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The future of airway management: a selection of recent advances — Narrative review

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Abstract

Airway management represents an essential yet huge chapter in the field of anesthesiology and critical care, being a pillar in a variety of scheduled, elective and/or urgent situations. It implies a multidisciplinary approach, a holistic vision, and a wide-ranging set of subskills. Specific relevant areas regarding airway have been arbitrarily selected for this narrative review and are noteworthy for their potential future use as breakthrough technologies. Airway ultrasonography (US) provides additional useful information about the anatomy and by combining that with classical clinical tests, improves the capacity to predict and anticipate a potential difficult intubation. High Flow Nasal Oxygenation (HFNO) can provide a high concentration of oxygen not only during preoxygenation in spontaneously breathing patients but also during the apneic phase, showcasing its abilities to produce positive airway pressure maintaining positive end-expiratory pressure (PEEP) and a high fraction of inspired oxygen. Furthermore, this technique provides minimal interference with the technical execution of bag-mask ventilation, laryngoscopy, and surgical interventions in the oropharynx. Intravenous oxygen (IVO2) is a new technique, already demonstrated in China and Asia, but present only with preliminary laboratory data in Europe and the United States. New technologies for delivery of this novel oxygen administration are currently being studied. Emerging data shows the application of these, and thus of IVO2, if effective and safe, could be extended to emergency settings to gain some bridging time to ExtraCorporeal Membrane Oxygenation (ECMO) or other interventions. Following approval there appears to be great scope as to how IVO2 could be implemented in perioperative medicine, e.g., as a tool used in pre-oxygenation before induction of general anesthesia, especially in critical ill patients.
A continuum of these relatively new techniques – US, HFNO, IVO2 – used in combination in the practice of perioperative medicine may change the way we plan for anticipated or unanticipated complications and manage the difficult airway, allowing us to offer the best possible pioneering care to our patients.

Keywords: **Surgery, intubation, airway, airway management, preoxygenation, oxygen, intravenous, ultrasound, induction of anesthesia, high flow nasal oxygenation.**

Introduction

Airway management represents an essential yet huge chapter in the field of anesthesiology and critical care, being a pillar in a variety of scheduled, elective and/or urgent situations. It is well established that the highest morbidity and mortality in anesthesia is related to the patient's airway, the management of which has been rapidly advancing over the years. Progressively, a standardization in preoperative reassessments ensures that possible problems in oxygenation, ventilation and intubation would be more frequently detected, while numerous new devices and procedures have appeared on the market and in emerging protocols. Airway management definitely warrants a multidisciplinary approach, as anesthesiologists often have to share the patient's airways with colleagues of other specialties (ENT/ Head and Neck surgeons, endoscopists, intensivists, pneumologists, etc.), and a holistic vision, as it involves a wide-ranging set of subskills in the so-called difficult airway management (e.g. pediatric airway, obstetric airway, morbid obesity airway, management outside the operating-room or in the Intensive Care Unit (ICU), etc.).

A detailed description of any single sector is beyond the scope of this text; thus a few specific relevant topics have been selected.

This narrative review is based on searches in PubMed, Embase and Cochrane Library databases. Search terms used were 'preoxygenation', 'airway', 'intubation', 'airway management', 'airway updates', 'induction' of 'general anesthesia', 'difficult airway', 'ultrasound', 'intravenous oxygen', 'high flow nasal oxygenation', in different combinations. The selected articles were cross-referenced. The latest search was performed in February 2023 and the time range covers approximately the last 5-8 years. The following number of articles has been selected and retained: 18 references regarding the paragraph "Ultrasonography", 27 regarding the paragraph "Oxygenation/preoxygenation 1" and 22 regarding the paragraph "Oxygenation/preoxygenation 2".

All the articles were screened for relevance on title, abstract and full text.

Ultrasonography

Airway ultrasonography can be a helpful and quick tool for assessing and managing possible difficult airway (DA) provided that an ultrasound machine is freely available where trained personnel is ready to scan and comes with many obvious advantages: ultrasound is cheap, fast, non-invasive, repeatable, portable, although a disadvantage is that it is operator-dependent. In 2019 a test accuracy systematic review analyzed pre-specified bedside tests such as: the Mallampati test (6 studies); modified Mallampati test (MMT) (105 studies); Wilson risk score (6 studies); thyromental distance (TMD) (52 studies); sternomental distance (SMD) (18 studies); mouth opening test (34 studies); and the upper lip bite test (ULBT) (30 studies)[1]. Standard bedside airway examination tests for DA in patients with no apparent airway abnormalities might not represent a reliable screening[1]. Ultrasound can be a strategic aid together with clinical tests in order to determine the predictive capacity for difficult intubation and it is useful to locate the trachea or the cricothyroid membrane especially when they are not identifiable by palpation or due to anatomical alterations. Some ultrasound indices for assessing DA are related to quantitative measures of soft tissue in the neck, other indices assess the visualization of anatomical structures qualitatively or measure the distance between them.

1. SOFT TISSUE THICKNESS – Wu J et al. evaluated the correlation between difficult laryngoscopy (DL) and the distance from skin to the hyoid bone (DSHB) measured by ultrasound[2]. They also included the distance from skin to epiglottis midway (DSEM, or DSE), and the distance from skin to anterior commissure (DSAC). They analyzed 203 patients and found the optimal cut-off values with the best discriminatory power was a DSHB of 1.28 cm (sensitivity 85.7%, specificity 85.1%), concluding this ultrasound parameter was an independent predictor of difficult airway; yet both the positive predictive value (PPV) and diagnostic odds ratio (DOR) are of moderate clinical utility (39% and 35%, respectively). The areas under the ROC curve (AUCs or AUC-ROC, ROC = receiver operating characteristic) of MMT, DSHB, DSEM, and DSAC were all over 0.7, indicating they are all good parameters in predicting difficult laryngoscopy. The AUCs of TMD and inter-incisor gap (IIG) were less than 0.7, suggesting that those two were poor parameters in predicting difficult laryngoscopy. This study measured anterior neck soft tissue at three levels – hyoid bone, thyrohyoid membrane, and anterior commissure.

Ezri et al. measured the distance from the skin to the anterior trachea at the vocal cords (ANS-VC) in a sample of 50 obese patients[3]. They observed an ANS-VC of 28 mm as the ideal cut-off with a PPV of nearly 100%. Nevertheless, a sample of 50 patients with a characteristic such as obesity is rather small, and the limit of the study was a low prevalence of difficult intubation because only 9 patients presented with a Cormack-Lehane (CL) grade III-IV during direct laryngoscopy. Reddy PB et al. conducted a study with the same ultrasound parameter but in a larger sample (100 obese patients)[4] and obtained an ANS-VC cut-off of 23 mm. An ANS-VC > 23 mm had a sensitivity of 85.7% in predicting a CL grade of III or IV, which was higher than that of Mallampati class, TMD and SMD. However, the specificity (57%), PPV (24.5%) and accuracy (61%) were lower than the physical parameters. The negative predictive value (NPV) was comparable (95.6% in ANS-VC vs. 94.7% in Mallampati class ≥ 3). The ultrasound quantification of pretracheal soft tissue seems to be promising in obese patients but more studies and a larger population are needed considering the difference of fat distribution between sexes and ethnic groups[5].

Kaul et al.[6] enrolled 100 Asian patients (39 categorized as difficult laryngoscopy) in 2021 and measured thickness at hyoid bone (DSHB), at thyrohyoid membrane level (DSEM), and DSAC as the study of Wu et al did. The optimal cut-off values for DSEM, DSHB, and DSAC were 1.34 cm, 0.98 cm (1.28 in Wu), and 1.68 cm respectively. Ultrasonography and traditional screening tests were compared in predicting DL. It was found

the AUCs of DSHB, DSEM, DSAC, MMT and TMD were > 0.7, indicating good parameters to predict DL. But IIG, SMD, neck circumference (NC), ULBT had AUCs < 0.7, making them poor parameters for DL prediction.

Pinto J et al. measured the amount of soft tissue between the skin and the epiglottis (distance from skin to epiglottis, DSE) in 74 patients and its relation to a possible difficult intubation[7]. They included a comparison with other clinical assessments such as MMT, IIG, TMD, cervical perimeter. For a DSE cut-off of 27.5 mm (2.75 cm) the study showed relatively poor statistical significance (PPV of DSE 45.8% [26-67] vs. PPV of MMT 42.9% [26-62]) and none of the highest values was significantly better than all the values of the remaining performance metrics. However, the parameters improved dramatically by combining DSE with MMT: MMT-DSE PPV 71.4% [45-94], specificity 93% [86-98], accuracy 85.1% [76-93]; vs. Naguib score (which combines IIG, TMD and Mallampati score) with a PPV of 32.5% [19-48], specificity 52.6% [39-66], accuracy 58.1% [47-70]. The sensitivity of Naguib score was higher (76.5% compared to 58.8% of MMT-DSE). DSE is concretely one of the most studied indexes in literature to predict difficult direct laryngoscopy. Fernandez-Vaquero et al.[8] included 209 patients to perform preoperatively 3 ultrasound measurements with the head in "sniffing" position: DSE, DSHB, DSAC. The DSE was the best predictor of direct DL (defined as CL grade ≥ 2b) with a cut-off of 2.48 cm and a PPV of 89.36% (95% CI 79.5–99.2%), sensitivity 91.3%, specificity 96.93%, and a range for DL corresponding to 2.70 ± 0.19 cm. The diagnostic accuracy for DSE was expressed as area under the ROC curve corresponding to 0.96 [95% CI 0.94–0.99], p < 0.001. DSE performed better than any clinical airway assessment parameter. The AUC for the MMT was 0.74 (95% CI 0.66–0.82, sensitivity 32.61%, specificity of 92.02%), as the best clinical airway assessment predictor (PPV MMS 53.57%). The DSHB cut-off was at 1.19 cm with moderate correlation (sensitivity 80.4%; specificity 60.1%). No correlation was found for the DSAC (cut-off of 0.82 cm with a PPV of 35.6% (95% CI 25.0–46.3%) and a NPV of 87.7% (95% CI 81.5–93.9%)). Interestingly in women compared to men, the skin to the epiglottis distance was more sensitive (92.3% vs. 90.9%) and specific (98.8% vs. 95.2%). The systematic review of Carsetti et al.[9] reinforced the hypothesis that a DSE > 2 to 2.5 cm seems to identify difficult direct laryngoscopies. They considered 15 studies for statistical analysis and concluded that airway ultrasound index tests are significantly different comparing easy versus difficult direct laryngoscopy. DSE had a sensitivity of 82% [74-87], a specificity of 79% [70-87], a positive likelihood ratio of 3.91 [2.65–5.76], an AUC of 0.87 [0.84-0.90]. DSHB had a sensitivity of 71% [58-82], a specificity of 71% [57-82], a positive likelihood ratio of 2.46 [1.50-4.04], an AUC of 0.77 [0.73-0.81]. ANS-VC showed sensitivity 75% [62-84], specificity 72% [45-89], positive likelihood ratio 2.63 [1.16-5.98], AUC 0.78 [0.74-0.81]. Those data are also mentioned in the review published by Vasconcelos Pereira et al[10]. A high clinical and methodological heterogeneity has been found between studies, though. It may be probably due to the inter-variability between patients and to differences in the technical execution of US assessment (e.g., head position). External airway manipulation (such as Backwards Upwards Rightwards Pressure or BURP maneuver) was not uniformly applied, and several studies did not mention if it was allowed during DL. This aspect may affect the results as BURP may improve laryngeal visualization and consequently change CL classification. Unfortunately, the relatively limited number of studies did not allow further analysis to investigate the source of heterogeneity.

Finally, Hui CM et al.[11] performed a sublingual ultrasound identifying the non-visualization of the hyoid bone as a predictor of difficult intubation in 110 patients (PPV 71%, DOR 76%).

2. ANATOMICAL QUALITATIVE EVALUATION (ORAL SPACE/TONGUE) – Yao W et al.[12] enrolled 2254 patients and analyzed the tongue thickness to predict a difficult tracheal intubation (DTI). It was pointed out a tongue hypertrophy (> 6.1 cm) could indicate a difficult airway, but a PPV of 11% was obtained. The predictive capacity remained low even by combining this ultrasound measure with the clinical TMD (PPV ratio tongue thickness-TMD 18%). Other single clinical parameters analyzed were MMT (PPV 10%), IIG (PPV 11%, but the best sensitivity at 86% [79-91]), TMD (PPV 11%). The same team published in 2022 another single-center study with 1000 patients establishing a multiparameter ultrasound model for difficult airway assessment (ultrasound model, including tongue thickness > 61 mm, mandibular condylar mobility ≤ 10 mm, and hyomental distance ≤ 51 mm) and positively evaluating its ability to predict difficult airways[13]. The area under the ROC curve for the ultrasound model to predict DL was 0.84 (95% confidence interval [CI]: 0.82–0.87), and the sensitivity and specificity were 0.75 (95% CI: 0.60–0.86) and 0.82 (95% CI: 0.79–0.84), respectively. The AUC for predicting DTI was 0.89 (95% CI: 0.87–0.91), and the sensitivity and

specificity were 0.85 (95% CI: 0.65–0.96) and 0.81 (95% CI: 0.78–0.83), respectively. Compared with mouth opening, TMD, and MMT, the ultrasound model predicted a greater AUC for DL ($P < 0.05$). Compared with mouth opening and MMT, the ultrasound model predicted a greater AUC for DTI ($P < 0.05$). The PPV of the ultrasound model for DL and DTI stagnated at 18% and 11%, respectively. The best clinical predictor was a mouth opening < 3 cm (PPV 36% for DL and 28% for DTI; specificity 98% and 97%). The most sensitive test was MMT (sensitivity 80% for DL, PPV 10%).

3. ANATOMICAL QUANTITATIVE EVALUATION – Moving away from the measurement of soft tissue thickness and oral cavity, the literature also evaluates other different parameters, such as in the study of Andruszkiewicz et al[14]. In this case, the authors analyzed particularly the hyomental distance in extension (HMDE) in 199 patients to predict DA and identified the best discriminatory power in an HMDE value of less than 4.28 cm (PPV 66.7%). Other clinical and sonographic parameters were included. The diagnostic validity profiles showed poor sensitivity (9.1%-42.9%) and positive predictive value (4.5%-66.7%), but good specificity (71.8%-97.7%) and negative predictive value (87.1%-94.5%). The low sensitivity of the HMDE (38.1%) shows that the airway assessment must not rely on these predictors only. A high proportion of false negative results carries a risk of missing several patients with difficult intubation potential. The poor sensitivity of a single test proves that laryngoscopy depends on a complex dynamic interaction between the anatomic and functional factors. Thus, no one individual predictor can represent all the unfavorable functional or anatomic characteristics that have an impact on DL. The accuracy and specificity of the hyomental distance–related tests in this study were good. The low false positive predictions based on this test reduce the risk of subjecting many patients to unnecessary advanced airway procedures.

Kalezić et al.[15] focused on the hyomental distance ratio (HMDR) – the ratio between the hyomental distance (HMD) at the extreme of head extension (HMDe) and the one in the neutral position (HMDn) – and examined the predictive value, sensitivity, and specificity of HMDe, HMDn, and HMDR in predicting DTI. The cut-off points for the difficult laryngoscopy predictors were HMDe <5.3 cm, HMDn ≤5.5 cm, and HMDR ≤1.2 cm, with HMDR as the best predictor with a sensitivity of 95.6% and specificity of 69.2%.

4. SUMMARY – Therefore, it can be concluded that there is no ultrasound index yet that replaces the typical clinical tests significantly, but ultrasonography provides additional useful information and combining that with classical tests does improve the capacity to predict and anticipate a potential difficult intubation. Further studies are needed with better standardization of ultrasound assessment (e.g., head position, technique, etc.), considering the differences between patients (e.g., sex, geographical background, body constitution, etc.). Similar thoughts were expressed in the latest systematic review by Giordano et al.[16] which included 31 observational studies and reported 41 single parameters and 12 combinations of clinical and ultrasound measures. 33 studies with 8409 adult patients and 27 unique indices were included in the meta-analysis of Bhargava et al[17]. Here the authors examine airway ultrasound measurements within methodologically related domains. Ultrasound variables assessed in each study were grouped into three domains, similarly to the subheadings of the current section "Ultrasonography" in this manuscript. The domains were as follows: (1) ultrasound tests evaluating anterior neck soft-tissue thickness (tissue thickness domain), (2) ultrasound tests evaluating the dynamic motion of the neck or tongue or position of the hyoid bone to the mentum (anatomical position domain), and (3) ultrasound tests evaluating for space in the floor of mouth such as the size of the tongue (oral space domain). Anterior tissue thickness demonstrated a pooled sensitivity of 76% (95% CI, 71–81%), specificity of 77% (95% CI, 72–81%), and an AUC-ROC of 0.83 (95% CI, 0.80–0.86). Anatomical position demonstrated a pooled sensitivity of 74% (95% CI, 61–84%), specificity of 86% (95% CI, 78–91%), and an AUC-ROC of 0.87 (95% CI, 0.84–0.90). Oral space demonstrated a pooled sensitivity of 53% (95% CI, 0.36–0.69), specificity of 77% (95% CI, 0.67–0.85), and an AUC-ROC of 0.73 (95% CI, 0.69–0.77). The anatomical position domain, which includes sonographic assessment of HMD(e), may be more accurate than other domains. See (Table I) for an overview of the studies mentioned herewith.

In practice the combination of measurements seems to be the key: the use of scores combining clinical predictors and ultrasound measurements, or a systematic coupling of several ultrasound parameters, is very promising although possibly time-consuming. The current guidelines recommend in fact to use a combination of the validated tests to predict DA as no single test is sufficient alone[18], thus the search for the ideal radiological parameter – or the optimal outstanding combination of tests – is still on. On a side note, data regarding a correlation between ultrasound parameters and difficult mask ventilation are limited and the role of ultrasound is still unclear.

Oxygenation/preoxygenation

1. HFNO new standard of care?

Whenever possible, preoxygenation should precede any airway intervention[19,20]. Oxygen is routinely delivered by mask for several minutes prior to anesthetic induction. In this way the patient's oxygen reserve denoted by the functional residual capacity (FRC) is purged of nitrogen. Up to 90% of the normal FRC of ~2 L following preoxygenation is filled with oxygen and at the same time some micro-atelectasis may occur. In fact the use of high inspiratory oxygen concentration (high FiO2) during induction and maintenance of general anesthesia is the major cause to resorptive atelectasis. Nitrogen from room air is slowly absorbed into the blood and therefore helps maintain alveolar patency; in contrast, oxygen is rapidly absorbed into the blood[21]. Considering the normal oxygen demand of 200 to 250 mL/min (~3 ml/kg/min) which remains rather constant in an anesthetized patient, oxygen reserves allow a maximum of 3 minutes of apnea without serious impact on the saturation after ventilation with room air. This time can be doubled by performing a correct preoxygenation: the preoxygenated patient may have approximately 5 to 8 min oxygen reserve. Increasing the duration of apnea without desaturation (safe apnea time) improves safety when active oxygenation following anesthetic induction is delayed for any reason. Before upper airway control, desaturation occurs when the O2 reserve is depleted to support oxygen consumption during the apnea period[22]. After induction, oxygen will enter the blood from the FRC at a rate faster than carbon dioxide (CO2) leaves the blood and this mechanism will generate a negative (subatmospheric) pressure in the alveolus and a mass flow from the upper airway to alveoli, via diffusion, thus drawing oxygen into the lungs. This is how supplemental oxygen during apnea (or apneic oxygenation) provides the O2 gradient to maintain arterial oxygen saturation and optimize safe apnea time[23]. The potential risks of preoxygenation are absorption atelectasis, delayed recognition of esophageal intubation, and production of reactive oxygen species.

Oxygenation via High-Flow Nasal Cannula (HFNC), or transnasal humidified oxygen delivery system (Optiflow™), is a promising new technique that can be implemented in many settings around the hospital. The use of HFNC has been implemented for many years in the ICU and has arrived in the operating room during the induction and maintenance of anesthesia and upper airway surgeries. The advantages of this technique include its acceptable tolerability, easy installation and its ability to produce positive airway pressure maintaining PEEP and a high fraction of inspired oxygen: this way the micro-atelectasis caused by pre-oxygenation could be mitigated or reversed. HFNC can be used effective to preoxygenate patients breathing spontaneously and then provide passive oxygenation during the apneic period too; furthermore, this technique seems to be appealing because it interferes minimally with the technical execution of bag-mask ventilation, laryngoscopy and surgical interventions in the oropharynx. The use of High Flow Nasal Oxygenation (HFNO) has been described to provide preoxygenation and to extend the apnea time of patients with difficult airways in the THRIVE study[24] that described the continuous insufflation through HFNC facilitating oxygenation and CO2 clearance through gaseous mixing and flushing of the deadspace. The median (IQR [range]) apnea time was 14 (9–19 [5–65]) min. No patient experienced arterial desaturation < 90%. Mean (SD [range]) post-apnea end-tidal CO2 (EtCO2) level was 7.8 (2.4 [4.9–15.3]) kPa. In 2017, Ang et al.[25] conducted an observational pilot study with 21 healthy volunteers to evaluate the performance of HFNC in preoxygenating patients concluding that it was able to rapidly increase end-tidal oxygen (EtO2), however pointing out the variability in the extent of denitrogenation. The median [IQR (range)] EtO2 for each time interval (30, 60, 90, 120, 150 and 180 s) was 72% [66–79% (45–82%)], 79% [71–86% (65–89%)], 84% [77–88% (64–91%)], 87% [80–91% (72–93%)], 88% [83–90% (75–94%)] and 86% [84–90% (78–92%)] respectively. Only 50% of the volunteers achieved an EtO2 of 90% within 3 minutes. Pillai et al.[26] concluded that 3 minutes of humidified oxygen delivered at 60 L/min via nasal cannula with the mouth closed was as effective as 3 minutes oxygen at 10 L/min via face mask. However, they recruited only 10 healthy patients. Tremey et al.[27] stated that inducing general anesthesia "without the hands" using HFNO is safe for preoxygenation and peroxygenation and is as reliable as usual care. Esophageal intubation occurred twice in the HFNO group, allowing a correct reintubation without desaturation despite the prolonged apnea time. Lyons et al.[28] enrolled 79 patients requiring intubation for an elective surgical procedure and assigned them to 3 groups. Median (IQR [range]) times to desaturate to 92% after pre-oxygenation with facemask oxygen, high-flow nasal oxygen only and high-flow nasal oxygen with mouthpiece, were: 309 (208-417 [107-544]) s; 344 (250-393 [194-585]) s; and 386 (328-498 [182-852]) s, respectively, $p = 0.014$. Median (IQR [range]) arterial oxygen partial pressure after 3 minutes of pre-oxygenation by facemask, nasal cannula, and nasal cannula plus mouthpiece, was:

49 (36-61 [24-66]) kPa; 57 (48-62 [30-69]) kPa; and 61 (55-64 [36-72]) kPa, respectively, p = 0.003. 100 healthy parturients scheduled for a C-section under general anesthesia were included in the study of Osman et al.[29] The safe apnea time was significantly longer under HFNO with median of 7 min compared to facemask ventilation with 4 min. The median of arterial oxygen partial pressure (PaO2) with the facemask was 101 mmHg (range 74-215) after 3 min of apnea vs. 355 mmHg (120-498) with HFNO (P < 0.01). No statistically significant difference was found for the partial pressure of carbon dioxide (PaCO2) between the two groups. Other healthy volunteers were considered for the randomized crossover study by Hanouz JL et al[30]. 50 patients were included to compare the EtO2 following a 3 min pre-oxygenation with high-flow nasal oxygenation versus spontaneous breathing of 100% O2 via face mask, demonstrating that HFNO is not a reliable pre-oxygenation method before induction. According to their results the EtO2 after 3 min of pre-oxygenation was 89 (2) % in the face mask group and 77 (12) % in the HFNO group [difference 12% (95% CI 8-15); P < 0.001]. The median (IQR) time to obtain an EtO2 = 90% was 172 [120-250] seconds, and 360 [240-360] seconds in the face mask and HFNO groups, respectively. The article received an on-point criticism from an editorial[31] as the crossover design may have led to bias; EtO2 is quite challenging to measure directly during HFNO; and the clinical benefit of the high-flow (pre)oxygenation is already well described in the literature.

The integrative literature review of Gleason et al.[32] in 2018 examined 18 studies through a standardized literature search in order to endorse the benefit of nasal cannula apneic oxygenation. Methodologically, all studies show congruence and consistent findings heading towards a favorable position that supports the systematic implementation of this technique. Despite patients having various medical conditions, nasal cannula use during intubation extended the duration of safe apnea in patients undergoing elective surgery. Four studies[33-36] found no benefit with the HFNC method but the sample population considered (ICU patients or patients with hypoxic respiratory failure) is rather specific and differs from the elective uncomplicated cases: this may suggest lack of benefit of HFNC when hypoxic respiratory failure is the indication for intubation in critically ill patients. These patients are likely to have developed pathological changes on a structural level (pulmonary circulatory shunting) and even though preoxygenation may be utilized (via non-invasive ventilation [NIV] or HFNO), they might not respond further to supplemental oxygen; underlying cardiopulmonary conditions and abnormal lung function reduce the efficacy of preoxygenation and impact the apneic oxygenation too. Moreover, many critically ill patients may have an increased oxygen consumption that may deplete their reserve much more quickly. Finally, patients intubated in a critical care setting are typically in the supine position, which results in a decrease of FRC, and limits the effectiveness of preoxygenation ab initio compared to the upright position[37,38]. In 2019 a narrative review by Kim HJ et al described the state of knowledge regarding techniques based on HFNC with pro's and con's, leading to the conclusion that it seems reasonable to implement the high-flow oxygenation in standard settings, but under reserve in relation to critically ill patients given the conflicting evidence and the insufficient number of reported clinical trials[39].

Eight randomized controlled trials (8 RCTs for a total of 2314 patients) were included in a systematic review by Spence et al[40], who found the risk of O2 desaturation (defined as O2 saturation < 90% in 4 studies and 93% in 1 study) was lower in HFNO versus conventional oxygenation control group, at induction and intraoperatively. At induction with an odds ratio (OR; 95% confidence interval (CI)) of 0.06 (0.01-0.59, P = .02), and during procedure with an OR (95% CI) of 0.09 (0.05-0.18; P < .001). Other remarks in favor of HFNO were minimum recorded intraoperative O2 saturation (higher, compared to the group that received conventional oxygenation) at induction by a mean difference (MD) (95% CI) of 5.1% (3.3-6.9; P < .001), and during procedure, by a MD (95% CI) of 4.0% (1.8-6.2; P < .001). Safe apnea time was significantly longer with HFNO compared to facemask oxygen by a MD (95% CI) of 33.4 (16.8–50.1; P < .001) seconds. There are concerns that if a patient is apneic during treatment with HFNO, rising EtCO2 and acidosis may ensue. In this meta-analysis there was no significant difference in EtCO2 and no evidence of significant hypercapnia.

The largest number of RCTs published on this topic was included in the systematic review conducted by Song et al.[41] in 2022, which supported the use of HFNC for pre-oxygenation and its maintenance during induction, underlining its superiority compared to standard facemask ventilation. The PaO2 was higher in HFNO group than standard facemask group with a MD (95% CI) of 57.38 mmHg (25.65-89.10; p = 0.0004) after preoxygenation and the safe apnea time was significantly longer with a MD (95% CI) of 86.93 s (44.35-129.51; p < 0.0001) during anesthesia induction. Safe apnea time was significantly longer in HFNO compared with standard facemask group

by a MD (95% CI) of 86.93 s (44.35-129.51; $p<0.0001$), after reduction of heterogeneity. There was no significant statistical difference in the CO2 accumulation, EtO2 and desaturation rate during induction between the two groups.

Ricard JD et al.[42] suggested their practical approach on pre-oxygenation and apneic oxygenation keeping HFNC throughout the entire induction and laryngoscopy or adding it to the NIV during laryngoscopy. The population they considered was rather specific (ICU hypoxemic patients, thus an opposing view to what the 4 studies cited in the article of Gleason[32]) and their enthusiasm for HFNC was supported by current literature including the study of Guitton et al.[43] and it was focused on the fact that this approach led to a reduction in intubation-related adverse events.

The measurement of end-tidal oxygen fraction after securing a definitive airway and time to secure an airway appear as secondary end-points in a randomized controlled trial by Merry et al[44], who allocated 199 patients (> 10 years old) undergoing elective surgery to pre-oxygenation using either HFNO or facemask. Ease and comfort were assessed by anesthetists and patients and in relation to patient comfort and user-friendliness this study favors HFNO over mask pre-oxygenation (and markedly over non-invasive ventilation), after the comparison of the 10-cm visual analogue scale and six-point smiley face scale. It is also the first study to explicitly compare ease-of-use from the perspective of the anesthetist and has evaluation of comfort and ease of use as its primary objective. There was no significant difference between groups in the number of patients with hypoxemia or severe hypoxemia lasting ≥ 1 min or ≥ 2 min, in the proportion of patients with an end-tidal oxygen fraction $<87\%$ in the first 5 min after tracheal intubation (52.2% vs. 58.9% in facemask and high-flow nasal oxygen groups, respectively; $p=0.31$), or in time taken to secure an airway (11.6 vs. 12.2 min in facemask and high-flow nasal oxygen groups, respectively; $p=0.65$).

It is safe to assume that HFNO could and should be considered for anesthesia induction in patients at high risk of hypoxemia. More supportive data will be necessary – or confuting data, given the fact that in medicine anything is true until proven otherwise. More evidence is also needed concerning the differential implementation in standard "easy" airway and expected difficult airway, testing on a population with ongoing hypoxic respiratory failure, possible necessity to introduce HFNO in the future DAS (Difficult Airway Society) difficult airway algorithm[45] or future airway management guidelines, alone or in simultaneous combination with a tight-fitting facemask. It has been proposed that the next generation of anesthetic machines will have HFNO fitted as standard.

The gaps in current research include the following: the use of varying levels of oxygen flow such as 5L vs. 70L O2 HFNO, direct comparison and investigation of superiority between NIV and HFNO, and whether HFNO is efficacious – and if it can be standardized – in diverse presenting medical conditions such as pregnancy, obesity, trauma, anaphylaxis and other comorbidities.

2. Intravenous Oxygen (IVO2) – application in ICU and in the OR?

The oxygen administration for therapeutic and prophylactic strategies (pre-oxygenation, ventilation of a patient during elective surgery, supportive care and ventilation during respiratory insufficiency, etc.) has always been conventionally and unequivocally inhalational. This poses a problem in case of anatomical deformities or inability to access the airway or respiratory diseases impairing the diffusion of O2 to the bloodstream via respiratory tract. Exploring alternative routes of administration that bypass the lungs and deliver oxygen closer to its cellular target may be the goal for the future. IVO2 may accomplish the same benefits of hyperbaric oxygen therapy without the technical challenges, costs, and potential side effects (barotrauma, direct oxygen toxicity) which are associated with hyperbaric chambers. However, a safe and effective way for intravenous delivery of O2 still represents a challenge for research groups. Currently, different ways to provide IVO2 have been studied or developed over time, corresponding to different devices or technologies: (1) direct injection of free oxygen gas into the blood stream, resulted in pulmonary emboli even at low infusion rates[46,52], (2) physiologic solutions containing dissolved oxygen artificially added at hyperbaric concentration (supersaturated intravenous fluids)[47], (3) hyperoxygenated solutions (HOS) produced after being treated with ultraviolet light that creates an O2/O3 mixture flowing into the airtight base solution, (4) use of artificial carriers such as hemoglobin-based carriers[48,49] or Perfluorocarbon (PFC)-based carriers in emulsions , (5) use of nanotechnology[51,65]. Of note over the past century some authors explored the possibility of giving intravenous oxygen[52] or O2-enemata for absorption through the intestinal mucosa[53], both of which were not followed by further studies. Research in China and South-East Asia has investigated the efficacy of intravenous HOS as auxiliary oxygen supplies in several hypoxic states[54], with good therapeutic effects. In 1999 a special equipment called GY-1,

used to dissolve oxygen in solutions and administer that in medical hyperoxygenated infusions, was invented and patented by Chinese researchers and has been used to treat millions of hypoxic patients since then[54]. GY-1 equipment has been distributed to several hospitals in China, and some devices have been exported to other southeast Asian countries. IVO2 for systemic administration is not yet at the stage of clinical testing in Europe and USA, neither in the form of HOS nor as supersaturated solutions with the exception of SuperSaturated Oxygen (SSO2) therapy, mentioned further in the text. Possible application has been encouraged by some preliminary laboratory data, such as in mechanically ventilated rabbits (Kim et al.[55], Spears et al.[56]), and in a porcine model (Gao et al.[57] , Grady DJ et al.[58]). On the contrary, in 2016 the study of Damiani et al.[59] suggested the inadequacy of intravenous oxygenated fluids or intestinal insufflation of O2 as alternative ways for oxygen administration in hypoxemic rats. Gehlbach et al.[60] summarized the current evidence regarding IVO2 a few years ago underlining the potential benefit of this method and the application of HOS in Asia. Currently the ongoing application of IVO2 in Europe, which was also recently approved by the United States Food and Drug Administration (FDA), concerns the SSO2 therapy, a proprietary medical technology developed by TherOx®. SSO2 therapy creates a highly oxygenated saline solution and combines it with the patient's arterial blood to provide focal hyperoxemic oxygen environment to ischemic tissue[61], by injecting it into a patient's coronary artery. The focus of SSO2 therapy is for the treatment of acute myocardial infarction. The FDA's approval for this system was based on the results of multiple clinical trials, including the pivotal AMIHOT II trial[62], which enrolled 301 patients with anterior acute myocardial infarction, and the IC-HOT study[63,64] which enrolled 100 patients.

In a more advanced initiative, a new nanotechnology is currently in development: lipid-based microparticles surrounding a core of pure oxygen (lipid-coated microbubbles)[51], or polymer-based hollow microparticles[65]. Vutha et al.[66] claimed in 2022 to have designed a microfluidic device that administers oxygen gas directly to the bloodstream in real time and on demand using a sequential shear-induced bubble breakup. If successful, the described technology which was tested in vivo on rodent models, may help to reduce the incidence of ventilator-related lung injury from refractory hypoxemia. The application of this device and of IVO2, if effective and safe, could be extended to emergency settings to gain some bridging time to ECMO for example or other interventions[67], but it is important to realize researchers have not performed any in vivo human studies yet. It remains an exciting prospective challenge to see how IVO2 could be implemented in perioperative medicine and anesthesia in any setting where supplemental oxygen is required by the patient.

Conclusion

The oxygenation of the patient undergoing anesthesia and the management of the airway remains a keystone in anesthesia. As our knowledge and skills develop over time, increasingly new technology and scientific advances bring new possibilities in mastering this challenging domain. Provided that more studies and research are carried out, the implementation of US, HFNO and IVO2 in a continuum during perioperative medicine as well as the integration of tools for anticipating the difficult airway could change the way we offer the best possible pioneering care to our patients. Whilst this list is not exhaustive, it provides an exciting glimpse of what may lie on the horizon in the future of airway management.

List of abbreviations in chronological order:

US: Ultrasound/ultrasonography
HFNO: High Flow Nasal Oxygenation
PEEP: Positive End-Expiratory Pressure
IVO2: Intravenous Oxygen
ECMO: ExtraCorporeal Membrane Oxygenation
ENT: Ear-nose-throat
ICU: Intensive Care Unit
DA: Difficult Airway
MMT: Modified Mallampati Test
TMD: Thyromental Distance
SMD: Sternomental Distance
ULBT: Upper Lip Bite Test
DL: Difficult Laryngoscopy
DSHB: Distance from Skin to the Hyoid Bone
DSEM: Distance from Skin to Epiglottis Midway
DSE: Distance from Skin to Epiglottis
DSAC: Distance from Skin to Anterior Commissure
PPV: predictive value
DOR: diagnostic odds ratio
AUC: Area Under the ROC Curve
ROC: Receiver Operating Characteristic
IIG: Inter-Incisor Gap
ANS-VC: distance from the skin to the Anterior Trachea at the Vocal Cords
CL: Cormack-Lehane
NPV: Negative Predictive Value
NC: Neck Circumference
BURP: Backwards Upwards Rightwards Pressure
DTI: Difficult Tracheal Intubation
HMDE: Hyomental Distance in Extension
HMDR: Hyomental Distance Ratio
HMD: Hyomental Distance

FRC: Functional Residual Capacity
O2: Oxygen
CO2: Carbon Dioxide
FiO2: Inspiratory Fraction of O2
HFNC: High-Flow Nasal Cannula
IQR: InterQuartile Range
SD: Standard Deviation
EtCO2: End-Tidal CO2
EtO2: End-Tidal O2
PaO2: Arterial oxygen partial pressure
PaCO2: Arterial partial pressure of Carbon dioxide
NIV: Non-Invasive Ventilation
RCTs: Randomized Controlled Trials
OR: Odds Ratio
OR: Operating Room (according to the context)
CI: Confidence Interval
MD: Mean Difference
DAS: Difficult Airway Society
HOS: HyperOxygenated Solutions
SSO2: SuperSaturated Oxygen
FDA: Food and Drug Administration

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