



**HAL**  
open science

## Zero-inflated models for identifying disease risk factors when case detection is imperfect: Application to highly pathogenic avian influenza H5N1 in Thailand

Timothée Vergne, Mathilde C. Paul, Wanida Chaengprachak, Benoit Durand, Marius Gilbert, Barbara Dufour, François Roger, Suwicha Kasemsuwan, Vladimir Grosbois

### ► To cite this version:

Timothée Vergne, Mathilde C. Paul, Wanida Chaengprachak, Benoit Durand, Marius Gilbert, et al.. Zero-inflated models for identifying disease risk factors when case detection is imperfect: Application to highly pathogenic avian influenza H5N1 in Thailand. Preventive Veterinary Medicine, 2014, 114 (1), pp.28-36. 10.1016/j.prevetmed.2014.01.011 . hal-02630698

**HAL Id: hal-02630698**

**<https://hal.inrae.fr/hal-02630698>**

Submitted on 3 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

1 Negative-pressure pulmonary edema in 35 dogs

2

3 Abstract

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

8 Design: Retrospective study.

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

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

11 Interventions: None

12 Measurements and Main Results: Data collected included patient characteristics,  
13 clinical history, clinicopathological abnormalities, radiographic features,  
14 treatments and outcome. Median age was 4 months (range 2-90) and median  
15 weight was 7.1 kg (range 1.7-37.2). There were many causes of NPPE including  
16 leash tugs, near hanging, accidental choking, anatomical obstruction to airflow  
17 and purposeful airway obstruction by people. The most common cause of NPPE  
18 was accidental choking (40% of cases). Dogs with an anatomical obstruction  
19 were older than 24 months. Hypoxemia with an increased alveolar-arterial  
20 gradient was common on presentation. The majority of thoracic radiographs  
21 (65.7%) showed an alveolar or interstitial pattern in the caudodorsal area as  
22 previously described in the literature. Oxygen therapy was administered to 33  
23 (94.3%) dogs. Furosemide was administered to 18 (51.4%) dogs. Median length  
24 of hospitalization was 2 days (range 0-14). Twenty-eight (80%) dogs survived to  
25 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

34 Abbreviation List

35 ARDS: acute respiratory distress syndrome

36 A-a: alveolar-arterial (gradient)

37 BAL: bronchoalveolar lavage

38 BP: blood pressure

39 BOAS: brachycephalic obstructive airway syndrome

40 CT: computed tomography

41 NPPE: negative-pressure pulmonary edema

42 PBF: pulmonary blood flow

43 PE: pulmonary edema

44 SpO<sub>2</sub>: blood oxygen saturation measured with pulse oximetry

45 TP: total protein

46

47 Introduction

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

59 produced by concurrent changes in pulmonary vascular pressures and  
60 permeability of the vascular beds. Mixed-cause PE include neurogenic PE  
61 (produced by seizures, traumatic brain injury or electrocution), re-expansion PE  
62 and negative-pressure PE (NPPE).<sup>2</sup>

63 NPPE, also called “post-obstructive PE”, occurs due to vigorous inspiratory  
64 efforts against an obstructed airway. In human medicine this is known as the  
65 Müller maneuver and is used diagnostically in certain settings.<sup>3</sup> These efforts  
66 produce large negative pleural pressures that increase transvascular fluid  
67 filtration and precipitate interstitial and alveolar edema. The pathophysiology of  
68 NPPE could be explained by a rise in pulmonary capillary pressure associated with  
69 the transient drop in intrathoracic pressure and subsequent increase in venous  
70 return to the right side of the heart. In addition, the negative pleural pressure  
71 transmits to the pericardium increasing cardiac afterload. The increase in  
72 afterload elevates left ventricular, left atrial and hence pulmonary capillary  
73 pressures. This upsurge in pressure promotes fluid movement from the  
74 pulmonary capillaries towards the pulmonary interstitial space and alveoli.  
75 Moreover, nervousness associated with airway obstruction and hypoxemia may  
76 produce sympathetic activation contributing towards further increases in cardiac  
77 afterload.<sup>4-6</sup> In the majority of human patients these mechanisms produce a low-  
78 protein edema fluid, demonstrated by a low edema fluid-to-plasma protein ratio  
79 (<0.65), although a small subset of patients present with values above this cutoff  
80 suggesting an additional increased permeability mechanism. This may be due to  
81 pressure-induced rupture of pulmonary capillaries as some patients present with  
82 blood-tinged pulmonary secretions.<sup>5,7</sup>

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

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

99

## 100 Materials and Methods

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

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

109 Data collected included patient demographics, clinical history, admission  
110 physical examination findings, blood test results [arterial and venous blood gases,  
111 PCV and refractometric total protein (TP), WBC, platelet count, serum  
112 biochemistry], blood pressure (systolic Doppler blood pressure or mean  
113 oscillometric blood pressure), blood oxygen saturation (SpO<sub>2</sub>) with pulse  
114 oximetry, thoracic radiographs and computed tomography (CT) scans,  
115 echocardiograms, cytological and microbiological results of bronchoalveolar  
116 lavage, treatments performed including medications and type of oxygen  
117 administration, length of hospitalization and outcome. A board-certified  
118 radiologist (XX) reviewed all available radiographs. In patients where arterial  
119 blood gas analysis was performed on room air, these results are reported as PaO<sub>2</sub>  
120 and alveolar-arterial (A-a) gradient. In patients where arterial blood gas analysis  
121 was performed on supplemental oxygen, these results are reported as PaO<sub>2</sub>/FiO<sub>2</sub>  
122 ratio. A-a gradients were calculated in patients breathing room air at sea level  
123 using the following formula: (A-a) gradient= P<sub>A</sub>O<sub>2</sub> - P<sub>a</sub>O<sub>2</sub> = [150 - P<sub>a</sub>CO<sub>2</sub>/0.8] - P<sub>a</sub>O<sub>2</sub>

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

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

132

133 Statistical methods

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

144 Results

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

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



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

168 On physical examination 15 (42.9%) dogs were reported as alert, 10  
169 (25.7%) were obtunded and one arrived anesthetized to the hospital (2.9%).  
170 Mucous membranes were pale in 5 (14.3%), pink in 20 (57.1%), cyanotic in 4  
171 (11.4%) and white in 2 (5.7%). The median heart rate was 142 beats per minute  
172 (range 56-180), the median respiratory rate 80 breaths per minute (range 20-  
173 180) and the median rectal temperature 38.1°C (range 34.9-38.8). Eight dogs  
174 were hypothermic on presentation (rectal temperature < 37.9°C) and there were  
175 no hyperthermic dogs.

176 Blood pressure (BP) was measured on presentation using the Doppler  
177 method in 7 dogs and oscillometric method in 4 dogs. The median Doppler BP was  
178 110 mmHg (range 80-120) and the median mean arterial pressure with the  
179 oscillometric method was 90 mmHg (range 72-130). Only 2 dogs were classified  
180 as hypotensive on presentation (Doppler BP < 100).

181 Pulse oximetry was performed in 15 dogs (42%). Median SpO<sub>2</sub> was 90%  
182 (range 56-99). FiO<sub>2</sub> could only be obtained from the medical records from 5 dogs  
183 who had pulse oximetry performed; 3 of them were breathing room air and 2 of  
184 them were on mechanical ventilation with various FiO<sub>2</sub>. One dog had a FiO<sub>2</sub> of 0.6  
185 with a SpO<sub>2</sub> of 99% and another dog had a FiO<sub>2</sub> of 1 with a SpO<sub>2</sub> of 91%. Arterial  
186 blood gas analysis was performed on 9 patients, 6 of them breathing room air and  
187 3 on supplemental oxygen. Patients breathing room air had a low mean PaO<sub>2</sub> [7.5  
188 ± 2.5 KPa, RI 10.6-14 (56 ± 19 mmHg, RI 80-105)] with an increased mean (A-a)  
189 gradient [6.9 ± 2.4 KPa, RI <2 (52 ± 18 mmHg, RI <15)]. Patients on supplemental  
190 oxygen had a low median PaO<sub>2</sub>/FiO<sub>2</sub> ratio {10 (10-61) kPa, RI 50.5-66.5 [75 (75-  
191 458)]}. Two of these patients had a PaO<sub>2</sub> of 75mmHg with a FiO<sub>2</sub> of 1 and the  
192 remaining patient had a PaO<sub>2</sub> of 275mmHg with an FiO<sub>2</sub> of 0.6. The rest of blood  
193 test results are displayed in Table 1.

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

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

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

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

212 Oxygen therapy was administered to 33 (94.3%) dogs. Two (5.7%) dogs  
213 received nasal oxygen through cannulae and 24 (68.6%) dogs via oxygen cages.  
214 Seven (20%) dogs had endotracheal intubation and mechanical ventilation. Two  
215 (5.7%) dogs had tachypnea and radiographic features of NPPE but improved  
216 soon after presentation and did not require oxygen therapy. Antibiotics were  
217 administered to 12 (34.2%) dogs. Eight dogs received amoxicillin-clavulanic  
218 acid<sup>b</sup> and 4 dogs received cefuroxime<sup>c</sup>. Eighteen (51.4%) dogs received  
219 furosemide<sup>d</sup> at any time point. In 10 (28.5%) dogs this was prior to referral and  
220 8 (22.9%) dogs at the referral hospital. Median dose of furosemide was 2 mg/kg  
221 (range 0.5-6.5).

222 Nine (25.7%) dogs received corticosteroid at any time point.  
223 Dexamethasone<sup>e</sup> was administered to 5 (14.3%) dogs prior to referral and to 4  
224 (11.4%) dogs at the referral hospitals. Median dose of dexamethasone was 0.2  
225 mg/kg (range 0.13-0.37).

226 Twenty-eight (80%) dogs survived to discharge. Of the 7 (20%) dogs that  
227 did not survive, 4 were euthanized and 3 died naturally. It was not possible to  
228 tell from the medical records if euthanasia was financially driven or if it was due  
229 to a perceived poor prognosis. Dogs that were mechanically ventilated had a  
230 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<sub>2</sub>, A-a  
235 gradient, PaO<sub>2</sub>/FiO<sub>2</sub> 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.<sup>10-12</sup> 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<sub>2</sub>O of negative intrathoracic  
253 pressure.<sup>13</sup> 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

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

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

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

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

283 In human medicine it is common to measure protein concentration of the  
284 edema fluid to then calculate the edema fluid-to-plasma protein ratio.<sup>21</sup> A ratio of  
285  $<0.65$  suggests a low-protein edema as seen in cases of cardiogenic PE but also in  
286 the majority of humans with NPPE.<sup>5</sup> Higher ratios are consistent with increased-  
287 permeability PE and mixed-cause PE.<sup>21</sup> This is uncommonly performed in  
288 veterinary medicine and the majority of clinicians perform BAL infusing sterile  
289 saline solution into the airway, which would affect the fluid-to-plasma protein  
290 ration. The bronchoalveolar fluid obtained in our cases revealed neutrophilic  
291 inflammation. This inflammatory response may be due to rupture of pulmonary  
292 capillaries resulting from large negative pulmonary pressures.

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

306 Glucocorticoids are not indicated.<sup>5</sup> 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%).<sup>8,9</sup> 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%)<sup>22</sup> but is higher  
319 than the overall canine ARDS population requiring mechanical ventilation (8.3%  
320 and 16%).<sup>23,24</sup> 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

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

338

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

345



346 Acknowledgments

347

348 Footnotes

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

360 References

- 361 1. Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema. N Engl J  
362 Med 2005;353(26):2788-2796.
- 363 2. Adamantos S, Hughes D. Pulmonary edema. In: Silverstein D, Hopper K,  
364 editors. Small Animal Critical Care Medicine. 2nd ed. Philadelphia: WB  
365 Saunders Co; 2015, pp. 116-120.
- 366 3. Faber CE, Grymer L. Available techniques for objective assessment of  
367 upper airway narrowing in snoring and sleep apnea. Sleep Breath  
368 2003;7(2):77-86.

- 369 4. Fremont RD, Kallet RH, Matthay MA, Ware LB. Postobstructive Pulmonary  
370 Edema: A Case for Hydrostatic Mechanisms. *Chest* 2007;131(6):1742-  
371 1746.
- 372 5. Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-pressure  
373 pulmonary edema. *Chest* 2016;150(4):927-933.
- 374 6. Lemyze M, Mallat J. Understanding negative pressure pulmonary edema.  
375 *Intensive Care Med* 2014;40(8):1140-1143.
- 376 7. West JB, Tsukimoto K, Mathieu-Costello, Prediletto R. Stress failure in  
377 pulmonary capillaries. *J Appl Physiol* 1991;70(4):1731-1742.
- 378 8. Kerr LY. Pulmonary edema secondary to upper airway obstruction in the  
379 dog: a review of nine cases. *J Am Anim Hosp Assoc* 1982;25(2):207-212.
- 380 9. Drobotz KJ, Saunders HM, Pugh CR, Hendricks JC. Noncardiogenic  
381 pulmonary edema in dogs and cats: 26 cases (1987-1993). *J Am Vet Med*  
382 *Assoc* 1995;206(11):1732-6.
- 383 10. Toukan Y, Gur M, Bentur L. Negative pressure pulmonary edema  
384 following choking on a cookie. *Pediatr Pulmonol* 2016;51(7):E25-27.
- 385 11. Miyazaki S, Matsui T, Inoue M, Ikeda T. Negative-pressure pulmonary  
386 oedema following choking on a rice ball. *BMJ Case Rep* 2018  
387 doi:10.1136/bcr-2017- 222520.
- 388 12. Berdai AM, Labib S, Harandou M. Postobstructive pulmonary edema  
389 following accidental near-hanging. *Am J Case Rep* 2013;14:350-353.
- 390 13. Cook CD, Mead J. Maximum and minimum airway pressures at various  
391 lung volumes in normal children and adults. *Fed Proc* 1960;19:377.
- 392 14. Bouyssou S, Specchi S, Desquilbet I, Pascaline P. Radiographic appearance  
393 of presumed noncardiogenic pulmonary edema and correlation with the

- 394 underlying cause in dogs and cats. *Vet radiol ultrasound* 2017;58(3):259-  
395 265.
- 396 15. Amis TC, Jones HA, Hughes JM. A conscious dog model for study of  
397 regional lung function. *J Appl Physiol Respir Environ Exerc Physiol*  
398 1982;53(4):1050-1054.
- 399 16. Robinson NE. Pulmonary blood flow. In: Cunningham JG, Klein BG,  
400 editors. *Textbook of Veterinary Physiology*. 4th ed. Saunders  
401 Elsevier; 2007, pp 578-586.
- 402 17. Chon D, Beck KC, Larsen RL et al. Regional pulmonary blood flow in dogs  
403 by 4D-X-ray CT. *J Appl Physiol* 2006;101(5):1451-1465.
- 404 18. Hoi BW, Choe KO, Kim HJ et al. Characterization of the pulmonary  
405 circulation according to hemodynamic changes by computed tomography.  
406 *Yonsei Med J* 2003;44(6):968-978.
- 407 19. West JB. Blood flow and metabolism. In: *Respiratory physiology: The*  
408 *essentials*. 9th ed. Lippincott Williams & Wilkins; 2012, pp 36-56.
- 409 20. Casha AR, Caruana-Gauci R, Manche A et al. Pleural pressure theory  
410 revisited: a role for capillary equilibrium. *J Thorac Dis* 2017; 9(4): 979-  
411 989.
- 412 21. Ware LB, Fremont RD, Bastarache JA et al. Determining the aetiology of  
413 pulmonary oedema by the oedema fluid-to-plasma protein ratio. *Eur*  
414 *Respir J* 2010;35(2):331-337.
- 415 22. Edwards TH, Coleman AE, Brainard BM et al. Outcome of positive-  
416 pressure ventilation in dogs and cats with congestive heart failure: 16  
417 cases (1992-2012). *J Vet Emerg Crit Care* 2014;24(5):586-593.

418 23. Balakrishnan A, Drobatz KJ, Silverstein DC. Retrospective evaluation of  
 419 the prevalence, risk factors, management, outcome, and necropsy findings  
 420 of acute lung injury and acute respiratory distress syndrome in dogs and  
 421 cats: 29 cases (2011-2013). J Vet Emerg Crit Care 2017;27(6):662-673.

422 24. Boiron L, Hopper K, Borchers A. Risk factors, characteristics, and  
 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 $\pm$ SD Median (range)	Reference interval	Conventional units Mean $\pm$ SD Median (range)	Reference interval
PCV	25	0.39 $\pm$ 0.06	0.37-0.55	39.7 $\pm$ 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 <sub>2</sub>	18	4.9 (3.7-12) KPa	4.3-5.7	37 (27.6-89.5) mmHg	32-43
HCO <sub>3</sub> <sup>-</sup>	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 <sup>9</sup> /L	5.3-19.8	17.6 ± 5.4 10 <sup>3</sup> /uL	5.3-19.8

Platelet count	14	360 ± 127 10 <sup>9</sup> /L	177-398	360 ± 127 10 <sup>3</sup> /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 (°C)		38.2(35.9- 38.8)	37.7 (34.9- 39.7)	0.358

439

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<sub>2</sub>: blood oxygen saturation measured  
 444 with pulse oximetry, TP: total protein.  
 445

Parameter	Survivors	Non-survivors	p value
PCO <sub>2</sub>	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 <sub>2</sub>	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 <sup>3</sup> /uL	15.9 ± 2.8 10 <sup>3</sup> /uL	0.828
Platelet count		381 ± 121 (10 <sup>3</sup> /uL)	230 ± 87 (10 <sup>3</sup> /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