University of Szeged, Albert Szent-Györgyi Medical School

Doctoral School of Multidisciplinary Medical Sciences

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

Summary of the Ph.D. Thesis

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Abbreviations

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

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

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

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

III. Furák, J., **Szabó, Z.,** Tánczos, T., Paszt, A., Rieth, A., Németh, T., . . . Molnár, Z. (2020). Conversion method to manage surgical difficulties in non-intubated uniportal video-assisted thoracic surgery for major lung resection: Simple thoracotomy without intubation. *JOURNAL OF THORACIC DISEASE, 12*(5), 2061-2069. doi:10.21037/jtd-19-3830

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

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

II. Molnár, Z., **Szabó, Z.**, & Németh, M. F. (2017). Multimodal individualized concept of hemodynamic monitoring. *CURRENT OPINION IN ANAESTHESIOLOGY, 30*(2), 171-177. doi:10.1097/ACO.0000000000000440

III. Gárgyán, I., Furák, J., **Szabó, Z**., & Varga, E. (2020). Serratus plane block improves pulmonary function of patients with multiple rib fractures. *EUROPEAN JOURNAL OF TRAUMA AND EMERGENCY SURGERY, 46*(S90), S90.

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

VI. Furák, J., **Szabó, Z**., Theodor, H., Géczi, T., Pécsy, B., Németh, T., . . . Lázár, G. i. (2017). Nem intubált, spontán légző betegnél, egy metszésből, minimálisan invazív módon elvégzett tüdőlebeny-eltávolítás mint új műtéti eljárás klinikánk gyakorlatában. Non-intubated, uniportal, video assisted thoracic surgery (VATS) lobectomy, as a new procedure in our department. *MAGYAR SEBÉSZET, 70*(2), 113-117. doi:10.1556/1046.70.2017.2.1

VII. Németh, T., **Szabó, Z.**, Pécsy, B., Barta, Z. V., Lázár, G. i., Torday, L., . . . Furák, J. (2020). A tüdőmetastasisok sebészi kezelésében történt változások az elmúlt 12 évben [Changes in the surgical treatment of pulmonary metastases during the last 12 years]. *ORVOSI HETILAP, 161*(29), 1215-1220. doi:10.1556/650.2020.3177

Introduction

High-risk surgical interventions present an increased risk of mortality and morbidity, especially for the elderly patients or for patients living with severe comorbidities**.** According to a 2008 estimate, approximately 234 million**, and in 2016, already 310 million** surgeries were performed worldwide each year**, in addition,** the average age of the patients**, and** the complexity, thus the risk of the surgical interventions are constantly increasing**.**

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

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

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

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

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

Open points

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

avoiding or radically reducing the duration of positive pressure ventilation may still seem to be a patient safety endangering practice for many. So the questions to be answered are as follows:

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

2. Will there be fewer respiratory complications?

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

Research aims and objectives

- Is the use of the open NITS technique effective and successful in patients for whom conventional surgical techniques are not recommended according to the international recommendations, due to the patients' severely decreased respiratory function values and severe underlying diseases, comorbidities? (Study 1)

- Is NITS safe to use in patients who require thoracotomy because of the expected surgical difficulties, and is there a benefit to using minimally invasive techniques regarding the perioperative complications and oncological success? (Study 2)

- Comparison of the intra- and postoperative results of thoracic surgeries performed intubated, with maintaining the patient's spontaneous breathing and intubated, but applying positive pressure ventilation. (Study 3)

Materials and methods

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

Study 2: Prospective, observational study. Patients undergoing NITS surgery using the uniportal technique between January 2017 and November 2018.

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

Measurements

Study 1: Recording of blood gas and oxygenation parameters before surgery, during surgery (before and after resection), at the end of surgery, in the PACU room (post anaesthesia care unit), and in the hospital ward.

Study 2: Physiological parameters, heart rate, systolic and diastolic blood pressure values, and end-tidal carbon dioxide values were recorded during the intraoperative period.

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

Statistics

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

Results

Study 1- NITS thoracotomy

The patient was a 73-year-old man who had lost more than 20 kgs of weight in the 2 months prior to his visit and developed haemoptysis. A 4x2.8 cm lesion compressing the right main bronchus was detected during the examination, and cytological examination confirmed basaloid adenocarcinoma. During routine preoperative pulmonary examination, his respiratory function values were dramatically decreased: FEV1 27%, Tiffeneau-index 43%, DLCO 26%, VO_2 max 13,9 ml/kg body weight/min. Due to his severe comorbidities (underwent coronary artery bypass graft surgery, CABG and has aortic aneurysm) and respiratory function, the current recommendation (European Society of Thoracic Surgeons, ESTS) did not recommend one-lung ventilation (OLV) in his case. After the patient had signed the informed consent form, a right bilobectomy was performed with the NITS technique, as an elective surgery in the knowledge of the atypical pathological lesion, in an open surgery.

When planning the surgery, we prepared for an open surgery due to the location of the lesion and the difficulty of the surgical technique. We also used our achievements in the field of analgesia - obtained during the non-intubated surgeries-, in the course of intubated surgeries, namely that the routinely applied intercostal, paravertebral and vagus blockade is perfect for blocking the pain in open surgeries as well. The gas exchange and acid-base parameters show that there was no oxygenation problem in the intraoperative period and the hypercapnia is a normal sub-phenomenon of NITS surgeries.

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

Blood gas values	**T_{Pre}**	**T_{BR}**	**T_{AR}**	**T_{Post}**	**T_{RR}**	**T_A**	**T_W**
FiO_2 (%)	21	100	100	40	40	40	21
pH	7.434	7.195	7.153	7.243	7.294	7.325	7.357
pCO_2 (mmHg)	32	64	67	49	40	38	35
pO_2 (mmHg)	68	217	325	118	182	204	62

BE (mmol/L)	−3.6	−4.7	−6.1	−6.7	−7.1	−6.0	−5.7
HCO_3 (mmol/L)	22	24	23	21	19	19	19
Lactate (mmol/L)	2.0	1.0	1.1	1.3	1.9	2.6	3.0
SaO_2 (%)	95	99	99	97	99	99	92
p50 (mmHg)	24	39	48	31	24	35	26
Haemoglobin (g/dl)	10.4	10.0	10.5	11.0	11.1	10.8	11.1

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

Study 2 – NITS and the conversion method

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

Of the 160 patients, intubation was necessary in 6 cases: in 1 case due to pronounced diaphragmatic and mediastinal movements, and in 2 cases due to respiratory tract bleeding. For surgical reasons, we opted for conversion in 3 cases due to extensive adhesions.

Based on our previous experience, lung resections with lymphadenectomy can be performed in open NITS surgeries as well as using traditional techniques. There were no R1-2 resection cases. The duration of surgery was longer in the unplanned conversion group, which includes the exploration time until conversion became necessary. The postoperative chest drain time was longer in the planned NITS group, due to the fact that these patients were in the most severe general condition, they had severe underlying diseases and comorbidities, and the radicality of their surgeries were the most extensive. Three patients had a drain time of more than 5 days, and drain time

for all patients was 4.2 days (1-14 days). Our average conversion rate was 7.5% (12/160).

Data of these interventions are summarized in Table 2.

Table 2: NITS thoracotomy data

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

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

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

Study 3 - VATS SVI

Data from patients enrolled in our VATS-SVI study and data related to surgery are summarized in Table 3.

Table 3: Surgical parameters of patients who underwent VATS-SVI

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

Right lower lobectomy	9	7	2
Left upper lobectomy	4	3	1
Left lower lobectomy	3	3	0
Segmentectomy	2	1	1
Wedge resection	4	3	1

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

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

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

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

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

The patients' intraoperative parameters are summarized in Tables 4 and 5.

Table 4: Respiratory parameters during VATS-SVI

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

Table 5: Gas exchange parameters during VATS-SVI

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

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

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

The kinetics of the inflammatory response was similar to those observed with other methods. The changes in the measured inflammatory markers are summarized in Table 6.

Table 6: Changes in inflammatory parameters in patients who underwent VATS-SVI

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

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

Discussion

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

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

We observed that the $EtCO_2$ levels were stabilized at higher values in cases of NITS surgeries compared to ventilated patients. Exclusion criteria include an $EtCO_2$ value significantly higher than normal by about 30 mmHg. This phenomenon is permissive hypercapnia, which is well known in the treatment of ARDS and status asthmaticus, as well as in thoracic anaesthesia. Our understanding of the physiological effects of hypercapnia grows through the understanding of both the cellular and molecular mechanisms induced by hypercapnia. Acute hypercapnia and the consequent acidosis have had protective effects in a number of studies - in cases of non-septic lungs -, such as reduction of pulmonary hypertension, reduction of ischaemia-reperfusion injury, reduction of endothelial barrier damage by preventing an increase in the permeability of pulmonary capillaries. This effect is due in part to a reduction in the endocytosis of the Na/K-ATPase pump, and inhibition of the NF-κB pathway, however, it is important to note that the same mechanism is responsible for regulating a number of adverse effects, such as delayed wound healing and weakening of the local immune response.

From a clinical point of view, vasodilation due to acidosis, - which manifests itself mainly in an increase in cerebral blood flow and in an increased right heart strain-, remains within a tolerable range up to 70 mmHg $EtCO_2$ or pH> 7.15, and in such cases we do not yet have to reckon with adverse physiological effects.

NITS – with laryngeal mask

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

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

A very important finding from research over the past decade is that intraoperative IPPV (intermittent positive-pressure ventilation) can cause alveolar damage even in healthy individuals, which increases perioperative morbidity and mortality. The pathomechanism of ventilation-induced lung damage is mainly due to baro- and

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

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

Hypercapnia is a common phenomenon that occurs in both the non-intubated and the intubated, ventilated surgery patients. One cause for this is that during NITS, the alveolar gas mixture mixes with the gas mixture of the dependent and non-dependent lungs, resulting in the so-called carbon dioxide rebreathing. The other cause is

hypoventilation, which, on the one hand, is related to the collapsed, operated state of the lung, and, on the other hand, to the respiratory depressant effects of drugs administered during anaesthesia. Experience has shown that carbon dioxide accumulation during surgery does not cause damage if $PaCO_2$ does not exceed 70 mmHg or pH does not fall below 7.15, however, hypercapnia should be avoided in patients with pulmonary hypertension, or severe valvular heart disease or increased intracranial pressure. It is important to note that these values are such threshold levels/values from the literature that are to be flexibly interpreted by the clinician, especially in procedures where we try to reduce the stressful conditions that test the patient's load-bearing capacity, while maintaining the surgical radicality of the operation.

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

non-elective) surgical conversion. In our 2nd examination, we've reviewed medical data from 10 months of surgeries and analysed the effects of complicated and extensive lung resections - performed while maintaining spontaneous breathing (SB)-, on postoperative outcome.

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

The next very important aspect in judging the effectiveness of open NITS surgeries is

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

Intubation and maintenance of spontaneous breathing (SB)

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

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

Based on our results, the durations of VATS-SVI lobectomies, and the duration of need for chest drainage (mean duration of surgery: 85.6 minutes and mean drain time: 2,2 days) were shorter than those reported in the literature for NITS lobectomies (130.9 minutes and 5,6 days) and for intubated lobectomies (146 minutes and 5.4 days), in addition, the average length of hospital stay (3.7 days) was shorter than reported in the

literature (7.6 days) [61]. According to a recent meta-analysis, diaphragmatic movements necessitated intubation in 4%, while mediastinal movements in 7% of the patients undergoing NITS surgery. In our report, 1 of the 26 VATS-SVI patients showed excessive mediastinal movements (3.84%) that required relaxation and positive pressure ventilation. There was no conversion for oncological reasons, which may make the procedure suitable for technically more difficult surgeries in the future. Following the return of spontaneous breathing, both diagnostic and therapeutic interventions can be performed through the double-lumen tube. Blood gas parameters measured during VATS-SVI are similar to those in the NITS group, with evidence of permissive hypercapnia and a slight decrease in PaO_2, which can be compensated by an increase in FiO2 and / or applying PEEP in the dependent lung's airways.

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

During SVI, the duration of controlled ventilation could be reduced by 76.6%. In their study, Misthos et al. found that oxidative stress in conventional surgeries may be due to OLV lasting more than 1 hour, and therefore we hypothesize that reducing the duration of OLV induces less pathophysiological changes in the lung tissue, thus oxidative stress may also be less pronounced. The duration of OLV is also a major factor, according to a report by Mineo et al. In our patients, the mean leukocyte count increased on the first postoperative day and then decreased below baseline on the second day, showing similar kinetics as reported by Mineo et al. in their patients undergoing VATS and NITS. The inflammatory response elicited by VATS-SVI appears to trigger a very similar reaction to that observed in NITS. Although, according to a study by Leaver et al., there was no measurable change in the postoperative lymphocyte count on the first

postoperative day, and the largest difference was seen on the second day for VATS surgeries. In our study, serum CRP levels doubled on day 1 and remained unchanged on day 2. The results reported by Dongel et al. showed that in conventional VATS surgeries, the CRP levels were more than four times higher than baseline on day 1 and more than three times higher even on day 2, which also suggests less inflammatory mediator release in our patients undergoing VATS-SVI.

Conclusion

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

The dissertation's new findings

1. Even in high-risk patients with severe comorbidities, anaesthesia without intubation and with spontaneous breathing is a safe alternative also for patients undergoing thoracotomy.

2. NITS can be used safely also in patients who have to undergo thoracotomy due to surgical difficulties, even in the case of conversion, patient safety is not compromised, and it is a better alternative to traditional methods in terms of oncology efficacy and length of hospital stay, while it is at least an equivalent alternative to the conventional methods in terms of incidence of perioperative complications.

3. The VATS-SVI technique offers the possibility to maintain spontaneous breathing during thoracic resections also in patients who, due to the need to maintain a secure airway, and a number of exclusion criteria (a suspected difficult airway, abnormal anatomy, respiratory tract bleeding, severe GERD) that have been used so far, could not be operated on in this way until now, thus, the inclusion criteria have been significantly broadened and can also be applied to patients who have not been eligible for NITS surgeries, and we can take advantage of the benefits provided by a safe airway and the possibility of isolating the lungs without the need for positive pressure ventilation.

4. By applying the VATS-SVI technique, the duration of positive pressure ventilation during thoracic surgery was reduced to almost ¼, thus, it can be applied while retaining the physiological benefits of non-intubated procedures, and furthermore, this procedure represents a real alternative in terms of both the kinetics of the inflammatory response and the perioperative complications. It is important to note that, although the concept is not new, the technical implementation is novel, so further research is needed to determine the effectiveness of the procedure.

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