL	0.480
Na	145±5 mmol/L 145±5 mEq/L	143±1 mmol/L 143±1 mEq/L	0.660

K	4.1±0.5 mmol/L 4.1±0.5 mEq/L	3.5±0.1 mmol/L 3.5±0.1 mEq/L	0.153
Cl	111±5 mmol/L 111±5 mEq/L	110±6 mmol/L 110±6 mEq/L	0.775
Blood glucose	6.7 (5.6-11) mmol/L 120.7(100.9-198.2) (mg/dL)	7.1 (6.6-7.6) mmol/L 127.9(118.9-136.9) (mg/dL)	1
Creatinine	70.7 ± 17.7 mmol/L 0.8 ± 0.2 mg/dL	44.2 ± 35.4 mmol/L 0.5 ± 0.4 (mg/dL)	0.311
PCV	0.4 ± 0.05 40 ± 5 %	0.39 ± 0.09 39 ± 9 %	0.832
TP	60 (44-72) g/L 6 (4.4-7.2) (g/dL)	56 (52-85) g/L 5.6 (5.2-8.5) (g/dL)	0.667

WBC		16.8 ± 5.6 10^3/uL	15.9 ± 2.8 10^3/uL	0.828
Platelet count		381 ± 121 (10^3/uL)	230 ± 87 (10^3/uL)	0.119
All lung lobes affected		9	4	0.174
Pattern of infiltrate	Alveolar	22	4	0.406
	Interstitial	1	0	
	Interstitial to alveolar	3	1	
Oxygen administered		26	7	1.000
Treatment with furosemide		15	3	0.466
Treatment with glucocorticoids		6	3	0.242
Mechanical ventilation		2	5	<0.001

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