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A New Trick for an Old Dog: L-Epinephrine Delivered Continuously in the Vapor Phase

OBJECTIVES: Inhaled L-epinephrine is a known treatment of severe croup and postextubation upper airway obstruction. L-epinephrine can be delivered continuously in the vapor phase, but the indications, safety, and efficacy of this novel practice have yet to be evaluated. Theoretical risks are tachycardia, hypertension, and dysrhythmias. The study objective was to describe patient characteristics and vital sign changes related to continuous vaporized L-epinephrine use in critically ill children with the hypothesis that it can be practically and safely administered to children with subglottic edema and lower airway obstruction.

DESIGN: Retrospective cohort study.

SETTING: PICU and cardiothoracic ICU in a tertiary academic children's hospital.

PATIENTS: Patients age 0–21 years treated with continuous vaporized L-epinephrine from 2013 to 2019.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Continuous vaporized L-epinephrine was administered 140 times to 129 subjects via a high-flow nasal oxygen device. The median age was 10.6 months (1.3; interquartile range, 4.8–17.1 mo). The most common indications were lower respiratory tract obstruction (45%), postextubation subglottic edema (31%), and croup (16%). Eighty-eight percent had no escalation of respiratory support within 24 hours of initiation of continuous vaporized L-epinephrine, 5% progressed to require endotracheal intubation, and 3% were reintubated within 24 hours of initiation of continuous vaporized L-epinephrine following an extubation attempt. After starting continuous vaporized L-epinephrine, 85% of subjects had a decrease in heart rate and 80% had a decrease in respiratory rate. Six subjects had an increase in heart rate, and eight had an increase in blood pressure of more than 20% from baseline. These subjects did not receive interventions specific to these vital sign changes, including discontinuation of continuous vaporized L-epinephrine.

CONCLUSIONS: Continuous vaporized L-epinephrine was safely administered to critically ill children with most subjects demonstrating a decrease in heart rate, blood pressure, and respiratory rate.

KEY WORDS: airway obstruction; bronchiolitis, viral; croup; drug delivery systems; epinephrine; nebulizers and vaporizers

Intermittent inhalation of nebulized epinephrine in racemic and laevo forms has been a known treatment for children with moderate-to-severe croup and postextubation upper airway obstruction for over 60 years (1–5). Inhaled nebulized epinephrine has also been shown to improve symptoms and respiratory mechanics in children with lower respiratory tract obstruction from infections (6–8), although the outcome benefits have been variable (9–11). The mechanism of its effect in postextubation subglottic edema and bronchiolitis seems likely to be its alpha-adrenergic effect of vasoconstriction to reduce

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mucosal edema in the subglottic region or bronchioles, thereby reducing airway resistance by increasing airway caliber (12).

The onset of action of inhaled nebulized epinephrine is rapid, but with typical intermittent administration, the effect is short-lived, often requiring multiple doses (2, 3, 13). Continuous administration of nebulized medication may be advantageous, but delivery through a nasal oxygen device is challenging due to deposition of medication at various points in the circuit (14, 15). Bhashyam et al (14) demonstrated medication losses in the cannula, nebulizer, connectors, heated tube, and liquid trap. Ari et al (15) showed that delivery was worse with higher flows and thought to be due to impactive losses. Kim et al (11) and Dailey et al (16) suggest improved delivery when administered with heliox. An alternative method of delivery was considered after Leung et al (17) demonstrated that continuous epinephrine could be more reliably delivered in the vapor phase—rather than in nebulized form—using the Vapotherm (Exeter, NH) heated high-flow nasal oxygen (HHFNO) device (Vapotherm). The authors demonstrated dose-dependent delivery of continuous vaporized L-epinephrine (CVE) with increasing flows in a range accepted as therapeutic and safe, and without thermal destabilization of the drug. The study was inspired, as stated by the study authors, by detailed observation in two subjects that demonstrated improved upper airway obstruction with CVE delivered via HHFNO of 20L/min. This improvement could not be sustained by HHFNO alone when the epinephrine was removed.

The safety and efficacy of repeated doses or continuous administration of inhaled epinephrine have not been evaluated (1, 18). Theoretical risks include tachycardia, hypertension, and dysrhythmias (19). Nonetheless, clinical observations after intermittent dosing of both L-epinephrine and the 11 times more potent racemic epinephrine usually record that as the patient's effort of breathing decreases, so does respiratory rate, and heart rates either decrease (20) or remain unchanged (18). Two case studies have reported ventricular tachycardia in children after administration of inhaled epinephrine, although there is no evidence of causality (21, 22). No studies to date have described the clinical use of L-epinephrine delivered in the vapor form.

We aim to provide our institution's experience with CVE delivered via the Vapotherm HHFNO device. Our

objective is to describe the patient characteristics, indications, and physiologic effects related to CVE administration in critically ill children. We hypothesize that CVE can be safely and practically administered to children with upper airway and lower respiratory tract obstruction.

MATERIALS AND METHODS

This study is a retrospective analysis of data previously collected for clinical use and was considered exempt from review by the Institutional Review Board, Children's Hospital Los Angeles (CHLA) Human Subjects Protection Program (CHLA-20-0079). As with many other drugs and techniques used in pediatric practice, including the administration of racemic epinephrine to children, the Vapotherm product is not labeled for the described use.

Setting and Subjects

CHLA is a large tertiary academic pediatric hospital with 391 inpatient beds, 106 of which are critical care beds. Critically ill children beyond the neonatal period receive care in a 24-bed PICU or a 24-bed cardiothoracic ICU (CTICU).

All patients 0–21 years old who were admitted to the CHLA PICU or CTICU and treated with CVE for at least 1 hour from 2013 to 2019 were included. Subjects were identified in the ICU's electronic medical record (EMR, Cerner, Kansas City, MO) by a pharmacist.

Medication Administration

CVE was delivered via HHFNO device in the identical fashion described by Leung et al (17). The Vapotherm HHFNO device was selected when CVE administration was anticipated. The standard preparation by the pharmacists at CHLA was 30 mg of L-epinephrine (1 mg/mL) diluted in a 1-L bag of sterile water (epinephrine 0.003%), which provided the humidification for the HHFNO device. This practice was established by one of the authors (CN) at CHLA, and it has been increasingly adopted as clinical management for upper and lower airway obstructions. Initiation and titration of CVE were at the discretion of the attending on service.

Data Collection and Variables

Patient characteristics were abstracted from the CHLA PICU Database (Microsoft SQL Server, Redmond,

WA). The CHLA PICU Database is maintained in real time by critical care physicians and data entry specialists and includes admission source and discharge disposition, *International Classification of Diseases*, 9th Edition diagnoses, procedures and interventions, ventilatory support and duration, physician notes, and mortality score data. Admission, discharge, transfer, radiology, microbiology, and laboratory data are electronically transferred from the hospital informatics system to the database. There are built-in methods of quality control for missing data elements, and accuracy of diagnoses is continuously updated by physicians. Medication data were abstracted from the EMR by a pharmacist. Provider notes were reviewed to identify the indication(s) for CVE and any adverse effects. Physiologic parameters were abstracted from monitor data (Philips HL7 feed [Amsterdam, the Netherlands], Microsoft SQL Server). Heart rate, respiratory rate, and oxygen saturation were captured every 30 seconds, and blood pressure and temperature were captured every hour. Vital signs were collected for the time period of 2 hours prior to CVE initiation through 6 hours after CVE initiation. Continuous monitor printouts of telemetry alarms were reviewed for evidence of dysrhythmias when available. Electrocardiography strips are routinely printed once per shift and when there is an abnormal rhythm.

RESULTS

Over the 7-year study period, CVE was administered 140 times to 129 unique subjects. Subject characteristics appear in **Table 1**. The median age was 10.6 months (interquartile range [IQR], 4.8–17.1 mo). The median ICU length of stay was 4.6 days.

Subjects received CVE via HHFNO device. All but two subjects received 30 mg of L-epinephrine (1 mg/mL) diluted in a 1-L bag of sterile water (epinephrine 0.003%). Two subjects had alternative preparations: one with half the standard dilution (epinephrine 0.0015%) and one with double the standard dilution (epinephrine 0.006%).

The most common indications were lower respiratory tract obstruction ($n = 63$, 45%), postextubation upper airway obstruction ($n = 43$, 31%), and croup ($n = 23$, 16%). Among the subjects who had postextubation upper airway obstruction, 49% had concomitant structural airway anomalies or were extubated

after airway surgery. The median duration of CVE was 24.2 hours (IQR, 14.4–42.2 hr).

Eighty-eight percent had no escalation of respiratory support within 24 hours of initiation of CVE, 4% progressed to heliox or noninvasive positive pressure, 5% progressed to intubation, and 3% were reintubated within 24 hours of initiation of CVE following an extubation attempt.

Subjects were treated with an average of two doses of inhaled racemic epinephrine prior to initiation of CVE (range 0–10). Eighty-six percent of the subjects with upper airway obstruction (croup or postextubation) were treated with systemic steroids in addition to CVE.

In the first 6 hours after initiation of CVE, 85% of subjects had a decrease in heart rate, 80% had a decrease in respiratory rate, 69% had a small increase in oxygen saturation, and 70% had a small decrease in blood pressure, as demonstrated in the locally weighted scatterplot smoothing curves in **Figure 1**. Among all subjects, there was a moderate decrease in median heart rate (–12.5% [IQR, –20.5 to –1.8]) and respiratory rate (–7.5% [IQR, –25.3 to 6.3]). There was a minor decrease in mean arterial blood pressure (–0.5% [IQR, –18.5 to 18.0]). There was no change in oxygen saturation (0% [IQR, 0.0–2.0]).

Due to the hypothetical risk of pathologically increased heart rate and blood pressure secondary to systemic absorption of epinephrine, we evaluated these vital signs in more detail. Six subjects (4%) had an increase in heart rate of more than 20% from baseline heart rate prior to CVE initiation. None of these subjects was given a fluid bolus in response to this tachycardia. Two of these subjects had fevers close to the time of their tachycardia. One of these subjects was escalated to heliox; the remaining five did not have any escalation of respiratory support. Eight subjects (6%) had an increase in blood pressure more than 20% from baseline. Only one was given an antihypertensive medication, and this patient was receiving frequent, as needed, doses of a calcium channel blocker prior to the initiation of CVE. Two of these subjects had concomitant administration of systemic steroids. Among these subjects, there was no evidence that CVE was discontinued due to vital sign changes.

One patient with congenital heart disease had a brief hemodynamically stable episode of ventricular tachycardia 12 hours after the initiation of CVE.

TABLE 1.
Characteristics of Subjects Treated With Continuous Vaporized L-Epinephrine

Characteristic	<i>n</i> = 140
Age, <i>n</i> (%)	
< 1 mo	2 (1)
1 to < 12 mo	77 (55)
12 to < 24 mo	38 (27)
24 mo to 6 yr	20 (14)
≥ 6 yr	3 (2)
Sex, <i>n</i> (%)	
Female	55 (39)
Location, <i>n</i> (%)	
PICU	126 (90)
Cardiothoracic ICU	14 (10)
ICU admission source, <i>n</i> (%)	
Emergency department	51 (36)
General care floor	45 (32)
Operating room	22 (16)
Outside hospital	21 (15)
Another ICU	1 (1)
ICU length of stay, median days (IQR)	4.6 (3.0–10.9)
Primary indication for CVE, <i>n</i> (%)	
Lower respiratory tract obstruction	63 (45)
Post-extubation	43 (31)
Croup	23 (16)
Anatomical anomaly	4 (3)
Postairway or facial surgery	4 (3)
Poor tone or neurologic compromise	1 (1)
Other	2 (1)
Duration of CVE, median hours (IQR)	24.2 (14.4–42.2)
Number of racemic epinephrine doses prior to starting CVE, mean doses (range)	2 (0–10)
Use of systemic steroids, <i>n</i> (%)	
None	62 (44)
One dose	14 (10)
24 hr	35 (25)
> 24 hr	29 (21)
Escalation of support within 24 hr, <i>n</i> (%)	
No escalation	123 (88)
Intubation or reintubation	11 (8)
Noninvasive positive-pressure ventilation	2 (1)
Heliox	4 (3)

CVE = continuous vaporized L-epinephrine, IQR = interquartile range.

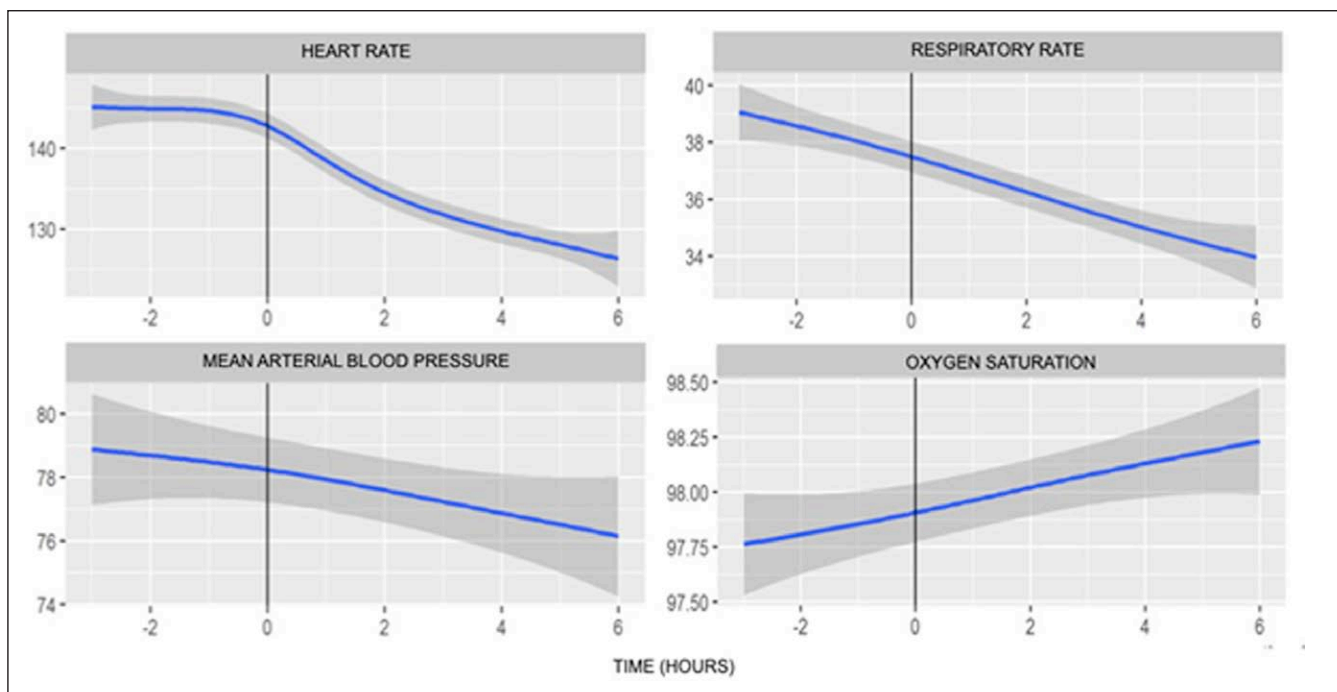


Figure 1. Locally weighted scatterplot smoothing curves showing vital sign changes 2 hr before and 6 hr after initiation of continuous vaporized L-epinephrine at time = 0. The *solid line* represents the mean, and the *shaded area* represents the 95% CI. N = 140 episodes of continuous vaporized L-epinephrine administration.

He had no further dysrhythmias after the discontinuation of the medication.

DISCUSSION

CVE was safely delivered 140 times to 129 unique subjects over a 7-year study period for the indications of lower respiratory tract obstruction, postextubation subglottic edema, and croup. The delivery method in this study is novel; we could not confirm a prior clinical report of L-epinephrine being delivered in the vapor phase. The Vaportherm HHFNO device is not yet approved for this use.

We did not observe an elevation in heart rate or blood pressure in the majority of the subjects; these vital signs remained steady or declined. This was true even for a patient who received CVE for 123 hours, the maximum duration in this cohort. This refutes the theoretical risks of tachycardia and hypertension due to systemic absorption, despite delivering an amount of epinephrine to the respiratory system that is considered therapeutic for cardiovascular effects when administered intravenously (approximately 0.03–0.04 $\mu\text{g}/\text{kg}/\text{min}$ based on air flow) (17).

Patients with bronchiolitis, postextubation subglottic edema, and croup had higher rates of concomitant

decrease in heart rate and respiratory rate than the other indications for use (postoperative, anatomical anomaly, and neurologic compromise). We propose that the observed decline in these vital signs is due to a significant improvement in the individual patient's effort of breathing, the effect of which outstrips the catecholaminergic effect of the medication. Prior work by Argent et al (23) has demonstrated that subjects with severe croup manifest a high pressure-rate product (peak-to-trough change in esophageal pressure with respiratory effort multiplied by the respiratory rate, a surrogate for increased effort of breathing) in order to maintain minute ventilation. In a sample patient from our cohort who had an esophageal manometer, the improvement in pressure-rate product (with a concomitant decline in heart and respiratory rates) after administration of CVE is demonstrated in **Figure 2**. The lesser benefit in patients with fixed obstruction or poor tone can be similarly anticipated.

It can be argued that high-flow conditions alone could provide enough continuous positive airway pressure to improve the pressure-rate product, as proposed by Klein and Reynolds (24). However, our group, while finding that HHFNO does decrease pressure-rate product, particularly in infants (25), the effect is not of the dramatic order seen by Argent et al (2).

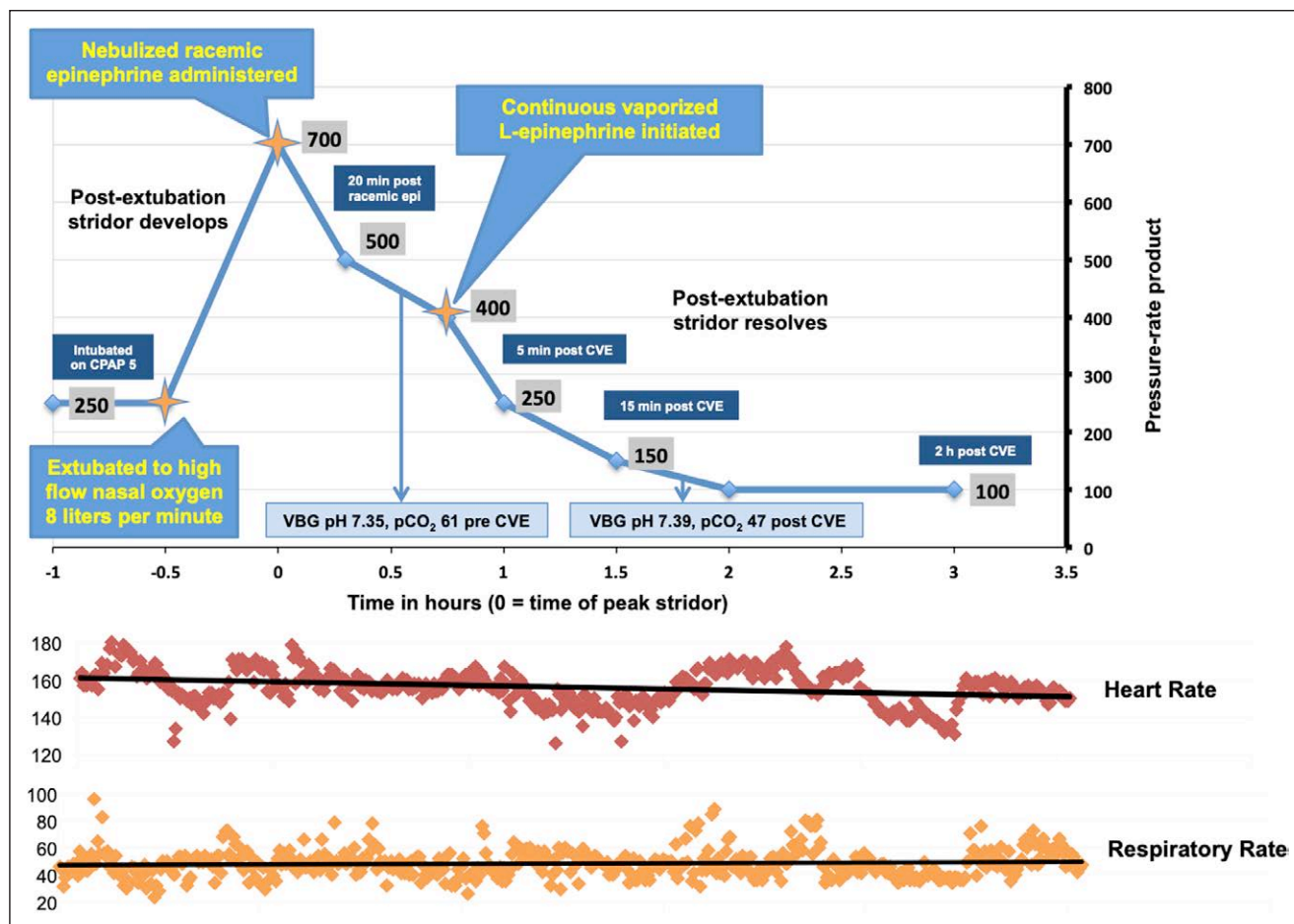


Figure 2. Postextubation stridor in a 6-mo-old patient: pressure-rate product (PRP) in response to treatment with continuous vaporized L-epinephrine. PRP is calculated as peak-to-trough change in esophageal pressure with respiratory effort multiplied by the respiratory rate. Esophageal pressure is used as a surrogate for pleural pressure. At a PRP of 700, patients are symptomatic of increased effort of breathing. At a PRP of 200, effort of breathing is minimal to absent and is considered normal. CPAP = continuous positive airway pressure, CVE = continuous vaporized L-epinephrine, VBG = central venous blood gas.

As noted earlier, Leung et al (17) reported in their article that HHFNO alone was not enough to overcome the effect of postextubation subglottic edema and required the addition of CVE, as also shown in the patient in Figure 2. At our institution, CVE is considered an escalation from HHFNO, and we anticipated that the cohort would represent a group of subjects at higher risk of decompensation. Nevertheless, the treatment failure rate in the cohort was 12%, similar to the rate of treatment failure with HHFNO alone (26).

Among the few subjects who had an increase in heart rate or blood pressure 20% above their baseline after administration of CVE, none of them required intervention or discontinuation of the medication related to these vital sign changes. The rate of escalation of respiratory support, including intubation, did not vary depending on vital sign response to CVE in this cohort.

After discontinuation of the CVE, eight subjects had epinephrine restarted; there was no identified pattern of vital sign changes among these patients. The average time to reinitiation of CVE among these subjects was 43 hours. This time period is long beyond the proposed duration of inhaled epinephrine's clinical effect (1–2 hr) and was, therefore, not considered to be consistent with a rebound stridor effect, as anticipated by other authors (27).

The findings of our study suggest that CVE may reduce subglottic airway edema and treat lower airway mucosal edema from viral bronchiolitis in a similar fashion to intermittent aerosolized epinephrine. From a patient care standpoint, the continuous delivery method offers multiple benefits. Nasal cannula devices are frequently tolerated by toddlers. Clinician time spent delivering inhaled medication doses can be reduced compared with hourly intermittent

administrations. The patient receives a consistent therapy rather than an episodic one.

There are important limitations to our study. We were limited by factors common to single-center reviews, including sample size and generalizability. Our sample size was large enough to show clear vital sign trends but may have been too small to detect rare complications of treatment with CVE. Although the indications for CVE were common pediatric problems like bronchiolitis and croup, these illnesses are often superimposed on chronic complex conditions in a tertiary-care children's hospital. Furthermore, nearly half the subjects who had postextubation upper airway obstruction had concomitant structural airway anomalies or were extubated after airway surgery. These features may not reflect the general pediatric population. In addition, our study was limited by its retrospective nature. We believe the reduction in heart rate and respiratory rate was due to improved effort of breathing, but this mechanism could not be fully elucidated in an observational study, and there is confounding due to prior administration of racemic epinephrine and systemic steroids in some subjects. Further, data were collected as part of clinical care, and concomitant therapies were administered per usual practice. Therefore, vital sign changes may have been influenced by other medications such as albuterol (which would have the effect of increasing heart and respiratory rates [28, 29]) or, in later years of the study period, dexmedetomidine, which could slow heart rate (30, 31).

There are several opportunities for future research based on this study. The initial dose of 30-mg L-epinephrine in 1 L of sterile water was empiric, and dose delivery varies with gas flow rates (17). CVE may be effective with lower epinephrine doses, and medication delivery may be augmented with heliox (15, 16, 32, 33). Dose-response and delivery optimization need to be evaluated, as well as randomized controlled trials comparing outcomes on HHFNO with CVE to HHFNO alone or with heliox as the carrier for L-epinephrine. Future studies should also investigate whether other medications can be administered continuously in the vaporized form.

CONCLUSIONS

CVE was safely administered to critically ill children with upper airway and lower airway obstruction with most subjects demonstrating a decrease in heart rate,

blood pressure, and respiratory rate, along with a mild improvement in arterial oxygen saturation.

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