Supplementary File-4. Summary tables of the studies (5 tables).

Table 1. Summaries of Studies Comparing Different Preoxygenation Methods in Patients Undergoing Rapid Sequence Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies in which oxygenation was not applied during the apneic period (pure preoxygenation studies)						
Baillard	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients admitted to medical or surgical ICUs with acute respiratory failure and hypoxemia (PaO_2 <100 mmHg while receiving 10 L/min oxygen via face mask).. Exclusion Criteria: Encephalopathy, coma, cardiac resuscitation, hyperkalemia (≥5.5 mEq/L), and patients with a prior failed trial of NIV.	Group 1 (NIV): Preoxygenation with NIV using an ICU ventilator via face mask (FiO_2 100%, PEEP 5 cmH_2O), with tidal volume set at 7–10 mL/kg. Group 2 (BVM): Preoxygenation with a non-rebreather bag-valve-mask at 15 L/min oxygen, allowing spontaneous breathing with intermittent assistance as needed.	Primary outcome: Mean decrease in SpO_2 during intubation. Secondary outcomes: PaO_2 measured at 5 and 30 minutes after intubation.	A total of 57 patients were included (29 in the NIMV group, 28 in the control group). After preoxygenation, SpO_2 increased significantly more in the NIMV group (from 89 ± 6% to 98 ± 2%) compared with the control group (from 90 ± 5% to 93 ± 6%) ($p < 0.05$). The lowest SpO_2 during intubation was higher in the NIMV group (93 ± 8% vs 81 ± 15%; $p < 0.001$), and fewer patients experienced SpO_2 < 80% (2 vs 12; $p < 0.01$). PaO_2 values at the end of preoxygenation and at 5 and 30 minutes after intubation were also significantly higher in the NIMV group ($p < 0.01$).	None

Baillard	Multicenter, assessor-blinded, randomized controlled trial.	Inclusion Criteria: Adult ICU patients with acute hypoxemic respiratory failure requiring intubation (PaO_2/FiO_2 ≤300 mmHg and SpO_2 ≤95% on room air). Exclusion Criteria: Age <18 years, pregnancy, cardiac arrest, facial trauma or deformity, respiratory arrest, do-not-intubate decision, and need for urgent/emergent intubation.	Group 1 (NIMV): Preoxygenation for 3 minutes before intubation using NIMV via a face mask with 100% FiO_2 (pressure support 8 cmH_2O, PEEP 5 cmH_2O). Group 2 (Face mask): Preoxygenation for 3 minutes using a nonrebreather face mask with 100% oxygen at a flow rate of 15 L/min.	Primary outcome: Maximum Sequential Organ Failure Assessment (SOFA) score within 7 days after intubation. Secondary outcomes: Severe hypoxemia during intubation (SpO_2 <80%), adverse events (arrhythmia associated with hemodynamic deterioration, regurgitation, myocardial ischemia, failure of preoxygenation), number of organ failures, ICU-free and ventilator-free days within 28 days, ICU mortality within 28 days.	Total number of patients: 201 (NIMV: 99, Face mask: 102). Median maximum SOFA score within the first 7 days: NIMV group 9 [IQR 6–12], Face mask group 10 [IQR 6–12]; p=0.65. Number of organ failures per patient: 1 [0–2] in both groups; p=0.42. Severe hypoxemia during intubation (SpO_2 <80%): NIMV 18.4% vs Face mask 27.7%; p=0.10. Preoxygenation failure: 5 patients (4.9%) in the Face mask group, 0 in the NIMV group. Among patients previously receiving NIMV, intubation-related adverse events were more frequent in the Face mask group compared with the NIMV group (OR 5.2; 95% CI 1.4–19.5; p=0.006). There were no significant differences between groups in 28-day mortality, ventilator-free days, or ICU-free days.	None

Guitton	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) admitted to the ICU who required endotracheal intubation and had a PaO_2/FiO_2 ≥200 within the 4 hours prior to enrollment. Exclusion Criteria: Anatomical nasopharyngeal obstruction, Cormack–Lehane grade 4 glottic view, patients under legal protection, pregnancy, lack of informed consent, prior endotracheal intubation in the ICU, intubation without rapid sequence induction (e.g., during cardiac arrest), fiberoptic intubation, and conditions requiring emergent airway management due to asphyxia.	Group 1 (HFNO): Preoxygenation using high-flow nasal oxygen therapy at a flow rate of 60 L/min. Group 2 (BVM): Standard preoxygenation using a disposable, self-inflating bag-valve-mask with reservoir, delivering 100% oxygen at 15 L/min.	Primary outcome: Median lowest SpO_2 measured during intubation. Secondary outcomes: SpO_2 levels from the start of preoxygenation to the end of intubation; episodes of SpO_2 dropping below 95%, 90%, and 80%; incidence of difficult intubation; adverse events and organ failure within the first 5 days; duration of mechanical ventilation; length of ICU stay; incidence of ventilator-associated pneumonia; 28-day mortality.	Total of 183 patients (HFNO: 94, BVM: 89). The median [IQR] lowest SpO_2 during intubation was 100% [97–100] in the HFNO group and 99% [95–100] in the BVM group, with no statistically significant difference between groups (p=0.30). In multivariable analysis, HFNO was associated with a lower frequency of desaturation below 90% and fewer intubation-related complications, as well as a trend toward reduced oxygen desaturation below 80% (p=0.058).	None .

Gibbs	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Critically ill patients aged ≥18 years undergoing tracheal intubation with sedation and laryngoscopy in 7 emergency departments and 17 intensive care units. Exclusion Criteria: Pregnant patients, prisoners, patients already receiving positive-pressure ventilation, presence of apnea/hypopnea, need for emergent intubation, and cases in which the operator deemed noninvasive mechanical ventilation or an oxygen mask to be mandatory or contraindicated.	Group 1 (NIMV): NIMV delivered via a tight-fitting mask using a mechanical or dedicated NIMV ventilator; FiO_2 100%, EPAP ≥5 cmH_2O, IPAP ≥10 cmH_2O, respiratory rate ≥10/min; applied from the start of preoxygenation until laryngoscopy. Group 2 (Oxygen Mask): Supplemental oxygen via a non-rebreather mask or bag-valve-mask device (without manual ventilation); highest available oxygen flow (≥15 L/min); applied until laryngoscopy.	Primary outcome: Hypoxemia (SpO_2 <85%) from induction of anesthesia until the 2nd minute after intubation. Secondary outcomes: Lowest SpO_2 during the same interval; hemodynamic events (hypotension, vasopressor use, cardiac arrest); markers of aspiration (clinical, radiologic, physiologic).	Total of 1301 patients (645 NIMV, 656 oxygen mask). Hypoxemia occurred in 9.1% (57/624) of the NIMV group and 18.5% (118/637) of the oxygen mask group (absolute risk difference: −9.4%, 95% CI −13.2 to −5.6; P<0.001). Median lowest SpO_2: 99% [IQR 95–100] with NIMV versus 97% [IQR 89–100] with oxygen mask (median difference: 2%; 95% CI 1–3). The effect of NIMV was more pronounced in patients with higher BMI.	None

Li	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adults aged 18–60 years of either sex, requiring emergency surgery; fasting duration <8 hours and no fluid intake within the last <2 hours; body mass index (BMI) 18–35 kg/m²; ASA Physical Status I–III; NYHA functional class I–II. Exclusion Criteria: Pregnancy; high risk of aspiration (e.g., bowel obstruction, diaphragmatic hernia, altered mental status); presence of a gastric tube; contraindications to nasopharyngeal airway placement.	Group 1 (HFNO): 100% oxygen delivered via a nasopharyngeal airway at a flow rate of 30–60 L/min. Group 2 (Mask Group): 100% oxygen delivered via a face mask securely fixed with a four-point head strap at a flow rate of 8 L/min. Preoxygenation was applied for 3 minutes with instructions for deep breathing.	Primary outcome: Arterial partial pressure of carbon dioxide ($PaCO_2$) at T1, T2, and T3. Secondary outcomes: Arterial partial pressure of oxygen (PaO_2) at T1–T3; gastric antrum cross-sectional area (CSA) at T1 and T3; complication rate. Timeline: Preoxygenation (T0), post-induction (T1), post-intubation (T2), post-initiation of mechanical ventilation (T3).	Total of 115 patients (58 HFNO, 57 Mask). $PaCO_2$ was significantly lower in the HFNO group at all time points: T1 (32.3 vs 34.6 mmHg, P=0.045), T2 (45.0 vs 49.4 mmHg, P<0.001), T3 (47.9 vs 52.9 mmHg, P<0.001). PaO_2 was significantly higher in the HFNO group at T1 (median 404.5 vs 358.9 mmHg, P=0.007), T2 (343.0 vs 258.3 mmHg, P<0.001), and T3 (333.5 vs 149.8 mmHg, P<0.001). There was no significant difference between groups in CSA measurements. Hypoxemia occurred in 1 patient (1.7%) in the HFNO group and in 9 patients (15.8%) in the mask group (P=0.019). There were no significant differences between groups with respect to other complications.	None
Studies in which preoxygenation was continued throughout the apneic period						

Frat	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged ≥18 years admitted to the ICU with acute hypoxemic respiratory failure requiring intubation. Exclusion Criteria: Intubation due to cardiac arrest, Glasgow Coma Scale <8, contraindications to NIMV, pregnant or breastfeeding women, and patients who refused participation.	Group 1 (NIMV): Preoxygenation was performed using a face mask connected to an ICU ventilator. Pressure support was adjusted to achieve an expiratory tidal volume of 6–8 mL/kg of predicted body weight; PEEP 5 cmH_2O, FiO_2 1.0. Group 2 (HFNO): Preoxygenation was performed by delivering continuous oxygen at a flow of 60 L/min via a bi-nasal cannula. High-flow oxygen provides oxygenation during preoxygenation,	Primary outcome: PaO_2 after tracheal intubation.	There were 142 patients in Group 1 and 171 patients in Group 2. The mean (SD) PaO_2 was 43.7 (15.2) kPa in the apneic oxygenation group and 41.9 (16.2) kPa in the control group (p=0.722); $PaCO_2$ values were 5.8 (1.1) kPa and 5.6 (1.0) kPa, respectively (p=0.631); arterial pH values were 7.36 (0.05) and 7.34 (0.06), respectively (p=0.447).	The study was not blinded, and the authors noted that the more controlled and careful laryngoscopy/intubation performed in the intervention group may have attenuated any potential superiority of the technique with respect to arterial blood gas outcomes. Because patients with pre-existing respiratory distress were excluded in this study, the degree of indirectness is high.

Chua	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged ≥21 years requiring RSI for any indication. Exclusion Criteria: Active do-not-resuscitate order; crash, awake, or delayed sequence intubations; need for NIV; cardiac arrest; suspected or confirmed skull base fracture or severe facial trauma preventing nasal cannula placement; pregnancy; incarceration.	Group 1 (NRB Group): Preoxygenation with NRB mask at flush flow only, followed by apneic oxygenation via nasal cannula at ≥15 L/min HFNO. Group 2 (HFNO): The HFNO group received heated and humidified oxygen at 37 °C with a flow of 60 L/min and >90% FiO_2 during both the preoxygenation and apneic oxygenation phases.	Primary outcome: The lowest SpO_2 recorded during the first intubation attempt. Secondary outcomes: Incidence of SpO_2 dropping below 90% and safe apnea time (the duration until successful intubation while SpO_2 remained ≥90%).	There were 93 patients in the control group and 97 patients in the intervention group. There was no statistically significant difference between the intervention and control groups in terms of the lowest SpO_2 recorded during the first intubation attempt (median SpO_2 100% [96.0–100] vs 100% [91.0–100], p=0.138). In quantile regression analysis adjusting for significant covariates, the first quartile of the lowest SpO_2 achieved during the first intubation attempt was 5.5% higher in the intervention group compared with the control group (95% CI 1.5–9.5, p=0.007). The median safe apnea time was 10 minutes in the intervention group and 7 minutes in the control group, corresponding to a 3.0-minute longer duration in the intervention group (p=0.082).	The use of HFNO for preoxygenation and apneic oxygenation did not improve the median lowest SpO_2 achieved during the first intubation attempt compared with usual care. However, this approach may prolong the safe apnea time.

Tarigonda	Randomized clinical trial	Inclusion Criteria: ICU-admitted patients aged 18–65 years with hypoxemic respiratory failure who were hemodynamically stable. Exclusion Criteria: Suspected difficult airway, contraindication to nasopharyngeal airway placement, contraindication to NIMV, pregnancy/breastfeeding.	Group 1 (NIMV + NC): Preoxygenation for 5 minutes with NIMV using FiO_2 100%, 5 cmH_2O PEEP, and 10 cmH_2O pressure support. Apneic oxygenation was provided using a nasal cannula at a flow rate of 15 L/min. Group 2 (NIMV + NPA): Preoxygenation again for 5 minutes with NIMV using FiO_2 100%, 5 cmH_2O PEEP, and 10 cmH_2O pressure support. Apneic oxygenation was provided via a nasopharyngeal airway connected to the ventilator circuit with 10 cmH_2O CPAP	Primary outcome: The decrease in SpO_2 between peri-intubation oxygenation techniques when oxygen is delivered via nasal cannula versus CPAP delivered via a nasopharyngeal airway. Secondary outcomes: Intubation difficulty assessed using the Intubation Difficulty Scale (IDS); incidence of adverse events such as bradyarrhythmia/tachyarrhythmia and cardiac arrest.	Twenty-five patients were included in each group. The lowest SpO_2 recorded after intubation was 93.96 ± 4.38 in Group 1 and 96.08 ± 4.6 in Group 2 ($p = 0.104$).	None

Karlupia	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients requiring rapid sequence intubation (RSI) for emergency abdominopelvic surgery. Exclusion Criteria: Pregnancy, severe cardiopulmonary disease, laryngotracheal stenosis, suspected or confirmed skull base fracture or facial trauma preventing nasal cannula placement, hypopharyngeal obstruction, BMI ≥40 kg/m².	Group 1 (HFNO): Preoxygenation was performed using HFNO at a flow rate of 60 L/min and was continued throughout the apneic period and during laryngoscopy. Group 2 (Face Mask): Preoxygenation was performed using a face mask delivering oxygen at 12 L/min and was continued throughout the apneic period.	Primary outcome: PaO_2 measured immediately after intubation (ABG). Secondary outcomes: Lowest SpO_2 within the first 5 minutes after intubation, apnea duration, number of laryngoscopy attempts, use of rescue maneuvers, and adverse events such as desaturation (SpO_2 ≤90%) or hemodynamic instability.	A total of 80 patients were included (40 in each group). The mean PaO_2 was 258 ± 106 mmHg in Group 1 and 239 ± 107 mmHg in Group 2 (P > 0.05). There were no significant differences between the groups in terms of $PaCO_2$, pH, HCO_3, or lactate values. The median lowest SpO_2 was similar between groups (97% in Group 1 vs 97.5% in Group 2, P > 0.05). There were no significant differences with respect to adverse events or the use of rescue maneuvers.	None

RSI: Rapid sequence intubation, ICU: Intensive care unit, NC: Nasal cannula, NRB: Non-rebreather mask, BiPAP: Bilevel Positive Airway Pressure, BVM: Bag-valve-mask, HFNC: High-flow nasal cannula, SpO_2: Oxygen saturation, NIMV: Non-invasive mechanical ventilation, ASA: American Society of Anesthesiologists, NYHA: New York Heart Association, NPA: Nasopharyngeal airway.

Table 2. Summaries of Studies Investigating the Effectiveness of Apneic Oxygenation in Patients Undergoing Rapid Sequence Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies Using the Same Preoxygenation Techniques						
Semler 2016	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged ≥18 years who will undergo endotracheal intubation in the medical ICU. Exclusion Criteria: Planned awake intubation, cases requiring intubation too urgently to allow randomization, and situations in which the use of a specific intraprocedural oxygenation method or laryngoscopy device is mandatory.	Control: Usual preoxygenation method (NRB, BiPAP, BVM, or standard nasal cannula). Apneic Oxygenation arm: In addition to the usual preoxygenation method, HFNC (15 L/min) was initiated prior to induction.	Primary outcome: Lowest SpO_2 level at 0 minutes after intubation. Secondary outcomes: Rates of severe desaturation defined as SpO_2 <80% and SpO_2 <90%.	There were 73 patients in the control group and 77 patients in the apneic oxygenation group. The median lowest SpO_2 was measured as 90% (80–96%) in the control group and 92% (84–99%) in the intervention group; there was no statistically significant difference between the groups (p=0.16). Apneic oxygenation did not affect the proportion of patients who experienced oxygen saturation <90%, <80%, or a desaturation greater than 3% during the procedure.	The results of this clinical study show that, in critically ill adult patients, apneic oxygenation during endotracheal intubation does not increase the lowest arterial oxygen saturation compared with usual care. Routine use of apneic oxygenation during emergency intubations is not recommended.

Caputo 2017	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: All adult patients aged ≥18 years presenting to the emergency department who required endotracheal intubation were included in the study. Exclusion Criteria: Patients who did not undergo 3 minutes of preoxygenation with 100% FiO_2 according to standard RSI protocol (via BVM, BiPAP, or NRB), patients in cardiac or traumatic arrest, and patients intubated without an apneic period were excluded from the study.	Control: Usual preoxygenation method (NRB, BiPAP, or BVM). Apneic Oxygenation: In addition to the usual preoxygenation method, HFNO (>15 L/min) was started simultaneously and continued until the end of intubation (apneic phase).	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: SpO_2 <80% (severe desaturation), SpO_2 <90% desaturation, and first-attempt intubation success rate.	There were 102 patients in the control group and 104 patients in the intervention group. The mean lowest SpO_2 was 93% (SD 5.1) in the control group and 92% (SD 5.1) in the apneic oxygenation group, with no statistically significant difference between groups (p=0.08). Severe desaturation (SpO_2 <80%) occurred in 4 patients in the control group and 3 patients in the apneic oxygenation group.	This study demonstrated that, in patients who received adequate preoxygenation during rapid sequence intubation in the emergency department, the use of apneic oxygenation did not result in a significant difference in mean lowest oxygen saturation, rates of desaturation, or successful intubation without hypoxemia.

Shahul Hameed 2024	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged ≥18 years presenting to the emergency department with acute hypoxemic respiratory failure requiring RSI were included in the study. Exclusion Criteria: Patients whose relatives did not provide consent, pregnancy, contraindication to nasopharyngeal cannula placement, and patients assessed as having a difficult airway were excluded from the study.	Control: Standard preoxygenation using a BVM. Apneic Oxygenation: In addition to preoxygenation via BVM, nasopharyngeal oxygen therapy (>15 L/min) was initiated simultaneously and continued until the completion of intubation (apneic phase).	Primary outcome: Lowest SpO_2 levels immediately after intubation (0 minute).	There were 38 patients in the control group and 38 patients in the intervention group. The median SpO_2 was 89% (76–98%) in the control group and 95% (80–99%) in the intervention group, with no statistically significant difference between groups (p=0.27).	In the intervention group, there was no significant difference in the incidence of hypoxemia during intubation or in the prevention of post-intubation adverse events.
Studies Using Different Preoxygenation Techniques						

Vourc'h 2015	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients aged ≥18 years with acute hypoxemic respiratory failure requiring endotracheal intubation. Exclusion Criteria: Contraindication to orotracheal intubation; intubation without rapid sequence induction (RSI); pregnancy or lack of informed consent.	Control: Preoxygenation using only a face mask with 15 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at a flow rate of 60 L/min.	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcome: SpO_2 <90% (desaturation).	A total of 62 patients were included in the intervention group and 57 patients in the control group. The median lowest SpO_2 was 89.5% (81–95) in the control group and 91.5% (80–96) in the intervention group, with no significant difference between groups (p=0.44). Severe desaturation (SpO_2 <90%) occurred in 2 patients (3.5%) in the control group and 4 patients (6.5%) in the intervention group (p=0.49).	Despite its theoretical advantages, HFNO therapy in acutely severely hypoxemic patients was not found to be more effective than a high-FiO_2 face mask in preventing desaturation during endotracheal intubation.

Jaber 2016	Single-center, double-blind, randomized controlled trial.	Inclusion Criteria: Patients admitted to the intensive care unit requiring mechanical ventilation via an orotracheal tube were included in the study. Exclusion Criteria: Patients under 18 years of age, pregnant or breastfeeding women, individuals under legal protection, patients in cardiocirculatory arrest, nasopharyngeal obstruction preventing HFNO use, and patients with standard contraindications to NIMV were excluded.	Control: Preoxygenation for 4 minutes in a 30° head-up position using NIMV alone (PS 10 cmH_2O, PEEP 5 cmH_2O, FiO_2 100%). Apneic Oxygenation: In addition to NIMV, HFNO (60 L/min) was started simultaneously with preoxygenation and continued until the completion of intubation (apneic phase).	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: SpO_2 <80% (severe desaturation), intubation-related complications, and ICU morbidity.	A total of 25 patients were included in the apneic oxygenation group and 24 patients in the control group. The mean lowest SpO_2 was 91.5% (SD 12.5) in the control group and 94.6% (SD 15) in the intervention group; the difference was not statistically significant (p=0.08). Severe desaturation (SpO_2 <80%) occurred in 5 patients (21%) in the control group and 4 patients (16%) in the intervention group.	The results did not indicate any safety concerns and suggest that this novel approach may be more effective than the reference method using NIMV alone in increasing the minimal SpO_2 values during intubation in critically ill patients with severe hypoxemic respiratory failure.

Simon 2016	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) admitted to the ICU with acute hypoxemic respiratory failure (PaO_2/FiO_2 ≤300 mmHg) requiring endotracheal intubation. Exclusion Criteria: Contraindications to HFNO or BVM, nasopharyngeal obstruction, need for emergent intubation, and difficult or known difficult airway.	Control: Standard preoxygenation method using BVM with 10 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at a flow rate of 50 L/min.	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: Intubation-related complications and severe desaturation (SpO_2 <80%).	Her grupta 20 hasta yer aldı. Kontrol grubunda ortalama en düşük SpO_2 %86 (SS 11), apneik oksijenasyon grubunda %89 (SS 18) idi; fark anlamlı değildi (p=0.56). Ciddi desatürasyon (%<80), her iki grupta da 5 hastada (%25) görüldü (p=0.99). Hiçbir advers olay bildirilmedi.	None

Cırıl 2024	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) presenting to the emergency department who required RSI. Exclusion Criteria: Patients with a "do-not-resuscitate" order, trauma patients, cardiac arrest, delayed or crash intubation, history of facial trauma or surgery, prior use of HFNO or NIMV, need for a surgical airway, pregnancy, or missing 30-day mortality data.	Control: Preoxygenation using BVM with 15 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at 60 L/min.	Primary outcome: Lowest SpO_2 during RSI. Secondary outcomes: SpO_2 <90% (desaturation), SpO_2 <80% (severe hypoxemia), intubation duration, rate of failed intubation, 30-day mortality.	A total of 135 patients were included (HFNO group: 68, BVM group: 67). The median lowest SpO_2 was 92% (86–98) in the control group and 96% (89–99) in the apneic oxygenation group; the difference was not statistically significant (p=0.16). Severe desaturation (SpO_2 <80%) occurred in 6 patients (9%) in the control group and 9 patients (13.2%) in the apneic oxygenation group (p=0.4).	None
Studies Evaluating the Effectiveness of Apneic Oxygenation in Patients Intubated for Emergency Surgery						

Mir 2017	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged >16 years requiring rapid sequence induction (RSI) for general anesthesia in emergency surgery were included. Exclusion Criteria: Patients under 16 years of age, those unable to provide informed consent due to language barriers, or patients with severe respiratory disease were excluded.	Control: Patients in the face mask group received preoxygenation via face mask at an oxygen flow rate of 12 L/min for 3 minutes. Apneic Oxygenation: Preoxygenation was performed using HFNO at 30 L/min, and apneic oxygenation was provided using HFNO at 70 L/min.	Primary outcome: PaO_2 at the end of tracheal intubation.	Primary outcome: PaO_2 measured after intubation. A total of 40 patients were included in the study (20 in each group). The mean (SD) PaO_2 was 43.7 (15.2) kPa in the apneic oxygenation group and 41.9 (16.2) kPa in the control group (p=0.722). $PaCO_2$ values were 5.8 (1.1) kPa and 5.6 (1.0) kPa, respectively (p=0.631), and arterial pH values were 7.36 (0.05) and 7.34 (0.06) (p=0.447).	The study was not blinded, and the authors noted that this may have led to more controlled and careful laryngoscopy and intubation in the intervention group, potentially attenuating any advantage of the method with respect to arterial blood gases. Because patients with pre-existing respiratory distress were excluded, the level of indirectness in this study is high.

Lodenius 2018	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) requiring rapid sequence induction (RSI) under anesthesia for emergency surgery during daytime hours. Exclusion Criteria: BMI >35 kg/m², pregnancy, need for non-invasive ventilation to maintain oxygenation, or inability to provide consent.	Control: Preoxygenation was performed via a face mask for at least 3 minutes using 100% oxygen delivered at 10 L/min from a circle system. Apneic Oxygenation: Preoxygenation was performed using HFNO at 40 L/min, increased to 70 L/min during the apneic phase. The nasal cannula was left in place during intubation.	Primary outcome: Lowest SpO_2 during the RSI procedure.	A total of 79 patients were included in the study (39 in the control group, 40 in the apneic oxygenation group). The median lowest SpO_2 was 99% (range: 70–100) in the control group and 99% (range: 96–100) in the apneic oxygenation group; the difference was not statistically significant (p=0.09).	None

Preya 2023	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged 18–60 years, ASA Physical Status I–III, requiring emergency laparotomy, and who provided written consent were included in the study. Exclusion Criteria: Patients with anatomically difficult airway, SpO_2 <95% on room air, hemoglobin <8 g/dL, hemodynamic instability (systolic blood pressure <90 mmHg and on vasopressor support), or coronary artery disease were excluded.	Control: Patients received preoxygenation via face mask at an oxygen flow rate of 5 L/min for 3 minutes. Apneic Oxygenation: In addition to preoxygenation via face mask, nasopharyngeal oxygen therapy (>10 L/min) was started simultaneously and continued until the completion of intubation (throughout the apneic phase).	Primary outcome: Decrease in the partial pressure of oxygen (PaO_2) after 90 seconds of apnea.	Primary outcome: Magnitude of decrease in partial pressure of oxygen (PaO_2) after 90 seconds of apnea. During the 90-second apneic period following preoxygenation, PaO_2 decreased by 38% in the control group and by 12% in the intervention group (P<0.001).	In this study, patients with pre-existing respiratory distress and baseline SpO_2 <95% were excluded, resulting in a high degree of indirectness.

RSI: Rapid Sequence Intubation, ICU: Intensive Care Unit, NRB: Non-rebreather Mask, BiPAP: Bilevel Positive Airway Pressure, BVM: Bag-Valve-Mask, HFNO: High-Flow Nasal Oxygen, SpO_2: Oxygen Saturation, NIMV: Non-invasive Mechanical Ventilation

Table 3. Summary of Studies Comparing Gum Elastic Bougie with Standard Intubation (with or without Stylet) in Tracheal Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Ghai 2022	Randomized clinical trial	Participants: 80 patients undergoing elective surgery. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Success rate of intubation. Secondary outcomes: Intubation duration, complications.	Results: First-attempt success: Bougie 50% (20 of 40 patients), standard intubation 60% (24 of 40 patients). Duration: Bougie 62.80 ± 20.74 seconds, standard intubation 52.44 ± 14.23 seconds (p=0.01). Overall success within two attempts was similar (Bougie 90% vs Standard 95%, p=0.55).	Randomization was reported, but the allocation concealment was not described. No serious adverse events were reported.
Bawa 2022	Randomized clinical trial	Participants: 100 patients (50 per group) undergoing elective or emergency surgery, ASA Physical Status I–II. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Intubation duration. Secondary outcomes: Number of attempts, hemodynamic changes, sore throat.	Results: First-attempt success: Bougie 80% (40 of 50 patients), Stylet 82% (41 of 50 patients) (p=0.196). Duration: Bougie 33.78 ± 20.49 seconds, standard intubation 22.16 ± 6.65 seconds (p<0.05).	Sore throat was more frequent in the Stylet group (12 vs 6 patients, p=0.02). Desaturation: 0 vs 1; esophageal intubation: 1 vs 0. Randomization was reported.

Driver 2021	Randomized clinical trial	Participants: 1,102 critically ill patients undergoing emergency intubation. Study setting: Emergency department and ICU (7 emergency departments and 8 ICUs).	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt success rate. Secondary outcomes: Hypoxemia, esophageal intubation, trauma.	First-attempt success: Bougie 80.4% (447/556), Stylet 83% (453/546) (p=0.27). Absolute risk difference: −2.6% [95% CI, −7.3 to 2.2]. Median time from induction to intubation: Bougie 124 sec (IQR 97–180), Stylet 112 sec (IQR 85–157). Mean ± SD time: Bougie 133.7 ± 61.5 sec; Stylet 118 ± 53.3 sec.	Severe hypoxemia: Bougie 11.0% (58/556), Stylet 8.8% (46/546). Esophageal intubation: Bougie 0.7% (4), Stylet 0.9% (5). Pneumothorax: Bougie 2.5% (14), Stylet 2.7% (15). Oral, glottic, or thoracic injury: Bougie 0%, Stylet 0.5% (3). No significant differences were observed in complications.

Driver 2018	Randomized clinical trial	Participants: 757 patients (>17 years) undergoing intubation in the emergency department, including both difficult and non-difficult airways. Study setting: Emergency department.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt success rate. Secondary outcomes: Duration, hypoxemia, esophageal intubation.	Results: First-attempt success: Bougie 98% (373/381), Stylet 87% (328/376) (absolute difference 11% [95% CI, 7–14], p<0.001). No differences were observed regarding hypoxemia or trauma. Subgroups: Difficult airway: Bougie 96% (191/198), Stylet 82% (150/182). Non-difficult airway: Bougie 99% (182/183), Stylet 92% (178/194). First-attempt durations: Bougie 38 sec (29–51), Stylet 36 sec (25–54). Mean ± SD: Bougie 39.3 ± 16.3 sec; Stylet 38.3 ± 21.5 sec.	The incidence of hypoxemia was similar (13% vs 14%). This is a multicenter, methodologically robust randomized controlled trial.

Dutta 2020	Randomized clinical trial (3-arm).	Participants: 450 patients aged 18–65 years, ASA Physical Status I–II, undergoing laparoscopic or open general surgery. Study setting: Operating room.	Intervention 1: Intubation assisted by a rigid tracheal tube introducer (TTI). Intervention 2: Intubation assisted by a flexible (non-rigid) TTI (gum elastic bougie). Control: Standard intubation (use of stylet not specified).	Primary outcome: Postoperative sore throat (POST) scored from 0–3. Secondary outcomes: Laryngoscopy quality, number of attempts, intubation duration, minor complications (airway obstruction, stridor).	Results: POST incidence was lowest in the rigid TTI group (29%), significantly lower than standard intubation (45.1%, p=0.005); no significant difference was observed between the rigid TTI and non-rigid TTI (bougie) groups (37.9%, p=0.117). Intubation duration: Standard 20.7 ± 5.3 sec, rigid TTI 25.7 ± 4.6 sec, bougie (non-rigid TTI) 26.6 ± 7.5 sec (p=0.000). Patients requiring more than one attempt: Standard 8.5%, rigid TTI 1.4%, bougie 1.4% (p=0.011).	First-attempt success rate was not reported. No differences were observed in complications such as laryngospasm or stridor. Analysis was conducted per protocol.

Sut 2016	Randomized clinical trial (3-arm).	Participants: Elective surgical patients aged 18–65 years, ASA Physical Status I–II, with a cervical collar applied to simulate a difficult airway.	Intervention 1: Gum elastic bougie. Intervention 2: ILMA (intubating laryngeal mask). Control: Standard intubation (use of stylet not specified).	Primary outcome: Intubation success. Secondary outcomes: Intubation duration, number of attempts, Cormack–Lehane classification. (The study does not clearly specify which outcome was primary.)	Results: First-attempt success: Bougie 93%, ILMA 45%, standard intubation 60% ($p<0.001$). Mean intubation duration: Bougie 36.0 ± 0.6 sec, Standard 41.0 ± 1.1 sec, ILMA 92.0 ± 1.0 sec (all comparisons $p<0.05$). Intraoperative complications: Bougie 6%, Standard 13%, ILMA 34% ($p=0.02$). Postoperative sore throat: Bougie 73%, Standard 64%, ILMA 50% ($p=0.07$).	No differences were observed between groups in systolic/diastolic blood pressure, heart rate, SpO_2, or $EtCO_2$ values.

Khan 2014	Randomized clinical trial	Participants: 56 patients aged >11 years, ASA Physical Status I–II, with a rigid Philadelphia cervical collar applied to simulate a difficult airway. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Overall success rate. Secondary outcomes: Number of attempts, need for alternative airway, complications.	Results: Overall success: Bougie 100%, standard intubation 71.4% (p=0.002). Fewer attempts were required in the Bougie group. First-attempt success: Bougie 78.5% (22/32), standard 50% (10/20). First-attempt duration was not measured.	Due to the small sample size, the statistical power was limited. No adverse events were reported.
Heegaard 2003	Randomized clinical trial	Participants: 51 critically ill patients aged >11 years requiring emergency intubation. (Criteria for “critically ill” were not explicitly defined.) Study setting: Prehospital environment.	Treatment group: Gum elastic bougie. Control group: Standard intubation (use of stylet not specified).	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, number of attempts, complications.	Results: First-attempt success: Bougie 70% (16/20), standard 65% (20/31) (p=0.67). No differences were observed in complications. Mean total intubation duration was 62 seconds (no difference between groups, p=0.4).	Complications: One esophageal intubation occurred in the Bougie group, and two in the standard group.

Noguchi 2003	Randomized clinical trial	Participants: 60 patients undergoing elective surgery, ASA Physical Status I–III. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, ease of intubation, failure rate.	Results: Intubation success: Bougie 96.7% (29/30), Stylet 96.7% (29/30). (It is not specified whether this represents first-attempt or overall success.) Mean duration: Bougie 31 ± 7 sec, Stylet 27 ± 3 sec (p=0.09).	No adverse events were reported.
Gataure 1996	Randomized clinical trial	Participants: 100 elective surgical patients, ASA Physical Status I–II. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, complications.	Results: Overall success within two attempts: Bougie 96%, standard intubation 66% (p<0.001). First-attempt success: Bougie 82%, Stylet 48%. First-attempt duration: Bougie 14.4 ± 0.3 sec, Stylet 15.1 ± 0.6 sec.	No adverse events were reported.

Nolan 1993	Randomized clinical trial	Participants: 157 elective surgical patients with cervical spine immobilization using a cervical collar. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Standard intubation (use of stylet not specified).	Primary outcome: Intubation duration. Secondary outcomes: Success rate, complications, number of failed attempts.	Results: Success: Bougie 100% (83/83), standard intubation 93% (69/74). Mean duration: Bougie 26 sec (range 15–45), standard 20 sec (range 13–95).	The study demonstrates that bougie use increases intubation success in patients with cervical spine injuries. No adverse events were reported.

ASA: American Society of Anesthesiologists classification, ICU: Intensive Care Unit, CI: Confidence Interval, IQR: Interquartile Range, SD: Standard Deviation, TTI: Tracheal Tube Introducer, POST: Postoperative Sore Throat, ILMA: Intubating Laryngeal Mask Airway, SpO_2: Oxygen Saturation, $EtCO_2$: End-tidal Carbon Dioxide.

Table 4. Summary of Studies Evaluating Bolus Dose Vasopressor Use During Rapid Sequence Intubation in Critically Ill or Hypotensive Patients

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies on Bolus Dose Vasopressor Use During RSI or the Peri-Intubation Period						
Panchal 2015	Retrospective observational study (single-arm).	Participants: 20 adult patients in the emergency department requiring intubation with systolic blood pressure (SBP) <90 mmHg; received a bolus dose of phenylephrine during the 30-minute period before or after intubation. Mean age: 64 ± 16 years; 50% male. Diagnoses: Respiratory failure, pneumonia, sepsis, trauma.	Intervention: Bolus phenylephrine (100 mcg/mL, IV). Thirteen patients (65%) received more than one dose; median administration time was 2 minutes after intubation (range −18 to +29 minutes). Seventy percent additionally received other vasopressors (norepinephrine, dopamine, etc.).	Outcome measures: Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) before and after the first phenylephrine bolus; data were recorded up to 60 minutes post-intubation.	Results: Mean SBP increased from 73 to 93 mmHg ($p < 0.01$). Mean DBP increased from 42 to 52 mmHg ($p < 0.01$). Heart rate did not change (114 → 115 bpm, $p > 0.05$). No arrhythmias or adverse events were reported.	Bolus phenylephrine during RSI produced a significant increase in blood pressure. The application was not standardized; in most patients, it served as a bridge to continuous vasopressor infusion. This supports the rapid effect of phenylephrine but highlights the need for standardization and further research.

Schwartz 2016	Retrospective observational study (single-arm).	Participants: 73 adults in the emergency department receiving bolus-dose phenylephrine for acute hypotension (71.2% received vasopressors around RSI). Median age: 65 years. Diagnoses: Septic shock (45.2%), respiratory failure (19.2%), stroke, cardiac arrest, pulmonary embolism.	Intervention: IV phenylephrine 100–200 mcg administered from prefilled syringes. Timing relative to intubation (±60 minutes) was recorded. Administration was assessed in the context of at least 30 mL/kg fluid resuscitation prior to phenylephrine.	Primary outcome: Initiation rate of continuous vasopressor infusion (CVI) within 30 minutes after the first phenylephrine dose. Secondary outcomes: Hemodynamic response (SBP, HR), number of doses administered, adverse events.	Results: Continuous vasopressor infusion (CVI) was initiated within 30 minutes in 46.5% of patients. Sixty-seven point one percent received fluids prior to phenylephrine; patients with adequate fluid resuscitation required fewer doses (1.5 vs 2.3 doses, p=0.01). SBP increased from 56.5 to 79.3 mmHg ($p < 0.05$). Adverse events occurred in 20.5% of patients: bradycardia 9.6%, reactive hypertension 8.2%, ventricular tachycardia (VT) 2.7%.	Highlights the relationship between fluid status and vasopressor response: inadequate fluid resuscitation is associated with higher vasopressor requirements. Hypotension related to RSI occurred in 71.2% of patients. The study is limited by its retrospective design and generalizability.

Swenson 2018	Retrospective observational study (single-arm).	Participants: 181 adults in the emergency department receiving bolus-dose phenylephrine, 62 (34%) administered around RSI. Mean age: 53.6 years; 59% male. Diagnoses: Sepsis, respiratory failure, trauma, cardiac arrest, drug overdose.	Intervention: Prefilled 1000 mcg/10 mL phenylephrine syringes; doses 10–500 mcg IV at the clinician's discretion. Repeated dosing was administered in 81 patients. Vital signs were recorded 30 minutes before and after administration.	Primary outcome: Adverse events: SBP >180 mmHg, DBP >110 mmHg, HR <50 bpm within 30 minutes. Secondary outcomes: Changes in MAP, SBP, DBP, HR; dose-response relationship.	Results: MAP increased in all dose groups; the greatest increase occurred in the 200–500 mcg group (+12 mmHg, p = 0.02). Five patients (2.8%) met the adverse event threshold: 3 with high SBP, 2 with bradycardia; no serious adverse events (SAE) occurred. Phenylephrine increased MAP even in patients with HR <50 bpm.	Phenylephrine is safe and produces a short-term effect in hypotensive emergency patients, including those undergoing RSI. Adverse events were rare and clinically insignificant. Limitations include the absence of a control group and a standardized dosing protocol.

Fuchita 2018	Secondary analyses of two multicenter RCTs (BOUGIE and PREPARE II) using propensity score matching.	Participants: 1,798 critically ill patients undergoing emergency intubation in the ED or ICU. 187 patients (10%) received prophylactic vasopressors and were matched 1:1 with 187 controls. Patients in cardiac arrest prior to intubation were excluded.	Intervention: Prophylactic vasopressor administration before intubation or during induction (bolus or infusion dose titration). The intervention was non-randomized; agent and dose were at the clinician's discretion.	Primary outcome: Development of SBP <90 mmHg within 2 minutes after intubation (peri-intubation hypotension). Secondary outcomes: ΔSBP, need for new vasopressors, cardiac arrest within 1 hour, 30-day mortality, ventilator-free and ICU-free days.	Results: In 374 matched patients, incidence of hypotension: Vasopressor 41% vs Control 32% (p = 0.08). ΔSBP: −12 vs −11 mmHg (p = 0.66). 30-day mortality: Vasopressor 57% vs Control 47% (p = 0.08). Need for new vasopressors: 40% vs 29% (p = 0.03). Low SBP was associated with increased mortality risk (OR 1.08 per 10 mmHg decrease, p = 0.001).	This represents the largest analysis conducted in RSI patients. Although non-randomized, it closely reflects clinical practice. Prophylactic vasopressor use did not reduce peri-intubation hypotension. Findings are limited by confounding variables, heterogeneity of agents used, and short follow-up duration.
Rotando 2019	Prospective observational study (single-arm).	Participants: 146 adults in the emergency department receiving bolus-dose phenylephrine or ephedrine for hypotension. 43% received the drug around RSI, 37% before procedures such as cardioversion, 20% for spontaneous hypotension.	Intervention: Phenylephrine (50–200 mcg IV) or ephedrine (5–10 mg IV) at the clinician's discretion. No standardized dilution protocol was used. Doses related to RSI were administered during or immediately after induction.	Outcomes: Changes in SBP before and after drug administration; adverse events (reactive hypertension, arrhythmia, ischemic events).	Results: Mean SBP increased from 80 to 106 mmHg (+26 mmHg, p < 0.001). Adverse events occurred in 11.6% of patients: reactive hypertension 7.5%, arrhythmia 4.1%, ischemia 0%.	This ED-based study includes 43% of cases associated with RSI. Both agents produced consistent increases in SBP. Although limited by lack of randomization and standardized protocol, it provides valuable real-world data.

Schmitt 2021	Retrospective matched cohort (propensity score matching).	Participants: 105 adults in the emergency department who developed peri-intubation hypotension (SBP <90 mmHg). Bolus-dose phenylephrine (PDPE), norepinephrine (NE), or PDPE + NE were administered within 30 minutes before or after intubation.	Groups: 1.PDPE (100 mcg/mL bolus) 2.NE infusion (0.02–0.1 mcg/kg/min) 3.PDPE + NE combination Agent selection and timing were at the clinician's discretion. RSI was mostly performed using etomidate and rocuronium.	Primary outcome: Cardiovascular instability within 2 hours after vasopressor initiation (SBP <90 mmHg, HR <60 bpm, cardiac arrest, or death).	Results: Composite outcome frequency: NE 88.6%, PDPE 80.0%, PDPE + NE 88.6% (p = 0.50). Hypotension 83.7%, bradycardia 19.4%, cardiac arrest 4.9%. In the sepsis subgroup, adverse events were more frequent (p = 0.045); bradycardia was notable in the NE group (p = 0.048).	Despite the high rate of instability, there were no differences among the three strategies. PDPE and NE were commonly used, yet clinical outcomes were similar. The small sample size and retrospective design are limitations, but the findings remain applicable to emergency intubation practice.
Davis 2023	Prospective observational study (multicenter).	Participants: 523 critically ill patients with hypotension during RSI in the air ambulance setting. 344 received arginine-vasopressin (aVP) for trauma, 179 received phenylephrine (PI) for non-trauma indications.	Intervention: Bolus-dose vasopressors during RSI: aVP 2 U IV/IO (every 5 min in trauma patients) or PI 200 mcg IV/IO (every 5 min in non-trauma patients). Administered according to protocol; repeat doses allowed.	Outcomes: Changes in SBP after drug administration, resolution of hypotension, need for repeat dosing, rebound hypertension, or cardiac arrest within 20 minutes.	Results: SBP increased from 61 → 109 mmHg (aVP) and 64 → 107 mmHg (PI). Hypotension resolution: aVP 79.1%, PI 82.1%. Recurrent hypotension: aVP 50.6%, PI 60.9%. Reactive hypertension 4.5%, cardiac arrest approximately 15%.	This is a large, field-based study focusing on RSI-related hypotension. Both agents rapidly increased SBP. However, being single-arm, the effects on clinically significant outcomes such as cardiac arrest remain unclear.
Studies Evaluating Bolus-Dose Vasopressor Efficacy in Hypotensive Situations Outside of RSI						

NAWROCKI 2019	Retrospective observational study (single-arm).	Participants: 52 critically ill patients transported by air ambulance who received bolus-dose adrenaline for hypotension (total 94 doses). Average age ~65.5 years.	Intervention: Adrenaline 10–20 mcg/dose (1:100,000), IV every 2 minutes as needed. Used as a bridge while preparing continuous infusion. Administered by nurse–nurse teams according to protocol.	Primary outcome: Changes in mean arterial pressure (MAP) and heart rate (HR). Secondary outcomes: Adverse events (tachycardia, arrhythmia, hypertension, cardiac arrest).	Results: MAP increased by +13 mmHg (IQR 5–34); HR increased by +2 bpm. Hypotension resolved in 58.5% of patients. Repeat doses were 50% effective; sequential doses 70% effective. Three post-bolus cardiac arrests were considered expected clinical events.	Adrenaline is effective as a bridge to infusion in prehospital care. Most patients were intubated. Adverse event rates were low, and administration protocols were clear. This is not specific to RSI but is contextually relevant.
SINGER 2022	Retrospective observational study (single-arm).	Participants: A total of 2,183 bolus-dose vasopressor administrations in critically ill patients in ICU or emergency department settings (2,041 phenylephrine, 142 adrenaline). Both agents were not used concurrently in the same patient; operating room administrations were excluded.	Intervention: Phenylephrine (100–200 mcg) or adrenaline (10–20 mcg) IV bolus using prefilled syringes. No bedside dilution was performed.	Primary outcome: ≥25% increase in SBP (defined as response). Secondary outcomes: Changes in MAP/DBP, adverse events (hypertension, bradycardia, tachycardia), cardiac arrest within 60 minutes, need for infusion, ICU/hospital length of stay, in-hospital mortality.	Results: Response rate: Phenylephrine 55.9%, Adrenaline 71.8% ($p < 0.001$). SBP increase: Phenylephrine +45 mmHg, Adrenaline +60 mmHg. Adverse events: Hypertension 6.5% (PE) vs 12% (Epi), tachycardia 35% vs 45%. ICU length of stay longer in PE responders ($p = 0.007$). Mortality ≈ 28% (no difference).	This represents the largest series of bolus-dose vasopressors to date. Adrenaline is more effective but has a higher rate of adverse events. Use of prefilled syringes improved safety. This is not specific to RSI but provides important real-world data on hypotension management.

NAM 2022	Retrospective observational study (single-arm).	Participants: 135 adults in the emergency department with SBP < 90 mmHg or MAP < 65 mmHg, including both intubated and non-intubated patients. Each patient received only one agent; those receiving both agents were excluded.	Intervention: Phenylephrine (100–200 mcg) or adrenaline (10–20 mcg) IV bolus, using prefilled syringes.	Primary outcome: Heart rate (HR) change within 30 minutes after drug administration. Secondary outcomes: SBP, DBP, MAP, shock index, adverse events, ICU/hospital length of stay, mortality, dosing errors.	Results: No significant change in HR (p = 0.139). SBP increase was greater with epinephrine: 33 vs 26 mmHg (p = 0.049). Percentage change in SBP was also higher with epinephrine (p = 0.039). Dosing errors: epinephrine 12.8%, phenylephrine 2.1% (p = 0.021). No differences in adverse events, ICU stay, or mortality.	Epinephrine produces a stronger SBP increase but carries a higher risk of dosing errors. Its use emphasizes the need for careful administration and standardization. Findings are not HAE-specific but provide comparative insights for managing hypotension in the emergency department.

HAE: Rapid Sequence Intubation, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, HR: Heart Rate, ICU: Intensive Care Unit, RCT: Randomized Controlled Trial, PDPE: Push-Dose Phenylephrine, NE: Norepinephrine, aVP: Arginine Vasopressin, Post-Intubation (PI), PDP: Push-Dose Vasopressor, PE: Phenylephrine, Epi: Epinephrine, LOS: Length of Stay.

Table 5. Summary of Studies Evaluating the Efficacy of Ketamine in Patients with Acute Brain Injury

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Randomized controlled trials conducted in patients with acute brain injury						
Burman 2025	Randomized controlled trial	Inclusion criteria: Patients with severe traumatic brain injury, Glasgow Coma Scale (GCS) score between 3–8, aged 18–49, under mechanical ventilation, and with an intracranial pressure (ICP) monitoring probe in place were included in the study.	Both groups received fentanyl (1 µg/kg/h) and midazolam (0.05–1 mg/kg/h). Treatment group: Ketamine infusion (3 mg/kg/h for 36 hours). Control group: 0.9% saline infusion (for 36 hours).	Primary outcome: Neurologic outcomes at 3 months. Secondary outcomes: Intracranial and systemic pressure dynamics in severe TBI patients.	Main findings: ICP values in the ketamine group remained lower over the 36-hour observation period. Statistically significant ICP reductions were observed at the 4th and 6th hours compared to the control group. Similarly, CPP values in the ketamine group were generally higher, with a significant difference observed between the 4th and 6th hours. There was no difference in 3-month neurological outcomes.	None

Bourgoin 2005	Randomized controlled trial	Inclusion criteria: Severe traumatic brain injury patients aged 18–75 years with Glasgow Coma Scale (GCS) <9 after resuscitation, and with cerebral perfusion pressure (CPP) monitoring.	Treatment group: Target plasma concentration: Ketamine 1.0 µg/mL + Midazolam 100 ng/mL. Control group: Target plasma concentration: Sufentanil 0.3 ng/mL + Midazolam 100 ng/mL.	Outcomes: Cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were continuously measured.	Main Findings: Total 30 patients (15 per group). On day 1, mean ICP: Ketamine group 14.6 ± 8.3 mmHg, Sufentanil group 18.7 ± 6.8 mmHg. Mean CPP: Ketamine group 83.2 ± 14.3 mmHg, Sufentanil group 75.6 ± 11 mmHg. No statistically significant differences between groups.	None
Bourgoin 2003	Randomized, double-blind, placebo-controlled study	Inclusion Criteria: Patients with traumatic brain injury, aged 16–75 years, post-resuscitation GCS score 3–8, requiring mechanical ventilation and ICP monitoring. Patients with high ICP risk based on computed tomography (CT) were included. Treatment Group: Midazolam 1 µg/kg/min + ketamine 50 µg/kg/min infusion.	Control Group: Midazolam 1 µg/kg/min + sufentanil 0.005 µg/kg/min infusion.	Outcomes: Continuous measurement of cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP).	Main Findings: Total 25 patients (12 ketamine, 13 sufentanil). Day 1 average ICP: Ketamine group 19 ± 8.4 mmHg, Sufentanil group 15.7 ± 6.8 mmHg. Day 2 average CPP: Ketamine 81 ± 7 mmHg, Sufentanil 80.4 ± 5.7 mmHg. No significant difference observed. Due to uncontrolled intracranial hypertension, additional sedation was required in 4/12 ketamine patients and 4/13 sufentanil patients.	None

Kolenda 1996	Randomized controlled trial	Inclusion Criteria: Patients aged 16–72 years with moderate or severe head trauma, undergoing ICP, MAP, and CPP monitoring.	Treatment Group: Midazolam 6.5 mg/kg/day + Ketamine 65 mg/kg/day. Control Group: Midazolam 6.5 mg/kg/day + Fentanyl 65 µg/kg/day.	Outcomes: Continuous monitoring of SPB, IKB, and mean arterial pressure (MAP). Additionally, neurological examinations were performed twice daily according to the Glasgow Coma Scale (GCS).	Main Findings: Total 24 patients (12 per group). Day 1 mean IKB: Ketamine 12 ± 2.2 mmHg, Fentanyl 13 ± 1.2 mmHg. Mean SPB: Ketamine 59 ± 5.2 mmHg, Fentanyl 67 ± 2.2 mmHg. No significant difference between groups. SPB was higher in the ketamine group compared to fentanyl due to increases in MAP.	Ketamine provided a supportive effect on cerebral perfusion pressure (CPP) due to its blood pressure–increasing properties.
Schmittner 2007	Randomized controlled trial	Inclusion Criteria: Patients diagnosed with severe traumatic brain injury (TBI) (Glasgow Coma Scale <9) or aneurysmal subarachnoid hemorrhage (Hunt-Hess > II).	Treatment Group: Ketamine 0.5 mg/kg IV bolus, followed by continuous infusion. Control Group: Fentanyl 3 µg/kg IV bolus, followed by continuous infusion. Doses were individually titrated to achieve adequate sedation.	Outcomes: Cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were continuously monitored.	Main Findings: Total 24 patients (12 per group). Day 1 mean ICP: Ketamine 15.9 ± 5.8 mmHg, Fentanyl 14.7 ± 3.4 mmHg. Mean CPP: Ketamine 82.5 ± 9.9 mmHg, Fentanyl 84.1 ± 12.2 mmHg. No significant differences between groups.	None

Michalczyk 2013	Randomized controlled trial	Inclusion Criteria: Pediatric patients with oncologic diagnoses scheduled for sedation prior to lumbar puncture.	Groups: Group A: Midazolam 0.1 mg/kg (max 4 mg) + ketamine 1 mg/kg Group B: Ketamine 1 mg/kg only Group C: Propofol + fentanyl combination	Outcome: Lumbar puncture opening pressure.	Main Findings: Total 25 patients, 84 procedures (Group A: 35, B: 39, C: 10). Mean opening pressures: A: 22 ± 7.56 mmHg B: 26.5 ± 8.03 mmHg C: 17.3 ± 6.92 mmHg The ketamine groups had significantly higher opening pressures.	Groups A and B were randomized, while the randomization method for Group C was not specified.
Yehuda 2006	Randomized controlled trial	Inclusion criteria: Pediatric patients undergoing lumbar puncture for suspected aseptic meningitis; sedation was administered prior to the procedure.	Groups: Group A: Ketamine 1 mg/kg + Midazolam 0.05 mg/kg Group B: Midazolam 0.1 mg/kg only	Outcome: Opening pressure measured after lumbar puncture.	Main Results: Total 39 patients (A: 26, B: 13). Mean opening pressures: A: 24.4 ± 8.87 mmHg, B: 20 ± 3.74 mmHg (p = 0.011).	None
Observational Studies on Ketamine Use						
Observational Studies Demonstrating the Effect of Ketamine in Patients with Acute Brain Injury Under Continuous ICP Monitoring						

Bar-Joseph 2009	Prospective, open-label clinical study	Inclusion Criteria: Children aged 1–16 years with sustained intracranial hypertension (ICP > 18 mmHg), unresponsive to first- and usually second-line treatments, currently under sedation and receiving mechanical ventilation.	Treatment Groups: Group 1: Patients receiving ketamine to prevent ICP increases during painful procedures. Group 2: Patients receiving ketamine as an additional intervention to reduce markedly elevated ICP.	Outcomes: Changes in ICP and CPP, hemodynamic stability.	Main Results: In 30 patients, a total of 82 ketamine administrations were evaluated. Overall, ICP decreased by 30% (25.8 ± 8.4 → 18.0 ± 8.5 mmHg, $p < 0.001$), CPP increased (54.4 ± 11.7 → 58.3 ± 13.4 mmHg, $p < 0.005$). • Group 1 (n=17): During intervention, only one case showed an ICP increase >2 mmHg. • Group 2: Ketamine administered for refractory intracranial hypertension resulted in a 33% decrease in ICP (26.0 ± 9.1 → 17.5 ± 9.1 mmHg, $p < 0.0001$).	This study directly challenges historical concerns that ketamine increases ICP. The results demonstrate that ketamine lowered ICP without causing hemodynamic adverse effects, suggesting it may be a potentially safe option in pediatric patients with TBI and intracranial hypertension.

Caricato 2013	Prospective observational study	Inclusion Criteria: Patients aged 18–75 years with closed head trauma within 72 hours post-injury, Glasgow Coma Scale (GCS) ≤ 8; patients with ICP monitoring in place receiving sedation with propofol + remifentanil targeting a Ramsay score of 5–6.	Treatment Arms: •Control Phase: Endotracheal suctioning (ETS) under propofol + remifentanil infusion. •Intervention Phase: In patients exhibiting a cough reflex, a 10-minute racemic ketamine infusion at 100 µg/kg/min was administered in addition to the existing sedation before ETS.	Outcomes: ICP, CPP, jugular venous oxygen saturation (SjO_2), mean flow velocity of the middle cerebral artery (mVMCA), cough reflex score, hemodynamic changes.	Main Findings: In the control group after ETS, mean arterial pressure (MAP) increased (89.0 ± 11.6 → 96.4 ± 13.1 mmHg, $p < 0.001$), intracranial pressure (ICP) increased (11.0 ± 6.7 → 18.5 ± 8.9 mmHg, $p < 0.001$), jugular venous oxygen saturation (SjO_2) increased (82.3 ± 7.5 → 89.1 ± 5.4, $p = 0.01$), and mean middle cerebral artery velocity (mVMCA) increased (76.8 ± 20.4 → 90.2 ± 30.2 cm/s, $p = 0.04$), while cerebral perfusion pressure (CPP) remained unchanged. Median cough score was 2 [IQR 1–2]. In the ketamine group, only ICP increased (11.0 ± 6.4 → 15.1 ± 9.4 mmHg, $p < 0.05$); other parameters did not change significantly. The cough score was significantly lower compared to the control group ($p < 0.0001$).	None

Dengler 2022	Retrospective observational study	Inclusion Criteria: Patients with severe traumatic brain injury (TBI) who had invasive ICP monitoring, were intubated and mechanically ventilated, and received at least one bolus of ketamine.	Treatment Arm: In 43 patients, a total of 216 administrations of ketamine were given as 2 mg/kg IV bolus; used as rescue therapy for elevated ICP.	Outcomes: Changes in ICP and CPP; proportion of administrations achieving both ICP reduction and CPP increase.	Main Findings: 44 patients (median age 30 years, median GCS 5). A total of 216 ketamine boluses were administered. Both ICP decrease and CPP increase were observed in 46% of administrations. Median ICP change: −3.5 mmHg (IQR −9 to +1, $p < 0.001$). Median CPP change: +2 mmHg (IQR −5 to +12, $p < 0.001$).	None
Laws 2023	Retrospective observational study	Inclusion Criteria: Pediatric patients under 18 years old, admitted to the intensive care unit, with severe traumatic brain injury (sTBI) and invasive ICP monitoring.	Treatment Arms: Ketamine group: Patients receiving ketamine bolus (subgroups: for ICP management and not for ICP management). Non-ketamine group: 17 patients with ICP > 20 mmHg treated with non-ketamine strategies.	Outcomes: Changes in ICP and MAP after ketamine administration; comparison of measured MAP values against age-specific thresholds; analysis of ICP and MAP trends over time.	Main Findings: A total of 33 pediatric patients; 127 ketamine boluses were administered to 22 patients. In the 18 ICP-targeted applications (11 patients, ICP > 20 mmHg for ≥5 min), mean ICP decreased significantly (−5.00 ± 7.44 mmHg, $p = 0.046$) and MAP increased. In applications given solely for sedation purposes, ICP or MAP did not change. Within the first 5 minutes, the MAP difference was not significant.	This study demonstrates, using high-frequency physiological data, that ketamine does not increase ICP in children and may reduce ICP during crisis periods.
Observational studies evaluating the effect of ketamine during rapid sequence intubation (RSI) in patients with acute brain injury.						

Lyon 2015	Comparative cohort study	Inclusion Criteria: All consecutive trauma patients who underwent prehospital rapid sequence intubation (RSI) during the defined study periods.	Treatment Groups: Group 1: Etomidate + Succinylcholine Group 2: Fentanyl + Ketamine + Rocuronium (Doses of fentanyl and ketamine were reduced in hemodynamically unstable patients.)	Outcomes: Intubation success, acute hemodynamic response, laryngoscopic view, survival until hospital discharge.	Main Results: Group 1: 116 patients, Group 2: 145 patients. Group 2 had better laryngoscopic view ($p = 0.013$) and higher first-attempt success (100% vs 95%, $p = 0.007$). Hypertensive response was less frequent (37% vs 79%, $p < 0.0001$). Hypotension was rare in both groups (1% vs 6%, $p = 0.05$). Mean arterial pressure ($p = 0.148$) and systolic blood pressure ($p = 0.257$) did not change.	None
Cornelius 2018	Retrospective observational study	Inclusion Criteria: Patients over 18 years old with suspected increased intracranial pressure (ICP) who required intubation.	Treatment Arms: Etomidate, midazolam, and ketamine were used for induction or sedation during rapid sequence intubation (RSI).	Outcomes: Mortality rate, time of death, discharge rate, and Glasgow Coma Scale (GCS).	Main Results: There were no significant differences between the groups for any of the outcomes.	None

Mudri 2020	Retrospective observational study	Inclusion Criteria: Pediatric trauma patients aged 0–17 years with traumatic brain injury; rapid sequence intubation (RSI) performed.	Treatment Arms: Propofol, ketamine, midazolam, and etomidate (used alone or in combination), administered with or without neuromuscular blockers.	Outcomes: Mortality rate, Hemodynamic stability measured by Pediatric Adjusted Shock Index (PASI), First-attempt intubation success.	Main Results: A total of 107 pediatric trauma patients. First-attempt intubation success was 88.5%, overall survival 87%. Mean hospital stay 21 days, ICU stay 7.5 days. Midazolam was the most frequently used agent; ketamine used alone in 7 patients. Propofol was associated with post-intubation hypotension. Blood pressure decrease observed with propofol or ketamine/midazolam combination; no change in blood pressure when ketamine used alone. No statistically significant hemodynamic differences were found between agents.	When ketamine was used alone, no change in blood pressure was observed; however, no direct statistical comparison was made between induction agents. An increase in PASI scores was also observed in the ketamine group, but the highest increase occurred in patients receiving propofol or propofol/midazolam.

Fouche 2021	Retrospective observational study	Inclusion Criteria: Patients aged ≥12 years with suspected traumatic brain injury (TBI) by paramedics, who underwent prehospital rapid sequence intubation (RSI).	Intervention Groups: Pre-Ketamine period (before January 2015): RSI primarily performed using fentanyl and midazolam. Ketamine period (after January 2015): Ketamine (1.5 mg/kg) used as the primary induction agent for RSI.	Outcomes: Incidence of hypotension after RSI, changes in systolic blood pressure (SBP), shock index.	Main Results: A total of 1,619 patients were analyzed (792 pre-ketamine period, 827 ketamine period). After transitioning to ketamine use, post-HAE hypotension increased by 5% (p = 0.046) with an additional 0.5% rise per quarter (p = 0.004). Mean SBP decreased by 7.8 mmHg (p = 0.04) and showed a quarterly downward trend. In sensitivity analysis, the adjusted increase in hypotension was 5.6% (p = 0.02). Intubation success remained stable at 97.5%.	None
Mazandi 2023	Retrospective observational study	Inclusion Criteria: Pediatric patients <18 years old with a risk of intracranial hypertension due to neurological conditions (e.g., TBI, hydrocephalus, intracranial hemorrhage) requiring tracheal intubation.	Intervention Arms: Ketamine as the primary induction agent for intubation was compared with non-ketamine agents (e.g., etomidate or propofol).	Outcomes: Assessment of whether ketamine administration in this patient group increased the risk of neurological, hemodynamic, or respiratory events within 5 hours after induction.	Main results: A total of 143 patients (70 ketamine, 73 non-ketamine). No increase in neurological, hemodynamic, or respiratory adverse events was observed with ketamine. No mortality occurred within 24 hours. In the subgroup with ICP monitoring (n = 23), no ICP increase was observed; MAP remained stable. In 3 patients with elevated ICP, ketamine administration followed by intubation resulted in improvement of ICP.	None

Mansvelder 2024	Retrospective observational study	Inclusion criteria: Prehospital patients with Glasgow Coma Scale (GCS) ≤ 8 and suspected severe traumatic brain injury (TBI) based on trauma mechanism or clinical findings, who received prehospital advanced airway management using etomidate or S(+)-ketamine.	Intervention groups: Comparison between etomidate and S(+)-ketamine.	Outcomes: Relationship between induction agent and 30-day mortality; Systolic blood pressure after induction; Glasgow Coma Scale (GCS) at discharge; ICU length of stay and hospital length of stay.	Main results: A total of 1,451 patients (955 etomidate, 496 ketamine). No significant difference in 30-day mortality (32.9% vs 33.8%, p = 0.716). No differences were observed in post-induction blood pressure, ICU length of stay, or functional outcomes at discharge. In adjusted analysis, hospital length of stay was slightly longer in the ketamine group. No significant differences were found in definitive or isolated traumatic brain injury subgroups.	None

Loi 2024	Retrospective observational study	Inclusion criteria: Children under 18 years old who were intubated for a primary neurological indication in pediatric intensive care units (PICU), pediatric cardiac ICU, or emergency department.	Intervention arms: Patients who received ketamine as the induction agent for tracheal intubation were compared with those who received other induction agents.	Outcomes: Association of ketamine use with combined adverse events (SpO_2 < 80% hypoxemia, hemodynamic instability) occurring within 20 minutes after intubation.	Main results: A total of 2,073 intubations (495 ketamine, 1,578 other agents). Combined adverse events: 17% (ketamine) vs 13% (other agents) (p = 0.026); however, in the adjusted analysis, not statistically significant (aOR 1.34, 95% CI 0.99–1.81, p = 0.057). No difference in first-attempt intubation success. In the traumatic brain injury (TBI) subgroup, adverse event rates were similar between ketamine and non-ketamine groups.	None

TBI: Traumatic Brain Injury, sTBI: Severe Traumatic Brain Injury, ICP: Intracranial Pressure, CPP: Cerebral Perfusion Pressure, MAP: Mean Arterial Pressure, SBP: Systolic Blood Pressure, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, ICU: Intensive Care Unit, PICU: Pediatric Intensive Care Unit, ETS: Endotracheal Suctioning, SjO_2: Jugular Venous Oxygen Saturation, mVMCA: Middle Cerebral Artery Mean Flow Velocity, PASI: Pediatric Adjusted Shock Index, $PbtO_2$: Brain Tissue Oxygen Pressure, aOR: Adjusted Odds Ratio, RSI: Rapid Sequence Intubation, IQR: Interquartile Range.