REVIEW

Rapid sequence induction of anesthesia: works in progress and steps forward with focus to oxygenation and monitoring techniques

Tommaso DEL SANTO, Alessandro DI FILIPPO *, Stefano ROMAGNOLI

Department of Health Sciences, University of Florence, Florence, Italy

*Corresponding author: Alessandro Di Filippo, Department of Health Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy. E-mail: alessandro.difilippo@unifi.it

ABSTRACT

The description of the main scientifically consolidated innovations in recent years on Rapid Sequence Induction have been the subject of this narrative review. Data sources were PubMed, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and ClinicaTrials.gov, searched up to March 21st, 2023; rapid sequence induction and anesthesia were used as key word for the research. In recent years at least three significant innovations which have improved the procedure: firstly the possibility of using drugs which rapidly reverse the action of the myorelaxants and which have made it possible to give up the use of succinylcholine, replaced by rocuronium; secondly, the possibility of using much more effective pre-oxygenation methods than in the past, also through apneic oxygenation techniques which allow longer apnea time, and finally new monitoring systems much more effective than pulse oximetry in identifying and predicting periprocedural hypoxemia and indicating the need for ventilation in patients at risk of hypoxemia and preventing it. The description of three main scientifically consolidated innovations in recent years, in pharmacology, oxygen method of administration and monitoring, have been the subject of this narrative review.

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Aspiration of gastric content: past, actuality, physiopathology, and consequences

The first concept of rapid sequence induction (RSI) of anesthesia to prevent aspiration of gastric content was first formulated in the 1950s (although the first formal description of the RSI technique was done by Stept and Safar in the 1970); in those years a study on the death causes related to anesthesia on more than 1000 patients showed that one of the main causes was aspiration of gastric content.[1] Despite advances in anesthetic techniques, aspiration of gastric contents is still one of the main complications of anesthesia. It mostly occurs in patients with risk factors.[2]

Induction of anesthesia induces a loss of protective upper airway reflexes that facilitate pulmonary aspiration.[3] Mask ventilation is a technique that is routinely used after induction of anesthesia, while waiting for the neuromuscular

blocker to act before proceeding to orotracheal intubation and mechanical ventilation. Despite being a widely used technique, it is the main cause of gastric aspiration during anesthesia, excluding those that occur when a supraglottic device is used.[4]

Ultrasound confirmed that aspiration occurs mainly in patients ventilated with facemask. It also showed that 28% of patients, despite observation of the preoperative fasting, arrive at the surgery with a high gastric volume, which is a risk for gastric content aspiration.[5]

Lung aspiration of gastric contents can cause various consequences, the nature and severity of which depend on the type of material aspirated and its quantity. Large food fragments cause bronchial obstruction. If the food fragments are small enough to enter the distal airways, they induce a foreign body reaction with inflammation and granuloma formation.

The aspiration of acidic material, such as gastric juice, causes an inflammatory response that begins in a few minutes and progresses over 24-36 hours with consequent edema and alveolar hemorrhage. At the bronchial level there is desquamation of the lining epithelium.

Type II pneumocytes are destroyed both by acid and inflammation, resulting in a reduction of surfactant production which causes a progressive collapse of the alveolar units involved. The resulting picture is a chemical pneumonia that can progress to acute respiratory distress syndrome (ARDS).[6] Overall mortality due to pulmonary aspiration is between 5% to 20%.[7, 8]

The RSI technique: indications, controversies, and critical elements

RSI is a technique used to achieve patient intubation in situations where induction of anesthesia is required quickly and when it is necessary to minimize the risk of gastric content aspiration.

RSI aims with the shortest intubation time after induction after induction, to reduce the chances of active or passive aspiration.

The induction of anesthesia causes the loss of reflexes that protect the airways, resulting in the risk of pulmonary aspiration especially in the time interval between loss of consciousness and the start of ventilation after cuffing the tube.[9]

RSI is indicated for patients who are at increased risk of aspiration during the induction of anesthesia, as patients with a full stomach (*i.e.* emergency surgery, trauma patients, non-observance of preoperative fasting), patients with gastrointestinal pathology at high risk of regurgitation (*i.e.* gastroparesis, intestinal occlusion, gastric occlusion, esophageal stricture, symptomatic gastroesophageal reflux disease, hiatal hernia), patients with increased intra-abdominal pressure (obese, ascites) and pregnant women over 20th week or with gastroesophageal symptoms.[10]

The technique consists in the administration of a hypnotic agent with rapid action onset associated with drugs to ensure adequate analgesia for laryngoscopy and the administration of a neuromuscular blocker (usually succinylcholine or rocuronium at an increased dose).[11]

Unlike standard tracheal intubation, in which manual ventilations are carried out with the balloon-mask while waiting for suitable intubation conditions, in RSI these are not performed, although some authors suggest that a gentle bag/facemask ventilation (maximal inflation pressure <20 cmH$_2$O) can be performed to reduce oxygen desaturation and to provide an estimation of the likelihood of successful bag–facemask ventilation following prolonged or failed intubation attempts.[12, 13]

A possible technique to reduce even more the risk of regurgitation in RSI is Sellick maneuver, that consists in applying pressure on cricoid ring to compress the esophagus between the cricoid cartilage and the fifth cervical vertebra to prevent stomach contents from reaching the pharynx.[14] Although Sellick and other authors confirmed the efficacy of the technique to prevent gastric content aspiration in both adult and pediatric population[14-16] there is still no consensus of its benefits among anesthesiologists worldwide and the application of the technique in RSI is very debated.[17]

The critical element of RSI is to provide adequate pre-oxygenation and apneic oxygenation to ensure an effective safe apnea: muscle paralysis without manual ventilation determines a period of apnea during the attempt (or attempts) of tracheal intubation. During this apnea, desaturation may arise, with potentially fatal consequences.[18]

Maximal preoxygenation is achieved when the alveolar, arterial, tissue, and venous compartments are all filled with oxygen.

Some patients tend to desaturate quicker than others: these are patients with an increased oxygen extraction or with decreased capacity for oxygen loading. This may depend, for example, on the presence of cardio-pulmonary pathologies or, as for obese patients and pregnant women, on a pathological or paraphysiological reduction of the residual functional capacity.[19]

Neuromuscular blockade during RSI

Neuromuscular blockade (NMB) is very important in RSI, since it facilitates the intubation maneuver, reducing complications associated with airway management.[20-22]

Fast-acting, rapid metabolism neuromuscular blockers should be used for RSI.

The most used in the setting of RSI are high dose rocuronium (non-depolarizing neuromuscular blocker) and succinylcholine (depolarizing neuromuscular blocker).[23] Compared to succinylcholine, rocuronium has the benefit to avoids the risk of myalgia, hyperkaliemia, and malignant hyperthermia.[24]

The problem of rocuronium is its long duration of action, especially when used at dosage (1.2 mg/kg)[23] for RSI (30-65 minutes), which for many years has limited its use in short surgical procedures. One concern with the use of NMB agents (NMBA) during general anesthesia is that it puts the patient at risk of residual paralysis, that can lead to hypoxemia and postoperative pulmonary complications.[25]

The conventional treatment for reversal of NMB is via acetylcholinesterase inhibitors who are associated to an increase of parasympathetic effects due to their action on muscarinic synapsis throughout the body. Currently, it is possible to quickly antagonize rocuronium effect thanks to sugammadex, a cyclodextrin first approved in 2008 in Europe that binds in a 1:1 ratio to a steroidal NMBA and has 2.5 times greater affinity for rocuronium than vecuronium and pancuronium.[26] The dose of sugammadex is based on body weight and the degree of neuromuscular blockade at the time of reversal. A dose of 16.0 mg/kg administered 3, 5 or 15 min after a high dose of rocuronium, cause complete reversal in less than 3 min, without signs of recurrence of neuromuscular blockade.[27, 28]

The reversal speed of rocuronium with sugammadex is comparable to or shorter than the spontaneous recovery from succinylcholine:[29-33] this can provide an advantage in "cannot intubate, cannot ventilate" situations, although some patients could develop ventilatory depression despite the administration of sugammadex.[34]

Pre-oxygenation

In RSI the patient is not ventilated unless it is necessary for the onset of hypoxemia, in order not to cause aspiration of gastric contents. Consequentially, the critical element of RSI is to provide adequate pre-oxygenation and apneic oxygenation to ensure a valid period of safe apnea, defined as the time before the patient reaches a saturation of 88-90%: muscle paralysis without manual ventilation determines a period of apnea during tracheal intubation attempt (s) during which desaturation may occur.[18, 35]

In healthy patients who breathes ambient air prior to RSI, desaturation usually begins within 60 seconds.[35] Compared to the simple breathing of ambient air, an optimal pre-oxygenation can guarantee oxygen reserves up to 6 times greater, depending on the patient's characteristics such as gender, Body Mass Index (BMI), age and comorbidities.[36]

Pre-oxygenation in RSI has three main objectives:

• bring arterial oxygen saturation (SaO_2) as close as possible to 100%;

• increase the reserve of O_2 inside the lung as much as possible, replacing nitrogen in the dead space with oxygen (process called denitrogenation);

• increase the oxygen dissolved in the blood as much as possible.[35, 37]

A method to prolong safe apnea is to provide oxygen during the apnea period; after cessation of spontaneous ventilation, the alveoli continue to absorb O_2. In apnea approximately 250 mL/min of O_2 passes from the alveoli to the blood, while only 8 to 20 mL/min of CO_2 passes from

the blood to the alveoli, with most of the CO_2 that remains inside the blood and is buffered by it.[35, 38]

The current standard in clinical practice provides that pre-oxygenation, in RSI procedures, is carried out using a face mask or a non-rebreather mask, delivering an oxygen flow of 15 L/min at an inspired fraction of oxygen (FiO_2) of 1.00 until reaching an end tidal O_2 (EtO_2) concentration of 90% prior to administration of drugs used in RSI.

Alternatives that do not require EtO_2 measurement are to ask the patient to breathe at tidal volume for 3 minutes, or to take eight vital capacity breaths in one minute.[10] An alternative method to obtain preoxygenation and apneic oxygenation is to use the standard low-flow nasal cannula, which can deliver oxygen up to 15 L/min. At last, a newer oxygenation technique for RSI is the use of high flow nasal oxygenation (HFNO), that allows administration of O_2 with a maximum flow of 60-70 L/min and a FiO_2 up to 100%.[39, 40]

High flow nasal oxygen: description, physiological effects, efficacy and use in RSI

Oxygenation with high flow nasal cannula (HFNC), called HFNO, is a non-invasive method to dispense oxygen. The delivery system consists of an air-oxygen mixer with adjustable FiO_2 (21-100%) which delivers a gas flow, also adjustable between 2 and 60-70 L/min, to a chamber where it is heated and humidified. The gas mixture is then administered to the patient through special nasal cannulas.

The system can increase FiO_2 by administering a higher flow than would occur during normal inhalation, thereby decreasing entry into the ambient air circuit, which commonly occurs with standard low flow nasal cannulas and facemasks.[41]

There are various physiological effects of HFNO that can provide benefits in patients undergoing RSI. HFNO has shown to create a positive airway pressure up to 5 cmH_2O: this pressure could recruit collapsed alveoli, reduce the work of breathing and reduce airway resistance by creation of a small positive end-expiratory pressure

(PEEP);[42, 43] the use of HFNO increases both tidal volume and end-expiratory lung volume with larger increases in patients with high BMI, who mostly benefit from this effect;[44] the difference between the patient's inspiratory flow and the flow provided by the cannula is small, and the FiO_2 remains relatively constant, especially when administering high flows;[45] at last, the humidified and heated gas determines an improvement of the mucociliary function, facilitates the clearance of secretions and is associated with the reduction of atelectasis, resulting in a better ventilation/perfusion ratio and better oxygenation.[46]

A debated possible effect of HFNO is the generation of a ventilatory exchange, with a clearing of CO_2, in apnea patients called THRIVE (trans nasal humidified rapid insufflation ventilatory exchange).[47-49] However, THRIVE has been recently refuted by Riva *et al.*, who demonstrated that different levels of flow (from 0.25 L/min to 70 L/min) administered *via* HFNO are not associated with significant differences in CO_2 clearance.[50] Studies have been carried out on the use of HFNO as a pre-oxygenation method before induction of the anesthesia for surgical interventions. In RSI performed for emergency abdominal surgery, HFNO was found to be an effective and safe method for preoxygenation.[51]

During the induction of anesthesia in morbidly obese surgical patients, and therefore with a greater tendency to desaturation during the apnea period, the use of HFNO compared to pre-oxygenation with facemask allowed to increase the safe apnea interval by an average of 40%, and the minimum SpO_2 obtained in the population was higher.[52]

In a 2021 multicenter study, HFNO and facemask were compared as pre-oxygenation methods in patients undergoing emergency surgery in which RSI was used. In the study, there were no differences in the risk of desaturation during pre-intubation apnea, in the $EtCO_2$ detected after intubation and in the percentage of patients who showed signs of gastric regurgitation.[53]

In patients undergoing emergency surgery, 3 further studies were carried out which compared HFNO and facemask in RSI:

• the first one showed a non-significant difference between the two groups in the arterial oxy-

gen pressure (PaO_2) values reached at the time of intubation, compared to a significantly longer apnea time in the HFNO group;[54]

• in the second study, the number of patients who desaturated (SpO_2 <93%) was significantly lower in the oxygenated group with HFNO;[55]

• the third one showed that, compared to usual care, HFNO did not improve lowest SpO_2 during the first intubation attempt but prolong safe apnea time.[56]

In a study carried out in pregnant women that received RSI, HFNO has shown to be superior to facemask for preoxygenation, since PaO_2 and EtO_2 values at intubation were higher in HFNO group than facemask group.[57]

To provide apneic oxygenation during orotracheal intubation, HFNO is a very effective device. This provides a limited FiO_2 in a patient who breathes spontaneously, but in an apneic patient the absence of breathing allows the pharynx to be filled with a high FiO_2 gas. As the flow of O_2 administered increases, there is an increase in the FiO_2 supplied to the patient, as when using HFNO, up to 100%. A further advantage of using HFNO is that they can be left in place during intubation attempts, continuing to provide beneficial effects on apneic oxygenation (Figure 1).

This feature is particularly important in situations in which intubation is difficult, and therefore requires a greater number of attempts at intubation and/or more airway management time. Furthermore, HFNO does not interfere with the application of a facemask when mask ventilation is needed due to desaturation.

On the contrary, oxygenation with face masks, although they can provide high levels of FiO_2 to the patient who breathes spontaneously, during apnea provide reduced quantities of oxygen, since the masks may not adhere perfectly to the patient's face, causing ambient air to enter; furthermore, some masks, such as nonrebreathing masks, are equipped with 2 ventilation holes which, for safety reasons, are not completely unidirectional and determine further entry of ambient air. Finally, these masks must be removed during intubation attempts, resulting in a decrease in apneic oxygenation during the maneuver.[35, 58, 59]

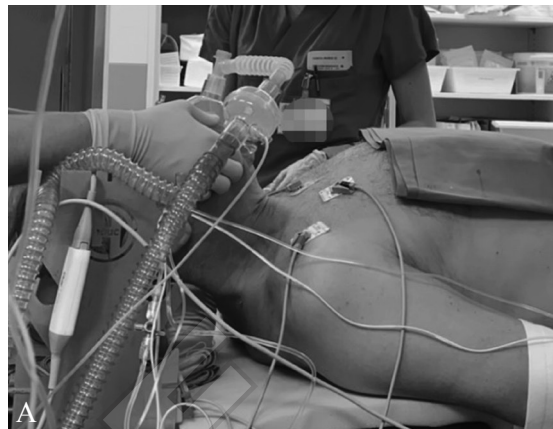

Figure 1.—Oxygenation with facemask (A) and with high flow nasal cannula (B).

Oxygenation monitoring during RSI: what's new?

Since desaturation is the main criticality in RSI, it is therefore important monitoring blood oxygenation to ensure preoxygenation is effective and to detect need for oxygenation during apnea period. Monitoring of hyperoxemia would also be very useful to detect imminent desaturation and to assess safe apnea time. The gold standard test for monitoring oxygenation status is arterial blood gas analysis. However, it is an invasive and

expensive test, that does not allow to have results in real time and its utility in RSI is limited.[60]

Measurement of arterial hemoglobin saturation (SaO_2), along with measurement of expired oxygen, is part of the American Society of Anesthesiologists (ASA) standards of monitoring for anesthesia.[61]

While pulse oximetry is useful for monitoring hypoxemia, its utility in determining oxygenation status above a PaO_2 of 90-100 mmHg is limited. In this situation, O_2 saturation is almost complete, and further increases in PaO_2 no longer affect SpO_2. Consequently, when SpO_2 is $\geq97\%$, patients' PaO_2 could be anything >90 mmHg.[62]

During preoxygenation for RSI, we aim to reach high value of PaO_2 to prolong safe apnea and reduce the incidence of desaturation. While SpO_2 is not useful to detect the level of hyperoxia and to predict desaturation, new technologies, as Oxygen Reserve Index, can be used for this purpose.

Oxygen Reserve Index

The Oxygen Reserve Index (ORi) is a recently invented tool that reflects, in real time and noninvasively, the patient's oxygenation status in a range of hyperoxia (PaO_2 >100 mmHg).[63]

In the hyperoxemic range a significant amount of oxygen is not bound to hemoglobin but is dissolved in the blood; this quota can satisfy part of the metabolic needs of the tissues, reducing the release of oxygen from hemoglobin and thus increasing the saturation of venous hemoglobin (SvO_2). Consequently, under conditions of 100% SaO_2, an increase in PaO_2 results in an increase in SvO_2, and therefore a change in the absorption of light emitted by the sensor. The absorption rate of light emitted at various wavelengths is related to the level of hyperoxia; this allows, by means of an algorithm, the calculation of the ORi.

ORi is not a direct measurement of PaO_2, but a dimensionless measurement between 0.00 and 1.00 that is determined by the absorption of emitted light and, therefore, is related to PaO_2. The ORi value is usually 0.0 when SpO_2 is 98% or lower; the maximum sensitivity of ORi is for PaO_2 between 100 and 200 mmHg. Nonetheless, ORi can detect PaO_2 changes even above >200 mmHg.

The correlation between ORi and PaO_2 values is strong when PaO_2 is < 240 mmHg, while it is weaker when PaO_2 is >240 mmHg; when PaO_2 <240 mmHg there is also strong agreement between PaO_2 and ORi trend[64, 65] (Figure 2). Among its many possible applications, such as monitoring the response to oxygen administration and detecting impending hypoxemia, ORi can be useful during preoxygenation which is performed before tracheal intubation and to monitor apnea period. Unlike arterial saturation measuring (that is useless in hyperoxemic

Figure 2.—Example of continuous intraoperative Oxygen Reserve Index trend (ORI), continuous pulse oxygen saturation trend (SpO_2), and intermittent arterial partial pressure of oxygen determination (PaO_2) obtained during surgery. ORI decreased during 30 minutes before a documented large decrease in PaO_2.[64]
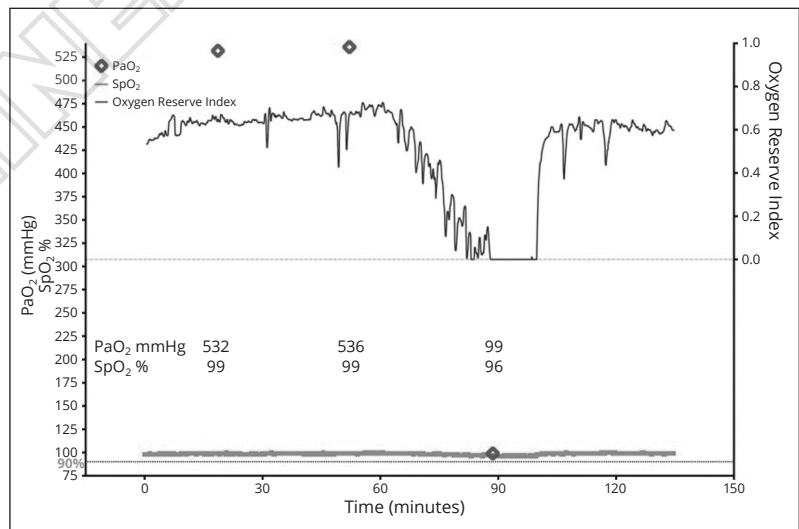
range), ORi can be useful in identifying patients who do not increase their oxyemia during pre-oxygenation, as well as highlighting incorrect preoxygenation technique.[66]

Current standards recommend using EtO_2 as an indicator of adequate pre-oxygenation; pre-oxygenation is considered adequate when EtO_2 >90%. There is a strong correlation between EtO_2 and ORi, suggesting that ORi can be used as an effective non-invasive monitoring tool during pre-oxygenation.[67]

ORi is also a useful tool to predict desaturation and drop in oxygen blood levels. Compared to pulse oximetry, ORi is able to detect the drop in oxygenation about 30-45 seconds in advance, allowing earlier detection of desaturation risk and more timely changes in patient's airway management plan to prevent desaturation.[65, 68]

Hille and colleagues investigated the efficacy of ORi as a tool to predict the onset of mild hypoxemia (defined as SpO_2 <97%) during the tracheal intubation procedure in 56 non-hypoxemic patients admitted to the intensive care unit. This study shows that the mean time between when ORi drops below 0.40 and when SpO_2 drops below 97% is 81 seconds, and that higher ORi values during pre-oxygenation are associated with lower risk of hypoxemia during the intubation procedure, confirming the possible role of ORi in monitoring pre-oxygenation and apnea even in an ICU setting.[69]

Conclusions

Although the RSI procedure was proposed and described many years ago,[70] over time, many innovations have occurred with the aim of making it safer and more effective.

Waiting for the scientific community to produce prospective randomized controlled trials demonstrating the superiority of video laryngoscopes in performing the RSI procedure,[71] given the doubts that, instead, their use in the first instance had raised,[72] in our opinion, in recent years at least three significant innovations have improved the procedure: firstly the possibility of using drugs which rapidly reverse the action of the myorelaxants and which have made it possible to give up the use of succinyl-choline, replaced by rocuronium;[32] secondly, the possibility of using much more effective pre-oxygenation methods than in the past, also through apneic oxygenation techniques which allow longer apnea time[54] and finally new monitoring systems much more effective than pulse oximetry in identifying and predicting periprocedural hypoxemia and indicating the need for ventilation in patients at risk of hypoxemia and preventing it.[69]

The historical location, indications and procedure description of the RSI and the description of the main scientifically consolidated innovations in recent years have been the subject of this narrative review.

Key messages

• Rapid sequence induction of anesthesia for tracheal intubation has seen some scientifically consolidated innovations in recent years.
• The first innovation is the possibility of using drugs which rapidly reverse the action of the myorelaxants.
• The second innovation is that providing apneic oxygenation during rapid sequence induction High Flow Nasal Oxygenation proved to be the more effective device.
• Lastly, new monitoring systems that are much more effective than pulse oximetry in identifying and predicting periprocedural hypoxemia and indicating the need for ventilation.

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