The effects of flow settings during high-flow nasal cannula oxygen therapy for neonates and young children

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Tailoring flow settings based on individual factors like peak inspiratory flow, respiratory rate, work of breathing and clinical status helps to optimise high-flow nasal cannula treatment for paediatric patients https://bit.ly/3UcXuta

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Abstract

Background During neonatal and paediatric high-flow nasal cannula therapy, optimising the flow setting is crucial for favourable physiological and clinical outcomes. However, considerable variability exists in clinical practice regarding initial flows and subsequent adjustments for these patients. Our review aimed to summarise the impact of various flows during high-flow nasal cannula treatment in neonates and children.

Methods Two investigators independently searched PubMed, Embase, Web of Science, Scopus and Cochrane for *in vitro* and *in vivo* studies published in English before 30 April 2023. Studies enrolling adults (⩾18 years) or those using a single flow setting were excluded. Data extraction and risk of bias assessments were performed independently by two investigators. The study protocol was prospectively registered with PROSPERO (CRD42022345419).

Results 38 406 studies were identified, with 44 included. *In vitro* studies explored flow settings' effects on airway pressures, humidity and carbon dioxide clearance; all were flow-dependent. Observational clinical studies consistently reported that higher flows led to increased pharyngeal pressure and potentially increased intrathoracic airway pressure (especially among neonates), improved oxygenation, and reduced respiratory rate and work of breathing up to a certain threshold. Three randomised controlled trials found no significant differences in treatment failure among different flow settings. Flow impacts exhibited significant heterogeneity among different patients.

Conclusion Individualising flow settings in neonates and young children requires consideration of the patient's peak inspiratory flow, respiratory rate, heart rate, tolerance, work of breathing and lung aeration for optimal care.

Introduction

Noninvasive respiratory support, including nasal continuous positive airway pressure (CPAP), high-flow nasal cannula (HFNC) and noninvasive ventilation (NIV), are commonly used in paediatrics to reduce the need for intubation or the risk of reintubation after liberation from invasive mechanical ventilation [1–3]. Among these treatments, HFNC provides high-flow gas mixtures heated to near-body temperature and

humidified to levels exceeding 99% relative humidity, which offers several potential advantages over nasal CPAP and NIV, including ease of installation and setup, greater patient tolerance and a lower risk of nasal tissue injury [4]. HFNC is particularly beneficial for preterm neonates with respiratory distress due to immature lung development or other aetiologies, as well as infants with bronchiolitis or other respiratory diseases [4, 5]. The selection of flow settings for HFNC therapy has been evaluated in numerous studies because it can improve upper airway flow dynamics, affect the positive end-expiratory pressure (PEEP) (*i.e.* increase functional residual capacity (FRC)), improve oxygenation, increase dead space washout, augment minute ventilation and reduce work of breathing (WOB) [6–9]. However, the optimal flow setting for HFNC in children remains unclear. Thus, we conducted a review aiming to investigate the physiological and clinical effects of various flow settings during HFNC treatment in paediatric patients.

Literature search strategy and results

The literature search was conducted independently by two authors (CY and PL) in six electronic databases, CINAHL, Cochrane Library, Embase, PubMed, Scopus and Web of Science, using the following keywords: ("high-flow nasal cannul*" OR "high flow cannul*" OR "high flow oxygen therapy" OR "high flow oxygen" OR "high flow therapy" OR "HFNC" OR "nasal high flow" OR "NHF") AND ("flow") AND ("child" OR "children" OR "pediatric" OR "infants" OR "newborn" OR "neonates" OR "adolescents" OR "youth" OR "teenagers"). The search was limited to papers published in English before 30 April 2023. Original studies investigating more than one HFNC flow setting were included. Studies that only included adult (⩾18 years of age) subjects or used only one flow setting during HFNC treatment and review articles, letters, abstracts and editorials were excluded. Study titles and abstracts were initially screened, and full texts were subsequently reviewed to select eligible studies. The review protocol was registered *a priori* with PROSPERO (registration number: CRD42022345419). Two authors (CY and PL) independently assessed the quality of included studies using the Cochrane Collaboration risk of bias tool 2.0 (RoB2) [10] for randomised controlled trials (RCTs) and the Newcastle–Ottawa Scale [11] for nonrandomised trials. Any disagreements regarding study selection, data extraction or quality assessments were resolved through consensus discussions with a third author (WH).

A total of 38 406 studies were identified and 37 851 studies were excluded after screening by titles and abstracts (figure 1). After assessing the eligibility of 555 full-text studies, 505 studies were excluded for using a single flow setting, four for investigating the effects of different flows on aerosol delivery and two because they were animal studies. Consequently, 44 studies were included: 15 were *in vitro* studies [12–26], two combined *in vitro* and *in vivo* studies were conducted on neonates [27, 28] and 27 were clinical studies [6–8, 29–52]. In the clinical studies (supplementary table S1), 14 were conducted on neonates [29–41, 51] including preterm infants with [29, 31, 34, 35, 37, 38, 51] or without [30, 32, 33, 36, 39–41] lung disease, while 13 focused on paediatric patients with bronchiolitis [6–8, 44, 46–48, 50, 52] or requiring HFNC for various reasons [42, 43, 45, 49], with most the patients younger than 2 years. Four of these studies were RCTs [48–51], and ten were randomised crossover studies [31, 33, 34, 37, 39–41, 43, 45, 46].

Of the 14 randomised trials, all had a low risk of missing outcome data and selection bias in reported results, 13 showed a low risk of deviation from the intended intervention, and three exhibited a low risk in the randomisation process. All RCTs had a clear description of random sequence generation, but only two explained the study allocation concealment. All the randomised crossover trials demonstrated a low risk of bias arising from period and carryover effects. Blinding of participants and/or the treating clinicians was conducted in only one study (supplementary figure S1). Among the 13 nonrandomised trials, 12 were of good quality and one had poor quality in comparability on the most important factors and other risk factors (supplementary table S2).

Peak tidal inspiratory flow for neonates and children younger than 2 years

HFNC delivers gas mixtures at flows that match or exceed a patient's peak tidal inspiratory flow (PTIF), thus it is crucial to understand a patient's inspiratory flow demand to provide appropriate flow. Available evidence [44, 53–55] suggests that PTIF varies across different ages and diseases among neonates and children younger than 2 years (supplementary table S3). The PTIF indexed to body weight declines as subjects grow.

The effects of flow settings: *in vitro* findings

In vitro studies investigated the effects of different flow settings on several variables, including PEEP [13–18, 20, 23, 24, 26–28], humidity and condensation [19, 22, 25, 26], carbon dioxide (CO_2) clearance [21, 23], tidal volume (V_T) [17, 24], delivered inspiratory oxygen fraction (F_{IO_2}) [25] and noise level [12].

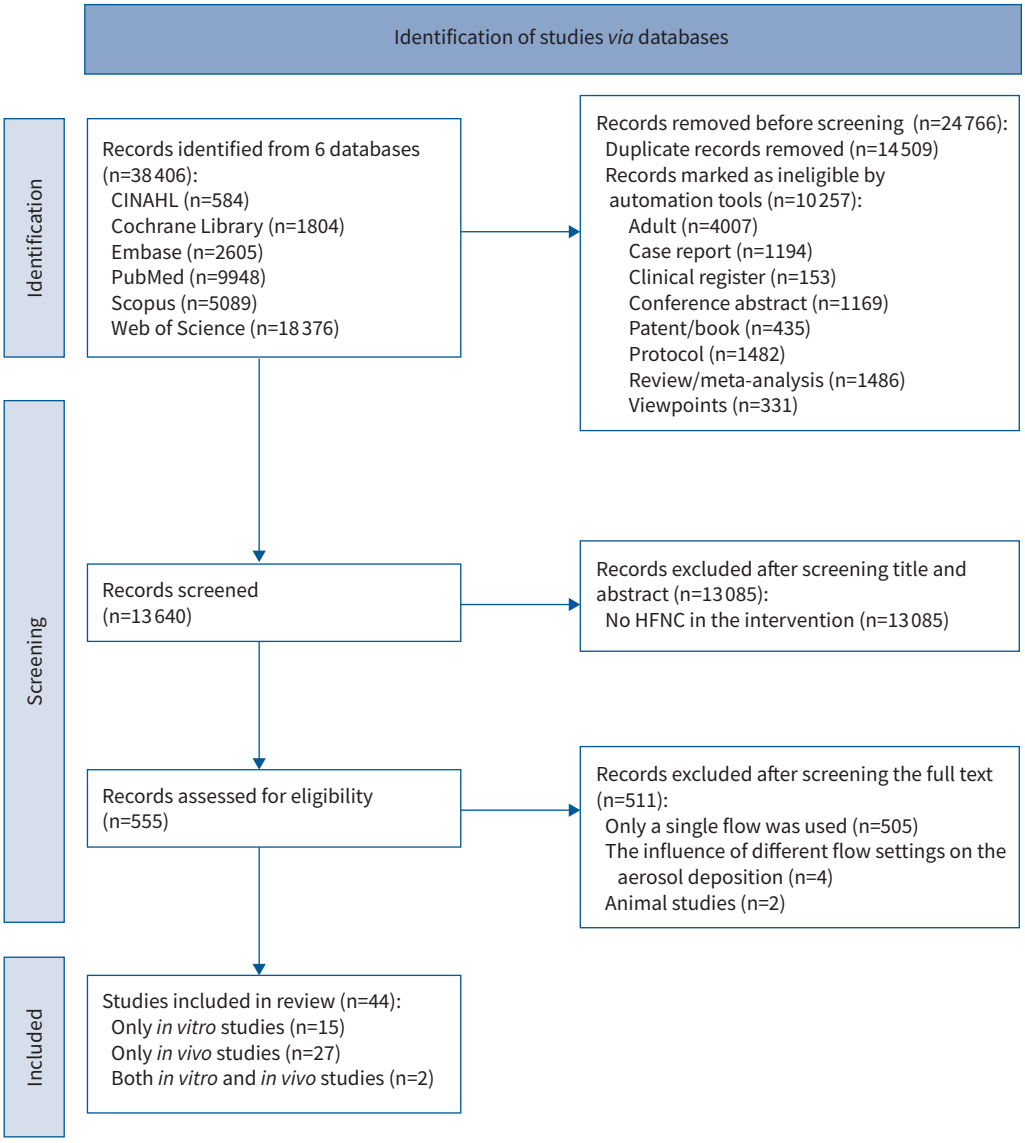

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. HFNC: high-flow nasal cannula.

PEEP

Studies consistently reported that PEEP increased as flow increased [13–18, 20, 23, 24, 26–28]. Several other factors, including HFNC devices [14, 23, 28], prong-to-nares ratio [13, 14, 16, 20, 28], mouth status [15, 16, 20, 23, 27] and gas types [24], have been found to affect the level of PEEP.

Nielsen *et al.* [23] conducted a study using simulated three-dimensional paediatric anatomic airway models of preterm neonates, term neonates, toddlers and small children. They compared PEEP levels at different flows using the Optiflow (Fisher & Paykel Healthcare) and Precision Flow (Vapotherm Inc.) HFNC systems. They observed change points in the flow in all models except for the open-mouth preterm model. Change points were defined as the flow where the PEEP increment started to decrease, meaning the PEEP increment with flow beyond the change point was smaller compared to flows below the change point. The change points varied across different models, with a change point of 4 $L \cdot min^{-1}$ in the preterm and term neonates, and 10 $L \cdot min^{-1}$ in the toddler and small child with mouth closed.

In paediatric patients, the HFNC devices manufactured by Fisher & Paykel and Vapotherm are commonly used. Three studies [14, 23, 28] compared the PEEP levels generated by these two devices. When the

nasal cannula size was used according to the manufacturer's instructions, with a minimum prong-to-nares ratio of 1:1.25, both devices produced minimal and similar PEEP levels at low gas flows. This similarity was observed when the flow was below the change point in the models of Nielsen *et al.* [23], $\leqslant$6 L·min^{-1} in the neonatal model of Hasan *et al.* [14], and $\leqslant$4 L·min^{-1} in the infant model of Kubicka *et al.* [28]. However, at higher set flows, the Vapotherm device generated higher PEEP levels than the Fisher & Paykel device [14, 23], probably due to the pressure relief feature by the latter device.

Notably, PEEP is affected by several factors beyond flow. PEEP increased as the prong-to-nares ratio decreased [13, 14, 16, 20, 28], while PEEP decreased significantly when the mouth was open [15, 16, 20, 23, 27]. Moreover, using helium-oxygen (a gas mixture lighter than air) during HFNC treatment resulted in lower PEEP levels compared to air [24].

CO_2 clearance

CO_2 clearance increased as flow increased with the mouth closed [21, 23]. However, during open-mouth breathing, expiratory CO_2 significantly decreased at minimally tested flows (*e.g.* 3 L·min^{-1} in the preterm neonate model and 8 L·min^{-1} in the toddler model) compared to baseline, then remained near constant as the HFNC flow increased. There was no significant difference in expiratory CO_2 clearance between the Vapotherm and Fisher & Paykel devices across all testing conditions [23]. When the prong was half inserted into the nares, CO_2 washout time was longer with the mouth closed but similar with the mouth open, compared to the fully inserted condition [21].

Humidity and condensation

When the study models and HFNC circuits were placed inside an incubator, absolute humidity remained stable across various flows. Conversely, absolute humidity and condensate volume increased with flow when the circuits were placed in ambient air, regardless of V_T [25].

V_T, F_{IO_2} and noise level

Moore *et al.* [24] found that, as flow was increased from 1 to 2 L·kg^{-1}·min^{-1}, V_T tended to decrease when air was used during HFNC treatment, but the change was minimal when helium-oxygen was used. As flow increased, the measured F_{IO_2} approached the set F_{IO_2} more closely [25]. König *et al.* [12] reported that noise levels increased as the HFNC flow increased from 4 to 8 L·min^{-1}, and that noise levels were higher with the Vapotherm device compared to the Fisher & Paykel device.

The effects of different flow settings in neonates

Oxygenation and ventilation

The effects of different flow settings on oxygenation were evaluated in five studies involving preterm infants. Regardless of the HFNC device used in the studies, the oxygen saturation measured by pulse oximetry (S_{pO_2})/F_{IO_2} ratio and S_{pO_2} showed improvement as the flow increased (figure 2a and supplementary table S4) [27, 33, 34, 39, 40]. Notably, the S_{pO_2}/F_{IO_2} ratio has been shown in children to predict NIV failure [56, 57].

Two studies reported no significant changes of V_T with different flows [31, 33]. However, Liew *et al.* [33] reported a significant reduction in respiratory rate (figure 2b) and minute ventilation (supplementary table S5) when the mean flow was increased from 1.4 to 2.1 L·kg^{-1}·min^{-1}. These values remained stable thereafter. Additionally, there were no observable changes in transcutaneous CO_2 measurements with different flows. In contrast, Lavizzari *et al.* [34] reported increased V_T and minute ventilation, along with a reduction in respiratory rate, when the flow was increased from 2–4 to 4–6 L·min^{-1} using Vapotherm for preterm infants with mild to moderate respiratory distress syndrome and an average birth weight of 1.5 kg. However, no changes were observed in transcutaneous CO_2 measurements. It is important to note that, in these studies, respiratory rate either increased or remained stable when flow exceeded 4 L·kg^{-1}·min^{-1} [27, 33, 39]. Furthermore, in the same studies, an increase in heart rate was observed (figure 2c), which could potentially indicate patient discomfort at such high flow settings [27, 33].

Airway pressure

Multiple studies [2, 27–31, 33, 34, 36, 40, 41] have investigated the relationship between flows and airway pressure measured at various locations, including the oral cavity [28], thoracic oesophagus [2, 27, 31, 40] and pharynx [29, 30, 33, 34, 36, 40, 41] (figure 2d). Additionally, different HFNC devices were used across studies. Comparing the Fisher & Paykel to the Vapotherm device, two studies found no significant differences in pharyngeal pressure [41] or oral cavity pressure [28]. Additionally, Liew *et al.* [33] reported that nasopharyngeal pressure during open-mouth breathing was approximately two thirds of that observed during closed-mouth breathing across various flows. They also found only mild differences in intratracheal pressure between <0.7 and >0.7 prong-to-nares sizes.

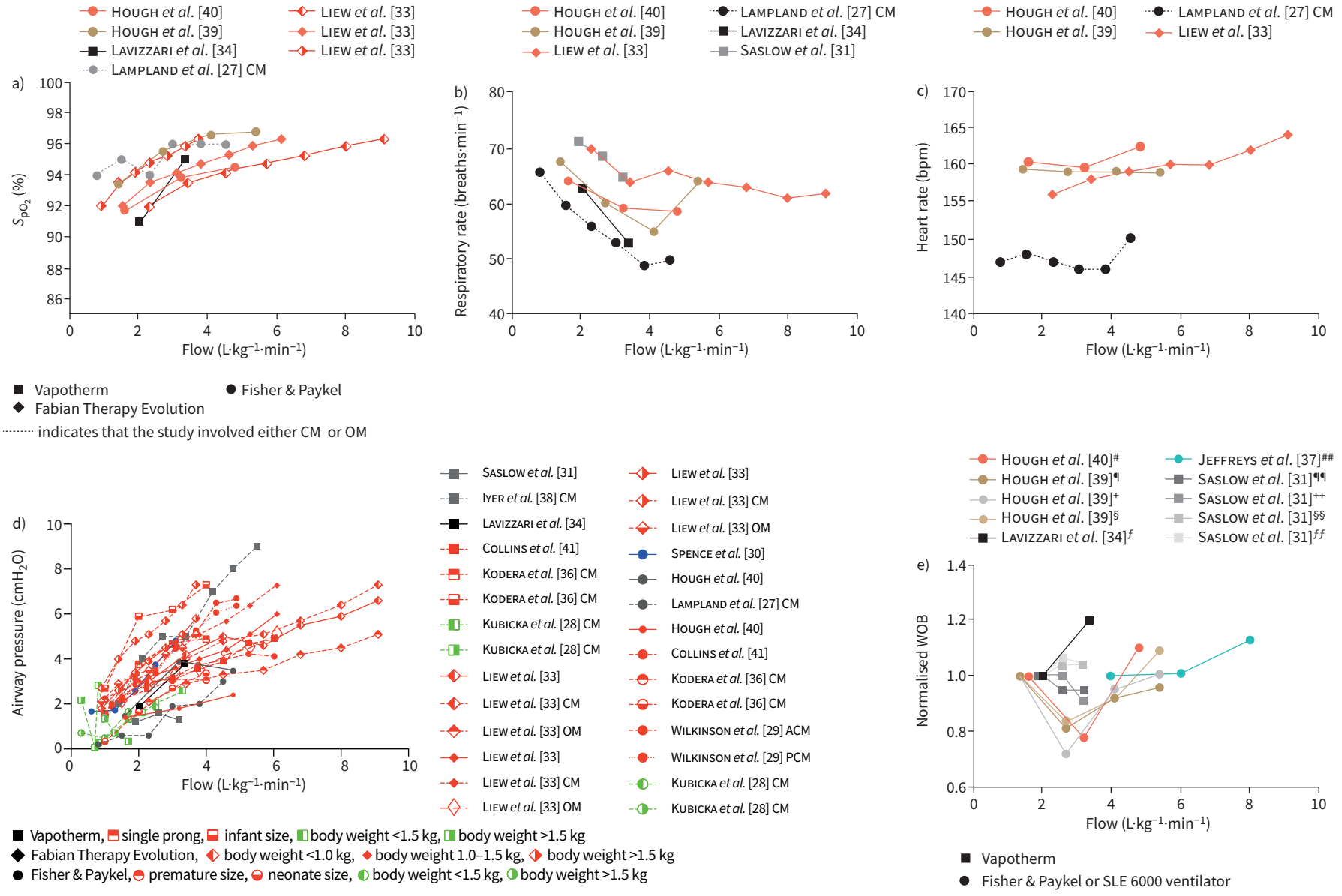
Hough et al. [40]
Hough et al. [39]
Lavizzari et al. [34]
Lampland et al. [27] CM
Liew et al. [33]
Liew et al. [33]
Liew et al. [33]
a)
S_{pO_2} (%)
Flow (L·kg⁻¹·min⁻¹)
Hough et al. [40]
Hough et al. [39]
Liew et al. [33]
Lampland et al. [27] CM
Lavizzari et al. [34]
Saslow et al. [31]
b)
Respiratory rate (breaths·min⁻¹)
Flow (L·kg⁻¹·min⁻¹)
Hough et al. [40]
Hough et al. [39]
Lampland et al. [27] CM
Liew et al. [33]
c)
Heart rate (bpm)
Flow (L·kg⁻¹·min⁻¹)
Vapotherm
Fisher & Paykel
Fabian Therapy Evolution
indicates that the study involved either CM or OM
d)
Airway pressure (cmH2O)
Flow (L·kg⁻¹·min⁻¹)
Saslow et al. [31]
Iyer et al. [38] CM
Lavizzari et al. [34]
Collins et al. [41]
Kodera et al. [36] CM
Kodera et al. [36] CM
Kubicka et al. [28] CM
Kubicka et al. [28] CM
Liew et al. [33]
Liew et al. [33] CM
Liew et al. [33] OM
Liew et al. [33]
Liew et al. [33] CM
Liew et al. [33] OM
Liew et al. [33]
Liew et al. [33] CM
Liew et al. [33] OM
Spence et al. [30]
Hough et al. [40]
Lampland et al. [27] CM
Hough et al. [40]
Collins et al. [41]
Kodera et al. [36] CM
Kodera et al. [36] CM
Wilkinson et al. [29] ACM
Wilkinson et al. [29] PCM
Kubicka et al. [28] CM
Kubicka et al. [28] CM
Vapotherm, single prong, infant size, body weight <1.5 kg, body weight >1.5 kg
Fabian Therapy Evolution, body weight <1.0 kg, body weight 1.0–1.5 kg, body weight >1.5 kg
Fisher & Paykel, premature size, neonate size, body weight <1.5 kg, body weight >1.5 kg
Oral cavity pressure
Oesophageal pressure
Nasopharyngeal pressure
Intrapharyngeal pressure
Retropharyngeal pressure
indicates that the study involved either CM or OM status, empty shapes indicate OM status, and solid shapes indicate CM status
Hough et al. [40]#
Hough et al. [39]¶
Hough et al. [39]+
Hough et al. [39]§
Lavizzari et al. [34]ƒ
Jeffreys et al. [37]##
Saslow et al. [31]¶¶
Saslow et al. [31]++
Saslow et al. [31]§§
Saslow et al. [31]ƒƒ
e)
Normalised WOB
Flow (L·kg⁻¹·min⁻¹)
Vapotherm
Fisher & Paykel or SLE 6000 ventilator

FIGURE 2 The association between flow settings and recorded outcomes in neonates. a) Oxygen saturation measured by pulse oximetry (S_{pO_2}). b) Respiratory rate. c) Heart rate. d) Airway pressure measured at various locations, using different high-flow nasal cannula (HFNC) devices with different breathing patterns (mouth open *versus* closed). For a–d, all data are presented as mean/median. ACM: active closed mouth; CM: closed mouth; OM: open mouth; PCM: passive closed mouth. e) Work of breathing (WOB) presented in various variables. All the WOB variables are normalised using the WOB at the lowest flows in each study. WOB was reflected by the following. [#]: pressure rate product; [¶]: root mean square (RMS) of the electromyogram (EMG) signal from the entire muscle groups reflected in respiration; [+]: RMS of the EMG signal from posterior diaphragm; [§]: RMS of the EMG signal from the intercostal muscles; [ƒ]: pressure-time product; [##]: EMG of the diaphragm amplitude; [¶¶]: inspiratory WOB; [++]: elastic WOB; [§§]: RWOB; and [ƒƒ]: phase angle.

Regardless of the devices used, the patient's mouth status [29, 33] and the locations where pressure measurements were taken, airway pressure consistently increased proportionally to the flow in a near-linear relationship [2, 27–31, 33, 34, 36, 40, 41]. Notably, at high flow settings, airway pressure measurements could become very high. For instance, during closed-mouth breathing, Iyer *et al.* [38] reported end-expiratory oesophageal pressure as high as 9 cmH_2O (interquartile range (IQR) 6–15 cmH_2O) at a mean flow of 5.5 $L \cdot kg^{-1} \cdot min^{-1}$ in preterm infants using Vapotherm. Such elevated oesophageal pressure raises concerns about the potential for lung injury, necessitating careful evaluation of the benefits *versus* harms if flows of that magnitude are used clinically [58]. A single study measured ventilation distribution and end-expiratory levels using electrical impedance tomography (supplementary table S6). This study found no significant differences in these measurements with flows of 2, 4 and 6 $L \cdot min^{-1}$. The lack of significant differences may be attributed to the relatively low oesophageal pressures generated by the three flows, with the highest mean oesophageal pressure reported as 3.9 cmH_2O [40].

Work of breathing

Hough *et al.* [39, 40] conducted studies using various measurement tools to assess WOB (figure 2e). In one study [40], WOB was assessed using the pressure rate product (PRP) obtained through an oesophageal catheter under three tested flow conditions (2, 4 and 6 $L \cdot min^{-1}$), with the lowest PRP noted when flow was set at 4 $L \cdot min^{-1}$. The corresponding flows per kilogram, calculated based on the mean weight of the included patients, were 1.6, 3.2 and 4.8 $L \cdot kg^{-1} \cdot min^{-1}$, respectively. Another study by Hough *et al.* [39] employed respiratory inductance plethysmography and transcutaneous electromyography to assess changes in the electrical activity of the diaphragm as surrogates for WOB (supplementary table S6). Overall muscle activity decreased as the flow increased from 2 to 4 $L \cdot min^{-1}$, followed by an increase in overall muscle activity for flows of 6 and 8 $L \cdot min^{-1}$, with significant differences noted between 4 and 8 $L \cdot min^{-1}$. The corresponding flows per kilogram were 1.4, 2.7, 4.1 and 5.4 $L \cdot kg^{-1} \cdot min^{-1}$ for the four flows (2, 4, 6 and 8 $L \cdot min^{-1}$), respectively. In these two studies, WOB was found to be lowest at flows of 3.2 and 2.7 $L \cdot kg^{-1} \cdot min^{-1}$, respectively, with an increase in WOB observed when flow exceeded 4 $L \cdot kg^{-1} \cdot min^{-1}$.

Similarly, Jeffreys *et al.* [37] employed noninvasive diaphragm electromyography (EMG) to assess WOB, with EMG amplitude serving as a surrogate measure. The EMG amplitude increased as the flow increased from 4 to 6 and 8 $L \cdot min^{-1}$, corresponding to flows per kilogram of 4, 6 and 8 $L \cdot kg^{-1} \cdot min^{-1}$. Conversely, Saslow *et al.* [31] did not observe significant differences in WOB with flows of 3, 4 and 5 $L \cdot min^{-1}$ using Vapotherm, which corresponded to 1.9, 2.6 and 3.2 $L \cdot kg^{-1} \cdot min^{-1}$, respectively.

Collectively, these studies suggest the existence of a potential optimal range for the relationship between flow settings and WOB, with WOB being lowest within the flow range of 2–3 $L \cdot kg^{-1} \cdot min^{-1}$ [31, 37, 39, 40].

Noise

Noise exposure from medical equipment is believed to be a risk factor for hearing loss in neonates. Roberts *et al.* [32] measured the noise level near the infant's ear during HFNC treatment using Optiflow, showing a nonsignificant increase in noise levels with higher HFNC flows, that were comparable to those generated by CPAP therapy.

Treatment failure

In a RCT involving 212 preterm neonates with a gestational age of ⩾28 weeks, Balasubramanian *et al.* [51] compared HFNC therapy under two different flows (5 *versus* 8 $L \cdot min^{-1}$) and found no significant difference in treatment failure rates between the two groups (29% in the 5 $L \cdot min^{-1}$ group *versus* 22% in the 8 $L \cdot min^{-1}$ group, p=0.22) (table 1). Treatment failure was defined as the need for higher respiratory support (CPAP or invasive ventilation) or surfactant therapy. Furthermore, none of the patients developed air leak syndromes. However, it is important to note that more patients in the 5 $L \cdot min^{-1}$ group required increased flows compared to the 8 $L \cdot min^{-1}$ group (64% *versus* 43%, p=0.004). Interestingly, in a

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TABLE 1 Comparison of different flow settings in randomised controlled trials (RCTs) reporting treatment failure

Author/year	Country	Study design	Population	Intervention	Control	Comparisons between intervention and control groups						Other outcomes
						Age	Patients, n	Male gender, n (%)	Weight, kg	Treatment failure n (%)		
Balasubramanian *et al.* 2021 [51]	India	RCT, S, DB	Moderately and late preterm infants with RDS and/or F_{IO_2} of 0.3 within the first 6 h of birth	8 L·min^{-1}	5 L·min^{-1}	GA: 28–30$^{6/7}$ weeks	28 *versus* 24	58 (56) *versus* 64 (59)	1.66±0.47 *versus* 1.63±0.42	11 (42) *versus* 12 (52)	Overall: 22 (22) *versus* 31 (29)	Median HFNC flow (L·min^{-1}): 7 (7–8) *versus* 6 (5–7), p=0.008 Max HFNC flow (L·min^{-1}): 8 (8–10) *versus* 7 (5–7), p=0.001 Need for flow increments: 44 (43%) *versus* 68 (64%), p=0.005 Need for flow increments in patients with treatment success: 27% (22/80) *versus* 49% (37/76)
						GA: 31–33$^{6/7}$ weeks	61 *versus* 67			11 (18) *versus* 14 (21)		
						GA: 34–36$^{6/7}$ weeks	15 *versus* 17			0 (0) *versus* 5 (29)		
Milési *et al.* 2018 [50]	France	RCT, M	Infants up to 6 months with acute bronchiolitis	3 L·kg^{-1}·min^{-1}	2 L·kg^{-1}·min^{-1}	1.6 ±1.80 *versus* 1.92±1.75 months	144 *versus* 142	86 (60) *versus* 84 (60)	4.4±1.2 *versus* 4.5±1.1	56 (38.9) *versus* 55 (38.7)		NIV: 48 (33.1%) *versus* 48 (33.8%) Intubation: 10 (6.9%) *versus* 4 (2.8%) PICU LOS: 6.4±4.9 days *versus* 5.3±2.8 days Skin lesions: 0 (0) *versus* 4 (2.8%)
Yurtseven *et al.* 2019 [48]	Turkey	RCT, S	Paediatrics with acute bronchiolitis	2 L·kg^{-1}·min^{-1}	1 L·kg^{-1}·min^{-1}	9.2±6.7 *versus* 10.9±6.5 months	80 *versus* 88	60 (75) *versus* 63 (72)	NR	8 (10) *versus* 10 (11.4)		At the 2nd hour of HFNC: Weaning: 28 (35%) *versus* 47 (53.4%), p=0.017 Reduction in CRS: −1.5 (−1.7– −1.2) *versus* −2.1 (−2.3– −1.8)[¶], p<0.001 Reduction in RR: −11.8 (−13.9– −9.7) *versus* −15.2 (−17.4– −13)[¶], p<0.001 Rise in S_{pO_2}: 3.6 (2.4–4.8) *versus* 4.8 (3.9–5.7)[¶], p<0.001

S: single centre; DB: double blinded; RDS: respiratory distress syndrome; F_{IO_2}: inspiratory oxygen fraction; GA: gestational age; HFNC: high-flow nasal cannula; M: multicentre; NIV: noninvasive ventilation; PICU: paediatric intensive care unit; LOS: length of stay; NR: not reported; CRS: clinical respiratory score; RR: respiratory rate (breaths·min^{-1}); S_{pO_2}: oxygen saturation measured by pulse oximetry (%). [#]: values reported as median (interquartile range); [¶]: values reported as mean (95% CI).

subgroup analysis specifically focusing on patients with a gestational age of 34–$36^{6/7}$ weeks, the treatment failure rate was lower in the 8 L·min^{-1} group compared to the 5 L·min^{-1} group (0% *versus* 29%, p=0.03). This observation may be attributed to the potential inadequacy of the lower flow (5 L·min^{-1}) in neonates of this age who typically have a higher body weight. Although their exact weights were not reported, considering the average weight of the overall included neonates (1.6±0.4 kg), if a weight of 2 kg was used to calculate the flows, the actual flows in the two groups would be 4 *versus* 2.5 L·kg^{-1}·min^{-1}. The 2.5 L·kg^{-1}·min^{-1} flow was likely insufficient for the neonates at this age. Conversely, for the other two age groups (28–$30^{6/7}$ and 31–$33^{6/7}$ weeks of gestational age), if one used weights of 1 and 1.5 kg to calculate the flows in the two groups, both would have exceeded 3 L·kg^{-1}·min^{-1}, which could explain the similar treatment failure rates observed in both groups.

These findings highlight the potential impact of flows relative to body weight on treatment outcomes in preterm neonates receiving HFNC therapy. Further research is warranted to explore the optimal flow based on individual gestational age and body weight, ensuring appropriate and effective management for this vulnerable population.

The effects of different flow settings in young children

Oxygenation and ventilation

In the two studies involving infants with bronchiolitis, an increase in flow was associated with an improvement in the patient's S_{pO_2}/F_{IO_2} ratio (supplementary table S4) [7, 8]. When the flow was increased from 0.5 to 2 L·kg^{-1}·min^{-1} [44, 46], no significant differences were observed in V_T and minute ventilation, as assessed by respiratory inductance plethysmography [45], pneumotachography [44] or electric impedance tomography [46]. Moreover, when flow was increased from 0.4 to 2 L·kg^{-1}·min^{-1}, a reduction in respiratory rate was observed in six studies (figure 3a) [6, 8, 43–46], except for the study conducted by Nascimento *et al.* [7], in which no significant differences in respiratory rate were observed across flows of 0.5–2 L·kg^{-1}·min^{-1} when using the Vapotherm device.

Airway pressure

Similar to studies conducted in preterm infants, airway pressure was measured at different locations in paediatric patients (figure 3b). In the two studies that measured pharyngeal pressure, an increase in pressure was observed with increasing flows [6, 47]. Notably, Arora *et al.* [47] compared pharyngeal pressure during open- and closed-mouth breathing and found a slight pressure reduction with open-mouth breathing.

Three studies measured oesophageal pressure at the end of expiration (*P*ese) [8, 43, 46], and two reported an increase in *P*ese with increasing flows [8, 43]. However, the extent of this increase was less pronounced in the Rubin *et al.* [43] study, which included post-extubated children with a median age of 6.5 months (IQR 1.3–15.5 months), compared to the Hough *et al.* study [8], which included infants with bronchiolitis and a mean age of 3.2±2.1 months. Interestingly, in the study conducted by Guglielmo *et al.* [46] with bronchiolitis patients aged 9.5 months (IQR 5.8–19.5 months), no significant differences in *P*ese were found across flows of 0.5–2 L·kg^{-1}·min^{-1}. However, it is worth noting that in Guglielmo *et al.* study [46], *P*ese measured at the lowest flow settings (⩽0.5 L·kg^{-1}·min^{-1}) was higher (10.0 cmH_2O, IQR 7.2–15.2 cmH_2O) compared to the values reported in the Rubin *et al.* [43] study (4.8±4.3 cmH_2O) and the Hough *et al.* [8] study (−0.2±7.6 cmH_2O). Additionally, in Guglielmo *et al.* [46], 84% of patients showed hyperinflation in chest radiography findings. These findings suggest varying degrees of air trapping in different studies, with *P*ese potentially reflecting intrinsic PEEP rather than the external PEEP created by HFNC.

Work of breathing

In the aforementioned five studies [6, 8, 43, 46, 47] that reported pharyngeal pressure or *P*ese, four measured PRP (figure 3c) [8, 43, 46] or pressure-time product (supplementary table S7) [6] as surrogate markers of WOB, and all reported a reduction in WOB with increasing flows. Additionally, Papoff *et al.* [44] measured PRP and pressure-time product, and both values decreased with increasing flows. Weiler *et al.* [42] also reported a 21% reduction in PRP as the flow increased from 0.5 to 2 L·kg^{-1}·min^{-1}. However, it is important to note that not all patients responded optimally to the highest flow. Weiler *et al.* [42] observed that the flow with the lowest WOB varied for different patients, with 51%, 35% and 12% patients responding best at 2.0, 1.5 and 1.0 L·kg^{-1}·min^{-1}, respectively. Stratified analysis based on studies with patients of different mean ages indicated that patients with higher baseline WOB had a more substantial reduction with increasing flows (supplementary figure S2). However, Hough *et al.* [8] found that patients with very high WOB at baseline exhibited minimal responses between flows of 0.4 and 1.7 L·kg^{-1}·min^{-1}. Notably, patients with lower baseline PRP demonstrated a plateau response at lower flows, *e.g.* those with a mean baseline PRP around 400 cmH_2O·min^{-1} had a PRP plateau at flows of 0.8

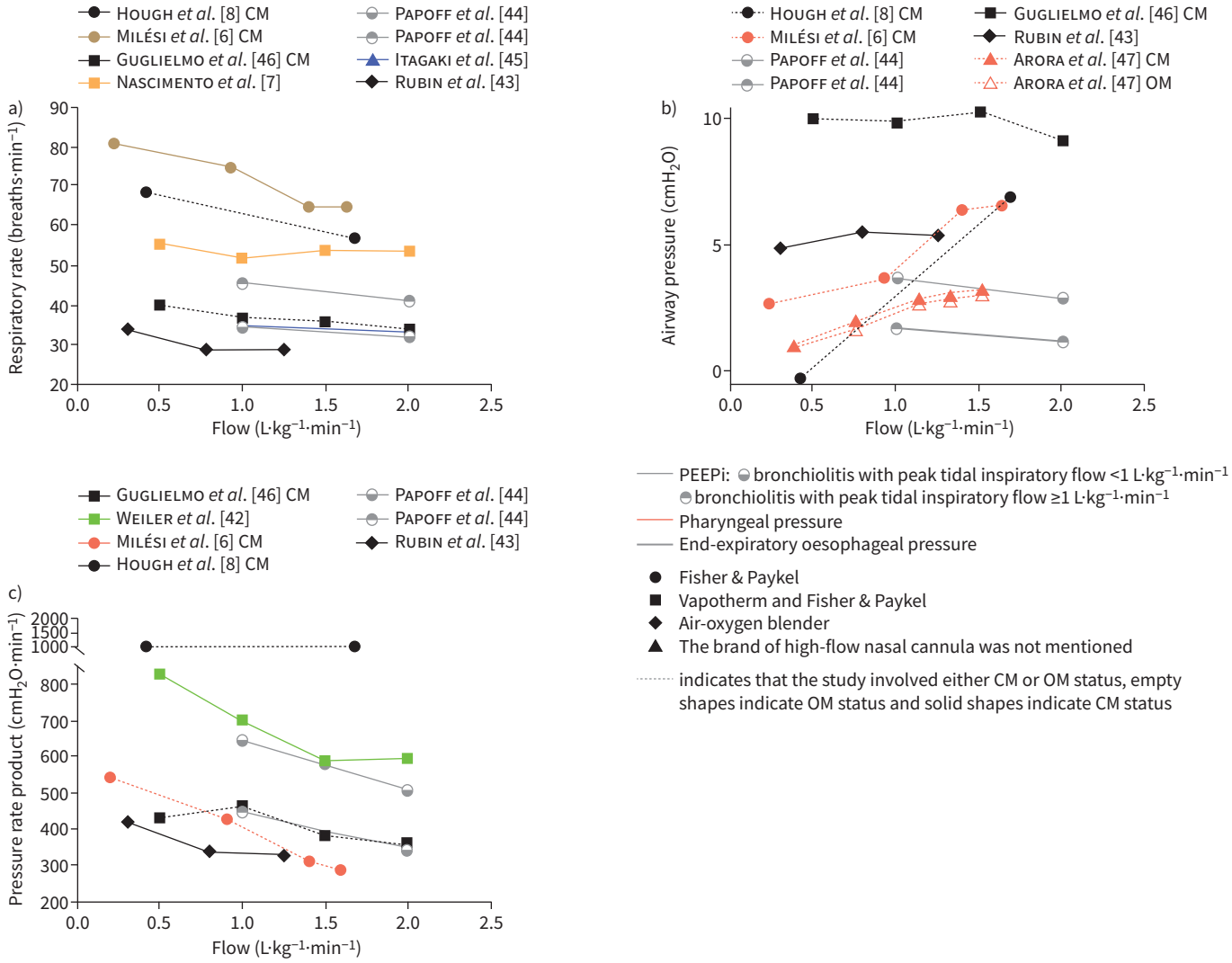

FIGURE 3 The association between flow settings with a) respiratory rate, b) airway pressure and c) pressure rate product in young children. All data are presented as mean/median. CM: closed mouth; OM: open mouth; PEEPi: intrinsic positive end-expiratory pressure, calculated as the difference between peak oesophageal pressure and oesophageal pressure at the start of inspiratory flow.

and 1.25 $L \cdot kg^{-1} \cdot min^{-1}$. In contrast, patients with a baseline PRP around 800 $cmH_2O \cdot min^{-1}$ reached a PRP plateau at flows of 1.5 and 2.0 $L \cdot kg^{-1} \cdot min^{-1}$.

Three studies [43, 44, 46] reported decreased inspiratory effort, as measured by change in oesophageal pressure swings, with increasing flows. Moreover, the modified Wood's clinical asthma score and respiratory distress score also decreased with increasing flows [6, 7].

Treatment failure

Two RCTs compared different HFNC flow settings for patients with acute bronchiolitis (table 1). Yurtseven *et al.* [48] compared HFNC therapy at a flow of 1 *versus* 2 $L \cdot kg^{-1} \cdot min^{-1}$ in 168 children with a mean age of 10.1±6.7 months, while Milési *et al.* [50] compared 2 *versus* 3 $L \cdot kg^{-1} \cdot min^{-1}$ in 286 infants with a mean age of 1.6±1.9 months. Neither study found any significant differences in treatment failure rates between the two flow groups, and both reported a proportion of patients who could not tolerate the higher flows and required flow reduction. Yurtseven *et al.* [48] found that patients in the 1 $L \cdot kg^{-1} \cdot min^{-1}$ group had faster clinical improvement and weaning from HFNC, but this should be interpreted with caution because there may be a cognitive bias related to weaning speed.

It is worth noting that the two studies used different definitions for treatment failure (supplementary table S8) and, more importantly, included patients with different disease severity. Patients in the Yurtseven *et al.* [48] study were likely less sick than those in the Milési *et al.* [50] study, as reflected by 45% of patients being weaned from HFNC within 2 h of initiation and fewer instances of treatment failure in the former. This suggests that the inspiratory flow demand of the patients in the Yurtseven *et al.* [48] study might have been lower. Additionally, patients in that study were older and, as mentioned earlier, children's PTIF calculated using weight declines as they grow. Interestingly, in a retrospective study of 251 infants with bronchiolitis with a median age of 5.3 months (IQR 2.4–9.1 months) treated with HFNC, most patients (75%) received a flow of 1.5 $L \cdot kg^{-1} \cdot min^{-1}$, 18% received 1 $L \cdot kg^{-1} \cdot min^{-1}$ and 7% received 2 $L \cdot kg^{-1} \cdot min^{-1}$ [52]. Patients receiving 1.5 $L \cdot kg^{-1} \cdot min^{-1}$ had lower treatment failure rates (13%) than the other two groups (33% and 26%, respectively) and shorter length of stay [52]. However, fewer patients required increased flow in the group of 2 $L \cdot kg^{-1} \cdot min^{-1}$ (5%) than the groups of 1.5 $L \cdot kg^{-1} \cdot min^{-1}$ (59%) and 1 $L \cdot kg^{-1} \cdot min^{-1}$ (84%) [52].

Therefore, among young children, one should cautiously conclude that a flow of 1 $L \cdot kg^{-1} \cdot min^{-1}$ is appropriate. However, for younger infants or sicker children, a higher flow, such as 1.5–2 $L \cdot kg^{-1} \cdot min^{-1}$, might be necessary for optimal effect. Regardless, close monitoring of treatment response and tolerance, and flow titration based on individual needs, are crucial for the success of HFNC therapy.

Apnoeic ventilation

In a RCT conducted by Riva *et al.* [49], 30 children weighing 10–15 kg and requiring elective surgery were randomised to receive HFNC at a flow of either 2 or 4 $L \cdot kg^{-1} \cdot min^{-1}$ following the induction of anaesthesia. Transcutaneous CO_2 level was measured for 10 mins, but no significant differences were observed between the two groups, suggesting that a flow of 2 $L \cdot kg^{-1} \cdot min^{-1}$ is likely sufficient to generate ventilatory effects during apnoeic ventilation in this population.

Discussion

In this systematic review, we assessed both *in vitro* and *in vivo* studies investigating the impacts of various flows among paediatric populations. We also discussed the short-term physiological effects, including oxygenation, ventilation, airway pressure and WOB, along with long-term treatment failures in both neonates and young children.

Similarities and differences in the effects of flow settings in neonates and young children

In both neonates and children under 2 years of age, an increase in flow resulted in improved oxygenation and decreased respiratory rates (table 2). Interestingly, the impact of open-mouth breathing on airway pressure was less pronounced in neonates and young children compared to *in vitro* models and adult patients [59]. This difference may be explained by the innate anatomic differences in the airway structure and physiological functions between adult and paediatric patients, as well as between human beings and simulated models. Innate anatomic differences between the airways of adults and young children may also contribute to this disparity.

However, there are notable differences in the evidence assessed between neonates and young children in terms of HFNC therapy flows used in the available studies. Neonatal studies generally employed higher flows when indexed to body weight ($L \cdot kg^{-1} \cdot min^{-1}$) compared to paediatric studies. For instance, the maximum flow investigated in neonates was 9 $L \cdot kg^{-1} \cdot min^{-1}$, compared to 3 $L \cdot kg^{-1} \cdot min^{-1}$ in young children. Another difference lies in the airway pressure generated during HFNC treatment. In neonates, as HFNC flow was increased, airway pressure increased proportionally to the flows, demonstrating a near-linear relationship, irrespective of the locations where pressure measurements were taken [2, 27–31, 33, 34, 36, 40, 41]. Conversely, in young children, as HFNC flow was increased, airway pressure varied significantly and had no clear, consistent relationship, depending on whether the patients had hyperinflation [6, 8, 43, 46, 47]. Moreover, when evaluating WOB, the optimal flow with the lowest WOB generally was higher in neonates (2–3 $L \cdot kg^{-1} \cdot min^{-1}$) compared to young children (1.5–2.0 $L \cdot kg^{-1} \cdot min^{-1}$) [42, 50]. It must be noted that individual patients responded differently to these flows in both populations, possibly due to varying inspiratory flow demands. HFNC therapy continues to be used clinically in heterogeneous disease processes and the exact physiological effects show variance based on patient size, flow demands, disease type (*i.e.* obstructive lung disease *versus* parenchymal lung disease) and disease severity, among other factors.

Future research directions

For preterm infants, RCTs are needed to investigate the effect of weight-based flows ($L \cdot kg^{-1} \cdot min^{-1}$) on clinical outcomes, such as treatment failure and the need for advanced respiratory support (*i.e.* NIV,

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TABLE 2 Summary of *in vitro* and clinical evidence of flow settings during high-flow nasal cannula (HFNC) treatment for neonates and young children

Effects	*In vitro* evidence	Clinical evidence	Explanation	Take-home message
Airway pressure	PEEP increased as flow increased [13–18, 20, 23, 24, 26–28]	In neonates, airway pressures increased proportionally to the flows in a near-linear relationship [2, 27–31, 33, 34, 36, 40, 41] In children, pharyngeal pressure increased as flow increased [6, 47], but oesophageal pressure varied in patients with different ages and diseases [8, 43, 46]	The impact of flow on airway pressure follows Poiseuille's law, but for patients with hyperinflation, oesophageal pressure is affected by PEEPi	When true CPAP is needed, HFNC should be considered as a second-line therapy
	PEEP decreased significantly when the mouth was open [15, 16, 20, 23, 27]	The differences in the airway pressures between open- and closed-mouth breathing were minimal [33, 47]	Discrepancies between *in vitro* models and human subjects regarding leak effects on airway pressure can be attributed to the anatomical and physiological differences	HFNC can be employed for mouth-breathing patients
	PEEP increased as the prong-to-nares ratio decreased [13, 14, 16, 20, 28]	Only mild differences in the airway pressure were observed between different prong-to-nares ratios [33]		Nasal cannula should be ⩽50% of patient's nares
CO_2 clearance	CO_2 clearance was enhanced with increasing flow during closed-mouth breathing [21, 23]	During apnoeic ventilation, no significant differences in transcutaneous CO_2 levels were observed between flows of 2 *versus* 4 $L \cdot kg^{-1} \cdot min^{-1}$ [49]	Increasing flow helps wash out dead space and reduce air entrainment	2 $L \cdot kg^{-1} \cdot min^{-1}$ is likely sufficient during apnoeic ventilation
Respiratory rate	NR	Respiratory rates decreased as flow increased up to a certain level, after which respiratory rates started to increase or remained stable [6, 8, 27, 31, 33, 34, 39, 40, 43–46]		Titrate flow based on respiratory rate, oxygenation and tolerance
Oxygenation	NR	Oxygenation increased as flow increased [7, 8, 27, 33, 34, 39, 40]		
WOB	NR	Individual patients responded differently to flows in terms of WOB Neonates generally responded optimally at 2–3 $L \cdot kg^{-1} \cdot min^{-1}$ [31, 37, 39, 40], while children showed favourable responses at 1.5–2.0 $L \cdot kg^{-1} \cdot min^{-1}$ [6, 8, 42–44, 46]	WOB reduction is likely attributed to improved ventilation, decreased upper airway resistance, counteracting PEEPi, stenting effect on small bronchi and increased FRC Different patients had different inspiratory flow demand, contributing to their variable responses	It is essential to individualise flow settings to optimise WOB and overall effectiveness
Humidity and condensation	The amount of condensation depended on the temperature gradient between the gas and the circuit wall [25]	NR	When fully saturated gas encounters a decrease in temperature, condensation occurs	Place the HFNC circuits inside the incubator to mitigate the condensation

PEEP: positive end-expiratory pressure; PEEPi: intrinsic PEEP; CPAP: continuous positive airway pressure; CO_2: carbon dioxide; NR: not reported; WOB: work of breathing; FRC: functional residual capacity.

invasive ventilation). Promising results from physiological studies and a subgroup analysis from the RCT conducted by Balasubramanian *et al.* [51] suggest a flow of 3–4 $L \cdot kg^{-1} \cdot min^{-1}$ may be beneficial for some neonates. However, further RCTs are required to more definitively evaluate this higher flow strategy relative to patient outcomes. In the paediatric population, flows higher than 2 $L \cdot kg^{-1} \cdot min^{-1}$ have not been shown to be helpful [50].

In children aged between 28 days and 2 years of age, the PTIF exhibits large variance relative to patient size and disease severity, especially in pathological conditions with obstructive lung disease, often marked by hyperinflation. Therefore, individualised flow settings based on inspiratory flow demand (PTIF) and physiological responses, such as respiratory rate, heart rate, tolerance, WOB and lung aeration, should be investigated. Further research is needed to explore these aspects across various pathological conditions. Additionally, it is important to note that the current evidence predominantly stems from patients with a clinical diagnosis of bronchiolitis, so studies exploring the effects of different HFNC flows on other respiratory conditions are sorely needed. Lastly, for children older than 2 years, the effects of various flows on their physiological responses, tolerances and clinical outcomes are largely unknown from the evidence at hand. Therefore, further studies to address these knowledge gaps are needed in older children.

Conclusion

In neonates and young children, the PTIF varies based on age and disease severity. Calculated PTIF using weight ($L \cdot kg^{-1} \cdot min^{-1}$) declines as children grow. During HFNC treatment, increasing flow has been shown to improve oxygenation. However, other physiological responses, such as respiratory rate, airway pressure, WOB and lung aeration, may differ between neonates and older children. Given the variability in PTIF and other physiological responses, individualised flow settings based on the patient's inspiratory flow demand and other factors, such as respiratory rate, heart rate, tolerance, WOB, lung aeration and pathological conditions, may be necessary for optimal treatment application.

Provenance: Submitted article, peer reviewed.

Availability of data and materials: Data will be available 36 months after article publication to researchers who provide a methodologically sound and ethically approved proposal, for any purpose of analysis.

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