UNIVERSITY OF SZEGED
ALBERT-SZENTGYÖRGYI MEDICAL SCHOOL
DOCTORAL SCHOOL OF CLINICAL MEDICINE

SLEEP-RELATED BREATHING DISORDERS AND THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA IN PEDIATRIC POPULATION

Ph.D. Thesis

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Szeged, 2023

SCIENTIFIC METRICS

Number of publications related to the subject of the thesis:	3
Cumulative impact factor of publications related to the thesis:	7.415
D1: 0, Q1: 1, Q2: 1, Q3: -, Q4: 1	

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

1. Benedek P, Keserü F, Kiss G, Bella Z, Rovó L, Katona G, Bikov A, Csoma B, Lázár Z. Postoperative respiratory complications in children with obstructive sleep apnoea syndrome. Acta Otorhinolaryngol Ital. 2022 Apr;42(2):162-168. doi: 10.14639/0392-100X-N1803. PMID: 35612508; PMCID: PMC9132002. SJR: Q2. IF: 2.618
2. Keserű F, Sipos Z, Farkas N, Hegyi P, Juhász MF, Jászai VA, Párniczky A, Benedek PE. The risk of postoperative respiratory complications following adenotonsillar surgery in children with or without obstructive sleep apnea: A systematic review and meta-analysis. Pediatr Pulmonol. 2022 Dec;57(12):2889-2902. doi: 10.1002/ppul.26121. Epub 2022 Sep 19. PMID: 36030550. SJR: Q1. IF: 4.09
3. Keserű F, Párniczky A, Gács É, Katona G, Benedek PE. Személyre szabott, pozitív nyomású légzésterápia cystás fibrosisban [Personalised positive-pressure ventilation in cystic fibrosis]. Orv Hetil. 2021 May 9;162(19):760-765. Hungarian. doi: 10.1556/650.2021.32060. PMID: 33965910. SJR: Q4. IF: 0.707.

INTRODUCTION

Pediatric sleep medicine is continuously outgrowing itself due to the rapid development of science and undiscovered areas of the discipline. Clinical interest in the diagnosis and management of obstructive sleep apnea (OSA) or other sleep-related breathing disorders (SBD) are increasing due to the significant prevalence in pediatric population. OSA syndrome is the most severe sleep-related breathing disorder, manifested in 2-5% of the pediatric population, mostly occurring between the ages of two to six years. Underlaying the pathophysiology of the disease in children, most commonly adenotonsillar (AT) hypertrophy can be found causing anatomical narrowing in the oropharynx.

Symptoms of OSA are not just present during sleep, but also additional changes can be noticed during daytime. Based on the history provided by the parents, most commonly snoring, impairment of cognition and behavioral changes can be registered. In the process of establishing the diagnosis, an algorithm should be followed, including exploring the symptoms, carrying out additional non-specified examination and using specified sleep-related diagnostic tools. The gold standard for establishing the presence and severity of the disease is polysomnography (PSG). Consensus guideline for implementing the examination and analyzing sleep structure was defined by the American Academy of Sleep Medicine (AASM). Respiratory movements are monitored by thoracic and abdominal excursion helping the differentiation of central and obstructive events. Through nasal cannula airflow, and with pulse oximetry gas exchange with end tidal CO_2 can be measured giving precise information of breathing during sleep, flow limitation, the absence or presence of apneas and hypopneas. Arousal can be detected, and sleep stages can be determined based on the frequency and amplitude of the waves registered from the age of 2-3 months through electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG).

The diagnosis of OSA can be established if any one of the following criteria is met: 1. apnea-hypopnea index (AHI, average number of apneas and hypopneas occurring per hour of sleep) is greater than one, 2. obstructive hypoventilation for >25% of total sleep time is registered manifested in partial pressure of carbon dioxide >50 mm Hg. Children can be categorized in three severity groups based on the AHI according to the AASM: mild OSA (OSA I): 1<AHI<5, moderate OSA (OSA II): 5≤AHI<10, severe OSA (OSA III): AHI≥10.

When the diagnosis is confirmed but the characteristic of the obstruction is undefined, in order to determine the exact location, configuration, and degree of obstruction in the upper airways during sleep, additional specific examination should be performed, such as drug-induced sleep

endoscopy (DISE). During the procedure anatomical, functional, or mixed disfunction can be identified with the degree of the occlusion. When needed, further CT or MRI imaging can be carried out.

Since most commonly AT hypertrophy stands in the background of pediatric OSA, AT surgery has been accepted as first line treatment. Previous guidelines suggest that adenoidectomy alone may not be sufficient and either tonsillotomy or tonsillectomy should be carried out along with it. Consequential of the intermittent hypoxia in OSA, downregulation of genes responsible for identifying and reacting to hypoxia and hypercapnia can result the desensitization of the respiratory system leading to serious postoperative adverse events. Not only minor complications such as desaturations without the need of intervention can occur, but there is a possibility of laryngospasm, bronchospasm, or pulmonary oedema, that can lead to respiratory distress syndrome with the need of consequential naso-oropharyngeal airway management, re-intubation, and ventilation as major adverse events. If respiratory complications are not promptly recognized, then serious complications may occur, such as myocardial ischemia, cardiac arrythmia, hypoxic encephalopathy or even death. Therefore, postoperative monitoring is crucial. Several regional consensus statements can be found regarding postoperative monitoring, but there is not a generally accepted agreement.

In some cases, such as residual OSA, when surgery can not be performed, or in case of lack parental compliance CPAP therapy is recommended in the first place. To be able to ensure an effective therapy, the titration of positive pressure and oxygen flow should be set individually in sleep laboratories under the supervision of sleep technicians along polysomnographic monitoring. In Hungary 12 accredited laboratory can be registered in 2023 by the European Sleep Research Society (ESRS), among which the only one particularly for children is the Sleep Laboratory of Heim Pal National Pediatric Institute.

AIMS OF PHD WORK

Although, sleep medicine related science is evolving, still many unresolved question and undiscovered potential can be found in the topic. OSA is a common disorder in children, usually caused by adenotonsillar hypertrophy and requiring surgical treatment. However, several studies suggest that OSA increases the risk of postoperative respiratory complications (PoRC) after adenoid and/or tonsil surgery, but contradiction can be found and also the correlation with the presence and severity of OSA is unclear. With an appropriate postoperative monitoring system and protocol PoRC could be detected in time with avoiding major complications, but there is currently no consensus statement, only regional guidelines are available.

Sleep medicine, being a multi-disciplinary science, can play a role in the treatment of diseases where breathing support is needed due to rapid pulmonary progression with personalised positive pressure ventilation adjusted individually in a sleep laboratory. Although, the care of children with cystic fibrosis is improving with the development of biological therapy, it remains difficult to access. In my work, my aim was to describe the impact and benefits of CPAP therapy on respiratory function through a case study.

My aims in my Ph.D. work were:

1. *Prospective analysis based on our own data*
   - The effect of comorbidities and OSA on PoRCs after AT surgery.
   - The effect of OSA severity on PoRCs after AT surgery.
2. *Meta-analysis based on international data*
   - Occurrence rate of PoRCs in OSA compared to non-OSA children following AT surgery.
   - Connection between the appearance rate of PoRCs, the severity of OSA, the severity of respiratory complications.
   - Major and minor PoRCs in pediatric patients following AT surgery in OSA and non-OSA.
   - The role of comorbidities in PoRCs in OSA and non-OSA pediatric patients following AT surgery.
3. *Potential advantages of CPAP therapy*

Our aim was to establish a case report on the advantages and positive effects of personalized positive airway pressure therapy prior lung transplantation in cystic fibrosis based on our results.

METHODS

1. Prospective analysis based on our own data

Prospective data collection

577 children were included who underwent polysomnography (PSG) followed by adenoid and/or tonsil surgery at Heim Pal National Pediatric Institute, Budapest, Hungary due to symptoms of sleep-related breathing disorders between 1 January 2015 and 31 December 2018. The indications for surgery were clinical symptoms of OSA and abnormal findings on polysomnography. Details from past medical history, physical status, results of PSG, treatment and postoperative complications were recorded.

Polysomnography

PSG was performed with a Somnomedics Somnoscreen Plus device (Somnomedics, Randersacker, Germany) according to guidelines and data was evaluated by a physician experienced in sleep medicine. The severity of OSA was defined by the AHI as mild ($1<AHI<5$), moderate ($5\leq AHI<10$), or severe ($AHI\geq 10$). Clinical data were analysed with regards to PSG parameters including AHI and DI.

Physical examination

Obesity was defined by body mass index (BMI), ENT examination included the examination of the nose (ala nasi, septum nasi, inferior turbinate), nasopharynx, and oropharynx with the size of the tonsils, which was categorized by the Brodsky scale. Patients with laryngeal abnormalities diagnosed with fiberoptic laryngoscopy were excluded.

Statistical analysis

Data normality was tested (D'Agostino test) and data are shown as mean ± standard deviation or median (interquartile range). Groups were compared with t-test, analysis of variance (ANOVA), Mann-Whitney and Kruskal-Wallis tests. Categorical data were analysed with chi-square or Fisher's exact tests (GraphPad Prism 7.0, GraphPad Software, San Diego, USA). The association between clinical variables and demographics as well as PoRCs was evaluated with multivariate logistic regression. This was investigated separately in patients with and without comorbidities. We calculated the required sample size for Fisher exact test of independence using the G*Power software version 3 (Heinrich Heine University Dusseldorf, Dusseldorf, Germany). We used the results of a previous study that prospectively evaluated the incidence of postoperative airway-related complications between children with and without comorbidities as input. We expected a difference between the sample sizes of the two groups, so we utilized the findings of another study, in which the incidence of craniofacial abnormalities was

investigated in children with obstructive sleep apnea. The calculated minimum total sample size for the study was 131 (1-β=0.80, α=0.05; group with comorbidities N=21, group without comorbidities N=110). However, due to the lower prevalence of comorbid conditions than expected initially, we continued to recruit children to reach the minimal sample size in the comorbid group.

Study characteristics

We recruited 577 patients for the study, 357 boys and 220 girls from the age of 8 months to 18 years. Twenty-four children (4.2%) presented with comorbidities including obesity (13 patients, 4 of whom suffered from Prader Willi syndrome), prematurity with bronchopulmonary dysplasia (3 patients), hypotonic neuromuscular disorder (3 patients), Down syndrome (3 patients), Pfeiffer syndrome (1 patient) and Fragile X syndrome (1 patient) There were no differences in age and gender between patients with and without comorbidities, however, patients with comorbidities suffered from more severe OSA ($p< 0.001$).

2. Meta-analysis based on international data

Eligibility criteria

Observational studies that examined PoRCs in pediatric patients (aged 0–18 years) undergoing any kind of AT surgery were considered. Only studies that provided adequate data on PoRCs in both the OSA and non-OSA groups were eligible. No other restriction was put in place.

Eligibility was based on the following PECO:

P – Population: Studies that examined pediatric patients (aged 0–18 years) undergoing any kind of AT surgery.

E – Exposure: Children with a diagnosis of OSA undergoing AT surgery.

C – Comparator: Children undergoing AT surgery without OSA.

O – Outcome: The presence of PoRCs following AT surgery in the pediatric OSA and non-OSA population.

Systematic search and selection

The systematic search was conducted in MEDLINE (via PubMed), Embase and the Cochrane Library (CENTRAL). The date of the last systematic search was 3 March 2021. No language restriction was applied.

Data extraction

For both groups (OSA and non-OSA), extracted data from the eligible articles contained first author, publication year, study design, number of patients, age, and gender distribution, PoRCs (minor and major), and patients' characteristics, such as comorbidities and severity of OSA. Subgroups were formed to be able to decide whether children with OSA (at a mild, moderate, or severe stage) or with additional comorbidities carry a higher risk of developing respiratory complications following AT surgeries. As regards PoRCs, two subgroups were formed: major and minor complications. Based on the included articles, desaturations for any reason without the need for intervention were listed as minor complications, while desaturation, laryngospasm, bronchospasm, pulmonary oedema, or pneumonia requiring interventions, such as re-intubation, naso- or oropharyngeal airway management, or ventilation were listed as major complications in the postoperative period prior to discharge. In the OSA group, three subgroups were created based on severity: mild ($1<AHI<5$), moderate ($5\leq AHI<10$) and severe ($AHI\geq 10$).

Risk of bias assessment

The studies included in our meta-analysis were analysed using the Quality in Prognostic Studies (QUIPS) modified table to assess risk of bias.

Statistical analysis

Odds ratios (OR) were calculated, with 95% confidence intervals (CI) and a p-value of $p<0.05$ indicating statistical significance. If at least three articles reported on the same outcome in a comparable manner, a meta-analysis was performed using the DerSimonian–Laird random effects model. Results of the meta-analyses are displayed graphically with Forest plots. Heterogeneity was tested with the chi-squared test (with $p<0.1$ indicating statistically significant heterogeneity) and the I^2 statistic, where an I^2 value of 30–60% represents a moderate risk of heterogeneity, 50–90% indicates a substantial risk and 75–100% suggests a considerable risk. All meta-analytical calculations were performed using the Stata 15 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

Systematic search and selection

The systematic search yielded 672 hits, of which 474 studies were screened after removing duplicates. 198 studies were also excluded by title, leaving 276 for screening based on abstracts

and leading to the exclusion of a further 190 papers. Out of the remaining 86 studies, based on a review of the full texts, 19 were included.

Study characteristics

Data of 120,544 patients, with 59,323 of them involving OSA, were examined based on the included 19 studies regarding PoRCs following AT surgery in. Thirteen of the included studies were retrospective observational, two retrospective case-control, one ambidirectional, one prospective and two cross-sectional.

3. Potential advantages of CPAP therapy

We present a case report on the effectiveness of personalized positive pressure ventilation, used in the Sleep Laboratory of the Heim Pál National Institute of Pediatrics as a bridging option in preparing children for transplantation with cystic fibrosis.

RESULTS

1. Prospective analysis based on our own data

Effect of comorbidities on postoperative respiratory complications

The incidence of postoperative respiratory complications in our cohort was 4.3% (25/577). The prevalence of complications was significantly higher in patients with comorbidities (58.3%, 14/24 vs. 2%, 11/553; $p<0.001$). The presence of comorbidity increased the risk for PoRCs with an odds ratio (OR) of 4 (95% confidence interval 3.6-5.2).

In the group without comorbidities, complications occurred in all 11 cases as desaturation, in 5 cases without requiring supplemental oxygen therapy, in 6 cases with requiring it, and one patient was diagnosed with bronchopneumonia. Complications appeared within two hours after surgery, with no need for reintubation.

In the group of patients with comorbidities, desaturations occurred in all 14 cases and was associated with more severe postoperative nadir oxygen desaturations compared to patients without comorbidity (72% ± 12% vs. 83% ± 12%, $p=0.005$). Specifically, apnea worsened in 6 cases, while three of these patients suffered only from mild OSA, two being obese and one having a craniofacial malformation. Moreover, 4 patients required reintubation and mechanical ventilation due to laryngospasm, bronchospasm, or pulmonary oedema, showing the more severe nature of complications in this subgroup.

Association of PoRCs with clinical parameters

Twenty-five patients had PoRCs, among whom 9 suffered from mild, 1 from moderate and 15 from severe OSA. When all subjects were analysed together, AHI ($\beta=0.044$) and the presence of comorbidities ($\beta=4.047$) were independently associated with PoRCs (both $p<0.001$). According to stepwise analysis, the presence of a comorbidity was more strongly related to the risk of complications than OSA severity ($\beta=4.234$).

In patients with comorbidities, no significant difference was observed in OSA severity [AHI values (8.2 (3.8-50.2) events/hour vs. 14.3 (11.7-23.3) events/hour, $p=0.37$], or BMI (20.7 ± 4.9 vs. 18.0 ± 4.6 kg/m^2, $p=0.20$), preoperative nadir O_2 saturation (74% ± 18% vs. 78% ± 15%, $p=0.57$) and oxygen desaturation index [5.9 (4.8-41.8) events/hour vs. 12.5 (7.5-22.8) events/hour, $p=0.67$] between cases with and without complications. In contrast, in patients without comorbidities, AHI was increased in patients with PoRCs [14.7 (3.4-51.3) events/hour vs. 3.9 (2.0-8.0) events/hour, $p<0.001$] (Figure 4). Using stepwise approach, we can conclude

that AHI was the most strongly related factor to complications (β=0.037, p=0.004). None of the other parameters investigated were associated with the incidence of PoRCs (all p>0.05).

2. *Meta-analysis based on international data*

Postoperative respiratory complications in pediatric patients following AT surgery shows higher occurrence in OSA than in non-OSA.

Based on our analysis of all 19 included studies, PoRCs following AT surgery show a significantly higher occurrence rate in children with OSA (OR: 2.24, 95% CI (1.60, 3.15), p<0.001).

Moderate and severe OSA is associated with a higher risk of postoperative respiratory complications in pediatric patients following AT surgery.

With the inclusion of five studies that supplied precise information about the severity of OSA, the PoRCs rate was analysed in each OSA severity subgroup and compared individually to non-OSA patients. Based on the analysis, no significant difference was found in the case of mild OSA (p=0.619, OR: 1.15, 95% CI (0.651, 2.058)), but a significantly higher probability of PoRCs was observed in moderate (p=0.048, OR: 1.79, 95% CI (1.004, 3.194)) and severe OSA (p=0.002, OR: 4.06, 95% CI (1.68, 9.81)) compared to non-OSA patients.

Major postoperative respiratory complications in pediatric patients following AT surgery in OSA and non-OSA.

Nine studies with sufficient data on major PoRCs were examined. No significant difference was found in the rate of major PoRCs in pediatric patients with OSA compared to children without it (p=0.200, OR: 2.14, 95% CI (0.67, 6.86)) (I-squared 61.7%, chi-squared test p=0.008), suggesting that OSA does not elevate the risk for major respiratory complications postoperatively.

Major and minor postoperative respiratory complications in pediatric patients following AT surgery in OSA and non-OSA.

In the seven studies included, no statistically significant difference (p=0.904, OR: 0.94, 95% CI (0.36, 2.45)) was found in the likelihood of the complication being major among children experiencing PoRCs in the OSA group compared to the non-OSA groups, suggesting that mostly minor events occur.

The role of comorbidities in postoperative respiratory complications in OSA and non-OSA pediatric patients following AT surgery.

A statistical analysis of four studies showed no significant difference (p=0.669, OR: 1.29, 95% CI (0.40, 4.14)) in additional comorbidities in children with OSA compared to children without it in the PoRCs group. Based on our results, the presence of other comorbidities was not more common in the OSA group among pediatric patients with respiratory complications postoperatively, strengthening our hypothesis that OSA alone can increase the risk of respiratory complications after AT surgery. Only comorbidities associated with craniofacial malformations or affecting the respiratory system (e.g. obesity, Down syndrome, and bronchial asthma) were collected.

3. Potential advantages of CPAP therapy

At our institute, we have successfully used personalized positive pressure ventilation therapy as part of the preparation for lung transplantation in three children with cystic fibrosis. The 13-year-old adolescent boy (born in February 2006) presented here has been under the care of our hospital's mucoviscidosis unit since the age of 8 months due to cystic fibrosis with homozygous genotype R553X confirmed by genetic typification. Initially, respiratory symptoms were manageable, respiratory function parameters in November 2013 included FEV1 of 57% and FVC of 88%. The slow progression of the disease was replaced in 2017 by exacerbations with recurrent pneumonia, progressively worsening general condition and pulmonary progression. Due to increased oxygen demand and deepening desaturation ($SpO2 \geq 88\%$) during sleep, nocturnal oxygen therapy with a continuous flow of 2 liters/min became necessary. The worsening respiratory function, poor general condition, and significant dyspnea even with treatment raised the need for lung transplantation. He was presented to the Hungarian Transplantation Committee in August 2018, where he was not yet considered eligible for listing. The increasing incidence of exacerbations, progressively worsening lung capacity and general condition made the need of lung transplantation clear. In January 2019 the Hungarian Transplant Committee refused to perform the transplantation because of the poor general condition and rapidly deteriorating respiratory function values, and recommended referral of the case to Vienna, two months later. Consequential to the rapid progression observed previously, it was questionable whether the general condition of the child would allow the transplantation and given the significant dyspnea and progressively worsening general condition, a bridging solution was required. After somnological consultation polysomnography was recommended to obtain an objective picture of the nocturnal respiratory disturbance and to be able to adjust the

pressure needed for the ventilation by manual titration. A polysomnography performed on 18 February 2019 in the Sleep Laboratory of our institute confirmed severe obstructive sleep apnoea-hypopnoea syndrome with significant alveolar hypoventilation. Due to the failure of noninvasive ventilation previously, titration was performed with a BiPAP device (S7VPAP III ST) with a lower, initial pressure of 2 water centimeters. Finally, with the administration of 1 liter/min of oxygen at 4 water centimeters, the patient's breathing normalized, alongside the apnoea-hypopnoea index and desaturation index. With the use of the device the nightly mean oxygen saturation was 96%, and the patient spent 100% of the total sleep time with an oxygen saturation above 90%.

Compared to the FVC 36% and FEV1 28% measured before therapy, FVC 39% and FEV1 31% were registered after two months usage of the device. More than 4 months after the start of the personalized positive pressure ventilation therapy, a lung transplantation was performed in Vienna in July 2019, after which the use of a breathing support device was no longer necessary.

DISCUSSION

OSA is a common disorder in childhood, and the pediatric OSA population has come to be the primary indication for AT surgeries, where adverse respiratory events are a known side effect. Mostly minor events occur without the need of intervention, but in severe cases laryngospasm, bronchospasm, acute respiratory distress syndrome, with the need of re-intubation, ventilation, and ICU admission or even death can occur. According to our statistical analysis PoRCs after AT surgery is increased significantly and occurred in 58.3% of the patients with comorbidity compared to otherwise healthy children with the diagnosis of OSA, where complication rate was 2%, and these complications are more severe than in patients without comorbidities. Also, we can conclude that the occurrence of pulmonary complications increases with the severity of OSA in children without comorbidities, but these complications can be registered mostly within the first two hours postoperatively without the need of intervention or intensive care unit observation. After processing our data, a meta-analysis was carried out to compare our results with international findings. However, in mild OSA no significant difference was found in the appearance rate of PoRCs with a 0.5 times higher occurrence rate, the severity of OSA was associated. In moderate OSA 1.79 times higher and in severe OSA 4.06 times higher risk was found for PoRCs compared to non-OSA patients.

When surgery is not a solution for managing the disease, or residual OSA occurs, CPAP therapy is recommended as first line therapy. Because of its beneficial effects on the lungs, it can be an effective therapy in diseases, such as cystic fibrosis, where in respiratory capacity an unmanageable, rapid deterioration can be registered and ventilatory support is needed to improve breathing function. With the continuous positive pressure provided in both expiration and inspiration expectoration increases and air retention decreases. Based on the international literature and our own results, we can conclude that personalized positive pressure ventilation with polysomnographic monitoring helps the management of sleep-dependent breathing disorders and to overcome the critical condition of patients with cystic fibrosis who are about to undergo transplantation by improving compliance and respiratory function through decreasing respiratory effort and evolving lung capacity, therefore helping to stabilize the general condition of the children. Personalised adjustment is important and should be performed in the sleep laboratories.

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to my supervisor habil. Pálma Benedek MD, PhD, who have supported my research, motivated me, gave guidance through my PhD training, taught me with patience from the very beginning and not only became my mentor, but also took care of my life and career as a mother would have taken care of her own child.

I am obliged to Professor Lajos Kemény MD and to the Doctoral School of Clinical Medicine University of Szeged for providing the resources to fulfill my PhD work.

I am also grateful to Professor Péter Hegyi for the opportunity to be a part of the Economic Development and Innovation Operational Programme Grant and a Human Resources Development Operational Programme Grant, to Assistant Professor Andrea Párniczky PhD, Félix Márk Juhász PhD, Viktória Jászai, and to all the other co-workers at the Institute for Translational Medicine for all the help they gave me, especially in the early stages of my research.

I would like to acknowledge to Professor Gábor Katona who has guided me since my first day of my work, to Zsuzsanna Csákányi PhD, Head of Department of Otorhinolaryngology and to the leadership of Heim Pál National Pediatric Institute to support my participation in the program.

I appreciate all the help and both practical and professional knowledge I got from my colleagues at the Department of Sleep Diagnostic and Therapeutic Laboratory and all the language assistance from Lili Kökényesi MD.

And finally, my heartfelt thanks to my family. My parents who have always been there for me from the beginning of my life and sacrificed so much for my success. My fiancé, actually already my husband, who supported me all the way and encouraged to achieve my dreams.