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Efficiency and safety of nasal positive airway pressure systems during endoscopic procedures in high-risk patients: Endo-Breath study

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Trial registration: NCT05972304, ClinicalTrials.gov (http://www.clinicaltrials.gov/), Prospective, Randomized, Single-Center

Abstract:
Background and study aims: Sedation of high-risk patients is a relevant issue in interventional endoscopy. This is especially because standard oximetric monitors display only hypoxia and not the preceding hypercapnia. Therefore, the question arises whether use of a nasal positive airway pressure (nPAP) system can decrease the rate of sedation-associated events.
Patients and methods: A randomized, prospective trial was conducted at University Hospital Ulm, including 98 consecutive patients, identified as high-risk (American Society of Anesthesiologists physical status ≥ 3) and scheduled for prolonged (> 15 minutes) endoscopic procedures. Patients underwent 1:1 randomization to two groups: interventional (nPAP-Mask) and control (conventional oxygen supplementation). Levels of CO₂ were measured noninvasively by transcutaneous capnometry device. The primary outcome was incidence of hypoxia (SpO₂ < 90% over 10 seconds) and incidence of severe hypoxia was incidence of SpO₂< 80% over 10 seconds. One of our secondary objectives was to determine if the nPAP-Mask could result in significant CO₂ retention among high-risk patients.
Results: Data analysis showed lower incidence of hypoxia in the interventional group (10/47 vs. 31/251) P < 0.05. Episodes of severe hypoxia (SpO₂ < 80% over 10 seconds) were more frequent in the control group (8/51) compared with the intervention group (2/47) P < 0.05. There was no significant difference in ΔCO₂ levels in the interventional vs. control group (-6.01 ± 7.66 vs. -7.35 ± 8.59 mm Hg).
Conclusions: In high-risk patients use of a nasal positive airway pressure system could significantly lower risk of hypoxia, especially in prolonged procedures. The nPAP-Mask does not induce CO₂ retention when compared with conventional oxygen supplementation.

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Efficiency and Safety of nasal positive airway pressure System during endoscopic procedures in high-risk patients: The Endo-Breath-Study.

1. Introduction:

Patient safety is imperative in all types of endoscopic procedures, particularly for those categorized as high-risk due to underlying chronic diseases (classified as ASA III or ASA IV). Ensuring a safe intervention becomes even more challenging in such cases. Hypoxia, a potentially life-threatening complication, can arise during endoscopic procedures when patients are under deep sedation. Previous studies support the fact that episodes of hypoxia are more prevalent among patients with multiple comorbidities and elderly individuals. One of leading causes of acute respiratory failure during endoscopy is insufficient ventilation due to airway obstruction caused by soft palate and epiglottis falling back to the posterior pharynx.

Hypercarbia, resulting from insufficient clearance of CO_2 due to hypoventilation associated ineffective gas exchange, can also have drastic consequences. However, unlike hypoxia, which manifests immediately, the accumulation of CO_2 takes time. Elevated levels of carbon dioxide can lead to altered mental status, respiratory acidosis, fasciculations, arrhythmias, and coma. Detecting hypercapnia in sedated patients is nearly impossible through standard monitoring. It requires specialized equipment for accurate measurement, which is not usually available in an endoscopy unit.

Endotracheal intubation remains the gold standard for optimal airway support due to its recognized safety. However, resource constraints might hamper the adoption of endotracheal intubation and continuous anaesthesiologic support for routine endoscopy even in high-risk patients. Indeed, the invasive nature of general anaesthesia has led to concerns regarding the efficiency of resource management within endoscopy units when considering performing endotracheal intubation on every high-risk patient scheduled for an endoscopic intervention.

In the pursuit of a safe and efficient alternative for airway management previous studies have demonstrated promising results in significantly reducing the occurrence of hypoxia using non-invasive devices. One such device is the positive airway pressure system SuperNO2VA (Vyaire Medical Inc., USA), which has already demonstrated feasibility and safety in diagnostic endoscopic procedures for bariatric patients [1].

It remains unclear, whether SuperNO2VA-Mask can decrease the incidence of hypoxia during prolonged endoscopic procedures in (non-)bariatric high-risk patients. Furthermore, the incidence and severity of hypercarbia using nasal-PAP Systems are poorly understood.

CO_2 levels are typically assessed by analysing blood samples (venous, arterial, or capillary) or through the detection of exhaled CO_2 using nasal capnography. In case of upper gastrointestinal endoscopy, the utility of nasal capnography appears limited, given by the fact, that many modern endoscopes use CO_2 for insufflation, which may lead to inconclusive data. Blood sampling for hypercarbia detection is invasive and does not provide real-time monitoring of CO_2 levels during the interventions.

Novel non-invasive methods of CO_2 measurement, such as transcutaneous capnometry, have demonstrated high sensitivity and specificity when compared to capillary blood CO_2 levels. This method has already proven to be safe and effective in detection of hypercarbia during endoscopic procedures in the presence of high-flow nasal cannula oxygen [2].

This prospective study aims to investigate whether positive airway pressure systems can mitigate the risk of hypoxia and prevent hypercabia compared to conventional nasal oxygen cannulation in high-risk patients. Furthermore, we intend to analyse the relationship between various factors such as age, sex, procedure duration, type of procedure, sedation agent dosage and type, underlying chronic disease, and the occurrence of hypercarbia during prolonged endoscopic procedures.

2. Methods:

Design:

This single centre, randomised, controlled trial was performed at the University Hospital Ulm, Germany. The study protocol was approved by the local ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and the established best clinical practice. The study was also registered on the Clinical Trials Database under the identifier NCT05972304.

Study protocol:

A total of 98 consecutive patients with underlying chronic diseases were included in the study. These patients were stratified as high-periprocedural risk individuals based on the American Society of Anaesthesiologists physical status classification system (ASA III and ASA IV) [3]. They were scheduled for prolonged endoscopic procedures, including colonoscopy, gastroscopy, colonoscopy and gastroscopy, endosonographic ultrasound of the upper gastrointestinal tract, and endoscopic retrograde cholangiopancreatography (ERCP). Prolonged endoscopic procedure was defined as diagnostic or interventional procedure with a duration longer than 15 minutes.

Study randomization was conducted using Study Randomizer (Version 2017, Phase Locked Software, Netherlands), a web-based randomization service. The participants were divided into two groups in a 1:1 ratio. The interventional group received nasal positive airway pressure with the SuperNO2VA system, which involved insufflation of 10 liters of oxygen per minute. This flow rate was determined as the minimum insufflation required for the system to function properly, recommended by the manufacturer of the mask. In the control group, participants received conventional oxygen supplementation with a maximum flow rate of 6 liters of oxygen per minute, as advised by the manufacturer to prevent potential damage to the nasal mucosa. None of the patients received preoxygenation therapy except those, who were already using supplemental oxygen. After the endoscopic procedure, the patients were transferred to the recovery room. The oxygen levels were maintained at the same level as at the end of the procedure. The observation was discontinued when the patients reached full recovery, as indicated by the achievement of a Richmond Agitation Sedation Scale (RASS) Level of 0.

SuperNO2VA is a positive airway pressure device that consists of a tightly sealed nasal mask and 2-litre reservoir bag. When completely inflated and firmly applied, it generates intermittent positive airway pressure, which enables pneumatic stenting of upper respiratory tract. This on itself leads to optimising oxygen flow and reducing dead space [1]. However, it was not previously documented, whether such mechanism could lead to entrapment of CO_2 in the reservoir bag, thus increasing the

risk of hypercarbia. It is also unknown whether such devices could reduce the risk of hypercarbia by lowering CO_2 levels through intermittent positive airway pressure, which could lead to increased ventilation of pulmonary dead space.

The procedures were performed by two experienced endoscopists, each with an extensive clinical experience of over 10 years. One endoscopist was responsible for conducting the intervention, while the other one was in charge of administering sedation. The sedation protocol adhered to the German national guidelines and represents the standard practice for endoscopic procedures conducted in university hospitals. The procedural sedation and analgesia were administered by an experienced Endoscopist certified in ALS (Advanced Life Support), adhering to guidelines outlined by the "European Society of Anaesthesiology and the European Board of Anaesthesiology" for procedural sedation and analgesia in adults [4]. The sedation was administered using either the intermittent Propofol-Bolus-Application Method alone or in combination with Midazolam Bolus Application [5].

All patients were monitored in accordance with a standardized protocol, which included monitoring of blood pressure, oxygen saturation (SpO_2) and heart rate. Additionally, a transcutaneous capnometry system (TCM 5 by Radiometer GmbH, Krefeld, Germany) was used for monitoring. Invasive capnometry was not used in this study. The transcutaneous CO_2 probe was attached to the forehead of each participant, and the system was set to the minimum testing temperature of 42 degrees Celsius. The duration of the endoscopic procedure was calculated from the initiation of sedation until the end of endoscopic procedure and transfer of the patient to the recovery room. Continuous observation was carried out in the recovery room as well, to ensure the absence of any severe adverse events. However, the data collected during this observation period was not intended for use in the statistical analysis. Observation in the recovery room was discontinued once the patient achieved a RASS (Richmond Agitation-Sedation Scale) score of 0.

Participant recruitment:

Recruitment of patients was performed regarding further inclusion and exclusion criteria. Inclusion Criteria were:

- Estimated duration of endoscopic procedure equal or longer than 15 minutes
- Patients where older than 18 years old at the time of recruitment
- Patients with underlying chronic disease, stratified as ASA III (poorly controlled diabetes mellitus or arterial hypertension, chronic obstructive pulmonary disease, morbid obesity (BMI≥40), active hepatitis, advanced chronic liver disease, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, end-stage renal disease undergoing regularly scheduled dialysis, history (>3 months) of myocardial Infarction, transient ischemic attack, or coronary atherosclerotic disease.
- Patients with underlying chronic disease, stratified as ASA IV (recent (<3 months myocardial infarction, transient ischemic attack or coronary atherosclerotic disease, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, acute renal damage or end stage renal diseases not undergoing regularly scheduled dialysis
- Existence of active malignancy (ECOG Performance Status ≥ 2)
- Severe obesity (BMI ≥ 35 kg/m2)

Exclusion Criteria were as follows:

- Patients with tracheotomy
- Pregnancy
- Intubation assisted endoscopy
- Procedure without sedation

Outcomes:

Our primary outcome was the incidence of hypoxia episodes (SpO_2 < 90% over 10 seconds) as well as occurrence of severe hypoxia (SpO_2 < 80% over 10 seconds) during the procedure. The determined SpO_2 cut-off values were based in the accordance with AWMF S3 German Guideline [6]. Our secondary outcomes were the difference of $tcpCO_2$ values from the beginning of the intervention to the mean $tpCO_2$ levels observed throughout the procedure, the number of manipulations/manoeuvres needed to provide upper airway support, the rate of severe complications such as manual bag ventilation, intubation, reanimation or death. Furthermore, the correlation between type of the procedure and $tcpCO_2$-Levels was performed. Lastly, we intended to investigate impact multimorbidity on the severity of CO_2 retention. Other factors such as duration of the procedure and amount and type of the sedation agent were also analysed in regards to their influence on hypercarbia.

Data collection:

Data collection was performed with the assistance of the principal investigators' study assistants, who used "on-site" documentation of vital parameters while observing patients during endoscopy. The acquired data was then validated through a post-procedural analysis of CO_2 and SpO_2 measurements stored in the TOSCA TCM5 monitor capnometry device memory unit. After enrolling the patients in the study and obtaining their previous medical history, they were assigned an identification number and kept blinded to the physicians conducting the endoscopy. All patient data was pseudonymized, making it completely traceable only for the principal investigator and the principal investigator's study assistants.

Statistics:

Descriptive statistics using absolute amounts and percentages of categorical variables, or mean and standard deviation of numeric variables were performed to characterise the collective. To investigate the difference of hypoxia episodes between two groups Fisher Exact Test was performed. Analysing CO_2 levels was conducted using Student t-Test. Correlation matrix to investigate the correlation and effect between type of procedure, comorbidities, procedural length and types of the seduction agent the Spearmen correlation factor was applied. P-value under 0.05 was considered to be statistically significant. The statistical analysis was performed using open-source statistical software RStudio (Version 4.2.2; Posit, PBC; Austria).

Results:

This study was conducted at the Endoscopy Unit of University Hospital Ulm from April 2022 until November 2022. Out of the initially enrolled 107 patients, 9 were subsequently excluded from the study due to the following reasons: In one case, a change in the method of oxygen supplementation (from conventional to Nasal PAP Mask) was performed directly during the endoscopic procedure based on the endoscopist's decision. In four cases, the endoscopic procedure lasted less than 15 minutes. In three cases, capnometry electrodes were disconnected for a prolonged period of time (>30 seconds). In one case, the stored data on the device became damaged and therefore was not

suitable for analysis. Descriptive statistics as well as detailed data about the population of this study are demonstrated in table 1.

Primary outcomes:

We observed that 10.6% (5/47) of patients in the SuperNO2VA Group experienced hypoxia episodes, while 25.5% (13/51) of patients in the conventional oxygen supplementation group had episodes of hypoxia. The difference was statistically significant, with a p-value of 0.034 (95% CI for the odds ratio 0.105 - 1.079). The difference in the number of hypoxia episodes (SpO_2 < 90% over 10 seconds) between the intervention group (10/47) and the control group (31/51) was also statistically significant, with a p-value of 0.00015 (95% CI for the odds ratio 1.737 - ∞). Episodes of severe hypoxia (SpO_2 < 80% over 10 seconds) were more frequent in the control group (8/51) compared to the intervention group (2/47), with a p-value of 0.0346 (95% CI for the odds ratio 0.1805 - 2.7547). Not only the frequency of hypoxia episodes but also the duration of hypoxia was significantly longer in control group (p-value = 0.0004). The data is presented in table 2, as well as in image 1.

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Secondary outcomes:

There was no significant difference in the initial levels of CO_2 between the two groups (p-value = 0.615; 95% CI (-2.437 to 4.096)), which could be interpreted as an optimal starting point for the analysis, indicating that patients in both groups started at the same level. However, no statistically significant difference was detected in the mean transcutaneous CO_2 levels between the groups (p-value = 0.734; 95% CI (-3.487 to 2.464)). The results of the measured transcutaneous delta CO_2 levels (tcpΔ CO_2) did also not show any statistically significant difference (p-value = 0.416; 95% CI (-4.594 to 1.914)). The number of manoeuvres aimed at upper respiratory tract support (head tilt, jaw thrust, repositioning of the nPAP-mask) was comparable in both groups. Suction to remove mucus was used at almost the same rate in both groups. There was only one severe adverse event - manual bag ventilation -, which occurred in the conventional oxygenation group in the recovery room. The data is presented in table 3.

Analysis of the CO_2 levels in relation to the type of endoscopic procedures showed no significant differences in mean tcpCO2 levels (p-value = 0.633; 95% CI (-4.539 to 7.339)) or ΔtcpCO_2 levels (p-value = 0.618; 95% CI (-4.981 to 8.241)) during upper gastrointestinal endoscopy between the SuperNO2VA Group and the control group. No statistical significance was detected when analyzing data of patients who underwent only lower gastrointestinal colonoscopy [mean tcpCO2 (p-value = 0.754; 95% CI (-5.208 to 3.808))]; [ΔtcpCO_2 (p-value = 0.921; 95% CI (-7.019 to 6.357))]. Interestingly, we did observe a statistically significant result in favour of the intervention group when comparing ΔtcpCO_2 levels between the groups during the combined endoscopic procedure (p-value = 0.019; 95% CI (-5.646 to -0.533)). Detailed data are demonstrated in Table 4.

We conducted a univariate analysis to investigate whether any of the variables exhibit statistically significant correlations with the frequency of hypoxic episodes. After processing the data, we isolated those variables that demonstrated statistical significance or approached significance (p-value < 0.1) in correlation (positive or negative) with the number of hypoxia episodes (SpO2 < 90 sec). These included: sex (male), height, colonoscopy, ASA Status, and the use of nPAP-mask. These variables were subjected to multivariate analysis, revealing that the most significant determinant

leading to a higher frequency of hypoxia episodes was the ASA Status. The utilization of the nPAP-mask displayed a negative correlation with hypoxia episodes; however, it did not reach statistical significance (p-value = 0.0831). The results are shown in the table 6 and 7.

Additional investigation into the comparison of different endoscopic procedures in relation to hypoxia events yielded interesting results. The incidence of events, including severe hypoxia episodes, was notably lower in the nPAP-Mask group compared to the conventional oxygen therapy group. This trend was particularly noticeable in the oral endoscopy group (comprising procedures such as EGD or EUS, or a combination of both), as well as in the ERCP and ERCP + EUS subgroups, where results were statistically significant. However, due to the small sample sizes of the subgroups, we couldn't find any other statistically significant results in other types of endoscopic procedures. Further data is demonstrated in table 5.

To investigate the factors contributing to the development of hypercarbia, a correlation analysis was conducted using Spearman's correlation coefficient. The analysis revealed a weak correlation between the mean transcutaneous carbon dioxide ($tcpCO_2$) levels and the delta (Δ) $tcpCO_2$ levels observed during upper gastrointestinal endoscopy in patients. Furthermore, a weak correlation was observed between the amount of propofol administered during the procedure and both variables. Remarkably, a weak correlation was also identified in patients who underwent suction during the procedure. Conversely, no significant correlation was observed between the occurrence of hypoxia episodes and CO_2 levels. Additionally, the duration of hypoxia episodes did not exhibit any correlation on both the mean transcutaneous carbon dioxide ($tcpCO_2$) level and the delta (Δ) $tcpCO_2$. For a more comprehensive understanding of these findings, refer to table 8, which presents detailed results.

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Discussion:

Hypoxia is a major adverse event that can occur during endoscopic procedures when using sedatives. In our literature research, we have found that the reported incidence of hypoxia in endoscopy varies greatly. The rates of hypoxia (defined as an oxygen-saturation below 90% for more than 10 seconds) in the general population undergoing endoscopy with sedation have been documented as low as 10% and as high as 50%. Furthermore, in patients with chronic comorbidities, it tends to be even more frequent and is reported to be as high as 80% [7].

Invasive positive airway pressure systems, such as the SuperNO2VA, have been studied in a highly selective patient collective for their efficacy in preventing hypoxia during endoscopic procedures, and encouraging findings have been documented in prior research [1, 8]. However, the application of SuperNO2VA masks in procedures involving a broader collective of non- bariatric patients with high periprocedural risk has not been previously explored.

In our study, we evaluated the efficacy of the SuperNO2VA Mask in comparison with conventional nasal oxygen supplementation in reducing the risk of hypoxia (SpO_2 <90%) in high-risk patients undergoing endoscopic procedures. The use of the SuperNO2VA Mask demonstrated superiority over conventional supplementation, with significantly fewer episodes of severe hypoxia (SpO_2 <80%) observed in the control group. Not only did the frequency of hypoxia episodes decrease, but the duration of insufficient oxygenation was also shorter when the nPAP-System was applied. This effect is presumed to be achieved by generating sufficient positive intermittent airway pressure, which prevents the collapse of small airways and facilitates additional ventilation surface in the lungs.

To evaluate the severity and incidence of hypercarbia in our patients, we assessed changes in transcutaneous carbon dioxide (Δ $tcpCO_2$) levels during the procedure, as well as the mean $tcpCO_2$ levels throughout the entire procedure. This method proved to be more reliable in indicating susceptibility to CO_2 retention compared to simply counting the number of episodes where CO_2 levels exceeded 60 mmHg. Considering that some patients in our study already exhibited elevated baseline CO_2 levels due to underlying diseases, comparing absolute values of CO_2 seemed inadequate.

Statistical analysis revealed no significant differences in mean and Δ$tcpCO_2$ between the intervention and control groups. Furthermore, the use of the nPAP-Mask did not result in clinically relevant CO_2 entrapment in the reservoir bag or the emergence of hypercarbia. When considering the type of endoscopic procedure and $tcpCO_2$ levels, it was observed that patients undergoing lower GI endoscopy tended to exhibit smaller mean and Δ $tcpCO_2$ levels compared to patients undergoing upper GI endoscopy alone.

The number of standard manipulations performed to secure the upper airway, such as jaw thrust, head tilt, application of a nasopharyngeal tube, mask adjustment, and repositioning of the nasal oxygen cannula, was more frequent in the control group than in the intervention group. However, it is important to interpret this data cautiously as the specific type of airway support employed was not documented. Additionally, due to the novelty of the nPAP-Mask in our endoscopy unit, there were frequent instances of mask dislocation during the initial stages of the study, likely attributable to a lack of experience with the device.

Only one severe adverse event, involving manual bag ventilation due to refractory hypoxia, occurred in the recovery room after the endoscopic procedure, and this event was observed in the control group. Following the procedure, patients in interventional group were kept on the SuperNO2VA - Mask in the recovery room, considering that the majority of peri-interventional hypoxia episodes occur during this period [9]. However, it is worth noting that this study did not specifically collect data during the recovery period, which could be an important area for investigation in future studies.

The analysis of the impact of different factors and their correlation with the emergence of hypercarbia did not reveal any strong correlations. This is partially attributed to the small number of cohorts in this study. However, a weak correlation was observed between the dosage of propofol and Δ $tcpCO_2$. It can be suggested that the dosage of sedative is associated with decreased respiratory drive and, therefore, with the frequency and depth of respirations. It is important to notice that the duration of the procedure did not correlate with hypercarbia. Interestingly, the amount of suction episodes also weakly correlated with the mean and Δ $tcpCO_2$. However, the exact mechanism of this finding is not clear. It is also unclear whether the higher mean CO_2 levels led to hypersalivation or if hypersalivation and frequently applied suction led to the obstruction of small airways, which then caused CO_2 retention, based on the gathered data.

Our study has several limitations. Firstly, a significant number of patients were excluded from the study due to practical issues, such as the prolonged dislocation of the transcutaneous monitor sensor during the interventions, resulting in a loss of a considerable amount of data.

Secondly, oxygenation was only observed using pulse oximetry. The levels of true diluted oxygen in arterial or venous blood (paO_2 or pvO_2) remained unknown. It has been well-studied that oversaturation with oxygen could potentially be harmful to patients due to the accumulation of

Reactive Oxygen Species (ROS) [10]. Such species could be even more damaging for patients with multimorbidity.

Thirdly, the initial setup process, which involved the placement of the nPAP-System, the $tpCO_2$ sensor, and the calibration of transcutaneous monitoring devices, was performed by one of our trained study assistants. If the nPAP-System became dislocated during the procedure, the endoscopy nurse was the first responder and attempted to reposition the mask for optimal respiratory support. During the initial stages of our study, this led to frequent incorrect placements of the device. It is evident that the implementation of SuperNO2VA masks during endoscopy does require a certain level of initial experience to ensure the provision of optimal support.

With this study we have intended to provide valuable insight safety aspects in regards to incidence hypoxia and hypercarbia during endoscopy in high-risk-patients. The analysed data shows that hypoxia, as well as severe hypoxia can still occur while using non-invasive airway support devices.

In a search for a non-invasive alternative, High-Flow-Nasal-Cannulation-Therapy (HFNC) has been shown to be a safe alternative [11, 12, 13]. A significant number of studies have proven its efficacy in low- to moderate-risk patients, as well as in high-risk patients [14].

It is also known that HFNC therapy generates positive end-expiratory pressure [15], leading to passive ventilation of dead space volume and contributing to the clearance of CO2 from the lungs [16, 17]. Although technically easy to use, HFNC still requires qualified maintenance and cleaning by trained personnel. Therefore, its practicability, especially in centres with a high turnover of patients, would be questionable.

Head-to-head studies comparing SuperNO2VA-Masks and High-Flow-Nasal-Cannulation-Therapy (HFNC) during endoscopic procedures in their influence oh hypoxia, hypercarbia, as well as their cost efficiency should be performed to bring new data on safety and feasibility of such devices in endoscopy units.

Conclusion:

The implication of SuperNO2VA masks during endoscopy has been shown to significantly reduce the risk of hypoxia in high-risk patients when compared to conventional oxygen supplementation therapy.

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Attachment: (Tables and Images)

Table 1: Descriptive statistic and general population of the study.

SD – Standard Deviation; EGD – Esophagogastroduodenoscopy; ERCP - Endoscopic retrograde cholangiopancreatography

* Midazolam was only applied in combination with propofol. The application was performed based on the decision of the endoscopist.

Table 2: Demonstration of the data analysis preformed to compare hypoxia events and hypoxia severity in interventional and control group.

* - IQR (inter-quartile range) could not be calculated due to small sample size. ** - The shortest hypoxia episode, detected by the TOSCA Monitor system, lasted for only 5 seconds. There was only one instance of a

hypoxia episode with SpO2 < 90% that lasted less than 10 seconds. This particular episode was included in the statistical analysis. SD – Standard deviation.

Table 3: Data analysis performed on rates of hypercarbia, number of episodes of upper respiratory tract support and number of severe adverse events in the interventional and control groups.

Image 1: Graphic demonstration of hypoxia and severe hypoxia event SuperNO2VA-Group and in Conventional Oxygen Supplementation (Control) Group.

Table 4: Comparison of rates hypercarbia in dependence of preformed procedure in interventional and control group

Table 5: Representation of hypoxia and severe hypoxia episodes in relation to the type of endoscopic procedure.

Table 6: Univariate analysis of variables and their impact on the number of hypoxia episodes (SpO2 < 90%)

Table 7: Representation of most significant multivariate analysis of variables and their impact on the frequency of hypoxia Episodes.

Legend: Green color is indicative of a moderate negative coefficient, while red signifies a moderate positive coefficient. Orange, conversely, represents the absence of coefficient

Table 8: Correlation between different factors and mean transcutaneous carbon dioxide (tcpCO2) levels and the delta (Δ) tcpCO2 were examined.

It should be noted that the delta (Δ) tcpCO2 variable was calculated as a negative value, but the observed correlation indicated a negative relationship, contrary to the actual direct proportionality.

Tables and Images

	SuperNO2VA	Supplemental Oxygen
Total number of patients (n = 98)	47	51
Gender (Male/Female) n = M/F (%)	27/20 (57%/43%)	24/27 (47%/53%)
Age (Years) Mean ± (Standard deviation)	70.34/ ± 12.3 Max 90 Min 40 IQR (60.6 – 81.5)	73.7/ ± 10.8 Max 93 Min 40 IQR (66.9 – 80.7)
BMI (kg/m2) Mean ± (Standard deviation)	26.2/ ± 5.43 Max 44.4 Min 17.6 IQR (22.2 – 29.2)	26.09/ ± 5.04 Max 44.6 Min 18.8 IQR (24.4 – 28.7)
ASA Classification		
n (%) **ASA III** **ASA IV**	 44 (94%) 3 (6%)	 43 (84%) 8 (15%)
Duration of Intervention (Minutes) Mean ± (Standard deviation)	33.8/ ± 25.2 Max 115 Min 15 IQR (16 – 38.5)	33.92/ ± 38.72 Max 270 Min 15 IQR (17.5 – 34.0)
Types of the Intervention		
n (%) **EGD** **EGD + Endosonography** **EGD + Colonoscopy** **Colonoscopy** **ERCP** **Endosonography + ERCP**	 7 (15%) 2 (4%) 15 (32%) 20 (42%) 2 (4%) 2(1%)	 10 (19%) 2 (4%) 16 (31%) 15 (29%) 7 (13%) 1 (2%)
Underling chronic conditions		
n (%) **Heart disease:** **Pulmonary disease:** **Terminal renal disease:** **Vascular disease:** **Poorly controlled Diabetes or Hypertension:**	27 (57%) 10 (21%) 1 (2%) 21 (44%) 22 (47%) 10 (21%)	21 (41%) 7 (14%) 0 (0%) 25 (50%) 26 (51%) 13 (25%)

Chronic liver disease:		
	Sedative agent	
Propofol (mg) Mean ± (Standard deviation)	287.71/ ± 168.34 (Max. 800. Min. 80) IQR (175 – 355)	297.2/ ± 282.06 (Max. 1930.Min. 80) IQR (160 – 315)
Midazolam (mg)*	2 cases – 1 mg 5 cases – 2 mg 1 case – 4 mg	5 cases – 2 mg 3 cases – 3 mg 1 case – 4 mg

Table 1: Descriptive statistic and general population of the study.

SD – Standard Deviation; EGD – Esophagogastroduodenoscopy; ERCP - Endoscopic retrograde cholangiopancreatography

* Midazolam was only applied in combination with propofol. The application was performed based on the decision of the endoscopist.

	SuperNO2VA	Supplemental Oxygen	p-value
Hypoxia episodes (SpO2 < 90% over 10 seconds) (n)	10	31	0.00015
Number of severe hypoxia episodes (SpO2 < 80% over 10 seconds) (n)	2	8	0.0346
Number of patients with hypoxia episodes (n)	5	13	0.034
Corelation	1 Patient (5 Episodes)	1 Patient (6 Episodes)	-

between each patient and number of hypoxia episodes	1 Patient (2 Episodes) 3 Patients (1 Episode)	2 Patients (4 Episodes) 2 Patients (3 Episodes) 3 Patients (2 Episodes) 5 Patients (1 Episode)	
Duration of Hypoxia (sec) Mean/± Standard deviation (SD) *	174.6/ ± 154.4 Max: 424 Min: 16	390/ ± 696.9 Max: 2544 Min: 5**	0.0004
SpO2 initial (%) Mean/± Standard deviation (SD)	97.81/ ± 2.82	97.46/ ± 1.93	0.4693
SpO2 max (%) Mean/± Standard deviation (SD)	99.92/ ± 2.82	99.74/ ± 0.55	0.0766
SpO2 min (%) Mean/± Standard deviation (SD)	94.65/ ± 8.06	91.90/ ± 6.75	0.112

Table 2: Demonstration of the data analysis preformed to compare hypoxia events and hypoxia severity in interventional and control group.

* - IQR (inter-quartile range) could not be calculated due to small sample size. ** - The shortest hypoxia episode, detected by the TOSCA Monitor system, lasted for only 5 seconds. There was only one instance of a hypoxia episode with SpO2 < 90% that lasted less than 10 seconds. This particular episode was included in the statistical analysis. SD – Standard deviation.

	SuperNO2VA	Supplemental Oxygen	p-value
CO2 initial (mmHG) Mean/± Standard deviation (SD)	33.53/ ± 8.87 Max: 65.3 Min: 16.3 IQR: (30.1- 36.8)	32.72/ ± 7.24 Max: 67.9 Min: 18.7 IQR: (29.3 – 35.4)	0.6151 95% CI (-2.4373 - 4.0966)
CO2 mean (mmHG)	39.6/ ± 7.62 Max: 62.0	40.08/ ± 7.18 Max: 60.7	0.7336 95% CI (-3.4875 -

Mean/± Standard deviation (SD)	Min: 23.7 IQR: (35.1 - 43.0)	Min: 23.2 IQR: (35.1 – 46.1)	2.4642)
Delta Co2 (mmHG) (Initial CO2 – Mean CO2) Mean/± Standard deviation (SD)	- 6.01/ ± 7.66 Max: 17.6 Min: -27.7 IQR: (-8.15 – (-2.51))	- 7.35/ ± 8.59 Max: 26.0 Min: - 33.6 IQR: (- 10.7 – (-3.67))	0.4159 95% CI (-4.5946 - 1.9146)
Number of episodes securing upper airway (n)	22	29	0.672
Number of patients were upper airway securement was needed (n)	15	18	0.641
Number of episodes using suction (n)	12	12	0.721
Number of patients were suction was needed (n)	6	8	0.678
Severe adverse event (n)	0	1	0.117

Table 3: Data analysis performed on rates of hypercarbia, number of episodes of upper respiratory tract support and number of severe adverse events in the interventional and control groups.

	SuperNO2VA	Supplemental Oxygen	p-value

Upper GI endoscopy (EGD, EGD and endosonography, endosonography and ERCP, ERCP) n = 32			
Number of Patients (n)	n = 12	n = 20	
CO2 mean (mmHG) Mean/± Standard deviation (SD)	42.01 / ± 10.0	43.41/ ± 6.50	0.6337 95% CI (-4.5390 - 7.3390)
Delta (Δ) CO2 (mmHG) Mean/± Standard deviation (SD)	- 11.1/ ± 9.29	-9.47/ ± 8.61	0.6183 95% CI (-4.9812 - 8.2412)
Lower GI endoscopy (Colonoscopy) n = 35			
Number of Patients (n)	n = 20	n = 15	
CO2 mean (mmHG) Mean/± Standard deviation (SD)	40.09/ ± 5.01	39.39/ ± 8.07	0.7540 95% CI (-5.2079 - 3.8079)
Delta (Δ) CO2 (mmHG) Mean/± Standard deviation (SD)	- 5.14 / ± 7.63	- 5.47/ ± 11.8	0.9206 95% CI (-7.0168 - 6.3568)
Combined upper and lower GI endoscopy (EGD and Colonoscopy) n = 31			
Number of Patients (n)	n = 15	n = 16	
CO2 mean (mmHG) Mean/± Standard deviation (SD)	36.79/ ± 3.60	36.58/ ± 3.35	0.8676 95% CI (-2.7628 - 2.3428)
Delta (Δ) CO2 (mmHG) Mean/± Standard deviation (SD)	- 3.07/ ± 3.61	- 6.16/ ± 3.35	0.0195 95% CI -(5.6465 - - 0.5335)

Table 4: Comparison of rates hypercarbia in dependence of preformed procedure in interventional and control group

	SuperNO2VA	Supplemental Oxygen	p-value

Upper GI endoscopy (EGD, EGD and endosonography) n = 21			
Number of Patients (n)	n = 9	n = 12	
Number of hypoxia episodes SpO2 < 90%	2	11	0.099
Number of severe hypoxia episodes SpO2 < 80%	1	0	0.717
Upper GI endoscopy (Endosonography and ERCP, ERCP) n = 11			
Number of Patients (n)	n = 3	n = 8	
Number of hypoxia episodes SpO2 < 90%	0	8	**0.001**
Number of severe hypoxia episodes SpO2 < 80%	0	3	0.214
Lower GI endoscopy (Colonoscopy) n = 35			
Number of Patients (n)	n = 20	n = 15	
Number of hypoxia episodes SpO2 < 90%	0	4	0.087
Number of severe hypoxia episodes SpO2 < 80%	0	1	0.981
Combined upper and lower GI endoscopy (EGD and Colonoscopy) n = 31			
Number of Patients (n)	n = 15	n = 16	
Number of hypoxia episodes SpO2 < 90%	8	8	0.971

Number of severe hypoxia episodes SpO2 < 80%	1	3	0.064

Table 5: Representation of hypoxia and severe hypoxia episodes in relation to the type of endoscopic procedure.

Variable	Coefficient	Standard Error	t-value	p-value
Alter	0.02884	0.02657	1.085	0.278
Geschlecht	-1.2131	0.5825	-2.082	0.0373
Size	-0.09238	0.03220	-2.869	0.00412
Weight	-0.02373	0.02002	-1.186	0.236
ASA Grade	1.5180	0.7762	1.956	0.0505
Duration	0.007823	0.008292	0.943	0.3455
EGD	0.7940	0.7269	1.092	0.27471
EGD + EUS	-17.4729	0.7663	-0.006	0.99512
EGD + Clonoscopy	0.3244	0.6276	0.517	0.60519
Colonoscopy	-1.6368	0.7024	-2.330	0.0198
ERCP	0.8743	0.9386	0.932	0.35158
EUS + ERCP	-16.4518	0.1469	-0.007	0.99465
Supernova	-1.0497	0.5932	-1.770	0.0768
Nasal Cannula	1.0497	0.5932	1.770	0.076803
Initial Co2	0.02065	0.03632	0.569	0.570
Midazolam	-17.8068	0.3122	-0.004	0.9968
Propofol	-0.001479	0.001754	-0.843	0.399
Suction	0.4833	0.3876	1.247	0.21249
Upper Airway Manoveur	0.3315	0.2845	1.165	0.24399
Cardiac disease	0.4463	0.5923	0.754	0.45112
Pulmonary Disease	-0.9777	0.8837	-1.106	0.2685
Vascular Disease	0.4674	0.5907	0.791	0.4287
Liver disease	0.5829	0.6788	0.859	0.39048
Diabetes Melitus or poorly controlled hypertension	0.8808	0.6008	1.466	0.142598
Oncologic disease ECOG 1	-0.70026	0.64472	-1.086	0.277
Oncologic disease ECOG 2	0.04594	0.88552	0.052	0.959
Oncologic disease ECOG 3	0.95266	1.52150	0.626	0.531

Table 6: Univariate analysis of variables and their impact on the number of hypoxia episodes (SpO2 < 90%)

Variable	Coefficient	Std. Error	t-value	p-alue
Sex (Male)	**-0.57961**	0.80840	-0.717	**0.4734**
Height	**-0.06027**	0.03923	-1.536	**0.1244**
ASA Grade	**1.47484**	0.68511	2.153	**0.0313**
Colonoscopy	**-1.16990**	0.72841	-1.606	**0.1083**
Supernova	**-1.03404**	0.59673	-1.733	**0.0831**

Table 7: Representation of most significant multivariate analysis of variables and their impact on the frequency of hypoxia Episodes.

Legend: Green color is indicative of a moderate negative coefficient, while red signifies a moderate positive coefficient. Orange, conversely, represents the absence of coefficient

Impact of variables on the development of hypercarbia during endoscopy			
	Mean tcCO2 (**ρ(rho);** df; p-value)	**Delta (Δ) tcCO2*** (**ρ(rho);** df; p-value)	**Chaddock scale** Mean tcCO2 Delta (Δ) tcCO2
Age	**0.129;** 96; 0.205	**-0.009;** 96; 0.929	Negligible correlation Absence of correlation
Sex (Male/Female)	**0.196;** 96; 0.096	**-0.049;** 96; 0.629	Negligible correlation Absence of correlation
BMI	**0.063;** 96; 0.001	**0.019**; 96; 0.852	Absence of correlation Absence of correlation
Episodes of Hypoxia	**0.058;** 96; 0.572	**-0.079**; 96; 0.438	Absence of correlation Absence of correlation

Duration of Hypoxia	**0.058;** 96; 0.559	**0.028;** 96; 0.784	Absence of correlation Absence of correlation
Upper GI Endoscopy	**0.299;** 96; 0.004	**-0.291;** 96; 0.004	*Weak correlation* *Weak correlation*
Lower GI Endoscopy	**-0.003;** 96; 0.975	**0.119;** 96; 0.244	Absence of correlation Negligible correlation
Combined upper and lower GI Endoscopy	**-0.289;** 96; 0.004	**0.172;** 96; 0.091	*Weak correlation* Negligible correlation
Suction	**0.292;** 96; 0.004	**-0.444;** 96; 0.001	*Weak correlation* *Weak correlation*
Manouvers for upper airway support	**-0.051;** 96; 0.619	**0.156;** 96; 0.125	Absence of correlation Negligible correlation
Duration of the procedure	**0.162;** 96; 0.112	**-0.191**; 96; 0.061	Negligible correlation Negligible correlation
Multiborbidity	**-0.109;** 96; 0.284	**0.214**; 96; 0.035	Negligible correlation Negligible correlation
	Sedation agent		
Propofol	**0.210;** 96; 0.038	**-0.424;** 96; 0.001	Negligible correlation *Weak correlation*
Midazolam in combination with Propofol	**0.074;** 96; 0.572	**- 0.175**; 96; 0.085	Absence of correlation Negligible correlation

Table 8: Correlation between different factors and mean transcutaneous carbon dioxide (tcpCO2) levels and the delta (Δ) tcpCO2 were examined. It should be noted that the delta (Δ) tcpCO2 variable was calculated as a negative value, but the observed correlation indicated a negative relationship, contrary to the actual direct proportionality.

Image 1: Graphic demonstration of hypoxia and severe hypoxia event SuperNO2VA-Group and in Conventional Oxygen Supplementation (Control) Group.