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INVESTIGATION OF LESS INVASIVE APPROACHES IN PERIOPERATIVE MANAGEMENT ON ENHANCED RECOVERY AFTER SURGERY IN LUNG SURGERY PATIENTS

Doctoral (Ph.D.) dissertation

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Abbreviations

BIS	Bispectral scale
BMI	Body mass index
Ch	Charrier
CPAP	Continuous positive airway pressure
DLCO	Diffusion capacity of the lung for carbon-monoxide
DO_2	Delivered oxygen
ERAS	Enhanced recovery after surgery
$EtCO_2$	End tidal carbon dioxide level/end-expiratory carbon dioxide concentration
FEV_1	Forced expiratory volume in one second
FiO_2	Fraction of inspired oxygen
HFNC	High flow nasal cannula
IPPV	Intermittent positive-pressure ventilation
LMA	Laryngeal mask airway
MAP	Mean arterial pressure
NITS	Non-intubated thoracoscopic/thoracic surgery
OLV	One-lung ventilation
PaO_2	Partial pressure of oxygen
PEEP	Positive end-expiratory pressure
POCD	Postoperative cognitive dysfunction
SPI	Surgical pleth index
SVI	Spontaneous ventilation combined with double-lumen tube intubation
SVR	Systemic vascular resistance
TCI	Target controlled infusion
TOF	Train of four
VAS	Visual analogue scale
VATS	Video assisted thoracoscopy
$VO_{2\ max}$	Maximal oxygen consumption

International publications on which the Ph.D. thesis is based

I. Furák, J., & **Szabó, Z**. (2021). Spontaneous ventilation combined with double-lumen tube intubation in thoracic surgery. *GENERAL THORACIC AND CARDIOVASCULAR SURGERY*. doi:10.1007/s11748-020-01572-3

II. **Szabó, Z.,** Tánczos, T., Lebák, G., Molnár, Z., & Furák, J. (2018). Non-intubated anaesthetic technique in open bilobectomy in a patient with severely impaired lung function. [case report]. *JOURNAL OF THORACIC DISEASE, 10*(4), E275-E280. doi:10.21037/jtd.2018.04.80

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International and Hungarian publications related to the topic of the Ph.D. thesis

I. Furák, J., Paróczai, D., Burián, K., **Szabó, Z.,** & Zombori, T. (2020). Oncological advantage of nonintubated thoracic surgery. Better compliance of adjuvant treatment after lung lobectomy. *THORACIC CANCER, 11,* 3309-3316.

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V. Furák, J., **Szabó, Z.,** Géczi, T., Pécsy, B., Németh, T., Molnár, Z., & Lázár, G. i. (2017). Nem intubált, spontán lélegző betegnél, egy metszésből minimál invazív módon elvégzett tüdőlebeny-eltávolítás klinikánk gyakorlatában. *MAGYAR SEBÉSZET, 70*(2), 165-166.

- **VI.** Furák, J., **<u>Szabó, Z.,</u>** Theodor, H., Géczi, T., Pécsy, B., Németh, T., . . . Lázár, G. i. (2017). Nem intubált, spontán légző betegnél, egy metszésből, minimálisan invazív módon elvégzett tüdőlebeny-eltávolítás mint új műtéti eljárás klinikánk gyakorlatában. Non-intubated, uniportal, video assisted thoracic surgery (VATS) lobectomy, as a new procedure in our department. *MAGYAR SEBÉSZET*, *70*(2), 113-117. doi:10.1556/1046.70.2017.2.1
- **VII.** Németh, T., **<u>Szabó, Z.,</u>** Pécsy, B., Barta, Z. V., Lázár, G. i., Torday, L., . . . Furák, J. (2020). A tüdőmetastasisok sebészi kezelésében történt változások az elmúlt 12 évben [Changes in the surgical treatment of pulmonary metastases during the last 12 years]. *ORVOSI HETILAP*, *161*(29), 1215-1220. doi:10.1556/650.2020.3177

International and Hungarian publications not related to the Ph.D. thesis topic

- **I.** Korsós, A., Kupcsulik, S., Lovas, A., Hankovszky, P., Molnár, T., **<u>Szabó, Z.</u>**, & Babik, B. (2020). Diagnosztikus lépések és a betegség prognózisának becslése COVID–19-fertőzött betegeken. *ORVOSI HETILAP, 161*(17), 667-671. doi:10.1556/650.2020.31815
- **II.** Lovas, A., Hankovszky, P., Korsós, A., Kupcsulik, S., Molnár, T., **<u>Szabó, Z.</u>**, & Babik, B. (2020). A képalkotó diagnosztika jelentősége a COVID–19-fertőzött betegek ellátásában. *ORVOSI HETILAP, 161*(17), 672-677. doi:10.1556/650.2020.31814
- **III.** Novák, T., Andrási, L., **<u>Szabó, Z.,</u>** & Németh, G. L. (2017). Succesfully treated case of a patient with giant benign ovarian tumor and suicide attempt. *MAGYAR NŐORVOSOK LAPJA, 80*(5), 231-233.

Introduction

High-risk surgical interventions present an increased risk of mortality and morbidity, especially for the elderly patients or for patients living with severe comorbidities. According to a 2008 estimate, approximately 234 million [1], and in 2016, already 310 million surgeries were performed worldwide each year, in addition, the average age of the patients, and the complexity, thus the risk of the surgical interventions are constantly increasing. However, it is important to note that billions of people do not have access to safe treatment procedures and at least 143 million interventions take place in the low- and middle-income countries (LMICs) each year [2]. The hospital structure is unable to keep up with the ever-increasing number of surgeries, so it is particularly important to review the existing procedural strategies and look for points where we can raise the quality of patient care while rationalizing the cost of treatments. An important step in this direction could be to examine those procedures that attempt to preserve the physiological processes while carrying out the interventions that place a heavy burden on the body.

Overall, the anaesthesia-related mortality and morbidity have declined significantly in the last decades of the previous millennium, but are still significant [3]. Perioperative mortality ranges from 3 to 17%, depending on the type of surgery and region [4,5]. According to a 7-day survey conducted in 2011 in 28 European countries, the mortality rate associated with major surgery is 4%. Two other studies have found that high-risk surgical patients account for about 12.5% of all interventions, however, about 80% of total mortality comes from this patient group [6,7].

Thoracic surgery in itself is a high-risk intervention, which risk is further exacerbated by co-morbidities in the majority of patients. Studies have shown that renal insufficiency, chronic obstructive pulmonary disease (COPD), certain liver diseases, as well as age, body mass index (BMI), and smoking has the strongest association with the development of perioperative complications [8,9].

In recent decades, the “minimally invasive” or “less invasive” perioperative care strategy has become the focus of interest in modern perioperative medicine. Its essence is the coordinated application of preoperative preparation, minimally invasive intraoperative surgical and anaesthetic techniques, as well as the postoperative care strategy, which has become known in the international literature as “Enhanced Recovery After Surgery” (ERAS) and become a concept [10]. It was an important step in our practice to introduce the multimodal, individualized monitoring concept, which is used in high-risk interventions and/or in the care of high-risk patients, and which concept is in line with the treatment recommendations proposed by ERAS [11]. These guidelines also apply to thoracic anaesthesia.

From a surgical perspective, video-assisted thoracoscopic surgery (VATS) has become an increasingly common and globally accepted procedure in thoracic surgery. Traditionally, for these operations, isolated ventilation of the lungs is performed with a double-lumen endotracheal tube (DLT) or a bronchial blocker (BB). Recently, a novel anaesthetic procedure, non-intubated thoracoscopic surgery (NITS), has been published, which applies intravenous sedation and regional anaesthesia techniques without intubation, while maintaining spontaneous respiration when performing VATS surgery for the removal of mediastinal tumours and in patients undergoing anatomical resections [12,13]. This technique radically differs from the conventional “one lung” (OLV) positive pressure ventilation technique, as the patient breathes spontaneously during surgery, thereby the physiological respiratory pressure conditions are only slightly affected.

Numerous studies have confirmed that the use of protective lung ventilation (PLV) strategies, minimally invasive anaesthetic and surgical techniques induce less tissue damage (barotrauma in case of ventilation) and inflammatory response, resulting in shorter recovery times and fewer complications [14–16]. Based on these, it can be assumed that intraoperative respiratory support closest to physiological respiration may also yield favourable outcomes. Of course, the method also has potential disadvantages, such as the lack of a secure airway, the risk of aspiration, and acid-base abnormalities due to hypercapnia, as a result of which its widespread use, or widespread implementation in daily routine is yet to come.

A number of other risk factors have been identified in recent decades, some of which are briefly described below.

Factors influencing patient recovery

Surgical stress response

The stress response to surgical trauma is one of the primary mechanisms that can lead to the development of organ dysfunction in the postoperative period, which consists of neuroendocrine and inflammatory components. The endocrine metabolic response results in catabolism and consequent negative nitrogen balance, which, however, can be reduced by the sympatholytic effects of regional anaesthetic techniques [17,18]. However, recent research suggests that complex inflammatory immunological changes induced by surgical trauma exert an even more pronounced effect on the development of postoperative complications [19,20].

Pain

Adequate analgesia is also an important element of the ERAS concept, although there is no single "gold standard", "ideal" analgesic procedure fit for all interventions. What is common ground is that it is desirable to prioritize the multimodal, " opioid sparing" analgesic techniques [21,22]. However, further studies are needed in patients with a different-than-average pain threshold (opioid users, pain-sensitized patients), therefore, organ dysfunction due to inadequate doses of medication may be more common in this group of patients, which may significantly increase recovery time compared to that of other patient populations [23,24].

Postoperative cognitive dysfunction (POCD)

Postoperative cognitive dysfunction (POCD) has received considerable attention in recent years as a postoperative complication that can be caused by a number of factors [25]. Almost all of the recently published randomized prospective studies have neglected the multifactorial pathogenesis of the dysfunction, including pain, sleep disorder, opioid use, and the inflammatory response due to surgery, and instead, typically, the immunological and receptor-level lesions were examined [26]. However, these factors are very closely related to the post-operative pathophysiological processes, and may lead to the development of POCD, especially in the elderly. [27,28]. Several studies have shown that the development of POCD is not age-dependent, but affects virtually all age groups, in similar proportions, and only the duration of dysfunction decreases with age [29]. Therefore, it is particularly important to identify the individual risk factors, assess patient risk, and build a treatment and monitoring strategy based on this.

Perioperative fluid therapy

One of the Holy Grails of medicine is the parameter by which a patient's fluid therapy can be tailored to its actual needs. Unfortunately, just as we cannot find the relic, finding this parameter is yet to come. However, several important grips, guiding indicators are known to optimize our patient's fluid intake at any given time.

Tissue oxygenation is based on a balance between oxygen supply, oxygen transport capacity, and oxygen uptake [30]. The main factors determining these are illustrated in Figure 1.

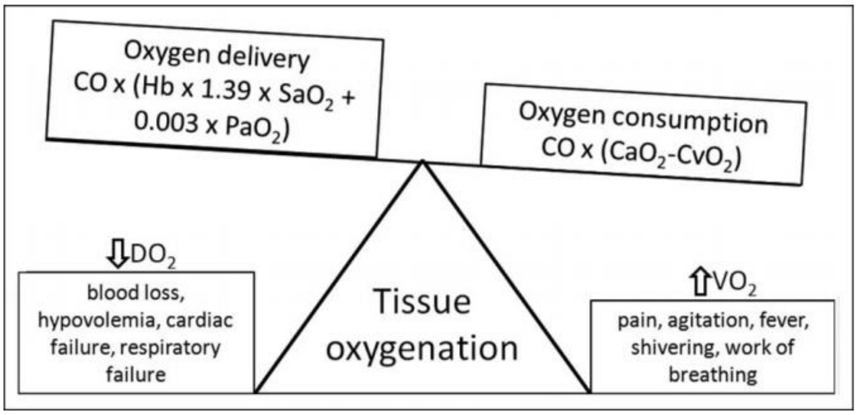

Figure 1: Factors influencing tissue oxygenation [11].

DO_2: delivered oxygen, VO_2: oxygen uptake (oxygen consumption, oxygen demand), CaO_2 arterial oxygen content, CvO_2: oxygen content of mixed venous blood, CO: „cardiac output"; SaO_2: oxygen saturation as measured by blood analysis (e.g., arterial blood gas analysis), PaO_2: arterial oxygen tension. Explanation in the text.

The tissue oxygenation balance is based on a balance between the oxygen transport capacity and the actual oxygen demand (Fig. 1). The delivered oxygen/systemic oxygen transport for an average adult at rest is four times the oxygen demand (DO_2~1000 ml/min, VO_2~250 ml/min), however, factors that increase oxygen demand (pain, work of breathing /WOB/, etc.) and the supply-reducing effects (blood loss, decreased cardiac output, respiratory failure, hypoxia) can easily lead to destabilization and tissue oxygen deprivation, which exacerbates the situation as a vicious circle.

During thoracic anaesthesia, it is particularly difficult to balance the tissue oxygen supply, as the conditions required for advanced haemodynamic monitoring are not constant. In this regard, I am thinking here primarily of the cessation of negative chest pressure, the lateral position, the gravitational displacement of the mediastinum toward the dependent lung. Therefore, a multimodal approach is needed that puts the patient's altered individual tissue perfusion and oxygen consumption in context with the adjustment of oxygen transport capacity/delivered oxygen. The concept of multimodal, individualized haemodynamic support developed by Molnár et al. can help in this, the detailed description of which goes far beyond the scope of the present dissertation [11].

Thromboembolic complications

Deep vein thrombosis and pulmonary embolism are classic and dreaded postoperative complications. The main pathogenesis of thromboembolism is immobilization and the altered postoperative rheological and coagulation conditions. It is no coincidence that thrombosis prophylaxis is an important chapter in all perioperative guidelines. However, the ERAS guidelines that we also apply allow us to minimize the time of immobilization, thereby minimizing the significance of this major risk factor. Of course, it is still necessary to give thromboprophylaxis, but the incidence of thromboembolic complications, the duration of prophylaxis as well as the costs can be reduced [31,32].

Orthostatic intolerance

Thus, early mobilization is essential in the elimination of pulmonary and thromboembolic complications, but it also plays an equally important role in reducing postoperative muscle loss.

However, it is a well-known problem that early mobilization causes dizziness and nausea in some patients, which is called orthostatic intolerance and may affect 40-50% of the patients. This phenomenon may be due to an imbalance between the sympathetic and parasympathetic responses and may occur regardless of the duration of surgery. Several studies have shown that this is not a complaint caused by hypovolemia per se, but may be due to other factors such as vasoplegia caused by the inflammatory response or the use of opioids [33].

Open points

Based on the above, minimally invasive procedures appear to have a beneficial effect on the incidence of perioperative complications, reducing the mortality and length of hospital stay [34]. A paradigm shift has begun in thoracic anaesthesia in the last decade, which had already taken place in the field of intensive care. The ever-evolving technological background, as well as our growing work experience in the operating room allow us to look for alternative ways to solve problems that have hitherto seemed almost unthinkable: avoiding muscle relaxation, maintaining spontaneous breathing, avoiding or radically reducing the duration of positive pressure ventilation may still seem to be a patient safety endangering practice for many. So the questions to be answered are as follows:

1. Will the alternative techniques outlined above actually reduce the magnitude of the surgical stress response?

2. Will there be fewer respiratory complications?

3. Will the oncological outcomes remain at least (”non-inferior”) compared to the gold standard procedures?

Research aims and objectives

- Is the use of the open NITS technique effective and successful in patients for whom conventional surgical techniques are not recommended according to the international recommendations, due to the patients' severely decreased respiratory function values and severe underlying diseases, comorbidities? (Examination 1)
- Is NITS safe to use in patients who require thoracotomy because of the expected surgical difficulties, and is there a benefit to using minimally invasive techniques regarding the perioperative complications and oncological success? (Examination 2)
- Comparison of the intra- and postoperative results of thoracic surgeries performed intubated, with maintaining the patient's spontaneous breathing and intubated, but applying positive pressure ventilation. (Examination 3)

Materials and methods

Patients

Study 1: Case report. A patient with severely impaired respiratory function in whom anatomical resection of a lung tumour is planned.

Study 2: Prospective, observational study. Patients undergoing NITS surgery using the uniportal technique between January 2017 and November 2018. Ethical license number: 111/2017-SZTE

Study 3: Patients operated between March 2020 and September 2020 who underwent lung surgery with either applying VATS or thoracotomy, and all of whom underwent surgery where airway management was conducted with a double-lumen tube (DLT) and following the return of spontaneous breathing, the operation was performed by maintaining it. Ethical license number: 4703/2020-SZTE

Inclusion and exclusion criteria were grouped according to the anaesthetic and surgical considerations. All aspects had to be met for inclusion of the patient.

Anaesthetic and surgical inclusion criteria:

1, Hungarian citizen over 18 years of age

2, resection surgeries involving thoracotomy

3, mechanical isolation of the lungs is not required (Examination 1, Examination 2).

Anaesthetic exclusion criteria:

1, lack of patient consent

2, a score of 4 or higher according to the American Society of Anesthesiology (ASA) classification

3, BMI>30

4, awake, case of a suspected difficult airway suggestive of fiberoscopic intubation

5, decompensated heart disease/ decompensated heart failure

7, bronchiectasis

8, clinically relevant amount of sputum

9, presence of a blood clotting disorder

10, pregnancy

11, imperfect lung isolation (Examination 3)

12, long-term administration of a vasoactive drug > 20 min

13, PEEP is need to maintain oxygenation (Examination 3)

14, a rescue manoeuvre was required until the blood samples were taken

15, hypothermia. Temperature <35.5 °C

16, PCO_2> 70 mmHg or pH < 7.15

17, Hgb< 7 g/dl.

Surgical exclusion criteria:

Patients to be excluded according to the recommendation of the European Society of Thoracic Surgery (ESTS) [35] are featured by:

1, the size of the lesion is greater than 7 cm

2, considering the TNM stage classification (TNM Classification of Malignant Tumours), a patient with a higher than N1 stage tumour

3, patient undergoing neoadjuvant therapy.

Perioperative management

All patients underwent routine examination according to the SZTE AITI (Institute of Anaesthesiology and Intensive Care, University of Szeged) preoperative preparation protocol. Upon arrival at the operating room, routine monitoring (ECG, non-invasive blood pressure measurement, and pulse oximetry) was initiated, and after undertaking peripheral venous cannulation, an arterial cannula was inserted into the left radial artery, under local anaesthesia, for continuous invasive blood pressure measurement and blood gas testing. In all patients, continuous core temperature measurements were performed.

Intraoperative fluid therapy

Restrictive fluid replacement was used for all three types of surgeries, using a balanced crystalloid infusion as maintenance fluid, administered via volumetric pump at a dose of 1.5-2 ml/kg body weight/h, and the postoperative fluid intake was maximized at 20 ml/kg body weight/24 h.

Mechanically ventilated patient, intubated with double-lumen tube (VATS)

Anaesthesia induction

For entropy- based (Bispectral index scale, BIS Vista, Medtronic, USA) sleep depth monitoring, a sensor was placed on the patient's forehead. After 3 minutes of preoxygenation, target-controlled infusion (TCI) of propofol based anaesthesia was initiated until achieving a target BIS (bispectral index, BIS) of 40 to 60, and then the patient was relaxed with rocuronium (0.6 mg/kg body weight). After complete muscle relaxation, which was checked with a relaxometer (TOF=0), a double-lumen tube (39 Ch-37 Ch for men, 37 Ch-35 Ch for women) was placed in the patient's trachea, and the position of the tube was checked with a bronchoscope.

Intraoperative care

Intermittent positive pressure ventilation was started with a tidal volume of 8-10 ml/kg body weight, with an inspiration-expiration ratio (I:E) of 1:2, a FiO2 varying between 21 and 100% to achieve a saturation above 92%. The respiratory rate was chosen to keep the $EtCO_2$ between 30 and 35 mmHg. During one-lung ventilation (OLV), the tidal volume was reduced to 4-6 ml/kg body weight, the FiO_2, and I:E ratio were not changed, positive end-expiratory pressure (PEEP) was not applied.

Rescue intervention in case of hypoxia

If SpO_2 fell below 90%, an alveolar recruitment manoeuvre was performed on the dependent lung with the Mapleson-C system. We tried to fix the patient's oxygenation by manual ventilation using PEEP. And in the event of failure of the manoeuvre, we returned to two-lung ventilation (TLV).

Treatment in case of haemodynamic instability

In both procedures, in case of haemodynamic instability, the haemodynamic support protocol of SZTE AITI was followed. In case of a suspected low cardiac output, inotropic therapy was used, while in the event of a suspected low systemic vascular resistance (SVR), fluid bolus and noradrenaline therapy were administered until MAP > 60 mmHg was reached. Whereas, as these agents alter the value of both pulmonary vascular resistance and shunt fraction, patients in need of continuous circulatory support therapy were excluded from the study.

Non-intubated, spontaneously breathing patient (NITS)

Anaesthesia induction

For entropy-based (BIS, SPI, PSI, etc.) sleep depth monitoring, a sensor was placed on the patient's forehead and target-controlled infusion (TCI) of propofol based anaesthesia was initiated. After reaching the target BIS range, a laryngeal mask was inserted.

Intraoperative care

Oxygen supply was provided by a T-piece attached to the end of the laryngeal mask, through which the inhaled oxygen concentration (FiO_2) could be varied between 21 and 100% so that the patient's oxygen saturation be above 92%. A gas analyser was connected to the connector end of the T-piece for continuous monitoring of the end-expiratory carbon dioxide concentration/end-tidal carbon dioxide level and FiO_2 value.

After local anaesthesia of the skin with 2% Lidocaine and intercostal nerve blockade at the 4/5th intercostal segment were performed, an incision was made and the chest was opened. Following lung collapse, intercostal, paravertebral, and vagus nerve blocking injections were administered under eye control for analgesia and to abolish the cough reflex. Surgical treatment was then provided according to the uniportal VATS care rules.

Rescue intervention in case of hypoxia

It is the same technique as used during VATS surgery.

Conversion - endotracheal intubation

For cases of rescue manoeuvre fail or apparently inevitable intubation due to surgical reasons, the following protocol was used:

Indications

Hypoxaemia: SpO_2<92% or PaO_2<60 mmHg, FiO_2=1.0 and upon reinflation of the nondependent lung.

Hypercapnia: In cases of $PaCO_2$>70 mmHg or pH<7.15, the nondependent lung was reinflated, and in CPAP mode, we ensured an adequate minute ventilation (MV) required to resolve respiratory acidosis. If this proved unsuccessful we intubated the patient.

Respiratory tract bleeding: intubation is necessary at the first sign of blood/bleeding if confirmed by airway fiberoscopy through the LMA.

If intubation is necessary, the patient is ventilated with 100% oxygen prior to the procedure, the surgical incision is covered with a sterile dressing, the operating table top is positioned in a straight position and the patient is positioned horizontally. Following the administration of a muscle relaxant, a double-lumen tube (DLT) is inserted into the trachea, its position is checked with a fiberoscope, and the operation is continued according to the “intubated, ventilated” (see above) method.

Spontaneously breathing patient, intubated with double-lumen tube (VATS-SVI)

Anaesthesia induction

In addition to routine monitoring (ECG, saturation), for entropy-based (BIS, SPI, PSI, etc.) sleep depth monitoring, a sensor was placed on the patient’s forehead and target-controlled infusion (TCI) of propofol based anaesthesia was initiated. After reaching the target BIS value of 40 to 60, the patient was relaxed with mivacurium at a dose of 0.06-0.10 mg/kg body weight and intubated with a double-lumen tube. Following fiberoscopic control of the tube position, pulmonary protective ventilation was initiated. The patient was then positioned in a lateral position and its surgical preparation was performed. After local anaesthesia of the skin with 2% Lidocaine and intercostal nerve blockade at the 4/5th intercostal segment were performed, the chest was opened. Following lung collapse, intercostal, paravertebral, and vagus nerve blocking injections were administered under eye control for analgesia and to abolish the cough reflex. Surgical treatment was then provided according to the uniportal VATS care rules.

Intraoperative care

Intermittent positive pressure ventilation was started with a tidal volume of 8-10 ml/kg body weight, with an inspiration-expiration ratio (I:E) of 1:2, a FiO2 varying between 21 and 100% to achieve a saturation above 92%. The respiratory rate was chosen to keep the $EtCO_2$ between 30 and 40 mmHg. During one-lung ventilation (OLV), the tidal volume was reduced to 4-6 ml/kg body weight, the FiO_2, and I:E ratio were not changed, the positive end-expiratory pressure (PEEP) was set between 0 and 10 cm H_2O. As the relaxant effect wears off, the patient's spontaneous breathing returns, however, coughing does not occur as a result of the vagus and paravertebral blockade, initially pressure support breathing will take place, then purely spontaneous breathing (SB) is achieved without pressure support after full muscle strength is regained.

Rescue intervention in case of hypoxia

It is the same technique as described for the VATS procedure.

In case of haemodynamic instability

In both procedures, in case of haemodynamic instability, the haemodynamic support protocol of SZTE AITI was followed. In case of a suspected low cardiac output, inotropic therapy was used, in the event of a low systemic vascular resistance (SVR), intermittent boli of phenylephrine were administered, while in the event of a suspected persistent low systemic vascular resistance (SVR), fluid bolus and noradrenaline therapy were administered until MAP > 60 mmHg was reached. Patients in need of continuous circulatory support therapy were excluded from the study.

At the end of the operation, the patient was extubated and then observed in a PACU room (PACU: Post anaesthesia care unit) for at least 2 hours. If necessary, intravenous analgesics were given according to the WHO's multimodal therapeutic recommendation until the visual analogue scale (VAS) score fell below 3. During the ward observation, the patients were able to consume oral liquids as early as 2 hours after surgery, and their in-bed mobilization, then full mobilization took place in the first 6 hours.

Measurements

Study 1:

Recording of blood gas and oxygenation parameters before surgery, during surgery (before and after resection), at the end of surgery, in the PACU room (post anaesthesia care unit), and in the hospital ward.

Study 2:

Physiological parameters, heart rate, systolic and diastolic blood pressure values, and end-tidal carbon dioxide values were recorded during the intraoperative period.

Study 3:

During surgery, ventilation parameters during relaxation (tidal volume, respiratory rate, I:E ratio, FIO_2), gas exchange parameters ($EtCO_2$, saturation) were recorded, which were also recorded in the spontaneous breathing phase, in addition, we made notes of the total medication, especially for vasopressor use. In the postoperative period, laboratory sampling was carried out on postoperative day 1, 2 and 3, measuring the differential leucocyte count, CRP and renal function values.

Statistics

Basically, descriptive statistical methods were used. Data were expressed as mean (minimum-maximum) or mean [95% confidence interval]. In the 2nd examination, data before and after chest opening were compared by two-way analysis of variance (ANOVA) and $p<0.05$ was considered statistically significant. Calculations were performed with IBM SPSS 24 software.

Results

Study 1

More than 80 anatomical resections were performed in 22 months applying the NITS technique. Due to the experience gained in this way, we chose this method for an extremely high-risk patient (for whom the current international recommendations contraindicated the traditional surgical procedure and OLV).

The patient was a 73-year-old man who had lost more than 20 kgs of weight in the 2 months prior to his visit and developed haemoptysis. A 4x2.8 cm lesion compressing the right main bronchus was detected during the examination, and cytological examination confirmed basaloid adenocarcinoma.

The patient's arterial blood gas values are summarized in Table 1.

Table 1: Arterial blood gas parameters in the perioperative period

Blood gas values	T_{Pre}	T_{BR}	T_{AR}	T_{Post}	T_{RR}	T_{A}	T_{W}
FiO_2 (%)	21	100	100	40	40	40	21
pH	7.434	7.195	7.153	7.243	7.294	7.325	7.357
pCO_2 (mmHg)	32	64	67	49	40	38	35
pO_2 (mmHg)	68	217	325	118	182	204	62
BE (mmol/L)	−3.6	−4.7	−6.1	−6.7	−7.1	−6.0	−5.7
HCO_3 (mmol/L)	22	24	23	21	19	19	19
Lactate (mmol/L)	2.0	1.0	1.1	1.3	1.9	2.6	3.0
SaO_2 (%)	95	99	99	97	99	99	92
p50 (mmHg)	24	39	48	31	24	35	26
Haemoglobin (g/dl)	10.4	10.0	10.5	11.0	11.1	10.8	11.1

T, sampling time; Pre, before induction; BR, before resection; AR, after resection; Post, at the end of surgery; RR, awakening A: awakening, at discharge from the postanaesthetic care unit (PACU), W: hospital ward sampling 12 hours after surgery; BE, base excess/deficit

During routine preoperative pulmonary examination, his respiratory function values were dramatically decreased: FEV1 27%, Tiffeneau-index 43%, DLCO 26%, VO_2 max 13,9 ml/kg body weight/min. Due to his severe comorbidities (underwent coronary artery bypass graft surgery, CABG and has aortic aneurysm) and respiratory function, the current recommendation (European Society of Thoracic Surgeons, ESTS) did not recommend one-lung ventilation (OLV) in his case. After the patient had signed the informed consent form, a right bilobectomy was performed with the NITS technique, as an elective surgery in the knowledge of the atypical pathological lesion, in an open surgery.

When planning the surgery, we prepared for an open surgery due to the location of the lesion and the difficulty of the surgical technique. We also used our achievements in the field of analgesia - obtained during the non-intubated surgeries-, in the course of intubated surgeries, namely that the routinely applied intercostal, paravertebral and vagus blockade is perfect for blocking the pain in open surgeries as well. Thus, not only during this operation, but also before it, we performed a so-called conversion in patients in whom it became necessary to open the chest during surgery or in whom a chest opening had already been planned after VATS exploration.

Study 2

We enrolled 160 patients in this study. Patient demographics and types of surgeries are summarized in Table 2.

Table 2: Demographic data and summary of types of surgeries

Features	N=160
Age (years)	63.9 [20-81]
Female/ male	102/58
All NITS surgeries	160
VATS-NITS surgeries	145
Conversion	15
Lobectomy	100
Segmentectomy	18
Wedge resection	22
Volume reduction	2
Empyema decortication	2
Rib resection	1

NITS, non-intubated thoracic surgery; VATS, video-assisted thoracic surgery. Age is shown as mean [min-max].

Of the 160 successful surgeries, 145 patients underwent uniportal VATS-NITS, but 15 patients required surgical conversion, i.e., NITS thoracotomy. Data from these patients are summarized in Tables 3 and 4.

Table 3: Summary of resection types in patients who underwent NITS thoracotomy due to unplanned conversion:

Unplanned / non-elective conversion to NITS thoracotomy	N=9
Pulmonectomy	2
Right upper sleeve resection	1
Lobectomy	5
Wedge resection	1

Table 4: Summary of resection types of patients who underwent NITS thoracotomy due to planned conversion

Planned / elective (or semi-elective) conversion to NITS thoracotomy	N=6
Bilobectomy	1
Lobectomy	2
Segmentectomy (anatomical)	2
Exploration	1

NITS: non-intubated thoracic surgery; VATS: video-assisted thoracic surgery.

Of the 160 patients, intubation was necessary in 6 cases: in 1 case due to pronounced diaphragmatic and mediastinal movements, and in 2 cases due to respiratory tract bleeding. For surgical reasons, we opted for conversion in 3 cases due to extensive adhesions. Based on our previous experience, lung resections with lymphadenectomy can be performed in open NITS surgeries as well as using traditional techniques. There were no R1-2 resection cases. The duration of surgery was longer in the unplanned conversion group, which includes the exploration time until conversion became necessary. The postoperative chest drain time was longer in the planned NITS group, due to the fact that these patients were in the most severe general condition, they had severe underlying diseases and comorbidities, and the radicality of their surgeries were the most extensive. Three patients had a drain time of more than 5 days, and drain time for all patients was 4.2 days (1-14 days). Our average conversion rate was 7.5% (12/160).

Data of these interventions are summarized in Table 5.

Table 5: NITS thoracotomy data

	Non-elective (unplanned NITS thoracotomy N=9	Elective (planned) NITS thoracotomy N=6
BMI	24.3 [19–31]	24.7 [20–32]
FEV1 (%)	61.7 [32–111]	60.3 [36–73]
DLCO (%)	60.5 [40–84]	47.5 [26–61]
Duration of surgery (min)	146.7 [105–225]	110 [75–190]
Drain time (days)	3.6 [1–14]	5.1 [2–13]
No. of N2 lymph nodes	9.6 [4–24]	21.6 [10–29]
Adenocarcinoma	4	3
Squamous carcinoma	1	2
Neuroendocrine tumour	2	1
Carcinosarcoma	1	0
Benign tumour	1	0
IA	1	2
IB	1	0
IIA	0	0
IIB	3	0
IIIA	3	3
IIIB	0	1

BMI, body mass index; DLCO, diffusion capacity of the lung for carbon-monoxide; FEV1, forced expiratory volume in one second; NITS, non-intubated thoracic surgery; N2 lymph node: mediastinal lymph node. Data are given as mean [95% confidence interval].

There were no significant differences among the 15 cases studied, regarding the systolic blood pressure, oxygen saturation levels, or the effective side propofol concentration values, however, we found significant differences between the pre- and post-thoracotomy values, e.g., the heart rate, diastolic blood pressure, and end-tidal carbon dioxide values. Despite the statistical results, these were not clinically relevant and did not require any change in anaesthesiology care. Four patients required temporary vasopressor therapy to maintain an adequate MAP value. Two patients who had underwent pulmonectomy were transferred to the intensive care unit (ICU) for observation, from where they returned 24 hours later, following an uneventful observation period, whereas the other 13 patients returned to the surgical ward according to protocol. The patients' haemodynamic and gas exchange parameters, as well as the TCI settings used are summarized in Tables 6 and 7.

Table 6: Haemodynamic data before and after NITS thoracotomy (planned/elective and unplanned/non-elective)

Patient	P_{before} (min)	P_{after} (min)	$sysRR_{before}$ (mmHg)	$sysRR_{after}$ (mmHg)	$diasRR_{before}$ (mmHg)	$diasRR_{after}$ (mmHg)
1	89	87	124	115	68	64
2	96	93	109	118	62	68
3	65	66	106	116	62	70
4	NA	NA	NA	NA	NA	NA
5	65	76	106	94	62	64
6	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA
8	NA	NA	NA	NA	NA	NA
9	78	89	104	116	62	70
10	83	87	94	116	48	68
11	65	80	112	106	60	68
12	65	66	112	112	68	72
13	66	76	104	104	62	64
14	65	75	102	115	62	64
15	80	89	104	102	62	66
P	0.007		0.316		0.013	

P_{before}: heart rate before NITS thoracotomy (NITS period), P_{after}, heart rate after NITS thoracotomy (open period), $sysRR_{before}$ systolic blood pressure before NITS thoracotomy, $sysRR_{after}$: systolic blood pressure after NITS thoracotomy; $diasRR_{before}$: diastolic blood pressure before NITS thoracotomy (NITS period) $diasRR_{after}$, diastolic blood pressure after

NITS thoracotomy (open period). Data are given as median, statistical analysis was performed using a two-way analysis of variance test with repetition, by the use of the IBM-SPSS-24 program.

Table 7: Gas exchange and anaesthetic TCI (Target-controlled infusion) data before and after NITS thoracotomy (planned and unplanned)

	O_2SAT_{before} (%)	O_2SAT_{after} (%)	$etCO_{2before}$ (mmHg)	$etCO_{2after}$ (mmHg)	Ce_{before} (mcg/ml)	Ce_{after} (mcg/ml)
1	97.0	97.6	50.0	49.4	2.62	3.02
2	96,6	97.6	48.2	63.0	3.02	3.20
3	98.8	99.2	35.2	34.2	3.16	2.80
4	NA	NA	NA	NA	NA	NA
5	98.6	98.4	43.2	46.4	2.5	2.52
6	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA
8	NA	NA	NA	NA	NA	NA
9	96.2	96.4	46.4	49.0	2.52	2.62
10	90.8	96.6	43.4	47.6	2.76	2.90
11	98.8	98.2	35.4	47.2	3.00	3.44
12	96.2	95.0	43.0	45.0	3.12	3.56
13	95.0	96.4	36.8	41.6	2.66	2.74
14	96.2	95.8	43.2	45.2	2.66	2.70
15	96.6	96.8	46.0	48.6	2.56	2.76
P	0.270		0.016		0.053	

O_2SAT_{before}, arterial oxygen saturation before NITS thoracotomy (NITS period), O_2SAT_{after}: oxygen saturation after NITS thoracotomy (open period); Ce: propofol effect concentration; $etCO_2$: end-tidal carbon dioxide pressure; NA: no data available. Statistical analysis was performed using a two-way analysis of variance test with repetition, by the use of the IBM-SPSS-24 program.

Study 3

Data from patients enrolled in our VATS-SVI study and data related to surgery are summarized in Table 8.

Table 8: Surgical parameters of patients who underwent VATS-SVI

	All cases N=26	VATS-SVI N=19	Open SVI N=7
Male/Female	14/12	9/10	5/2
Age	65.2 (43-80)	63.7 (43-80)	69.1 (56-75)
BMI	26.8 (19-35)	26.4 (19-32)	28 (24-35)
CCI	5.4 (2-10)	5.4 (2-10)	5.5 (4-7)
FEV1 (%)	86.2 (44-126)	87.7 (44-113)	82.7 (57-126)
Duration of surgery (min)	83.3 (55-130)	81.0 (55-110)	89.2 (60-130)
Drain time (days)	2.4 (1-10)	2.2 (1-10)	2.8 (1-6)
Right upper lobectomy	2	0	2
Right middle lobectomy	2	2	0
Right lower lobectomy	9	7	2
Left upper lobectomy	4	3	1
Left lower lobectomy	3	3	0
Segmentectomy	2	1	1
Wedge resection	4	3	1

CCI: Carlson Comorbidity Index. BMI: body mass index; FEV1: Forced expiratory volume in one second; SVI: spontaneous ventilation combined with intubation; VATS: video-assisted thoracic surgery. Data are given as mean (min-max).

Lobectomy was performed in 20 of the 26 cases. We had to induce repeated relaxation in 2 cases. In one case for surgical reasons and one case due to definitive haemorrhage control. Conversion occurred in two cases.

The demographic data of patients and the surgical parameters are summarized in Table 9.

Table 9: Summary of the summary demographic data and surgical results of patients who underwent VATS-SVI

	VATS-SVI lobectomies N=15	Open SVI lobectomies N=5
Male/Female	8/7	4/1
Age (years)	62.4 (46-79)	69.6 (56-75)
BMI	25.6 (22-32)	28 (24-35)
CCI	4.7 (2-8)	5.2 (4-7)
Duration of surgery (min)	85.6 (55-110)	86 (60-105)
Drain time (days)	2.2 (1-10)	2.4 (1-4)
Postoperative hospital stay (days)	3.7 (2-7)	4.8 (4-6)
FEV1 (%)	88.7 (78-113)	74 (57-104)
Right upper lobectomy	0	2
Right middle lobectomy	2	0
Right lower lobectomy	7	2
Left upper lobectomy	3	1
Left lower lobectomy	3	0

BMI: body mass index; CCI: Carlson Comorbidity Index.; FEV1: Forced expiratory volume in one second; SVI: spontaneous ventilation combined with intubation; VATS: video-assisted thoracic surgery. Data are given as mean (min-max).

None of our patients were admitted to intensive care unit, the postoperative period was uneventful, and neither airway aspiration nor bronchoscopy was needed. Chest X-ray revealed dystelectasis in 7 cases, infiltration in 1 case, minimal thoracic fluid and pneumothorax in 13 cases, which are considered to be of normal changes/alterations in this surgical group. In neither case was reoperation or other intervention needed.

We observed that the patients had a reduction in blood pressure 5–10 min after the vagus nerve puncture and blockade, which in 9 cases resulted in such a decrease in the mean arterial pressure (MAP) that it made phenylephrine administration necessary. In the other cases, the patients' haemodynamic autoregulation restored the mean arterial pressure required for (physiological) tissue perfusion.

In 26 cases, spontaneous breathing was restored after one-lung ventilation, and based on our data, the duration of mechanical ventilation could be reduced by 76.6%. In 24 cases, only the initial muscle relaxant dose administration (required for intubation) was needed.

The patients' intraoperative parameters are summarized in Tables 10 and 11.

Table 10: Respiratory parameters during VATS-SVI

Heart rate (1/min)		Average time period of one-lung ventilation (OLV) (min)	Average time period of spontaneous breathing (SB) (min)
Min	Max		
66.4 (48-90)	84.9 (65-120)	25.5 (15-115)	73.3 (45-100)

Table 11: Gas exchange parameters during VATS-SVI

Oxygen saturation (%)		pCO_2 (mmHg)		Respiratory rate (1/min)	
Min	Max	Min	Max	Min	Max
93.8 (86-99)	99.3 (89-100)	39.1 (28-50)	52.3 (38-66)	12.1 (10-15)	18.3 (14-25)

SVI: spontaneous ventilation combined with intubation; OLV: one-lung ventilation; pCO_2: partial carbon dioxide pressure. Data are given as mean (min-max).

Respiration rate was adjusted to the 10-25 / min range by modified dosing of the administered opioid, all patients were extubated without the use of an acetylcholinesterase inhibitor, and no reintubation was performed.

The kinetics of the inflammatory response was similar to those observed with other methods. The changes in the measured inflammatory markers are summarized in Table 12.

Table 12: Changes in inflammatory parameters in patients who underwent VATS-SVI

	Preoperative N=6	Postoperative 24 hours N=6	Postoperative 48 hours N=6
Leucocyte (10^9/L)	10.9 (100%) (7.1-13.8)	12.1 (111%) (10.1-15.9)	9.6 (88%) (8.3-10.4)
Lymphocyte (10^9/L)	1.31 (100%) (0.38-2.25)	1.29 (98%) (0.87-1.7)	1.56 (119%) (1.07-1.82)
CRP (mg/L)	29.6 (100%) (18.2-44.0)	68.6 (231%) (61.1-72.9)	69.7 (235%) (49.7-82.0)

CRP: C-reactive protein, VATS: video-assisted thoracic surgery; SVI: spontaneous ventilation combined with intubation; Data are given as mean (min-max).

Discussion

Reducing the chance of iatrogenic injuries caused by surgical interventions — i.e., the principle of" nil nocere" ("do no harm") — has also emerged as an important endeavour in thoracic surgery and in the practice of thoracic surgical anaesthesia in recent decades. This goal also guided our team when we introduced non-invasive and less-invasive methods into daily practice and examined their effectiveness. Our interest focused on the methods that most resemble physiological processes, i.e., maintaining the patient's spontaneous breathing (SB).

The tradition of this procedure dates back to the heroic age of surgery, when Ossipov operated on the lungs of spontaneously breathing patients in the absence of adequate anaesthetic procedures, facilities [36]. The development of anaesthesia made it possible to perform one-lung ventilation (OLV) with modern devices, which method created much better surgical conditions for the surgeon in addition to complete airway control, making this technique the gold standard for thoracic surgery for decades. However, the recognition that there is a strong link between reducing invasiveness and better outcome has led to the fact that some working groups such as Mineo et al. have again raised the possibility of reusing spontaneous breathing (SB) as a lung-protective strategy, which has since become a constantly evolving specialty [37]. Reduction of invasiveness has led to a paradigm shift in surgical technique also in the field of thoracic surgery, namely the widespread use of the VATS technique. Thus, the combination of the VATS technique with the non-intubated, spontaneous breathing anaesthesia seemed to be an ideal combination.

During the learning phase, we made a number of modifications different from the world's mainstream practice to the anaesthesia protocol of non-intubated thoracic surgery (NITS), in order to increase security of care. We also combined the NITS technique with the multimodal, individualized haemodynamic support introduced by Molnár et al., moreover, the monitoring of sleep depth by use of monitoring devices and the application of intravenous target-controlled infusion (TCI) based sedation technique became a routine of care. [11].

We observed that the $EtCO_2$ levels were stabilized at higher values in cases of NITS surgeries compared to ventilated patients. Exclusion criteria include an $EtCO_2$ value significantly higher than normal by about 30 mmHg. This phenomenon is permissive hypercapnia, which is well known in the treatment of ARDS and status asthmaticus, as well as in thoracic anaesthesia. Our understanding of the physiological effects of hypercapnia grows through the understanding of both the cellular and molecular mechanisms induced by hypercapnia. Acute hypercapnia and the consequent acidosis have had protective effects in a number of studies - in cases of non-septic lungs -, such as reduction of pulmonary hypertension, reduction of ischaemia-reperfusion injury, reduction of endothelial barrier damage by preventing an increase in the permeability of pulmonary capillaries [38–40]. This effect is due in part to a reduction in the endocytosis of the Na/K-ATPase pump, and inhibition of the NF-κB pathway, however, it is important to note that the same mechanism is responsible for regulating a number of adverse effects, such as delayed wound healing and weakening of the local immune response [41]. From a clinical point of view, vasodilation due to acidosis, - which manifests itself mainly in an increase in cerebral blood flow and in an increased right heart strain-, remains within a tolerable range up to 70 mmHg $EtCO_2$ or pH> 7.15, and in such cases we do not yet have to reckon with adverse physiological effects [42].

NITS – with laryngeal mask

The laryngeal mask technique we use differs from the previously reported practice in this type of non-intubated surgery. Elsewhere, the patient was oxygenated with a high-flow nasal cannula (HFNC) [43]. The laryngeal mask airway technique offered several advantages, such as easy access to the airway, continuous intraoperative bronchoscopy through the LMA, and the possibility of emergency airway management, as well as continuous measurement and analysis of the end-tidal carbon dioxide level (EtCO2).

We performed more than 160 anatomical resections with this technique, initially in low-risk patients. Thus, after gaining adequate experience, we were able to perform extensive anatomical resection in a very high-risk patient for whom the current European recommendations did not recommend the use of conventional one-lung ventilation because of his low dynamic and static respiratory function parameters, extremely low diffusion capacity, and delivered oxygen being at limit value. Current recommendations estimate the perioperative risk based on these parameters [44]. For our patient, this meant that there was a very high likelihood of postoperative respiratory failure and the need for long-term mechanical ventilation due to insufficient lung capacity. Our case was the first to demonstrate that our technique can be effective and safe even in such high-risk patients. Based on this, the need arises and it is justified to test the procedure in a prospective, randomized trial, which, in the event of a positive result, could lead to a modification of the current guidelines.

A very important finding from research over the past decade is that intraoperative IPPV (intermittent positive-pressure ventilation) can cause alveolar damage even in healthy individuals, which increases perioperative morbidity and mortality [45,46]. The pathomechanism of ventilation-induced lung damage is mainly due to baro- and volutrauma to the alveoli. Shear forces due to periodic opening-closing, synchronous with the respiratory cycle, result in damage that provokes an inflammatory stress response. Furthermore, severe ventilation-perfusion (V/Q) mismatch develops in patients lying in a lateral position during one-lung ventilation, since circulation of the nondependent lung is preserved, but its ventilation ceases. In contrast, in a spontaneously breathing patient, this mismatch is theoretically smaller because of the still intact diaphragmatic movements, which, of course, are absent where the patient is in a state of muscle relaxation. During OLV, perfusion is dramatically reduced in the nondependent lung due to a physiological process, namely hypoxic pulmonary vasoconstriction (HPV), induced by hypoxia, thus ensuring a sufficient V/Q ratio in the dependent lung [47]. In addition, due to surgical manipulation and gravitational forces acting on the lung tissue, a right-to-left shunt often develops [48,49]. The effectiveness of hypoxic pulmonary vasoconstriction (HPV) is substantially affected by lung volume. A set tidal volume and the resulting intrapulmonary pressure can overstretch the alveoli, diverting blood flow towards the unventilated alveoli, weakening the effect of HPV, leading to a shift in V/Q ratio and a deteriorating oxygenation status [50].

If a non-intubated, spontaneously breathing patient has undergone surgical chest opening, a pneumothorax has developed, and the physiologically negative intrathoracic pressure has been lost, a so-called paradoxical breathing movement (when movements of the chest and abdomen are out of phase) occurs. During inhalation, the normal atmospheric pressure pushes the mediastinum towards the dependent lung, on exhalation an opposite process takes place [51]. Perfusion of the dependent lung is greater during spontaneous breathing than during one-lung ventilation, as lower or negative pressure prevails. The intrapulmonary shunt may also be smaller by preserving the normal diaphragmatic function (intact diaphragmatic movements).

Hypercapnia is a common phenomenon that occurs in both the non-intubated and the intubated, ventilated surgery patients. One cause for this is that during NITS, the alveolar gas mixture mixes with the gas mixture of the dependent and non-dependent lungs, resulting in the so-called carbon dioxide rebreathing. The other cause is hypoventilation, which, on the one hand, is related to the collapsed, operated state of the lung, and, on the other hand, to the respiratory depressant effects of drugs administered during anaesthesia. Experience has shown that carbon dioxide accumulation during surgery does not cause damage if $PaCO_2$ does not exceed 70 mmHg or pH does not fall below 7.15, however, hypercapnia should be avoided in patients with pulmonary hypertension, or severe valvular heart disease or increased intracranial pressure [42,52]. It is important to note that these values are such threshold levels/values from the literature that are to be flexibly interpreted by the clinician, especially in procedures where we try to reduce the stressful conditions that test the patient's load-bearing capacity, while maintaining the surgical radicality of the operation.

The increase in the number of cases and the inevitable encounter with some complicated cases have raised several new issues to be addressed in the future. According to Mineo et al., the conversion rate ranges from 0 to 9%, but no difference was made between the causes [53]. There has been a clear improvement in our practice concerning the recognition of causes leading to conversion during surgery, assessing the severity of the problem, making an adequate decision, and the ever faster technical implementation. At the same time, however, we recognized that not all intraoperative complications necessarily lead to conversion. There are two major groups of problems. The first group of problems is related to gas exchange disturbances, which should lead to immediate, prompt conversion in certain cases, the protocol of which is described above. However, factors in the other group, typically surgical difficulties (adhesions, anatomical variants, pathological lesions, extensive anatomical resections, sleeve resections) are those that lead to surgical (switching from uniportal VATS to open surgery (thoracotomy)) rather than anaesthetic conversion (intubation and positive pressure ventilation, PPV). Our established anaesthesia practice, which includes intercostal, paravertebral, and ipsilateral vagus blockade, eliminates the need for any other anaesthetic intervention to perform thoracotomy, as the necessary adequate pain relief and safe anaesthetic techniques are also provided. We have performed an increasing number of non-intubated interventions, accepting the possibility of planned or unplanned (elective or non-elective) surgical conversion. In our 2nd examination, we've reviewed medical data from 10 months of surgeries and analysed the effects of complicated and extensive lung resections - performed while maintaining spontaneous breathing (SB)-, on postoperative outcome.

The most common counter-argument for NITS surgeries is the "unsafe airway" problem [54,55]. In the conventional design of non-intubated surgeries, i.e., in cases of HFNC (high-flow nasal cannula oxygen therapy) surgeries, airway patency is indeed mostly dependent on the patient's sedation status, however, with our modification, using the laryngeal mask, this problem did not arise because the airway was patent regardless of the sedation level. Another advantage of using a laryngeal mask is that both for the diagnostic steps (bronchoscopy) and in the management of possible complications, an immediately accessible airway and the possibility of ventilation were of great help [56]. Liu et al. reported a conversion rate of 7% in their scientific paper, however, the causes were not identified there either, basically, the operator skill was identified as the main predisposing factor for it [57]. In our practice, the conversion rate is 7.5%, similar to the results of other large centres. We consider it a useful innovation that during conversion – unlike the practice of other centres [53,58]-, following the immediate dressing of the surgical wound, the patient is placed on his/her back from the lateral position for intubation and tube positioning. Although we found statistically significant differences in heart rate, diastolic blood pressure, and pre- and post-conversion end-tidal carbon dioxide values, these were not such as to require any therapeutic intervention. The confidence interval for the differences have shown that although the difference was statistically significant, but given that the values remained within a physiologically acceptable range, the result was not clinically relevant. No systematic review or meta-analysis has been found in the literature to date that summarizes the long-term experiences gained from the non-intubated versus intubated open thoracic surgeries [52,57,58]. This is due to the lack of prospective randomized trials in this area, which should definitely be one of the goals for the future in the light of the present results.

The next very important aspect in judging the effectiveness of open NITS surgeries is the oncological outcome. Based on our study, the number of mediastinal lymph nodes (N2) removed during open NITS is equal to - and in some cases exceeds (N1 and N2: 9.6 and 21.6) - the number of lymph nodes (N1+N2) removed during VATS-NITS (as reported by other centres), although a meta-analysis suggests that the main difficulty during NITS is the correct execution of mediastinal lymphadenectomy [52,59].

Intubation and maintenance of spontaneous breathing (SB)

Following the previous two examinations, further modifications were introduced in the daily practice. For patients operated on by conventional methods, based on the exclusion criteria used for non-intubated techniques, there have been an increasing number of patients for whom, based on our results to date, surgery with spontaneous breathing would have been the optimal solution, but, mainly due to high BMI, we opted for conventional surgery. Therefore, by combining the experience gained with non-intubated techniques and the practice of conventional airway management, positive pressure ventilation, we created the intubated, spontaneous ventilation VATS surgery (VATS-SVI) technique, which combines the benefits of spontaneous breathing with safe intubated conditions. The main limiting factor so far, the cough reflex (both tracheal and pleural), has been eliminated by the use of nerve blockades [35,60].

The intubated patient is able to breathe spontaneously again by breaking down the short acting muscle relaxant, and in theory, any anaesthetic or surgical intervention may be carried out that can be performed by the use of conventional techniques. Furthermore, there was no need for conversion due to airway loss, or other anaesthetic causes observed with non-intubated techniques, which, according to the literature data, can occur in up to 9% of the cases [53].

Based on our results, the durations of VATS-SVI lobectomies, and the duration of need for chest drainage (mean duration of surgery: 85.6 minutes and mean drain time: 2,2 days) were shorter than those reported in the literature for NITS lobectomies (130.9 minutes and 5,6 days) and for intubated lobectomies (146 minutes and 5.4 days), in addition, the average length of hospital stay (3.7 days) was shorter than reported in the literature (7.6 days) [61]. According to a recent meta-analysis, diaphragmatic movements necessitated intubation in 4%, while mediastinal movements in 7% of the patients undergoing NITS surgery [62]. In our report, 1 of the 26 VATS-SVI patients showed excessive mediastinal movements (3.84%) that required relaxation and positive pressure ventilation. There was no conversion for oncological reasons, which may make the procedure suitable for technically more difficult surgeries in the future. Following the return of spontaneous breathing, both diagnostic and therapeutic interventions can be performed through the double-lumen tube. Blood gas parameters measured during VATS-SVI are similar to those in the NITS group, with evidence of permissive hypercapnia and a slight decrease in PaO_2, which can be compensated by an increase in FiO2 and / or applying PEEP in the dependent lung's airways.

Following the vagus blockade, a decrease in blood pressure was observed and 34% of patients needed transient circulatory support. Blood pressure resolved spontaneously in 66% of patients. In both animal and human experiments, increasing the vagal tone has led to reduced left ventricular contractility [63], and by reducing the sympathetic tone, beta-adrenergic antagonists are well-established therapeutic agents for the treatment of heart failure [64]. Vagal activity has a similar effect to beta-adrenoceptor antagonists and reduces heart rate and contractility [65].

During SVI, the duration of controlled ventilation could be reduced by 76.6%. In their study, Misthos et al. found that oxidative stress in conventional surgeries may be due to OLV lasting more than 1 hour, and therefore we hypothesize that reducing the duration of OLV induces less pathophysiological changes in the lung tissue, thus oxidative stress may also be less pronounced. The duration of OLV is also a major factor, according to a report by Mineo et al [66]. In our patients, the mean leukocyte count increased on the first postoperative day and then decreased below baseline on the second day, showing similar kinetics as reported by Mineo et al. in their patients undergoing VATS and NITS [67]. The inflammatory response elicited by VATS-SVI appears to trigger a very similar reaction to that observed in NITS. Although, according to a study by Leaver et al., there was no measurable change in the postoperative lymphocyte count on the first postoperative day, and the largest difference was seen on the second day for VATS surgeries [68]. In our study, serum CRP levels doubled on day 1 and remained unchanged on day 2. The results reported by Dongel et al. showed that in conventional VATS surgeries, the CRP levels were more than four times higher than baseline on day 1 and more than three times higher even on day 2, which also suggests less inflammatory mediator release in our patients undergoing VATS-SVI [69].

Conclusion

The rise of minimally invasive procedures has brought fundamental changes to patient care in recent decades. In my thesis, I aimed to present a holistic view that combines the approach of a surgeon and an anaesthetist, presenting their collaboration and which, in my view, could lead to further improvements in care in the future. The use of thoracoscopic surgical techniques has already led to significant advances in itself in reducing the incidence of perioperative risks and complications, as well as in shortening the nursing time. However, anaesthesiology has been deprived of such paradigm-shifting developments for a long time. The procedural methods listed in our studies may break this barrier. Performing thoracic surgeries without intubation while preserving the patient’s spontaneous breathing may lead to a fundamental change in anaesthetic care, which may improve the outcome as well, based on our preliminary results. However, as experience grew, the method's limitations attracted increasing attention, which necessitated further changes. For these reasons, our team has developed an alternative procedure that enables to maintain the patient’s spontaneous respiration and, at the same time, to perform OLV for airway management, which may provide a safe, effective, yet less invasive alternative for these particularly high-risk patients awaiting thoracic surgery. Our results so far clearly support the need for conducting prospective, randomised trials with large numbers of patients, comparing the conventional technique with the alternative methods outlined in the dissertation.

The dissertation's new findings

1. Even in high-risk patients with severe comorbidities, anaesthesia without intubation and with spontaneous breathing is a safe alternative also for patients undergoing thoracotomy.
2. NITS can be used safely also in patients who have to undergo thoracotomy due to surgical difficulties, even in the case of conversion, patient safety is not compromised, and it is a better alternative to traditional methods in terms of oncology efficacy and length of hospital stay, while it is at least an equivalent alternative to the conventional methods in terms of incidence of perioperative complications.
3. The VATS-SVI technique offers the possibility to maintain spontaneous breathing during thoracic resections also in patients who, due to the need to maintain a secure airway, and a number of exclusion criteria (a suspected difficult airway, abnormal anatomy, respiratory tract bleeding, severe GERD) that have been used so far, could not be operated on in this way until now, thus, the inclusion criteria have been significantly broadened and can also be applied to patients who have not been eligible for NITS surgeries, and we can take advantage of the benefits provided by a safe airway and the possibility of isolating the lungs without the need for positive pressure ventilation.
4. By applying the VATS-SVI technique, the duration of positive pressure ventilation during thoracic surgery was reduced to almost ¼, thus, it can be applied while retaining the physiological benefits of non-intubated procedures, and furthermore, this procedure represents a real alternative in terms of both the kinetics of the inflammatory response and the perioperative complications. It is important to note that, although the concept is not new, the technical implementation is novel, so further research is needed to determine the effectiveness of the procedure.

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I.

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ORIGINAL ARTICLE

Spontaneous ventilation combined with double-lumen tube intubation in thoracic surgery

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Abstract

Objective We present the combination of spontaneous ventilation and double-lumen tube intubation in thoracic surgery.

Methods At the beginning of the procedures, the patients with a body mass index of ≤ 30 were relaxed for a short time, and a double-lumen tube was inserted. After the utility incision or thoracotomy, the vagus nerve was blocked (in right side in the upper mediastinum; in left side in the aorto-pulmonary window) with 3–5 ml of 0.5% bupivacaine. The patients had a bispectral index of 40–60. After the short relaxation period, the patients were ventilating spontaneously without any cough during the manipulation.

Results Between March 10 and September 18. 2020, 26 spontaneous ventilation combined with intubation surgeries were performed: 19 uniportal video-assisted thoracic surgery (15 lobectomies, 1 segmentectomy, and 3 wedge resections) and 7 open (5 lobectomies and 1 sleeve segmentectomy, 1 wedge resection). The mean mechanical and spontaneous one-lung ventilation time was 25.5 (15–115) and 73.3 (45–100) minutes, respectively. In 2 cases conversion to relaxation were necessary (2/26; 7.7%). The mean maximal carbon dioxide pressure was 52.3 (38–66) Hgmm and the mean lowest oxygen saturation was 93.8 (86–99) %. Breathing frequency ranged between 10–25/minute. The mean surgical times was 83.3 (55–130) minutes.

Conclusions Spontaneous ventilation combined with intubation in video-assisted thoracic surgery or open resections is a safe method in selected patients. It can reduce the mechanical one-lung ventilation period with 76.6% and give safe airway for spontaneous ventilation thoracic procedures.

Keywords Spontaneous ventilation · Intubation · Video-assisted thoracic surgery · Non-intubated

Introduction

Video-assisted thoracic surgery (VATS) combined with spontaneous ventilation (SV) provides the least potential stress and fewer complications [1, 2]. In the case of relaxation and mechanical ventilation, the immunological advantages of spontaneous ventilation surgery (the lower negative impact on lymphocytes and natural killer cells) are lost [3], and the disadvantages of the mechanical one-lung ventilation (OLV), such as alveolar damage (injury of the endothelial glycocalyx and capillary shear stress, oxidative stress, and edema formation) may develop [4, 5]. The longer the mechanical OLV, the more severe the oxidative stress [6].

From an anesthesiologist's perspective, several trials combined spontaneous ventilation with the intubation to prevent the negative side effects of relaxation and mechanical ventilation; however, none of them were fully successful [7]. To tolerate an endotracheal tube as a foreign body in the trachea without cough, the cough reflex must be stopped by blocking the vagus nerve [8]. Although the vagal block is well known in SV surgery [9], the combination of the vagus blockade and intubation is not published in the literature.

We developed a new technique, spontaneous ventilation combined with double-lumen tube intubation (SVI), to reduce the length of the mechanical OLV and provide a 'safe airway' for the SV thoracic surgeries. To the best of our knowledge, this is the first study to report this kind of surgical operation.

József Furák and Zsolt Szabó contributed equally to this work.

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Methods

Patients

Between March 10 and September 18. 2020, 26 SVI surgeries were performed (14 male; 12 female) with a mean age of 65.2 (43–80) years (Table 1.) The follow-up period lasted until September 29, 2020.

The pre-operative pulmonological examination was the same as in a VATS, non-intubated thoracic surgery (NITS), or normal open cases, and patients were not selected based on their comorbidities (Table 1). The SVI procedure and its risks were explained to each patient. Additional informed consent was obtained from all patients for which identifying information is included in this article If the patients agreed to this method, written informed consent was obtained. Patient data were retrieved retrospectively from our medical record system (Medsolution) and the patients' personal data were secured. The Ethical Committee of the Human Investigation Review Board in the University of Szeged approved this study (permission no.: 4703/2020.01.20).

Table 1 Surgical parameters of the SVI patients

	All cases $n=26$	VATS SVI $n=19$	Open SVI $n=7$
Male/female	14/12	9/10	5/2
Age	65.2 (43–80)	63.7 (43–80)	69.1 (56–75)
BMI	26.8 (19–35)	26.4 (19–32)	28 (24–35)
CCI	5.4 (2–10)	5.4 (2–10)	5.5 (4–7)
FEV1 (%)	86.2 (44–126)	87.7 (44–113)	82.7 (57–126)
Surgical time (minutes)	83.3 (55–130)	81.0 (55–110)	89.2 (60–130)
Drainage time (days)	2.4 (1–10)	2.2 (1–10)	2.8 (1–6)
Right upper lobectomy	2	0	2
Right middle lobectomy	2	2	0
Right lower lobectomy	9	7	2
Left upper lobectomy	4	3	1
Left lower lobectomy	3	3	0
Segmentectomy	2	1	1
Wedge resection	4	3	1

CCI Carlson Comorbidity Index, *BMI* body mass index, *FEV1* Forced exspiratory volume in 1 s, *SVI* spontaneous ventilation combined with intubation, *VATS* video-assisted thoracic surgery

Patient selection

The inclusion criteria are similar to the indications for the NITS, however, several exclusion criteria of the NITS (suspicion of difficult intubation, full anticoagulation, reflux disease, cardiac instability, mental problem) can be omitted [5]. In our current practice, patients with body mass index (BMI) of < 30 are indicated for SVI.

Oncologically, the patient's selections for VATS SVI was performed as for normal VATS. According to a consensus meeting recommendations, patients without advanced stage lung cancer (< 7 cm, N0, and N1 patients) were scheduled [10]. For open SVI, we accepted simple cases, i.e. extended resections, and patients who underwent neoadjuvant treatment were excluded.

Surgical procedure: VATS SVI

Regarding the surgical steps, the same VATS uniportal method was performed as we published in our VATS NITS paper [11], but at the beginning of the surgery for a short time, the patients were relaxed and intubated with a double-lumen tube. At the incision site of the fifth intercostal space in the middle axillary line, 2% lidocaine (5 mg/kg) was administered. After entering into the thoracic cavity, vagus and intercostal nerve blockades were performed. The total amount of bupivacaine used was 0.5 ml/kg: 3–5 ml of 0.5% bupivacaine was administered near the vagus nerve (right side in the upper mediastinum; left side in the aortopulmonary window) (Fig. 1.) and 4–5 ml near each intercostal nerve between 2 and 5, close to the spine (paravertebral blockade). Due to this local anaesthesia, if the relaxation stopped, the patient could spontaneously ventilate without

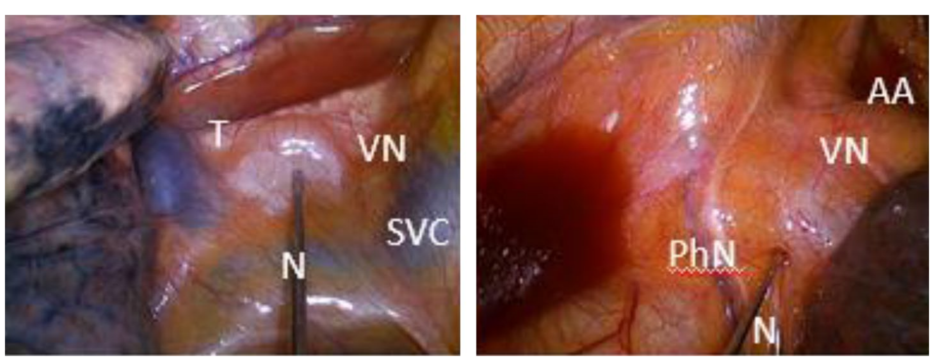

Fig. 1 Vagus blockade on right and left sides. *AA* aortic arch, *N* needle for injection, *PhN* phrenic nerve, *SVC* superior vena cava, *T* trachea, *VN* vagus nerve

cough, and the mediastinal and diaphragmatic movements did not disturb during the resection. After the resection, the chest was drained and closed. The types of VATS SVI resections are listed in Table 1.

Surgical procedure: open SVI

In open cases, the patient was relaxed for a short time and intubated with a double-lumen tube. During the thoracotomy, an intercostal nerve blockade was performed using 4–5 ml of 0.5% bupivacaine between the 3.–6. ribs. After entering into the chest cavity, the same vagus nerve blockade was performed as in VATS SVI. After stopping the relaxation and resuming spontaneous breathing, all resections and mediastinal lymph node dissections could be performed. After the resection, the chest was drained and closed. The types of open SVI resections are presented in Table 1.

Anaesthesiology

The standard monitoring (ECG, O_2 saturation, and depth of anaesthesia monitoring by bispectral index (BIS, Medtronic Vista) and invasive blood pressure measurements were performed. Preoperatively, midazolam and fentanyl were administered. Anaesthesia was induced and maintained with propofol, administered via the target-controlled infusion titrated to keep the BIS between 40 and 60, according to recommendations [9].

After the induction, the gold standard intubated technique for muscle relaxation and mechanical ventilation was performed. The difference in the period of muscle relaxation was determined using mivacurium instead of rocuronium, and the spontaneous breathing was allowed after eliminating the muscle relaxant. This ensured adequate time to perform vagal blockade to prevent cough reflex. After the return of spontaneous breathing, the patient did not cough due to regional blockades despite the double-lumen tube in the trachea. The oxygen saturation and pCO_2 were kept within normal or close to the normal range with higher FIO_2 (40–100%) with 3–5 positive end-expiratory pressure in the dependent lung, which was easily measured through the double-lumen tube.

All of our patients have been observed in the post anaesthesia care unit for at least 2 h and until their visual analogue scale (VAS) went under 3. Oxygen was administered all of them via face mask usually with 2–4 l/min to exceed 94% of oxygen saturation and 88% for patients with severe chronic obstructive pulmonary disease (COPD). Oxygen support was carried on with the same algorithm in the ward for 2–3 h. None of our patients required a higher level of oxygen support or advanced non-invasive respiratory support in the post anaesthesia care unit and later in the postoperative period.

Some patients, during the operation had hypotensive periods that might have been caused by the vagal blockade and its negative chronotropic effects. According to our protocol, we give 50–100 mcg phenylephrine in divided dose if systolic blood pressure goes down below 100 mmHg or decreases more than 25% or the mean arterial pressure is less than 60 mmHg.

Inflammatory response

On the preoperative-, and first- and second postoperative days (POD1; POD2) the inflammatory response to SVI was measured among six patients with leucocyte and lymphocyte counts, and level of C-reactive protein.

Results

Surgery

No perioperative mortality occurred. There were 2 conversions from SVI to relaxation method: in a patient, who underwent open SVI left sleeve 6 segmentectomy because of a 1 cm endobronchial lesion in the origin of the left 6. segmental bronchus, due to the preparation and anastomosis suture, and in one other patient who underwent a conversion from SVI VATS to relaxation open lobectomy due to a bleeding. Therefore, the conversion rate from SVI to relaxation is 7.7% (2/26). Without changing from SVI to relaxation two additional conversions occurred. With keeping the SVI method, VATS approach was changed to open surgery due to oncological/technical reasons.

After terminating the relaxation, the patients breathe spontaneously, the diaphragm and the mediastinum movement were not disturbing, and surgeries were the same as in NITS cases. Perioperative data are presented in Table 1. The surgical and drainage times were 83.3 (55–130) minutes and 2.4 (1–10) days, respectively. The length of postoperative hospital stay was 4.1 (2–7) days. One patient went home with Heimlich-valve on the 7^{th} postoperative day. The mean number of the removed mediastinal lymph nodes is 9.8 (1–22). 16 primary lung cancers, 4 metastasis and 6 benign lesions were removed (Table 2.). In the 16 lung cancer cases, the mean number of the removed mediastinal lymph nodes is 10.1 (1–22): in a patient with removed brain metastasis from lung cancer, an SVI VATS wedge resection with hilar lymph node dissection and mediastinal sampling with 1 subcarinal mediastinal lymph node removal was performed (pT1aN1M1b). For the patient with 22 removed mediastinal lymph nodes, an open SVI right lower lobectomy was performed after neoadjuvant treatment (ypT1bN0) Data of the 20 patients who underwent lobectomies were presented in the Table 3.

Table 2 Pathological results of the SVI resections

	All cases $n=26$	VATS SVI $n=19$	Open SVI $n=7$
Lung cancers	$n=16$	$n=10$	$n=6$
Adenocarcinoma	7	6	1
Squamous cell carcinoma	6	2	4
Large cell neuroendocrine carcinoma	1	1	0
Carcinoid (typical)	1	1	0
Carcinosarcoma	1	0	1
Lung metastases	$n=4$	$n=4$	$n=0$
Colorectal carcinoma metastasis	2	2	0
Melanoma metastasis	1	1	0
Urinary bladder carcinoma metastasis	1	1	0
Benign lesion	$n=6$	$n=5$	$n=1$
Tubecrulosis	1	1	0
Actinomycosis	1	1	0
Inflammation	2	1	1
Hamartochondroma	1	1	0
Sarcoidosis	1	1	0
Stages of the lung cancers	$n=16$	$n=10$	$n=6$
IA	7	4	3
IB	2	2	0
IIA	1	1	0
IIB	2	2	0
IIIA	3	0	3
IVA (with removed brain metastasis)	1	1	0

SVI spontaneous ventilation combined with intubation, *VATS* video-assisted thoracic surgery

Table 3 Results of the lobectomies in the SVI patients

	VATS SVI lobectomies $n=15$	Open SVI lobectomies $n=5$
Male/female	8/7	4/1
Age	62.4 (46–79)	69.6 (56–75)
BMI	25.6 (22–32)	28 (24–35)
CCI	4.7 (2–8)	5.2 (4–7)
Surgical time (minutes)	85.6 (55–110)	86 (60–105)
Drainage time (days)	2.2 (1–10)	2.4 (1–4)
Postoperative length of hospital stay (days)	3.7 (2–7)	4.8 (4–6)
FEV1 (%)	88.7 (78–113)	74 (57–104)
Right upper	0	2
Right middle	2	0
Right lower	7	2
Left upper	3	1
Left lower	3	0

BMI body mass index, *CCI* Carlson Comorbidity Index, *FEV1* Forced exspiratory volume in 1 s, *SVI* spontaneous ventilation combined with intubation, *VATS* video-assisted thoracic surgery

None of our patients were observed in the ICU, and all of them were transported to the ward after a short observation in the post anaesthesia care unit. All the postoperative periods were uneventful, the patients could cough, and none of them had a fever or required bronchial cleaning. All the postoperative chest X-ray reports of all patients, before and after the chest tube removal were studied, and if any of them mentioned any size of atelectasis/dystelectasis, infiltration, pneumothorax or pleural fluid in the chest, the results were respected as an abnormal finding. Of the 26 patients, in 7 cases dystelectasis, in 0 case atelectasis, in 1 case infiltration, in 13 cases pneumothorax and in 13 cases pleural fluid were mentioned. None of the above-mentioned abnormalities required surgical interventions, such as drainage or puncture. There were 2 prolonged air leak cases (7.7%) (6 and 10 days). No readmission or intervention was necessary for the follow-up period.

Anaesthesiology

About 5–10 min after the vagus nerve blockade, the blood pressure decreased; however, only 9 of 26 (34%) patients were supported with phenylephrine. The remaining 15 patients had only temporary hypotension.

In the 26 cases, the mean mechanical one-lung ventilation time was 25.5 (15–115) minutes, and thereafter, the mean spontaneous one-lung ventilation time was 73.3 (45–100) minutes, so the mechanical OLV time was reduced with 76.6% (50–87). In 92.3% of patients (24/26), only the initial relaxation drug for the intubation was required (Table 4.)

Hypercapnia was kept in a tolerable range, without any complication such as respiratory acidosis, right ventricular failure, or increased intracranial pressure. The mean maximal pCO_2 was 52.3 (38–66) Hgmm and the mean lowest oxygen saturation was 93.8 (86–99) %. (Table 4.)

The breathing frequency could be maintained for 10–25/min with opioid administration. Postoperatively, all patients were extubated without using an acetylcholinesterase inhibitor and after an hour of observation in the recovery room, they were transported to the general ward.

None of them required re-intubation.

Inflammatory response

During the POD1 leucocyte count increased with 11%, however, on the POD2 it dropped (88%) below the preoperative level. Very limited change was seen in the lymphocyte count: on the POD1 it was almost the same as preoperatively (98% vs 100%), however, on the POD2 it was higher than the preoperative level (119%). Compared to baseline measures, on POD1 CRP level elevated to 231%, however, it did not significantly change on POD2 (235%). (Table 5.)

Discussion

The SVI procedure was developed as the combination of the NITS/spontaneous ventilation thoracic surgery and intubated thoracic procedures. The key point of the SVI is the vagus nerve blockade with bupivacaine [9, 11]. With this local anaesthesia, the function of the vagus is blocked, and the cough reflex is suspended during the lung resection [8]. If the patient came out from the initial relaxation administered due to intubation, they can breathe spontaneously without any cough, and from this point, the surgery is the same as in NITS cases. It was not necessary to repeat the bupivacaine for the vagus blockade during the 73.3 min mean spontaneous one-lung ventilation time.

Table 4 Anaesthesiologic parameters during SVI surgeries

Pulse/minute		Mech OLV (minute)	Spontan OLV (minute)	Oxygen saturation %		pCO2 Hgmm		Breath/minute	
Min	Max			Min	Max	Min	Max	Min	Max
66.4 48–90	84.9 65–120	25.5 15–115	73.3 45–100	93.8 86–99	99.3 98–100	39.1 28–50	52.3 38–66	12.1 10–15	18.3 14–25

SVI spontaneous ventilation combined with intubation, *Max* maximal, *Mech* Mechanical, *min.* minimal, *OLV* one-lung ventilation, *pCO2* carbon dioxide pressure, *spontan.* spontaneous

Table 5 Inflammatory parameters during SVI surgeries

	Preoperative $n=6$	Postoperative 24 h $n=6$	Postoperative 48 h $n=6$
Leucocytes (10^9/L)	10.9 (100%) (7.1–13.8)	12.1 (111%) (10.1–15.9)	9.6 (88%) (8.3–10.4)
Lymphocytes (10^9/L)	1.31 (100%) (0.38–2.25)	1.29 (98%) (0.87–1.7)	1.56 (119%) (1.07–1.82)
CRP (mg/L)	29.6 (100%) (18.2–44.0)	68.6 (231%) (61.1–72.9)	69.7 (235%) (49.7–82.0)

CRP C-reactive protein, *L* liter, *VATS* video-assisted thoracic surgery, *SVI* spontaneous ventilation combined with intubation

Local anesthesia in thoracic surgery is not a new method. Ossipov [12] presented 3265 thoracic interventions under local anesthesia. He performed an extended infiltration in the following sequence. First, he performed vagosympathetic blockade on the neck and then wide local infiltration in the skin incision, followed by infiltration under the scapula, blockade of the Th2-Th9 intercostal and sympathetic nerves, and finally, the same vagus blockade that is used in the NITS procedures [9] and in the SVI.

Any risk of SVI can be temporary if it occurs. In the period of spontaneous one-lung ventilation, a double-lumen tube is located in its properly placed, giving chance to all interventions and medications as the situation requires.

If any surgical difficulty or complication occurred, the patient could be relaxed and the surgery would continue under a mechanical one-lung ventilation, as a 'normal thoracic surgery', and the uncomfortable conversion procedure (0–9% of the cases) [13] from NITS to intubation is prevented with the SVI. Moreover, as demonstrated, the relaxation was not absolutely necessary for thoracotomy: six open thoracotomies were performed with the SVI method.

Regarding postoperative results, mean operative- and drainage time was shorter after our SVI VATS lobectomy cases compared to AlGhambi's study on non-intubated and intubated/relaxed VATS lobectomies: 85.6, 130.9 and 146.0 min and 2.2, 5.6 and 5.4 days, respectively [14]. In our study, the mean postoperative length of hospital stay after VATS SVI and open SVI lobectomies were 3.7 and 4.8 days, which is shorter than the same data in the above-mentioned study after non-intubated and intubated/relaxed VATS lobectomies: 6.9 and 7.6 days [14].

In VATS NITS/SV patients, a disturbing mediastinal and diaphragmatic movements were the most common complication requiring intubation, occurring in 7% and 4% of a meta-analysis article in Shi et al. [15]. In our short series of SVI, this kind of disturbing movement rate was 1/26 (2.8%) requiring conversion from SVI to the relaxation and permanent mechanical one-lung ventilation (4 weeks later a smooth SVI VATS lobectomy was performed on the other side for this patient). The other conversion to relaxation performed due to a bleeding, from a segmental artery demanding thoracotomy. However, other 92.3% did not require additional relaxation after the induction. We had no conversion from SVI to relaxation due to oncological reason (only the previously mentioned technical reason and bleeding). The 2 conversion from VATS SVI to open SVI happened due to oncological/technical reason without any complication; however, the patients required 200 and 400 micg of phenylephrine as the circulation support. The postoperative periods were smooth.

If any anaesthesiologic difficulties occur, additional oxygen support, air-way cleaning, or relaxation can be performed in seconds due to the double-lumen tube located in the trachea and main bronchus, and all problems can be managed on a 'traditional way'. We have seen the same hypercapnia and hypoxia during the SVI as in patients with NITS [15]; however, it was easy to compensate with higher FIO_2 through the double-lumen tube.

At 5–10 min after the vagus blockade, the blood pressure was reduced, but only in 34% of the patients required circulation support. In the remaining 66%s, the self-regulation of the circulation normalized the blood pressure.

With the SVI, we could reduce the period of mechanical OLV by 76.6%. Misthos et al. reported that mechanical OLV for longer than 1 h could be a reason for the severe oxidative stress [6]. The OLV lung plays a major role in oxidative stress [3] and in SVI cases the reduced mechanical OLV time may produce less changes in lung physiology. In our cases, the tendency of inflammatory response to SVI was similar to the data of Mineo [3]. Among our patients, mean leucocyte count elevated on the POD1 to 111%, which was 138% among non-intubated and intubated VATS cases in Mineo's reports. On the POD1, mean lymphocyte count decreased to 98% among our patients, which data showed the same pattern with 92% and 83% in non-intubated and intubated cases of Mineo [3]. It seems, that the inflammatory response to SVI may be very close to the response after non-intubated procedures. Although in the study of Leaver, changes in lymphocyte count were not detected on POD1 and the highest deviation from baseline was detected on POD2 [16], our study with SVI cases showed that the leucocyte- and lymphocyte counts on POD2 are closer to baseline after the highest deviation seen on POD1.

In our study, the CRP levels doubled on POD1 and did not show significant elevation on POD2. But in the study of Dongel, patients undergoing thoracotomy and intubation with relaxation, CRP levels elevated until reaching 425% on POD1 and 353% on POD3, compared to baseline level [17].

With the SVI procedure, the indications of the spontaneous ventilation thoracic procedures can be more widespread, and because of the safe airway with the double-lumen tube, several previous exclusion criteria of the NITS can be accepted as an indication criteria for SVI: abnormal airway anatomy and anticipated difficult intubation, reflux disease, risk of blood or other fluid in the airway, mental problem [5, 9]. More patients can be selected for spontaneous ventilation surgery.

Conclusion

The SVI technique is a safe method for VATS and open thoracic surgeries for patients with BMI of < 30. There are less exclusion criteria for SVI than for NITS. The SVI could reduce the period of mechanical OLV with 77%. No complications were observed in patients during the SVI surgery because of the safe airway with a double-lumen tube that provides chance for all anaesthesiologic procedures as it is in normally relaxed patients, and the conversion can be very simple. After the vagus blockade, no cough occurred at all despite the double-lumen tube location in the trachea and main bronchus. Regarding leucocyte- and lymphocyte counts, the inflammatory response in SVI cases is very similar to the effect of non-intubated procedures.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest: FJ has no conflict of interest; SzZs has no conflict of interest.

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II.

Case Report

Non-intubated anaesthetic technique in open bilobectomy in a patient with severely impaired lung function

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Abstract: General anaesthesia has been the most commonly used method for almost all types of thoracic surgery. Recently, there has been a growing interest in non-intubated anaesthetic techniques. The rationale being, to prevent complications related to general anaesthesia and positive pressure ventilation such as barotrauma or ventilation-perfusion mismatch. We present a case with severely impaired forced expiration volume (26%), carbon monoxide diffusing capacity (26%) and VO_2max (13.9 mL/kg/min). According to current guidelines, this patient was suitable to undergo one-lung ventilation only with high risk of morbidity and mortality. Therefore, we chose the non-intubated technique for thoracotomy. Oxygenation was satisfactory throughout, the patient remained hemodynamically stable and the operation was uneventful. Oxygen supplementation was stopped from day 2 and he was discharged on day 7. To our knowledge, this is the first case report where a planned non-intubated method was applied for thoracotomy, and our results suggest that it might be a feasible and safe approach for open thoracotomy in difficult cases where severely impaired lung function indicates that one lung ventilation may carry significant risks.

Keywords: Non-intubated thoracoscopy; thoracotomy; impaired lung function; serratus block; lobectomy

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Introduction

Minimally invasive surgical and anaesthetic techniques have become increasingly popular and undergone major developments over the last decade. One of these is non-intubated thoracic surgery (NITS), especially for video-assisted thoracic surgery (VATS) (1). This technique enables the maintenance of spontaneous ventilation throughout the operation, which has several theoretical advantages as compared to intermittent positive pressure ventilation (IPPV), including the avoidance of baro-, and volu-trauma (2). This may become even more important in patients with long standing history of chronic obstructive pulmonary disease (COPD), which requires particular protection from the harmful effects of IPPV. In the current case report we present the perioperative course of a patient scheduled for open bilobectomy.

Case presentation

A 73-year-old man (height: 178 cm, weight: 62 kg, BMI: 19.6) visited his local hospital due to extensive weight loss of more than 20 kg over 2 months and repeated serious hemoptysis. His past medical history included coronary artery bypass operation after an acute myocardial infarction, aortic abdominal aneurysm and hypertension. He was also a heavy smoker with two packs per day for 50 years.

During the course of routine investigations, the chest computed tomography (CT) indicated bilateral emphysema and a 4.0 cm × 2.8 cm irregular solid tumour, which compressed the right main bronchus (*Figure 1*). The lower lobe was atelectatic, and the tumour infiltrated also the intermedial bronchus. Tissue mass was found in the right lower lobe and the intermedial bronchus with bronchoscopy and cytology showed basaloid adenocarcinoma (p40 positive,

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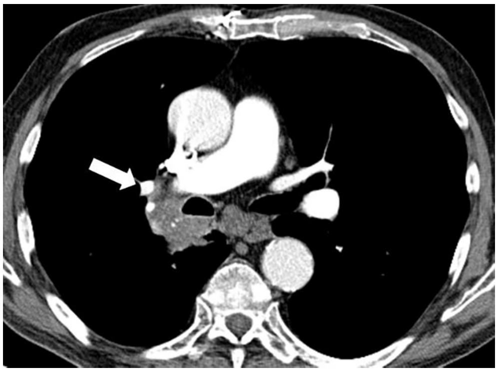

Figure 1 Preoperative chest CT scan. The white arrow indicates the tumour compressing the right main bronchus.

CK7 and TTF1 negative), which was later diagnosed—after surgery—as carcinoma epidermoides cornescens with peribronchiolar metastatic lymph nodes. The bone scintigraphy did not show any metastases. The results of pulmonary function test indicated severely impaired lung function with the forced expiratory volume in 1 second of 27%, the Tiffeneau index of 43% and the carbon monoxide diffusing capacity (DLCO) of 26%. The maximal oxygen consumption (VO_2max) was 13.9 mL/kg/min. However, the calculated postoperative DLCO—preopDLCO × [1− (total number of segments to be resected/total number of lung segments)]—worked out of 19.16% and the predicted postoperative VO_2max—preopVO_2max × [1− (total number of segments to be resected/total number of lung segments)]—was 10.24 mL/kg/min indicating high postoperative risk for cardio-respiratory complications (3,4).

As we have gained substantial experience with NITS over the last year (more than 80 cases so far) with good results, we decided to choose this approach in order to avoid intubation and positive pressure one lung ventilation. Once this decision was made and discussed with the patient he was then scheduled for NITS open bilobectomy because of the previous frequent massive hemoptysis and due to the location and the extended infiltration of the tumour.

On arriving at the operating room standard monitoring of non-invasive blood pressure, electrocardiogram (ECG) and pulse oximetry was complemented with bispectral index (BIS) analysis. For continuous arterial blood pressure measurements and arterial blood sampling an indwelling arterial catheter was placed in the left radial artery. The patient was sedated with midazolam, fentanyl and asked to turn onto his left side. Anaesthesia was induced and maintained with propofol, which was administrated via target-controlled infusion titrated to a BIS of 40 to 60 throughout surgery. When the target BIS was achieved the airway was secured with a size 5.0 laryngeal mask. Spontaneous breathing was maintained throughout. Oxygen and air mixture was supplemented via T-piece at a fraction of inspired oxygen (FiO_2) of 50% starting at flow rate of 6 L/min. FiO_2 had to be increased to 100% before the resection. End tidal CO_2 and FiO_2 was continuously monitored via a side stream gas sampling, with the sampling line inserted into the laryngeal mask through an elastic seal on the T-piece.

Surgery

After skin infiltration with 2% lidocaine, the utility incision for VATS exploration at the 5th intercostals space was performed, followed by the 2–6th intercostal and vagal nerve infiltration above the azygos vein with 20 mL 0.5% bupivacaine under direct vision. Performing the block is facilitated by the total collapse of non-dependent lung, which takes place within a few minutes after opening the chest. On exploration the lower lobe seemed atelectatic and the tumour invaded the intermedius bronchus till beginning of the upper lobe bronchus containing the middle lobe bronchus as well, therefore the previously planned anterolateral thoracotomy and lower bilobectomy was performed. The intermedius bronchus was closed with hand sutures, at the level of the upper lobe. A mediastinal radical lymphadenectomy was also performed. The thorax was closed over a chest drain and a catheter was placed by the surgeons for continuous serratus anterior blockade in order to complement paravertebral blockade as our standard practice in NITS for postoperative pain relief.

Regarding anaesthesia, the NITS technique was well tolerated, hence conversion to endotracheal intubation was not required. The patient remained hemodynamically stable during the whole operation. Respiratory acidosis occurred (*Table 1*), but it remained in the tolerable range and it did not cause any respiratory distress to the patient. He maintained an oxygen saturation (SpO_2) of 97–99% with a respiratory rate of 18–22/min.

After the surgery was completed the patient was woken up then asked to cough and breathe deeply to re-expand the collapsed lung. Then he was transferred to the recovery room. Soon after arrival the first blood gas was taken, which showed that his respiratory acidosis was resolving. After

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Table 1 Arterial blood gas results in the perioperative period

Blood gas parameters	T_{Pre}	T_{BR}	T_{AR}	T_{Post}	T_{RR}	T_D	T_W
FiO_2 (%)	21	100	100	40	40	40	21
pH	7.434	7.195	7.153	7.243	7.294	7.325	7.357
pCO_2 (mmHg)	32	64	67	49	40	38	35
pO_2 (mmHg)	68	217	325	118	182	204	62
BE (mmol/L)	–3.6	–4.7	–6.1	–6.7	–7.1	–6.0	–5.7
HCO_3 (mmol/L)	22	24	23	21	19	19	19
Lactate (mmol/L)	2.0	1.0	1.1	1.3	1.9	2.6	3.0
SaO_2 (%)	95	99	99	97	99	99	92
p50 (mmHg)	24	39	48	31	24	35	26
Haemoglobin (g/dL)	10.4	10.0	10.5	11.0	11.1	10.8	11.1

T, time of sampling; Pre, preoperatively before induction of anaesthesia; BR, before lung resection; AR, after lung resection; Post, at the end of surgery; RR, recovery room; D, discharge from recovery; W, on the ward at 8 p.m.; BE, base excess.

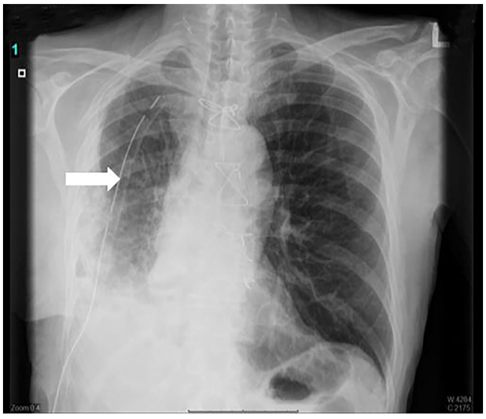

Figure 2 Postoperative chest X-ray on day 3. The white arrow indicates the chest drain.

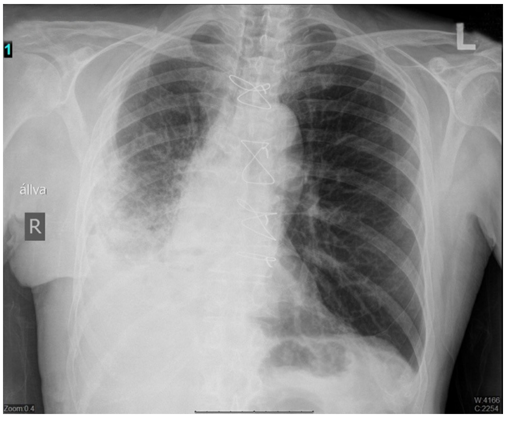

Figure 3 Chest X-ray on discharge. See text for explanation.

one hour he drank water and in bed mobilisation was also started. He was discharged from recovery with stable vital signs 5 hours after the operation.

Postoperative pain was well controlled by the serratus anterior blockade with 0.5% bupivacaine infused at 5 mL/h, which was also supplemented with intravenous or oral paracetamol and tramadol as indicated by visual analogue scores (VAS) of more than 4. The VAS varied between 1 to 5 during the first postoperative day. The patient's mobilisation was continued and the chest tube was removed on postoperative day 5 (*Figure 2*) and he has transferred to a pulmonology ward on day 7 (*Figure 3*), fully mobilised and without any oxygen demand after day 2.

Discussion

Minimally invasive surgical and anaesthetic techniques are becoming more and more popular even for major surgery. In thoracic surgery, general anaesthesia with endotracheal intubation and one-lung ventilation (OLV) has been the gold standard technique for decades. However, minimally invasive thoracic surgery has opened up new frontiers, which renders the need for the development of novel anaesthetic techniques.

Numerous type of thoracic procedures can be carried out with non-intubated techniques. Patients for NITS should be selected carefully but most of the exclusion criteria are relative contraindications depending on the team's experience (5) (*Table 2*). It is important to note that instead

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Table 2 Advantages and risks of intubated and non-intubated thoracic surgery

Properties	Intubated thoracic surgery	Non-intubated thoracic surgery
Advantages	Secured airway	Avoidance of intubation and one lung ventilation
	Quiet operation field	Avoidance of positive pressure ventilation
	Total control of tidal and minute volumes	Avoidance of muscle relaxants
		Potentially better V/Q matching
		Better lung collapse (easier for surgeons)
Disadvantages	Residual inflation in the operated lung	Maintained diaphragm movement
		Mediastinal movement
Risks	Intubation related complications	Hypoxemia and hypercapnia
	Positive pressure ventilation associated complications	Aspiration
	Residual muscle relaxant effect	Increased technical difficulties (surgical and anaesthetics too)
		Conversion to tracheal intubation and lung separation

Table 3 The exclusion criteria used in our institute

Exclusion criteria in non-intubated VATS major pulmonary resections
Patient with expected difficult airway
Obesity (body mass index >30)
Hypoxaemia (PaO_2 <60 mmHg) or hypercarbia (pCO_2 >50 mmHg) on room air
Coagulopathy (international normalized ratio >1.5)
Persistent cough or high amount of airway secretion
Haemodynamically unstable patient
Elevated risk of gastric regurgitation, GERD
Central hypoventilation syndrome, sleep apnoea syndrome
Neurological disorders: seizure, raised ICP, intracranial mass, unable to cooperate
Procedures requiring lung isolation to protect the contralateral lung from contamination
Any contraindications for use of regional anaesthetic technique
Extensive pleural adhesions

GERD, gastroesophageal reflux disease; ICP, intracranial pressure; VATS, video-assisted thoracic surgery.

of sedation—a technique most often used in previous reports (6)—we aimed for surgical depth of anaesthesia (confirmed by BIS monitoring), hence insertion of laryngeal mask could be performed, which provided airway patency and safer control of the airway.

General anaesthesia with one-lung IPPV also has several complications, which can increase perioperative morbidity and even mortality (7). Mechanical ventilation itself might cause pressure induced lung injury, damage caused by lung overdistension, shear stress of repetitive opening, closing of alveoli and increased inflammatory response due to elevated release of pro-inflammatory mediators (8,9).

In a mechanically ventilated patient, OLV in lateral decubitus position produces ventilation/perfusion (V/Q) mismatch, because the non-dependent lung is perfused but not ventilated. In a spontaneously breathing patient theoretically, there is a better match between ventilation and perfusion due to the more efficient diaphragmatic movements. During OLV the non-dependent lung is not ventilated, its perfusion decreases rapidly due to hypoxic pulmonary vasoconstriction (HPV), which is important to maintain acceptable V/Q results in the dependent lung (10). However, it is often the case that due to lung tissue gravity and surgical manipulations significant right to left intrapulmonary shunt occurs. The effectivity of HPV is influenced by the lung volume. If the delivered tidal volumes and intrapulmonary pressures overstretch the ventilated alveoli, blood flow may be diverted to the non-ventilated alveoli attenuating the HPV response and leading to increased V/Q mismatch and worsening hypoxemia (11).

In non-intubated patients, once the surgical pneumothorax is present, the negative pressure is lost

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and paradoxical breathing pattern occurs (12). During inspiration the normal atmospheric pressure in the open thorax pushes the mediastinum towards the dependent hemithorax and on expiration a reverse phenomenon occurs. Perfusion to the dependent lung is better as compared to OLV due to the low or negative pressure in this lung. Intrapulmonary shunt may also be reduced due to the intact diaphragmatic movements.

One of the possible complications of this technique is that after resection of the lung, the airway remains open until the bronchi are sutured. During this phase blood can enter into the airways and may cause aspiration pneumonia in the postoperative period. Therefore, to keep the airways clean requests delicate handling of the lung by the surgeon, and the anaesthetist can also perform fiberoptic bronchoscopy via the laryngeal mask if needed.

Hypercapnia is a common phenomenon during NITS procedures, but this is often present during OLV as well. During NITS, alveolar gases may communicate between the dependent and non-dependent lungs while surgical pneumothorax is present, causing carbon dioxide rebreathing causing hypercapnia (13). Another factor is hypoventilation, which is due on the one hand to the collapsed operated lung and on the second hand to anaesthesia related central respiratory depression. Fortunately, accumulation of CO_2 is not necessarily harmful in the perioperative period (13,14). $PaCO_2$ levels up to 70 mmHg are likely to be well tolerated by most patients. However, in patients with pulmonary hypertension, severe cardiac comorbidities or in case of increased intracranial pressure, acute hypercapnia should be avoided.

One of the most important message of this report is the risk stratification. According to our experience NITS is a safe approach, but the selection of patients is important. Our general exclusion criteria are summarized in *Table 3*. In this particular case, although preoperative VO_2max of 13.9 mL/kg/min is regarded as borderline by current guidelines, but the calculated postoperative DLCO and VO_2max indicated high postoperative risks of complications. To avoid it we decided to proceed with the NITS technique, taking into consideration all of the potential benefits of maintained spontaneous breathing.

Finally, we also have a "contingency plan" for unforeseen events during the NITS procedures, including fiberoptic intubation via the laryngeal mask and lung separation with a bronchial blocker. Fortunately, there was no need for any rescue interventions in this case.

Conclusions

In the current case report we presented a high-risk patient with severely impaired lung function in whom NITS was applied successfully even during open thoracotomy. To our knowledge this is the first case report to show that NITS is a feasible and safe approach in open thoracotomy.

It is expected that the less invasive non-intubated techniques will gain ground in the future in thoracic surgery for most thoracoscopic interventions but may also become a feasible less invasive alternative in certain procedures requiring thoracotomy. Our case report may serve as some reassurance for those who are willing implement this technique in their practice.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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III.

Original Article

Conversion method to manage surgical difficulties in non-intubated uniportal video-assisted thoracic surgery for major lung resection: simple thoracotomy without intubation

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Background: The major limitations of widespread use of non-intubated thoracic surgery (NITS) is the fear of managing complications. Here we present our practice of converting from uniportal video-assisted thoracic surgery (VATS) NITS to open NITS in cases of surgical complications.

Methods: The study period was from January 26, 2017, to November 30, 2018. Total intravenous anesthesia was provided with propofol guided by bispectral index, and the airway was maintained with a laryngeal mask with spontaneous breathing. Local anesthesia with 2% lidocaine at the skin incision, and intercostal and vagus nerve blockades were induced using 0.5% bupivacaine. For conversion with surgical indications, a thoracotomy was performed at the incision without additional local or general anesthetics.

Results: In 160 complete NITS procedures, there were 145 VATS NITS and 15 open NITS (9 conversions to open NITS and 6 intended NITS thoracotomies). In the 15 open NITS cases (2 pneumonectomies, 1 bilobectomy, 1 sleeve lobectomy, 7 lobectomies, 3 sublobar resections, 1 exploration), the mean operative time was 146.7 (105–225) and 110 (75–190) minutes in the converted and intended open NITS groups, respectively. There were no significant differences between systolic blood pressure (P=0.316; 95% CI, −10.469 to 3.742), sat O2% (P=0.27; 95% CI, −1.902 to 0.593), or propofol concentration in the effect site (P=0.053; 95% CI, −0.307 to 0.002) but significant differences in pulse (P=0.007; 95% CI, −10.001 to −2.72), diastolic blood pressure (P=0.013; 95% CI, −9.489 to −1.420) and in end-tidal CO2 (P=0.016; 95% CI, −7.484 to −0.952) before versus after thoracotomy, but there was no clinical relevance of the differences.

Conclusions: For conversion with surgical indications during the VATS-NITS procedure, NITS thoracotomy can be performed safely at the site of the utility incision without the need for additional drugs, and the major lung resections can be performed through this approach.

Keywords: Non-intubated thoracic surgery (NITS); video-assisted thoracic surgery (VATS); conversion; thoracotomy

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Introduction

Video-assisted thoracic surgery (VATS) has been developed to minimize surgery-inflicted tissue injury, thereby improving patient outcomes (1). Theoretically, combining VATS with the non-intubated thoracic surgical (NITS) approach, especially when spontaneous breathing is

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maintained throughout, induces the least potential stress on patients; hence, it could be most beneficial for patients undergoing lung resection (2). The VATS-NITS method for major lung resections is used mainly in dedicated centers, and its widespread use is mainly inhibited by a doubt: "Is this procedure safe enough for patients, and how could we perform a quick conversion if needed?" Currently, in the case of unexpected complications during NITS, the recommended solution is the conversion to open thoracotomy that is preceded by muscle relaxation, the insertion of a double-lumen endotracheal tube and controlled mechanical ventilation has been the gold standard and routine for several decades (3,4). Complications during NITS may be due to anesthesiologic and surgical reasons alike. In cases of surgical complications, which are mainly technical difficulties, intubation and conversion to thoracotomy is the recommended method (4), but intubation can sometimes be very difficult and even planned endotracheal intubation with a double-lumen tube has a significant complication rate (5).

Here we report our practice of managing surgical difficulties during uniportal VATS-NITS major lung resection.

Table 1 Patient characteristics

Characteristics	N=166
Female/male	104/62 (62.6%/37.4%)
Mean age (years)	63.9 [20–81]
Conversion to intubation (3 anesthesia and 3 surgical indications)	6 (3.7%; 6/166)
Complete NITS procedure	160 (96.3%)
VATS-NITS procedures	145
Lobectomy	100
Segmentectomy	18
Wedge resection	22
Lung volume reduction	2
Empyema decortication	2
Rib resection	1
Open NITS procedures	15
Conversion from VATS to NITS thoracotomy (surgical indication)	9 (5.8%; 9/154)
Intended NITS thoracotomy	6

NITS, non-intubated thoracic surgery; VATS, video-assisted thoracic surgery.

Methods

Patients

Between January 26, 2017 and November 30, 2018, 166 thoracic surgical procedures were performed using the uniportal VATS-NITS method. Patient characteristics are summarized in *Table 1*. Six of the 166 patients required intubation during surgery: 1 had serious diaphragm and mediastinal movements, 2 had blood in the airways (anesthesiologic indications for conversion), and 3 had severe adhesions (surgical indication for conversion) requiring isolation with a double-lumen tube. The conversion rate to intubation with anesthesiologic indication and the following thoracotomy was 1.8% (3/166). In 160 cases, the NITS procedure was completed. In 145 NITS-VATS cases, the uniportal procedure was performed; however, 15 cases required conversion to open NITS (NITS with thoracotomy). The characteristics of these 15 open NITS patients are shown in *Tables 2* and *3*. For each patient, the NITS procedure was explained and the risks were detailed. If the patients agreed with this method, written informed consent was obtained from all patients.

Surgical selection criteria for VATS-NITS procedure

Because the surgical technique of the VATS-NITS procedure is the same as in intubated cases, the indications are also similar. According to the recommendations of a recent consensus meeting, patients mainly with lung cancer less than 7 cm, N0 and N1 cases are scheduled for VATS in our practice as well (1). Regarding the NITS itself, patients who are otherwise planned to undergo the VATS procedure with a body mass index (BMI) less than 30 without other exclusion criterias are indicated for NITS operation (*Table 4*).

Surgical procedure

We performed the same VATS uniportal method during the NITS procedures as was mentioned in the literature (6); in our uniportal practice, we follow the recommendation and work of Gonzales-Rivas (7,8). The "uniportal" terminology is debated in the literature due to the size of the incision (9).

Due to the NITS, at the incision site in the 5th intercostal space in the middle axillary line, 2% lidocaine (5 mg/kg) skin and subcutaneous infiltration is administered. A few

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Table 2 Characteristics of open NITS patients

Characteristics	N=15
Female/male	8/7
Mean age (year)	61.1 [52–73]
Conversion from VATS NITS to open NITS	9
Pneumonectomy	2
Sleeve right upper lobectomy	1
Lobectomy	5
Wedge resection	1
Intended NITS thoracotomy	6
Bilobectomy	1
Lobectomy	2
Segmentectomy (anatomical)	2
Exploration	1

NITS, non-intubated thoracic surgery; VATS, video-assisted thoracic surgery.

minutes later, the incision is performed. The size of the utility incision depends on the patient's BMI. If the chest wall is 3–6 cm wide due to the fat, the incision is about 6 cm, but in a thin patient, the incision can be 4 cm. Thus, incision size is unrelated to uniportal VATS if a single incision is made without rib retraction. After entering the thoracic cavity, the lung gradually becomes atelectatic. A plastic ring retractor is inserted to hold the soft tissue. The complete atelectasis develops in 7–10 minutes, but during this time an intercostal nerve blockade is given with 0.5% bupivacaine between the 2^{nd} and 5^{th} intercostal nerves and near the vagus nerve (right side in the upper mediastinum; left side in the aortopulmonary window). The total amount of bupivacaine is 0.5 mL/kg. We usually administer 4–5 mL 0.5% bupivacaine near the 2^{nd} to 5^{th} intercostal nerves. To deliver local infiltration close to the vagus nerve, we administer 0.5% bupivacaine 3–5 mL with a long or butterfly needle. The left side the vagus blockade is a little more difficult. In the aortopulmonary window, the pleura is

Table 3 Data of the open NITS patients

	Converted NITS thoracotomy (n=9)	Intended NITS thoracotomy (n=6)
BMI	24.3 [19–31]	24.7 [20–32]
FEV_1 (%)	61.7 [32–111]	60.3 [36–73]
DLCO (%)	60.5 [40–84]	47.5 [26–61]
Surgical time (min)	146.7 [105–225]	110 [75–190]
Drainage time (days)	3.6 [1–14]	5.1 [2–13]
Number of N2 lymph nodes	9.6 [4–24]	21.6 [10–29]
Adenocarcinoma	4	3
Squamous cell carcinoma	1	2
Neuroendocrine tumor	2	1
Carcinosarcoma	1	0
Benign lesion	1	0
IA	1	2
IB	1	0
IIA	0	0
IIB	3	0
IIIA	3	3
IIIB	0	1

BMI, body mass index; DLCO, carbon monoxide diffusion; FEV_1, forced expiratory volume in 1 second; NITS, non-intubated thoracic surgery; N2 lymph nodes, mediastinal lymph nodes.

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Table 4 Exclusion criteria from non-intubated thoracic surgery

Hemodynamically unstable patients
INR >1.5
Sleep apnea syndrome
Anticipated difficult airway
BMI ≥30 kg/m^2
Persistent cough or high airway secretion
Elevated risk of regurgitation
Raised intracranial pressure, unable to cooperate
Procedures requiring lung isolation to protect the contralateral lung
Full anticoagulation before surgery

BMI, body mass index; INR, international normalized ratio.

elevated a little and the needle is inserted under the elevated pleura into the fatty tissue close to the vagus nerve, and 3–5 mL bupivacaine is injected toward the vagus nerve. This is not painful, and patients do not react during this maneuver. To the vagus nerve blockade, the lung must be touched gently because it is very sensitive to manipulation. We just lift up the lung with an instrument or sponge to visualize the vagus. At 2–3 minutes after the vagus blockade, the lung can be held with the ring forceps without coughing. After this point, the manipulations are the same as in an intubated VATS surgery. There was no cough at the time of the manipulation near or in the bronchus.

Conversion from VATS NITS to open NITS

At the beginning of our NITS practice, when any kind of complications or difficulties occurred during the resection that were difficult to manage using the VATS-NITS approach, the anesthesiologist was asked to intubate the trachea with a double-lumen tube and a thoracotomy was performed. This was done in six cases.

In one case, the reason for conversion was a metastatic lymph node around the right upper lobe; we asked the anesthesiologist to intubate the patient. Because the intubation was a little more difficult and longer than usual, we simply extended the skin incision and used a rib retractor to enlarge the wound to provide a better view to the thoracic cavity. Because the patient remained stable and there were no signs of anesthetic complications, we gradually performed a regular axillary thoracotomy and a right upper sleeve lobectomy without complications.

After this operation, we changed our practice: In case of any surgical difficulties during the VATS-NITS surgery that were not manageable through the VATS method and the patient was stable, we disregarded endotracheal intubation and proceeded with a regular axillary thoracotomy and resection as usual. At the end of the surgery, the thoracotomy is closed, a chest tube is inserted via another incision, and a serratus cannula is inserted for postoperative pain management.

Conversion to open NITS was required in 9 cases due to oncological reasons (lymph node infiltration) in 4, bleeding in 2, technical difficulty to the sleeve in 1, extended adhesion in 1, and palpation difficulty in 1. In cases of major bleeding, the judgment and management of the conversion is the same as in intubated VATS. In our practice, if we cannot control the bleeding with compression of the distal artery or it is on the main pulmonary artery (even if it can be control with compression), a thoracotomy is indicated. As the bleeding begins, if the patient is stable, there is no indication for intubation. Theoretically, if the situation was catastrophic (fortunately none of our cases), the thorax would be opened immediately, the bleeding controlled with a clamp or by hand, and intubation requested of the anesthesiologist with the patient in a lateral position : it would be performed via a laryngeal mask with a single-lumen tube and bronchial blocker under fiberoptic guidance.

However, we must stress that the real-life threatening situation is not the major bleeding from a large vessel; rather, it is bleeding into the airway. This is an immediately indication for intubation. In this situation, the bleeding volume is not serious, so we have time to turn the patient and intubate them normally. Using the LMA (LMA; Ambu Aura-i laryngeal mask), we can completely control the airway.

Intended open NITS

After the excellent results of the first 4 conversion cases from VATS-NITS to open NITS, in 6 patients with a low forced expiratory volume in 1 second [60.3% (36–73%)] and carbon monoxide diffusion [47.5% (26–61%)], we decided to perform a direct/planned/intended open NITS surgery after receiving patient permission. We performed intended axillary thoracotomies after VATS-NITS exploration of the thorax and infiltration of the intercostal spaces and the vagus nerve. Using this method, normal resections

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were possible. The chest was closed over a drain, and a serratus cannula was inserted for pain management. The serratus anterior plane (SAP) block with cannula, which can be inserted intraoperatively or under ultrasonography guidance, provides prolonged anesthesia of the hemithorax with numbness over the thoracic area supplied by the lateral cutaneous branches of the T2–T9 spinal nerves. This can provide adequate pain relief effect after a thoracotomy. It is filled intraoperatively with bupivacaine (0.5 mg/mL) and followed by a continuous infusion of 5 mL/h for the first 36 hours (10). Patient data are shown in *Tables 2* and *3*.

Anesthesiology

The exclusion criteria of NITS are summarized in *Table 4*. In the operating room, in addition to standard monitoring (ECG, O_2 saturation, non-invasive blood pressure), depth of anesthesia monitoring by bispectral index (BIS; Medtronic Vista) and invasive blood pressure measurements are performed. Midazolam and fentanyl are administered prior to the surgery. Anesthesia is induced and maintained with propofol administrated via target-controlled infusion titrated to keep the BIS at 40–60 according to published recommendations (5). After adequate depth of anesthesia is achieved, a laryngeal mask is inserted for airway maintenance. Spontaneous breathing is also maintained throughout and ventilation is monitored with capnography. Oxygen and air mixture are supplemented via a T-piece and FiO_2 is titrated to keep the SpO_2 at above 92%.

Anesthetic indications for conversion

The most frequently occurring indications for intubation are the following:

(I) Hypoxemia: In case of SpO_2 <92% or PaO_2 <60 mmHg on 100% O_2, the operated (non-dependent) lung is reinflated. If this procedure cannot correct the hypoxemia, then endotracheal intubation is performed.

(II) Hypercapnia: If $PaCO_2$ >75 mmHg or pH <7.15, the operated lung is reinflated to eliminate CO_2: patients breathe spontaneously via LMA and we adjust the low PEEP and pressure support on the circle and the lung reinflates due to this positive pressure. If it fails, conversion is necessary.

(III) Bleeding in the airways: At the first sign of blood in the airway, immediate intubation is required. The airways are always checked via LMA with a fiber optic bronchoscope before and after the resection. If there is any sign of blood or other secretions, it must be suctioned prior to the reinflation.

Method of conversion from NITS to intubation

At the start of our NITS experience, the correct procedure for intubation was as follows: rotation of the operation table to backward as we could, intubation of the trachea with a single-lumen tube, and placement of a bronchial blocker under fiber optic guidance or the insertion of a double-lumen tube. After we had more experience with patient tolerability and difficulties with urgent intubations in the lateral decubitus position, our protocols changed. Currently, if conversion to intubation is necessary, an urgent chest tube is inserted, the wound is covered with a temporary bandage, and the patient is returned to the supine position. In this supine position, intubation is a simple procedure. The time from the decision of the intubation to the supine position is generally less than 2 minutes.

Method of anesthesiology in open NITS cases

If the patient is stable and there is no indication for intubation but the surgical difficulties cannot be managed with the VATS-NITS method, a thoracotomy can be done in NITS circumstances. For the thoracotomy, we do not change the anesthesia and no additional drugs are necessary. Generally, with the same drug administration as in the pre-thoracotomy period, we can keep the patient parameters in the normal range. We follow the ERAS (enhanced recovery after surgery) principles and try to avoid TEA (thoracic epidural anaesthesia) and its possibly hard sympatholytic effect. Therefore, we use TPB (thoracic paravertebral blockade) and the new SAP block. This block is in the new ERAS guidelines with TPB and might be useful after thoracotomies. Our experience absolutely confirmed this theory.

We use the same protocol for intended open cases. In 4 of 15 cases, some noradrenaline was necessary for a short period of time. The indication for the administration of noradrenaline is the low systolic blood pressure or the low mean arterial pressure (MAP). According to our practice, the MAP must be higher than 60 mmHg or the systolic blood pressure higher than 90 mmHg to ensure adequate organ and tissue filling pressure and blood flow. This practice is similar in intubated and non-intubated patients (*Table 5*).

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Table 5 Anesthesia data before versus after NITS thoracotomy (converted and intended open NITS group)

Patient	PB/min	PA/min	sysRRB, mmHg	sysRRA, mmHg	diasRRB, mmHg	diasRRA, mmHg	O_2SATB%	O_2SATA%	etCO_2B, mmHg	etCO_2A, mmHg	CeB, mcg/mL	CeA, mcg/mL
1	89.4	87.4	124	115	68	64	97	97.6	50	49.4	2.62	3.02
2	96.6	93.8	109	118	62	68	96.6	97.6	48.2	63	3.02	3.2
3	65.2	66	106	116	62	70	98.8	99.2	35.2	34.2	3.16	2.8
4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	65.6	76.8	106	94	62	64	98.6	98.4	43.2	46.4	2.5	2.52
6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	78.8	89.8	104	116	62	70	96.2	96.4	46.4	49	2.52	2.62
10	83	87.4	94	116	48	68	90.8	96.6	43.4	47.6	2.76	2.9
11	65.6	80	112	106	60	68	98.8	98.2	35.4	47.2	3	3.44
12	65.2	66.6	112	112	68	72	96.2	95	43	45	3.12	3.56
13	66.6	76	104	104	62	64	95	96.4	36.8	41.6	2.66	2.74
14	65.8	75.4	102	115	62	64	96.2	95.8	43.2	45.2	2.66	2.7
15	80.4	89.4	104	102	62	66	96.6	96.8	46	48.6	2.56	2.76
P value	0.007		0.316		0.013		0.270		0.016		0.053	
95% CI	−10.001 to −2.72		−10.469 to 3.742		−9.489 to −1.420		−1.902 to 0.593		−7.484 to −0.952		−0.307 to 0.002	

CeA, propofol concentration in the effect site after NITS thoracotomy (open NITS period); CeB, propofol concentration in the effect site before NITS thoracotomy (VATS-NITS period); CI, confidence interval for mean difference; diasRRA, diastolic blood pressure after NITS thoracotomy (open NITS period); diasRRB, diastolic blood pressure before NITS thoracotomy (VATS-NITS period); etCO_2A, end-tidal carbon dioxide pressure after NITS thoracotomy (open NITS period); etCO_2B, end-tidal carbon dioxide pressure before NITS thoracotomy (VATS-NITS period); NA, no data because the patients received minor and temporal noradrenalin to keep a mean arterial pressure (noradrenalin administration was ceased during surgery); NITS, non-intubated thoracic surgery; O2SATA, oxygen saturation after NITS thoracotomy (open NITS period); O2SATB, oxygen saturation before NITS thoracotomy (VATS-NITS period); PA, pulse after the NITS thoracotomy (open NITS period); PB, pulse before the NITS thoracotomy (VATS-NITS period); sysRRA, systolic blood pressure after NITS thoracotomy (open NITS period); sysRRB, systolic blood pressure before NITS thoracotomy (VATS-NITS period).

Statistical methods

Data of the pulse, systolic and diastolic blood pressure, sat O_2, end-tidal carbon dioxide pressure (etCO_2), and propofol concentration in the effect were collected from the anesthesiologic documentation. Two-way repeated measures analysis of variance was used to compare the means of the above noted variables before versus after thoracotomy during the NITS open surgery. The 95% CIs for the mean differences were calculated. Values of $P<0.05$ were considered statistically significant. The analysis was performed using IBM SPSS 24 statistical software.

Results

Among the open NITS cases, there were almost identical numbers of female and male patients; in contrast, among the VATS-NITS cases, there were almost twice as many female as male patients (*Tables 1* and *2*). There were no cases of perioperative mortality.

Anesthesiology

Regarding the 15 open NITS cases, there were no significant differences in systolic blood pressure (P=0.316; 95% CI,

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–10.469 to 3.742), satO_2% (P=0.27; 95% CI, –1.902 to 0.593), or propofol concentration in the effect site (P=0.053; 95% CI, –0.307 to 0.002) but there were significant differences in pulse (P=0.007; 95% CI, –10.001 to –2.72), diastolic blood pressure (P=0.013; 95% CI, –9.489 to –1.420) and etCO_2 (P=0.016; 95% CI, –7.484 to –0.952) during the NITS surgery or before and after the thoracotomy. Despite these statistical findings, due to the open NITS procedure use in 11 patients, it was not necessary to change the anesthesiologic treatment after thoracotomy. In 4 patients, noradrenaline administration was necessary to maintain adequate MAP, but it was ceased toward the end of the surgery. Two patients after pneumonectomy were admitted to the intensive care for observation, but the other 13 were transferred from the recovery room to the ward.

Surgery

According to our preliminary experience, all parts of a lung resection including lymphadenectomy can be performed via open NITS just as with the conventional intubated way without complications (*Table 3*). We had no R1–2 resections. The operative time was a little longer in the converted cases because of the exploration until conversion (*Table 3*). The majority of the resections were lobectomies, and in the patients with a BMI ≤30, the mediastinum and the diaphragm movement did not disturb the resection. The only new experience was the softness of the airways without the endotracheal tube, which requires special attention during mediastinal lymphadenectomy. Most of our patients had advanced lung cancer with lymph node metastasis. There were 3 patients with a prolonged air leak longer than 5 days (20%; 3/15), and the mean drainage time in the 15 open NITS cases was 4.2 days (range, 1–14). The overall conversion rate with surgical indications (3 to intubation and thoracotomy; 9 to open NITS) was 7.5% (12/160). One patient who underwent surgery due to a serious hemoptysis for which a lower bilobectomy was done died 25 days postoperative of cardiac insufficiency. His preoperative lung functions were very limited as follows: forced expiratory volume in 1 second (26%), carbon monoxide diffusing capacity (26%), and VO_2max (13.9 mL/kg/min). His postoperative period was uneventful, and he was discharged on postoperative day 7 to rehabilitation.

Discussion

The most criticized part of the NITS procedure is the "unsafe" airway. Although the conversion from NITS to an intubated method depends on anesthesiologic and surgical indications, it is recommended in any difficulties during the NITS thoracic surgery that the patient be intubated and the surgical procedure continue in that manner (11). With our experiences and practice, we recommended distinguishing between anesthesiologic and surgical indications for the conversion because the different problems should be managed differently.

In a review article from Mineo, the overall conversion rate to general anesthesia was 0–9%, but it did not detail the rates of surgical versus anesthesiologic indications (11). The conversion rate of the Liua study was 7%, which could be reduced with more experience, but this article did not distinguish between anesthesiologic and surgical indications for conversion; rather, intubation was required for both (5).

Intubation in the lateral decubitus position can be difficult. In our practice, in case of conversion with anesthesiologic indication, we quickly cover the wound over a chest tube and turn the patient to the supine position, in which intubation is very easy, taking less than 2 minutes. In difficult intubation cases, we do not perform intubation in the lateral position. Other authors reported inserting a chest drainage tube during the intubation to prevent tension pneumothorax, but they did not turn the patients to the supine position first (11,12).

In our practice, the overall surgical indication for conversion was 7.5%, which is very similar to the data of other centers; most frequently, serious adhesion, mediastinal movement, and bleeding cause the conversion (11). At the beginning of our NITS procedure, we intubated for any complication, and surgical reasons caused 1.8% (3/166) of cases. Later we realized that in surgical difficulties, when the patient is stable, intubation is not necessary from the anesthesiologic point of view and a thoracotomy and all resections can be performed without it.

Although there were statistically significant differences between the data of pulse, diastolic blood pressure, and etCO_2 before versus after NITS thoracotomy, the changes were not dramatic and did not require any serious modification in the drug administration in 11 patients. Confidence intervals for the differences clearly present that, despite statistical significance, there is no clinical relevance of the differences. In 4 patients, to maintain MAP, minor and temporal noradrenalin administration was necessary but could be ceased during surgery. This shows that, in adequate intercostal and vagus nerve blockade, the thoracotomy procedure itself does not require any modification in the

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NITS anesthesiology. In the literature, we did not find any articles analyzing long-term experiences or presenting metanalysis about open NITS procedures (5,11,12).

An open NITS surgery is feasible for any minor and major lung resection. As we demonstrated here, the pneumonectomy and even a sleeve resection can be performed under open NITS, but attention must be paid to prevent blood from entering the airway.

The other part of the oncological principles is lymph node management. As we demonstrated, a good number of mediastinal lymph nodes (N2) can be removed during open NITS (9.6 and 21.6) versus VATS-NITS in other centers (all the lymph nodes N1+N2: 17.2) (5). In a review article of NITS metastasectomy from Migliore (13) it is mentioned, that the main criticisms against the NITS is the difficulty of the mediastinal lymphadenectomy. In our practice, we did not find any difficulties in performing lymphadenectomy. The only technical difference from intubated cases is that in open NITS patients, the airways are soft because of the absence of the intratracheal tube, so preparation around this soft airway must be done carefully. Using our technique, no cases of cough or airway injury occurred during the peribronchial manipulation.

In conclusion, the anesthesiologic and surgical indications in cases of conversion in VATS-NITS should be strictly distinguished because of the different management approaches to these problems. The anesthesiologic difficulties required intubation, but if the patient's oxygenation and circulation are normal, intubation is not necessary to manage surgical difficulties and a simple thoracotomy can be performed. Using open NITS thoracotomy, every step of a major lung resection can be completed without additional risk for patients. Although we worked out a safety way for conversion in NITS procedures, we can't predict if the NITS or awake surgery for major lung resection will become more common in the future or not. Currently mainly the technical questions of the procedure are discussed in the literature, and only few studies are published with physiological and the positive immune effect of the NITS (14). As a safe conversion practice was presented and the long term physiological and cancer-related effect of the NITS are proved, the current judgment of the non-intubated thoracic procedures will be changed.

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Footnote

Conflicts of Interest: Al authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-19-3830). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The authors confirm that the research adhered to the conditions of the ethics committee of the institutions and confirm the provisions of the Helsinki Declaration. Patient data were retrieved retrospectively from our medical record system (Medsolution) and the patients' personal data were secured. Ethical permission number: 111/2017-SZTE.

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