INTEGRATIVE REVIEW OF THE EFFICACY OF THRIVE

IN EXTENDING THE APNEIC WINDOW

by

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ABSTRACT

Maintaining ventilation is vital for patients under general anesthesia. However, establishing a patent airway can prove problematic: repeated attempts to intubate can lead to airway trauma that makes subsequent attempts far more difficult. Anesthesia-care providers (ACPs) must prevent hypoxic injury and establish an airway during the "apneic window," which stretches from the administration of a neuromuscular blocking agent to the establishment of a definitive airway and effective ventilation. Should intubation prove impossible, ACPs find themselves in the dangerous "can't intubate, can't ventilate" scenario (Patel et al., 2015). Various methods of prolonging the tolerance of the apneic window have focused on the period of time prior to intubation. Some patients are at increased risk of aspirating stomach contents into their lungs during intubation, and this expedited version of induction and intubation is known as *rapid sequence induction* (RSI). Since this procedure does not include administering positive pressure breaths to verify their airway patency prior to the administration of muscular blocking agents, there is a heightened concern regarding the ability to secure an airway- thus prolonging the apneic window- for these patients.

Within the last ten years, a new method of prolonging the apneic window, Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE), has shown promising results related to maintaining oxygen saturation and preventing excess accumulation of CO_2 during RSI (Doyle et al., 2016; Gustafsson et al., 2017). The THRIVE technique involves the administration of 40-70 liters per minute of warmed, humidified 100% oxygen via a nasal cannula. The high flow rate helps entrain and expel CO_2 from the lungs and fosters apneic oxygenation with the 100% oxygen contained in the pharynx (Gustafsson et al., 2017).

Because it is still considered a novel technique, it has not yet been widely adopted in the United States, despite its promising results in studies thus far. This review includes: 1) the physiological basis for the mechanism of THRIVE, 2) the length of the apneic window in comparison with traditional methods of preoxygenation, and 3) the incidence of significant desaturation and hypoxemia in patients utilizing THRIVE vs. other traditional methods of preoxygenation. Databases searched included Pubmed, Embase, CINAHL. The terms included *transnasal humidified rapid insufflation ventilatory exchange, rapid sequence induction, apneic window, hypoxemia,* and *pre-oxygenation.* 12 articles were identified and reviewed. According to the results of the 12 articles and studies, THRIVE is capable of lengthening the mean apneic time in many patients and reducing the incidence of significant desaturation and hypoxemia.

Keywords: transnasal humidified rapid insufflation ventilatory exchange, rapid sequence induction, apnea, desaturation

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INTRODUCTION

Rapid sequence induction is a process implemented during the induction of anesthesia that helps to protect the airway of patients at an increased risk of aspiration; these patients may have recently eaten, may be actively vomiting, have a gastrointestinal obstruction, have gastroparesis, or be pregnant. Rapid induction involves monitoring vital signs, inserting an intravenous line, proper positioning of the patient prior to induction, preoxygenation, and the administration of an IV anesthetic and a fast-acting neuromuscular blockade (Klucka, et al, 2020). The apneic window begins when the neuromuscular blockade is administered and concludes when a definitive airway is secured and positive-pressure ventilation begins or when spontaneous ventilation resumes. This procedure and the associated apneic window carry with it the risk for significant desaturation and hypoxemia. The human brain cannot endure significant hypoxemia for long; most patients begin to suffer negative effects after one to two minutes, with more permanent damage setting in after three to six minutes. For this reason, preoxygenation is an essential component in traditional RSI. The goal of preoxygenation is to increase the oxygen reservoir available to the patient prior to the induction of anesthesia. The typical method of preoxygenation is spontaneous facemask ventilation with 100% oxygen. This increases the amount of oxygen held within the functional residual capacity (FRC) of the patient. FRC is the volume of air in the lungs when there is no exertion of the diaphragm or other respiratory muscles. Head-up patient positioning and increasing the mean airway pressure can also help to improve the size of this reservoir and reduces atelectasis. At the end of preoxygenation, the oxygen content contained in the FRC is fixed and begins to dwindle from that point. Prior to the advent of apneic oxygenation, there has been no standardly used method of continuing to provide oxygen during the apneic period.

THRIVE makes use of a physiologic phenomenon known as “apneic oxygenation,” which enables the system to push more oxygen into the lungs during the apneic window. Apneic oxygenation works on a system of total pressure gradients. Assuming airway patency, “the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH_20 that drives oxygen into the lungs” (Patel et al., 2015). Essentially, if there is a reservoir of oxygen in the pharyngeal space, the body can draw that oxygen down into the lungs, via a positive pressure gradient, to replenish the FRC’s oxygen reservoir and continuously supply fresh oxygen. THRIVE’s high flow rate creates a constant supply of oxygen to the upper airways that then diffuses down to the alveoli, thereby lengthening the apneic window and reducing the incidence of desaturation and hypoxemia. This review aims to answer the question: “Does THRIVE create better patient outcomes in patients who require an RSI?”

Variables:

- Significant desaturation – oxygen saturations below 94%
- Hypoxemia: PaO_2 less than 80
- Apneic window: Period during anesthesia induction that stretches from the administration of a neuromuscular blocking agent to the establishment of a definitive airway and effective ventilation
- THRIVE: Involves the administration of 40-70 liters per minute of warmed, humidified 100% oxygen via a nasal cannula

Focused review questions:

- What is the physiologic mechanism behind THRIVE?
- Was the length of the apneic window extended in comparison with traditional methods of preoxygenation?
- What was the incidence of significant desaturation and hypoxemia in patients utilizing THRIVE as opposed to other traditional methods of preoxygenation?

METHODS

Elements of Population

The population reviewed was treated with THRIVE prior to RSI and the induction of anesthesia. The population had a variety of comorbidities, and some had difficult airways contributing to discrepancies in the results. Some reviews included patients who did not require RSI's; such studies were used in this review solely to speak to the physiological basis of THRIVE, rather than its use in RSI.

Inclusion and Exclusion Criteria

Inclusion criteria for this review include human studies, randomized-control trials, observational studies, physiological studies, clinical trials, and surveys. A wide variety of research is included in order to gather and present the greatest amount of relevant information possible. THRIVE is still a relatively new technique, and thus, inclusion criteria were kept broad. Exclusion criteria included non-English abstracts or manuscripts, pediatric populations (18 years of age and younger), and articles written more than ten years ago.

Search Strategies

EMBASE was searched using the EBSCOhost provider on 02/24/2020

- Search terms: "transnasal humidified rapid insufflation ventilatory exchange" and “rapid sequence induction” and “apneic window”

- 112 articles

CINAHL was searched on 03/15/2021

- Searched “transnasal humidified rapid insufflation ventilatory exchange” and “rapid sequence induction” and “apneic window”
- 5 articles ➐ all had previously been found in the EMBASE search

Pubmed was searched on 03/15/2021

- Same search terms
- 4 articles ➐ all had previously been found
- Search term: “transnasal humidified rapid insufflation ventilatory exchange” alone gave 32 results
    - Found one new usable article

Handpicked search from references in relevant articles. Saturation point met. Discarded duplicates.

Eleven articles met the research criteria.

Evidence Appraisal

The Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Research Evidence Appraisal tool was employed to evaluate the validity and reliability of the chosen literature (John Hopkins). According to the model, the strength of the evidence is rated from Level 1 (the strongest) to Level 4 (the weakest). This classification system helps to determine if the evidence put forth by each article is considered high-quality, applicable, consistent, and generalizable. *Table 1: Critique of Literature* displays the findings of this appraisal.

Data Analysis

The evidence was organized and analyzed based on how it applied to the focused review questions. Physiologic studies explained the reasons why THRIVE is a successful and scientifically-sound technique. Randomized control trials, prospective-observational trials, and clinical trials all serve to determine the efficacy of THRIVE in prolonging the apneic window and preventing significant desaturation and hypoxemia.

RESULTS

Physiologic basis for THRIVE

THRIVE is used to both preoxygenate patients prior to the induction of anesthesia and to provide apneic oxygenation after. Preoxygenation is a well-established practice that increases the concentration of oxygen contained in the client's FRC. This provides a larger oxygen reservoir to draw from during the period of apnea and helps stave off desaturation and hypoxemia. THRIVE has been shown to be equally effective in preoxygenating patients as traditional methods (Miguel, 2015). Though preoxygenation is vital, THRIVE's true efficacy in extending the apneic window and preventing significant desaturation is based on its ability to foster apneic oxygenation. Apneic oxygenation is driven by the diffusion of oxygen and carbon dioxide down their total pressure gradients, a concept known as "bulk flow". During apnea, the differences in the rates of excretion of carbon dioxide and the absorption of oxygen create pressure gradients. Oxygen and carbon dioxide will both move according to their own individual partial pressures. Oxygen is absorbed into the blood more readily than carbon dioxide is excreted into the lungs, thereby creating a negative pressure gradient that draws air down into the lungs, even during periods of apnea. The high flow of THRIVE facilitates apneic oxygenation by constantly supplying or insufflating the pharynx with 100% oxygen that can then diffuse into the lungs according to the principles of bulk flow.

Another question raised particularly by Patel's study, is how does THRIVE promote carbon dioxide clearance? A problem associated with traditional apneic oxygenation methods is the accumulation of carbon dioxide (hypercapnia) and associated progressive respiratory acidosis. If not treated, this condition can lead to myocardial depression, arrhythmias, and ultimately death (Patel et al., 2015). Though carbon dioxide accumulation is not a pressing issue during short periods of apnea, it becomes problematic when attempting to extend the apneic window. Typically, rates of carbon dioxide accumulation during apneic oxygenation range between 0.35 and 0.46 kPa/min (measuring $ETCO_2$ against time). However, in Patel's study, THRIVE achieved a rate of carbon dioxide increase of only 0.15 kPa/min. Another study by Gustafsson found the rate of increase to be 0.24 kPa/min (2017). A physiological study was performed to examine the mechanism by which THRIVE impacted carbon dioxide clearance. Using three laboratory air models, it was found that the combination of the turbulent supraglottic vortices created by the high flow rate interacted with the changes in airway gas flow and pressure created by the cardiac cycle (cardiogenic oscillations) to help entrain and expel carbon dioxide (Hermez, 2019). THRIVE does not achieve a steady-state carbon dioxide level, but there is evidence that it improves carbon dioxide clearance, which can be vital during prolonged periods of apneic oxygenation.

Recent literature increasingly recommends the use of nasal cannula for preoxygenation and continuous oxygenation rather than a facemask. Nasal cannula can reduce the risk of gastric insufflation and aspiration (Mir, 2016). They also make it possible to maintain oxygenation during laryngoscopy and intubation, which is not possible with a facemask (Miguel, 2015). Until the advent of THRIVE, conscious patients could not tolerate flow rates of dry oxygen over 15 L/min due to mucosal drying and headaches. However, warming and humidifying the oxygen and delivering it through specifically crafted nasal cannula has enabled patients to easily tolerate flow rates of 70L/min and more (Mir, 2016). These high flow rates are vital to the insufflation of the pharynx and subsequent effective apneic oxygenation.

Length of apneic window

One of THRIVE's most important benefits is its ability to prolong the apneic window. Das et al performed a randomized controlled trial that tested how long THRIVE could maintain oxygen saturations of over 94% as compared with traditional methods of preoxygenation and apneic oxygenation (facemask and nasal cannula with oxygen flow at 15 L/min). THRIVE has administered at 70 l/min. It was found that the THRIVE group's safe apnea time was significantly longer than the facemask group (approximately 24 minutes vs. 16 minutes). Rajan et al. also performed a similar prospective, randomized, single-blinded study that investigated how long it would take for patients to desaturate below 90% during apnea with THRIVE compared to traditional preoxygenation and apneic oxygenation methods. Again, the results of the study displayed that THRIVE maintained SpO_2 far longer than traditional methods (769 seconds v 444 seconds). Patients undergoing THRIVE maintained saturations of 100% even after 12 minutes of apnea, while 80% of patients using traditional methods desaturated below 90% after 6 minutes of apnea. However, at 12 minutes of apnea, the researchers also saw a significant increase in PCO_2 and subsequent fall in pH. A randomized controlled trial performed by Hua et al. investigated whether THRIVE would produce the same extension of the apneic window in elderly patients (65-80 years of age). The primary outcome investigated was the apnea time, defined as the length of time from the cessation of breathing until SpO_2 decreased to 90% or until 10 minutes elapsed. The trial revealed that the apnea time was significantly increased by the use of THRIVE. 25 out of 30 patients (83.3%) in the THRIVE group lasted all 10 minutes without desaturating below 90%, while only 15 out of 28 patients (53.6%) in the facemask group made it through 10 minutes. Patel et al. also investigated the viability of THRIVE in maintaining oxygenation in patients with difficult airways. In this non-experimental, retrospective study, they reviewed the use of THRIVE on 25 patients who qualified as difficult to intubate, including obese and stridulous patients who needed RSIs. They maintained two patients on THRIVE alone for 32 minutes and 65 minutes, while maintaining oxygen saturations of approximately 99% and 95% respectively (Patel et al., 2017.

Incidence of significant desaturation and hypoxemia

While the ability of THRIVE to extend the apneic window is evident, it is also vital that it be able to do so without allowing any significant desaturation or hypoxemia to occur. Some studies included in this review did not investigate the length of the apneic window, but rather focused on the incidence of desaturation when using THRIVE during intubation procedures verses other methods of oxygenation. A study performed by Doyle et al.
hypothesized that using THRIVE for preoxygenation and apneic oxygenation would produce low incidences of desaturation during rapid sequence induction. The study found that the median decrease in SpO2 was 1% over a median apneic window of 80 seconds. Five patients (7%) in the study experienced significant desaturation. However, three of those patients had difficulty maintaining their airway patency, which is vital for the efficacy of THRIVE, and another had a preinduction SpO2 of 90% caused by acute respiratory failure. Another finding of the study was that there was no correlation between the BMI of the patient and the incidence of desaturation,

showing that this technique may not be limited by a patient's BMI. Though these results are promising, this study was weakened by the fact that the researchers collected no data regarding the incidence of significant desaturation prior to the implementation of THRIVE, and thus the results could not be compared to other methods.

Studies by Lodenius et al. (2018), Sjoblum et al. (2021), and Miguel et al. (2015) also monitored and reported the effect of THRIVE on SpO_2 during apnea. Lodenius et al. (2018) found no differences in median oxygen saturations between the THRIVE group and the facemask group; both produced a median lowest SpO_2 of 99%. However, it was noted that fewer patients in the THRIVE group desaturated below 93%. Sjoblum et al. (2021) also found no difference in the number of patients who desaturated below 93% and thus concluded that THRIVE is a valid and adequate method of preoxygenation and apneic oxygenation during RSI. Miguel et al. (2015) compared the lowest SpO_2 recorded during intubation, as opposed to the median SpO_2. This study also recorded the number of patients that experienced saturations lower than 80%. It was reported that the median lowest SpO_2 of patients in the nonrebreathing bag reservoir facemask group was 94% while the THRIVE group's median lowest SpO_2 was 100%. Additionally, patients in the facemask groups experienced more episodes of severe hypoxemia. These three studies serve to further the evidence that THRIVE does indeed maintain oxygen saturations just as well and perhaps better than a variety of current methods of oxygenation.

Studies by Mir et al. (2016) and Rajan et al. (2018) specifically investigated the ability of THRIVE to prevent hypoxemia during apnea. Mir's study primarily assessed PaO_2 levels after intubation and compared the levels found in the THRIVE group to those of a group oxygenated with a facemask. Interestingly, the mean PaO_2 of both groups was quite similar (43.7 kPa in the THRIVE group vs. 41.9 kPa in the facemask group). However, when reviewing the procedures, the researchers discovered that the THRIVE group experienced significantly longer periods of apnea than the face mask group (248 seconds v 123 seconds), yet still managed to maintain slightly higher mean PaO_2. Thus, Mir concluded that even during longer periods of apnea, THRIVE is able to stave off hypoxemia effectively. It was proposed that the reason for the discrepancy in the apneic time between the two groups was due to the feeling of security that THRIVE gave the anesthesia care providers. Researchers believed that this feeling of security led to more controlled, measured, and cautious laryngoscopy and intubation procedures, thus explaining the longer apneic window. Rajan et al. (2018) also looked primarily at PaO_2 to draw conclusions about THRIVE's efficacy. This study once again compared the PaO_2 levels of patients after spending some time in the apneic window. The THRIVE group produced significantly higher PaO2 levels, even at apnea times of greater than six minutes. However, Rajan et al. (2018) also found that $PaCO_2$ levels were higher in the THRIVE group, which prompted a drop in pH six minutes into the apneic window. This finding is concerning as respiratory acidosis can cause myocardial depression. It also contradicts other literature in which researchers reported slower rates of CO_2 increase and physiological studies investigating and displaying how CO_2 is expelled from the lungs during the use of THRIVE (Patel et al., 2015 & Hermez et al., 2019). These findings regarding CO_2 warrant further investigation.

DISCUSSION

THRIVE is shown to be highly effective in prolonging the apneic window and preventing desaturation and hypoxemia during that extended time. These positive results from multiple studies highlight the fact that this new technique has incredible ramifications for anesthesia induction. THRIVE serves as one of the first and only ways currently available to provide continuous fresh oxygen to the lungs even during times of complete apnea. By doing so, it helps to improve patient outcomes in those undergoing general anesthesia. Additionally, it improves the experience of the ACPs. THRIVE is reported to be easy to use and seamlessly integrated, and it also relieves the strain and hurriedness of the intubation process. By safely extending the apneic window and providing effective apneic oxygenation, ACPs are able to intubate carefully and without time constraints or the fear of hypoxic injury.

Currently, THRIVE is not widely used, especially in the United States of America. Most studies are centered in the United Kingdom, Australia, New Zealand, and India. The research for this review shows that THRIVE can be easily and safely implemented to improve patient outcomes, and thus, advocates for the increasing education about and use of THRIVE in the United States. THRIVE also requires further research, particularly more randomized controlled trials with larger sample sizes to increase the generalizability of the findings and strengthen the level of evidence found. This review also discovered conflicting evidence regarding the efficacy of THRIVE in clearing carbon dioxide from the lungs and preventing hypercapnia and subsequent respiratory acidosis. Some studies reported favorable findings in which CO_2 clearance was more effective when using THRIVE (Patel et al., 2015 & Hermez et al., 2019), but others reported dramatic rises in CO_2 and significant accompanying respiratory acidosis (Rajan et al., 2018). Further research needs to be done to assess the true effect of THRIVE on carbon dioxide clearance.

Limitations

This review was limited by the dearth of studies done specifically about the use of THRIVE in anesthesia to extend the apneic window. This technique is still relatively new and thus, the body of literature surrounding this topic is still growing. A systematic review of this information has not been performed. The literature in this review included all the most applicable and relevant studies available at this time.

CONCLUSION

THRIVE is a promising new technique that combines traditional concepts of preoxygenation with a novel approach to apneic oxygenation. THRIVE allows fresh oxygen to be continuously delivered to the lungs to replenish the oxygen content available in the FRC and maintain arterial oxygenation and oxygen saturations in completely apneic patients. This new approach has been shown to be effective in extending the apneic window and preventing desaturation and hypoxemia, even in patients with high BMIs and difficult airways. In order for this technique to be effective, it is absolutely vital that a patent airway is maintained. There is a need for increasing education regarding this topic, especially in the United States, as it is a valid and useful tool in improving the outcomes of patients who undergo general anesthesia and RSI.

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APPENDICES

Figure 1: Critique of Literature

Author(s)/Date	Design	Participants	Conclusion	Strength of Evidence
Das et al. (2020)	Experimental: RCT	N = 48 Patients were randomly assigned to either face mask ventilation at 15L/min or THRIVE at 70L/min. Primary endpoint was safe apnea time.	The safe apnea time was significantly longer in the group undergoing THRIVE protocol.	Level 1 – High Quality of Evidence
Doyle et al. (2016).	Non-experimental: Prospective, observational study	N = 71 THRIVE protocol was implemented in the CCU, OR, and ED for patients at high risk for hypoxia during intubation	Preoxygenation and apneic oxygenation with THRIVE were associated with low incidence of desaturation during emergency intubation of patients at high risk for hypoxia	Level 2 – Good Quality of Evidence
Gustafsson et al (2017)	Non-experimental: Physiological study	N = 31 Patients undergoing shorter laryngeal surgery under general anesthesia; mild systemic disease and BMI <30	Able to keep this population well oxygenated and with a pH at or above 7.13 for 30 minutes; successfully extends apneic window	Level II – Good Quality of Evidence
Hermez et al. (2019)	Non-experimental: Physiological Study	Used three laboratory airway models to investigate the method of CO_2 clearance in apneic patients while using THRIVE	Postulated that CO_2 clearance occurred due to the interaction between the high flow supraglottic vortex created by THRIVE and cardiogenic oscillations	Level III – Good Quality of Evidence

Hua et al. (2020)	Experimental: RCT	N = 60 Patients aged 65-80 without pulmonary dysfunction were randomly assigned to preoxygenation via facemask or THRIVE	THRIVE extended duration of apneic window and provided better preoxygenation than the facemask	Level 1 – High Quality of Evidence
Lodenius et al (2018)	Experimental: Prospective randomized non-blinded clinical trial (RCT)	N = 80 Patients were randomly assigned to preoxygenation with a face mask or with THRIVE prior to emergency surgery	No difference in lowest SpO_2 between facemask and THRIVE preoxygenation; lower incidence of patients desaturating below 93% in the THRIVE group indicating it may prevent hypoxia during prolong apnea (i.e. difficult intubations)	Level 1 – High Quality of Evidence
Miguel-Montanes et al. (2015)	Quasi Experimental: Prospective Before-After Study	N = 101 Patients requiring tracheal intubation in the ICU of Louis Mourier University Hospital, Colombes, France	THRIVE improved preoxygenation and reduced incidence of severe hypoxemia compared to a nonrebreathing bag reservoir facemask	Level 2 – Good Quality of Evidence
Mir et al. (2016)	Experimental: RCT	N = 40 Patients undergoing emergency surgery were randomly assigned to preoxygenation via facemask or THRIVE	There was no difference between the facemask ventilation group and the THRIVE group in terms of PaO_2, $PaCO_2$, or arterial pH. However, the mean apnea time was 125s longer in the THRIVE group	Level 1 – High Quality of Evidence

Patel et al (2015)	Non-experimental: Retrospective study	N = 25 Patients with difficult airways undergoing general anesthesia for hypopharyngeal or laryngotracheal surgery	THRIVE so successfully maintains oxygen saturations during the apneic window that it lessens	Level 2 – Good Quality of Evidence
			the stress of difficult intubations	
Rajan et al (2018)	Experimental: Prospective, randomized, single blinded study	N = 10 Patients presenting for directly laryngoscopy under general anesthesia	THRIVE significantly prolonged the apneic windows; cannot be recommended beyond 6 minutes of apnea because of development of hypercarbia and respiratory acidosis	Level 1 – High Quality of Evidence
Sjöblom et al (2021)	Experimental: RCT	N = 350 Adult patients from 6 centers in Sweden and 1 in Switzerland undergoing emergency surgery were randomly allocated to preoxygenation with a facemask or with THRIVE	THRIVE (or HFNC) is a suitable alternative to facemask preoxygenation for pre- and peri-oxygenation during RSI	Level 1 – High Quality of Evidence