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Nebulization of epinephrine to reduce the severity of brachycephalic obstructive airway syndrome in dogs

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Abstract

Objective: To determine the preoperative and postoperative effect of nebulized epinephrine on brachycephalic obstructive airway syndrome (BOAS) severity in dogs.

Study design: Prospective clinical study.

Sample population: Thirty-one client-owned pugs, French bulldogs, and English bulldogs with moderate to severe BOAS.

Methods: Whole body barometric plethysmography was used to determine BOAS severity (BOAS index; 0%–100%) prior to and after nebulization with 0.05 mg/kg epinephrine diluted in 0.9% saline preoperatively. The same protocol was repeated postoperatively (within 24 hours of surgery).

Results: Five dogs were excluded because they did not tolerate nebulization, and postoperative data were available for 13 dogs. Epinephrine nebulization resulted in a decreased BOAS index across all breeds of dog both before (9.6% [3.1% to −30.2%], n = 26) and after surgery (14.3% [0.9% to −24.3%], n = 13). The preoperative reduction in BOAS index was greater (17.3% [1.8% to −27.4%]) in dogs with a baseline BOAS index >70% ($P = .006$) and in pugs (16.9% [0.8% to −27.4%]) compared with French bulldogs (5.2% [3.1% to −30.2%], $P = .03$). Simple linear regression was used to identify a positive relationship between baseline BOAS index and reduction in BOAS index for pugs (n = 10, $P = .001$). Nausea was noted as a side effect in four dogs.

Conclusion: Nebulized epinephrine reduced the BOAS index of dogs in this study. This effect was clinically significant in preoperative dogs with a BOAS index >70% and in dogs recovering from surgery.

Clinical significance: This study provides evidence to support the use of nebulized epinephrine in the perioperative management of BOAS-affected dogs.

1 | INTRODUCTION

The prevalence of brachycephalic obstructive airway syndrome (BOAS) has increased in recent years because of the soaring popularity of brachycephalic breeds.[1] Affected dogs will often exhibit increased respiratory noise and effort alongside exercise and heat intolerance; these symptoms tend to be progressive and can lead to acute

respiratory distress. Emergency stabilization of dogs with BOAS presenting in acute respiratory distress frequently involves sedation, active cooling, and supportive oxygen therapy (with or without intubation).[2-4] Surgical treatment is indicated to alleviate components of upper airway obstruction in dogs affected with BOAS.[3-5] While surgery has the potential to significantly improve the quality of life of affected dogs, numerous surgical complications can occur. Most of these complications result from inflammation and edema of the pharynx, larynx, and surrounding soft tissues secondary to surgical manipulation. Severe inflammation can lead to dyspnea and hypoxemia, requiring interventions such as systemic anti-inflammatory medications, sedation, flow-by oxygen supplementation, or temporary tracheostomy tube placement.[6,7]

Nebulized epinephrine is hypothesized to cause vasoconstriction of vessels within the mucosa of the upper airways via its action at α-adrenergic receptors, leading to decreased edema and, therefore, decreased upper airway obstruction.[2,8] In human medicine, nebulized epinephrine is used to improve respiratory function in patients experiencing moderate to severe croup, a disease characterized by swelling of the larynx, trachea, and bronchi, which can lead to inspiratory stridor and coughing.[8-11] Conflicting evidence exists for its application in post-intubation stridor, another human syndrome characterized by laryngeal edema.[12-14] In dogs recovering from BOAS surgery, nebulized epinephrine has been used to reduce mucosal edema throughout the upper airway.[2,15] According to one case report, the administration of nebulized epinephrine in a pug experiencing acute upper airway obstruction after surgery helped alleviate dyspnea and avoid temporary tracheostomy tube placement.[2]

The use of nebulized epinephrine in man is associated with low morbidity; reported side effects include mild increases in heart rate, pallor, and, occasionally, tremors or nausea.[10,12,16-17] Despite the widespread use of nebulized epinephrine, only one instance of a major complication has been reported, in which the patient developed ventricular tachycardia after nebulization.[18] To the best of the authors' knowledge, there are no reports in the veterinary literature describing the side effects of nebulized epinephrine in dogs.

Whole-body barometric plethysmography (WBBP) is a diagnostic tool that provides objective, noninvasive, respiratory assessment in fully conscious and minimally restrained dogs.[19,20] This technique is particularly relevant in client-owned brachycephalic breeds because it eliminates the requirement for a face mask, which is often poorly tolerated in these dogs when they are conscious.[19,21] Brachycephalic obstructive airway syndrome index, a measure of relative BOAS severity, can be calculated from the WBBP respiratory variables and has been used for diagnosis of BOAS as well as evaluation of surgical outcome.[22,23] The BOAS index is an ascending scale ranging from 0% to 100%, with 100% indicating severe BOAS.

No reports of objective studies on the efficacy of nebulized epinephrine in dogs have been published to date. In this study, therefore, we sought to determine the effect of nebulized epinephrine on BOAS severity in dogs both preoperatively and postoperatively. In addition, any side effects of nebulized epinephrine are reported. Based on clinical impressions and comparative human studies, our hypothesis was that there would be a significant reduction in BOAS index (%) after nebulization with epinephrine in both preoperative and postoperative cohorts, with minimal side effects.

2 | MATERIALS AND METHODS

2.1 | Animals

Brachycephalic dogs (pugs, French bulldogs, and English bulldogs) with moderate to severe BOAS that presented at a single specialist referral hospital for BOAS surgery were recruited to the study. Dogs that had already undergone BOAS surgery and those with concurrent cardiovascular or lower airway disease were excluded from the study. Dogs were continuously enrolled until 26 suitable dogs that tolerated WBBP and nebulization were found. The study was approved by the University of Cambridge Ethical and Welfare Committee (reference No. CR312a), with informed consent signed by the owners.

2.2 | Study design

2.2.1 | Brachycephalic obstructive airway syndrome functional grading

Each dog underwent a general clinical examination, followed by BOAS functional grading performed by one of the authors in accordance with a previously published 4-point grading system (Table 1).[19] Dogs were included when they were assessed as functional grade II (moderate) or III (severe).

2.2.2 | Whole body barometric plethysmography

Each dog then underwent WBBP testing according to previously published protocols.[19,20,22] Briefly, WBBP measurements were generated by a barometric chamber

TABLE 1 Functional grading system of BOAS based on respiratory signs before and after an ETT

Grade	Time	Respiratory noise[a]	Inspiratory effort[b]	Dyspnea/cyanosis/syncope[c]
0	Pre-ETT	Not audible	Not present	Not present
	Post-ETT	Not audible	Not present	Not present
1	Pre-ETT	Not audible or mild	Not present	Not present
	Post-ETT	Mild	Not present to mild	Not present
2	Pre-ETT	Mild to moderate	Mild to moderate	Not present
	Post-ETT	Moderate to severe	Moderate to severe	Mild dyspnea; cyanosis or syncope not present
3	Pre-ETT	Moderate to severe	Moderate to severe	Moderate to severe dyspnea; may or may not present cyanosis; inability to exercise
	Post-ETT	Severe	Severe	Severe dyspnea

Notes: Table adapted from Liu et al.[19]

Abbreviations: BOAS, brachycephalic obstructive airway syndrome; ETT, exercise tolerance test.

[a]Respiratory noise was diagnosed by pharyngolaryngeal auscultation. Mild, only audible on auscultation; moderate, intermittent audible noise that can be heard without stethoscope; severe, constant audible noise that can be heard without stethoscope.

[b]An abnormal respiratory cycle characterized by evidence of increased effort to inhale the air with the use of diaphragm and/or accessory muscles of respiration and/or nasal flaring with increased breathing rate. Mild, regular breathing patterns with minimal use of diaphragm; moderate, evidence of use of diaphragm and accessory muscles of respiration; severe, marked movement of diaphragm and accessory muscles of respiration.

[c]Dogs that have had episodes of syncope and/or cyanosis as documented by owner's report are classified as grade III without ETT. Mild dyspnea, presents sign of discomfort; moderate dyspnea, irregular breathing, signs of discomfort; severe dyspnea, irregular breathing with signs of breathing discomfort and difficulty in breathing.

(model PLY370 and model PL360; Electro-Medical Measurement Systems [EMMS], Bordon, United Kingdom) supplied by a balanced bias airflow of room air (20 L/min, bias flow regulator BFL0404; EMMS). The pressure signals were amplified and sampled in commercial software (ESS-102, eDacq - EMMS Data Acquisition for Microsoft Windows XP; EMMS) and translated to pseudoflow signals. Each dog stayed in the chamber, and data were recorded for approximately 20 to 40 minutes. A surveillance video was used to identify vocalizations, sniffing, and body movements that produce artefacts in the trace, which were then manually removed. Twenty consecutive, representative resting breaths were selected during wakefulness for analysis. A BOAS index (%) was then generated as previously described.[22]

2.2.3 | Nebulization

Each dog was nebulized with 0.05 mg/kg epinephrine (Macarthys Laboratories, Romford, United Kingdom) added to 0.9% saline to make up a 5-mL nebulization solution. This was delivered in a flow-by manner by using a mesh nebulizer (DELBio DK010 nebuliser; DELBio, Taiyuan City, Taiwan) producing droplets with an average diameter of 3.5 μm at a rate of 0.25 mL/minute for 10 minutes. The dosing was adapted from that used in the previously discussed case report.[2] A second WBBP test was then performed immediately after the nebulization finished, and a postnebulization BOAS index was calculated.[22] The dogs were closely monitored during the procedure and for 60 minutes after nebulization. Incidences of pallor, tremors, excitement, and/or nausea were all recorded along with pulse rate. Monitoring for arrythmias via three-lead electrocardiogram (ECG) was performed by a veterinarian (P.H.F) in dogs in which it was tolerated. The procedure was then repeated postoperatively (within 24 hours of surgery) for any dogs in which the investigations would not negatively impact their recovery and the investigators were available. Functional BOAS grading was not repeated because of clinical concerns regarding the potential exercise-induced stress in dogs after surgery. Surgical interventions and postoperative medications were recorded.

2.3 | Statistical analysis

Statistical analysis was performed in R 3.5.3.[24] Nonparametric statistical tests were used throughout because of the small sample and because the data were not normally distributed. Wilcoxon signed-ranks tests were used to compare baseline and postnebulization BOAS indices for overall data in both the preoperative and postoperative cohorts. Within the preoperative cohort, Wilcoxon signed-ranks tests were used to compare baseline and postnebulization BOAS indices in the following subgroups: severity of BOAS (BOAS index >70% and BOAS index

TABLE 2 Surgical variables of the postoperative cohort

Surgical intervention	Dogs, n	Breed, n	Change in BOAS index after surgery, median (IQR), %	Change in BOAS index in response to nebulization, median (IQR), %
BT, FFP, BS, AFR, TTR	8	P = 1, FB = 6, EB = 1	−7.9 (33.7)	−12.5 (9.1)
BT, FFP, BS, AFR, BPC, TTR	3	P = 3	−16.6 (27.9)	−14.4 (5)
BT, FFP, AFR, TTR	1	FB = 1	26.6 (N/A)	0.9 (N/A)
BT, FFP, BS, AFR, TTR, LGR	1	FB =1	−2.3 (N/A)	−21.2 (N/A)

Abbreviations: AFR, alar fold resection; BOAS, brachycephalic obstructive airway syndrome; BPC, bilateral partial cuneiformectomy; BS, bilateral sacculectomy; BT, bilateral tonsillectomy; EB, English bulldog; FB, French bulldog; FFP, folding flap palatoplasty; LGR, laryngeal granuloma resection; N/A, not applicable; P, pug; TTR, Trader technique rhinoplasty.

TABLE 3 Adverse events after epinephrine nebulization detected in 26 dogs preoperatively

Adverse event	Event observed, n/N (%)
Pallor	0/26 (0)
Tremor	0/26 (0)
Excitement	4/26 (12)
Arrythmia[a,b]	0/23 (0%)
Nausea[c]	4/26 (12)

[a]Average change in heart rate = 7 ± 19.5 beats per minute.
[b]Three dogs did not tolerate electrocardiogram monitoring.
[c]Three dogs regurgitated, one dog lip smacked; of these four dogs, three had a history of regurgitation due to brachycephalic obstructive airway syndrome.

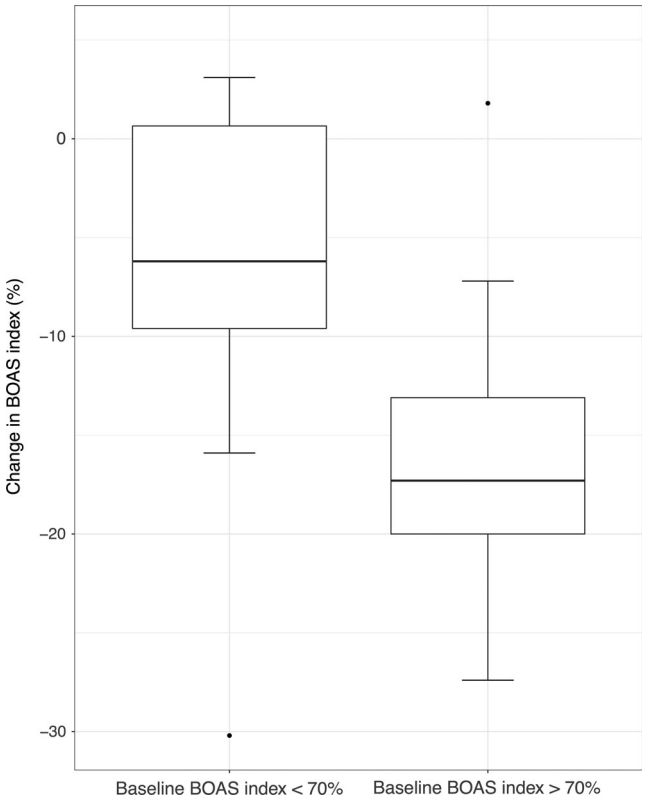

FIGURE 1 Box plots of the preoperative change in BOAS index in response to nebulized epinephrine (postnebulization–baseline). The cohort is divided into two groups according to baseline BOAS index (BOAS index >70% and BOAS index ≤70%). The box illustrates the interquartile range, and the whiskers represent 95% central range. Outliers are also marked. BOAS, brachycephalic obstructive airway syndrome

≤70%), breeds (pugs and French bulldogs), functional grades (grade II and grade III), and grades of laryngeal collapse (grade 0/I and grade II/III).[25] The changes in BOAS indices were compared between the related subgroups by using the Wilcoxon rank-sum test. The preoperative cohort was divided by severity of BOAS with a cut-off value of BOAS index at 70% based on a receiver operating characteristic curve, where the sum of sensitivity and specificity was maximized in terms of detecting clinically significant decrease in BOAS index (ie, over 10%) in response to nebulized epinephrine. The association between baseline BOAS index and change in BOAS index postnebulization was analyzed by using simple linear regressions both overall and within individual breeds.

In the postoperative cohort, descriptive statistics were used to analyze relationships between the surgeries performed, surgeons, postoperative medications, and change in BOAS index after nebulization (Table 2). Side effects were also analyzed by using descriptive statistics (Table 3).

Results were considered statistically significant when $P < .05$. Changes in BOAS index of less than 10% were not considered to be clinically significant because of respiratory dynamics and intraobserver/interobserver variability.[19]

Results of preliminary power analysis performed in R (package "pwr")[24] indicated that 26 dogs (preoperative

cohort) would be required to detect a > 10% change in BOAS index after nebulization to achieve a power of 80% and the significance level of $P = .05$.

3 | RESULTS

3.1 | Demographics

In total, 31 dogs were enrolled in the preoperative cohort between October 2018 and July 2019. Five of these dogs were subsequently excluded because they did not tolerate nebulization. Consequently the results of the 26 dogs that did tolerate nebulization are reported. Thirteen of the dogs in the preoperative cohort were enrolled in the postoperative cohort.

3.2 | Preoperative cohort

Ten pugs, 14 French bulldogs, and two English bulldogs were enrolled. The median age of all dogs was 19 months (range, 10-83), and each sex was equally represented (13 male, of which five were neutered, and 13 female, of which 10 were neutered).

Nineteen (73%) dogs were functional grade 2, while seven (27%) dogs were functional grade 3. The median baseline BOAS index was 67% (IQR, 23%). The median reduction in BOAS index after preoperative nebulization in this cohort was 9.6% (95% CI, 6.2%–13.5%, $P < .0001$). According to WBBP, 15 dogs had a BOAS index ≤70%, and 11 dogs had a BOAS index >70%. Dogs with a baseline BOAS index >70% had a median reduction of 17.3% after nebulization (95% CI, 9.5%–20.8%, $P = .002$), while those with a baseline BOAS index ≤70% had a median reduction of 6.2% (95% CI, 1.3%–8.9%, $P = .02$; Figure 1). There was a difference between these two groups ($P = .006$; Table 4). There was an association between baseline BOAS index and change in BOAS index after nebulization, providing evidence that dogs with a higher baseline BOAS index had a larger reduction in BOAS index after nebulization ($\beta = -.26$ [95% CI, −0.09 to −0.43], $R^2 = 0.29$, $P = .005$; Figure 2). There was a particularly strong association between the same variables specifically for pugs ($\beta = -.50$ [95% CI, −0.26 to −0.74], $R^2 = 0.74$, $P = .001$). Pugs with a BOAS index >70% had a median reduction of 19.2% (95% CI, 14.5%–24.1%, $P = .02$) after nebulization, while the remaining preoperative cohort had a median reduction in BOAS index of 6.7% (95% CI, 2.7%–9.5%, $P = .005$). Other notable relationships between changes in BOAS index and assessed variables were present (Table 4). These variables displayed marked collinearity with baseline BOAS index, preventing them from being used in multilinear analysis with baseline BOAS index and limiting the conclusions that could be drawn from these findings.

TABLE 4 Characteristics and results of Wilcoxon signed-ranks test comparing baseline BOAS index and postepinephrine nebulization BOAS index in 26 preoperative dogs

Variables	Breed, n	Baseline BI, median (IQR), %	Postnebulization BI, median (IQR), %	Change in BI, median (IQR), %
Breed[a]				
P	10	87.5 (25.2)	67.6 (12)	−16.9 (12.1)
FB	14	65.3 (18.5)	60 (25.7)	−5.2 (11)*
Baseline BI				
BI ≤70%	P = 3, FB = 11, EB = 1	64.7 (15.6)	54.1 (25.4)	−6.2 (10.2)
BI >70%	P = 7, FB = 3, EB = 1	91.4 (13.3)	67.5 (9)	−17.3 (6.9)**
Functional respiratory grade				
II	P = 4, FB = 13, EB = 2	66.7 (23.3)	64.6 (22.4)	−8.3 (15.3)
III	P = 6, FB = 1, EB = 0	83.6 (25.8)	68 (9.3)	−16.5 (11.1)
Laryngeal collapse				
Grade 0-1	P = 0, FB = 14, EB = 2	66.3 (19.7)	60 (25.4)	−7.8 (12.4)
Grade 2-3	P = 10, FB = 0, EB = 0	87.5 (25.2)	67.6 (12)	−16.9 (12.1)*

Abbreviations: BI, BOAS index; BOAS, brachycephalic airway obstructive syndrome; EB, English bulldog; FB, French bulldog; IQR, interquartile range; P, pug.

[a]English bulldogs have been excluded from this analysis because of their small sample size (n = 2).

*$P < .05$, change in BOAS index between related subgroups.

**$P < .01$.

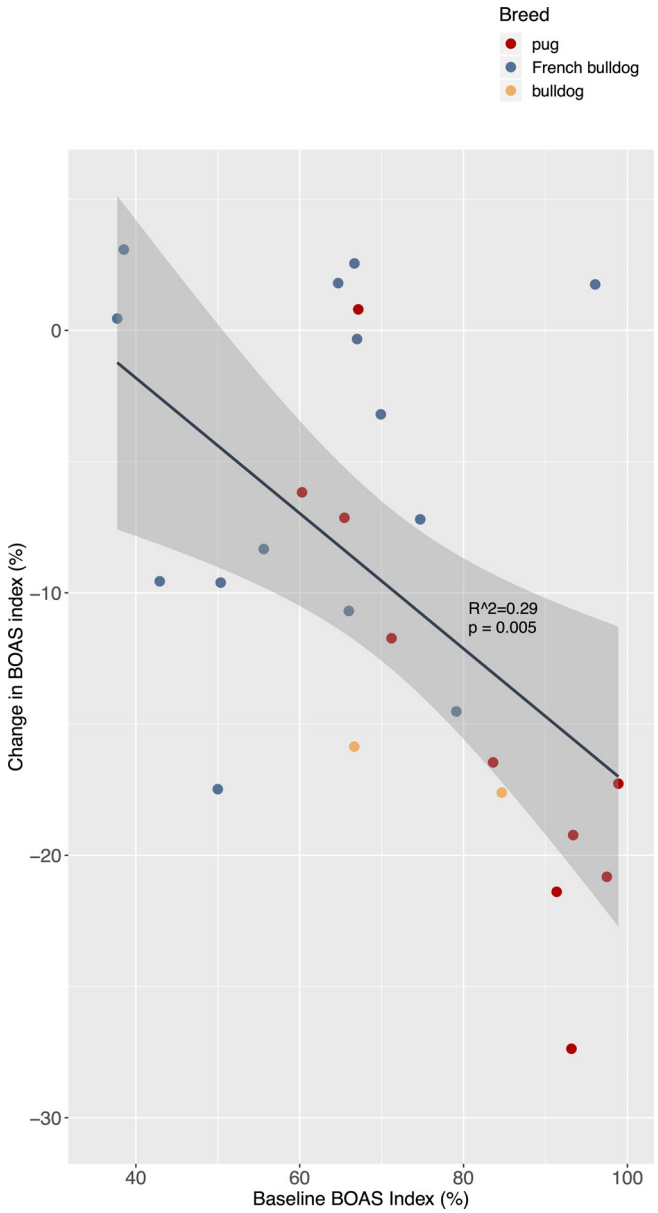

FIGURE 2 Scatterplot of the preoperative cohort illustrating baseline BOAS index plotted against change in BOAS index after epinephrine nebulization (postnebulization–baseline) with the fitted linear regression line (black) and 95% CI (gray shadow). BOAS, brachycephalic obstructive airway syndrome

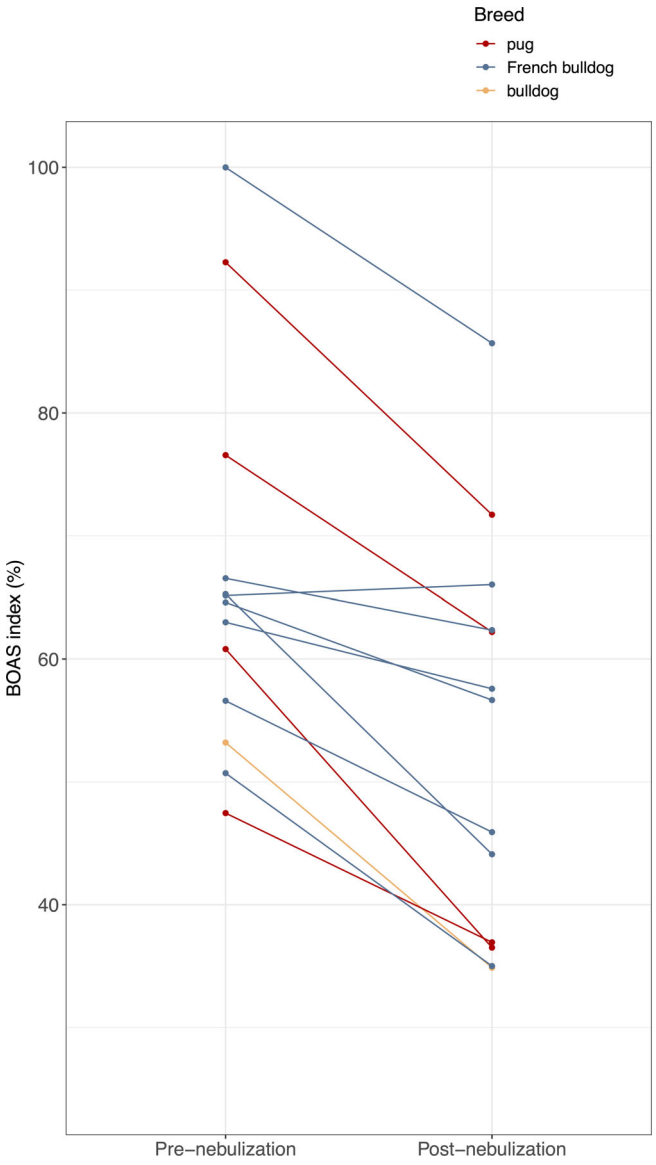

FIGURE 3 Line graph of the postoperative cohort plotting paired prenebulization and postnebulization BOAS indices. BOAS, brachycephalic obstructive airway syndrome

Neither pallor nor tremors were noted in any of the dogs. Three dogs were excluded from ECG monitoring because it was not tolerated; however, arrhythmias were not observed in any of the remaining 23 dogs (Table 3). Evidence of nausea was detected in four dogs; three dogs regurgitated, and lip smacking was noted in one dog. Three of these four dogs had a history of regurgitation that was attributed to BOAS. No noted side effects required intervention or cessation of nebulization.

3.3 | Postoperative cohort

Thirteen dogs from the preoperative cohort were enrolled in the postoperative cohort. The other thirteen dogs were excluded because the authors were unavailable to collect the data or clinical status, precluding the dog from leaving the intensive care unit. The postoperative cohort comprised four pugs, eight French bulldogs, and one English bulldog. All dogs underwent bilateral tonsillectomy, folding flap palatoplasty, vestibuloplasty (alar fold resection), and rhinoplasty (Trader technique; Table 2). All but one dog had laryngeal surgery (bilateral sacculectomy and/or bilateral partial cuneiformectomy and/or granuloma resection). The median BOAS index

within 24 hours after surgery was 65% (IQR, 10%). The median reduction in BOAS index (prenebulization) after surgery compared with the baseline BOAS index prior to surgery was 2.4% (IQR, 36%), although five dogs had an increased BOAS index. Within the postoperative cohort, the median reduction in BOAS index after nebulization was 14.3% (95% CI, 8%–17.5%, $P < .001$; Figure 3). All dogs received the following medications during surgery or within 24-hours postoperatively: metoclopramide (1-2 mg/kg/day IV delivered as a continuous rate infusion), omeprazole (1 mg/kg IV once daily), maropitant (1 mg/kg IV once daily), dexamethasone (0.2 mg/kg IV once daily), and paracetamol (10 mg/kg IV twice daily). Two dogs required additional antibiotics because of previous aspiration pneumonia, three dogs required additional pain relief (buprenorphine, 0.02 mg/kg IV), and four dogs required sedation. The single French bulldog that required no laryngeal surgery was the only dog that did not have a reduction in BOAS index after nebulization (change in BOAS index = 0.9%).

4 | DISCUSSION

Perioperative management of dogs with severe BOAS can be challenging because of the potentially life-threatening respiratory complications that can occur. Our results provide evidence that nebulized epinephrine reduces airway obstruction in severely affected dogs with BOAS preoperatively and in most dogs with BOAS postoperatively. Recorded side effects of this technique were minimal.

In the preoperative cohort, a clinically significant reduction in BOAS index in response to nebulized epinephrine was seen only in dogs with a baseline BOAS index >70%; a clinically significant improvement was seen in pugs compared with French bulldogs. The most marked reduction in BOAS index was documented when these two variables were combined (ie, in pugs with a baseline BOAS index >70%). In human medicine, nebulized epinephrine has been reported to be effective only in cases of moderate to severe croup rather than mild croup, and our findings mimic this observation.[8-11] We hypothesize that mucosal edema may be more severe in dogs with a higher BOAS index and, thus, the improvement produced by nebulized epinephrine is more marked and consistent. The previously discussed case report[2] described the effectiveness of nebulized epinephrine in a pug, and our findings add further weight to the argument that this treatment may be particularly effective in this breed. Because pugs have a smaller glottic height and width compared with French bulldogs,[26] it may be that mucosal edema causes a proportionally larger reduction in glottic size. Reducing mucosal edema would therefore cause a proportionally larger increase in the glottic opening in pugs compared with French bulldogs, explaining the greater improvement observed in the breed. However, pugs also had a higher average baseline BOAS index and a higher proportion of dogs with grade 2 or grade 3 laryngeal collapse compared with French bulldogs. These issues of collinearity make it impossible to untangle (and indeed attribute separate significance to) these variables. Additional studies in which researchers examine the effect of mucosal edema on glottic size and the effect of laryngeal collapse on mucosal edema are warranted to investigate this. A larger sample including more pugs with lower BOAS indices and French bulldogs with higher BOAS indices would also help to investigate these variables separately. Other investigated variables, presented in Table 4, were also collinear with the baseline BOAS index, meaning their individual relevance could not be ascertained. From a clinical perspective, our findings provide evidence that nebulized epinephrine may assist in the emergency stabilization of dogs experiencing acute respiratory distress due to BOAS prior to surgical intervention. Our understanding that nebulized epinephrine may be more effective in pugs might also be used to direct treatment.

The clinically significant improvement of BOAS indices after epinephrine nebulization was much more consistent in the postoperative cohort than in the preoperative cohort. Mucosal swelling and edema may be more prevalent among the population of dogs as a consequence of surgical interventions, explaining the more consistent response. The only dog that did not require laryngeal surgery was the only dog that did not have a reduction in BOAS index after nebulization. This may be an indication that laryngeal edema is particularly responsive to nebulized epinephrine; however, additional studies are required to investigate this. Five of the 13 dogs included in the postoperative part of the study had higher baseline BOAS indices compared with their BOAS indices preoperatively. This likely reflects the fact that significant soft tissue swelling can occur after surgical manipulation, worsening upper respiratory tract obstruction. Epinephrine nebulization should therefore be considered immediately postoperatively when significant mucosal edema and upper airway obstruction are clinically suspected or observed.

No side effects requiring intervention were observed in any of the preoperative cohort. This supports the hypothesis that epinephrine nebulization is an intervention with minimal side effects, as has already been documented in the human literature.[10,12,16-17] The main side effect was nausea, which may have been induced by stress associated with nebulization or, alternatively, may have been a side effect of the epinephrine itself. Most

dogs that became nauseous were known to regurgitate previously, attributed to their BOAS; however, one dog that became nauseous had no history of regurgitation, so the side effect in this dog was likely directly related to nebulization. Although no specific interventions were required for these dogs, the fact that regurgitation is a risk factor for aspiration pneumonia development must be considered.[5] Furthermore, five dogs that were initially enrolled to the study had to be excluded because they became very stressed during nebulization. Stress is known to exacerbate upper respiratory tract obstruction in BOAS-affected dogs and should be avoided. The dogs that did not tolerate the nebulization all exhibited particularly excitable characteristics at clinical examination, so consideration should be given to not attempting nebulization in such dogs. The sample in this study was not large enough to detect rare but potentially life threatening adverse events, such as those reported in the human literature.[18] Rebound edema is one such event that may occur after prolonged or repetitive dosing of nebulized epinephrine[27]; however, a recent article highlighted the lack of any reported cases.[28] In the study reported here, neither prolonged nor repetitive dosing was investigated, so the effect of this on adverse events or efficacy was not ascertained. The only reported case of a life-threatening tachyarrhythmia in human medicine was experienced when doses higher than those described here were administered three times within 90 minutes.[18] Having taken into account the observed and potential side effects of epinephrine nebulization, the authors recommend that it not be used universally, repetitively, or in dogs with a history of frequent regurgitation. Rather, its use should be reserved for those dogs in which it is clinically indicated, well tolerated, and likely to have an appreciable effect, and it should be administered at sensible intervals.

This study has several limitations. Although power calculations supported the reliability of preoperative results, the overall sample was still small, and a larger cohort would be useful in confirming the findings, separating variables which were collinear in this study, further defining the risk of side effects, and assessing for rare but life-threatening complications. The postoperative variables such as surgical interventions and postoperative medications are reported descriptively to avoid reporting type II errors. This study did not compare the effect of nebulized epinephrine to nebulized saline; a double-blinded placebo study would be required to investigate this further. The ECG monitoring was performed by a general practitioner (P.H.F) rather than a specialist, which may have led to rare or mild abnormalities being missed. Hypertension is a potential side effect of nebulized epinephrine; however, blood pressure of the nebulized dogs was not monitored. Although studies in man have provided evidence that nebulized epinephrine is unlikely to cause hypertension, we cannot be sure that this is the case in dogs.[10,17] In the postoperative cohort, there was an unavoidable selection bias because dogs that were deemed less stable within 24 hours of surgery were excluded. Some dogs were also excluded when none of the authors were available to collect postoperative data within the specified timeframe, although this was likely to have a random rather than a biasing effect. Postoperative medications could not be standardized, and sedation was required in some dogs. This will have affected the comparison between preoperative and postoperative BOAS indices but should have had a minimal effect on paired postoperative data. The incidence of complications was not specifically assessed in the postoperative cohort because of the possibility that recent anesthesia and analgesia drug administration may confound the results. Finally, throughout the study, the dogs underwent WBBP immediately after nebulization. Therefore, the duration of action of nebulized epinephrine was not investigated; in the human literature, it has been reported as between 30 and 120 minutes.[10] Additional studies are warranted to determine whether this is similar for dogs because it may impact the frequency of dosing of nebulized epinephrine.

In conclusion the findings of this study provide evidence that nebulized epinephrine causes a clinically significant reduction in BOAS index in preoperative dogs with a BOAS index >70% and in dogs recovering from surgery. Reduction of mucosal edema in both of these groups is thought to explain these findings, although additional studies are required to support this.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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