Bronchial Thermoplasty in severe asthma

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CHAPTER 1

General introduction and aims of the thesis
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GENERAL INTRODUCTION AND AIMS OF THE THESIS

This thesis evolves around Bronchial Thermoplasty, a novel device based bronchoscopic treatment for severe asthma patients, and innovative imaging of the airway wall by Optical Coherence Tomography (OCT).

SEVERE ASTHMA

The global prevalence of asthma is estimated at 334 million and in the Netherlands approximately 610,000 people are affected (1, 2). 3.6%-10% of all asthma patients suffer from difficult to treat- or severe asthma (3-6). Severe asthma is defined as asthma requiring, the use of high dose inhaled corticosteroids (ICS) next to a second controller and/or systemic oral corticosteroids (OCS) to prevent it from becoming uncontrolled or is uncontrolled despite this therapy (7, 8). Patients with severe asthma are often young, have significant morbidity, experience substantial disability (including reduced workforce participation) (9) and have an excessive utilisation of health care resources (10).

Despite the increasing knowledge in the pathophysiology of severe asthma and the awareness of the heterogeneity of this disease, the pathogenesis is incompletely understood. It composes a complex interplay between various airway pathophysiological components including inflammation, airway remodeling, innervation and vascular activation. In order to develop optimal future treatments for severe asthma patients the pathogenesis needs to be further clarified and biomarkers need to be discovered for optimized patient selection with the aim to achieve personalized and improved treatment. Recently, novel treatments have become clinically available including immunotherapy such as anti-interleukin 5 (anti-IL5) (11), targeting chronic airway inflammation and Bronchial Thermoplasty, targeting airway remodeling including airway smooth muscle.

BRONCHIAL THERMOPLASTY

Bronchial Thermoplasty is a medical device based therapy for severe asthma patients that delivers radiofrequency (RF) energy to the larger airways (2 – 10mm) during bronchoscopy (12). An asthmatic airway is characterized by airway wall changes such as a thickened epithelium, increased extracellular matrix and an increased and enlarged airway smooth muscle (ASM) mass/layer (13-15). The altered ASM mass is likely to play an important role in bronchoconstriction and airway hyper responsiveness resulting in asthma symptoms (16, 17). Furthermore, an increased ASM mass was found to be associated with asthma severity, including decrease in FEV₁ (18). Based on this problem a new treatment, Bronchial Thermoplasty, was developed with the aim to reduce the ASM mass and thereby to reduce airway constriction / hyper responsiveness and improve asthma control and quality-of-life.
BRONCHIAL THERMOPLASTY PROCEDURE AND CLINICAL EVIDENCE

Bronchial Thermoplasty is a bronchoscopic treatment that is performed under moderate-to-deep sedation or general anaesthesia. In three consecutive sessions with a minimum of three weeks interval all conducting airways of the right lower lobe, left lower lobe and both upper lobes are treated in this manner. The middle lobe is historically not treated for the fear of the development of a right middle lobe syndrome. During each Bronchial Thermoplasty procedure a basket catheter is distally placed in the airway (minimal airway diameter of 2-3 mm) and subsequently the basket catheter electrode array is expanded and the controller activated which results in 10 seconds of radiofrequency energy delivery to the airway, a so called “activation” (Figure 1 and 2).

![Figure 1](image1.png) A Alair Bronchial Thermoplasty system (Boston Scientific, Natick, MA, USA) is a radio frequency electrical generator with a food pedal activator switch; B controller to expand the basket catheter; C basket catheter with black marks; D expanded basket catheter. (Courtesy of P.I. Bonta)

Next, the electrode array is closed and withdrawn 5 mm proximal to the previous activation location (guided by the black marks on the catheter) where another activation is provided. This is repeated until all airways for that Bronchial Thermoplasty procedure are treated.

Initially, Bronchial Thermoplasty received a lot of attention as this was an entirely different treatment concept for patients with asthma.
Until then, virtually all asthma treatments where medication based targeting bronchomotor tone and airway inflammation. In contrast, Bronchial Thermoplasty was the first treatment which aimed to treat structural airway remodeling by ablation of the ASM (12). After Bronchial Thermoplasty was shown to be safe and able to reduce the ASM mass in dogs and in patients who needed to undergo a lobectomy, this treatment was performed in asthma patients (19, 20). In 3 randomized controlled trials, Bronchial Thermoplasty was shown to be safe and effective in mild to severe asthma patients (21-23). The main treatment outcomes were an improvement of quality-of-life and a reduction in asthma exacerbations, emergency visits and hospital admissions. Although proven effective on clinical outcomes in randomized trials, the mechanism that determines Bronchial Thermoplasty to be effective is incompletely understood and the specific asthma phenotype that responds best to this treatment is unknown. The available evidence of Bronchial Thermoplasty is discussed in more detail in Chapter 2.

SEVERE ASTHMA PHENOTYPING AND PATIENT SELECTION FOR BRONCHIAL THERMOPLASTY

According to the global initiative for asthma (GINA) guidelines the treatment for asthma is divided into 5 steps. GINA step 1 is for patients with only occasional (< 2 times a month) daytime symptoms of short duration who can be treated with an as-needed short-acting beta_2 agonist (SABA) only. GINA step 2 advises regular low dose ICS plus as-needed SABA. GINA step 3 consists of a combination of ICS/long acting beta_2 agonist (LABA) plus SABA as needed. For the more severe asthma patients GINA step 4 and 5 exist. GINA step 4 ranges from medium to high dose ICS/LABA and/or an extra controller such as tiotropium, leukotriene modifier or theophylline. GINA step 5 is for the most severe asthma patients with add on treatments such as tiotropium, anti-IgE, anti-IL5 and low dose oral corticosteroids (24).
Since asthma is a heterogenic disease, add on treatment options should ideally be selected based on individual patient characteristics. Anti-IgE should be considered in patients with a predominant allergic phenotype and anti-IL5 in patients with a predominant eosinophilic phenotype (25). Severe asthma patients with GINA step 4-5, who are not eligible for, or not responsive to anti-IgE or anti-IL5, might qualify for Bronchial Thermoplasty.

Bronchial Thermoplasty has been shown to improve quality of life, reduce exacerbation rates and the proportion of subjects experiencing severe exacerbations (21, 22, 26). Despite these favourable outcomes in many patients, a considerable proportion of patients have little or no benefit of Bronchial Thermoplasty treatment. Therefore, elucidating the asthma patient characteristics (or asthma phenotype) that is likely to respond to Bronchial Thermoplasty is of importance. Phenotyping asthma patients in daily practice is based on clinical data, most importantly; pulmonary function tests, high resolution chest-CT (HRCT) blood test and induced sputum analyses.

Since the ASM mass is the target of Bronchial Thermoplasty treatment, one could hypothesize that the amount of ASM mass at baseline could predict Bronchial Thermoplasty response. Quantification of the ASM mass is challenging. ASM mass can be measured precisely in biopsies taken during a bronchoscopy, however this is relatively invasive and time consuming. A HRCT is also able to image the airway wall, however the resolution is insufficient to provide detailed information about the smaller airways or the airway wall sublayers. New techniques to identify and quantify the airway remodeling and related ASM mass are therefore needed. A novel high resolution imaging technique called Optical Coherence Tomography (OCT) has the potential to improve current standards in airway wall imaging.

OPTICAL COHERENCE TOMOGRAPHY

Optical Coherence Tomography (OCT) is a light-based imaging technique which provides real-time high resolution images with a resolution of 10-15μm and a penetration depth of 2-3 mm (27, 28). OCT is used in clinical practice in ophthalmology (retina assessment) (29) and interventional cardiology (stent apposition and restenosis) (30, 31). In the pulmonary field, OCT has been shown to generate highly detailed near-histology images which enables identification and quantification of the airway wall and alveolar compartment (32-38).

In the studies described in this thesis, a 0.9 mm OCT probe (C7 Dragonfly, St. Jude Medical Inc., St. Paul, MN, USA) is used during a bronchoscopy and positioned in the airway(s) of interest. Near-infrared light from the catheter is scattered 360 degrees to the airway where the light is absorbed and backscattered by the airway wall tissue. The backscattering of the light is detected as a function of depth resulting in cross-sectional images of the airway wall. Cross-sectional images
(Figure 3) are obtained during an automated pullback over 5.4 cm (Figure 4). In this way, the airway wall of an entire airway segment can be visualised in a three dimensional way.

The capability of providing real-time, high-resolution images of the airway wall over a large airway segment gives a great advantage over the imaging techniques currently available. Therefore, OCT is a promising, minimal-invasive imaging tool for airway remodeling detection and quantification which could contribute to severe asthma phenotyping and subsequent patient selection for Bronchial Thermoplasty (36, 39-41). Next to OCT as a screening tool, OCT might qualify for monitoring and quantifying the (acute) treatment effects during and after Bronchial Thermoplasty. More background information on OCT can be found in Chapter 7 which reviews the available literature of novel imaging techniques OCT and confocal laser endomicroscopy (CLE) in pulmonary diseases.
TASMA STUDY

Bronchial Thermoplasty is applied as a bronchoscopic asthma treatment worldwide and in 2018 approximately 7000 patients in 33 countries have been treated. Although Bronchial Thermoplasty is positioned in GINA step 5, international guidelines state that evidence for its use is limited, with uncertainties in long-term consequences and incomplete understanding which phenotype of asthma patients will benefit most (42). Therefore, in 2014 the Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma (TASMA) trial (ClinicalTrials.gov, No.NCT02225392) was initiated. This investigator initiated study, aims to unravel pathophysiological targets of Bronchial Thermoplasty in severe asthma (how does it work?) and identify responder characteristics (who benefits most?) with the ultimate goal to identify leads to optimize Bronchial Thermoplasty performance (how to treat better?).

The TASMA study is an international, multicentre, randomized controlled trial in which 40 severe asthma patients were recruited for Bronchial Thermoplasty at 3 sites (in the Netherlands AMC, Amsterdam (n=26); UMCG, Groningen (n=4) and in the United Kingdom, Royal Brompton Hospital, London (n=10). This study is sponsored by the Dutch Lung Foundation, the Netherlands Organisation for Health Research and Development (ZonMW), the Academic Medical Center (AMC) Amsterdam and Boston Scientific.

The TASMA study design is illustrated in Figure 5. Recruited patients were discussed in a multidisciplinary team (MDT) meeting including asthma specialists.
and interventional pulmonologists, followed by extensive screening (blood test, pulmonary function test, imaging) to confirm the diagnosis of severe asthma. Subsequently, a bronchoscopy was performed during which baseline samples (including biopsies, bronchial wash, brushes) and high-resolution airway wall imaging (OCT and radial endobronchial ultrasound (rEBUS)) was obtained. Following bronchoscopy, patients were randomized to an immediate or delayed BT treatment group. The delayed BT treatment group which served as a control had to wait for 6 months, while receiving their standard asthma care after which the baseline investigations and research bronchoscopy were repeated. Both the immediate and delayed treatment groups received 3 Bronchial Thermoplasty procedures with a minimum of 3 week intervals. 6 months after the final Bronchial Thermoplasty procedure, baseline investigations and research bronchoscopy where repeated to be able to examine the Bronchial Thermoplasty induced changes.

In the first part of 2018 inclusion of patients in the TASMA trial was completed. The final results are expected in the second part of 2019. The TASMA trial aims to contribute to the following research questions; Is there a difference in change in ASM mass between the immediate Bronchial Thermoplasty group and the control group? What is the clinical responder profile? What is the effect of Bronchial Thermoplasty on airway remodeling including ASM and extra-cellular matrix (ECM), inflammation, neural innervation and vasculature? What is the effect of Bronchial Thermoplasty on airway gene expression? Are Bronchial Thermoplasty induced airway remodeling changes detectable with high-resolution imaging techniques OCT and rEBUS?
Figure 5. After informed consent baseline measurements and a screening bronchoscopy is performed. In the absence of endobronchial pathology, patients are randomized to an immediate or a delayed Bronchial Thermoplasty (BT) group. In the delayed Bronchial Thermoplasty treatment group, after 24 weeks, the endpoint measurements including research bronchoscopy are repeated to serve as controls (n=20). Both the immediate and delayed treatment groups receive 3 sessions of Bronchial Thermoplasty at a minimum of 3 week intervals and 6 months after the final Bronchial Thermoplasty procedure surveillance measurements and research bronchoscopy are repeated to investigate Bronchial Thermoplasty induced changes (n=40).
AIMS OF THIS THESIS

In 2014, when the TASMA study was initiated, there were many unanswered issues regarding Bronchial Thermoplasty (BT) in several domains. The following research questions will be addressed in this thesis:

1. Bronchial Thermoplasty procedure: is it safe and feasible to perform Bronchial Thermoplasty under moderate-to-deep sedation provided by specialized sedation anaesthesiology nurses?

2. What is the clinical response of Bronchial Thermoplasty in severe asthma patients? Can responder characteristics be identified?

3. Bronchial Thermoplasty treatment effect on the airway wall: does Bronchial Thermoplasty reduce airway smooth muscle mass in severe asthma patients?

4. Imaging of Bronchial Thermoplasty targets: can Optical Coherence Tomography (OCT) visualize airway wall layers and related airway remodeling including airway smooth muscle mass?

5. Bronchial Thermoplasty induced radiological side effects: what is the incidence and behaviour over time of radiological abnormalities seen directly after Bronchial Thermoplasty?
This thesis consists of four parts

PART I INTRODUCTION

- Introduction in severe asthma, Bronchial Thermoplasty (BT), Optical Coherence Tomography (OCT) and the TASMA study.

PART II BRONCHIAL THERMOPLASTY

- Review of the available literature on the mechanism of action of Bronchial Thermoplasty in asthma.
- Feasibility, safety and satisfaction rate of nurse administered propofol and remifentanil sedation for Bronchial Thermoplasty.
- Clinical response data in severe asthma patients treated with Bronchial Thermoplasty.
- The effect of Bronchial Thermoplasty on the airway smooth muscle and its correlation with clinical parameters.

PART III IMAGING OF THE AIRWAY WALL

- Review of the available literature of novel imaging techniques in pulmonary diseases; Optical Coherence Tomography and Confocal Laser Endomicroscopy (CLE).
- Identification and quantification of airway wall layers with Optical Coherence Tomography and its correlation with histology.
- Incidence and patterns of acute radiological abnormalities after Bronchial Thermoplasty.

PART IV DISCUSSION

- Discussion and summary in English and Dutch
REFERENCES

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42. Chung KF: Clinical management of severe therapy-resistant asthma. Expert review of respiratory medicine 2017