Perioperative pulmonary rehabilitation of patients with thoracic surgery

PhD thesis

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1. Introduction

The best long-term result can be achieved by thoracic surgery in early-stage lung cancer. The leading principle of pulmonary resection is the removal of the anatomical unit (lobectomy, pneumonectomy), with complete removal of all tumorous tissues (A evidence). Parallel with ageing, more comorbidities are present, which may result in an increased risk of surgical intervention in some cases. The incidence and order of postoperative complications of thoracic surgery are different from the general: the main cause of morbidity and mortality, the major perioperative risk, is 15–20% of respiratory complications, and cardiovascular complications as a second cause have 10–15% prevalence rate.

Some patients are operable based on oncology and technically term, but at the border because of lung function, exercise capacity and general clinical condition. There is a question about a method, which can improve the clinical condition and exercise capacity safely to reduce the risk of operations on behalf of the patient and the surgeon, and the patient will be eligible for the operation. In this dissertation, we are discussing this issue.

Pulmonary rehabilitation (PR) can be necessary if the patient's respiration is made to deteriorate by any of the causes. PR is a wider category than respiratory or pulmonological rehabilitation, whose ulterior is the pulmonologically indicated rehabilitation of patients with chronic respiratory disease (mostly with COPD). Pulmonary rehabilitation can be necessary during the treatment of musculoskeletal diseases, in connection with operations of the extremities and abdomen (basal hypoventilation caused by the deteriorated diaphragm-function, atelectasis, ventilatory dysfunction), or at injuries of the vertebral trunk. There is an especially important role of pulmonary rehabilitation associated with thoracic surgery.

The subject of *perioperative pulmonary rehabilitation* (PPR) includes the preoperative PR (immediately before thoracic surgery) and postoperative PR (started immediately after the emission from the surgery department or within a few weeks). Investigation of perioperative PR results in terms of chest hyperinflation, cardiovascular response, physical activity, general condition and quality of life of patients can provide useful information for the preparation of patients waiting for thoracic surgery or for the postoperative care of patients who have already undergone surgery. In our own study, we seek to find out how the beneficial effects of PR on patients with thoracic surgery are fulfilled. The examination of the capability of operation and the functional reserves of the patients may lead to more careful and accurate risk stratification.

The population that underwent PR in the present dissertation is special because every patient underwent *thoracic surgery* with intravenous narcosis. We investigate the favourable effects of perioperative PR associated with thoracic surgery by extending the analysis to the possible correlations of the examined parameters (functional variables, patient-, operation- and surgeon-dependent variables) with the complications. Analyzing the positive changes induced by PR and examining their correlation of serious postoperative complications may help to determine the importance of each functional parameter in risk stratification. During the most accurate preoperative risk stratification, we strive to assess with the utmost precision the anticipated effects of the planned surgical intervention on the patient's life functions, in the case of thoracic surgery, primarily in the respiratory and circulatory system. In addition, general effects have to be considered. The group of patients with COPD who have a particularly high proportion of pulmonary rehabilitated patients are particularly important for risk stratification. The risk stratification aims to find patients

with increased risk of surgery, and in general, the purpose of the risk assessment is to determine the intervention-specific risk as well. Preoperative identification of high-risk patients and indications of preoperative pulmonary rehabilitation in appropriate cases may reduce the rate of severe complications.

2. Objectives

1. The study aims to determine the *effectiveness* of pulmonary rehabilitation in connection with thoracic operations with intratracheal narcosis.

2. We investigate the effects of pulmonary rehabilitation on the cardiovascular system, muscles, lung mechanics, exercise capacity, lung function, exercise physiology, chest kinematics, muscle's strength and quality of life. We investigate the *changes* in functional parameters by follow-up, focusing on the significant *improvements* and positive effect of pulmonary rehabilitation. We are looking for the effectiveness of the 3-week supervised pulmonary rehabilitation program and the clinical significance.

3. We investigate the timing of the pulmonary rehabilitation program (pre- or postoperative) and the effectiveness of PR. We determine the effectiveness of *preoperative* PR.

4. We measure the effect of the *postoperative* PR program. Is it suitable for a patient who could not tolerate the operation well?

5. We investigate if the pre- and postoperative rehabilitations have an *additive* effect or not.

6. The maintenance of *quality of life* in connection with an operation is important. We use questionnaires to follow up the effectiveness of PR on symptoms, like dyspnea, fatigue and depression.

7. The study is based on clinical research, so it has timing. We investigate the data in different stages, analyze whether a trend can be observed in the change of the parameters examined in parallel with the *increase* in the number of cases. We investigate whether the changes can achieve clinical significance at a larger number of cases. We examine whether the inclusion of several variables of more patients in the analysis will change the results.

8. We are looking for the *correlation between improvements* of variables by statistical analysis.

9. We aim to determine the *discriminant* values of the severe complications developing.

10. We investigate the difference between severe and non-severe complications based on *starting* functional values.

11. Our aim is the development of a full-demand platform-independent database specially for thoracic surgery, including specifics of thoracic operations (diagnosis, type of operation), complications and parameters in perioperative PR, whose database structure is available for future analysis of different thoracic surgery analysis with small modifications. We aim to make an easier and more automated analysis for future studies.

3. Methods

Perioperative PR was based on the cooperation of three departments. The Department of Pulmonary Rehabilitation in the National Koranyi Hospital for Pulmonology (OKPI) was established in June 2008 and treats 600 to 700 patients every year. About a hundred patients take part in the perioperative pulmonary rehabilitation program each year. Department of Anaesthesiology and Intensive Care in our institute treats 1100–1200 patients every year.

We performed a literature review for risk stratification, focusing on lung function, lung mechanics, chest kinematics, exercise physiologic parameters and cardiovascular response. We investigated the effect of PR on cardiovascular system, muscles, lung mechanics, exercise tolerance and quality of life. We evaluated the risk of different laboratory results, co-morbidities, obesity, cachexia and smoking.
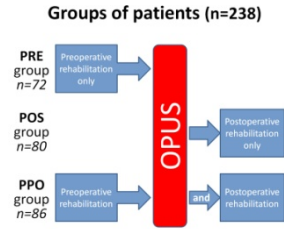
3.1. Ethical background of the investigation

Our investigation is based on clinical work, overseeing the general management of the patients. The study was primarily observational. The examination was performed with the informed consent of the patients. The study has satisfied the international registration requirements of the WHO ICTRP; it was registered according to the directives of the ICMJE and it was registered in the ISRCTN international registry with the title "Perioperative pulmonary rehabilitation in thoracic surgery" (study ID is: ISRCTN97596271). Local Ethics Approval was given on 20/NOV/2016 with registration number of 36/2016.

3.2. Patients

Two hundred and thirty-eight patients participated in the perioperative PR program at the Department of Thoracic Surgery at the National Koranyi Institute for Pulmonology during the 5-year observation period. Based on the timing around the thoracic operation, we separated three groups:

Figure 1. The 3 rehabilitation groups of the 238 patients. PRE group: preoperative PR only; POS group: postoperative PR only; PPO group: pre- and postoperative PR as well.

The first group of 72 patients performed preoperative pulmonary rehabilitation only (PRE). The second group consisted of 86 patients who performed only postoperative rehabilitation (POS). The third group comprised of 80 patients who performed both pre- and postoperative rehabilitation procedures (PPO) [Figure 1]. The control group had neither preoperative nor postoperative PR. The optimal number of groups was defined by a specialist of statistics.

The subject of our study is based on clinical work; therefore, it had temporality in line with the increasing case number. We analyzed the results in three stages. We investigated whether the changes became significant if we increase the number of patients in the PR program. Based on this question, we increased the number of patients for the same analysis and then we increased the number of variables in the three study periods. We involved 153 patients for the first, 208 for the second and 238 for the third analysis. We showed in the three PR group (PRE, POS and PPO) the consecutive periods with lower case signs (1./2./3.). In the third observation period, we made a correlation and discriminant analysis.

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3.3. Pulmonary rehabilitation program and measured variables

Our supervised inpatient PR program lasts 2–3 weeks with specialized healthcare professionals and devices. The PR program starts with a guide and education of the patients and includes 30 minutes breath training, learning controlled breathing techniques, chest wall mobilization with inhalation and expectoration and a personalized training. The patients learn specialized respiratory techniques (abdominal breathing, pursed-lip breathing, turn the trunk to 45 degrees) and passive-active chest mobilization. The patients perform specialized endurance training with strength respiratory muscle training. We offer the patients a personalized training 2/3 times/day for 10–25 minutes by cycle. We support the quitting of smoking by Smoking Cessation Center with psychologists in our institute. Initial parameters of the patients were registered with a detailed general checkup, changes in the values were recorded during functional follow-up, the results were analyzed by mathematical statistical analysis. We measured the following parameters: forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), chest wall expansion (CWE), 6-minute walking distance (6MWD), grip strength (GS), breath holding time (BHT), modified Medical Research Council dyspnoe scale (mMRC), COPD Assessment Test (CAT) and duration (in minutes), exercise tolerance (Watt) and distance (in km) of cycle-ergometry. We added some other parameter, for example, the extent of operation and degree of complications based on TM&M classification and ESTS Database.

3.4. Processing of data, mathematical and statistical analysis

We developed a database for analyzing and storage of data in thoracic surgery, including parameters of thoracic surgery, indication, type of surgical method, complications and measured variables in PR. We asked the help of a mathematician for statistical analysis. Analysis was preformed through a combination of t-tests, non-parametric sign tests on patient characteristics, functional markers, and health condition scores. 3D paired T probe (Sign test and Wilcoxon test) was made for start and post-rehabilitation values. We used Pearson chi-square analysis (χ2-probe) for discrete variables. The continuous variables were utilized to determine the continuous distribution. The distribution around the mean was expressed as ± SD. We used ANOVA statistics for the three groups. According to the patients' characteristics, the PR groups proved to be comparable. We evaluated the changes in functional parameters. Significance was recognized at $P<0.05$. Correlations of the changes were evaluated, connections in between variables and severity of complications were analyzed, discriminant-analysis was made for identifying the variables that can have connection with severity of complications.

4. Results

The average age of the patients was $63{,}7\pm8$ years, the man:woman proportion was 132:106, the average start value of FEV_1 was $62{,}3\pm14{,}6$ %pred. The average intensive care duration for all cases was $3{,}5\pm4{,}5$ days, it was $3{,}6\pm4{,}6$ days in the PRE_3 group, $3{,}1\pm3{,}7$ days in the POS_3 group, $3{,}8\pm5{,}3$ days in the PPO_3 group and for all preoperatively rehabilitated patients it was $3{,}7\pm5{,}0$ days (PRE_3 + PPO_3 groups together).

Indication of the 238 operations was primary lung cancer in 179 cases (75.2%), pulmonary metastasis in 11 (4.6%), benign disease in 10 (4.2%), infection in 16 (6.7%) and other causes in 22 cases (9,2%).

At the first stage of the study, by evaluating 153 patients' data, 6MWD showed *improving tendency* (PRE_1: 361±79 vs. 390±66 m; PPO_1: 369±93 vs. 423±74 m before surgery, 322±11 vs. 343±35 m after surgery; POS_1: 329±134 vs. 386±86 m). Chest wall extensions *improved significantly* (PRE_1: 3,9±1,2 vs. 5,9±0,7 cm; PPO_1: 3,5±1,0 vs. 5,7±0,8 cm before surgery, 4,2±1,0 vs. 5,7±0,8 cm after surgery; POS_1: 3,7±1,0 vs. 5,8±0,6 cm; $p < 0,05$).

At the second stage of the study, the improving trends became *clinically significant improvements* reaching 208 of patients. The FEV_1 value improved significantly by the effect of PR: PRE_2: 63,7±16,0 vs. 67,4±16,3 ref% ($p < 0,03$), PPO_2: 58,8±15,0 vs. 65,1±15,6 ref% before the operation ($p < 0,03$), 48,4±12,7 vs. 51,8±13,0 ref% after the operation ($p < 0,03$), POS_2: 55,6±16,2 vs. 60,8±14,2 ref%, ($p < 0,03$). 6MWD has improved significantly: PRE_2: 403±87 vs. 452±86 m ($p < 0,0001$); PPO_2: 388±86 vs. 439±83 m before surgery ($p < 0,0001$), 337±111 vs. 397±105 m after surgery ($p < 0,0001$); POS_2: 362±89 vs. 434±94 m ($p < 0,0001$). The chest wall extensions improved significantly in all PR groups: PRE_2: 4,4±2,3 vs. 5,9±2,2 cm ($p < 0,0001$); PPO_2: 4,2±2,3 vs. 5,7±2,8 cm preoperatively ($p < 0,0001$), 2,8±1,6 vs. 4,5±2,3 cm postoperatively ($p < 0,0001$); POS_2: 2,8±1,4 vs. 4,8±2,0 cm ($p < 0,0001$). The FVC, grip strength and results of quality of life tests improved significantly in all three PR groups.

At the third stage of the study, the analysis was performed on reaching the planned 238 patients. As a result of PR, a favourable change in each examined parameter was detected in all PR groups. The values of the PRE$_3$ and PPO$_3$ groups are shown in Table 1.

Table 1. The effectiveness of pulmonary rehabilitation is demonstrated by a significant improvement of the functional parameters in the *preoperative* pulmonary rehabilitation group (PRE$_3$) and in the *postoperative* pulmonary rehabilitation group as well (POS$_3$)

n=238	PRE$_3$ (preoperative rehabilitation only) n=72			n=238	POS$_3$ (postoperative rehabilitation only) n=80		
	Before PR	After PR	Change, Significance		Before PR	After PR	Change, Significance
FEV$_1$ (%pred)	63.2 ± 15.6	70.1 ± 16.6	[p<0.0001]	FEV$_1$ (%pred)	56.4 ± 15.6	64.6 ± 16.0	[p<0.0001]
FVC (%pred)	83.1 ± 15.9	90.9 ± 15.6	[p=0.0001]	FVC (%pred)	66.2 ± 18.7	76.1 ± 17.7	[p<0.0001]
Chest Wall Extension (cm)	4.2 ± 2.3	5.8 ± 2.2	[p<0.0001]	Chest Wall Extension (cm)	2.9 ± 1.4	5.0 ± 2.0	[p<0.0001]
6MWD (m)	392.9 ± 93.5	443.2 ± 86.6	[p<0.0001]	6MWD (m)	354.7 ± 90.7	437.0 ± 96.0	[p<0.0001]
mMRC	0.93 ± 0.70	0.61 ± 0.58	[p=0.0005]	mMRC	1.5 ± 1.0	1.0 ± 0.8	[p<0.0001]
Breath Holding Time (s)	29.7 ± 11.3	33.4 ± 13.8	[p=0.0177]	Breath Holding Time (s)	26.4 ± 12.2	32.1 ± 14.7	[p<0.0001]
Grip Strength (kg)	29.8 ± 9.8	31.7 ± 9.3	[p<0.0001]	Grip Strength (kg)	25.8 ± 7.7	28.1 ± 7.6	[p<0.0001]
CAT	8.3 ± 5.2	5.3 ± 4.6	[p<0.0001]	CAT	16.9 ± 8.1	11.4 ± 8.1	[p<0.0001]
Cycle ergometry - time (Minute)	6.9 ± 2.5	16.8 ± 4.7	[p<0.0001]	Cycle ergometry - time (Minute)	6.2 ± 2.8	14.6 ± 4.9	[p<0.0001]
Cycle ergometry - power (Watt)	31.5 ± 7.9	46.5 ± 14.4	[p<0.0001]	Cycle ergometry - power (Watt)	30.0 ± 8.2	40.8 ± 10.2	[p<0.0001]
Cycle ergometry - distance (Km)	3.3 ± 1.4	9.1 ± 2.7	[p<0.0001]	Cycle ergometry - distance (Km)	2.8 ± 1.8	7.8 ± 3.4	[p<0.0001]

The positive effects of PR were additive in those patients who underwent pre- and postoperative rehabilitation (PPO$_3$). In the table that shows the improvements of the PPO$_3$ group, 63% of the values are better than its initial value were before the operation and the preoperative PR, although a surgery — with major loss of lung parenchyma in most of the cases — were performed. [Table 2.]

According to our results, patients with severe complications are older (65.6 ± 7.8 vs. 63.1 ± 8.4 years) and taller (170.2 ± 10.5 vs. 164.7 ± 8.2 cm) [p<0.05]. In case of severe complications the initial 6MWD value is significantly lower (357.1 ± 91.4 vs. 394.3 ± 88.2 m), the mMRC is worse (1.3 ± 0.9 vs. 1.0 ± 0.9) and the distance value of cycle ergometry is significantly less (2.9 ± 1.2 vs. 3.6 ± 1.8 km) [p<0,05].

Table 2. Changes in functional parameters in the combined *pre- and postoperative* rehabilitation group (PPO$_3$.) demonstrate the effectiveness of PR before surgery and at operated patients as well. The value of postoperative and post-PR variables printed with bold letters and marked with a star is better than the preoperative start-value was (before the operation and the preoperative PR).

n=238	PPO$_3$. (pre- and postoperative rehabilitation as well) n=86						
	Before surgery				After surgery		
	Before PR	After PR	Change, Significance		Before PR	After PR	Change, Significance
FEV$_1$ (%pred)	58.2 ± 15.1	67.0 ± 14.6	[p<0.0001]		47.4 ± 13.0	53.4 ± 14.7	[p=0.0003]
FVC (%pred)	82.4 ± 16.7	93.3 ± 16.7	[p<0.0001]		63.6 ± 16.9	72.6 ± 18.6	[p=0.0001]
Chest Wall Extension (cm)	4.0 ± 2.1	5.6 ± 2.6	[p<0.0001]		2.7 ± 1.5	**4.4 ± 2.2***	[p<0.0001]
6MWD (m)	378.3 ± 90.5	441.3 ± 86.4	[p<0.0001]		341.4 ± 115.8	**403.3 ± 98.4***	[p<0.0001]
mMRC	1.2 ± 1.0	0.8 ± 0.8	[p<0.0001]		1.8 ± 0.9	1.4 ± 0.8	[p=0.0001]
Breath Holding Time (s)	29.3 ± 11.8	33.7 ± 11.8	[p<0.0001]		23.3 ± 10.4	28.1 ± 10.1	[p<0.0001]
Grip Strength (kg)	27.5 ± 7.7	29.6 ± 7.9	[p<0.0001]		26.9 ± 8.4	**27.7 ± 9.2***	[p=0.0376]
CAT	11.4 ± 6.8	7.7 ± 5.8	[p<0.0001]		15.4 ± 6.9	**9.9 ± 4.7***	[p<0.0001]
Cycle ergometry - time (Minute)	7.2 ± 3.2	17.8 ± 6.3	[p<0.0001]		7.1 ± 3.3	**14.5 ± 4.5***	[p<0.0001]
Cycle ergometry - power (Watt)	31.1 ± 8.7	44.1 ± 10.8	[p<0.0001]		30.4 ± 10.1	**39.7 ± 9.5***	[p<0.0001]
Cycle ergometry - distance (Km)	3.6 ± 1.9	9.3 ± 2.9	[p<0.0001]		3.3 ± 1.8	**7.5 ± 2.9***	[p<0.0001]

Looking at the correlations of the improvements, changes of four variable pairs correlate with Pearson's correlation coefficient. These include chest wall extensions with breath holding time, FEV$_1$ with FVC, 6MWD with CAT, and the time with the distance travelled via cycle ergometer.

According to Guilford form, we can conclude that all of these four correlations are moderate and the connection is significant.

The peak values after PR are significantly different at two variables: FEV_1: 70.1 ± 15.6 vs. 64.8 ± 16.2 %pred [p<0.05] and FVC: 93.8 ± 15.7 vs. 88.7 ± 17.5 %pred [p<0.05]. In terms of severe complications, 5 variables proved to have a discriminating value. In descending order of discriminating value, these are the following: gender, initial distance travelled via cycle ergometer in kilometres at the onset of the preoperative PR, peak value of FEV_1 after preoperative PR, extent of the operation and 6MWD before preoperative PR. These 5 values can discriminate severe complications correctly in 72,5 % of all cases, not severe in 64,2%; altogether they can discriminate between the 2 severity groups correctly in 66,4%. With a little bit more strict Jackknifed classification these values are 67,5% and 62,3% in order (altogether 63,7%).

5. Conclusions

1. Based on the result of the studies, *perioperative* PR has a positive effect in connection with thoracic surgery. It is indicated if the aim is the improvement of cardiopulmonary function, postoperative condition, quality of life or the tolerability of the operation.

2. Perioperative PR can decrease the chest hyperinflation as well as improve the cardiovascular response and physical activity.

3. PR has a favourable effect in pre- and postoperative condition as well. *Preoperative* PR can improve the clinical condition of the patients, quality of life and functional reserves. The PR used as a preparation contributes to the surgery by increasing reserve capacities. Preoperative PR is needed in terms of functional operability in about 20% of the patients. From the benefits of PR, most patients with high perioperative risk may benefit.

4. *Postoperative* PR can be indicated in those patients who have a worse clinical condition after the operation and are capable of the PR program. Postoperative PR can improve the clinical condition, lung mechanics, metabolism, and functioning of the cardiovascular system and muscles.

5. Pre- and postoperative rehabilitation together can be tolerable and have an additive effect. When pre- and postoperative PR are combined, better postoperative value can be achieved at some of the functional variables than before surgery and preoperative PR. Perioperative PR may reduce the function-depleting effect of the operation by improving the parameters, giving a better chance of the uncomplicated postoperative period and contributing to reducing the rate of severe complications.

6. Self-sufficiency, ability to carry out daily tasks, and overall quality of life of the patient is an important aspect of evaluating surgical effectiveness for the patient and the general practitioner as well. PR,

which has a beneficial effect on quality of life, helps patients to struggle with the disease, improve their wellbeing, and reduce symptoms (dyspnoe, fatigue and depression), making the difficulties of the post-operative period more tolerable.

7. In a larger patient population, PR has a clinically significant positive effect: in the case of patients who are expected to improve status by PR, it is recommended that the maximum proportion of perioperative pulmonary rehabilitation be used to maximize beneficial effects. The adverse effect of PR was not observed. Discriminant analysis of multiple variables can result in finding a combination of variables with a better discriminative value.

8. Correlation was observed between FEV_1 and FVC, chest wall extensions and breath holding time, 6MWD and CAT, and distance and time/power measured during ergometry.

9. The values measured during the general health check-up can be related to the severe postoperative complications. In terms of morbidity, it is interesting for the thoracic surgeon that such patient parameters and functional variables significantly determine the short- and medium-term outcomes of thoracic surgery that are independent of the operation and its features (surgical technique, skills, course and type of surgery). Nevertheless, by analysis extended with operation-dependent factors there can be found a group of variables with a better discriminative value for complication severity. Finding more variables with a predictive value can help to develop a more accurate preoperative risk stratification system.

10. According to our results, older age or higher body height is a risk factor for thoracic surgery. The worst starting 6MWD and mMRC values, as well as the smaller ergometer distance, are more common in

patients with severe complications. Therefore, the worse value of these variables can be interpreted as a warning sign for the likelihood of developing severe complications.

11.   The structured thoracic surgical database we use is suitable for jointly capturing data of any type of surgery, related indications, and specific values of other profession related to the treatment altogether with the postoperative complications. With the help of this system, we have simplified the steps for data entry and eliminated redundancies in a partly automated way. This does not require special target software, and no special computer technologist is required. Columns with automated formulas accelerate data entry. It may, therefore, be useful to describe in more detail the methodology of our thoracic surgical data processing system. The developed data storage system is suitable for processing the results of other fields (anesthesiology, pathology, pulmonology) together with thoracic surgery and for finding correlations.

12.   In the literature review of the dissertation, we presented the PR methodology and the surgical risk factors. We believe that with the help of the publications reviewed, we can provide a summary for pulmonologists, anaesthetists, thoracic surgeons and rehabilitation professionals that can serve as a reference for perioperative care of thoracic surgery and risk stratification, outlining the possibilities for improving the functional reserves of the patients; their surgical tolerance and risk thereby can be reduced.

6. Bibliography of the candidate's publications

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