Bronchial Thermoplasty in severe asthma

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Citation for published version (APA):
d’Hooghe, J. N. S. (2018). Bronchial Thermoplasty in severe asthma
CHAPTER 11

General discussion and summary
DISCUSSION OF THE THESIS

BACKGROUND

Asthma is a major global health concern affecting an estimated 334 million people. 3.6%-10% of asthma patients are diagnosed with difficult to treat - or severe asthma (1-5).

Therefore, there is a need for novel asthma treatments as well as improved asthma phenotyping / patient selection for available treatments in order to reduce disease burden and improve patient centred outcomes. In 2004, a novel bronchoscopic interventional treatment, called Bronchial Thermoplasty (BT) was introduced (6, 7). BT is a bronchoscopic device based treatment with the aim to reduce the amount of airway smooth muscle (ASM) in asthma patients using radiofrequency energy. BT has been shown to be feasible, safe and effective in 3 randomized controlled trials (RCTs) which led to FDA approval (8-10). In international guidelines BT is positioned as one of the add-on treatment options for patients with severe asthma. Today, BT treatment is available in more than 30 countries.

Although the RCTs outcomes showed an improved quality of life and reduction of severe exacerbation rate, a significant improvement in pulmonary function tests (e.g. FEV1 or bronchial hyper responsiveness (PC_{20} methacholine) could not be shown. Despite the efficacy of BT, many questions remain regarding the mechanism of action and related optimal patient selection. Does BT reduce ASM mass in severe asthma patients, and if so, to what extent? At the start of the TASMA project in 2014, BT had only shown to reduce the ASM mass in dogs and patients with lung cancer (7, 11) - not in patients with asthma. Does BT - besides an effect on the airway smooth muscle - have another or additional effect on the airways which could explain the clinical benefits? For example, is there a BT induced beneficial impact on remodeling (including extracellular matrix (ECM)), inflammation, innervation or vascularisation? In order to identify asthma phenotypes that will benefit most of BT treatment, understanding the mechanisms of action is considered crucial (12).

For this reason in 2014, the Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma (TASMA) study (ClinicalTrials.gov, No.NCT02225392), an investigator initiated international, multicentre, randomized controlled trial was conducted. With the inclusion being completed in early 2018, the final data including the delayed treatment randomisation arm will become available in 2019. This thesis presents and discusses current available data of the TASMA study and consists of four parts. After the Introduction (Part I, Chapter 1), in Part II (Chapter 2-6) titled “Bronchial Thermoplasty”, treatment-related issues including sedation strategy and BT treatment effects and outcomes are discussed. Part III, (Chapter 7-10) titled “Imaging of the airway wall” focuses on imaging of the airway wall with Optical Coherence Tomography and acute radiological BT treatment effects.
A general discussion and summary is provided in Part IV (Chapters 11 and 12).

PART II BRONCHIAL THERMOPLASTY

Research question 1 (Chapter 3): Is it safe and feasible to perform Bronchial Thermoplasty under moderate-to-deep sedation provided by specialized anaesthesiology nurses?

Although BT treatment is implemented worldwide, many treatment-related issues remain subject of discussion or are unknown, such as the optimal sedation strategy for BT. BT procedures require high precision, lasts longer than a regular bronchoscopy (~ 30- 45 min), need to take place 3 times with at least 3 week intervals for a full BT treatment and are performed in severe asthma patients with highly reactive airways. These aspects emphasize the need for optimal sedation ensuring patient comfort, safety and the absence of cough in order to optimally treat all airways.

Different sedation strategies are available ranging from mild sedation with midazolam to general anaesthesia with tracheal intubation. On the one hand, insufficient sedation or “under-sedation” involves the risk of patient distress and might lead to suboptimal treatment due to excess coughing of the patient (13). On the other hand, general anaesthesia including tracheal intubation could be seen as “over-sedation” as it is more invasive and complications such as hemodynamic collapse and/or respiratory depression can occur (14). Additionally, general anaesthesia is associated with higher costs and is more difficult to organize.

We performed a study to assess propofol/remifentanil sedation administered by specialized anaesthesiology nurses. Specialized sedation anaesthesiology nurses are nurses who perform self-reliant procedural sedations. An anaesthesiologist is available nearby as a back-up. Sedation specialists have followed a theoretical and practical sedation education program of 1 year that is completed by an examination that results in certification. In 13 severe asthma patients who were treated with BT, we showed that specialized sedation anaesthesiology nurse administered propofol and remifentanil sedation for BT treatment is feasible, safe and has high satisfaction rates for both patients and bronchoscopists (Chapter 3) (15). It should be noted however, that sedation administration by specialized sedation anesthesiology nurses is not yet commonly available.

Recently, one other study has described sedation strategies for BT (16). In 7 patients the majority of BT procedures were performed with monitored anesthetic care under moderate-to-deep sedation with propofol and/or dexmedetomidine. Due to occasionally episodes of hypoventilation and/or airway obstruction, which were short and resolved easily with airway manoeuvres, the auteurs preferred to perform the procedure under general anaesthesia with a laryngeal mask airway placement.
In conclusion, in current practice the selection of a sedation strategy will depend on institutional practice, local experience and resources. The two studies, although small in subject numbers, show the feasibility of moderate-to-deep sedation. The available results and detailed description will help starting centers to choose and implement the sedation strategy for BT procedures best suitable for their center. Comparison data regarding different sedation/anesthesia strategies in a larger population are needed in order to draw final conclusions regarding the optimal sedation/anesthesia strategy for BT.

Research question 2 (Chapter 5 and 6):
What is the clinical response of Bronchial Thermoplasty in asthma patients? And can responder characteristics be identified?
The ultimate goal of BT is to reduce asthma symptoms, decrease medication use and increase quality-of-life. These endpoints can be (partly) measured by asthma control and asthma quality-of-life questionnaires (ACQ and AQLQ respectively), where a difference of $>0.5$ points is considered a clinically relevant improvement. Also a reduction of the asthma exacerbation rate can be used as an endpoint of BT efficacy.

Published randomized and non-randomized trials with clinical response parameters as primary and main secondary endpoints including asthma control, asthma quality-of-life and exacerbation rate have shown beneficial effects of BT (8, 10, 17-19). The most debated results originate from the AIR-2 trial, a sham-controlled, randomized, multicentre trial including 297 subjects that were randomized 2:1 for BT versus sham. The primary endpoint AQLQ was significantly improved in the BT group compared with the sham group, however the between group difference did not achieve $>0.5$, which is considered to be clinically relevant (increase in AQLQ of 1.35 in the BT group versus 1.16 in the sham group). However, the proportion of patients achieving a clinical relevant difference in AQLQ of $>0.5$ was significantly larger in the BT group compared with the sham group (79% vs. 64% respectively) (20). Furthermore, there was a 32% reduction in the rate of severe exacerbations in the BT treated group.

Our preliminary data in 14 severe asthma patients (presented at the ERS 2017, Milan, Chapter 5) showed that 50% of the patients could be classified as clinical responders (defined as minimal clinical relevant difference of $>0.5$ points in both ACQ and AQLQ measured 6 months following BT treatment). A reduction of the calculated exacerbation rate/year was observed in 79% of patients. Further details of responder outcomes in the full TASMA study population ($n=40$) will be available in 2019. With these details additional effect of BT on airway remodeling, inflammation, neural innervation, vascularisation and gene expression will be investigated.
An important research aim of Chapter 6 was to challenge the hypothesis that clinical parameters correlate with baseline ASM mass and/or the change in ASM mass after BT. Literature shows that there is a relationship between ASM mass and FEV$_1$: an increased ASM mass is related to a decreased FEV$_1$ (21). Chakir et al. found that baseline ASM mass correlates with ASM mass reduction (19). In Chapter 6 we show that patients with a lower FEV$_1$ have an increased ASM mass at baseline and have a greater reduction in ASM mass following BT treatment. From these results it can be hypothesized that patients with a lower FEV$_1$ are the patients who will benefit most from BT treatment. Is a higher ASM mass at baseline and/or a greater ASM mass reduction after BT related with a positive clinical outcome? At present, the limited amount of patients evaluated is too small to challenge this research question.

Research question 3 (Chapter 6):
Does Bronchial Thermoplasty reduce ASM mass in asthma patients?
At the start of the TASMA study in 2014, the actual effect of BT on the ASM mass in severe asthma patients was unknown. In dogs, an altered ASM of 36% of the airway circumference was shown 6 weeks after BT (7). Furthermore, lung cancer patients undergoing lobectomy showed a reduction in ASM 3 weeks after BT in 50% of the circumference of the BT treated airway (11).

Since then, a few uncontrolled studies evaluated the histological changes in the airway wall following BT in asthma patients. The first results were demonstrated by Pretolani et al. who showed a 60% reduction of the ASM mass 3 months after BT in 10 patients (22). These results were confirmed by 2 other studies; one study (n=11) found a 58% reduction of ASM mass 6 weeks after BT (during the third BT session) (23) and the other study (n=17) found a 64% reduction 3 weeks after BT (during the second BT session) (19). Furthermore, Pretolani et al. showed a 73% reduction of the ASM mass in 15 patients (5 more than the earlier reported 10 patients) 3 months after BT (18). A more detailed review of these studies can be found in Chapter 2 (24).

In Chapter 6 we present our own histological biopsy data, comparing ASM mass % in airway biopsies 3 weeks before BT treatment with biopsies 6 months after BT treatment, using the untreated right middle lobe (RML) as a control. We conclude that in 16 severe asthma patients, the ASM mass significantly reduced following BT treatment with 55% measured with desmin staining and 40% reduction measured with α-SMA staining, while the untreated RML remained unchanged. In order to compare the various study results, it is necessary to use the same histological evaluation method, including the same staining. Currently, α-SMA staining is most frequently used and seen as the standard. However, in addition to ASM, α-SMA also stains myoepithelial cells located around glands, pericytes in capillaries and mucosal and perivascular myofibroblasts whereas desmin is a more specific
staining for ASM. Therefore, it seems logical to use desmin staining to assess the effect of BT on the ASM mass.

A drawback of the described studies is the lack of a control group, which restricts the assessment of the spontaneous time variation of ASM-mass. A significant difference in the ASM-mass change is ideally demonstrated between BT treated patients and control patients. The randomized control design of the TASMA study with a delayed treatment group will provide an answer to this question (primary endpoint).

A limitation of biopsies studies in general is risk of variability of biopsy samples (25). The current advised approach is to investigate at least two airway mucosa biopsies, more subjects (as many as possible) and relatively few sections per biopsy, also called the “do more less well” strategy (26). Using this approach we found an intraclass correlation coefficient of 0.52 regarding the variability of ASM mass within biopsies, which can be interpreted as moderate according to the Landis-Koch system.

To answer the question; does BT treatment reduce ASM mass in asthma patients? Yes, a reduction in ASM mass following BT is a consistent observation. The highest statistical evidence to answer the question, including a control group needs to be awaited. The randomized data from the TASMA study will be available in 2019 to answer this question.

PART III IMAGING OF THE AIRWAY WALL

Research question 4 (Chapter 8):
Can Optical Coherence Tomography (OCT) visualize airway wall layers and related airway remodelling including the airway smooth muscle?

An enlarged and increased airway smooth muscle (ASM) mass is considered an important component of airway remodeling in (severe) asthma and is the aimed target of BT. To assess the amount of ASM mass, the effect of BT on ASM mass and related airway remodeling, it would be of interest to have a high-resolution imaging technique that can accurately identify and quantify ASM and/or airway remodeling. In clinical practice, current techniques that can assess the airway wall are high-resolution computed tomography (HRCT)-scan of the chest, radial endobronchial ultrasound (rEBUS) and bronchial mucosal biopsies taken during bronchoscopy. HRCT requires patient exposure to ionizing radiation and has limited resolution that hampers visualization and quantification of the different airway wall layers. Radial EBUS is performed during a bronchoscopy and uses ultrasound waves to create real-time images of the airway wall at a single measure point. The clinical application of radial EBUS is currently under investigation. Biopsies taken during bronchoscopy can visualize the airway wall very precisely but this procedure is
relatively invasive, provides information of only a small selected site of the airways and in addition, the processing of biopsies is time consuming and often causes artefacts (27).

Optical Coherence Tomography (OCT) is a minimally invasive imaging technique that combined with bronchoscopy is able to generate real-time high-resolution, near-histology images of the airway wall. Therefore, OCT is a promising imaging technique to identify and quantify the airway wall, ASM and airway remodeling. The background and available evidence of the OCT technique in pulmonology is comprehensively reviewed in Chapter 7 (28). Previously, OCT has been shown to be able to visualize different airway wall layers (29-33) and to quantify the total airway wall area (27, 34). In Chapter 8 we report for the first time on the feasibility of OCT to quantify, next to the total airway wall area, the separate airway wall layers, demonstrating a good and significant correlation with histology for both ex-vivo and in-vivo OCT based quantification of the mucosa and submucosa (35). Furthermore, this is the first study to compare ex-vivo with in-vivo OCT imaging which correlated significantly. The results are strengthened by a high interobserver reproducibility.

These encouraging results are the outset for further investigations of this promising imaging technique. It would be of interest to see if OCT can differentiate between severe asthma patients, mild asthma patients and healthy subjects by airway wall characteristics including ASM mass. The next step is to investigate if OCT is able to identify airway wall characteristics of BT responders, e.g. a large ASM mass. As such, OCT might potentially serve as a screening tool that is able to identify patients that will benefit most of BT.

In addition to the above, OCT might qualify for monitoring and quantifying the treatment effects of BT on airway remodeling during and after BT. During BT treatment, there is no direct feedback in terms of imaging and/or physiological parameters. Which airway wall layers are affected and how far does the heat shock reach in the distal airways? OCT may fill this knowledge gap. In addition, after BT treatment, biopsy results have shown that there is a reduction of ASM mass (19, 22, 23). If OCT is able to detect BT changes in the ASM mass, this would make OCT more preferable as BT treatment evaluation/monitoring instrument because of its real-time and minimally invasive characteristics. OCT could also play a role in long term monitoring of BT treatment effect. Therefore, in the TASMA extension study OCT is performed 2 years after BT during a bronchoscopy.

Recently a new OCT technique was developed and validated; a novel birefringence microscopy platform which is able to visualize and quantify ASM fibers (36, 37). This technique, able to specifically image the ASM, could be of interest in patient selection/monitoring for treatments that target the ASM, such as BT.
Research question 5 (Chapter 9): What is the incidence and behaviour over time of radiological abnormalities seen directly after Bronchial Thermoplasty?

From our own experience we learned that impressive radiological abnormalities can occur directly after BT. This was the reason to investigate the incidence, patterns and behavior over time of radiological abnormalities after BT treatment in severe asthma patients, data that were lacking at the onset of the TASMA study. In Chapter 9 we report on the acute radiological abnormalities based on chest X-ray and ultralow dose CT after BT (38). We found that the incidence of acute radiological abnormalities after BT is high, 100% on ultralow dose chest CTs and 91% on chest X-rays. Four different radiological patterns were identified: peri-bronchial consolidations with surrounding ground glass opacities, atelectasis, partial bronchial occlusions and bronchial dilatations. The fact that these abnormalities were resolved in virtually all cases at 6 months’ follow-up was reassuring. One patient showed a focal bronchiectasis. Peri-procedural corticosteroid treatment was given to all patients.

Another study group investigated the same research question in a similar severe asthma population at the same time. Debray et al also found a high incidence of radiological abnormalities the day after BT and the described abnormalities were largely in line with ours (39). The contrary findings are discussed in a correspondence letter in Chapter 10. For example, we found a lower incidence of atelectasis in our cohort. We systematically scored endobronchial abnormalities before and immediately after BT by scoring the mucosal injury. A significantly higher median mucosal injury score was seen in patients with atelectasis. The observed difference in the occurrence of atelectasis directly after BT might be related to the vulnerability of the mucosa (40).

Routine chest X-ray or CT imaging after BT doesn’t seem necessary as it probably does not affect outcome or treatment. However, awareness of the pulmonary impact of BT directly after BT is important.
KEY FINDINGS OF THIS THESIS

BT results in a favorable clinical response in approximately half of the patients and reduces exacerbation rate by ~75%. It is feasible and safe to perform BT under moderate-to-deep sedation with spontaneous breathing provided by specialized sedation anesthesiology nurses. BT reduces the airway smooth muscle mass by >50% and the greatest reduction is seen in patients with a lower FEV₁. In all patients treated with BT acute radiological abnormalities occur, which resolve spontaneously over time. Optical Coherence Tomography might qualify as the airway wall imaging technique of choice to visualize airway wall layers and might be helpful in the selection and evaluation of patients for BT.

FUTURE PERSPECTIVES

Unravelling the mechanism of action of BT and further optimizing patient selection for BT are key priorities in the field. The complexity of asthma pathophysiology was highlighted in this thesis (24) and the reducing effect of BT on the ASM mass is demonstrated. However, it might well be possible that BT also influences the extracellular matrix, the inflammatory cascade, airway innervation and vascularisation. How BT affects these various pathophysiological components and how the impact of these components translate into clinical response needs further investigation. The full data of the TASMA trial might contribute to answer these research questions.

Long-term follow-up after BT is of importance to monitor safety and clinical efficacy and related patient response profile and to gain knowledge about the duration of BT effect on the airway remodelling. Long-term results about the impact of BT on ASM mass are rare. In a single study it was shown that there was a persistent reduction of the ASM mass 2 years after BT (41). Therefore the TASMA extension study (clinicalTrials.gov,No: NCT02975284) was initiated which will follow-up BT treated patients within the TASMA study for 5 years for clinical parameters. In the TASMA extension study we will also perform a bronchoscopy at 2 years to obtain airway biopsies and repeat OCT imaging. This will complement the 4 long-term studies currently available, which showed persisted efficacy and safety up to 5 years (42-45). For current clinical practice, it is advised to perform BT in specialised centres within registries or clinical studies (46).
SUMMARY

Chapter 1 is the introduction of the thesis providing a background on severe asthma, Bronchial Thermoplasty, Optical Coherence Tomography (a high resolution imaging technique), the TASMA study and the aims of this thesis.
Chapter 2 provides a detailed review of the current literature on mechanism of action and available evidence of Bronchial Thermoplasty.
Chapter 3 reports on the feasibility, safety and satisfaction rates for both patients and bronchoscopists using nurse administered propofol and remifentanil sedation for Bronchial Thermoplasty.
Chapter 4 contains a commentary on a study in which the effect of Bronchial Thermoplasty on the ASM mass in severe asthma patients was investigated for the first time.
Chapter 5 discusses the clinical response in severe asthma patients on Bronchial Thermoplasty.
Chapter 6 reports on the change of the airway smooth muscle after Bronchial Thermoplasty and the correlation between FEV$_1$ and ASM mass decrease.
Chapter 7 reviews the available literature of novel, innovative high resolution imaging techniques; Optical Coherence Tomography and confocal laser endomicroscopy in pulmonary diseases.
Chapter 8 reports on the feasibility of Optical Coherence Tomography to quantify separate airway wall layers and the correlation of both ex-vivo and in-vivo Optical Coherence Tomography based quantification of the mucosa and submucosa with histology.
Chapter 9 reports on acute radiological abnormalities observed on chest X-ray and ultralow dose CT after Bronchial Thermoplasty.
Chapter 10 contains a commentary on a study in which acute radiological abnormalities following Bronchial Thermoplasty are described.
Chapter 11 contains the general discussion and summary of this thesis.
Chapter 12 is the Dutch summary of this thesis.
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