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International ob**S**ervational s**T**udy on **A**i**R**way mana**G**ement in oper**A**ting room and non-opera**T**ing room ana**E**sthesia.

Study acronym identifier: **STARGATE**

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SUMMARY

LIST OF ABBREVIATIONS

ASA score	American Society of Anaesthesiology score
BMI	Body Mass Index
CICO	Can't intubate can't oxygenate
eFONA	Emergency front of neck access
FiO2	Fraction of inspired oxygen
ICU	Intensive Care Unit
NORA	Non-operating room anaesthesia
OR	Operating room
PEEP	Positive end-expiratory pressure
SAP	Systolic arterial pressure
SGA	Supraglottic Airway

PROTOCOL SYNOPSIS

Rationale	According to WHO, more than 230 million major surgical procedures are carried out under general anaesthesia each year worldwide. Despite important technological advances, airway management remains a major challenge in anaesthesiology. Data from large prospective studies on current incidence of major peri-intubation adverse events are lacking in the anaesthesia setting, especially on outcomes such as peri-intubation cardiovascular collapse, severe hypoxemia, and cardiac arrest. These events are more common in case of difficulties with airway management so that first pass intubation failure significantly increases the risks. Moreover, it has been documented that even transient hypotension during general anaesthesia, may have long-term consequences and may be associated with a worse outcome in patients undergoing non-cardiac surgery. The primary aim of the study is to assess the current incidence of major peri-intubation adverse events during anaesthesia in patients undergoing elective or emergency surgery performed in the operating room (OR) and non-OR setting and in the setting of nonoperating room anaesthesia. The secondary aim is to assess the current practice of airway management during anaesthesia worldwide.
Study design	International, multicentre, prospective cohort study
Inclusion criteria	We will include all adult (≥ 18 years old) patients undergoing advanced airway management for general anesthesia in the operating room (OR) or non-operating room anaesthesia (NORA) locations.
Exclusion criteria	● Airway management during cardiopulmonary resuscitation. ● Critically ill patients undergoing advanced airway management due to their underlying clinical condition
Primary outcome	At least one of the following major peri-intubation adverse events occurring within 30 minutes from induction or up to surgical incision: ○ Severe hypoxia (SpO_2 < 80%) ○ Cardiovascular collapse (at least one of the following): ■ Systolic arterial pressure < 65 mmHg ■ Systolic arterial pressure < 90 mmHg for > 15 minutes ■ Unplanned need of vasopressors or fluid load > 15 ml/kg to maintain the target blood pressure. ○ Cardiac arrest

Secondary outcomes	• Minor adverse events:
	  ○ Moderate hypoxia (SpO_2 < 93%)
	  ○ Airway injury
	  ○ Clinically relevant bleeding
	  ○ Oral aspiration of gastric contents
	  ○ Dental injury
	• Difficult facemask ventilation
	• First pass success rate
	• Early cardiovascular collapse
	• Late cardiovascular collapse

Others outcomes	• Emergency front of neck access (eFONA) • Cannot intubate cannot oxygenate scenario (CICO) • Unplanned need for ICU admission secondary to airway management related complications • In-hospital mortality • Post procedural severe hypertension • Difficult procedure (more than 2 attempts)
Study duration	All centers will enroll all consecutive patients meeting study criteria up to 50 maximum patients for each center.
Data collection	We will collect the following information: • Informed consent and admission data • Demographic and clinical characteristics • Type of procedure (time, setting, type of surgery, elective or emergency • Airway evaluation (anticipated difficult airway management) • Monitoring applied during the procedure • Patient's parameters • Preoxygenation method and use of apnoeic oxygenation (position during preoxygenation, rapid sequence induction applied) • Drugs used for induction (specific drug and doses) • Elective method for airway management • Operator 's characteristics • Method used for the second (and following) attempts • Method used for adequate tube placement confirmation • Duration of airway management procedure • Outcome of endotracheal intubation (total number of attempts, laryngoscopy view, minimum SpO_2 during laryngoscopy, need for SGA)

	• Advanced airway management-related complications (severe cardiovascular collapse, severe and mild hypoxemia, cardiac arrest, airway injury or any bleeding, aspiration of gastric contents, dental injury, emergency front of neck airway (FONA), cannot intubate cannot oxygenate scenario (CICO), unplanned need for ICU secondary to airway management complications) • Extubation procedure. • In hospital mortality
Sample size	Post-intubation hypotension has been reported in up to 10% of patients. We aim to collect data on 1000 major peri-intubation events during anesthesia therefore we plan to recruit a total of 10.000 patients. Considering 5% data lost, our final sample size will be of 10500 patients. We estimated an average number of 50 intubations/week at each center so we plan to recruit a total number of 210 centers.
Statistical analysis	We will report mean and standard deviation of normally distributed variables and we will compare them using the student T-test. We will report non-normally distributed variables as median and interquartile range, comparing them using the Mann-Whitney U test. Categorical variables will be expressed as proportion and compared using the Chi-square or Fisher exact test as appropriate. We will perform a bivariate analysis to identify variables associated with the composite outcome of major peri-intubation adverse events and significant variables will be then used to construct a multivariate logistic model in order to identify independent variables. The following planned secondary analyses will be performed: • Place of advanced airway management: OR vs outside OR • Type of surgery: cardiac vs non-cardiac surgery, ear-nose-throat surgery, thoracic surgery • Urgency of the procedure: planned intubation vs unplanned intubation • Type of hypnotic drug used: propofol vs different drug • Airway management procedure: difficult airway management vs not difficult • Patient's condition: ▪ ASA 1-2 vs ASA 3-4; ▪ BMI<30 vs BMI>30; A two-sided p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed by R 3.6.2 (http://www.R-project.org)

RATIONALE

According to WHO, more than 230 million major surgical procedures are carried out under general anaesthesia each year worldwide[1]. Despite important technological advances, airway management remains a major challenge in anaesthesiology.

The National Audit Project 4, published in 2011, for the first time addressed the need to systematically collect information on major airway-related complications in both the anaesthesia and critical care settings. While in the critical care setting the report provided important insights for improvement, incidence of major adverse events such as death, brain damage and need for emergency surgical airway appeared underestimated in anaesthesia [2] so that for every case captured by NAP4 there may be another 720 potential airway events if we consider hypoxemia and cardiovascular collapse [3].

Traditionally, airway management in anaesthesia has been described as *anatomically difficult* as opposed to airway management in critical care defined as *physiologically difficult*.

Indeed, the general population of patients undergoing elective surgery, has normally an adequate physiology reserve to cope the perioperative stress and most airway related complications are the consequence of potential difficulties at mask ventilation or intubation due to specific anatomic features (e.g. prognathism, large tongue, obesity).

On the other hand, critically ill patients are prone to a higher airway-related risk due to their underlying hypoxemia, shock, acidosis which expose them to the high incidence of adverse events, especially cardiovascular collapse, recently reported in the INTUBE study cohort [4].

Data from large prospective studies on current incidence of major peri-intubation adverse events are lacking in the anaesthesia setting, especially on outcomes such as peri-intubation cardiovascular collapse, severe hypoxemia, and cardiac arrest [5][6].

These events are more common in case of difficulties with airway management so that first pass intubation failure significantly increase the risks [7][8]. Moreover, it has been documented that even transient hypotension during general anaesthesia, may have long-term consequences and may be associated with a worse outcome in patients undergoing non-cardiac surgery [9][10].

The primary aim of the study is to assess the current incidence of major peri-intubation adverse events during anaesthesia in patients undergoing elective or emergency surgery and in the setting of nonoperating room anaesthesia. The secondary aim is to assess the current practice of airway management during anaesthesia worldwide.

STUDY DESIGN

International, multicenter, prospective cohort study.

POPULATION

Inclusion criteria

We will include all adult (≥ 18 years old) patients undergoing advanced airway management for general anaesthesia in operating room or non-operating room anaesthesia (NORA) locations. We will include all the procedures both diagnostic and therapeutic, elective, or emergency that will require an advanced airways management (either tracheal intubation or SGA placement).

All potentially eligible patients will be identified by local investigators by screening the OR schedule and the procedures performed outside the OR.

Exclusion criteria

We will exclude the airway management during cardiopulmonary resuscitation. Critical patients undergoing advanced airway management in ED, wards or ICU, due to their underlying clinical condition will not be included in the study.

PRIMARY OUTCOME

At least one of the following major adverse events occurring within 30 minutes from induction or up to surgical incision:

Major adverse event:

- Severe hypoxia (SpO_2 < 80%)
- Cardiovascular collapse (at least one of the following):
  - Systolic arterial pressure < 65 mmHg
  - Systolic arterial pressure < 90 mmHg for > 15 minutes
  - Unplanned need of vasopressors and/or fluid load > 15 ml/kg to maintain the target blood pressure.
- Cardiac arrest

Blood pressure values should be confirmed in two consecutive measurements on non-invasive blood pressure monitoring or for 10 seconds on invasive monitoring system.

SECONDARY OUTCOMES

- Minor adverse events:
  - Moderate hypoxia (SpO_2 < 93%)
  - Airway injury
  - Clinically relevant bleeding
  - Oral aspiration of gastric contents
  - Dental injury
- Difficult facemask ventilation
- First pass success rate
- Early cardiovascular collapse
- Late cardiovascular collapse

OTHER OUTCOMES

- Unplanned need for ICU admission secondary to airway management related complications
- Emergency front of neck airway (eFONA)
- Cannot intubate cannot oxygenate scenario (CICO)
- In-hospital mortality
- Post-procedural severe hypertension
- Difficult procedure (more than 2 attempts)

DATA COLLECTION

Data will be collected real-time by an investigator not involved in airway management using either the paper or the electronic version of the case report form on the Redcap.

The following variables will be collected:

- Informed consent and admission data
- Demographic and clinical characteristics
- Type of procedure (time, setting, type of surgery, elective or emergency

- Airway evaluation (anticipated difficult airway management)
- Monitoring applied during the procedure
- Ongoing respiratory and hemodynamical support before intubation
- Patient's parameters
- Preoxygenation method and use of apnoeic oxygenation (position during preoxygenation, rapid sequence induction applied)
- Fraction of expired O_2 (FeO_2) at the end of preoxygenation
- Application of any apnoeic oxygenation method
- Application of rapid sequence induction intubation
- Drugs used for induction (molecules and doses)
- Elective method for advanced airway management
- Operator's characteristics
- Method used for the second (and following) attempt
- Method used for adequate tube placement confirmation
- Duration of airway management procedure
- Outcome of endotracheal intubation (total number of attempts, laryngoscopic view, minimum SpO_2 during laryngoscopy, need for LMA)
- Advanced airway management-related complications (severe cardiovascular collapse, severe and mild hypoxemia, cardiac arrest, airway injury or any bleeding, aspiration of gastric contents, dental injury, emergency front of neck airway (FONA), cannot intubate cannot oxygenate scenario (CICO), unplanned need for ICU secondary to airway management complications)
- Extubation procedure
- In-hospital mortality

Local investigators are expected to transfer all collected data into an electronic CRF (eCRF, Research Electronic Data Capture – RedCap). Each local investigator will be trained on how to use the eCRF and will receive a personalized username and password. Each patient will be coded through a patient identification number generated by the eCRF and no patient names or initials will be present on the paper CRF.

Data will be handled confidentially and the paper CRF will be stored behind a lock at each local site. Any source of information which may allow to link a record with a patient will be destroyed at the end of the monitoring phase.

STATISTICAL ANALYSIS

We will report mean and standard deviation of normally distributed variables and we will compare them using the student T-test. We will report non-normally distributed variables as median and interquartile range, comparing them using the Mann-Whitney U test. Categorical variables will be expressed as proportion and compared using the Chi-square or Fisher exact test as appropriate. We will perform a bivariate analysis to identify variables associated with the composite outcome of major peri-intubation adverse events and significant variables will be then used to construct a multivariate logistic model in order to identify independent variables.

The following planned secondary analyses will be performed:

- Place of intubation: OR vs NORA
- Type of surgery: cardiac vs non-cardiac surgery, ear-nose-throat surgery, thoracic surgery
- Urgency of the procedure: planned advanced airway management vs unplanned advanced airway management
- Type of hypnotic drug used: propofol vs different drug
- Airway management procedure: difficult airway management vs not difficult
- Patient's condition:
    - ASA 1-2 vs ASA 3-4;
    - BMI<30 vs BMI>30;

A two-sided p-value < 0.05 will be considered statistically significant. Statistical analysis will be performed by R 3.6.2 (http://www.R-project.org)

Sample size

Post-intubation hypotension has been reported in up to 10% of patients [11].

We aim to collect data on 1000 major peri-intubation events during anesthesia in order to include at least 10 putative variables associated with this event in planned analyses and sub-analyses, therefore we plan to recruit a total of 10.000 patients. Considering a 5% data lost, our final sample size will be of 10500 patients. We estimated an average number of 50 intubations/week at each centre so we plan to recruit a total number of 210 centres.

CENTRES RECRUITMENT

We will recruit academic and non-academic hospitals worldwide. Any centre that performs advanced airway management in the context of general anesthesia for either surgery or diagnostic/therapeutic procedures will be eligible for participation. Centers characteristics (academic vs non-academic, workload etc.) will be collected.

We will launch a website (www.stargate.com) and a social media channel (@stargate_study) where we will publish study information and documents (e.g. protocol, case report form, national coordinator list) which will be available for potentially interested investigators.

The project will be presented and a call for centres will be announced during international meetings of anesthesiology..

We will also apply for receiving the endorsement of international scientific societies in order to promote and enhance participation to this study.

PATIENTS RECRUITMENT

After obtaining the local approval, each center will select a start date and screening for patients' eligibility will start. In order to avoid selection bias while addressing study feasibility and balance across different participating centers, a maximum number of 50 patients from each center will be enrolled.
To maintain data collection feasible, optimize enrolment of all consecutive patients, especially for high-volume centers, and balance number of enrolled patients across different centers, we suggest to focus screening for enrolment from a pre-defined number of operating rooms (3 to 5 according to local workload) up to the final enrollment of 40 patients/center in the anesthesia setting without any time limitation. All consecutive patients undergoing advanced airway management in the NORA setting will be screened up to the final enrollment of 10 patients/center without any time limitation. Local investigators will be involved in the screening of operating list of those selected areas.
Screening of all consecutive patients will involve all patients treated in the selected areas of each center. Screening and reporting of all consecutive treated patients will be interrupted only when the target number of patients/center will be reached.

PUBLICATION AND AUTHORSHIP POLICY

The main results of STARGATE study will be published in a peer–reviewed international medical journal. Authorship policy will follow the International Committee of Medical Journal Editors (ICMJE) recommendations. Authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Members of the Steering Committee will be part of the Writing Committee and listed as Authors. National Coordinators and particularly committed investigators fulfilling the previously exposed criteria will be part of the Writing Committee.

Each centre will designate local coordinators who will provide scientific and structural leadership in their centres. They will ensure that all local necessary ethical and regulatory approvals are obtained

before the start of patient inclusion. Local coordinators will guarantee the integrity of data collection and ensure timely completion of CRFs.

Local coordinators will be listed as study collaborators in proportion to the number of recruited patients at each center.

SECONDARY ANALYSES

After publication of the primary results, on request, the dataset will be available for investigators for secondary analyses, after submission of a substudy proposal which will be evaluated for approval by the Steering Committee after consideration of its scientific quality (i.e. originality and scientific priority).

Before submission, the final version of all manuscripts related to the STARGATE study dataset must be approved by the Steering Committee. The members of the Writing Committee will be authors of the publications derived from the STARGATE study dataset.

APPENDIX 1 – TABLE WITH STUDY DEFINITIONS

Airway injury	Any detectable and clinically relevant injury attributable to tracheal intubation procedure (e.g bleeding, tracheal or bronchial tear or laceration)
Advanced airway management	The use of either a supraglottic airway device or tracheal intubation as airway management method to provide general anesthesia
Cannot Intubate Cannot Oxygenate Scenario (CICO)	Impossibility to achieve a successful tracheal intubation and adequate patient's oxygenation.
Cardiac arrest	Pulseless dysrhythmia occurring during/after advanced airway management
Cardiovascular collapse	At least one of the following, occurring within 30 minutes from advanced airway management or up to surgical incision: • SAP < 65 mmHg • SAP < 90 mmHg for > 15 minutes or up to incision if it comes before 15 min • Unplanned need of vasopressors and/or fluid load > 15 ml/kg to maintain the target blood pressure.
Early cardiovascular collapse	Any cardiovascular collapse event occurring up to 10 minutes from induction (or surgical incision, whichever come first)
Late cardiovascular collapse	Any cardiovascular collapse event occurring from 11 to 30 minutes from induction (or surgical incision, whichever come first)
Clinically relevant airways bleeding	Any sign or symptom of airways haemorrhage that meet at least one of the following criteria: • requiring medical intervention by a healthcare professional • leading to hospitalization or increased level of care • Prompting a face to face evaluation
Dental trauma	Fracture or avulsion of tooth during airway management

Difficult mask ventilation	Impossibility to provide adequate ventilation because of one or more of the following problems: inadequate mask seal, excessive gas leak, or excessive resistance to the ingress or egress of gas
Difficult tracheal intubation	Procedure requiring > 2 laryngoscopy attempts
Duration of the airway management procedure	Difference between time of confirmed airway device placement and preoxygenation start
Emergency front of neck access (eFONA)	Emergency need for invasive access to the patient's neck to provide adequate oxygenation (e.g. cricothyroidotomy, percutaneous tracheostomy, surgical tracheostomy).
Severe hypertension	Systolic arterial pressure > 180 mmHg
Attempt	Each time a device (SGA, laryngoscope, fiberscope) is introduced in patient's mouth/nose.
Moderate Hypoxia	SpO_2 < 93%
Oral aspiration of gastric contents	Presence of vomit at the glottic inlet visualised during airway management in a previously clear airway
Rapid Sequence Induction- Intubation	Administration of rapid-onset induction agents and muscle relaxant with no ventilation between induction and laryngoscopy
Severe Hypoxia	SpO_2 < 80%
Unplanned need of vasopressor	Rescue administration of any vasopressor (either as a bolus or continuous infusion) due to hypotension after induction

APPENDIX 2 - DETAILED DESCRIPTION OF MEASUREMENTS.

Blood pressure monitoring

Blood pressure monitoring is a standard of care during airway management. Either noninvasive or invasive blood pressure monitoring is required for enrolled patients.

Noninvasive blood pressure monitoring

In case of noninvasive blood pressure monitoring, an appropriate size cuff (relative to the patient's arm circumference) is wrapped around the upper arm of the patient and the interval is set up according to clinical practice.

For the purposes of the current study, the hypotensive event (i.e. SAP < 90 mmHg) should be observed in at least two consecutive measurements.

In case of placement of an arterial line and invasive blood pressure monitoring start by 30 minutes following induction, the reference monitoring method for study outcome identification is the noninvasive blood pressure in place at the start of the procedure.

Invasive blood pressure monitoring

If an arterial line is already in place before intubation and invasive blood pressure monitoring is the standard of practice for the procedure, arterial pressure values from invasive monitoring must be registered and reported in the case report form.

For the purposes of the current study, the hypotensive event (i.e. SAP < 90 mmHg) should be observed in at least two consecutive measurements registered 10 seconds apart.

REFERENCES

[1] T. G. Weiser *et al.*, "An estimation of the global volume of surgery: a modelling strategy based on available data," *www.thelancet.com*, vol. 372, p. 139, 2008, doi: 10.1016/S0140.

[2] T. M. Cook, N. Woodall, and C. Frerk, "Major complications of airway management in the UK: Results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: Anaesthesia," *Br. J. Anaesth.*, vol. 106, no. 5, pp. 617–631, 2011, doi: 10.1093/bja/aer058.

[3] T. M. Cook, "Strategies for the prevention of airway complications – a narrative review," *Anaesthesia*, vol. 73, no. 1. Blackwell Publishing Ltd, pp. 93–111, Jan. 01, 2018. doi: 10.1111/anae.14123.

[4] V. Russotto *et al.*, "Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients from 29 Countries," *JAMA - J. Am. Med. Assoc.*, vol. 325, no. 12, pp. 1164–1172, Mar. 2021, doi: 10.1001/jama.2021.1727.

[5] R. S. Green and M. Erdogan, "Are outcomes worse in patients who develop post-intubation hypotension?," *Can. J. Emerg. Med.*, vol. 24, no. 5, pp. 465–466, Aug. 2022, doi: 10.1007/S43678-022-00340-X/METRICS.

[6] R. S. Green and M. B. Butler, "Postintubation Hypotension in General Anesthesia: A Retrospective Analysis," *J. Intensive Care Med.*, vol. 31, no. 10, pp. 667–675, Dec. 2016, doi: 10.1177/0885066615597198.

[7] J. L. Apfelbaum *et al.*, "2022 American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway," *Anesthesiology*, vol. 136, no. 1, pp. 31–81, Jan. 2022, doi: 10.1097/ALN.0000000000004002.

[8] D. K. Rose, M. M. Cohen, and K. Rose, "The incidence of air-way problems depends on the definition used."

[9] M. H. Nega, S. A. Ahmed, H. Y. Tawuye, and S. Y. Mustofa, "Incidence and factors associated with post-induction hypotension among adult surgical patients: Prospective follow-up study," *Int. J. Surg. Open*, vol. 49, p. 100565, Dec. 2022, doi: 10.1016/J.IJSO.2022.100565.

[10] S. Südfeld *et al.*, "Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia," *Br. J. Anaesth.*, vol. 119, no. 1, pp. 57–64, Jul. 2017, doi: 10.1093/bja/aex127.

[11] Bernatović N, Nesek Adam V, Professor A, Jurkić Msn N, Goranović T, Jakšić M, et al. Postintubation hypotension in elective surgery patients: a retrospective study. Signa vitae 2018; 14(SUPPL 1): 31-34