



## Dexmedetomidine for patients with croup

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### ABSTRACT

Agitation exacerbates symptoms in patients with croup, but the reports on the therapeutic effects of sedation in these patients without intubation are scarce. We describe a typical case of croup wherein light sedation with dexmedetomidine was effective in treating and discuss how agitation exacerbates and sedation improves symptoms from the viewpoint of fluid dynamics theory in addition to the conventional explanation. The mechanism of dynamic airway collapse during inspiration in these patients supports the effectiveness of sedation with dexmedetomidine.

### 1. Introduction

In patients with croup, agitation exacerbates symptoms further; therefore, agitation in these patients should be prevented [1]. However, the reports on the therapeutic effects of sedation in these patients without intubation are scarce. This is probably because sedatives in children often cause respiratory impairment, such as hypoxia and apnea [2] as a result of central nervous system depression, airway obstruction, reduced respiratory effort, and respiratory muscle weakness. On the other hand, light sedation with dexmedetomidine without intubation often improves respiratory status in patients with croup. We describe a typical case of croup wherein dexmedetomidine was effective in treating and discuss how agitation exacerbates and sedation improves symptoms of croup.

### 2. Case presentation

A 5-month-old boy with no underlying disease developed cough and nasal discharge. The next day, stridor and a barking cough were noted; the patient was referred to the clinic, and croup was diagnosed. The airway obstruction was improved by the inhalation of racemic epinephrine, and the patient returned home. The symptoms worsened, however, and the patient visited emergency room on the same day. The Westley croup score [3] was 11 points, which was high; the patient received inhaled racemic epinephrine and intravenous dexamethasone and was then admitted to the pediatric intensive care unit (PICU). On admission, the patient was agitated, exhibiting obvious inspiratory

stridor and marked chest wall retractions. Light sedation was induced with continuous administration of dexmedetomidine without intubation, and soon afterward, the sound of stridor decreased, and the chest wall retraction and air entry were improved. Supplementary Videos 1 and 2 show the patient before and after dexmedetomidine administration. During a total of 22 hours of continuous dexmedetomidine administration, the patient received two additional intravenous doses of dexamethasone, and his symptoms improved. He was discharged from the PICU 38 hours after admission.

#### 2.1. Ethics

The patient's parents gave informed consent to the publication of the patient's videos, which was approved by our institutional ethics committee.

### 3. Discussion

#### 3.1. Physiology of airway obstruction in patients with croup

In patients with croup, airway resistance is increased during inspiration and expiration, and inspiratory and expiratory flow are reduced. In addition, tidal volume is reduced, and chest wall distortion is increased. Argent et al. [4] listed possible explanations for increased airway resistance:

1. A "critical orifice" or choke point effect occurs at the subglottis.

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2. Turbulence in the airway limits flow.
3. The extrathoracic airways narrow during inspiration, which adds to the resistance at the subglottis.

One difference between being agitated and being sedated is the degree of the patient's inspiratory effort. The inspiratory effort is greater during agitation than during sedation, and the driving pressure and inspiratory flow increase accordingly [5]. Tidal volume is usually larger during agitation than during sedation, but in patients with croup as in our patient, air entry is actually improved after sedation. To account for this paradoxical result, the patient with croup must have higher airway resistance in the agitated state than in the sedated state. In this respect, we discuss the mechanism of dynamic airway collapse during inspiration in agitated patients with croup from the viewpoint of fluid dynamics theory in addition to the conventional explanation.

### 3.2. Fluid dynamics theory

The continuity equation and the Bernoulli equation for steady frictionless incompressible flow imply the following:

$$Q = Au \quad (1)$$

$$p + \frac{1}{2}\rho u^2 + \rho gz = \text{constant} \quad (2)$$

where  $Q$  is flow ( $\text{m}^3/\text{s}$ ),  $A$  is a cross-sectional area ( $\text{m}^2$ ),  $u$  is the flow velocity at a point on a streamline ( $\text{m}/\text{s}$ ),  $p$  is the static pressure at a chosen point (Pa,  $\text{N}/\text{m}^2$ , or  $\text{kg}/\text{m}\cdot\text{s}^2$ ),  $\rho$  is the density of the fluid at all points in the fluid ( $\text{kg}/\text{m}^3$ ),  $g$  is the acceleration caused by gravity ( $\text{m}/\text{s}^2$ ), and  $z$  is the elevation of point above a reference plane (m).

When the effect of gravity is removed, the following equation is obtained:

$$p + \frac{1}{2}\rho u^2 = \text{constant} \quad (3)$$

where  $\frac{1}{2}\rho u^2$  represents dynamic pressure.

Equation (3) represents the law of conservation of fluid energy in units of pressure.

### 3.3. Effect of dexmedetomidine

We first describe the physiology of inspiration when the patient is agitated and then explain how it changes after the patient is sedated with dexmedetomidine.

#### 3.3.1. Agitated state

1. During agitation, the patient's inspiratory effort is strong.
2. As high airway resistance due to the obstruction in the subglottis, the lung cannot expand along with the pleural cavity. This creates a large discrepancy between increased volume of the pleural cavity and the lung, causing much lower intrathoracic (and thus intra-tracheal) pressures.
3. Lower intra-tracheal pressures causes collapse of the extrathoracic c-shaped trachea.
4. The local airflow velocity at the collapsed trachea becomes faster, according to Eq. (1).
5. At that time, the dynamic pressure at the collapsed trachea extends high, which means that static pressure decreases significantly, according to Eq. (3).
6. The negative pressure produced by the patient's inspiration effort combines with the static pressure drop created by the rapid flow velocity leads to further dynamic airway collapse locally, and it does not improve until inspiration stops.
7. Air entry is severely restricted.

#### 3.3.2. Sedated state

1. Sedation with dexmedetomidine reduces the patient's inspiratory effort.
2. Despite high airway resistance due to the obstruction in the subglottis, intrathoracic pressure does not become excessively negative.
3. The extrathoracic c-shaped trachea does not collapse.
4. The local airflow velocity does not change.
5. No further dynamic airway collapse occurs.
6. Air entry improves.

#### 3.4. Brief review of literature

Croup is a common disease that causes upper airway obstruction in infants and ranges in severity from rhinorrhea and barking cough to stridor, respiratory distress, and, in the most severe cases, airway obstruction that necessitates intubation [6,7]. Among every 100 children younger than 6 years, croup affects 1.5 to 6 [8–10]. The rate of hospitalization for croup has been reported to range from 1.3% to 6% among pediatric outpatients [6,10]. It has also been reported that 9% of hospitalized patients are admitted to the PICU, of whom 23%–35% require intubation [7]. The mainstay of treatment is oral or inhaled glucocorticoids. Racemic epinephrine and humidified air can also be useful adjuncts [9,11]. For purposes of respiratory function testing, light sedation without intubation has been performed in patients with croup and has been shown to cause no clinical deterioration [4,12]; however, the therapeutic effects of light sedation in these patients have rarely been reported.

Dexmedetomidine is a newer sedative drug that is a selective  $\alpha_2$  agonist and acts as a central agent in the brain and spinal cord [13]. One of the most important advantages of dexmedetomidine is its low potential for respiratory depression. It has little effect on the structure of the upper respiratory tract [14]. Therefore, dexmedetomidine is preferred over other sedatives in patients at high risk of upper airway obstruction, such as those with a history of obstructive sleep apnea [13, 14]. For these reasons, we believe that dexmedetomidine is the safest and most suitable sedative for patients with croup. However, we do not recommend the use of sedatives for these patients when the patients are not properly monitored. While reduction of respiratory drive with sedation may reduce the effort generated by the patient and prevent further dynamic airway collapse, it will not actually improve the subglottic airway obstruction itself, and potentially could contribute to underestimation of the severity of airway obstruction in these patients. The clinicians have to be aware that while sedation may appear to make the patient "better", they may have to be vigilant that symptoms have been reduced without improving subglottic obstruction.

We have discussed respiratory physiologies in agitation and in sedation. Although this mechanism of dynamic airway collapse in patients with croup are conceptual and unproven, it is known that rapid airflow velocities lead to additional dynamic airway narrowing in other situations. For example, among patients with chronic obstructive pulmonary disease (COPD), the tracheas of nearly half of them collapsed during exhalation, which was confirmed by dynamic airway computed tomographic imaging and bronchoscopy [15,16]. Fluid dynamics theory revealed that positive pressure formed by hyperinflated lungs compressing the tracheal wall and negative changes in intratracheal static pressure due to rapid expiratory flow velocity on expiration leads to tracheal collapse in COPD patients [17,18]. Yuan et al. [19] also reported that patients with severe COPD have decreased forced vital capacity, in comparison with slow vital capacity. This paradoxical result is also well explained by the assumption that dynamic airway collapse is caused by rapid airflow velocity. For another example, in patients with tracheomalacia, tracheal stenosis becomes often more severe as respiratory effort increases; these patients rarely exhibit respiratory disturbances during calm spontaneous breathing, but severe cyanotic attacks develop during crying or coughing [20]. This can also be explained by a

similar mechanism.

Dynamic airway narrowing is assumed to occur in the extrathoracic airways during inspiration in patients with croup and in the intrathoracic airways during expiration in patients with COPD. In both cases, rapid airflow through the narrowed airways reduces local static pressures, leading to further airway narrowing. On the other hand, further airway collapse may not occur in patients with croup during the expiratory phase of crying. This is because they are exhaling against a relatively closed glottis, which will result in positive pressures within the subglottic airways. In patients with croup who are not intubated, it is theoretically difficult to measure subglottic central airway pressure during expiration, but intrathoracic pressure has been shown to exceed 20 cmH<sub>2</sub>O [4].

After intubation in patients with severe croup, differences in the outer and inner diameters of the endotracheal tube may narrow the airway; nonetheless, air entry improves. This is explained by the rigid structure of the endotracheal tube, which prevents further dynamic airway collapse even when dynamic pressure in the tube increases.

#### 4. Conclusion

In agitated patients with croup, the mechanism of dynamic airway collapse which further deteriorates their respiratory condition is explained from the viewpoint of fluid dynamics theory in addition to the conventional explanation. This mechanism supports the effectiveness of sedation with dexmedetomidine in these patients. Further studies are needed to determine whether the use of dexmedetomidine in patients with croup improves outcomes, such as reducing the proportion of patients who require intubation.

#### Author contributions

Norihiko Tsuboi: conceptualization, data curation, formal analysis, writing (original draft).

Tadashi Oi: conceptualization, supervision.

Kaoru Tsuboi: conceptualization, supervision, writing (review and editing).

Naoki Ebihara: conceptualization, supervision.

Satoshi Nakagawa: supervision, writing (review and editing).

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#### Declarations of competing interest

None.

#### Appendix A. Supplementary data

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