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High Flow Nasal Cannula Beyond Oxygenation A Narrative Review of Physiological Mechanisms and Clinical Relevance

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Abstract

High-flow nasal cannula (HFNC) provides more than oxygen delivery. Matching flow to inspiratory demand and anatomical dead-space washout influence the delivered fraction of inspired oxygen (FiO_2) and ventilatory efficiency. Modest positive airway pressure and adequate heating and humidification also affect end-expiratory lung volume and work of breathing. This review synthesizes evidence on respiratory, cardiovascular, and gastrointestinal physiology and examines clinical phenotypes, individualized flow and FiO_2 titration, and patient outcomes. Available studies suggest that HFNC can maintain lung aeration, improve ventilatory efficiency, and reduce inspiratory effort in selected patients, but provides limited support during ventilatory pump failure. Its hemodynamic effects depend on filling pressure, preload dependence, pulmonary vascular resistance, and right ventricular reserve. The short-term risk of gastric insufflation appears low in selected adults, but caution is warranted in children and patients with gastroesophageal dysfunction, enteral feeding, or concomitant airway devices. Flow should be titrated stepwise to inspiratory demand and respiratory load, whereas FiO_2 should be adjusted independently to a predefined oxygenation target. HFNC may reduce intubation or reintubation in some populations, but evidence for mortality and long-term resource benefits remains inconsistent. Clinical use should therefore be phenotype-based, with serial assessment of treatment response and timely recognition of patients who require escalation of respiratory support.

Keywords high-flow nasal cannula; physiological mechanisms; clinical phenotypes; respiratory mechanics; hemodynamics; individualized titration

1 Introduction

High-flow nasal cannula (HFNC) continuously delivers a heated and humidified air-oxygen mixture. It is widely used for acute hypoxemic respiratory failure, postextubation support, and perioperative oxygenation. Its effects extend beyond increasing the fraction of inspired oxygen. Flow, humidification, cannula geometry, and the patient's breathing pattern also modify upper-airway gas turnover, airway pressure, end-expiratory lung volume (EELV), and inspiratory effort[1-3].

Oxygen saturation alone cannot determine whether HFNC is effective. Hypoxemia may persist because of shunt or atelectasis, while respiratory load can continue to increase despite transiently improved oxygenation. Conversely, dead-space washout or closer matching of inspiratory demand may reduce breathing effort even when oxygenation changes little. Physiological assessment should therefore integrate gas exchange, breathing pattern, respiratory mechanics, circulatory reserve, and tolerance.

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The same mechanism may have opposing effects across phenotypes. Modest positive pressure can preserve lung volume but may also reduce venous return. Dead-space washout can improve ventilatory efficiency but cannot replace pressure support. Short perioperative studies generally found no substantial gastric insufflation, although severe gastrointestinal distension has occurred in susceptible patients[4-6]. These differences preclude the use of HFNC with fixed settings and a single response endpoint.

This review examines the respiratory, cardiovascular, and gastrointestinal effects of HFNC. It integrates clinical physiological phenotypes with individualized flow and FiO_2 titration and discusses outcomes, special applications, and evidential boundaries. We distinguish reproducible short-term physiological responses from context-dependent clinical inferences and unverified long-term benefits.

2 Literature Search and Scope

We conducted a focused search of PubMed, Web of Science, and Embase. Search concepts included HFNC, physiological effects, respiratory mechanics, dead-space washout, work of breathing, hemodynamics, cardiac function, gastric insufflation, clinical outcomes, flow titration, and FiO_2. We included physiological studies, randomized trials, observational studies, systematic reviews, meta-analyses, and relevant case reports that informed mechanisms, clinical implications, or safety boundaries.

Evidence was organized by clinical question and mechanism. Directionally consistent findings across methods and populations received greater interpretive weight, whereas isolated, small, or indirect observations mainly informed uncertainty. This review was not preregistered and included neither formal risk-of-bias assessment nor quantitative synthesis. Its conclusions support physiological reasoning and clinical monitoring rather than definitive estimates of comparative treatment effects.

3 Respiratory Physiological Effects

The respiratory effects of HFNC depend on the relationship between delivered flow and the patient's instantaneous inspiratory demand. When flow is insufficient, entrained room air dilutes the device-set FiO_2. As flow increases, dead-space washout, modest positive airway pressure, and respiratory unloading may all increase, although not in parallel.

3.1 Delivered FiO_2 and Airway Pressure

HFNC is an open system, so the device-set FiO_2 may not equal the concentration inhaled by the patient. Bench studies identify set FiO_2, device flow, and peak inspiratory flow as the main determinants. When inspiratory demand exceeds delivered flow, room-air entrainment increases and effective FiO_2 decreases[7,8]. Hypopharyngeal measurements in healthy volunteers further showed that mouth opening, hyperventilation, and altered breathing patterns increase variability in effective FiO_2 and airway pressure[9].

Higher flow generally increases positive pharyngeal pressure, but the pressure depends on the cannula-to-nares ratio, mouth opening, and expiratory flow. Clinicians should not equate a given flow with a fixed level of positive end-expiratory pressure. A systematic review showed that increasing flow can alter oxygenation, respiratory rate, inspiratory effort, airway pressure, and comfort. However, the optimal response point differs among these outcomes[10].

3.2 End-Expiratory Lung Volume and Lung Recruitment

Modest positive airway pressure can preserve EELV and reduce collapse in dependent lung regions. Randomized pediatric anesthesia trials, bronchoscopy studies, postoperative imaging, and lung ultrasound after chest trauma associate HFNC with preserved aeration or improved reaeration[11-15]. Electrical impedance tomography likewise shows that both body position and HFNC can modify EELV[16].

These surrogate outcomes do not establish that increased lung volume necessarily represents beneficial recruitment. With low recruitability, heterogeneous regional compliance, or excessive flow, regional overdistension may offset any benefit. A high FiO_2 may also increase the risk of absorption atelectasis. In adult laryngeal surgery, transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) caused no greater lung-volume loss during brief controlled apnea than mechanical ventilation. This finding does not establish that THRIVE actively recruits lung tissue[17].

3.3 Anatomical Dead-Space Washout and Ventilatory Efficiency

Continuous high flow displaces exhaled gas from the nasopharynx and reduces rebreathing from the upper airway. Washout efficiency depends on flow, respiratory rate, cannula size, and expiratory flow. With faster breathing, each expiration provides less time to clear dead space[18]. By altering bilateral nasal airflow, asymmetric cannulae may enhance carbon dioxide clearance and raise airway pressure at the same total flow. Evidence, however, is derived mainly from physiological models[19].

Dead-space washout may explain why respiratory rate

or carbon dioxide clearance improves in some patients without conventional pressure support. A small comparison in acute hypoxemic respiratory failure found distinct tidal volumes and breathing patterns with HFNC at 50 to 60 L/min and low-level continuous positive airway pressure (CPAP)[20]. This observation supports mechanistic differences but does not establish that HFNC prevents patient self-inflicted lung injury.

3.4 Respiratory Load and the Limits of Ventilatory Support

HFNC may reduce respiratory load through closer matching of inspiratory demand, less room-air entrainment, dead-space washout, and preservation of lung volume. Exercise trials in healthy volunteers, postextubation crossover studies, and flow-escalation studies in acute hypoxemic respiratory failure found reductions in esophageal pressure swings, pressure-time product, or diaphragmatic electrical activity[21-23]. The flow-escalation study enrolled only 17 patients and primarily demonstrates a short-term dose-response relationship, not clinical outcomes.

Respiratory unloading does not ensure adequate ventilation. In neuromuscular disease with nocturnal hypoventilation, HFNC provides limited correction of carbon dioxide retention and is less effective than noninvasive ventilation (NIV)[5]. A bilevel flow mode reduced energy expenditure associated with nasopharyngeal breathing in healthy volunteers. Its small sample and brief observation period preclude replacing patient-based trials[24]. During treatment, a lower respiratory rate may indicate improved efficiency or fatigue. Interpretation requires concurrent assessment of breathing effort, consciousness, gas exchange, and temporal trends.

4 Cardiovascular and Hemodynamic Effects

The circulatory effects of HFNC reflect several opposing mechanisms. A modest increase in intrathoracic pressure may reduce venous return. Improved oxygenation and lung volume can attenuate hypoxic pulmonary vasoconstriction. Reduced work of breathing may also decrease sympathetic stress and myocardial oxygen demand. The net effect depends on volume status, preload dependence, biventricular function, and pulmonary vascular resistance[4].

4.1 Filling Pressure and Acute Heart Failure

In acute heart failure with pulmonary congestion, a moderate reduction in venous return and work of breathing may relieve symptoms. A retrospective cohort associated HFNC with improvements in selected gas-exchange and echocardiographic measures[25]. Diuresis, vasoactive therapy, or reduced respiratory effort could also explain these changes, so they cannot be attributed directly to HFNC. Patients with stable blood pressure and elevated filling pressure may tolerate modest preload reduction, whereas those with limited circulatory reserve may deteriorate.

4.2 Pulmonary Hypertension and Right Ventricular Function

Responses in pulmonary hypertension depend particularly on right ventricular reserve. An observational study associated HFNC with improved right-heart structure and function and lower estimated pulmonary artery pressure[26]. Another retrospective cohort of 90 patients was stratified by the severity of right ventricular dysfunction. Outcomes with HFNC and NIV were similar in the mild-to-moderate subgroup, whereas HFNC was associated with higher intubation rates in the severe subgroup[27]. Given the small sample and residual confounding, these findings support risk stratification but cannot establish causal superiority of either treatment.

Congenital heart disease and single-ventricle physiology further illustrate the importance of context. Hemodynamics remained generally stable during HFNC in noncyanotic children undergoing transcatheter procedures[28]. A small study of Fontan circulation found lower heart rate and vascular resistance at 30 L/min, accompanied by improved cardiac output and cerebral perfusion indices[29]. These findings come from highly selected populations and do not support a universally applicable setting.

4.3 Monitoring and Clinical Interpretation

Available data show no consistent autonomic effect. Short-term HFNC in neuromuscular disease produced no clear changes in heart-rate variability, cardiac index, or peripheral resistance. In children with obstructive sleep apnea, CPAP attenuated obstruction-related pulse-rate responses more than HFNC[5,30]. Clinicians should repeatedly assess perfusion, congestion, right-heart tolerance, breathing effort, and the need to escalate support. Circulatory benefit should not be inferred from a single flow or oxygenation value.

5 Gastrointestinal Effects and Safety

Positive pharyngeal pressure generated by HFNC can be transmitted to the stomach when the esophagus is open. Actual risk depends on flow, mouth opening, lower esophageal sphincter function, gastric emptying, exposure

duration, and concomitant airway devices. Null findings in short-term studies and case reports in susceptible patients are not contradictory because they represent different risk conditions.

5.1 Short-Term Controlled Conditions

In healthy pregnant women at term, HFNC at 50 L/min for 20 min did not increase antral area or estimated gastric volume. Similarly, healthy volunteers showed no gastric distension or increased gastric fluid volume after 30 min at flows up to 70 L/min[31,32]. Peri-intubation computed tomography showed similar intragastric gas volumes after HFNC and face-mask ventilation[33]. During tubeless microlaryngeal surgery, brief apnea at 70 L/min did not increase ultrasound-estimated gastric volume despite an open mouth and neuromuscular blockade[34]. A study of awake craniotomy likewise reported no increase in gastric antral volume[35].

These studies support a low gastrointestinal risk in selected adults receiving short-term HFNC under monitored conditions. However, they cannot exclude rare events or be extrapolated to prolonged use, impaired gastroesophageal function, or critical illness. Gastric ultrasonography and computed tomography capture only specific time points, and negative findings are also constrained by sample size.

5.2 Susceptible Patients

A systematic review identified gastric distension as an uncommon complication of noninvasive respiratory support[6]. Severe abdominal distension has occurred in a child receiving HFNC with a nasopharyngeal airway inserted too deeply[36]. In critically ill patients receiving enteral nutrition after extubation, automated monitoring showed higher gastric residual volumes and more reflux signals during HFNC than during mechanical ventilation[37]. However, the change in treatment phase precluded confident causal attribution. Severe intestinal distension after HFNC-assisted awake intubation in an adult with hiatal hernia also suggests that anatomical susceptibility may increase risk[38].

Abdominal distension, vomiting, gastric residual volume, reflux, and unexplained respiratory deterioration should be monitored in patients at increased risk. Risk factors include childhood, prolonged high flow, impaired consciousness, delayed gastric emptying, enteral nutrition, hiatal hernia, severe reflux, and concomitant airway devices. Progressive abnormalities should prompt reassessment of flow, airway devices, and the mode of respiratory support.

6 Clinical Physiological Phenotypes and Their Potential Benefits and Risks

The net effect of HFNC depends on whether device settings match the patient's predominant pathophysiology. The same flow and FiO_2 may confer benefit, provide insufficient support, or cause adverse effects across different phenotypes. We group common phenotypes into respiratory, circulatory, and gastrointestinal categories, as detailed in Figure 1 and Table 1.

Patients with high inspiratory demand may benefit when delivered flow better matches demand and limits room-air entrainment. In patients with rapid shallow breathing,

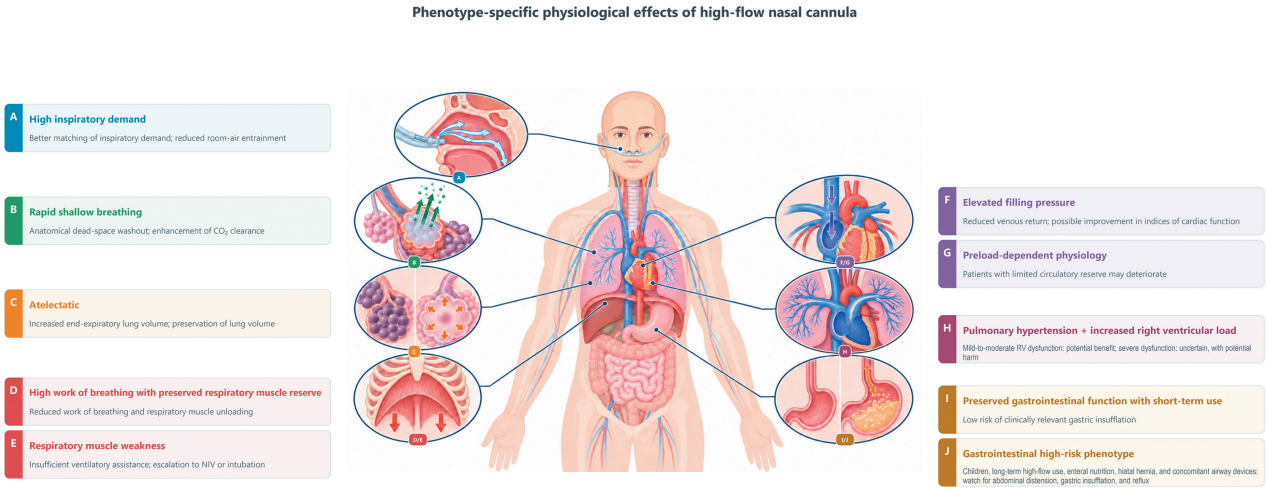


Figure 1 Clinical physiological phenotypes and potential benefits and risks of HFNC
Letters A to J in the figure correspond sequentially to the ten phenotypes listed in Table 1.

Table 1 Clinical physiological phenotypes, principal mechanisms, and potential benefits and risks of HFNC

Clinical physiological phenotype	Core pathophysiological problem	HFNC-related mechanism	Potential benefit	Principal risk or limitation
A High inspiratory demand or tachypnea	High instantaneous inspiratory flow increases room-air entrainment	Matches inspiratory demand and reduces room-air entrainment[7,10]	More stable effective FiO_2 and potentially lower inspiratory effort	Limited benefit when flow is insufficient; further increases should account for comfort and respiratory load
B Rapid shallow breathing or high dead-space burden	Reduced proportion of effective alveolar ventilation	Washes out upper-airway anatomical dead space[18,19]	May improve ventilatory efficiency and reduce respiratory rate and CO_2 rebreathing	Variable CO_2 response; cannot replace pressure support
C Atelectatic or recruitable phenotype	Reduced end-expiratory lung volume with gravitationally dependent collapse	Provides mild positive airway pressure and preserves end-expiratory lung volume[11,16]	May preserve lung aeration and reduce collapse in some dependent regions	Regional overdistension may occur; high FiO_2 may increase absorption atelectasis
D Increased work of breathing with preserved respiratory muscle reserve	Increased inspiratory effort and respiratory load	Matches inspiratory demand, washes out dead space, and provides mild positive pressure[22,23]	Unloads respiratory muscles and may relieve dyspnea	A lower respiratory rate may also indicate fatigue; serial reassessment is required
E Ventilatory pump failure or respiratory muscle weakness	Inadequate effective ventilation and CO_2 retention	Washes out dead space and provides limited unloading[5]	May provide limited adjunctive support	Insufficient ventilatory assistance may delay NIV or intubation
F Elevated filling pressure or pulmonary congestion	Pulmonary congestion, hypoxemia, and increased work of breathing	Provides mild positive pressure, respiratory unloading, and reduced venous return[25]	May improve congestion, oxygenation, and selected indices of cardiac function	Excessive preload reduction may be harmful; direct hemodynamic evidence is limited
G Preload-dependent state	Cardiac output depends heavily on venous return	Increased intrathoracic pressure interacts with improved oxygenation and lower respiratory load[4,29]	Some patients may maintain hemodynamic stability while respiratory load decreases	The net effect is difficult to predict; patients with limited circulatory reserve may deteriorate
H Pulmonary hypertension or increased right ventricular load	Increased pulmonary vascular resistance and right ventricular afterload	Reduces hypoxic pulmonary vasoconstriction and work of breathing and alters lung volume[26,27]	May benefit patients with mild-to-moderate right ventricular dysfunction	Support may be inadequate in severe dysfunction; overdistension or reduced venous return may be harmful
I Preserved gastrointestinal function with short-term use	Pharyngeal pressure may be transmitted to the gastrointestinal tract	Generates low-level positive pharyngeal pressure	Clinically relevant gastric insufflation is generally uncommon during short, controlled use in adults[31,32,34]	Gastric insufflation remains possible; evidence for prolonged exposure is limited
J Gastrointestinal high-risk phenotype	Greater gastrointestinal vulnerability or pressure transmission	Positive pharyngeal pressure may promote gas entry into the esophagus and stomach	No specific gastrointestinal benefit	Monitor for abdominal distension, gastric insufflation, and reflux in children or with prolonged high flow, enteral feeding, hiatal hernia, or concomitant airway devices[6,36-38]

anatomical dead-space washout may improve ventilatory efficiency[10,18]. HFNC can reduce inspiratory effort when respiratory muscle reserve is preserved. Its assistance is limited in ventilatory pump failure or marked respiratory muscle weakness and should not replace NIV or delay intubation[5]. A lower respiratory rate should be interpreted alongside respiratory effort, consciousness, and gas exchange.

The circulatory response is determined mainly by filling pressure, preload dependence, and right ventricular reserve. In hemodynamically stable patients with pulmonary congestion, mild positive pressure and respiratory unloading may be beneficial. In preload dependence, single-ventricle physiology, or severe right ventricular dysfunction, reduced venous return and inadequate support may offset respiratory benefits[4,25-27,29]. Because the evidence is largely observational or derived from small studies, it cannot establish a survival benefit.

Short-term use appears to carry a low overall risk in adults with intact gastroesophageal function. Closer monitoring is warranted in children and in patients with enteral nutrition, hiatal hernia, delayed gastric emptying, or concomitant airway devices[32,36-38]. The purpose of phenotyping is not to assign a fixed flow to each patient. Instead, it should define the expected mechanism, competing risks, and criteria for treatment escalation.

7 Physiology-Guided Individualized Titration of Flow and FiO_2

HFNC flow and FiO_2 should be adjusted to distinct targets. Flow is primarily used to match inspiratory demand, reduce room-air entrainment, and decrease respiratory load. FiO_2 is primarily adjusted to achieve a predefined oxygenation target. Although both influence effective oxygen delivery, their settings should not be increased automatically in tandem[3]. Key titration principles and monitoring variables are summarized in Table 2.

When hypoxemia persists with tachypnea, clinicians should assess both FiO_2 adequacy and whether flow matches inspiratory demand. Bench data indicate that when device flow is below peak inspiratory flow (PIF), increasing set FiO_2 alone cannot eliminate dilution from room-air entrainment[7,8]. Mouth opening and hyperventilation increase uncertainty between set and delivered FiO_2. Oxygenation and respiratory load should therefore be reassessed whenever the breathing pattern changes[9].

Flow should be increased stepwise according to the dynamic response. When measurable, peak tidal inspiratory flow (PTIF) can serve as a physiological reference. Decisions to increase flow should also consider oxygenation, respiratory rate, respiratory effort, ROX index trends, and comfort. In a 49-patient study with 5 to 10 min at each setting, the ROX index plateaued at flow-to-PTIF ratios of approximately 1.34 to 1.67[39]. This exploratory finding should not be treated as a universal threshold. Higher flow does not necessarily reduce comfort because temperature and disease severity also influence tolerance[40].

FiO_2 should be titrated to a predefined oxygen saturation target while considering the risk of oxygen-induced hypercapnia[41]. Once oxygenation is adequate, increasing FiO_2 cannot substitute for reassessing persistent tachypnea or inspiratory effort. Clinicians should evaluate flow adequacy, disease progression, and the need to escalate respiratory support. Apneic oxygenation usually requires both high FiO_2 and high flow. Specific settings should reflect the procedure, airway patency, and safety risks[42].

8 From Physiological Responses to Clinical Outcomes

HFNC can improve oxygenation, comfort, and respiratory effort within minutes. However, intubation, length of stay, and survival also depend on disease trajectory, concomitant treatment, and the timing of support escalation. Physiological improvement should not replace predefined criteria for treatment failure.

8.1 Intubation and Escalation of Respiratory Support

A systematic review and meta-analysis of adult acute respiratory failure suggested that HFNC may reduce

Table 2 Physiological target-guided titration of HFNC flow and FiO_2 and key monitoring variables

Physiological or clinical context	Flow titration	FiO_2 titration	Key monitoring variables
Initial settings	Adjust to inspiratory demand and respiratory load; avoid a fixed flow for all patients[3]	Adjust to the severity of hypoxemia and the prespecified oxygenation target[41]	SpO_2, respiratory rate, inspiratory effort, or work of breathing
Flow below inspiratory demand	Increase flow stepwise to reduce room-air entrainment and improve matching to inspiratory demand[7,8]	Reassess the FiO_2 requirement once flow is adequate	PTIF or PIF, SpO_2, and breathing pattern
Assessing the flow response	Increase flow stepwise. Near or above PTIF, use the physiological response to determine whether further increases remain beneficial[10,39]	Maintain or reduce FiO_2 after the oxygenation target is reached	ROX index trend, respiratory rate, inspiratory effort, or work of breathing
Change in breathing pattern	Greater flow may be needed as ventilatory demand increases; effective FiO_2 is less predictable with the mouth open[9]	Reassess the set FiO_2 against the observed response after the breathing pattern changes	Mouth-open or mouth-closed state, respiratory rate, and ventilatory demand
Tolerance	Adjust to individual comfort and temperature setting; do not assume that higher flow is necessarily less tolerable[40]	Not applicable	Comfort, dyspnea, and tolerance
Oxygenation target met but respiratory load remains high	Reassess flow adequacy and whether HFNC support is insufficient	Do not substitute further FiO_2 increases for assessment of respiratory load	SpO_2, respiratory rate, and inspiratory effort; blood gas analysis if needed
Specific clinical situations	Apneic oxygenation usually requires high flow, adjusted to the procedure and airway conditions[42]	Apneic oxygenation generally also requires high FiO_2; in spontaneously breathing patients, titrate to the oxygenation target	Respiratory status, airway patency, and the specific clinical setting

PIF, peak inspiratory flow; PTIF, peak tidal inspiratory flow; SpO_2, peripheral oxygen saturation. The ROX index supports dynamic risk assessment but should not replace clinical judgment or delay escalation of support.

intubation in some settings compared with conventional oxygen therapy (COT). Comparisons with NIV were less consistent[43]. In the randomized FLORALI trial, the primary outcome of intubation did not differ significantly between groups. This finding illustrates the influence of population and protocol on individual trial results[44].

Post-extubation evidence also depends on risk stratification. In patients at low risk of reintubation, HFNC reduced reintubation within 72 h compared with COT. In high-risk patients, HFNC was noninferior to NIV for reintubation[45,46]. However, these trials used different eligibility criteria and comparator strategies, precluding direct extrapolation across populations. Clinicians should prioritize assessment for more intensive ventilatory support when hypercapnia, impaired consciousness, inadequate airway protection, or respiratory muscle fatigue predominates.

Pooled evidence in immunocompromised patients with acute respiratory failure associated HFNC with a lower intubation rate but no clear survival benefit[47]. A meta-analysis in patients with obesity after cardiac surgery found no clear advantage for reintubation or intensive care unit stay[48]. Observational analyses in patients with brain injury likewise showed no consistent advantage of any noninvasive strategy[49]. Continuous monitoring and timely escalation may influence safety more than the initial device choice.

8.2 Mortality and Resource Use

Evidence for mortality and length of stay is weaker than that for intubation. Systematic reviews across heterogeneous populations have not shown consistent reductions in short-term mortality, and differences in length of stay are small and unstable[43,47,50]. Some perioperative or neurocritical care cohorts have reported fewer pulmonary complications or faster recovery. However, these findings are sensitive to case mix, treatment timing, and local workflows[14,51]. Future trials should standardize definitions of treatment failure, intubation criteria, and escalation timing. They should also report comfort, complications, mortality, and resource use.

9 Emerging and Procedure-Specific Applications

9.1 Breath-Hold Support During Radiotherapy

HFNC may increase oxygen reserve and improve tolerance of repeated inspiratory breath-holds in some patients. In locally advanced lung cancer, training increased breath-hold duration from approximately 39 to 78 s. In mediastinal lymphoma, mean duration increased from 34 to 60 s. Longer usable breath-hold periods were also reported during liver stereotactic body radiotherapy[52-54]. These specialized applications require training, visual guidance, and integration with radiotherapy workflows. Whether prolonged breath-holds consistently improve dosimetry, local control, or toxicity outcomes remains uncertain.

9.2 Neonatal Respiratory Strategies

A retrospective cohort of extremely preterm infants reported higher rates of normal brain magnetic resonance imaging and higher subsequent cognitive scores after combined neurally adjusted ventilatory assist and HFNC[55]. Because ventilation targets, sedation, nutrition, and developmental support changed concurrently, the independent contribution of HFNC cannot be isolated. These findings are hypothesis-generating and should not be interpreted as evidence of direct neuroprotection.

9.3 Short-Term Hyperoxic Exposure

During microlaryngoscopy, THRIVE did not increase measured markers of oxidative stress or organ injury relative to mechanical ventilation. Short-term high-flow oxygen during elective cardioversion likewise did not significantly alter high-sensitivity troponin concentrations[56,57]. These studies provide only limited safety information for brief procedural exposures and cannot be extrapolated to prolonged or repeated hyperoxia.

10 Limitations and Future Research

Available studies span healthy volunteers, neonates, perioperative adults, and patients with diverse forms of respiratory failure. Differences in airway anatomy, respiratory demand, lung recruitability, and circulatory reserve limit generalizability. Randomized trials also used different comparators, including conventional oxygen therapy and NIV. Initiation timing, flow, FiO_2, and escalation criteria were inconsistent[44-46]. Accordingly, average treatment effects should not substitute for individualized phenotypic assessment.

Much of the evidence relies on short-term surrogate endpoints, including esophageal pressure, electrical impedance tomography, lung ultrasound, echocardiography, or gastric imaging. Small cohorts, retrospective studies, and case reports help identify mechanisms and risks but remain susceptible to selection bias and confounding. Definitions of treatment failure, escalation, and intubation also vary across studies.

Flow-dependent effects further limit the applicability of fixed protocols. A 17-patient physiological study found different degrees of inspiratory unloading and lung-volume change at 30, 45, and 60 L/min. A 49-patient PTIF study suggested stepwise titration using oxygenation, the ROX index, and tolerance, while a systematic review found no standardized initiation or adjustment algorithm[10,23,39]. Together, these findings support individualized assessment but do not establish a single threshold applicable to all adults.

Future studies should comprehensively report flow, FiO_2, temperature, cannula size, mouth position, exposure duration, and co-interventions. They should also prespecify oxygenation targets and criteria for treatment failure and escalation. Prospective trials could stratify patients by respiratory drive, ventilatory pump function, lung recruitability, preload status, right ventricular reserve, and gastrointestinal risk. They should link serial physiological measures to intubation, comfort, complications, survival, and resource use.

11 Conclusions

HFNC is fundamentally a flow-based modality for providing respiratory support. Its relatively consistent short-term physiological effects include reduced room-air entrainment, anatomical dead-space washout, lower inspiratory load in some patients, and preserved end-expiratory lung volume. The magnitude of each effect depends on patient demand, interface characteristics, breathing pattern, and organ reserve.

Clinical use should match the intended mechanism to the patient's phenotype. Flow should be titrated to inspiratory demand and respiratory load, whereas FiO_2 should be adjusted to the oxygenation target. Gas exchange, respiratory effort, circulation, and tolerance require repeated reassessment. HFNC cannot replace NIV or invasive ventilation when either is clearly indicated. Current evidence supports lower intubation or reintubation rates in selected populations, but effects on mortality and long-term resource use remain inconsistent.

Declarations

Ethics Approval and Consent to Participate

This narrative review did not involve human participants, animal experiments, or identifiable personal data. Therefore, ethics approval and informed consent were not required.

Consent for Publication

Not applicable. This manuscript contains no identifiable personal information, images, or clinical case details.

Availability of Data and Materials

This narrative review is based on previously published literature and generated or analyzed no new primary data. All cited materials are available through the publications listed in the references.

Competing Interests

The authors declare that they have no competing interests.

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Author Contributions

Yuqi Cai conceptualized the review, conducted the literature search and evidence synthesis, drafted the original manuscript, and led the major revisions.
Xiaorui Zhou contributed to literature screening and evidence interpretation and participated in drafting and revising the manuscript.
Mu Jin assisted with data collection, verified key references, and advised on manuscript structure and clarity.
Chenghui Zhou contributed to evidence interpretation and synthesis and reviewed the manuscript for important intellectual content.
Sheng Wang supervised the project, contributed to its conceptual design, critically revised the manuscript for important intellectual content, and approved the final version as corresponding author.

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