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Effectiveness of chest physiotherapy using passive slow expiratory techniques in dogs with airway fluid accumulation: A randomized controlled trial

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[Correction added on 24-03-2021 after the first online publication: Removed the word "pilot" from title and article. The study as described does not meet the CONSORT guidelines for a "pilot" study as it is a hypothesis-driven study (randomized controlled trial) that draws conclusions.]

Abstract

Background: Prolonged slow expiration (PSE) and assisted cough (AC) are airway clearance techniques feasible and well tolerated in dogs.

Objectives: To evaluate the effectiveness of PSE and AC as chest physiotherapy (CP) techniques in dogs with airway fluid accumulation.

Animals: Thirty-one client-owned dogs hospitalized in an intensive care unit from October 2014 to May 2018.

Methods: Prospective randomized controlled trial. Dogs presented with or developing acute dyspnea during hospitalization associated with airway fluid accumulation were assigned to CP group (medical treatment and CP, 15 dogs) or control group (medical treatment alone, 16 dogs). The arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (P/F ratio; $PaO_2/FiO_2 \times 100$) was calculated daily for the 1st 48 hours of hospitalization and using the last arterial blood gas performed before discharge or death. The ratio of days of hospitalization with oxygen/total number of hospitalization days (ratio of oxygen-free-days [O_2Free]) was calculated.

Results: During the 1st 48 hours, the P/F ratio increased significantly in the CP group compared to the control group (+ 35.1 mm Hg/day; 95% confidence interval [CI] = 0.4-57.5; *P* = .03). The (median; 1st quartile to 3rd quartile) difference between the P/F ratio at discharge and inclusion was significantly higher in the CP group (178 mm Hg; 123-241) than in the control group (54 mm Hg; −19 - 109; *P* = .001). Mean O_2Free increased by 46.4% in the CP group compared with control group (95% CI = 16-59; *P* = .001). Mortality was 13% (2/15) in the CP group and 44% (7/16) in the control group (*P* = .07).

Conclusions and Clinical Importance: Prolonged slow expiration and AC improved P/F ratio within 48 hours and decreased need for oxygenation in dyspneic dogs with acute airway fluid accumulation.

KEYWORDS

canine, dyspnea, pneumonia, respiratory physiotherapy

1 | INTRODUCTION

Chest physiotherapy (CP) can be defined as the external application of a combination of forces to increase expiratory flow with the goal to optimize mucus transport.[1] In human medicine, CP is used in the treatment of conditions associated with the accumulation of secretions in the respiratory tract, such as pneumonia, acute bronchiolitis, community-acquired pneumonia, or cystic fibrosis.[1-4] These techniques frequently are used in intensive care units (ICU).[5,6] However, because of the heterogeneity of CP techniques and included patients, studies of CP described contradictory results regarding efficacy and tolerance.[2,7]

In the 1990s, new CP techniques were developed in Europe.[8-11] Expiratory flow increase techniques (EFIT) have been developed for the management of airway obstructions in children. These methods have been adapted to the small size of the individuals and their respiratory physiology.[11-14] In these patients, EFIT seem more effective than conventional techniques such as thorax percussion, manual vibration or postural drainage.[8,9,15,16] Among the EFIT, 2 manual techniques appear to be safe and effective in infants: prolonged slow expiration (PSE) and assisted cough (AC).[4,9,10,10,11,17]

Prolonged slow expiration and AC are of particular relevance to veterinary patients because they are passive techniques that do not require patient cooperation. A previous study was performed in dogs with naturally occurring airway fluid accumulation hospitalized in an ICU and showed that PSE associated with AC were easily adaptable and well-tolerated techniques in these species.[18] However, in this study, CP neither significantly improved survival rate nor decreased duration of hospitalization.[18] The lack of clear benefit of CP on mortality in this study may have reflected the small sample size of the population, the heterogeneous nature of the diseases of the enrolled dogs, and comparison between a group of prospectively recruited dogs and historical controls.[18] Moreover, respiratory function was not monitored by blood gas analysis.

The objectives of our randomized controlled trial were to assess whether CP with PSE and AC are effective airway clearance techniques in dogs with airway fluid accumulation hospitalized in an ICU. Our primary hypothesis was the use of CP would improve pulmonary gas exchange and be associated with more rapid improvement of the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen ratio (P/F ratio) during the 1st 48 hours. Our secondary hypotheses were that CP would be associated with an increased number of days without oxygen during hospitalization and would decrease mortality rate.

2 | MATERIALS AND METHODS

Our study was designed as a prospective randomized controlled trial conducted in the emergency and critical care unit of VetAgro Sup (SIAMU). The inclusion period was from October 2014 to May 2018. The study protocol was approved by the institutional ethic committee (approval number 1268). Owner consent was obtained before enrollment of dogs into the study.

2.1 | Inclusion and exclusion criteria

Client-owned dogs of any age, sex, or breed presented with or developing respiratory signs during hospitalization associated with clinical criteria of airway fluid accumulation were enrolled in the study.

Clinical criteria of airway fluid accumulation were defined as the association of dyspnea with the presence of crackles, cough, or fluid expectorations in a dog with a disease process considered likely to be associated with airway fluid accumulation. The disease processes identified included bronchopneumonia of any cause (eg, aspiration, infectious).

All enrolled dogs had thoracic radiographs performed and reviewed by a radiologist not associated with the study. If dogs were not stable enough to undergo thoracic radiography at the time of inclusion, thoracic point-of-care ultrasound examination was performed, and thoracic radiographs were postponed until the dog was stable. Radiological criteria of airway fluid accumulation included alveolar opacity of ≥1 lung lobes or an increased interstitial pattern. The ultrasound criterion of airway fluid accumulation was the presence of >3 B-lines in the field.[19] Because thoracic radiographs and ultrasound examination are of limited value to evaluate bronchial fluid accumulation, clinical criteria were mandatory to determine study eligibility. Thoracic radiographs and ultrasound examination were used to aid in diagnosis and to rule out nonpulmonary or neoplastic causes of dyspnea and were performed within the 1st 24 hours after inclusion.

Exclusion criteria included hospitalization for <24 hours; presence of thoracic or abdominal pain during manipulations; congestive heart failure; nonpulmonary or neoplastic causes of dyspnea; or a suspicion of zoonotic diseases that would necessitate limiting contact with the dog because of aerosolized transmission of the pathogen.

2.2 | Experimental protocol

Standard treatment for stabilization of respiratory distress was administered based on the most likely diagnosis, at the discretion of the

attending clinician. Initial stabilization included: oxygen delivered via a single or bilateral nasal cannula at 150 mL/kg/min[20,21] and administration of butorphanol (Torbugesic, Zoetis France, Malakoff, France; 0.2-0.4 mg/kg IM or IV).

After confirmation of airway fluid accumulation, dogs were randomly assigned to the intervention group (receiving medical treatment and CP as described below; CP group) or to the control group (receiving medical treatment only; control group). Before the start of the study, an Excel file was created for randomization. Each dog was represented by a number, starting from 1, and each number was assigned or 0 (control group) or 1 (CP group) using the RANDBETWEEN (0;1) Excel function.

From our experience and results of a previous study,[18] we anticipated that airway fluid accumulation would mainly be associated with aspiration pneumonia. Thus, treatment of dogs with aspiration pneumonia was standardized with the following medications:

- Oxygen supplementation.
- Ampicillin-sulbactam (Unacim, Pfizer, Paris, France; 30 mg/kg IV q8h).
- Butorphanol (Torbugesic, Zoetis France, Malakoff, France; 0.2 mg/kg IV q4h).
- Ten-minute session of nebulization q4h as follows:
  ○ Nebulization of gentamicin (Forticine, Vetoquinol, Lure, France; 6.6 mg/kg q12h)
  ○ Nebulization of isotonic saline (0.9% NaCl; B. Braun, B. Braun medical, Boulogne Billancourt, France) q12h.
  ○ Nebulization of hypertonic saline (10% NaCl; B. Braun, B. Braun medical, Boulogne Billancourt, France) q12h.
  ○ Nebulization was administered before the CP session for dogs in the CP group.

For other diseases, treatments were prescribed at the discretion of the attending clinician.

A decision to discontinue oxygen treatment was made by the attending clinician, based on the following criteria:

- No abnormal respiratory pattern or labored breathing at rest.
- Stable peripheral oxygen saturation (SpO_2) at 98% to 100% during gradual weaning of oxygen treatment.

2.3 | Chest physiotherapy techniques

All CP sessions were performed by veterinarians or technicians from the ICU team who received formal training in the CP techniques by a trained veterinarian (C. P. N.) before initiation of the study. Dogs were constantly monitored for discomfort or distress during CP and had pulse oximetry (SpO_2) recorded during all PSE and AC sessions. If a dog was on oxygen treatment, oxygen delivery was continued by the use of a nasal catheter during the CP session.

All dogs enrolled in the CP group received PSE and AC as CP techniques q4h until the absence of clinical criteria of airway fluid

accumulation as described above, hospital discharge, or death. These CP procedures, derived from well-described techniques used in humans[8,9,11] and adapted for use in dogs, previously have been described in detail.[18] Briefly, PSE involved the generation of synchronized thoracic-abdominal movement by the hands of the physiotherapist at the beginning of expiration with 1 hand on the thorax (5th to 6th intercostal spaces), and the other hand on the abdomen, centered behind the diaphragm to apply abdominal counterpressure (Figure 1). The maneuver began at the beginning of dog's spontaneous expiration and was pursued until the end of expiration. Sessions were started with the dog in lateral recumbency. In very small dogs (<2 kg) and in dogs that would not tolerate lateral recumbency, PSE was performed while the dog was standing. The PSE technique with the animal standing was performed by applying a continuous force with the 2 hands on 1 side of the dog's thorax. The body of the physiotherapist blocked the opposite side of the dog's thorax.

The PSE procedure was repeated for 5 to 10 successive forced expirations, then a break of 5 normal respiratory cycles was allowed. This cycle was repeated for a 5-minute period; the animal then was given a 1-minute break in sternal recumbency before repeating the 5-minute treatment in the opposite recumbency. The procedure was stopped if the dog had increased respiratory distress, vomited, showed signs of discomfort, or if the SpO_2 decreased below 85% during the CP session. Treatment was applied at least 1 hour after the last meal to avoid regurgitation or vomiting during expectoration. If no spontaneous coughing occurred during forced expirations, AC was induced by digital compression of the trachea at the end of the PSE session, with the dog in sternal recumbency.

FIGURE 1 Physiotherapist hand placement for the increased exhalation technique on the dog in lateral recumbency. In this position, increased exhalation technique involved the generation of synchronized thoracic-abdominal movement by the hands of the physiotherapist at the beginning of expiration with one hand on the thorax (5th to 6th intercostal spaces), and the other hand on the abdomen, centered behind the diaphragm in order to apply an abdominal counterweight. Arrows show the movement of the forces on the thorax

2.4 | Data recordings

An acute patient physiologic and laboratory evaluation (APPLE$_{fast}$) score was used for each dog at inclusion to stratify illness severity by mortality risk as previously described.[22]

Arterial blood gases (VetStat, IDEXX Laboratories Inc., Westbrook, Maine) were performed at inclusion, q24h during the 1st 48 hours of hospitalization and at discharge. If the dog died before discharge, the last arterial blood gas performed during hospitalization was considered as the arterial blood gas of discharge. Arterial blood samples were collected from the dorsal pedal or femoral artery, depending on the dog's compliance, comfort and body weight. Ultrasound guidance was used to facilitate arterial sampling. A 1-mL polypropylene syringe was heparinized by aspirating 1 mL of liquid sodium heparin (Héparine Choay 25000UI/5 mL; Sanofi-Aventis, Frankfurt, Germany) into the body of the syringe and then completely expelling it from the syringe, followed by 5 repetitions of 1 mL of air being drawn into and expelled from the syringe.

Arterial blood gases allowed determination of the ratio of arterial partial pressure of oxygen (PaO$_2$) to fraction of inspired oxygen (FiO$_2$) (P/F ratio, mm Hg), calculated by use of the following formula: P/F ratio = (PaO$_2$/FiO$_2$) × 100. The P/F ratios at inclusion (P/F-Incl), daily for the 1st 48 hours of hospitalization, and at discharge or death (P/F-Dis) were calculated. Fraction of inspired oxygen was defined as 40% for unilateral nasal cannula or 60% for bilateral nasal cannula.[20,21]

The differences in P/F ratio between discharge (P/F-Dis) and inclusion (P/F-Incl) were calculated as follows: (P/F-Diff) = (P/F-Dis) − (P/F-Incl).

The ratio of oxygen-free-days (O$_2$Free, %) was calculated as follows: O$_2$Free = ([number of hospitalization days with oxygen supply]/ [number of hospitalization days]) × 100.

2.5 | Outcomes

Over the time course of the intervention, the primary endpoint was improvement of oxygenation parameters (assessed by an increase in P/F ratio). The secondary outcomes were the increase of O$_2$Free, a decrease in mortality rate and CP tolerance assessed by the need to finish a session because of pain or stress induced by CP.

2.6 | Statistical analysis

Variables distribution was assessed using graphical representation (histograms and Q-Q plots) and the Shapiro-Wilk test. Because all parameters were not normally distributed, results were presented as median (1st quartile to 3rd quartile). Mann-Whitney-Wilcoxon tests were used to compare quantitative parameters. Chi-square tests were used to compare categorical parameters.

To test the association between CP and changes in the P/F ratio during the 1st 48 hours, a multivariable linear mixed model was computed. This model included the interaction between the variable "Group" (CP group vs control group) and the variable "Day" considered as a categorical variable (0 = admission, 1 = 1st day, 2 = 2nd day), the "APPLE$_{fast}$" and "Age" as fixed effects, and individuals as random effect (P/F ~ Group: Day + APPLE$_{fast}$ + Age + [1|individual]). Restricted maximum likelihood was used to estimate the variance and covariance parameters.

To test the association between O$_2$Free and CP, a multivariable linear model was computed. It included the variables "Group," "P/F-Incl," "Age," and "APPLE$_{fast}$" as explanatory variables (O$_2$Free-~ Group + P/F-Incl + APPLE$_{fast}$ + Age). Results of the multivariable linear models were presented with the estimation of the regression coefficients (estimate) and their 95% confidence interval (CI). The APPLE$_{fast}$ score was treated as an ordinal variable in the models.

For the linear mixed model, homoscedasticity and random distribution of residuals were checked by plotting residuals against fitted values.

To test the association between mortality and CP, a multivariable Cox model was computed, including the variables "Group," "P/F-Incl," and "Age" as explanatory variables ([hospitalization, mortality] ~ Group + P/F-Incl + Age). Results of the Cox model were presented with the values of the relative risk (risk ratio [RR]) and their 95% CI. Survival was assessed by Kaplan-Meier product limit estimates.

The influence of missing data was evaluated by a robustness analysis of the results by comparing them to those obtained after imputation of missing data. Missing data were imputed according to a method based on the fully conditional specification. The method chosen was predictive mean matching.
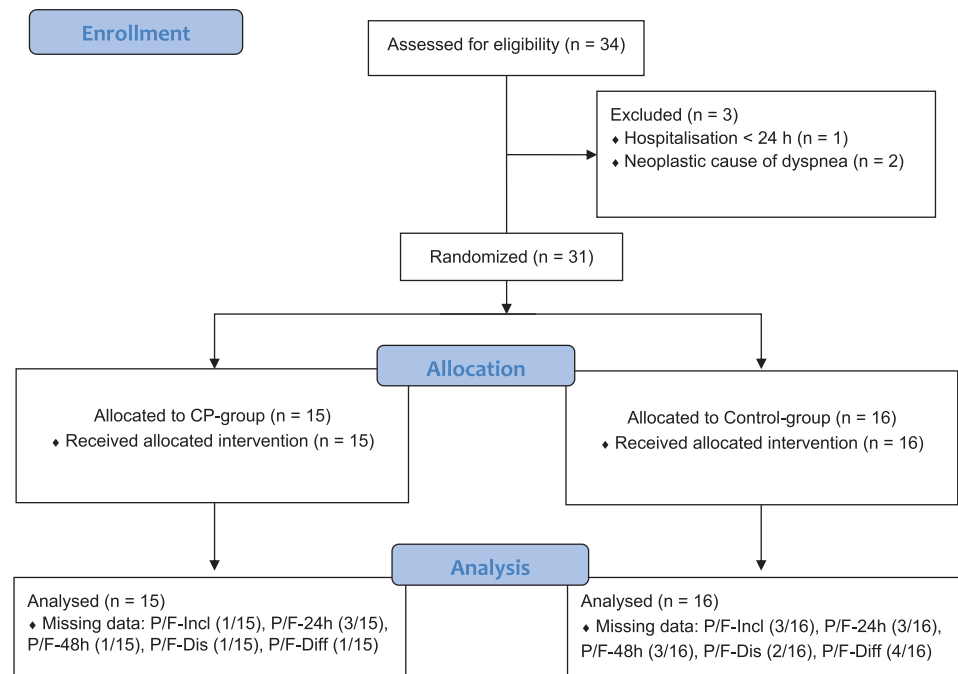
Statistical analyses were performed by 1 author (M. M.) using R 3.5.2 software (R Foundation for Statistical Computing, Vienna, Austria). The packages ggplot2, Lme4, Lmertest, gridExtra, survival, and MICE were used. A P value <.05 was considered significant.

3 | RESULTS

3.1 | Characteristics of the study population

Thirty-four dogs were enrolled in the study (Figure 2). Three dogs were excluded: 1 because of hospitalization for <24 hours, 2 because of neoplastic cause of dyspnea, leading to the final inclusion of 31 dogs. Fifteen dogs were included in the CP group. All dogs were purebred and belonged to the following breeds: French Bulldog (3), Australian Shepherd (2), Leonberger (2), and Malinois dog, Beauceron, Newfoundland, Pug, Bernese Mountain dog, Border Collie, Brittany and Staffordshire Bull Terrier (1 each). Sixteen dogs were included in the control group. Fifteen dogs were purebred and belonged to the following breeds: French Bulldog (4), Bulldog (2), and American Bulldog, Beauceron, Bernese Mountain dog, German Shepherd, Golden Retriever, Dachshund, Shih Tzu, Cocker Spaniel, and Basset Hound (1 each). In both groups, brachycephalic dogs were overrepresented (13/31 of the entire population, 42%).

FIGURE 2 CONSORT flow diagram: flow diagram of the progress through the phases of this randomized clinical trial. P/F-Diff = P/F-Dis − P/F-Incl; P/F ratio = PaO$_2$/FiO$_2$ * 100.Dis, at discharge; Incl, at inclusion; P/F, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO$_2$/FiO$_2$)

Enrollment

Assessed for eligibility (n = 34)

Excluded (n = 3)
♦ Hospitalisation < 24 h (n = 1)
♦ Neoplastic cause of dyspnea (n = 2)

Randomized (n = 31)

Allocation

Allocated to CP-group (n = 15)
♦ Received allocated intervention (n = 15)

Allocated to Control-group (n = 16)
♦ Received allocated intervention (n = 16)

Analysis

Analysed (n = 15)
♦ Missing data: P/F-Incl (1/15), P/F-24h (3/15), P/F-48h (1/15), P/F-Dis (1/15), P/F-Diff (1/15)

Analysed (n = 16)
♦ Missing data: P/F-Incl (3/16), P/F-24h (3/16), P/F-48h (3/16), P/F-Dis (2/16), P/F-Diff (4/16)

TABLE 1 Characteristics of the population at inclusion

Parameters	CP group (n = 15)	Control group (n = 16)	P value
Age (years)	5.0 (1.8-7.0)	4.5 (1.7-7.0)	.89[a]
Weight (kg)	23.0 (11.1-40.0)	17.5 (12.1-28.3)	.69[a]
Sex (female %)	7 (47%)	7 (44%)	1[b]
APPLE$_{fast}$ (AU)	27 (24-29)	25 (22-27)	.22[a]
P/F-Incl (mm Hg)	199 (160-252)	225 (125-273)	.92[a]

Note: Data are presented as median (range) or n (proportion).
Abbreviations: APPLE$_{fast}$, acute patient physiologic and laboratory evaluation; AU, arbitrary unit; CP, chest physiotherapy; Incl, inclusion; P/F, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO$_2$/FiO$_2$).
[a]*P* values obtained using the Mann-Whitney-Wilcoxon tests.
[b]*P* values obtained using the chi-square test.

According to the inclusion criteria, all dogs were dyspneic. Dyspnea was present at admission in 17/31 dogs (55%) and occurred during hospitalization in 14/31 dogs (45%). The definitive diagnoses were as follows: aspiration pneumonia in 29/31 dogs (94%; 14/15 dogs [93%] in the CP group and 15/16 dogs [94%] in the control group), drowning-induced pneumonia in 1/31 dog (3%; in the control group), and infectious pneumonia in 1/31 dog (3%; in the CP group).

Characteristics of the population are summarized in Table 1. No significant difference was observed between the groups for demographic characteristics (age, weight, and sex), for the severity of illness evaluated by APPLE$_{fast}$ score, and for the severity of hypoxemia evaluated by P/F-Incl.

3.2 | Tolerance of CP

Chest physiotherapy was well tolerated in all dogs without additional sedation. The CP sessions were discontinued in 1 dog

suffering from aspiration pneumonia, because of the occurrence of pneumothorax. Pneumothorax was treated successfully by 2 successive thoracocenteses, 6 hours apart, without further recurrence until the end of hospitalization.

3.3 | Impact of CP on oxygenation parameters

Arterial blood gases could not be obtained in 4 dogs at admission (1 in the CP group and 3 in the control group), 6 at 24 hours (3 in the CP group and 3 in the control group), 4 at 48 hours (1 in the CP group and 3 in the control group), and 3 at discharge (1 in the CP group and 2 in the control group). Thus, P/F-Diff was calculated for 14/15 dogs (93%) in the CP group and for 12/16 dogs (75%) in the control group.

Chest physiotherapy was associated with a significant increase in the P/F ratio during the 1st 48 hours of hospitalization, independent of APPLE$_{fast}$ score and age (*P* = .03; Table 2). In the CP group, the mean change in the P/F ratio was +35.1 mm Hg/day (95% CI, 0.4-
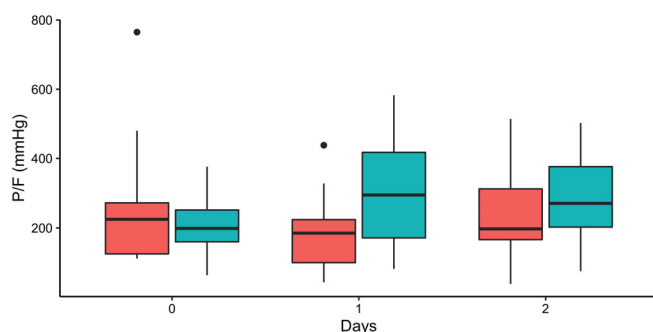
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Dependent variable	Explanatory variable	Estimate	95% CI	P value
P/F ratio (mm Hg)	CP group: day	35.1	0.4–57.5	.03[a]
	Control group: day	−25.1	−47.5 to 13.7	.14[a]
	Age	−5.9	−14.5 to 2.5	.40[a]
O_2Free (%)	CP group	46.4	16.1-59.1	**.001**[b]
	P/F-Incl	0.2	0.1-0.2	**.006**[b]
	Age	−3.2	−4.2 to 1.8	.07[b]

TABLE 2 Correlations between the P/F ratio during the 1st 48 hours and the number of oxygen-free-days with different explanatory variables according to multivariate analyses

Note: P values obtained using multivariate linear models. Bolded characters represent significant correlations.

Abbreviations: APPLE$_{fast}$, acute patient physiologic and laboratory evaluation; CI, confidence interval; CP, chest physiotherapy; Incl, inclusion; O_2Free, ratio of oxygen-free-days; P/F ratio, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO$_2$/FiO$_2$).

[a]P/F ratio ∼ Group: Day + APPLE$_{fast}$ + Age + (1|individual).

[b]O_2Free ∼ Group + P/F-Incl + APPLE$_{fast}$ + Age.

FIGURE 3 Evolution of the P/F ratio during the 1st 48 hours in dogs undergoing chest physiotherapy (blue boxplots, n = 15) and control dogs (red boxplots, n = 16). Chest physiotherapy was associated with a significant increase of the P/F ratio during the 1st 48 hours of hospitalization (P = .03). In the CP group, the mean change of the P/F ratio was +35.1 mm Hg/day (95% CI, 0.4-57.5). Boxplots show the 5-number summary of each group, including the minimum, the 1st quartile, the median, the 3rd quartile, and the maximum. CI, confidence interval; day 0, day of inclusion; P/F, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO$_2$/FiO$_2$)

57.5; Table 2 and Figure 3). No significant change in the P/F ratio was observed during the 1st 48 hours in the control group (Figure 3).

The P/F-Diff was significantly increased in dogs of the CP group (178 mmHg; 123-241) compared with those of the control group (54 mmHg; −19 - 109; P = .001; Figure 4A). Specifically, the P/F ratio increased in all dogs that had blood gas analysis in the CP group (14/14, 100%) and in 8/12 dogs (67%) that had blood gas analysis in the control group between inclusion and discharge (Figure 4B).

3.4 | Duration of hospitalization and oxygen supplementation during hospitalization

Duration of hospitalization was not different between the CP group (4 days; 4-6) and the control group (4 days; 3-6; P = .66). The O_2Free was significantly higher in the CP group (60%; 33-78) than in the control group (23%; 0-54; P = .001; Table 2) independently of APPLE$_{fast}$ score,

P/F-Incl, and age (Figure 5). The mean O_2Free increased by 46.4% in the CP group compared with control group (95% CI = 16-59; P = .001; Table 2). The P/F-Incl also was associated with O_2Free (P = .006; Table 2); when P/F-Incl increased by 10 mmHg, O_2Free increased by 2%.
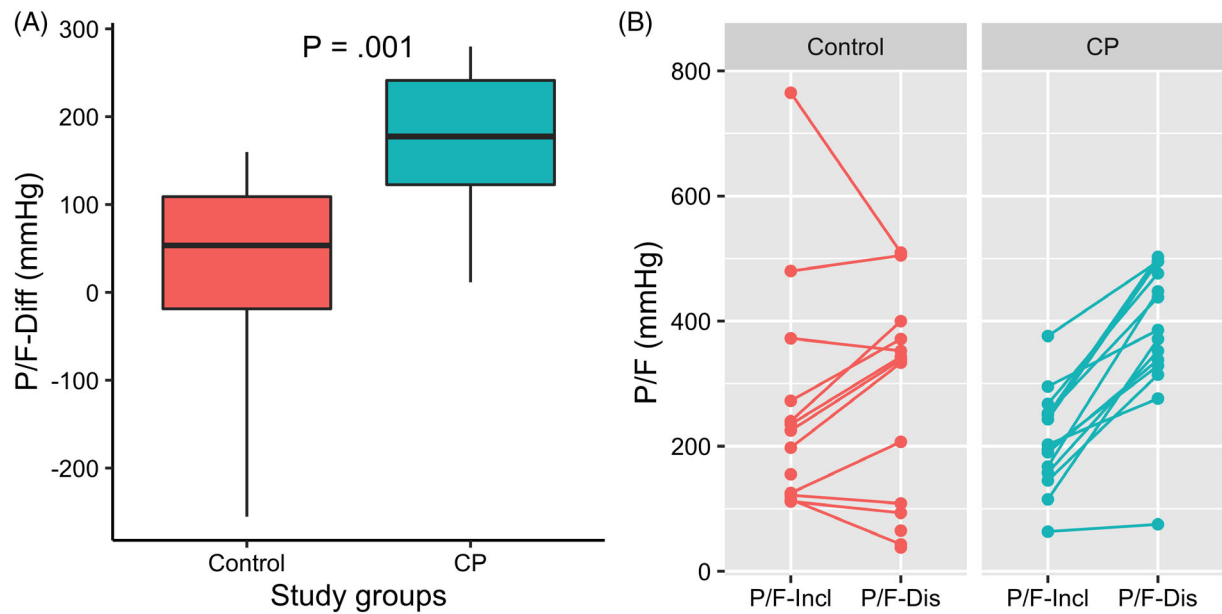
3.5 | Impact of CP on mortality

Mortality rate was 13% (2/15) in the CP group and 44% (7/16) in the control group (Figure 6). In the CP group, 1/15 dog (7%) died naturally, and 1/15 dog (7%) was euthanized. In the control group, 5/16 dogs (31%) died naturally, and 2/16 dogs (13%) were euthanized. Euthanasia was related to severe deterioration in the dogs' general condition and high associated costs. No association was found among mortality, APPLE$_{fast}$ score, P/F-Incl ratio, and age (Table 3). Mortality rate was decreased in the CP group, but this result did not reach statistical significance (RR, 0.05; 95% CI, 0.00-1.26; P = .07; Table 3). From the 4th day of hospitalization, no death was observed in the CP group (Figure 6).
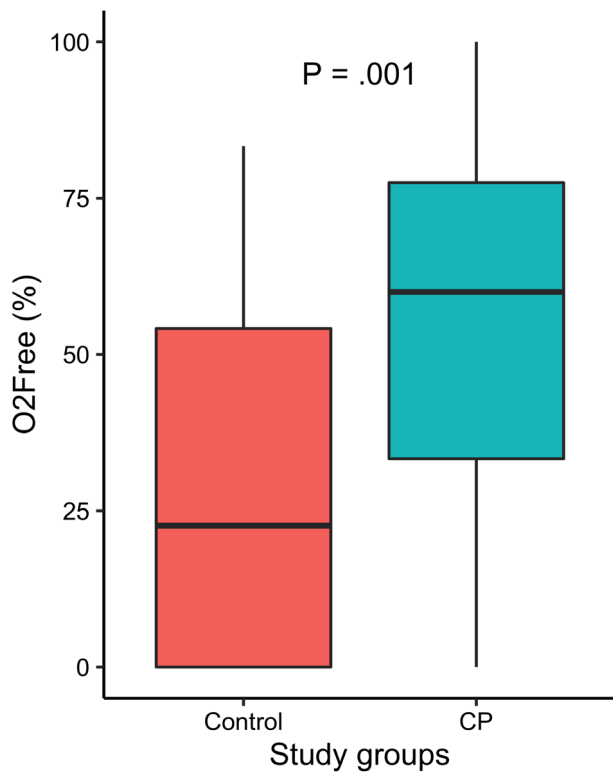
3.6 | Influence of missing data

Results obtained after imputing missing data did not modify the conclusions of our study. Chest physiotherapy always was associated with improvement in the P/F ratio during the 1st 48 hours and an increase in %O_2Free. The P/F-Diff variable was always significantly higher in the CP group as compared with the control group. The results obtained after missing data imputation are described in Appendix 1.

3.7 | Influence of the origin of fluid airway accumulation on outcome
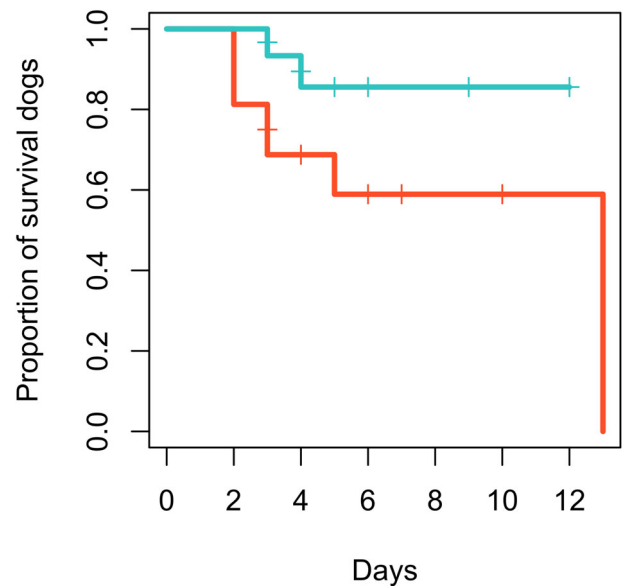
Only 2 dogs had airway fluid accumulation associated with medical conditions other than aspiration pneumonia. Neither of these 2 dogs had extreme values for all of the variables studied. The exclusion of these 2 dogs did not modify the results obtained (data not shown).

FIGURE 4 Evolution of the P/F ratio between inclusion (P/F-incl) and discharge (P/F-diff) 48 hours in dogs undergoing chest physiotherapy (CP, n = 15) and control dogs (n = 16). A, Box plots of P/F-diff in both groups (boxplots show the 5-number summary of each group, including the minimum, the 1st quartile, the median, the 3rd quartile, and the maximum); B, individual evolution of the P/F value between inclusion and discharge. Dis, discharge; Incl, inclusion; P/F, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO_2/FiO_2)

FIGURE 5 Comparison of the ratio of oxygen-free-days in dogs undergoing chest physiotherapy (CP, blue boxplots, n = 15) and control dogs (red boxplots, n = 16). The boxplots show the 5-number summary of each group, including the minimum, the 1st quartile, the median, the 3rd quartile, and the maximum. O2Free, ratio of oxygen-free-days

FIGURE 6 Survival curves in dogs undergoing chest physiotherapy (CP group, blue line, n = 15) and control dogs (red line, n = 16). On the plot, small vertical tick-marks indicate dogs withdrawn from the study (dogs discharged alive). The declining horizontal steps represent the death of dogs

4 | DISCUSSION

Our prospective randomized controlled study confirmed the effectiveness of CP, and more particularly of PSE and AC, on oxygenation

TABLE 3 Correlations between the mortality rate and different explanatory variables according to multivariate analyses

Explanatory variable	Relative risk	95% CI	P value
CP group	0.05	0.00-1.26	.07
P/F-Incl (mm Hg)	0.97	0.93-1.00	.07
Age (years)	1.15	0.80-1.64	.43

Note: P values obtained using a multivariate Cox model: (hospitalization, mortality) ∼ Group + P/F-Incl + Age.
Abbreviations: CI, confidence interval; CP, chest physiotherapy; Incl, Inclusion; P/F ratio, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO_2/FiO_2).

parameters in dogs with dyspnea associated with airway fluid accumulation. Our main findings are a significant improvement of hypoxemia within the 1st 48 hours and a significant increase in oxygen-free days during hospitalization when using CP.

As in a previous study,[18] we included in this prospective study many dogs with different signalment, ages varying from 1.7 to 7 years, body weight from 11.1 to 40 kg, and breeds from Pugs to Leonberg. Despite this heterogeneity, we found a well-tolerated position for performing PSE and AC in all cases. Because our CP technique could be performed with the animal standing or in lateral recumbency, it allows adaptability to dogs of different size and conformation. Based on our experience, lateral recumbency is recommended as the 1st choice when performing CP because it is more comfortable for the dog, and the physiotherapist can apply a more continuous force on the thorax.

The CP applied in our study has been adapted from techniques used in children during obstruction of the respiratory tract, especially during acute bronchiolitis. Expiratory flow increase techniques were developed specially for infants in accordance with their physiological characteristics (smaller airway diameter which produces a high resistance to air flow) and behavioral (not compliant).[8,12,17] These techniques are of particular relevance to veterinary patients because they are passive techniques that do not require patient cooperation. In addition, the results published for humans were rather encouraging because several studies reported rapid clinical improvement after sessions of PSE and AC.[9-11,13,17] A randomized controlled study in infants with acute bronchiolitis reported respiratory improvement from the 1st session with a decrease in the clinical severity score of approximately 50%.[13] Moreover, few adverse effects were reported in these studies. In veterinary medicine, standard treatments described in dogs is coupage and patient positioning, but no clinical study has evaluated the use of these techniques or compared different techniques. From our own clinical experience and the available literature, PSE and AC could be recommended as airway clearance techniques in dogs. However, additional studies are now required to compare PSE and AC with other CP techniques.

This new CP method is more attuned to pulmonary physiology and associated with few adverse effects. A previous study, using the same technique, reported a low discomfort rate, no adverse effects, and no deterioration of clinical parameters or desaturation during the

sessions.[18] In our study, no adverse effects were noted during the sessions. No dogs had to be excluded from the CP group because of intolerance of CP. One dog developed a spontaneous pneumothorax during hospitalization for aspiration pneumonia. Chest physiotherapy was not performed again during hospitalization because pneumothorax could have been a CP complication. This dog made a full recovery. However, this dog was presented to the ICU 1 month after the 1st hospitalization for deterioration of its respiratory status. Pneumothorax again was diagnosed, and the final diagnosis was spontaneous pneumothorax related to the bronchopneumonia.

Expiratory flow increase techniques are mainly described in children with acute bronchiolitis, which is associated with the presence of thick secretions of inflammatory origin in the respiratory tract.[9-11,13,23,24] They also have been used in children with pneumonia.[17] Their objective is to apply a slow and progressive pressure on the thorax (PSE) making it possible to force the secretions up along the respiratory tract until they can be swallowed, either spontaneously or after forced cough (AC). Most dogs enrolled in our study had aspiration pneumonia, which is also a disease process associated with increased airway fluid and mucus production in dogs. The efficacy of CP to clear these secretions has been described in humans, but also in dogs. A 1st study reported spontaneous swallowing or cough of the secretions after 60% of CP sessions, which increased by 21% after cough was triggered by compression of the trachea.[18] It is likely that the significant improvement in P/F ratio within the 1st 48 hours and the significantly different P/F-Diff between the 2 groups were because of secretion drainage. The P/F ratio conventionally is used to evaluate the efficiency of gas exchanges in dogs.[25-27]

In addition to CP, nebulization could play a major role in the elimination of respiratory secretions and the correction of hypoxemia.[10] Nebulization can promote the effectiveness of CP by increasing the fluidity of the secretions, thus promoting mechanical evacuation. The few studies of CP in infants that did not find benefit from EFIT techniques were carried out in children without nebulization.[23,24] In the studies describing a positive effect, nebulization was carried out with CP.[9-11,13,17] One study reported interest in coupling CP to nebulization, compared to nebulization alone.[28] In the aforementioned studies, different products were administered. However, it appears that the most important factor is the increase in water proportion in secretions, favoring expectoration and contributing to clinical improvement. A study in dogs found that water nebulization increased the transport of pulmonary mucus.[29] In our study, all dogs with aspiration pneumonia were nebulized according to in-house standard procedures. However, no consistent protocols for nebulization currently are available in dogs. Hypertonic solution nebulization is used for various causes of airway obstruction both in humans and dogs. It improves mucus rheologic properties and increases the rate of mucociliary clearance.[30,31] Gentamicin is a broad-spectrum antibiotic that eliminates the majority of bacteria encountered in pneumonia in dogs.[32] In 1 study, nebulization of gentamicin during infection with *Bordetella bronchiseptica* helped decrease morbidity in dogs.[33] This antibiotic is also widely used in humans with pneumonia.[31] Nebulization of gentamicin has the major advantages of increasing its pulmonary concentration and thus

effectiveness,[31] and minimizing its plasma concentration and renal toxicity.[34] Descriptions of other nebulization methods in dogs would be of value for the medical management of pneumonia.

In our study, CP significantly improved gas exchanges within the 1st 48 hours and allowed a 37.6% decrease in the number of days of oxygen treatment. This rapid improvement and decrease in oxygen requirement contribute to a decrease in hospitalization costs, and could motivate owners to accept the financial costs associated with severe illnesses.

Observation of the Kaplan-Meier curves (Figure 6) indicated a decrease in mortality in the CP group, but this result failed to reach significance. The absence of a significant difference between groups may reflect type II error because of a lack of statistical power related to the small study population. However, CP could help decrease mortality by improving pulmonary gas exchange and decreasing the amount of oxygen required. Indeed, improvement in the P/F ratio has been showed to be a favorable prognostic factor in several diseases in dogs.[35]

Missing data were present in our study related to the variable PaO_2 used in several models. These missing data were distributed in the 2 groups, but were more numerous in the control group. Inability to obtain an arterial blood gas was not associated with the condition of the dog but for technical reasons. These data can thus be considered as missing random data. Not taking missing data into account can be a source of bias in randomized controlled trials and can lead to false conclusions.[36] Therefore, we performed a robustness analysis of our results and after performance of a new statistical analysis with imputation of missing data, the result were similar (Appendix 1).

Our study had several limitations. First, the small sample of dogs decreased statistical power and limited certain conclusions. In addition, small samples weaken the results obtained by randomized controlled trials. Indeed, they often are associated with a low fragility index, which means that small modifications in the number of events in a group can change the significance of a result.[37] Our results therefore must be confirmed in a larger population. In addition, it would have been preferable to perform a power analysis to justify the sample size choice. However, the main objective of our study was to measure the impact of CP on changes in PaO_2. Because no published data are available on this subject in dogs, it was not possible to perform this analysis. The 2nd limitation concerns the absence of placebo. Indeed, it is possible that the presence of the physiotherapist during the session also played a role in the improvement of the dogs, by reassuring them and giving them attention. To control for a placebo effect, we could have organized the presence of a veterinarian or a technician at the same frequency in the CP group as in the control group. However, it was not possible to do so in a busy ICU. Moreover, all dogs received intensive care every 4 hours, whatever their allocated group. The 3rd limitation is the absence of blinding. Considering unstable patients and a busy ICU, we could not move every dog to a separate room for the CP sessions. Fourth, the calculation of the P/F ratio was based on a theoretical FiO_2 value from the literature[20,21] and obtained after administration of oxygen to healthy dogs by nasal tubes. Studies have shown that oxygen flow rate impacts the delivered FiO_2.[20,21] Oxygen rate usually is set at 150 mL/kg/min in our ICU, but we cannot exclude the use of higher flow rates in some dogs. It would have been more precise to measure FiO_2 for each individual, but it was not technically feasible in a clinical setting. In addition, the presence of open PO breathing or panting could have influenced FiO_2. These limitation could explain the extreme values of P/F ratio observed in 1 dog.

Finally, our study mainly included dogs with airway obstruction secondary to aspiration pneumonia. By making the studied population more homogeneous, the difference between groups could be mostly attributed to CP, because other treatments were similar. On the other hand, our results cannot be extended to all causes of respiratory obstruction. This overrepresentation of aspiration pneumonia as a cause of respiratory disease in dogs is consistent with the literature.[30]

In conclusion, our randomized controlled trial provided proof of the efficacy of PSE and AC in the management of respiratory distress secondary to airway fluid accumulation in dogs. We reported more improvement in hypoxemia and increase oxygen-free days in dogs receiving CP as compared with control dogs with similar medical treatment. Our findings confirmed that PSE and AC are easily adaptable and well tolerated techniques in dogs. Because this study was carried out mainly on acutely dyspneic dogs with aspiration pneumonia, these results should be validated in a more heterogeneous population or in the management of chronic airway obstruction.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study protocol was approved by the Université de Lyon institutional ethic committee (approval number 1268).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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APPENDIX A.: RESULTS OBTAINED AFTER IMPUTATION OF MISSING DATA BY FULLY CONDITIONAL SPECIFICATION-BASED METHOD ("MICE" R PACKAGE)

- Comparison of P/F-Diff

TABLE A1 Results obtained for the multivariable linear models

Dependent variable	Explanatory variable	Estimate	95% CI	P value
P/F ratio (mm Hg)	CP group: day	44.1	12.7-71.3	**.008**[a]
	Control group: day	−14.3	−40.9 to 16.1	.36[a]
	Age	−7.8	−15.6 to 0.6	.19[a]
O_2Free (%)	CP group	46.4	16.1-59.1	**.001**[b]
	P/F-Incl	0.2	0.1-0.2	**.006**[b]
	Age	−3.2	−4.2 to 1.8	.07[b]

Note: P values obtained using multivariate linear models.
Abbreviations: CI, confidence interval; CP, chest physiotherapy; Incl, inclusion; O_2Free, ratio of oxygen-free-days; P/F ratio, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO_2/FiO_2).
Bold values are the significant values for *p* < 0.05.
[a]P/F ratio ∼ Group: Day + $APPLE_{fast}$ + Age + (1|individual).
[b]O_2Free ∼ Group + P/F-Incl + $APPLE_{fast}$ + Age.

The median P/F-Diff was (median [IQR]: 185 (126-252) in the CP group and 53 (−19 to 109) in the Control group (Mann-Whitney-Wilcoxon test, *P* = .002).

TABLE A2 Results obtained for the Cox model

Explanatory variable	Relative risk	95% CI	P value
CP group	0.17	0.03-1.09	.06
P/F-Incl (mmHg)	0.98	0.96-0.99	**.02**
Age (years)	1.10	0.89-1.34	.35

Note: P values obtained using a multivariate Cox model: (hospitalization, mortality) ∼ Group + P/F-Incl + Age.
Abbreviations: CI, confidence interval; CP, chest physiotherapy; Incl, inclusion; O_2Free, ratio of oxygen-free-days; P/F ratio, arterial partial pressure of oxygen on fraction of inspired oxygen ratio (PaO_2/FiO_2).