Ventilation and Lung Injury.
Lung Protection in Anaesthesiology and Intensive Care Practice.

Theses of Doctoral (PhD) Dissertation

Dr. Gabriella Kecskés

Supervisor: Prof. Dr. Tamás F. Molnár
Program Director: Dr. Zalán Szántó
(2020-2023. Prof. Dr. Tamás F. Molnár)
Head of the Doctoral School: Prof. Dr. Lajos Bogár

Doctoral School of Clinical Medical Sciences
University of Pécs, Faculty of Medicine
Pécs, 2024

Table of contents

List of Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ASA	American Society of Anesthesiologists
BIS	Bispectral Index
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPAP	Continuous Positive Airway Pressure
CT	Computer Tomography
$EC_{CO2}R$	Extracorporeal carbon dioxide Removal
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
EESZT	Elektronikus Egészségügyi Szolgáltatási Tér
ERAS	Enhanced Recovery After Surgery
$EtCO_2$	End-tidal carbon-dioxide
FiO_2	Fraction of inspired oxygen
FRC	Functional Residual Capacity
GERD	GastroEsophageal Reflux Disease
HPV	Hypoxic Pulmonary Vasoconstriction
LMA	Laryngeal Mask Airway
MODS	Multiple Organ Dysfunction Syndrome
NITS	Non-intubated Thoracic Surgery
NIV	Non-invasive Ventilation
NIVATS	Non-intubated Video-assisted Thoracic Surgery
OLV	One Lung Ventilation
P-SILI	Patient Self-inflicted Lung Injury
PAEOK	Petz Aladár University Teaching Hospital
PaO_2	Partial Pressure of oxygen
pCO_2	partial pressure of carbon dioxide
PEEP	Positive End Expiratory Pressure
pH	potential of hydrogen
PM	Pneumomediastinum (mediastinal emphysema)
pO_2	partial pressure of oxygen
PONV	Postoperative Nausea and Vomiting
PPC	Postoperative Pulmonary Complication
PTE-ÁOK	University of Pécs, Faculty of General Medicine
PTX	Pneumothorax
RATS	Robotic-assisted Thoracic Surgery
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
TCI	Target Controlled Infusion
TOF	Train-of-Four
V-V ECMO	Veno-Venous Extracorporeal Membrane Oxygenation
V/Q	ventilation to perfusion
VATS	Video-Assisted Thoracoscopic Surgery
VATS-SVI	Video-Assisted Thoracoscopic Surgery-Spontaneous Ventilation Combined with Double Lumen Tube Intubation
VILI	Ventilator Induced Lung Injury
V_t	tidal volume
χ^2	Chi-Square(test)

1. Introduction

In my research, I dealt with the problem of positive pressure ventilation-related lung injury in a particular field of Anaesthesiology and Intensive Care. During the review of the current clinical practice, I also looked for relevant lessons from historical roots. Research questions were posed with the aim of resolving the perceived or real contradictions between canonised knowledge (received wisdom) and observed and analysed clinical experience.

The primary objective of anaesthesiologists and intensive care physicians is to ensure tissue oxygenation, which is a prerequisite for resolving any critical condition. The first necessary step for this is the uptake of oxygen by the lungs, the target organ. When lung function is impaired, regardless of the cause, oxygen therapy and artificial ventilation are employed to improve it. Positive pressure ventilation ensures gas exchange in a manner different from the physiological one. The risk of lung damage from its use has been recognised since its inception. Beyond the obvious complications diagnosed by physical examination, such as sudden pneumothorax or mediastinal emphysema causing immediate deterioration, we have increasingly detailed knowledge of the cellular-level harms and pathophysiology caused by ventilation. Research and publications on minimising these harms are a frequently discussed topic in contemporary literature, possibly sparked by the COVID-19 pandemic.

Thoracic surgical anaesthesia, due to airway management and one-lung ventilation (OLV), poses a particularly high risk for acute lung injury and subsequent respiratory complications. It is necessary to balance between the most lung-protective ventilation mode and ensuring adequate gas exchange. Taking the hitherto unexplored historical and current practices as examples, we examined how gas exchange and respiratory mechanics evolve in our patients during the phases of a newly developed thoracic surgical procedure: video-assisted thoracotomy performed with spontaneous ventilation using a double lumen tube (VATS-SVI).

Mechanical ventilation-related barotrauma caused an unusually high number and severity of intrapleural complications during the COVID-19 pandemic. The contradiction between our clinical experiences and the previous ideas of barotrauma prompted me to research the issue in more detail.

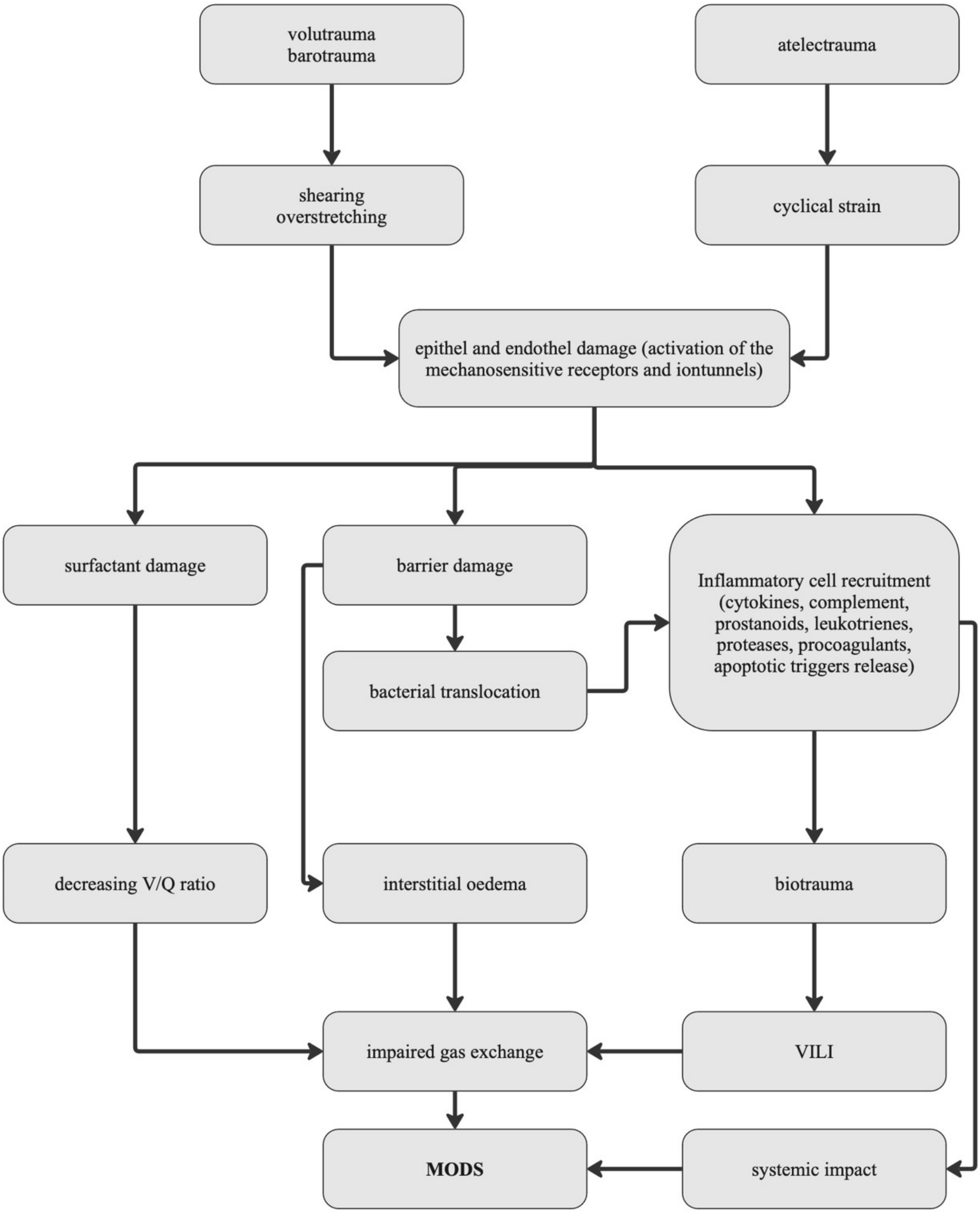
2. Objectives

In the scope of the dissertation, I sought answers to the following:

1. Before the era of intubation and positive pressure ventilation, what methods were used in the anaesthesia of thoracic surgeries and what were their outcomes? What lessons does past practice offer for today?
2. How do respiratory mechanics and gas exchange evolve from controlled ventilation to assisted ventilation to spontaneous breathing in a lateral decubitus position with an open chest and atmospheric pressure conditions? What parameters determine the patient group for whom the VATS-SVI technique can be safely applied?
3. Is there a difference in the incidence of pneumothorax (PTX) and pneumomediastinum (PM) in COVID-19 pneumonia based on whether the patient's lungs were originally healthy or damaged? Is pre-existing lung damage a risk factor?
4. How do pre-existing lung conditions affect outcomes?
5. How do PTX and PM related to barotrauma affect outcomes?
6. How did the choice of ventilation strategy influence outcomes in respiratory failure caused by COVID-19?

3. Foundation: Ventilation-induced Lung Injury

Ventilator-induced lung injury is an inflammatory response triggered by mechanical damage, causing increased alveolar permeability, alveolar and interstitial oedema, alveolar haemorrhage, hyaline membrane formation, surfactant damage, and consequent alveolar collapse. Predisposing factors include severe underlying diseases such as sepsis, polytrauma, or extensive surgical interventions in terms of timing or tissue volume, which already push the immune system into heightened activity. The main mechanisms causing mechanical damage are volutrauma, barotrauma, atelectrauma, and biotrauma. Ventilator-induced lung injury (VILI) is composed of the stress caused by the ventilator on the lung tissue and the lung tissue's response to this stress. The lung tissue damage can be described using a biomechanical analogy as mechanical energy, with its value per unit of time being mechanical power. Factors from the ventilator include delivered volume, pressure, flow, and respiratory rate, while from the lung, the amount of lung tissue involved in gas exchange, its inhomogeneity, the stress and strain in the airways, and their rates of change (i.e., their rate of change per unit time) play roles. Lung damage can potentially occur in both previously healthy and already damaged lung tissue. In the latter case, based on theoretical considerations more severe damage is expected. The VILI not only causes impaired gas exchange but as a trigger or part of Multiple Organ Dysfunction Syndrome (MODS) increases the morbidity and mortality of ventilated patients. The possible causes and connections leading to multi-organ failure, including the lungs, are illustrated in the following figure.



The concatenation of VILI and MODS

The pathomechanisms leading to ventilator-associated lung injury also offer the possibility of reduction:

1. Lung-protective ventilation

- Reducing tidal volume
- Reducing driving pressure
- “Open lung ventilation”: alveolar recruitment and PEEP
- Optimizing respiratory rate

Fewer complications can only be achieved by the combined application of these elements. When examining ventilation modes, none has been definitively proven to be superior to another.

2. Maintaining spontaneous breathing

2.1. Advantages of maintaining spontaneous breathing, i.e., preserving diaphragm function:

- Better ventilation of dependent lung areas
- Prevention of atelectasis tendency
- Preservation of mucociliary function
- Higher FRC (functional residual capacity)
- Preserved HPV (hypoxic pulmonary vasoconstriction) reflex
- Mitigation of the adverse haemodynamic consequences of ventilation
-

These collectively result in a more favourable V/Q ratio, ultimately better gas exchange, and reduce the chances of PPCs (postoperative pulmonary complications).

2.2. Possible disadvantages of maintaining spontaneous breathing:

2.2.1. Under surgical conditions

- Locally elevated transpulmonary pressure can cause heterogeneity in ventilation, with alveoli of differing time constants, resulting in consequent occult pendelluft
- Atelectrauma can occur in the dorsal lung regions due to the cyclic opening and closing of small airways
- Increased alveolo-capillary gradient predisposes to interstitial oedema
- Worsening haemodynamics

- Decreased reliability of respiratory parameter monitoring
- Difficulties in emergency conversion from VATS to thoracotomy
- The respiratory depression effects of anaesthetics, especially opioids, must be considered. In the absence of neuromuscular blockade, residual muscle weakness is not a concern.

2.2.2. In the intensive care unit

In the early stages of severe ARDS, the patient's uncontrolled inspiratory effort can lead to acute lung injury due to elevated transpulmonary pressures (Patient Self-Inflicted Lung Injury, P-SILI). In such cases, spontaneous breathing is undesirable, and deep sedation and muscle relaxation may be necessary. However, the positive impact of the latter on outcomes has not been unequivocally proven. Continuous muscle relaxation can result in respiratory muscle atrophy within as little as 18 hours, posing significant challenges in weaning from the ventilator. To preserve respiratory muscle function, myopathy resulting from inactivity must be avoided, thus it is essential to strive to maintain spontaneous breathing.

3. Extracorporeal life support treatments

- Veno-venous extracorporeal membrane oxygenation (V-V ECMO)
- Extracorporeal carbon dioxide removal ($ECCO_2R$)

4. Historical roots: Non-intubated Thoracic Surgery

4.1. István Sándor (Temesvár 1881-Budapest 1962)

Researching the literature on the history of anaesthesia in Hungary, István Sándor proved to be of pioneering importance in two aspects. He does not appear in the Hungarian Medical Biographical Lexicon, although through his publications and the medical instruments he played an important role in the development of Hungarian anaesthesiology and surgery as well.

4.2. Thoracotomy for penetrating chest injury 1908

István Sándor presented a series of surgeries performed due to thoracic gunshot, and massive pulmonary haemorrhage at the meeting of the Medical Section of the Transylvanian Museum Society. The anaesthesia was performed with ether maintenance after chloroform induction, under spontaneous breathing. The author provided the thirteenth case description in world literature, addressing the pathophysiological problem of an open chest under atmospheric conditions: "We have nothing to fear from the open pneumothorax created by chest exposure, as emphasised by König, Rehn, and others, even when no pneumatic apparatus is available to prevent lung collapse."

4.3. Infusion pump forty years before its "invention",1934

In Europe, anaesthesia and surgery developed along parallel paths, with initially surgeons taking the first steps in the field of anaesthesiology. Martin Kirschner (1879-1942) developed numerous surgical procedures and established the concepts of emergency and rescue care, intensive therapy, and the principles of modern anaesthesia and pain management. He proposed avoiding prolonged exposure to inhalational anaesthetics, which he implemented in his practice through a combination of total intravenous anaesthesia and regional anaesthetic techniques. For longer surgeries, he maintained anaesthesia using an infusion pump he invented, operated by a clockwork mechanism. István Sándor, as the director and chief surgeon of the Count Sándor Károlyi Foundation Public Hospital, improved Kirschner's apparatus. The "automatic syringe ejector" he designed operated with springs and pistons, making it simpler and cheaper than the clockwork mechanism. He complemented the pump with a side branch, allowing for the administration of infusions or additional medications. He did not favour the combined administration of the anaesthetic and morphine because "the effects of these drugs on the vital centres could unpleasantly add up.” Therefore, he combined general anaesthesia and local anaesthesia. In 1934, he published his treatise in the Medical Weekly titled “Remarks on Evipan-Sodium Anaesthesia and Description of a New Method Automatic Syringe Ejector”.

4.4 1908-1934-2024.

If we consider the case report on the gunshot chest injury and the report on intravenous anaesthesia - including the practice of multimodal anaesthesia - together, we can see the precursor of the non-intubated thoracic surgeries (NITS) that have regained ground in the past 20 years.

5. Clinical Studies: Lung and Pleural Space

5.1.Video-Assisted Thoracic Surgery with Double-Lumen Tube Intubation (VATS-SVI)

In line with the principles of minimal invasiveness and ERAS (Enhanced Recovery After Surgery), video-assisted thoracoscopic surgery (VATS) has become the gold standard in thoracic surgery for many procedures. Alongside VATS, robot-assisted surgery (RATS) is also emerging. Since the mid-1980s, the standard practice in thoracic anaesthesia has been one-lung ventilation (OLV) with double-lumen tubes or bronchus blockers, muscle relaxation, and controlled ventilation. This practice creates ideal conditions for the surgeon by ensuring the operated lung remains airless and the diaphragm remains immobile. However, lung-protective ventilation poses challenges because the respiratory minute volume required for total body gas exchange must be provided by one lung, while the tidal volume and FiO_2 levels are directly proportional to the frequency of postoperative airway complications. Considering other sources of complications from general anaesthesia, such as airway injury, residual relaxant effects, and postoperative nausea and vomiting (PONV), the need for “minimally invasive” anaesthesia has arisen. One potential solution is surgery without intubation, with maintained spontaneous breathing. This type of anaesthesia combines some regional anaesthesia techniques with intravenous sedation, with oxygen supplementation. The main criticism of NITS is the lack of a secure airway. This issue was eliminated by Dr. József Furák and his team at the Department of Thoracic Surgery, University of Szeged. They developed a new anaesthetic technique where patients were sedated with propofol administered by a TCI pump and intubated with a double-lumen tube under short-acting non-depolarizing muscle relaxants. For uniportal VATS surgery, intercostal blockade was performed in the fifth intercostal space, followed by paravertebral and vagus nerve blockade once inside the chest. The surgeries were performed under spontaneous breathing. VATS-SVI potentially offers a solution for performing thoracic surgeries in a minimally invasive manner from both anaesthetic and surgical perspectives. From the surgical perspective, a technical challenge with maintained spontaneous breathing is the moving diaphragm. From the anaesthetic perspective, dangers include respiratory depression and hypoventilation proportional to the level of sedation, and the resistance of the tube, which can result in increased respiratory effort and ultimately insufficient tidal volume.

We examined the applicability of VATS-SVI in our practice (Petz Aladár University Teaching Hospital) to see if:

1. acceptable gas exchange can be ensured in room air, with an open chest and spontaneous breathing.
2. based on routinely monitored parameters characterising respiratory mechanics, can it be determined whether the patient is suitable for thoracic surgery with spontaneous breathing.

Patients and Methods

After obtaining approval from the Regional Research Ethics Committee of the Health Science Council (Reference Number: 76-1-11/2022), we conducted a pilot study. Between August and October 2022, we included 13 patients.

Inclusion Criteria:

- Elective lung resection
- Patients over 18 years of age

Exclusion Criteria:

- ASA IV stage
- Oxygen saturation below 90% under OLV
- Hemodynamic instability for any reason

Anaesthesiology risk assessment: ASA I:1, ASA II:10, ASA III:2

Surgical procedures: segment resection:1, lobectomy:9, other:3

Anesthesia procedure: As a standard procedure, patients received 0.5 mg alprazolam preoperatively. Induction and maintenance of anaesthesia were performed with 1% propofol in TCI mode, following the Marsh model with a 2-minute induction time. Patients were intubated with a double-lumen tube under the effect of 0.15 mg/kg mivacurium, and the relaxant was not repeated during the surgery. If there was no contraindication, 75 mg diclofenac was administered intravenously before the incision. Surgically, an intercostal block was performed to open the chest, followed by paravertebral and vagus nerve block during the initial phase, using a total of 20 ml of 0.5% bupivacaine hydrochloride. If deeper anaesthesia was needed, the propofol rate was increased, and 50-100 µg fentanyl was administered. After lung separation, ventilation was performed in pressure-controlled mode, followed by pressure-assisted mode with a maximum peak pressure of 25 mbar, 5 mbar PEEP, adjusting FiO_2 based on arterial blood gas to achieve normocapnia. After satisfactory spontaneous breathing returned, 6 l/min O_2 supplementation was applied. Patient Monitoring: EKG, pulse oximetry, capnography, invasive and non-invasive blood pressure, muscle relaxation monitoring (TOF), depth of sleep measurement (BIS). The numerical data were recorded at 5-minute intervals: tidal volume, respiratory rate, minute volume, mean airway pressure, and peak airway pressure. Prospective data collection: from the anaesthesia records and arterial blood gas analyses

Collected Data:

- First arterial blood gas after chest opening, in lateral position, under controlled ventilation at TOF 0
- Second arterial blood gas at TOF 0.8
- Third arterial blood gas during spontaneous breathing at TOF 1
- Ventilation parameters

Postanaesthesia control: after awakening and at 4 PM, paying special attention to alertness and pain, based on a VAS scale of 1-10.

We compared the data obtained during the three phases of anaesthesia: tidal volume, respiratory rate, minute volume, mean airway pressure, O_2 saturation, $etCO_2$, pCO_2, pH, pairwise. Initially, we performed a Shapiro-Wilk test for normality. Based on this, the data did not always show a normal distribution. For normal distribution, we used the Student's t-test; for non-normal distribution, we used the Wilcoxon test.

Results

Regarding oxygenation, there was no statistically significant difference across the three phases of anaesthesia. There was a significant difference in minute volume, tidal volume, respiratory rate, $etCO_2$, pCO_2, and pH, with a decrease in minute volume accompanied by an increase in $etCO_2$ and pCO_2 and a decrease in pH. Airway pressure also significantly decreased towards spontaneous breathing.

The surgical method in all cases was VATS-SVI. In two cases, the surgery was converted to open thoracotomy due to technical difficulties. In all 13 cases, we achieved assisted/spontaneous or spontaneous breathing. In 5 cases, spontaneous breathing was not satisfactory, indicated by low tidal volume, minute volume, and a drop in saturation, so assisted ventilation was maintained until the end of the surgery. In the two cases where conversion occurred, spontaneous breathing ensured adequate gas exchange. No hemodynamic instability was observed during the surgeries, and no patient required vasopressors. All patients were extubated in the operating room and transferred to the postoperative care unit. During the afternoon anaesthetic visit, no pain above VAS 3 was observed; all patients were alert and started incentive spirometry physiotherapy. Chest X-rays performed 4-6 hours post-surgery and on the first postoperative day showed expanded lungs in all cases.

Discussion

Minimally invasive VATS and RATS surgeries cannot be performed without collapsing the operated lung. This can be achieved not only with a double-lumen tube or bronchus blocker. About a quarter of a century ago, we revisited historical roots and “rediscovered” non-intubated thoracic surgeries, which can also satisfy this surgical need. Beyond technical aspects, potential lung damage caused by positive pressure ventilation can also be reduced.

VATS-SVI meets the need for a secure airway and collapsing the operated lung simultaneously. The paravertebral block performed under visual control by the surgeon minimizes the need for intravenous major opioids during surgery by anaesthetizing the chest wall and pleura. The vagus nerve block eliminates the cough reflex and blocks mechanical stimuli from mediastinal organs. Combined with intravenous sedation, these measures ensure that the patient remains still during surgery. Airway security with a double-lumen tube provides safety, as it allows to assist the patient's breathing if necessary and protects the contralateral airway from aspiration. The lungs can be separated, preventing cross-flow of secretions or blood, as well as paradoxical respiratory movements induced by pendelluft. Maintaining diaphragm contraction results in better ventilation on the dependent side, making spontaneous breathing an optimal solution for gas exchange. If a patient is deemed suitable for thoracic surgery based on standard preoperative tests, spontaneous breathing can be allowed with an open chest. Anaesthesia monitoring of the patient and ventilation parameters, supplemented with arterial blood gas analysis, is sufficient to recognize if the patient's gas exchange is inadequate and spontaneous breathing needs to be assisted.

The results of the pilot study support the safe applicability of the method even with the low number of cases. Theoretically, they also pave the way for considering applications outside the university centre.

5.2.Pleural and Mediastinal Air Accumulation in COVID-19 Infection in Intubated Patients

Since the SARS-CoV-2 pandemic began in December 2019, an unusually large number of patients with viral pneumonia-induced ARDS has appeared in intensive care units. Complications associated with mechanical ventilation, such as pneumothorax (PTX) and pneumomediastinum (PM), have also become more common. Necrotizing viral pneumonia itself predisposes patients to pneumothorax, and it is reasonable to assume that the risk is even higher in individuals with pre-existing lung damage. In both secondary spontaneous pneumothorax and those considered as complications of mechanical ventilation, chronic obstructive pulmonary disease (COPD) is an independent risk factor according to the literature. Canonical teaching holds that the probability of pneumothorax is proportional to the severity of the underlying disease.

During the second wave of SARS-CoV-2 (2021), we observed a significant increase in cases among patients in the Central Anaesthesiology and Intensive Care Unit of Petz Aladár University Teaching Hospital. Among these patients, there was a higher proportion who did not have pre-existing lung disease. To clarify the discrepancy between our observations and the literature, we compared the clinical course of patients with initially healthy lungs versus those with pre-existing lung damage. We investigated whether pre-existing lung tissue damage increased the risk of barotrauma.

Patients and Methods

Between 1st March 2020, and 1st February 2021, we treated a total of 138 confirmed COVID-19 pneumonia patients in the COVID Intensive Care Unit at Petz Aladár University Teaching Hospital. With the approval of the Regional Scientific and Research Ethics Committee (No. 76-1-8/2021) and in accordance with the Helsinki Declaration, we performed a retrospective analysis of the data collected during their treatment. The criteria for intensive care unit admission were: PaO_2 <65 mmHg or O_2 saturation <92% with the use of a reservoir O_2 mask, hypotension (mean arterial pressure <70 mmHg), or acidosis, or rapidly worsening clinical status due to poor gas exchange. If the patient's consciousness permitted and cooperation was possible, we attempted full face mask mechanical ventilation. 60/138 patients had previous or current chest CT scans. Three independent reviewers examined the images. The primary focus was on existing lung tissue damage, apical bullae, bullous emphysema, fluid-free cysts, and pneumatocele. We categorized patients with pre-existing parenchymal damage into three stages based on the extent of lung involvement: Stage I <10%, 10%<Stage II <50%, Stage III >50%. We also categorized pneumothorax during ventilation into three grades based on extent: Grade 1 for less than 20% of the parietal surface involved, Grade 3 for total or tension pneumothorax, and Grade 2 for cases in between. Pneumomediastinum cases were treated as a separate group. We excluded patients where iatrogenic pneumothorax during central venous catheterization was suspected. We reviewed patient medical histories in the EESZT and the institution's electronic database, with particular attention to chronic respiratory diseases and pulmonary follow-up.

Data processing: IBM SPSS 28 statistical software.

Kruskal-Wallis test: if there were significant differences in the occurrence of PTX/PM between groups with initially healthy lungs and those with pre-existing lung damage. The null hypothesis was that patients with pre-existing lung damage were more susceptible to PTX/PM.

Spearman test: the relationship between existing lung damage and the occurrence of PTX/PM.

Logistic regression analysis: the effect of age, gender, existing lung pathology, invasive, and non-invasive on PTX/PM as an outcome.

Cox regression analysis: how lung damage affected the number of days until the development of PTX/PM?

Kruskal-Wallis test: differences in survival between patients with initially healthy lungs and those with previously damaged lungs?

Dwass-Steel-Critchlow-Fligner pairwise comparison: survival among patients with different severities of chronic lung disease

Mann-Whitney U test: effect of barotrauma on survival

Log-rank test: comparison of medial survival in non-invasive and invasive ventilated patients

Results

Out of the 60 patients, 44 were intubated and required controlled mechanical ventilation via endotracheal tube, while 16 pressure-supported ventilation with full face masks. Barotrauma developed in 13 patients. The average age of women and men was similar (66 and 65 years, respectively). Pre-existing lung damage was more common among older patients (70 years). The average age of patients with previously negative CT scans was 64 years. The average age of the patients with controlled ventilation was 67 years, while those who were assisted in ventilation were generally younger (61 years).

When considering the frequency of PTX/PM with respect to age, the difference decreased: the average age in the PTX/PM group was 66 years, compared to 65 years in those without barotrauma. The difference was not significant. Lung damage was found in the CT scans of 17 patients, 15 men and 2 women. This difference can be explained by the fact that more men than women were included in the study.

Among all COVID-19 ventilated patients, the occurrence of PTX/PM was 27.3%. In patients with pre-existing lung damage, 58.8% required intubation and controlled ventilation, with only 17.6% developing PTX/PM, compared to patients with initially healthy lungs, 79.1% of whom were invasively ventilated and 23.3% developed barotrauma. PTX and pneumomediastinum occurred in 23.25% of patients with initially healthy lungs and 17.64% of patients with pre-existing lung damage.

The Kruskal-Wallis test showed no difference in the extent of PTX or pneumomediastinum among patients with pre-existing lung damage.

The Spearman correlation indicated no relationship between pre-existing lung damage and the various degrees of barotrauma.

Cox regression did not show a statistically significant relationship between pre-existing lung damage and the development of barotrauma.

Logistic regression analysis did not reveal a statistically significant relationship between individual variables (age, gender, mode of ventilation, and extent of pre-existing lung damage) and PTX/PM as an outcome. The model's predictive value was 78.3% ($p<0.001$). There was no difference in survival between patients with initially healthy lungs and those with previously damaged lungs (37.20% versus 35.29%, Kruskal-Wallis test: $\chi^2=3.281$, $p=0.350$). This was also true when comparing survival among patients with different severities of lung damage.

Development of PTX or pneumomediastinum did not impair survival (Mann-Whitney U test: $U=235.500$, $p=0.127$).

The median survival time for the invasively ventilated group was significantly longer than for the non-invasively ventilated group: 22 days vs. 12 days. When examining exit days, there was no statistically significant difference between the two groups: 13 vs. 17 days.

Discussion

Our null hypothesis based on the literature was not confirmed. There is no relationship between barotraumas occurring in COVID-19 patients requiring mechanical ventilation and pre-existing lung damage prior to COVID-19 infection. In other words, pre-existing lung tissue damage, such as bullous emphysema or pneumatocele, did not indicate an increased risk of barotrauma in COVID-19 pneumonia.

Spontaneously occurring pneumothorax originates from the apical part of the lung and spreads toward the lateral surface. A common underlying condition is apical bullous changes, which could suggest a causal relationship between the two. However, the mechanism of PTX in viral pneumonia might differ from the increased transpulmonary pressure. Clinical observations support this, as minimal air outflow is often noted during chest drainage, and after drainage, the lung expansion is either slow or does not occur at all because the consolidated "shrinking" lung parenchyma does not fill the thoracic cavity.

Two non-exclusive explanations can account for why pre-existing damaged lung parenchyma does not predispose to barotrauma. According to the mechanical perspective, fibrotic components in inflamed tissues may increase, offering "protection" against increased transpulmonary pressure. A similar phenomenon was experimentally observed in patients with blunt abdominal trauma due to liver cirrhosis.

Another possible explanation relates to the known mechanisms of PTX formation. Traditionally, the visceral pleura covering bullous lung tissue is considered the weak point, ignoring that experimental conditions have shown that a pressure of at least 1938 cmH2O is required for bullous rupture. During the first wave of the COVID-19 pandemic, no histopathological studies were conducted. However, during the second wave, more data emerged from microscopic examinations of surgically resected bullous lung tissue and lung tissue from deceased COVID-19 patients. These studies confirmed that, in COVID-19 pneumonia, as in other necrotizing inflammatory lung processes, inflammation in capillary walls leads to microthrombosis and vascular wall thickening. Small bullae are formed. The air entering the lung interstitium through the wall of the necrotized bullae spreads further in the peribronchovascular sheath based on the Macklin effect, thus causing PTX or pneumomediastinum (PM).

Regardless of the mechanism of air accumulation in the pleural space, except for Grade 3 PTX, the lung's lateral surface is effectively "tethered" to the parietal pleura due to inflammatory processes. On the mediastinal surface, micro-vibrations from blood flowing in the heart and large vessels prevent adhesion formation, allowing localized air collections. The risk of patient self-induced lung injury is high during assisted spontaneous breathing. This lung damage, involving the breakdown of the interstitial matrix or capillary walls, is caused by significant fluctuations in transpulmonary pressure. It theoretically does not matter whether this fluctuation is caused by the patient's increased respiratory effort or external forces generated by the ventilator. There are numerous reports of PTX and pneumomediastinum occurring during spontaneous ventilation, often as the first symptom of viral pneumonia. Therefore, the inadequate explanation for barotrauma being due to non-protective mechanical ventilation does not hold. It might be hypothesized that pre-existing damaged lung tissue could be a contributing factor. However, in our patient cohort, we observed the opposite; paradoxically more patients with initially healthy lung tissue experienced barotrauma. Based on our results, PTX and PM accompanying COVID-19 pneumonia are primarily consequences of the viral pneumonia itself rather than mechanical ventilation. Comparing survival rates between invasively and non-invasively ventilated groups, the median survival was significantly better in the invasively ventilated group. This supports the role of P-SILI (Patient Self-Induced Lung Injury) in the latter theory. For patients on prolonged mechanical ventilation in the intensive care unit, morbidity and mortality are multifactorial. Comorbidities, intensive therapy, including ventilation, and infrastructural factors all play roles.

6. Connections between the topics discussed in the thesis

The two clinical studies discussed address the phenomenon of pneumothorax from different perspectives.

The approach to thoracic anaesthesia has evolved over the past twenty-five years, particularly concerning thoracic surgery performed with spontaneous ventilation. This development prompts a re-evaluation of the effects of surgical pneumothorax on circulation and gas exchange. Contrary to long-held beliefs that spontaneous ventilation during open chest surgery is inadvisable, it has been demonstrated that, with proper patient monitoring and considerations, this notion no longer holds. Controlled pneumothorax can be managed effectively without concern. Under standard conditions of intraoperative patient monitoring, it is possible to determine whether spontaneous ventilation alone is sufficient or how much assistance is needed to ensure proper gas exchange. Both assisted spontaneous ventilation and spontaneous ventilation can provide appropriate conditions for the surgeon to perform the procedure. The VATS-SVI technique integrates the benefits of paravertebral blockade, vagus nerve blockade, and intubation anaesthesia. It meets patient safety standards, provides optimal conditions for the surgeon, and minimizes potential harm from positive pressure ventilation while maintaining spontaneous breathing. This focus on ventilation-related lung damage extends beyond thoracic anaesthesia and suggests exploring how to reduce the duration of positive pressure ventilation during surgeries in other fields.

Necrotic processes in lung tissue, such as those seen in viral pneumonias, can cause air leak syndrome. Except in cases requiring immediate intervention for tension pneumothorax, PTX alone is not typically life-threatening. Before opting for invasive interventions, the consequences of fibrotic remodelling resulting from acute or chronic inflammation should be considered. Stiffened lung tissue is less prone to expansion, so it is not certain that interventions like chest drainage and suction are in the best interests of the patients, as opposed to conservative management ("wait and see"). The assessment and treatment of pneumothorax warrant a revision in daily practice. Historically, until the 1950s, treatment for tuberculosis often involved pneumothorax, which was well-tolerated by patients. However, ignoring empirical facts, it became an area of concern often leading to unnecessarily aggressive therapies and even iatrogenic complications.

7. Conclusion

1. By researching pre-intubation and positive pressure ventilation methods in thoracic surgery, I identified the first documented case in Hungary from 1908. This research illuminated Sándor István's pioneering work and established the historical roots of NITS (Non-Invasive Thoracic Surgery). This serves as a fundamental argument against the exclusive use of positive pressure ventilation in thoracic surgery.
2. In the context of lateral decubitus position, open chest, and atmospheric pressure conditions, examining controlled ventilation, assisted ventilation, and spontaneous breathing, we observed a decrease in tidal volume and minute ventilation, an increase in pCO_2, and a shift towards acidosis in pH. However, oxygenation remained stable. With proper airway management and standard patient monitoring, the VATS-SVI technique proved safe and effective for both patient parameters and surgical contexts. The results of the study theoretically pave the way for application outside university centres.
3. Contrary to general belief, our large-scale study showed no significant difference in the incidence of pneumothorax and pneumomediastinum in COVID-19 pneumonia between patients with originally healthy lungs and those with chronic lung damage. Prior lung damage does not represent a risk factor in ventilation.
4. We found no significant difference in survival between patients with originally healthy lungs and those with pathological lung changes in COVID-19 respiratory failure. The presence of damaged lung tissue does not serve as a prognostic factor, contrary to expectations.
5. There was no detectable correlation between barotrauma-related pneumothorax (PTX) or pneumomediastinum (PM) and mortality in COVID-19 infection.
6. In COVID-19 respiratory failure, the ventilation strategy did not significantly impact outcomes. Survival in the intensive care unit is influenced by multiple factors, with ventilation mode being just one among many, and certainly not the most critical.

8. Scientific Publications

8.1. Scientific Publications Underpinning the Dissertation

Molnár FT, Kecskés G. A magyar nem intubációs mellkassebészet kezdetei, Kolozsvár, 1908. Orvosi Hetilap. 2022. július 31.;163(31):1250–1. IF 0,6; SJR rank Q4

Kecskés G, Belágyi T, Molnár FT. Nihil novi sub sole: a Sándor István-féle automatikus fecskendő. Orvosi Hetilap. 2023. január 8.;164(1):38–40. IF 0,7; SJR rank Q4

Kecskes, G., Szabo, A., Sutori, D., Maroti, P., Marovics, G., Molnar, T. F. (2022). Pneumothorax/pneumomediastinum and pre-existing lung pathology in ventilated COVID-19 patients: a cohort study. J Thorac Dis 2022;14(12):4733-4740. doi:10.21037/jtd-22-817 IF 2,5; SJR rank Q2

8.2. Additional Scientific Publications

Wellner I, Banga P, Haulik L, Rácz I, Kecskés G. Distalis duodenum tumorok rezekciójával szerzett tapasztalataink Magy Sebészet. 2001 augusztus;54(4):215-8.

Kecskés G, Belágyi T, Oláh A. Korai jejunalis táplálás pre- és probiotikummal történő kombinálása akut pancreatitisben – Prospektív, randomizált, kettős-vak vizsgálatsorozat. Magy Sebészet. 2003 február;56(1):3-8

Belágyi, T., Issekutz, A., Paukovics, A., Kecskés, G., Oláh, A. Successful treatment of mediastinal pancreatic pseudocyst by pancreatic head resection. Journal of the pancreas, 2008; *9*(3), 346–349

Fodor, G., Gartner, B., Kecskés, G. Magas nyaki gerincvelősérült beteg komplex intenzív ellátása, rehabilitációja rekeszi pacemaker alkalmazásával. Ideggyógyászati szemle 2020; 73(7–8) 269–273. https://doi.org/10.18071/isz.73.0269

8.3. Prize

Kecskés G. Early Enteral Nutrition with Specific Lactobacillus and Fibre reduces Sepsis in Patients with Severe Acute Pancreatitis. Poster session presented at: Congress of the Hungarian Society of Gastroenterology, 2002, Budapest, Hungary.
First prize - "Ferenc Földes - prize"