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THE ROLE OF PRESERVED SPONTANEOUS BREATHING DURING THORACIC SURGERY

PhD Thesis

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Abbreviations

ALI	acute lung injury
ASA	American Society of Anesthesiologists
BB	bronchial blocker
BIS	bisprectal index
BMI	body mass index
CI	confidence interval
CMV	controlled mechanical ventilation
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DAMP	damage-associated molecular pattern
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	double-lumen tube
ECG	electrocardiogram
ERAS	enhanced recovery after surgery
FEV_1	forced expiratory volume in one second
FiO_2	fraction of inspired oxygen
FRC	functional residual capacity
FVC	forced vital capacity
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
IV	intravenous
LMA	laryngeal mask airway
MeSH	medical subject headings
mOLV	mechanical one-lung ventilation
NITS	non-intubated thoracic surgery
NIVATS	non-intubated video-assisted thoracic surgery
NK	natural killer
NMBAs	neuromuscular blocking agents
NPRS	numeric pain rating scale
OLV	one-lung ventilation
$PaCO_2$	arterial partial pressure of carbon dioxide

PACU	post-anesthesia care unit
PAMP	pathogen-associated molecular pattern
PaO_2	arterial partial pressure of oxygen
PAO_2	alveolar partial pressure of oxygen
PEEP	positive end-expiratory pressure
PPCs	post-anesthesia pulmonary complications
PPV	positive pressure ventilation
PSV	pressure support ventilation
Resp.R.	respiratory rate
RR_{dias}	diastolic blood pressure
RR_{sys}	systolic blood pressure
SAD	supraglottic airway devices
SB	spontaneous breathing
SD	standard deviation
Sp. OLV	spontaneous one-lung ventilation
SpO_2	oxygen saturation
SR	sarcoplasmic reticulum
SVI	spontaneous ventilation with double-lumen tube intubation
TCI	target-controlled infusion
V/Q	ventilation/perfusion ratio
VALI	ventilator-associated lung injury
VAS	visual analog scale
VATS	video-assisted thoracic surgery
WST	water submersion test

International publications on which the PhD thesis is based

1. Szabo Zsolt, **Fabo Csongor**, Oszlanyi Adam, Hawchar Fatime, Geczi Tibor, Lantos Judit, Furak Jozsef: Anesthetic (r)evolution from the conventional concept to the minimally invasive techniques in thoracic surgery-narrative review JOURNAL OF THORACIC DISEASE 14 : 8 pp., 16 p. (2022); SJR indicator: Q2

2. Szabo, Z.; **Fabo, C.**; Szarvas, M.; Matuz, M.; Oszlanyi, A.; Farkas, A.; Paroczai, D.; Lantos, J.; Furak, J. Spontaneous Ventilation Combined with Double-Lumen Tube Intubation during Thoracic Surgery: A New Anesthesiologic Method Based on 141 Cases over Three Years. J. Clin. Med. 2023, 12, 6457. SJR indicator: Q1

International and Hungarian publications related to the topic of the PhD thesis

3. Furák József, Németh Tibor, Lantos Judit, **Fabó Csongor**, Géczi Tibor, Zombori-Tóth Noémi, Paróczai Dóra, Szántó Zalán, Szabó Zsolt: Perioperative Systemic Inflammation in Lung Cancer Surgery FRONTIERS IN SURGERY 9 Paper: 883322, 7 p. (2022) SJR indicator: Q2

4. **Fabo Csongor**, Oszlanyi Adam, Lantos Judit, Rarosi Ferenc, Horvath Theodor, Barta Zsanett, Nemeth Tibor, Szabo Zsolt: Nonintubated Thoracoscopic Surgery-Tips and Tricks From Anesthesiological Aspects: A Mini Review FRONTIERS IN SURGERY 8 Paper: 818456, 8 p. (2022) SJR indicator: Q2

5. **Fabo Csongor**, Oszlanyi Adam, Barta Zsanett Virág, Nemeth Tibor, Lantos Judit, Vaida Stefan Nicolae, Szabo Zsolt: Anesthesiology of the spontaneous ventilation in thoracic surgery: a narrative review AME Surgical Journal 2 Paper: 14, 7 p. (2022)

6. Furák József, Barta Zsanett, Lantos Judit, Németh Tibor, Pécsy Balázs, Buzás András, Vas Márton, **Fabó Csongor**, Szabó Zsolt, Rieth Anna, Lázár György: Intubálással biztosított spontán légzés módszerével elvégzett sublobaris tüdőreszekciók korai műtét utáni eredményei. Új műtéti eljárás MAGYAR SEBÉSZET 75 : 2 pp. 117-120., 4 p. (2022)

7. Farkas A, Csókási T, **Fabó C**, Szabó Z, Lantos J, Pécsy B, Lázár G, Rárosi F, Kecskés L and Furák J (2023) Chronic postoperative pain after nonintubated uniportal VATS lobectomy. Front. Surg. 10: 1282937. (2023) SJR indicator: Q2

8. Furák J, Németh T, Budai K, Farkas A, Lantos J, Glenz JR, **Fabó C**, Shadmanian A, Buzás A. Spontaneous ventilation with double-lumen tube intubation for video-assisted thoracic surgery thymectomy: a pilot study. Video-assist. Thorac Surg: 8p (2023) SJR indicator: Q4

Summary

With advancements in medicine and healthcare systems, patients are undergoing surgeries at an older age and with more severe comorbidities. The development of perioperative complications is strongly associated with these patient factors. This, along with the growing number of surgeries, results in a significant financial and human burden on healthcare systems. To prevent perioperative complications and maintain the patient's physiological balance as much as possible, minimally invasive surgical and anesthetic approaches have been prioritized in the last few decades, although some aspects of the effects of the minimally invasive anesthetic strategies have remained unclear.

The focus of minimally invasive anesthesia in thoracic surgery is the maintenance of spontaneous breathing during procedures. This approach was known since the mid-1800s as the only option for thoracic interventions. However, with the development of modern anesthesia, this method disappeared from the anesthetic repertoire for decades. The revival of this technique began around the millennium when various research groups started to perform thoracic procedures on patients in mild sedation without endotracheal intubation. This strategy capitalizes on the advantages of spontaneous breathing, including enhanced physiological synchronization, reduced patient stress, and improved ventilation-perfusion matching, and the mitigation of adverse effects associated with general anesthesia and controlled mechanical ventilation such as barotrauma and volutrauma. In response to the concerns related to non-intubated thoracic procedures, significant advancements have been achieved in the last years, and several directions have emerged in this area. To address the issues associated with non-intubated techniques, Furák and Szabó in 2021 developed a method called spontaneous ventilation with double-lumen tube intubation (SVI). This approach combines the benefits of preserving spontaneous respiration with the safety provided by double-lumen tube insertion.

We aimed to review the evolution of thoracic anesthesia, with a primary focus on the benefits and drawbacks of various anesthetic techniques used by different teams for procedures involving spontaneous breathing. Following this, we examined the intraoperative and early postoperative outcomes of thoracic surgeries conducted with SVI. Our investigation focused on the safety and practicality of this anesthetic approach,

particularly in terms of intraoperative oxygenation, carbon dioxide elimination, and the resulting acid-base imbalances.

Several anesthetic management methods have been identified, and we found that our approach used for non-intubated thoracic procedures, including anesthesia depth guided propofol sedation with laryngeal mask insertion, represents a novel, safe, and practical technique, offering advantages such as a higher level of airway safety compared to NITS and the possibility of lung recruitment, fiberoptic manipulation, and water submersion testing.

Since SVI integrates maximal airway safety through double-lumen tube intubation with the maintenance of spontaneous breathing, this technique is both safe and feasible for various thoracic procedures and also for thoracotomies and has fewer exclusion criteria compared to non-intubated methods. The technique can reduce the duration of controlled positive pressure ventilation during thoracic surgery by up to 76.5% and has a low anesthetic conversion rate of 2.8%. While permissive hypercapnia and associated acid-base disturbances are common during SVI, these are also well-known phenomena during the classical technique, they are generally transient and resolve spontaneously in the early postoperative period without causing oxygenation issues.

We assert that conventional intubated anesthesia, NITS, and the SVI technique each have a valid role within the anesthesiological repertoire. It is crucial to recognize patient heterogeneity, which necessitates the customization of anesthetic strategies to suit individual patient profiles.

1. Introduction

High-risk surgical interventions such as thoracic procedures come with an increased risk of morbidity and mortality, which is more pronounced in frail patients with severe comorbidities. Several studies have proved that certain comorbidities and conditions, including chronic obstructive pulmonary disease (COPD), renal insufficiency, age, smoking, body mass index (BMI) have more pronounced effect on the development of perioperative complications. Due to the growing number of surgeries performed, the human and financial burden on the healthcare system can be almost intolerable, especially in low- and middle-income countries, where the greater part of the surgeries is performed, and billions of people have no access to a quality healthcare. [1,2]

Thus, rationalizing the financial burden on the healthcare system by preserving the physiological balance of patients with minimally invasive surgical and anesthetic techniques appears to be a reasonable effort. The concept of “Enhanced Recovery After Surgery” (ERAS) is a well-known collection of recommendations for healthcare professionals that aims to evolve a perspective in which the preoperative preparation, minimally invasive surgical and anesthetic approaches, and postoperative care are interdependent components of patient care and have to be applied in a coordinated manner. [3,4]

The video-assisted thoracic surgery (VATS) technique combines the advantages of minimally invasive interventions with an optimal view of the surgical field. Advantages arising from minimal invasivity such as reduced tissue trauma or reduced pain lead to shorter recovery time, better morbidity rates, improvement of pulmonary function parameters, and also smaller scars. [5] These benefits of VATS explain why video-assisted – preferably uniportal – thoracoscopic approach is the gold standard for major pulmonary resections as well. [6–9]

Thoracic anesthesia has also kept pace with the development of surgical techniques and undergone a paradigm shift. Traditionally, thoracic procedures require(d) general anesthesia, muscle relaxation, and controlled mechanical one-lung ventilation (mOLV). The functional separation of the lungs can be achieved with double-lumen tube (DLT) insertion or by bronchial blockers (BB). General anesthesia, muscle relaxation, and endotracheal intubation enhance the risk of pulmonary complications (for example, increased incidence of pneumonia and ventilator-associated lung injury [VALI]). Other complications, as well as postoperative nausea and vomiting, and the fortunately rare occurrence of intubation-related trauma are also associated with the above-mentioned anesthetic strategies. The POPULAR study demonstrated that the use of neuromuscular blocking agents (NMBAs) during general anesthesia increases the risk of post-anesthesia pulmonary complications (PPCs) [10]. One of the main recommendations of this study is that anesthetists need to find the balance between the beneficial effects of neuromuscular blockade and the maintenance of spontaneous breathing, for example by using supraglottic devices for minor surgeries.

During surgical interventions, innate and acquired immunity are damaged. The activation of innate immunity is primarily connected to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The activation of innate immunity helps to restore the integrity of homeostasis, and it is controlled by the compensatory anti-inflammatory immune responses. The activation of acquired immunity is associated with a higher leukocyte count with relative Th2 dominance, although the absolute number of the CD4+ and CD8+ lymphocytes decreases, which enhances the immunosuppressive effects. [11]

The stress experienced by the patient's body during surgical interventions essentially consists of two components: those associated with the surgical insult and the detrimental effects induced by anesthesia. Minimally invasive surgical and anesthetic approaches also offer immunological advantages. The effects of minimally invasive surgical approaches have been widely investigated, and VATS is associated with a lower postoperative complication rate than the open approach [12]. Moreover, in the matter of immunological effects (cytokine levels and natural killer (NK) and T cell counts), VATS has proved to be superior to thoracotomy. [13]

As a significant portion of the interventions is performed using the VATS method, further progress is expected from the minimally invasive anesthesiological techniques.

2. Background

2.1. History of spontaneous breathing thoracic procedures

Thoracic surgical interventions performed with maintaining spontaneous respiration are not a recent phenomenon. It is noteworthy that during the early endeavors in this field, performing thoracic surgical procedures while maintaining spontaneous respiration was not merely an elective option but rather the sole recourse.

This is particularly due to the fact that the first interventions trace back to an era preceding the advent of endotracheal tubes, mechanical ventilators, and modern anesthesia. Entries related to thoracoscopy as a procedure suitable for exploring the thoracic cavity ("exploration de la cavité thoracique") can be found in French encyclopedias as early as the mid-1800s. [14] The inception of thoracoscopy dates back to an 1866 report, which chronicled the inaugural endoscopic investigation of the pleural space by Richard Cruise in an 11-year-old girl suffering from empyema. [15]

The credit for its widespread application, primarily, but not exclusively for diagnostic purposes, is attributed to Swedish internist Hans Christian Jacobeus. The procedure attributed to Jacobeus, also known as Jacobeus operation, encompassed the dissolution of adhesions once the thoracic cavity has been opened. Consequently, the presence of complete pneumothorax and the resultant atelectasis facilitated a comprehensive examination of the thoracic cavity. Additionally, biopsies could be conducted as necessary to elucidate the origin of pleural effusion. [16–19] The successes of Jacobeus contributed to the broader adoption of the method across several European countries, primarily in the diagnosis of spontaneous pneumothorax, pleural effusion, focal lung diseases, and mediastinal tumors. Furthermore, it proved suitable for uncovering abnormalities in the heart and major vessels, as well as for a more precise examination of traumatic injuries.

After the initial steps in 1950, Buckingham successfully introduced and applied epidural anesthesia in thoracic surgical procedures for over 600 patients, without causing nerve damage or respiratory depression. These successes laid the foundation for the indispensability of epidural catheters in thoracic surgical anesthesia for many decades. [20,21]

Vischnevski employed a sophisticated regional anesthesiological technique to create optimal surgical conditions. His method included vagal and phrenic nerve blocks performed at the neck, followed by an extensive intercostal block supplemented with lung hilum blockade. With this approach, he successfully conducted major lung resections, cardiac surgeries, and esophageal surgeries on over 600 patients. [22] Grounding his results and methodology on the work of Vischnevski, Ossipov performed thoracic surgical interventions in 3265 cases, utilizing local anesthesia. [23]

These results unquestionably constitute the foundations of thoracic surgery and thoracic anesthesia. However, over time, with the introduction of the DLT by Bjork and Carlens, these foundations receded into the background, giving way to anesthesia management supplemented by controlled mechanical ventilation based on lung isolation.

For decades, thoracoscopic interventions performed under local anesthesia predominantly strengthened the arsenal of interventional pulmonology, and their use was limited to diagnostic procedures. However, advancements in surgical techniques such as the emergence of precision linear staplers and high-angle thoracoscopic cameras, have enabled surgeons and anesthesiologists dedicated to minimally invasive approaches to incorporate thoracic surgical procedures performed alongside spontaneous breathing into their daily practice again. The first attempts are connected to two Japanese workgroups who performed video-assisted wedge resections in patients with spontaneous pneumothorax. [24,25]

Around the millennium, T.C. Mineo et al. at Rome, Tor Vergata University, launched a scientific program to investigate opportunities for performing thoracic procedures without general anesthesia and selective OLV. They published the results of their first randomized controlled trial in 2004 with the title “Feasibility and results of awake thoracoscopic resection of solitary pulmonary nodules.” The early investigations were all focusing on minor procedures. [26] In 2007, Al-Abdullatief et al. presented the safety and feasibility of the non-intubated technique for major procedures such as pulmonary lobectomy and thymectomy in awake or minimally sedated patients. [27]

From this point, several research teams across the globe, leveraging shared experiences, have devised their distinct surgical and anesthesiological methodologies for the execution of non-intubated thoracic surgical interventions. These approaches, applied in an expanding set of cases, have scientifically demonstrated the benefits of the procedure, encompassing reduced surgical time and hospital stay, shorter drainage time, and lower incidence of postoperative pulmonary complications. [26–30]

To address the concerns of non-intubated technique discussed later, Furák and Szabó (University of Szeged, Hungary) in 2021 combined the advantages of maintained spontaneous respiration with the safety of double-lumen tube insertion in the method named spontaneous ventilation with double-lumen tube intubation (SVI). [31]

2.2. Physiological and pathophysiological changes during thoracic anesthesia

Thoracic anesthesia presents a unique combination of physiological problems caused by the factors that make thoracic surgery possible (lateral decubitus position, general anesthesia, muscle relaxation, open pneumothorax, one-lung ventilation, surgical manipulation). These factors all have an effect on patient ventilation-perfusion relationship.

In awake patients, the lateral decubitus position does not influence the ventilation-perfusion (V/Q) matching, which is explained by the more effective contraction of the dependent hemidiaphragm and by the fact that the dependent lung is in a more favorable part of the compliance curve, with greater perfusion in the dependent (lower) lung due to gravitational influence. (Figure 1)

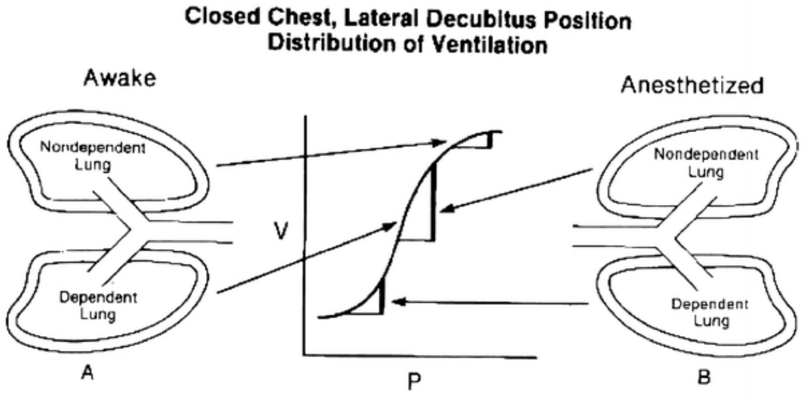

Figure 1 Effect of general anesthesia on lung compliance in lateral decubitus position.

Figure adopted from J. Lohser and S. Ishikawa, Physiology of the Lateral Decubitus Position, Open Chest and One-Lung Ventilation, in: Principles and Practice of Anesthesia for Thoracic Surgery, Springer New York, New York, NY, 2011: pp. 71–82. https://doi.org/10.1007/978-1-4419-0184-2_5 [32]

General anesthesia causes a decrease in functional residual capacity (FRC), and thus, shifts the dependent lung into a less favorable part of the compliance curve, while the distribution of perfusion in the lung is not affected by the induction of anesthesia (Figure 1). Muscle relaxation can worsen these effects as the static caudal displacement of the diaphragm by the abdominal content further reduces the compliance of the nondependent lung, while perfusion is not altered by muscle paralysis.

2.2.1. Effects of opening the thoracic cavity

By opening the thoracic cavity, iatrogenic pneumothorax develops, as the negative pleural pressure equalizes with atmospheric pressure and that results in atelectasis and a dramatic change in the ventilation of the affected (operated, nondependent) side of the lung. Opening the thoracic cavity with spontaneous breathing has two clear physiological consequences; namely, paradox ventilation (pendelluft phenomenon) and mediastinal shifting (Figure 2). As it happens in patients with pneumothorax, the dependent lung expands during inspiration, while the nondependent side is not able to. Under expiration, the carbon-dioxide-rich air from the dependent lung flows not only towards the trachea but also towards the nondependent lung. During inspiration, the fresh, oxygen-rich air from the trachea is mixed with the carbon-dioxide-rich air emanating from the non-dependent lung. This phenomenon is designated as paradoxical respiration or the pendelluft phenomenon. From a physiological standpoint, its significance lies in the development of hypercapnia, respiratory acidosis, and hypoxia attributable to the rebreathing of carbon dioxide and compromised gas exchange.

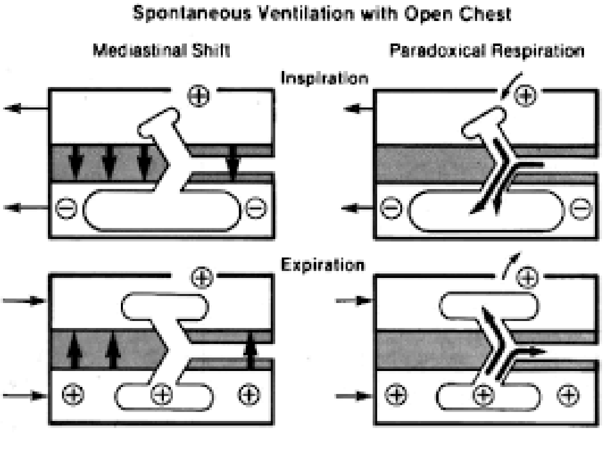

Figure 2 Effect of chest opening with spontaneous ventilation

Figure adopted from J. Lohser and S. Ishikawa, Physiology of the Lateral Decubitus Position, Open Chest and One-Lung Ventilation, in: Principles and Practice of Anesthesia for Thoracic Surgery, Springer New York, New York, NY, 2011: pp. 71–82. https://doi.org/10.1007/978-1-4419-0184-2_5 [32]

Due to the alterations in intrathoracic pressure dynamics caused by the pneumothorax, the mediastinum shifts towards the dependent side within the pleural cavity during inspiration. In contrast, during expiration, a shift in the opposite direction takes place. This phenomenon is referred to as mediastinal shifting, and it contributes to a further reduction in carbon dioxide elimination and deterioration of gas exchange.

2.2.2. Transpulmonary shunt and hypoxic pulmonary vasoconstriction

All the above-mentioned factors (general anesthesia, lateral decubitus, open pneumothorax, muscle relaxation) play a pivotal role in uncoupling the V/Q matching results in transpulmonary shunt and are responsible for the majority of pathophysiological changes seen under thoracic procedures. Transpulmonary shunt fraction is the proportion of the total cardiac output (pulmonary blood flow) that is not involved in gas exchange. Transpulmonary shunting exists under physiological circumstances as well, its range is normally between 6–10%, and it is triggered by the drainage of the Thebesian and bronchial veins and other right-left shunt pathways. [33] The rise of transpulmonary shunt fraction decreases the arterial oxygen content as a higher fraction of the total cardiac output is shunted from right to left without oxygenation, and what seems to be more important is the fact that the elevation of FiO_2 has less effect on oxygenation as shunt fraction increases as it is seen on Nunn's adapted iso-shunt diagram (Figure 3). [34,35] With increasing shunt fraction, the higher FiO_2 is unable to elevate the alveolar oxygen content in unventilated segments, and the extra oxygen content provided for the blood by ventilated segments is not enough to compensate for the effect of high shunt.

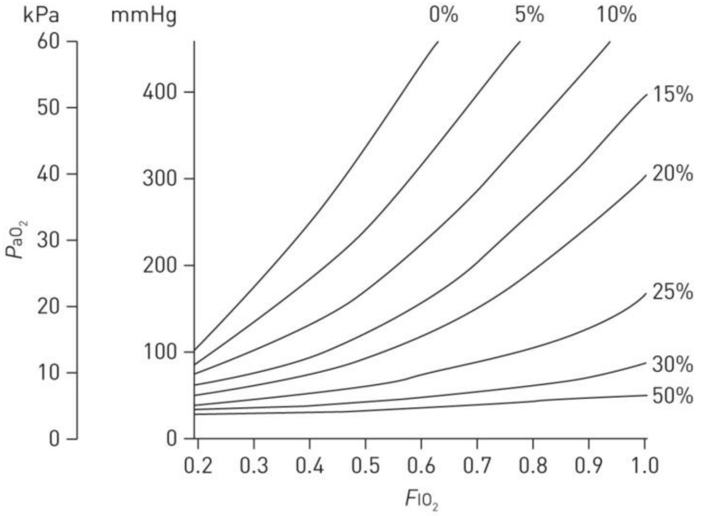

Figure 3 Iso-shunt diagram

Figure adopted from J. Petersson and R.W. Glenny, Gas exchange and ventilation–perfusion relationships in the lung, European Respiratory Journal 44 (2014) 1023–1041. https://doi.org/10.1183/09031936.00037014 [35]

During thoracic procedures, the transpulmonary shunt fraction could be as high as 20–30%, and if this V/Q mismatch remains uncompensated by the patient, it could lead to severe hypoxemia. The compensation mechanism is the hypoxic pulmonary vasoconstriction (HPV), also known as Euler–Liljestrand reflex, which involves the constriction of intrapulmonary arteries in response to a low alveolar oxygen tension. This phenomenon was first mentioned by Bradford and Dean [36], while the first detailed description of the mechanism of HPV was published by von Euler and Liljestrand. [37] The exact molecular mechanism of HPV is out of the focus of this thesis – essentially, it is the resting membrane potential (approx. −60 mV) in pulmonary artery smooth muscle cells maintained by the outward potassium current. In a hypoxic environment, this potassium current is inhibited, and by the depolarization of the membrane, the opening L-type calcium channels and the calcium efflux from the sarcoplasmic reticulum (SR) will lead to a rise in the cytoplasmic Ca^{2+} level, resulting in the contraction of pulmonary arteries. [38–40]

Hypoxic pulmonary vasoconstriction (HPV) operates within the physiological range (PAO_2 40–100 mmHg in adults) and directly correlates not only with the degree of hypoxia but also with the proportion of the hypoxic lung. The maximum effectiveness of HPV is achieved when 30 to 70% of the lung experiences hypoxia. [41]

HPV is biphasic, the early phase develops in minutes and reaches its plateau phase after fifteen minutes, while the later stage develops in hours and results in complete vasoconstriction. [10,42,43] Until vascular remodeling, HPV is reversible, and can either be global or local (it is the latter in the case of thoracic anesthesia). On HPV, blood flow is directed from the non-ventilated areas to open lung fields, thus optimizing the V/Q matching and systemic oxygen delivery. Adequate HPV is crucial for minimizing the perfusion of the nondependent lung, and by that, for decreasing shunt.

2.3. Pros and cons for spontaneous breathing

Based on the currently available evidence, the maintenance of spontaneous breathing seems to be advantageous during thoracoscopic and even in open thoracic procedures, although it has disadvantages as well. [26,44–49] The (patho)physiological background and potential benefits and disadvantages of maintained spontaneous breathing are briefly discussed below.

2.3.1. Physiology and advantages of spontaneous breathing

2.3.1.1. Fundamentals of spontaneous breathing

Spontaneous breathing is a consequence of the complex interaction between the chest wall, the lungs, and the contacting layers of the pleura, synchronized by the respiratory muscles. Pressure difference is a fundamental element of spontaneous breathing (and of controlled ventilation as well); thus, understanding the influential factors is essential. Under physiological conditions, inspiration is the result of the pressure difference between the alveolar space and the outer environment generated by the respiratory muscles. In contrast with this process, expiration occurs passively. During inspiration, the vertical and sagittal diameter of the thorax is also enlarged, in which the diaphragm and the external intercostal muscles have a pivotal role. The contraction of the diaphragm mainly alters the vertical dimension of the thoracic cavity. The diaphragm is a dome-shaped muscle that separates the thoracic and abdominal cavities, and structurally it can be divided to non-contractile (central) and muscular (costal and crural) parts (Figure 4). The contraction of the diaphragm alters the vertical dimension of the thoracic cavity. The dome of the diaphragm is displaced caudally by the muscle activation, resulting in an increase in vertical dimension, and this „piston-like” movement is responsible for approximately 90% of the volume expansion. Additionally, the contraction of the costal diaphragm lifts the lower six ribs, and this, owing to the shape and orientation of the ribs, results in an increase of the antero-posterior and lateral dimensions of the lower rib cage. Thirdly, as the diaphragm flattens, the elevation of the intra-abdominal pressure generates an expanding force on the lower rib

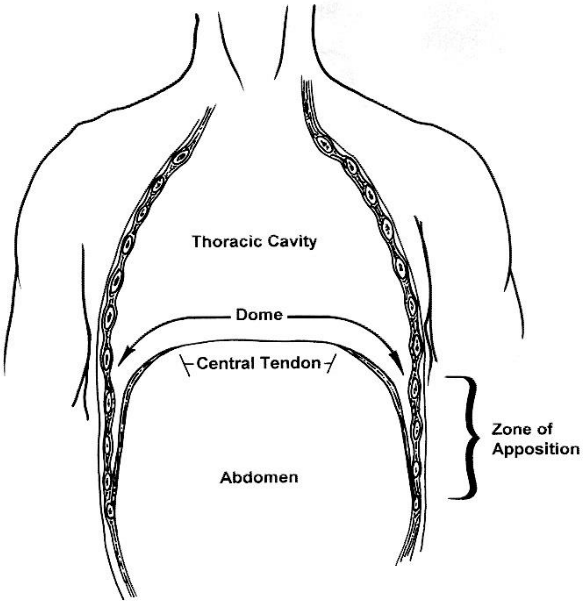

Figure 4 Schematic illustration of the diaphragm

cage as well [50]. The alteration in the volume of the thoracic cavity transferred by the pleural layers induces a change in the lung volume. This process generates subatmospheric pressure in the airways, thus promoting inspiration. Under physiological circumstances, the pressure difference between the alveolar space and the outer environment is generated by the respiratory muscles, the elastic components of the chest wall, and the lungs, resulting in an airflow and an opportunity for gas exchange.

The following universal equation describes the pressure gradient in the respiratory system, regardless of its origin:

$$\mathrm{Pao} + \mathrm{Pmus} = \mathrm{PEEP} + (\mathrm{Ers} \times \mathrm{V}) + (\mathrm{Rrs} \times \mathrm{Flow})$$

Pao, pressure at the airway opening; Pmus, pressure generated by respiratory muscles; PEEP, positive end-expiratory pressure; Ers, respiratory system elastance; Rrs, respiratory system resistance; V, tidal volume; Flow, airflow

2.3.1.2. The impact of ventilation on lung condition

The development of atelectasis in the dependent lung during OLV is a common phenomenon. [51,52] However, the grade of the atelectasis is highly unpredictable and may elevate the already higher shunt fraction; thus, worsen oxygenation. Therefore, preserving the physiological function of the diaphragm can be beneficial under surgical procedures. With spontaneous breathing, persistent negative or low airway pressures in the dependent lung support the improvement of the perfusion in the non-operated side. The grater amplitude movement of the dependent divisions of the diaphragm contributes to increased respiratory efficacy and lung recruitment by preventing alveolar compression and the consequential atelectasis in dependent lung zones; thus, leading to improved ventilation (oxygenation and carbon dioxide removal) [53,54]. The prevention of high alveolar pressure during spontaneous breathing increases the efficacy of hypoxic pulmonary vasoconstriction (HPV). [55] These effects together may lead to better V/Q matching in spontaneously breathing patients. [56,57]

The occurrence of acute lung injury (ALI) after thoracic procedures partly originates in controlled mechanical ventilation and one-lung ventilation. The incidence of ALI associated with OLV can be reduced by applying lung-protective ventilation strategies to prevent the presence of high pressures in the respiratory system (barotrauma), the overdistension of the lung (volutrauma), the shear stress caused by the cycling opening and closing of the alveoli (atelectotrauma), and the consequential activation of the inflammatory system (biotrauma). [51]

The effects of the aforementioned pathophysiological phenomena (barotrauma, volutrauma, atelectotrauma, biotrauma) can be mitigated/eliminated by partially or completely avoiding controlled mechanical ventilation and maintaining spontaneous breathing activity. Additionally, the use of muscle relaxation is associated with diaphragmatic dysfunction and a higher rate of postoperative pulmonary complications compared to procedures performed without the application of muscle relaxation. [10,58]

Furthermore, it is important to understand the dynamics that characterize breathing patterns, respiratory rate, and respiratory amplitude during spontaneous ventilation. These intricate changes in respiratory parameters aim to align the pulmonary function with the metabolic requirements, and the alignment is influenced by local factors, partial pressures of oxygen and carbon dioxide, the volumetric capacity of the lungs, and the chemical composition of the blood perfusing the respiratory tissues.

2.3.1.3. Control of the breathing pattern and dynamics, the influence of the cough reflex

Breathing activity is under neuronal influence. The primary areas responsible for generating the medullary rhythm were identified as the parafacial respiratory group, the pre-Bötzinger complex, and the ventral and dorsal respiratory groups. Interaction of the above-mentioned structures results in a rhythmically alternating inspiratory and expiratory activity [59,60]. This oscillatory activity is influenced by several factors. Sensory input occurs via both the vagal and sympathetic nerves, and airway receptors. Slowly adapting pulmonary stretch receptors perceive the airway pressure and its rate of change, and they are unresponsive to chemicals. They play a role in the Hering-Breuer reflex, influencing the frequency and amplitude of breathing. Rapidly adapting mechanoreceptors respond to both mechanical stimuli and certain chemicals, which leads to increased airway secretion and mucosal vasodilation. Activation of these receptors hinders inspiration, shortens expiration, and contributes to coughing [61,62]. Unmyelinated, chemosensitive C-fiber receptors are crucial for airway defense and hyper-responsiveness. Various chemicals including bradykinin, prostaglandins, hydrogen ions, and capsaicin, can activate these receptors, resulting in coughing and hypersecretion-induced bronchoconstriction [61–64]. Surgical interventions performed alongside spontaneous breathing require the crucial element of ensuring that the cough reflex is not triggered during surgical manipulation. This can be achieved during the interventions by unilaterally blocking the vagal nerve.

Spontaneous breathing comes with the phenomenon of physiological synchronization as the patient can control the respiratory rate and breathing amplitude, which helps to meet the current metabolic requirements.

2.3.1.4. Cardiorespiratory interactions

Heart-lung interaction can be described as the summary of the changes in the basic determinants of the left and right ventricular systolic and diastolic functions during positive pressure ventilation (PPV). PPV is associated with a cyclic change in airway pressure levels and it causes preload fluctuation and, consequently, pulse pressure and stroke volume variation. [65] Spontaneous respiration has less hemodynamic impact than mechanical ventilation, although in the case of thoracic surgeries, this hemodynamic effect is markedly influenced by the physiological and pathophysiological effects of one-lung ventilation.

2.3.2. Pathophysiology and disadvantages of spontaneous breathing

It has to be mentioned that maintained spontaneous breathing activity during thoracic surgeries present some disadvantages as well. With spontaneous breathing, the control over respiratory parameters such as the respiratory rate and tidal volume is limited. In the case of thoracic surgical interventions performed alongside spontaneous breathing, a significant deviation from the "gold standard" is observed in the direction of mediastinal shifting. During PPV, the mediastinum shifts towards the operated side at the time of inspiration, whereas in spontaneous breathing, this occurs in the opposite direction. Additionally, our observations indicate that the amplitude of mediastinal displacement is greater during maintained spontaneous breathing, potentially complicating surgical manipulation. The limited control over respiratory frequency deserves awareness since low respiratory rate may increase the extent of carbon dioxide retention, while an excessively high respiratory frequency can also pose challenges to surgical manipulation. The respiratory depression effect of major analgesics can be a problem that requires attention, although with the application of multimodal regional anesthesia, opiates can be used to optimize respiratory rate during surgeries. By blocking the vagal nerve as a required part of spontaneous breathing thoracic procedures, the tone of pulmonary vasculature and smooth muscles of the airway, as well as mucus secretion, are altered and may influence respiratory function in the postoperative period as well. [66]

Due to the aforementioned physiological changes, the respiratory system may have to bear an increased burden of stress. The stress in the context of lung mechanics is connected to the force applied to the lung tissue. As a part of this, transpulmonary pressure is a crucial parameter to understand lung mechanics and can be defined as the pressure difference between the alveolar and the intrapleural space. Stress and strain results in an inflammatory response as both the endothelial and epithelial cells and the extracellular matrix have a role in it. The cells respond to the mechanical deformation with cytokine production while the fragmentation of the extracellular hyaluronan results in an inflammatory response via Toll-like receptors, and it seems to be the link between the mechanical forces and the biological response. [67–70] The dispersion of the stress and strain in the lung is only theoretically homogeneous as there are inhomogeneities in the lung parenchyma (consolidation, collapse); therefore, the applied force impacts the affected lung zones differently. The lung field connected to the inhomogeneities have to bear more of the stress and strain than the homogenous lung fields. [71]

Volutrauma or barotrauma are not only related to controlled mechanical ventilation but can also be the result of the uncontrolled inspiratory efforts during spontaneous breathing in addition to the increased heterogeneity of ventilation, leading to a regional dorsal atelectrauma due to the cyclic opening and closing of small airways [72,73]. Spontaneous breathing under uncontrolled circumstances can cause lung injury, or at the least, can worsen existing lung injury. Dreyfuss et al. in their animal experiment showed that high tidal volumes and overinflation of the lung, regardless of the origin of the stress and strain (induced with positive pressure ventilation or by negative pressure), can result in pulmonary edema. [74]

Under normal circumstances, the hydrostatic pressure difference between the intra- and extravascular compartments of the lung results in fluid filtration from the capillaries to the interstitium. The resulting filtrate is cleared by the lymphatic drainage of the interstitial tissue. With maintained spontaneous breathing, the increased or uncontrolled inspiratory effort, especially when it comes with increased airway resistance, can result in significant drop in alveolar pressure and further changes in thoracic (transpulmonary) pressure. These can mimic the cardiothoracic relationship of negative pressure pulmonary edema, and the increase in the alveolar-capillary pressure gradient results in a higher rate of fluid filtration, and finally, when it exceeds the capacity of lymphatic drainage, it leads to interstitial edema. [75–77]

Fighting against lung damage is always challenging as there are several gray areas in the field of lung injury prevention. Additionally, in the case of maintained spontaneous breathing, we face extra difficulties in the feasible measurement of respiratory mechanics parameters (for example, driving pressure) [78]. In clinical practice, the decision to maintain spontaneous breathing or use mechanical ventilation depends on the condition and the underlying pathology of the patient, as well as the assessment of benefits and risks by the healthcare team.

3. Open points

Due to the paradigm shift that occurred in the last decades in the field of thoracic surgery and thoracic anesthesia, minimally invasive techniques have become more and more frequently applied. Bringing maintained spontaneous breathing to the fore has provided certainty about its relevance in thoracic anesthesia, although it has also raised some questions, and risks and concerns related to the non-intubated technique have also been identified. The main concern appears to be the question of the safe airway. This problem can possibly be resolved with the SVI method as we use double-lumen endotracheal tube for intubation with maintained spontaneous breathing.

1. Is there a non-intubated technique that allows conventional anesthesiological interventions (lung recruitment, fiberoptic manipulation, water submersion test) to be performed safely?

2. Is the use of the SVI technique a safe and feasible alternative to the gold standard method in thoracic anesthesia?

3. Is the SVI technique suitable for patients who are not candidates for a NITS procedure according to the applied exclusion criteria of NITS?

4. Is the SVI technique associated with temporary or permanent gas exchange abnormalities and/or acid-base disturbances?

5. Comparison of the intra- and early postoperative results of thoracic surgeries performed with SVI with data from the literature.

4. Research aims and objectives

Our main goal was to study the currently available spontaneous breathing anesthetic strategies and their influence on airway safety, as well as to investigate their potential effects on intraoperative and early postoperative results.

I. In the first narrative review published by us, we intended to survey the development of thoracic anesthesia, focusing primarily on the advantages and disadvantages of anesthetic techniques applied by different workgroups for spontaneous breathing thoracic procedures.

II. Secondly, in our prospective, nonconsequential case series, we investigated the intra- and early postoperative results of thoracic surgeries performed with SVI (maintained spontaneous breathing with double-lumen tube intubation), as well as the safety and feasibility of this anesthetic strategy, with specific focus on the intraoperative oxygenation, carbon dioxide removal, and the consequent acid-base disturbances.

We aimed to assess the following:

1. Can the SVI technique be a safe and feasible method for various types of thoracic procedures (minor and major resections)?

2. Can SVI reduce the mechanical ventilation time or alter the applied ventilation parameters?

3. Are there any differences in the intraoperative parameters (oxygenation, carbon dioxide removal, acid-base disturbances, hemodynamic parameters) compared with the gold standard and NITS methods?

4. Is SVI a useful and safe alternative if surgical conversion (thoracotomy) becomes necessary?

5. Materials and methods

5.1. Study I.

Multiple medical literature databases (PubMed, Google Scholar, Scopus) were searched, using the terms [(non-intubated) OR (non-intubated) OR (tubeless) OR (awake)] AND (thoracoscopic surgery)] as well as their Medical Subject Headings (MeSH) terms from 2004 to December 2021. Three hundred and six scientific papers were collected. The editorials, commentaries, and letters were excluded, similarly to papers focusing on topics other than the non-intubated (also known as awake or tubeless) VATS technique, as well as the full text scientific papers available in languages other than English. The selection process is illustrated in the Figure 5.

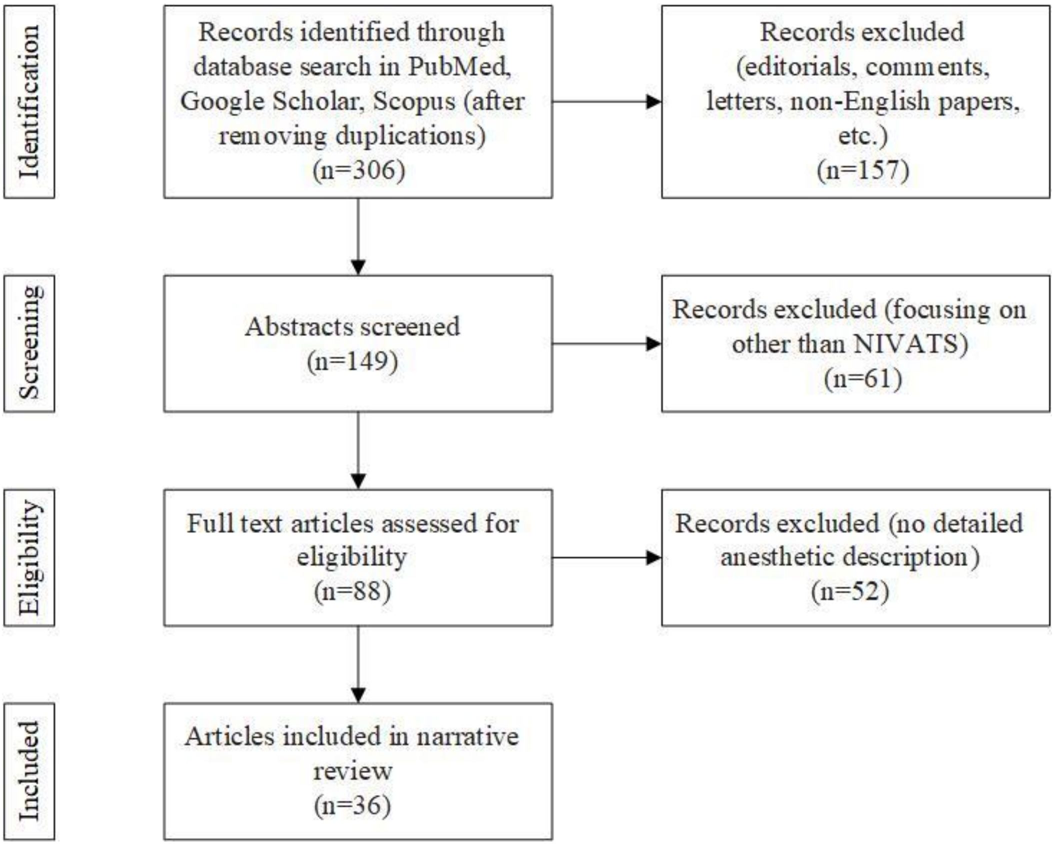

Figure 5 Flowchart of article selection.

5.2. Study II.

5.2.1. Ethical considerations

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethical Committee of the Human Investigation Review Board at the University of Szeged (protocol code: 4703; date of approval: 20 January, 2020). All patients were informed about the risks and benefits of the SVI method compared to classic anesthetic management before the operation. Informed consent was obtained from all subjects involved in this study.

5.2.2. Study Design and Patient Selection

In our case series, we applied the SVI method in a prospective, nonconsequential manner when patients met the inclusion and exclusion criteria (Table 1), and a dedicated anesthetist was assigned. Between 10 March, 2020 and 28 October, 2022, 141 surgeries were performed by our thoracic surgery team using the SVI approach for general anesthesia. All surgeries were performed by a single surgeon, and the patients were anesthetized by three anesthetists using the same procedural algorithm. Initially, we intended to perform 144 SVI procedures but three cases were excluded from the statistical analyses because spontaneous breathing did not return by the end of the surgery. Retrospective data including the intraoperative and early postoperative periods were collected and statistically analyzed to assess the feasibility of the SVI method as a primary endpoint and to identify any potential limiting factors.

For patient selection, we applied our previously published criteria for non-intubated thoracic procedures (Table 1).[79] However, the contraindications for NITS do not exclude the use of the SVI method. [31] In our daily clinical setting, patients with a body mass index < 34 without other contraindications were deemed suitable for SVI. The preoperative pulmonological and anesthesiologic examinations were the same as those in the normal or NITS cases. From a surgical perspective, we included all cases of SVI that would also be eligible for normal VATS according to consensus meeting recommendations. We included patients with no advanced lung cancer (< 7 cm, N0, or N1). [80]

Table 1. Exclusion criteria of spontaneous breathing anesthetic techniques.

NITS	SVI
Patient refusal	Patient refusal
Mental disorder (lack of compliance)	
Elevated intracranial pressure	Elevated intracranial pressure
Sleep apnea syndrome	
Airway abnormalities, anticipated difficult airway	
BMI ≥ 34 kg/m^2	BMI ≥ 34 kg/m^2
Persistent cough or high airway secretion	
Elevated risk of regurgitation	
Coagulation abnormality, INR > 1.5	
Hemodynamic instability, right heart failure	Hemodynamic instability, right heart failure

NITS, non-intubated thoracic surgery; SVI, spontaneous ventilation combined with double-lumen tube intubation; BMI, body mass index; INR, International Normalized Ratio.

5.2.3. Anesthetic management

Three-lead ECG, oxygen saturation (SpO_2) and invasive blood pressure measurements were performed. The depth of anesthesia was monitored using the bispectral index (BIS, Medtronic Vista). Anesthesia was induced with fentanyl (1–1.5 g/kg) and propofol using target-controlled infusion (Schnider model) with effect-site targeting. Considering the induction effect, the site target concentration was generally set between 4 and 6 µg/mL, depending on individual patient characteristics. Subsequently, the target concentration was modified to keep the BIS value between 40 and 60. Mivacurium chloride (0.1–0.15 µg/kg), a short-acting non-depolarizing muscle relaxant, was used to ensure optimal conditions for intubation. Although the dose of mivacurium that was used was below the recommended dose for intubation, we found that, 180 s after drug administration, the conditions for intubation were good or excellent. Similarly to the gold standard approach, fiberoptic equipment (aScope, Ambu, Ballerup, Denmark) was used to confirm the proper position of the DLT. Confirmation of the proper tube position was crucial because further manipulation of the tube after the effects of the muscle relaxant diminished would not be well tolerated. Muscle relaxation facilitated the DLT insertion and helped in early surgical steps. Although single-lumen intubation with a blocker may be considered less invasive, a bronchial blocker, according to our practice is used as a secondary option for situations in which the placement of the DLT is not possible. The potential advantages of DLTs include greater stability, they are also less prone to dislodgment during surgery, and provide more effective lung isolation. Furthermore, it is essential to consider the cost effectiveness of each approach and the available resources. After the thoracic cavity was opened, a paravertebral nerve blockade for pain relief and a vagal blockade to prevent the cough reflex were performed. Spontaneous breathing returned after the muscle relaxant effect was eliminated. In unexpected cases, when spontaneous breathing was unsatisfactory (low tidal volumes, bradypnea), temporary pressure support ventilation with a low-flow trigger (1.0 L/min) was used until the muscle relaxant effect was fully eliminated.

Intraoperatively, altering the FiO_2 (40–100%) and applying 3–5 cmH_2O PEEP to the dependent lung helped keep the SpO_2 and $PaCO_2$ within normal or close-to-normal ranges. Severe hypercapnia or hypoxia was also prevented or managed by applying PSV to the dependent lung. In case of necessity, the intraoperative evaluation of air leakage involved conducting a WST. After filling the thoracic cavity with saline, manual positive pressure ventilation was synchronized with the patient’s spontaneous breathing activity. Furthermore, if it was necessary, we were able to apply PSV to perform the leak test.

Rescue Maneuvers

Hypotension:

According to our intraoperative hemodynamic management protocol, when the mean arterial pressure was < 60 mmHg, the systolic blood pressure was < 90 mmHg or decreased by more than 25%, ephedrine (5–10 mg) or phenylephrine (50–100 µg) was administered in divided doses.

Hypoxia / Hypercapnia:

In patients with $SpO_2 < 92\%$ or $PaO_2 < 60$mmHg, 3–5 cmH_2O PEEP administration and FiO_2 alteration were used to increase oxygenation. In the cases of $PaCO_2 > 75$ mmHg or $pH < 7.15$, the nondependent lung was considered to be re-inflated for a short period to eliminate carbon dioxide and improve oxygenation. The effect of reinflation is partial and temporary. Thus, if the improvement was not satisfactory, or as an initial step, we administered PSV with 3–5 cmH_2O PEEP and 8–14 cmH_2O pressure support to assist in gas exchange. If hypercapnia and/or hypoxia were persistent, anesthetic conversion with muscle relaxation (0.05–0.1 µg/kg of mivacurium) and volume-controlled mechanical ventilation (PEEP: 3–5 cmH_2O, tidal volume: 3–4 mL/kg, Pmax: < 30 cmH_2O) were applied (Figure 6).

Technical Difficulties:

Paradoxical mediastinal shifting is an accompanying phenomenon of spontaneous ventilation surgery. The mediastinum moves downward during inspiration and vice versa during expiration. If it was intolerable, pressure support ventilation was applied to overcome the issue. An ineffective vagal nerve blockade may result in coughing. If repeated vagal nerve infiltration was not feasible, anesthetic conversion was applied (Figure 6).

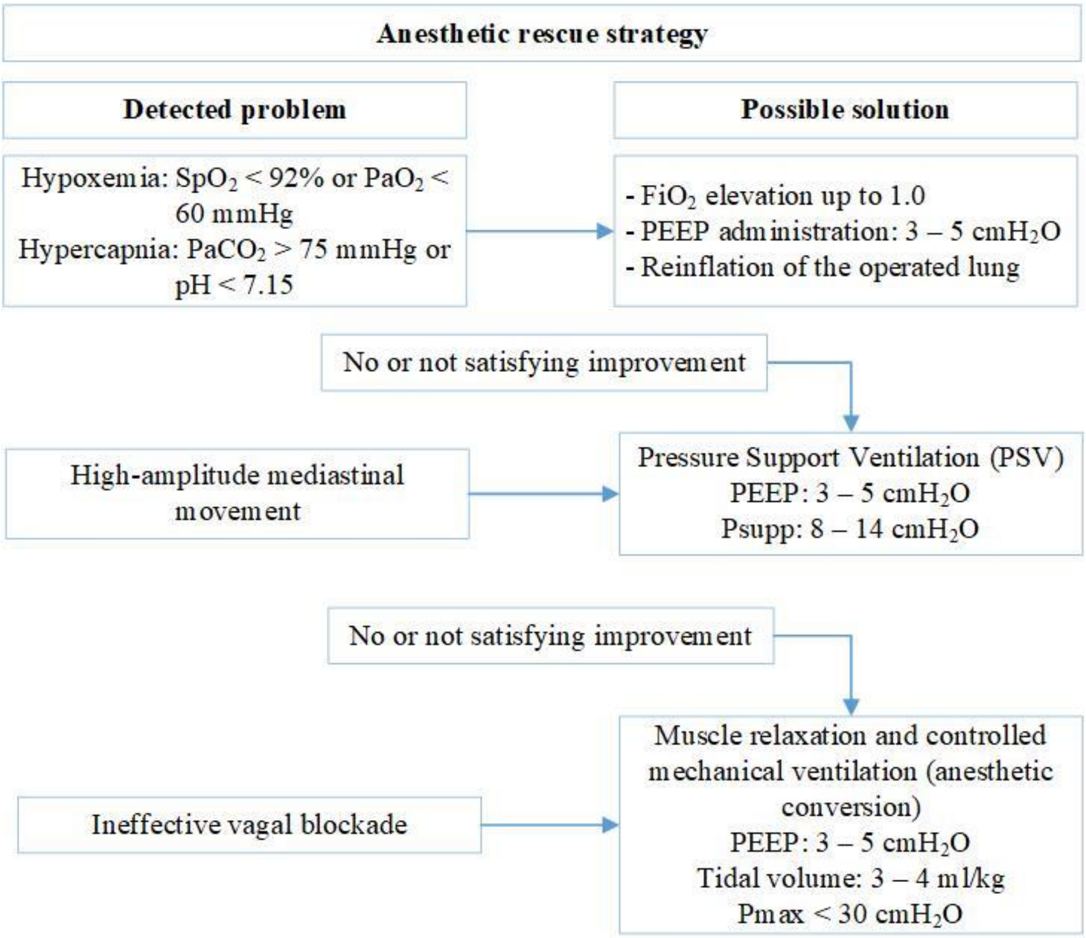

Figure 6 Anesthetic Rescue Strategy

5.2.4. Regional Anesthetic Techniques

In our study, all regional anesthetic techniques were performed by the surgeon under direct vision to decrease the risk of complications associated with a regional blockade and to reduce the length of stay in the operating room. During VATS with SVI in routine cases, 5 mg/kg of lidocaine (2%) was administered at the site of incision at the fifth intercostal space in the mid-axillary line. After opening the thoracic cavity under thoracoscopic guidance, vagal and paravertebral blocks were performed. For the vagal nerve blockade, 3–5 mL of bupivacaine (0.5%) was administered close to the nerve (aortopulmonary window, left side; upper mediastinum, right side). A deep intercostal or paravertebral blockade was achieved by administering 4–5 mL of bupivacaine (0.5%) close to each intercostal nerve (from the second to the fifth intercostal space). The maximum amount of bupivacaine used was 0.5 mL/kg (2.5 mg/kg). In cases of open SVI, an intercostal nerve blockade was guaranteed by administering 4–5 mL of bupivacaine (0.5%) between the third and sixth intercostal spaces.

5.2.5. Surgical Technique

We performed the same VATS uniportal method during the SVI procedures that we published in our NITS study [29,79] with indications based on the European Society of Thoracic Surgeons consensus report [6] and the recommendation of the NITS. [81,82]

5.2.6. Postoperative Care

Every patient was observed in the post-anesthesia care unit (PACU) for at least 2 h or until they met the criteria for leaving the PACU (visual analog scale (VAS) score < 3, Aldrete score > 9). Oxygen was administered to all patients via a face mask with 4–6 l/min O2 postoperatively to achieve a SpO_2 of > 94% or > 88% in patients with COPD. None of the patients required a higher level of oxygen or a higher degree of respiratory support (non-invasive ventilation) during the PACU stay or in the later postoperative period. None of the patients experienced fever or required bronchial secretion removal. Postoperatively, chest radiography was performed before and after the chest tube removal. Any pneumothorax, atelectasia/dystelectasia, infiltration, or pleural fluid observed in the radiography were considered abnormal findings. The pain intensity during hospitalization was assessed using a numeric pain rating scale (NPRS). An NPRS > 3 was the intervention point, and a minor analgesic agent prescribed by the anesthetist was administered orally as soon as possible. For patients who underwent thoracotomy, a pleural catheter was inserted for continuous local anesthetic (0.1 mL/h/kgbw bupivacaine 0.33%) administration.

5.2.7. Arterial Blood Sampling

In the cases of major pulmonary resection, blood samples were collected four times (T1, T2, T3, and T4; Figure 7). For T1, preoperative blood samples were collected before anesthesia induction, with a FiO_2 of 0.21. For T2, steady-state blood samples were collected 15 min after the vagal nerve blockade. For T3, blood samples were collected 15 min after anatomical resection (and only during anatomical resections). For T4, postoperative blood samples were collected 30 min after the patient arrived in the recovery room and at a FiO_2 of 0.5.

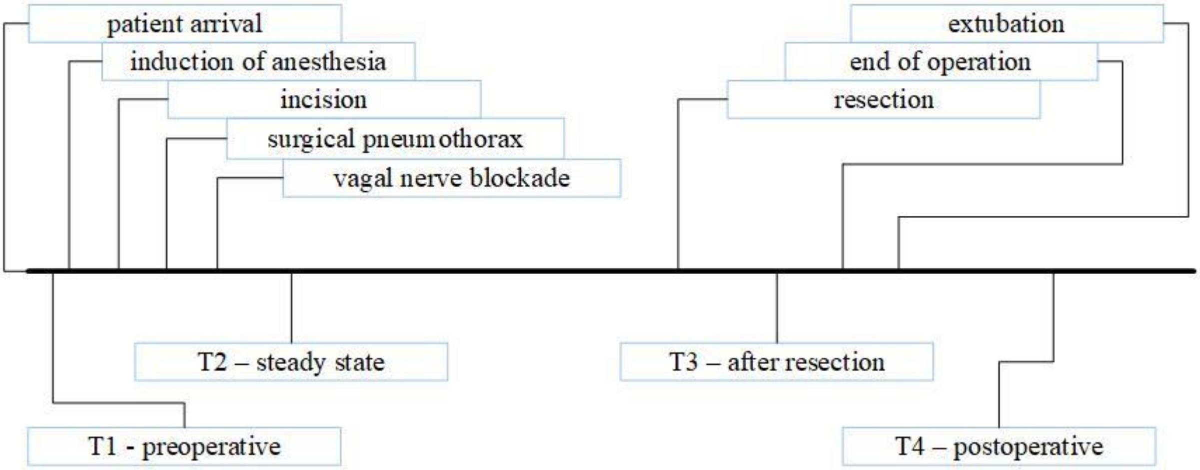

Figure 7 Timeline of blood gas sampling

5.2.8. Data Collection and Analyses

Data were retrospectively collected from our medical system (e-MedSolution) and personal patient documentation. Personal patient data were also collected. Descriptive statistics were performed using R statistical software, version 4.2.2 (R Foundation, Vienna, Austria), and SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as the mean ± standard deviation (SD) for continuous variables and as the count and percentage for categorical variables.

6. Results

6.1. Study I.

Based on the literature data, preserving spontaneous breathing can diminish the potential harmful effect of the conventional approach, but it is very important to emphasize that SB during thoracic procedures can be dangerous due to unusual circumstances (i.e., paradoxical breathing, mediastinal movement). This explains why the inclusion of NIVATS in the training programs for professional perioperative teams is essential to ensure maximal patient safety and comfort for the teams. [83,84] After reviewing the literature, we identified different methods with very similar clinical results.

6.1.1. The Italian technique

From the early 2000s, Pompeo and Mineo, two Italian researchers at Tor Vergata University, started to investigate their awake method. In the beginning, they used local and thoracic epidural anesthesia without sedation during VATS wedge resection of small pulmonary nodules. [26] They provided oxygen supplementation via face masks. It was found to be safe and feasible with better patient satisfaction, less nursing care, and shorter hospital stays. Through the years, the feasibility of this awake technique has been proven for increasingly complex VATS procedures (lung volume reduction surgeries, decortication, and bullectomy). Besides the fact that all their studies have found the technique to be feasible, further advantages have also been proven, such as the shorter operating room times, reduction of costs, less immunological and stress responses, and shorter air leak duration in the postoperative period. Their approach has evolved from awake to midazolam- or remifentanil-based, bispectral-index-(BIS-) guided, mildly sedated states over time, and thoracic epidural analgesia (TEA) was replaced with intercostal blockade. In order to obtund the cough reflex, Guarracino and Mineo used an aerosolized local anesthetic (lidocaine). [26,45,49,85–91]

6.1.2. The Asian technique

Asian researchers, in parallel with the work of their European colleagues, developed their own method, which differed from that of the Italians in several aspects. The pioneers of these studies applied intravenous propofol anesthesia with a target-controlled infusion system, depth of anesthesia monitoring, and targeted sedation maintaining a BIS value between 40 and 60 during their non-intubated anesthetic procedure. In the beginning, TEA was performed, but later they switched to the intercostal nerve blockade for its simplicity, safety, and to provide better hemodynamic stability. [28,47,92] In order to prevent coughing, intrathoracic vagal blockade was routinely applied. With their approach, intubation could be avoided in the course of major surgeries such as segmentectomy and lobectomy, not only during the VATS procedures, but also during thoracotomies and even in sternotomies (62). The way of oxygen supplementation has also changed from using face masks to transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) devices due to the larger oxygen reserve during OLV. [47,93,94]

Their results proved this method to be safe, feasible, even in the elderly and in children. However, obese patients whose BMI exceeds 25 kg/m^2 are not optimal candidates for NITS due to the excessive mediastinal movements, and encounter a higher risk of conversion to intubated anesthesia. [44,46,95–103]

6.1.3. The Hungarian technique

The previously introduced techniques have shown many advantages and disadvantages during thoracic procedures. The ever-growing experience has allowed us to perform increasingly challenging procedures, which required the same anesthetic abilities as the ones used in intubated thoracic surgeries such as the intraoperative re-insufflation of the lung or performing bronchoscopy. Our workgroup have presented a mixed technique using the laryngeal mask with targeted propofol sedation guided by the bispectral index scale, which allowed these intraoperative procedures and other complicated surgical treatments, including conversion to thoracotomy or complicated sleeve resections, to be performed. [29]

The same workgroup published a new method called VATS-SVI, which combined the positive physiological effects of SB with those of the gold standard technique applying double-lumen tube intubation and providing safe airway. Patients received premedication with midazolam and fentanyl. The induction and maintenance of anesthesia was guaranteed by propofol target-controlled infusion dosed to reach a BIS value between 40 and 60.

Better intraoperative cardiopulmonary stability and similar postoperative results were found with spontaneous ventilation combined with intubation compared to non-intubated thoracic surgery. [31,104] The duration of mechanical ventilation could be reduced by 76.6%, preserving all the beneficial effects of NITS. From the non-surgical aspects, Furák *et al.* have found advantages among oncology patients. Among the non-intubated patients, 92% completed the planned chemotherapy protocol, compared to 71% of patients in the intubated group. These results showed that the non-intubated procedure resulted in improved adjuvant chemotherapy compliance and lower toxicity rates after lobectomy. [105]

6.1.4. Other technique

Besides the Italian and Asian approaches, other modifications to the NITS procedure have also been developed. Al-Abdullatief *et al.* from Saudi Arabia performed major operations, such as lobectomy and thymectomy, in awake or mildly sedated individuals. After iv. midazolam-fentanyl premedication, thoracic epidural anesthesia was performed, and the ipsilateral stellate ganglion was blocked to diminish the cough reflex. [27]

In Table 2, we summarize, the most relevant characteristics of the different anesthetic approaches.

Table 2. Cornerstones of anesthetic management in thoracic surgery

Method	Approach	Airway	Level of sedation	Drugs for sedation	Type of analgesia	Advantages	Limitations
Conventional		DLT, BB	BIS 40-60	Fentanyl Propofol / volatile anesthetic agents Muscle relaxant	TEA	Safe airway Isolated lungs Possibility of fibroscopy Possibility of lung recruitment	Intubation trauma Muscle relaxation Hemodynamic consequences of TEA
Italian	NIVATS	Facemask/ (LMA)	Awake, BIS-guided sedation	None / midazolam, remifentanil	TEA/ICB + aerosolized lidocaine	No muscle relaxation Maintained spontaneous breathing	No safe airway
Asian	NIVATS	Facemask/ THRIVE	BIS 40-60	Propofol	TEA/ICB + vagal blockade	No muscle relaxation Maintained spontaneous breathing	No safe airway
Hungarian	NIVATS	LMA	BIS 40–60	Midazolam, fentanyl, propofol	ICB, PVB + vagal blockade	No muscle relaxation Possibility of lung recruitment	Semi-safe airway
	VATS-SVI	DLT	BIS 40–60	Midazolam, fentanyl, propofol	ICB, PVB + vagal blockade	Safe airway Spontaneous breathing after elimination of muscle relaxant Isolated lungs Possibility of fibroscopy and lung recruitment Higher BMI limit (< 32)	Intubation trauma Increased airway resistance
Other	NIVATS	Facemask	Light sedation	Midazolam, fentanyl	TEA + Stellate ganglion blockade	No muscle relaxation Maintained spontaneous breathing	No safe airway No DOA monitoring

DLT, double-lumen tube; BB, bronchial blocker; TEA, thoracic epidural anesthesia; NIVATS, non-intubated video-assisted thoracoscopic surgery; LMA, laryngeal mask airway; BIS, bi-spectral index; ICB, intercostal block; VATS-SVI, video-assisted thoracoscopic surgery with spontaneous ventilation combined with double-lumen tube intubation; THRIVE, transnasal humidified rapid-insufflation ventilatory exchange; PVB, paravertebral blockade; BMI, body mass index; DOA, depth of awareness

6.2. Study II.

6.2.1. Patient Characteristics

A total of 67 (47.52%) of the patients were men, and 74 (52.48%) were female patients. The mean age was 62.13 years (19–83), with a mean BMI of 25.82 (15.79–38.54) (Table 3). A total of 13 patients (9.22%) had previously undergone thoracic surgery.

Table 3. Demographic parameters of SVI patients

		All Cases	
		N = 141	**100%**
Sex	Male	67	47.52
	Female	74	52.48
Age	18–64	70	49.65
	65–	71	50.35
	mean ± SD	62.13 ± 13.56	
	min-max	19–83	
BMI	Underweight (BMI < 18.5)	6	4.26
	Normal weight (BMI: 18.5–24.9)	62	43.97
	Pre-obesity (BMI: 25–29.9)	49	34.75
	Obesity class I (BMI: 30–34.9)	19	13.48
	Obesity class II (BMI: 35–39.9)	5	3.55
	mean ± SD	25.82 ± 4.51	
	min-max	15.79–38.54	
ASA score	1	7	4.96
	2	95	67.38
	3	39	27.66
Smoking status (current)	Yes	57	40.43
	No	84	59.57
Smoking status (current or prev.)	No	49	34.75
	Yes	89	63.12
	NA	3	2.13
Smoking intensity	Less than 20/day	30	
	More than 20/day	37	

	NA	22	
Years of smoking	0–9 years	4	
	10–19 years	6	
	20–29 years	12	
	More than 30 years	44	
	NA	23	
Most relevant comorbidities	Hypertension	84	59.57
	Cardiovascular disease	41	29.08
	Asthma/COPD	38	26.95
	Diabetes mellitus	27	19.15
	Previous thoracic surgery	13	9.22
Preoperative medications	Anti-hypertensive agent	75	53.19
	Rhythm/frequency control agent	54	38.30
	Anticoagulants, antiaggregants	44	31.21
	Other cardiovascular drugs, diuretics	18	12.77
	Pulmonological drugs	29	20.57
	Statins	24	17.02
	Antidiabetics (incl. insulin)	19	13.48
	Psychiatric drugs	28	19.86
	Other medications	34	24.11

BMI, body mass index; ASA score, American Society of Anesthesiology score; COPD, chronic obstructive pulmonary disease.

The surgical procedures were mainly lung resections (76 lobectomies, 22 segmentectomies, 25 wedge resections and 5 other procedures) and 13 thymectomies (Table 4).

Table 4. Surgical parameters of SVI patients n = 141.

	Mean	**Range**
Charlson Comorbidity Index	5.51	0–12
FEV_1 (%) (n = 91)	82.45	22.3–126.4
DLCO (%) (n = 47)	73.67	35.3–106
Surgical time (min)	80.6	25–150
	N	**%**

Pneumonectomy	1	0.71%
Lobectomy	76	53.9%
Segmentectomy	22	15.6%
Wedge resection	25	17.73%
Pleural biopsy	2	1.42%
Exploration	2	1.42%
Thymectomy	13	9.22%

FEV_1, forced expiratory volume in one second; DLCO, diffusing capacity of the lungs for carbon monoxide.

6.2.2. Anesthetic Results

In 93 patients (93/141, 65.96%), spontaneous respiration, with or without 3–5 cmH_2O PEEP administration, produced satisfactory gas exchange. In 44 cases (44/141, 31.21%), temporary or permanent PSV administration was necessary for supportive oxygenation and carbon dioxide removal (Table 5). In four cases (4/141, 2.84%), repeated muscle relaxation and a return to a conventional anesthetic pathway were necessary. In one patient, high-amplitude mediastinal movement was intolerable despite the pressure support ventilation applied. In two cases, vagal blockade ineffectiveness resulted in coughing under surgical manipulation, and muscle relaxation was necessary. In one patient, endotracheal tube malposition was confirmed, and anesthetic conversion was necessary for correction (Table 5).

Table 5. Success of SVI and anesthetic conversions of SVI (N = 141).

Overall Success of SVI:	**N**	**%**
Spontaneous respiration with or without PEEP (non-PSV group)	93	65.96
Temporary/permanent pressure support ventilation (PSV group)	44	31.21
Anesthetic conversion (muscle relaxation, CMV)	4	2.84
Reasons for anesthetic conversion:	**N**	**%**
Intolerable mediastinal movement	1	0.71
Ineffective vagal blockade	2	1.42
DLT malposition	1	0.71

SVI, spontaneous ventilation combined with double-lumen tube intubation; PEEP, positive end-expiratory pressure; OLV, one-lung ventilation; DLT, double-lumen tube; CMV, controlled mechanical ventilation.

We compared the potentially relevant factors influencing the necessity of pressure support ventilation during an SVI procedure (Table 6). The mean BMI was 26.9 (18.75–37.81) and

25.39 (15.79–38.54) in the PSV and in non-PSV groups, respectively. The incidence of asthma or COPD in the PSV group was 31.48% (14/44), and in the non-PSV group, it was 24.73% (23/93). According to the respiratory test parameters of limited availability, the mean FEV$_1$ (83.77% ± 18.35% vs. 75.71% ± 22.75%; p = 0.043) and DLCO (76.55% ± 16.04% vs. 65.89% ± 22.04%; p = 0.044) values were significantly lower in the PSV group than in the non-PSV group. In the PSV group, thymectomy was performed in five cases (5/44, 11.36%), in which pressure support ventilation was necessary due to a bilateral surgical pneumothorax.

Table 6. Patient characteristics of the PSV and non-PSV groups.

		PSV Group	**Non-PSV Group**	***p***
		N = 44	**N = 93**	
Sex	Male	24 (54.55%)	40 (43.01%)	0.271$_{(1)}$
	Female	20 (45.45%)	53 (56.99%)	
Age	18–64	21 (47.73%)	47 (50.54%)	0.855$_{(1)}$
	65–	23 (52.27%)	46 (49.46%)	
	mean ± SD	62.59 ± 12.86	61.09 ± 15.55	0.553$_{(2)}$
	min-max	19–80	26–83	
BMI	Underweight (BMI < 18.5)	0 (0%)	6 (6.45%)	^{3} -$_{(3)}$
	Normal weight (BMI: 18.5–24.9)	17 (38.64%)	43 (46.24%)	
	Pre-obesity (BMI: 25.0–29.9)	18 (40.91%)	29 (31.18%)	
	Obesity class I (BMI: 30.0–34.9)	8 (18.18%)	11 (11.83%)	
	Obesity class II (BMI: 35.0–39.9)	1 (2.27%)	4 (4.3%)	
	mean ± SD	26.90 ± 4.18	25.39 ± 4.62	0.068$_{(2)}$
	min-max	18.75–37.81	15.79–38.54	
ASA score	1	2 (4.55%)	5 (5.38%)	0.936$_{(4)}$
	2	29 (65.91%)	63 (67.74%)	
	3	13 (29.55%)	25 (26.88%)	
Smoking status (current)	Yes	14 (31.82%)	40 (43.01%)	0.262$_{(1)}$
	No	30 (68.18%)	53 (56.99%)	
Smoking status (current or prev.)	No	17 (38.64%)	32 (35.56%)	0.849$_{(1)}$
	Yes	27 (61.36%)	58 (64.44%)	
	NA	0	3	-
	Hypertension	29 (65.91%)	53 (56.99%)	0.355$_{(1)}$

Most relevant comorbidities	Cardiovascular disease	11 (25%)	29 (31.18%)	0.547(1)
	Asthma/COPD	14 (31.82%)	23 (24.73%)	0.306(1)
	Diabetes mellitus	11 (25%)	16 (17.2%)	0.358(1)
	Previous thoracic surgery	6 (13.64%)	7 (7.53%)	0.349(1)
Spirometry	FEV$_1$ (%) N	26	61	0.043(2)
	FEV$_1$ (%) mean ± SD	75.71 ± 22.75	83.77 ± 18.35	
	DLCO (%) N	11	34	0.044(2)
	DLCO (%) mean ± SD	65.89 ± 22.04	76.55 ± 16.04	
	FVC (%) N	24	51	0.253(2)
	FVC (%) mean ± SD	88.45 ± 20.5	91.36 ± 16.01	
	FEV$_1$/FVC (%) N	22	37	0.215(2)
	FEV$_1$/FVC (%) mean ± SD	69.69 ± 11.84	71.94 ± 9.68	
Thymectomy	Yes	5 (11.36%)	8 (8.6%)	0.756(1)
	No	39 (88.64%)	85 (91.4%)	

[1] Fisher’s exact test; [2] *t*-test; [3] Does not meet the criteria for Pearson’s chi-squared test; [4] Pearson’s chi-squared. Normality was tested via visual interpretation (Q–Q plot). Continuous variables were tested via an independent samples *t*-test to compare differences between groups, whereas categorical variables were analyzed using Pearson’s chi-squared test and Fisher’s exact test to compare the proportions of groups. Four cases, in which muscle relaxation and conversion to the classic anesthetic method were necessary, have been excluded from the statistical analysis.

After anesthetic induction and 5–10 min following the vagal nerve blockade, hypotension was common. Of the 141 patients, 65 (46.1%) required phenylephrine or ephedrine due to hypotension. Ephedrine or phenylephrine administration was necessary in 49 cases (49/95, 51.58%) in patients with hypertension or other cardiovascular diseases (CV group), and it was administered for 15 patients (15/44, 34.09%) without any cardiovascular disease (non-CV group). The systolic blood pressure reduction was 33.45 mmHg ± 18.71 mmHg in the CV group, and it was 28.67 mmHg ± 19.55 mmHg in the non-CV group. Furthermore, the diastolic blood pressure reduction was 17.64 mmHg ± 10.68 mmHg and 15.49 mmHg ± 11.55 mmHg in the CV and non-CV groups, respectively (Table 7). However, none of our patients required continuous pharmacological hemodynamic support.

Table 7. Hemodynamic support parameters of SVI patients.

		CV Group	**Non-CV Group**	***p***
		N = 95	**N = 44**	
Ephedrin / Phenylephrin administration	Yes	49 (51.58%)	15 (34.09%)	$0.068_{(1)}$
	No	46 (48.42%)	29 (65.91%)	
Ephedrin dosage (mg)	N	28	8	$0.774_{(2)}$
	mean ± SD	17.5 ± 11.18	16.25 ± 9.16	
Phenylephrin dosage (µg)	N	28	7	$0.473_{(2)}$
	mean ± SD	257.14 ± 168.17	207.14 ± 136.71	
RRsys difference (mmHg)	N	91	43	$0.176_{(2)}$
	mean ± SD	33.45 ± 18.71	28.67 ± 19.55	
RRdias difference (mmHg)	N	91	43	$0.291_{(2)}$
	mean ± SD	17.64 ± 10.68	15.49 ± 11.55	

[1] Fisher’s exact test; [2] *t*-test; Normality was tested via visual interpretation (Q–Q plot). Continuous variables were tested via an independent samples *t*-test to compare differences between groups, whereas categorical variables were analyzed using Fisher’s exact test to compare the proportions of groups. RRsys, systolic blood pressure; RRdias, diastolic blood pressure. Two patients were excluded from the statistical analysis, as no data were available regarding their cardiovascular disease status.

The mean one-lung ventilation time was 74.88 min (20–140 min). The mean mechanical and spontaneous OLV times were 17.55 min (0–115 min) and 57.73 min (0–100 min), respectively. The mechanical OLV time was reduced by 76.5%. The respiratory rate altered between 4 and 36 min. The mean minimum respiratory rate was 12.19 (4–30), whereas the mean maximum respiratory rate was 19.19 (6–36) (Table 8).

Table 8. Anesthesiologic parameters of SVI patients (N = 141).

	Mean	**Median**	**Std. Deviation**	**Minimum**	**Maximum**
HR min	64.84	65.00	12.432	39	90
HR max	84.91	83.00	14.314	52	130
Pre RRSys	126.93	125.00	22.199	80	180
Pre RRDias	74.37	70.00	14.108	38	120
Post RRSys	94.92	90.00	20.594	46	145
Post RRDias	57.25	60.00	12.784	26	94
OLV time	74.88	75.00	25.521	20	140

Mech. OLV time	17.55	15.00	17.245	0	115
Sp. OLV time	57.73	60.00	24.685	0	130
Sp. OLV/OLV (%)	76.539	80.952	19.714	0	100
SpO$_2$ Min	93.96	94.00	4.060	81	100
SpO$_2$ Max	99.18	100.00	1.254	94	100
Resp. R. Min	12.19	12.00	3.302	4	30
Resp. R. Max	19.19	18.00	4.659	6	36

HR, heart rate; Pre RRSys, systolic blood pressure before vagal blockade; Pre RRDias, diastolic blood pressure before vagal blockade; Post RRSys, systolic blood pressure after vagal blockade; Post RRDias, diastolic blood pressure after vagal blockade; Mech. OLV, mechanical one-lung ventilation; Sp. OLV, spontaneous one-lung ventilation. OLV, one-lung ventilation; SpO$_2$, oxygen saturation; Resp. R, respiratory rate.

6.2.3. Blood Gas Results

At least one blood gas test result was available for 94 patients. According to the blood gas results, the mean PaO$_2$ level at time T2 was 115.97 mmHg (50.4–472.6 mmHg) and 143.831 mmHg (59.9–425.6 mmHg) at T3 (Table 9), and it was associated with a 93.96% (81–100%) mean minimal intraoperative oxygen saturation (Table 8). Hypercapnia, with or without respiratory acidosis, was a common but transient intraoperative complication. The mean PaCO$_2$ level at T2 was 59.05 mmHg (37.1–92.9 mmHg), with a mean pH of 7.27 (7.1–7.41). The mean PaCO$_2$ level at T3 was 58.17 mmHg (34.4–90.9 mmHg), accompanied by a mean pH of 7.27 (7.14–7.44). Hypercapnia and the acid-base discrepancy diminished in the early postoperative period. The mean PaCO$_2$ level at T4 was 47.44 mmHg (36.7–66.7 mmHg) (Table 9, Figure 8). Consequently, the mean pH was 7.332 (7.275–7.401) (Table 9, Figure 9). The mean intraoperative lactate level was 0.701 mmol/L (0.22–1.86 mmol/L) at T2 and 0.667 mmol/L (0.22–1.83 mmol/L) at T3.

Table 9. Blood gas results.

		Time	N	Mean	SD	Minimum	Maximum
FiO$_2$	1	preoperative	82	0.210	0.000	0.210	0.210
	2	steady state	89	0.821	0.200	0.500	1.000
	3	after resection	62	0.829	0.197	0.500	1.000
	4	postoperative	77	0.500	0.000	0.500	0.500
pH	1	preoperative	81	7.419	0.032	7.235	7.491
	2	steady state	90	7.270	0.054	7.100	7.412

	3	after resection	63	7.271	0.061	7.139	7.443
	4	postoperative	75	7.332	0.032	7.275	7.401
$PaCO_2$ (mmHg)	1	preoperative	83	38.619	5.642	28.300	66.900
	2	steady state	91	59.053	10.299	37.100	92.900
	3	after resection	64	58.167	11.293	34.400	90.900
	4	postoperative	77	47.438	5.670	36.700	66.700
PaO_2 (mmHg)	1	preoperative	81	79.459	11.519	57.900	130.700
	2	steady state	91	115.969	67.318	50.400	472.600
	3	after resection	64	143.831	78.665	59.900	425.600
	4	postoperative	77	149.543	55.581	48.600	262.100
Lactate (mmol/L)	1	preoperative	71	0.815	0.329	0.260	2.110
	2	steady state	72	0.701	0.322	0.220	1.860
	3	after resection	56	0.667	0.293	0.220	1.830
	4	postoperative	66	0.780	0.303	0.230	1.600

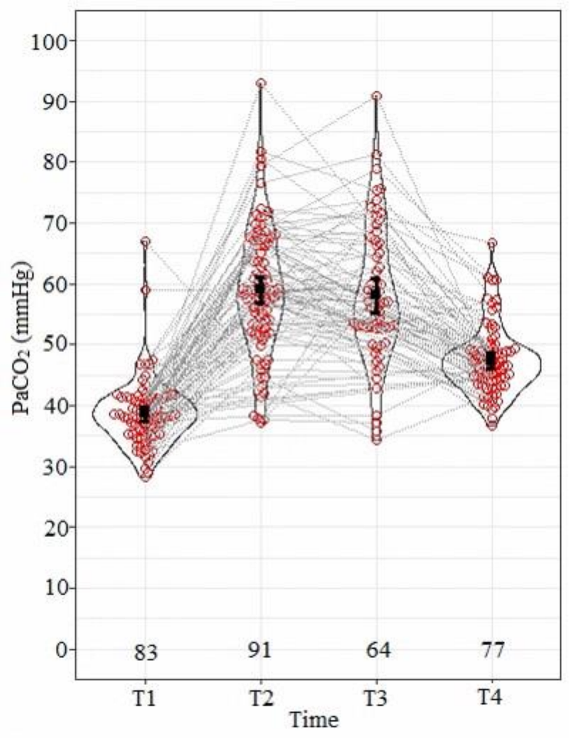

Figure 8 $PaCO_2$ levels

(Black square and lines: mean value ± 95% CI)

$PaCO_2$, partial pressure of carbon dioxide in arterial blood

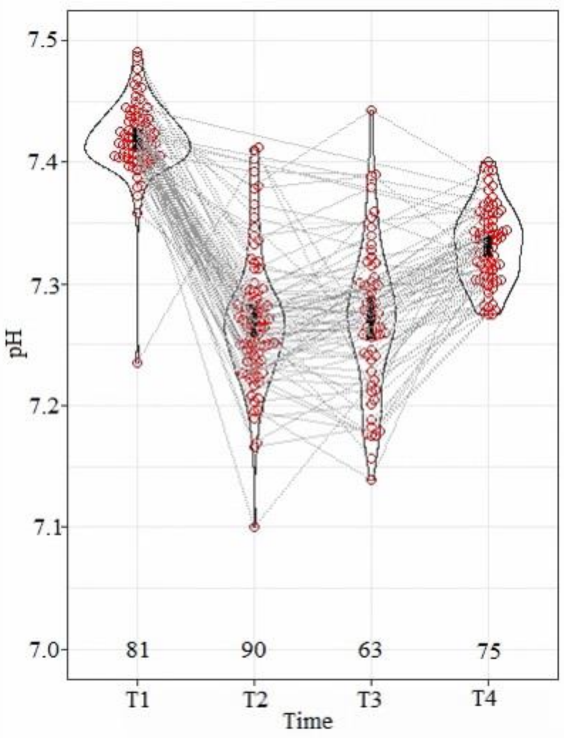

Figure 9 pH levels

(Black square and lines: mean value ± 95% CI)

Upon completion of the surgery, all patients were extubated. After a mean of 68.18 min (30–170 min) of observation in the recovery room, all patients were transported back to the thoracic surgical ward. None of the patients required a higher flow of oxygen therapy, non-invasive ventilation, reintubation, or intensive care unit admission. In the absence of contraindications, our patients routinely received 75 mg of diclofenac in the operating room as part of our multimodal pain management strategy. In the PACU, 25 of 141 patients did not require further analgesics. Metamizole (1 g, iv.) and paracetamol (1 g, iv.) were the most commonly administered analgesics postoperatively. A total of 94 (94/141, 66.67%) patients received metamizole, and 83 of the 141 patients (58.87%) received paracetamol. In half of the patients requiring metamizole, it was co-administered with paracetamol (47/141, 33.33%). The administration of approximately 10–75 µg of fentanyl was necessary in 8 (5.67%) patients to achieve a VAS score < 4. Tranexamic acid administration was necessary in 1 patient (1/141, 0.71%) because of the high rate of bleeding drained from the chest tube (Figure 10).

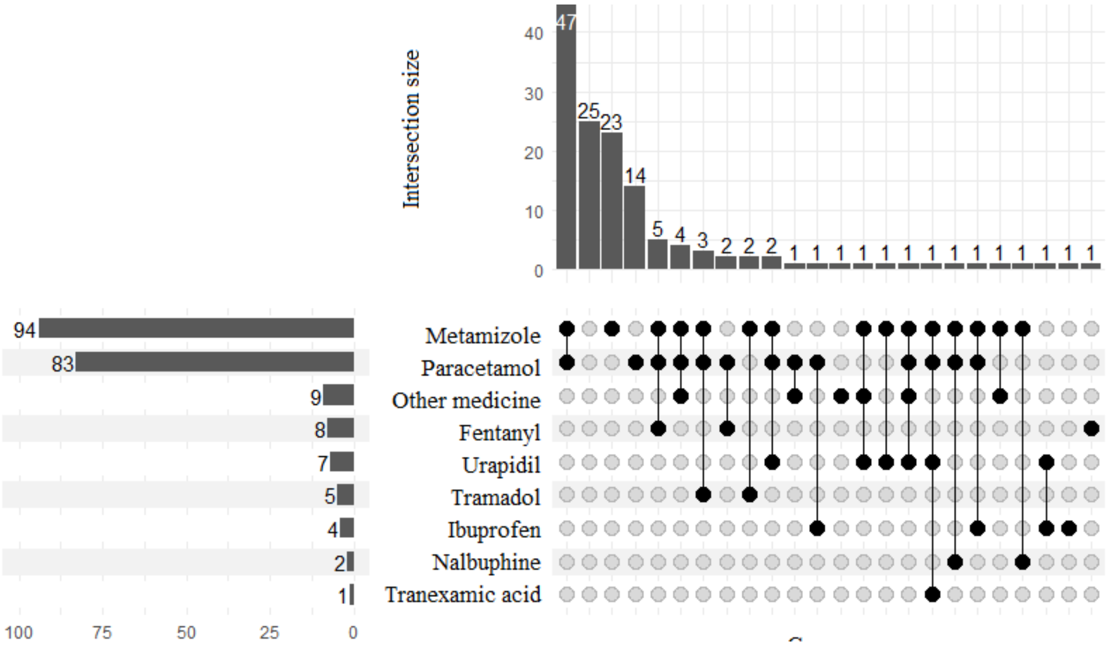

Figure 10 Drug administration at the post-anesthesia care unit

6.2.4 Surgical Intraoperative Results

A total of 3 of the 141 surgeries were intended for open SVI procedures. In 12 additional cases (12/138, 8.70%), conversion to thoracotomy was necessary, without anesthetic conversion (Table 10). Of these, 5 were due to oncological reasons (5/12, 41.67%), and 5 were due to technical difficulties (5/12, 41.67%). Bleeding also occurred in 2 cases (2/12, 16.67%). Overall, we performed 15 open thoracotomies (15/141, 10.64%) and 126 VATS (126/141, 89.36%)

procedures. The mean operation time was 80.6 min (25–150 min) and 80.2 min (25–150 min) in all cases and in cases without anesthetic conversion, respectively. The mean length of hospital stay was found to be 4.8 days (1–26 days) in all cases.

Table 10. Surgical conversions from VATS to open thoracotomy.

Reason for surgical conversion (n = 12)	**N**	**%**
Technical difficulties	5	41.67
Oncological consideration	5	41.67
Bleeding	2	16.67
Type of converted procedures (n = 12)	**N**	**%**
Atypical resection	1	8.34
Segmentectomy	2	16.67
Lobectomy (included 3 sleeve lobectomies)	9	75.00

7. Discussion

7.1. Airway management

One of the greatest concerns about the safety of non-intubated thoracic procedures is the lack of double-lumen tube insertion and lung isolation. After the investigation of the question of airway maintenance and oxygen supplementation and building upon the experiences of other workgroups, numerous modifications have been introduced, and all the workgroups have crafted their own method. At the onset of the NITS era, Italians used face masks during the operations, ensuring the administration of oxygen without allowing the application of positive end-expiratory pressure. In their case, the question of airway patency was less relevant, considering that their patients remained awake or were mildly sedated during the procedures. [26,91] The same airway management strategy was reported by Al-Abdullatief et al. from Saudi Arabia. [27]

The first step toward improving oxygenation and airway safety was the application of transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) by Asian workgroups. With the application of THRIVE, a flow-dependent PEEP can be generated, and it improves the oxygenation parameters in the intraoperative and postoperative period as well; however, THRIVE is inappropriate to facilitate the removal of carbon dioxide. [93]

Workgroups at the early stage of the learning curve of a new technique always look for the safest solution. Motivated by the uncertainty of a little-known method and with the increasing complexity of the procedures scheduled for non-intubated thoracic procedures, the need for providing a more secure airway was an immediate priority. Our workgroup introduced the use of supraglottic devices – the LMA carries numerous advantages that are often indispensable during thoracic surgical procedures. [29] The application of PEEP, the possibility of lung recruitment maneuvers, and the implementation of water submersion test (WST) for identifying intraoperative air leakage are all advantages associated with the use of laryngeal masks. Despite the continuous modification of the protocols for non-intubated procedures, a significant number of professionals still receive the method with reservation, and its dissemination has remained limited. Our new approach, the SVI method ensures maximal airway safety by double-lumen tube intubation combined with the possible advantageous effects of maintained spontaneous breathing. With DLT placement, the opportunity for all anesthetic interventions (recruitment maneuvers and fiberoptic control) with complete lung isolation are provided.

7.2. Sedation and regional anesthetic techniques

The early concept of non-intubated thoracic procedures included the avoidance of general anesthesia as well in order to prevent the pulmonary and extrapulmonary side effects associated with general anesthesia and one-lung ventilation. Italians initially performed the operations on awake patients or applied only mild sedation with midazolam and remifentanil. The fully awake approach may cause some discomfort to the patient and can result in patient stress with all its consequential negative effects. Al Abdullatief and his workgroup also opted for mild sedation with the administration of midazolam and fentanyl. To achieve painlessness, they used thoracic epidural anesthesia, or later, intercostal blockade. [27,49]

The Asian workgroups introduced the BIS-guided propofol sedation for non-intubated procedures. The target was to keep the BIS level between 40 to 60, and from that point, non-intubated procedures guaranteed the same comfort for patients as the conventional approach. The application of thoracic epidural anesthesia or intercostal blockade was also part of their non-intubated anesthetic protocol. [106]

The key element of non-intubated procedures is the prevention of coughing generally provoked by vagal nerve stretching, as it may disturb the surgical manipulation and expose the patient to the risk of an unsafe surgery. To minimize the risk of involuntary patient movement during the operation, several techniques have been developed, including intravenous or aerosolized administration of lidocaine, stellate ganglion blockade, or vagal nerve blockade. The latter became the most widespread method, thanks to its ease of execution under visual supervision by the surgeon at the early stage of the operation. Another advantage of vagal blockade is its high efficiency associated with a favorable side effect profile. [107]

In our NITS guideline, both patient comfort and patient safety are similarly emphasized in combining different protocols. The use of LMA mentioned above was combined with BIS-guided propofol sedation and supplemented with regional anesthetic techniques (intercostal and/or paravertebral blockade). During SVI, the same sedation and regional anesthetic protocol is applied. The essential differences between NITS and SVI are the short-term muscle relaxation at the early stage and the DLT insertion for maximal airway safety. To diminish cough reflex, we performed vagal nerve blockade during both SVI and NITS. The single-shot infiltration of the vagal nerve with 2–5 mL of bupivacaine (0.25–0.5%) in the thoracic cavity is a widely accepted method. [27,79,108–110] To control the respiratory frequency of the patient, fentanyl is administered in incremental doses in our practice, thus helping to create a calm surgical field. Other workgroups who apply only regional anesthetic techniques for non-intubated procedures (and their patients) may profit from general anesthesia itself. SVI is a hybrid anesthesiological technique that retains the benefits of spontaneous breathing known and utilized in non-intubated thoracic surgeries, while ensuring maximum patient safety by intubating the patient with double-lumen tubes (DLT), mirroring the gold standard procedure.

7.3. Anesthetic and surgical conversion

The part of the NITS procedure with the most risks is the conversion process under aggravated circumstances (2–11% of cases). [27,96,109,111–113] Furthermore, the incidence of unforeseen difficult airways and difficult intubation can reach a level as high as 20%. According to Langiano et al., the overall incidence of difficult airways is 16% in the thoracic surgical patient population, whereas the frequency of unexpected difficult airways is 5.2%. [114] Corso et al. reported in a retrospective study of 763 patients that difficult intubation occurred in 13.6% of the cases, challenging mask ventilation occurred in 9%, and a combination of both difficulties occurred in 2%. [115] In cases when anesthetic conversion is imminent, laryngeal mask provides the opportunity for emergency intubation even in lateral decubitus position and allows fiberoptic manipulation, although unforeseen difficult airway can make it challenging even for anesthetists experienced in NITS. In such instances, SVI provides a secure procedure for spontaneous ventilation as anesthetic conversion is safe and easy. In our SVI case series, muscle relaxation and permanently controlled mechanical OLV occurred in one patient due to intolerable mediastinal shifting (1/141, 0.71%). The incidence of disturbed mediastinal movement was higher, but these cases could be managed with pressure support ventilation. Two of our anesthetic conversions (2/141, 1.42%) were due to ineffective vagal nerve blockades, when repeated vagal nerve infiltration was technically infeasible. The fourth anesthetic conversion was due to DLT dislodgement (1/141, 0.71%). The remaining 97.16% of patients did not require further muscle relaxation after the initial dose of the muscle relaxant for induction.

From the surgeon’s perspective, there is no major difference between SVI and NITS, although spontaneous ventilation surgeries require surgeons to leave their comfort zone because paradoxical mediastinal shifting and diaphragmatic movements create an unusual surgical field. In their meta-analysis, Shi et al. reported that mediastinal and diaphragmatic factors were the most common complications leading to anesthetic conversion during NITS procedures (7% and 4%, respectively). [116]

The surgical conversion process is the same during SVI and NITS. It is known that surgical conversion does not necessarily come with an anesthetic conversion. [79] In our SVI case series, the twelve surgical conversions from VATS SVI to open SVI were uneventful and~~,~~ when the indication for conversion is surgical (thoracotomy), muscle relaxation and controlled mechanical ventilation are not required.

7.4. Gas exchange

Hypoxia and hypercapnia have also been observed during NITS, and the chance to improve gas exchange during NITS is often limited. [116] In SVI, hypoxia is easily compensated by a higher FiO_2, PEEP administration, or applying pressure support. However, it is important to emphasize that the peak airway pressure is lower during spontaneous ventilation, with or without pressure support, than during controlled ventilation. [31] Hypercapnia is a multifactorial condition. However, deepening the anesthesia affects respiratory activity negatively. In addition, mediastinal shifting reduces the tidal volume and lung compliance, and in the case of SVI, airway resistance is also increased by the use of a DLT. During NITS procedures, we do not have effective methods to improve carbon dioxide removal. In order to overcome hypercapnia during SVI, pressure support ventilation is an intermediate step before anesthetic conversion to maintain spontaneous breathing. Hypercapnia and associated respiratory acidosis tend to be temporary, and the acid-base aberration is generally spontaneously corrected after the operated lung is reinflated. [93,117–119] According to our blood gas results collected during SVI procedures at 30 min after extubation (T4), the mean $PaCO_2$ was 47.44 mmHg (36.7–66.7 mmHg), and the pH was 7.332 (7.275–7.401). However, hypercapnia itself may result in a better V/Q matching and may reduce intraoperative lung injury by suppressing inflammatory responses. [120,121] Furák et al. reasoned that SVI is more physiological in relation to gas exchange, and the authors found that a significantly lower minimum oxygen saturation and a higher maximum $PaCO_2$ level were found in the non-intubated group (vs. the SVI group). [104]

7.5. Hemodynamics

During spontaneous breathing thoracic procedures, hemodynamics is influenced by multiple factors. The lack of PPV leads to less significant changes in airway pressure levels, which in turn results in lower preload fluctuation, pulse pressure and stroke volume variation. [65] As opposed to this, surgical pneumothorax and the consequential changes in airway pressure levels and vascular resistance may significantly influence the pre- and afterload of the heart. As described earlier, SVI shows better hemodynamic stability than the non-intubated technique. [104] In our SVI series, hypotension commonly occurred after anesthesia induction and vagal nerve blockades. In total, 46.1% of our patients needed temporary pharmacological hemodynamic support. For the rest of the patients (53.9%), reductions in blood pressure were below our hemodynamic management cut-off value, and thus, self-regulation was sufficient to normalize blood pressure. The incidence of hypotension and the extent of intraoperative blood pressure reduction were higher among patients in the CV group. The elevated occurrence of hypotension can be attributed to the medications routinely used by patients in the CV group. Among these patients, 52 (52/95, 54.74%) were taking beta-blockers, 75 (75/95, 78.95%) were on antihypertensive medications (ACE inhibitors, ARBs, Ca^{2+} channel blockers, imidazoline/ α_2 receptor agonists), 30 (30/75, 40%) were on combinations of multiple antihypertensive drugs, and 15 patients (15/95, 15.79%) were regularly taking antidiuretic agents. The negative effects of controlled mechanical ventilation (CMV) have been extensively explored, and the decrease in the mechanical OLV time (76.5%) suggests that our patients suffered from less oxidative stress, which may offer some hemodynamic and immunological advantages. [57,122–124]

7.6. Interpretation of surgical results

Our workgroup previously published their results on SVI [31] and SVI lobectomies. [104] Their mean surgical time was 83.3 min (55–130 min) and 88.1 min (55–120 min), respectively. These times are similar to our mean surgical time of 80.2 min (25–150 min) and shorter than the ones reported in AlGhamdi’s study on non-intubated and intubated/relaxed VATS lobectomies (130.9, and 146.0 min). [125] Furthermore, Moon et al., in their study of 115 non-intubated thoracoscopic surgeries, reported that the mean operation time was 130 min. [113] Similarly, Hung et al., in their study of 109 non-intubated thoracic procedures, reported a mean operative time of 124.4 min. [28] Although the focus of this study is not on the detailed surgical results, by comparing Furak’s first SVI study with AlGhamdi’s study, it can be found that the mean postoperative length of hospital stay after VATS SVI lobectomies and open SVI lobectomies was shorter than the length of stay reported in AlGhamdi’s study after non-intubated and intubated/relaxed VATS lobectomies (3.7 and 4.8 days for SVI VATS/open lobectomies and 6.9 and 7.6 days for non-intubated and intubated/relaxed lobectomies). [31,125] Our conversion rate from VATS SVI to open (thoracotomy) SVI was 8.7%. All conversions were due to technical or oncological reasons or due to bleeding not associated with the SVI method. According to a systematic review and meta-analysis by Power et al. reporting on the results of 72.932 patients, the median conversion rate from VATS to thoracotomy for anatomical resections was 9.6%. [126]

7.7. Limitations of spontaneous breathing procedures

There are only a few established exclusion criteria for SVI, and patients indicated for VATS are also candidates for SVI. NITS has several exclusion criteria, such as potentially difficult airways or intubation, coagulation disorders or mental conditions, which are not exclusion criteria for SVI. [92,125,127] In our case series, the contraindications for SVI were a high BMI, patient refusal, elevated intracranial pressure, hemodynamic instability, and right heart failure (Table 2). In our daily practice, the most common limiting factor for spontaneous breathing thoracic procedures is the high BMI, which is an increasingly prevalent issue in Europe. We accepted a higher BMI threshold as a general exclusion criterion for SVI (as well as for NITS) compared to other workgroups because our national average BMI was slightly higher. Based on individual considerations, we sometimes made further concessions regarding the BMI if it was deemed justified by the patient's condition and respiratory function.

8. Conclusion

In the previous decades, surgical advancements such as the establishment of video-assisted thoracoscopy as the gold standard, the widespread adoption of uniportal techniques, and the evolution of surgical instrumentation all contributed to the extensive dissemination of minimally invasive surgical and anesthetic techniques. In my thesis, I aimed to focus on presenting various minimally invasive anesthesiological strategies, emphasizing their potential in reducing surgical stress for patients. The different anesthetic approaches of NITS described above have been applied in a large number of cases, and they appear to be safe and feasible. NITS in our practice entails the BIS-guided propofol TCI sedation of our patients, as well as the use of LMA. Supraglottic airway devices enable the application of anesthetic interventions crucial for thoracic anesthesia such as lung recruitment, fiberoptic manipulation, and WST. This approach is unique in the field of non-intubated techniques as it contributes to the enhancement of patient safety while the repertoire of interventions for anesthesiologists is expanded, and surgeons are less compelled to leave their comfort zone.

In order to reduce the number of patients excluded from thoracic surgical procedures performed with spontaneous breathing and to enhance patient safety, our workgroup developed the SVI technique, a hybrid technique established from the intersection of NITS and the gold standard method. The application of the SVI method holds the potential to combine the benefits of minimally invasive anesthesiological strategies with the safety provided by conventional approaches. Based on the available data, SVI is a safe and technically feasible option, with a low anesthetic conversion rate, and according to the intra- and early postoperative data, it supports the reduction of controlled mechanical OLV time, with normal oxygenation and permissive moderate hypercapnia, without any substantial hemodynamic complications.

According to our results, SVI appears to have a positive impact on patient outcome. However, it is crucial to underline that further randomized clinical trials, with large numbers of patients, are necessary to compare the different minimally invasive anesthesiological strategies presented in the thesis to the conventional method.

We believe that both conventional (intubated) and NITS, as well as the SVI technique, have their place in the anesthesiological repertoire. It is imperative to recognize the diversity among our patients, highlighting the need for individualizing the applied anesthesiological strategy.

9. New findings of the thesis

Study I.

1. Our method of NITS with BIS-guided propofol TCI and LMA is a novel, safe, and feasible technique, with the opportunity for lung recruitment, fiberoptic manipulation, and water submersion testing.

Study II.

1. SVI is a novel anesthetic technique in thoracic anesthesia, which combines maximal airway (patient) safety by double-lumen tube intubation with the preservation of spontaneous breathing activity. The SVI technique is safe and feasible for various types of thoracic procedures from wedge resections to major anatomical pulmonary resections (segmentectomies, lobectomies) and also for thymectomies. The SVI technique can be applied to a boarder range of patients than NITS as SVI has significantly fewer exclusion criteria.

2. By applying the SVI technique, the duration of controlled positive pressure ventilation during thoracic surgery can be reduced by 76.5%. Approximately two thirds of our patients had satisfactory gas exchange by spontaneous breathing with or without 3-5 cmH_2O PEEP administration, and one third of our patients needed temporary or permanent pressure support ventilation during the procedures, most commonly due to hypercapnia or high-amplitude mediastinal movement.

3. Oxygenation is within the normal range during SVI procedures, while permissive hypercapnia and the consequent acid-base disturbances are temporary and resolve spontaneously in the early postoperative period, similarly to the gold standard procedure.

4. The SVI technique can be safely applied even in cases where thoracotomy becomes necessary due to surgical difficulties or oncological reasons. Surgical conversion (from VATS to open) does not result in a mandatory anesthetic conversion (from SVI to relaxed) – SVI shows a low anesthetic conversion rate (2.8%).

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