Early computed tomography modifications following bronchial thermoplasty in patients with severe asthma

Marie-Pierre Debray[1], Marie-Christine Dombret[2], Marina Pretolani[3,4,5], Gabriel Thabut[3,4,5,6], Loubna Alavoine[7], Pierre-Yves Brillet[8,9], Camille Taillé[2,3,4,5], Antoine Khalil[1,4], Pascal Chanez[10] and Michel Aubier[2,3,4,5]

Affiliations: [1]Dept of Radiology, Bichat Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. [2]Dept of Pneumology A, Bichat Claude Bernard Hospital Assistance Publique-Hôpitaux de Paris, Paris, France. [3]Inserm UMR1152, Physiopathology and Epidemiology of Respiratory Diseases, Paris, France. [4]Faculty of Medicine, Paris Diderot University, Bichat Campus, Paris, France. [5]Laboratory of Excellence, INFLAMEX, Université Sorbonne Paris Cité and DHU FIRE, Paris, France. [6]Dept of Pneumology B, Bichat Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. [7]Clinical Investigation Center, Bichat-Claude Bernard University Hospital, Paris, France. [8]Dept of Radiology, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Bobigny, France. [9]Université Paris 13, PRES Sorbonne-Paris-Cité, UPRES EA 2363, Bobigny, France. [10]Dept of Respiratory Diseases, Inserm U1067 and CNRS UMR7733, Aix-Marseille University, Marseille, France.

Correspondence: Marie-Pierre Debray, Dept of Radiology, Bichat Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France. E-mail: marie-pierre.debray@aphp.fr

@ERSpublications
Consistent early transient peribronchial consolidations after bronchial thermoplasty do not require antibiotics http://ow.ly/Unzd307ckhL

Cite this article as: Debray M-P, Dombret M-C, Pretolani M, *et al*. Early computed tomography modifications following bronchial thermoplasty in patients with severe asthma. *Eur Respir J* 2017; 49: 1601565 [https://doi.org/10.1183/13993003.01565-2016].

ABSTRACT Bronchial thermoplasty (BT) is a recent, promising and well-tolerated technique for the treatment of severe asthma. By delivering thermal energy to the airway wall, this procedure can induce early pulmonary opacities seen on computed tomography (CT). We aimed to examine early CT modifications induced by BT and to determine their association with respiratory symptoms.

Unenhanced chest CT was performed the day after each BT session in 13 patients with severe asthma, leading to the examination of 38 treated lobes. A total of 15 BT-treated lobes were evaluated in 11 patients at 1 month. The first two patients also underwent CT at 1 week.

No symptoms suggestive of pulmonary infection were noted following BT in any patient. Peribronchial consolidations and ground-glass opacities were observed in all treated lobes on day 1, with three lower lobes showing complete collapse. Mild involvement of an adjacent untreated lobe was observed in 12 out of 38 (32%) cases. Opacities had decreased in 5 out of 15 (33%) and disappeared in 10 out of 15 (67%) at 1 month.

BT induced early pulmonary peribronchial hyperdensities in all treated lobes. These alterations were unrelated to clinical symptoms and spontaneously decreased or disappeared after 1 month.

Received: Aug 04 2016 | Accepted after revision: Nov 29 2016

This study was registered as a clinical trial with Clinicaltrials.gov identification number: NCT01777360.

Support statement: Funding for this study as provided by Legs Poix, Chancellerie des Universités, Paris, France and Boston Scientific, Natick, MA, USA. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Introduction

Current treatment of asthma is dominated by inhaled and oral corticosteroids in combination with bronchodilators. Although very effective in most patients with asthma, the disease remains poorly controlled in between 10 and 20% of patients with current standards of care [1]. The heterogeneity of airway inflammation in severe asthma has led to the recognition of multiple distinct endotypes, allowing the guidance of use of novel specific biologics, such as anti-IgE and anti-interleukin-5 monoclonal antibodies [2]. However, some patients experience severe exacerbations, despite treatment with these biologics, or even with undetectable inflammation [3].

Bronchial thermoplasty (BT) is a recent, promising non-pharmacological interventional approach for the treatment of severe asthma that aims to reduce airway smooth muscle mass, a main effector of airflow obstruction. This technique acts by delivering controlled thermal energy to the airway wall during bronchoscopy using a radiofrequency electrical generator, whose electrical energy is converted into heat when met with tissue resistance. BT, which has been available in the USA and Europe in selected patients for a few years [4], has been shown to improve patient's quality of life and asthma control and to reduce the number of exacerbations up to 5 years following treatment [5–8].

The procedure is usually well tolerated, although occurrence of asthma exacerbations is common in the early post-procedural time. Rare cases of lower respiratory tract infection and haemoptysis have been reported [5, 7].

Long-term computed tomography (CT) observations have been reported 1, 2 and 5 years after BT without any change in the majority of cases [8, 9]. In a recent study conducted in a group of 10 patients with severe asthma, we demonstrated that BT led to early CT alterations, such as consolidation and ground-glass opacities in the treated lobes and, in some cases, in the adjacent BT-untreated middle lung lobe [10]. A better knowledge of these events would be useful for the appropriate management of any short-term complication and for a better understanding of the mechanisms of action of this recent technique.

Therefore, the aim of the current study was to examine early CT findings following BT and to determine their association with respiratory symptoms.

Materials and methods

Patients

Patients were recruited from Bichat University Hospital in the setting of the prospective ASMATHERM trial (ClinicalTrials.gov identification number: NCT01777360), aimed at evaluating the effect of BT in patients with severe therapy-uncontrolled asthma. Because one patient showed extensive alveolar opacities on chest radiography on the day after the procedure, arguing for the onset of a pulmonary infection, but without any physical complaint or symptoms, thoracic CT was performed. CT examination showed peribronchial consolidations and ground-glass opacities in both BT-treated upper lobes [10] that spontaneously decreased after 1 week. These asymptomatic but extensive and impressive abnormalities occurring early after BT led us to perform a chest CT scan the day after BT sessions in the subsequent patients, to detect potential early pulmonary complications of the procedure. Therefore, between January and November 2014, 13 BT-treated patients with severe asthma underwent a chest CT on the day after each of three BT sessions, corresponding to 27 CT examinations. Eight out of these 13 patients were included in a previous report [10]. Demographic and clinical characteristics of the 13 patients included in this study, as well as the details related to the BT-treated lung lobes, are shown in table 1.

Bronchial thermoplasty

BT was performed as previously described [10] using the ALAIR® device (Boston Scientific, Natick, MA, USA), during three procedures separated by a 1-month interval. Each lower lobe was treated during one procedure, starting with the right lower lobe, then the left lower lobe, with both upper lobes being treated during the last procedure. The right middle lobe remained untreated to avoid the theoretical risk of obstruction and right middle lobe syndrome [10]. The system was adjusted to deliver a constant temperature of 65°C for 10 s at each treatment site, *i.e.* every 5 mm along the bronchial tree, from the small bronchi with a 3 mm diameter to the lobar bronchi. The total number of activations performed for each lobe was 46.7±15.1 (mean±SD). The procedure was performed under sedation during a short hospital stay. Patients received close clinical monitoring immediately after the procedure and were discharged the next day in the absence of persistent fever or respiratory symptoms. Prednisone (50 mg·day^{-1}) was systematically administered orally 2 days before and 3 days after each procedure.

Clinical status following bronchial thermoplasty

Any episode of fever, cough, chest pain, dyspnoea or desaturation occurring the day of the BT session or the following day, as well as any symptoms suggestive of bronchopulmonary infection occurring during the month following the BT session, were recorded from a systematic review of the clinical charts.

TABLE 1 Characteristics of patients with severe asthma treated by bronchial thermoplasty and details of the evaluated lung lobes

Parameter	
Patients	13
Men/women	6/7
Age years	40.8±7.8
Clinical status before BT	
Asthma duration years	27.4±13.5
FEV_1 pre-β_2-agonists % predicted	60.5±16.8
ACT score	7.2±2.2
Number of exacerbations in the previous year	10.1±6.4
Number of admissions to hospital in the previous year	3.5±3.7
Number of patients taking long-term oral corticosteroid therapy	11
Evaluated treated lobes (RUL/LUL/RLL/LLL)	
Day after the BT session	38 (10/11/6/11)
Follow-up at 1 week	3 (1/1/0/1)
Follow-up at 1 month	15 (0/0/6/9)

Data are presented as n or mean±SD. BT: bronchial thermoplasty; FEV_1: forced expiratory volume in 1 s; ACT: Asthma Control Test; RUL: right upper lobe; LUL: left upper lobe; RLL: right lower lobe; LLL: left lower lobe.

Computed tomography examinations

Thoracic CT was performed in each patient at inclusion in the ASMATHERM trial and the day after each BT session. Follow-up CT examinations were performed at 1 week in the first two patients to assess the evolution of opacities. For patients who had a subsequent BT session during the study period, the early post-procedural CT of this subsequent BT was also assessed for the 1-month follow-up of the previous BT session (n=11; seven patients had one and four patients had two follow-up CTs at 1 month).

CT examinations involved the acquisition of 0.6- to 1-mm-thick slices using a multidetector 64 raw CT device (GE Discovery 750 HD; GE Healthcare, Waukesha, WI, USA). These slices were volumetrically reconstructed using a high-spatial-frequency algorithm and obtained with the patient at full inspiration and lying supine. No contrast media were used.

Image evaluation

Images were analysed in each BT-treated lobe. One thoracic radiologist (MPD, 15 years of experience in thoracic diseases) semi-quantitatively evaluated peribronchial consolidations, ground-glass opacities, septal lines and filling of bronchial lumens. Their extent was graded as 1 when involving one segment, as 2 when involving more than one segment, and as 3 when involving all segments of the treated lobe. The thickness of consolidations (less or more than 1 cm) was further assessed further down the corresponding bronchial lumen. Any bubble-like lucency and cavitation in the consolidated lung were recorded. Volume lobe loss was also determined and graded as 1 when partial and as 2 in case of total lobar collapse. In addition to analysing the treated lobe, any involvement of another lobe adjacent to the treated one was determined. Pleural effusion, fissural thickening and completeness or incompleteness of fissures along the BT-treated lobes were documented.

The presence or the absence of chest opacities on the CT scout view (n=24) or on the day 1 chest radiograph, when available (n=14), was also recorded.

Finally, CT scans were assessed at follow-up at 1 week or 1 month, and at 4–5 months (mean 4.6 months) after the last BT session for those with persistent opacities to determine partial or complete regression of abnormalities, as well as the occurrence of new alterations, including bronchial dilatations or new infiltrates.

Statistical analysis

Analysis was performed per treated lobe. Continuous variables are reported as mean±SD and compared by Mann–Whitney U test, whereas categorical variables are reported as count and proportions. Statistical significance was considered at the $p<0.05$ level. Statistical analysis was performed using SAS 9.2 (SAS Inc., Cary, NC, USA).

Results

Computed tomography findings in the immediate post-procedural time

The rates of BT-induced CT alterations are summarised in table 2. Peribronchial consolidations were present on the day after BT in all treated lobes and their extent was proportional to the number of heat

TABLE 2 Early chest computed tomography findings obtained the day after bronchial thermoplasty

Parameter	Patients
Consolidations	38 (100)
All segments involved	25 (66)
>1 cm thickness away from bronchial lumen	11 (29)
Ground-glass opacities	38 (100)
All segments involved	23 (60)
Bubble-like lucencies or cavitation in consolidated lung#	26 (68)
Partial filling of bronchial lumen	36 (95)
Septal thickening	15 (39)
All segments involved	2 (5)
Pleural effusion or fissure thickening	26 (68)
Lobar volume loss	26 (68)
Complete lobar collapse¶	3 (8)
Non-treated lobe involvement+	12 (32)

Data are presented as n (%). BT: bronchial thermoplasty. #: microcavities that could correspond to minimal aerated bronchograms in predominantly filled bronchial lumen in 21 cases; ¶: all cases of complete lobar collapse involved the left lower lobe; +: BT-untreated lobes involved the middle lobe (n=5), right lower lobe (n=4), left lower lobe (n=2) and left upper lobe (n=1).

activations. Indeed, the mean number of BT activations was higher in lung lobes showing consolidation of all segments (*i.e.* grade 3) than in lobes with partial segment consolidation (*i.e.* grades 1 or 2) (52.1±13.5 *versus* 36.5±12.8, p=0.001).

Ground-glass opacities also involved all treated lobes along bronchi or on the edge of consolidations (figure 1). In addition, parenchymal opacities extended to another adjacent lobe in 12 out of 38 treated lobes (32%) (figure 2), fissures being most frequently incomplete (11 out of 12 cases, 92%). These alterations were always of mild intensity, representing only ground-glass opacities in one segment in most cases except one case in which both consolidation and ground-glass opacities were detected in the middle lobe the day after BT in the right lower lobe. Bubble-like lucencies or microcavities were frequently observed in the consolidated lung, barely distinguishable from minimal air bronchograms in predominantly filled bronchial lumen. Septal lines of limited extent were present in 15 out of 38 treated lobes (39%) and minimal fissural effusion or thickening adjacent to the treated lobe was present in 26 out of 38 cases (68%). Mild volume lobe loss was observed in 23 out of 38 treated lobes (61%), and three left lower lobes showed complete collapse (figure 3). None of these abnormalities were present in the CT scan performed before BT.

Overall, chest opacities were present in 27, questionable in three and absent in eight BT-treated lobes on the day 1 chest radiography or CT scout view.

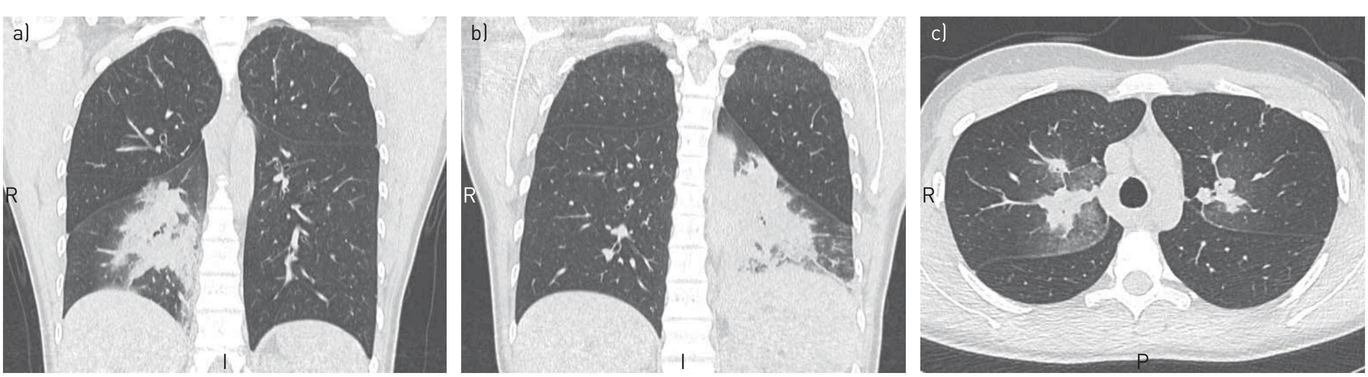

FIGURE 1 Chest computed tomography scans in the coronal plane the day after bronchial thermoplasty (BT) in a) the right lower lobe, showing peribronchial consolidations with bubble-like lucencies that completely disappeared 1 month later and b) the day after BT in the left lower lobe. Peribronchial consolidations are extensive and are associated with mild septal thickening and some lobar volume loss. c) Peribronchial opacities of limited extent are observed the day after BT in both upper lobes, which received the fewest number of activations. P: posterior; I: inferior; R: right.

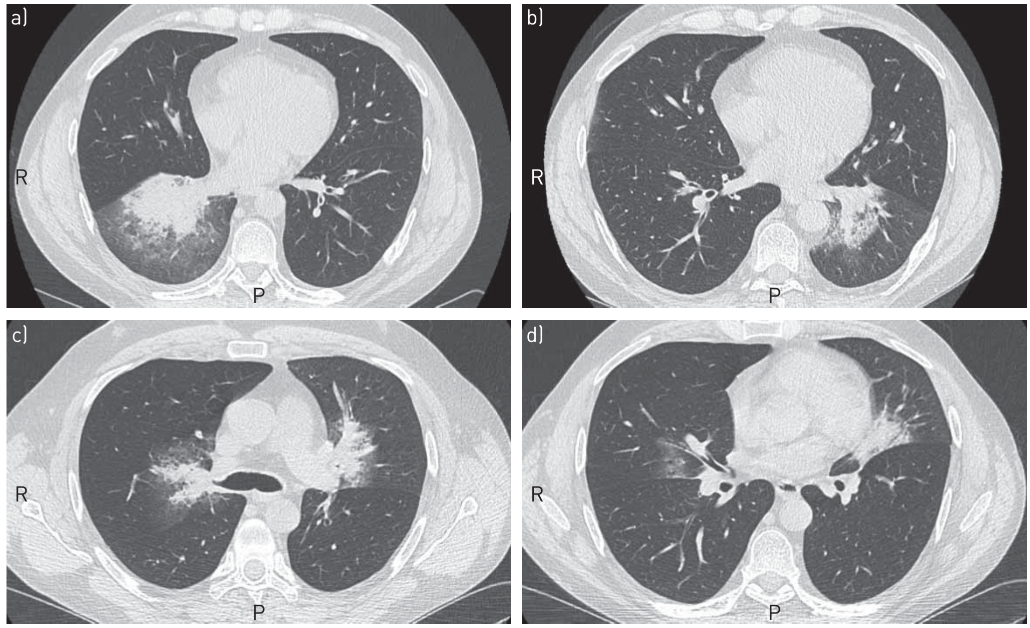

FIGURE 2 Chest computed tomography (CT) scans in the axial plane the day after bronchial thermoplasty (BT) in the a) right lower lobe, showing peribronchial consolidations surrounded by ground-glass opacities, filling of bronchial lumen and mild volume loss of the treated lobe. b) These abnormalities have disappeared 1 month later, when CT is performed the day after BT in the left lower lobe. Similar opacities are observed in this recently treated lobe. c) More limited opacities are observed the day after BT in both upper lobes, performed 1 month later. d) Mild ground-glass opacities are observed at that time in the middle lobe, despite the absence of any activation in this lobe.

Short-term evolution of computed tomography findings

Follow-up at 1 week showed a decrease of parenchymal opacities in both upper lobes in one patient and the disappearance of opacities in the left lower lobe of the second patient (figure 4).

One month after the last BT session, pulmonary opacities were resolved in 10 out of 15 treated lobes (67%) (figures 1 and 2) and decreased in the remaining 5 out of 15 lobes (33%). Discrete ground-glass opacities and a few distal atelectasis were still visible. Four out of five lobes with such persistent opacities at 1 month were evaluated with CT performed a few months later. It showed complete disappearance of opacities in all four lobes but occurrence of mild focal bronchial dilatation in three treated lobes, corresponding to two patients (both lower lobes of one patient and the left lower lobe of another patient). The three cases of complete lobar collapse had resolved (figure 3) and all microcavities had disappeared at 1 month, although one patient had bronchial dilatation in place of the microcavity.

Clinical status following bronchial thermoplasty

There were two cases of transient fever, six cases of wheezing dyspnoea and one case of transient chest pain in the immediate post-procedural time. There was no bronchopulmonary infection in the month following any BT session. Except for the first patient, for whom these imaging features suggested a pulmonary infection, no patient received antibiotics. All patients were discharged after 24 h, as scheduled,

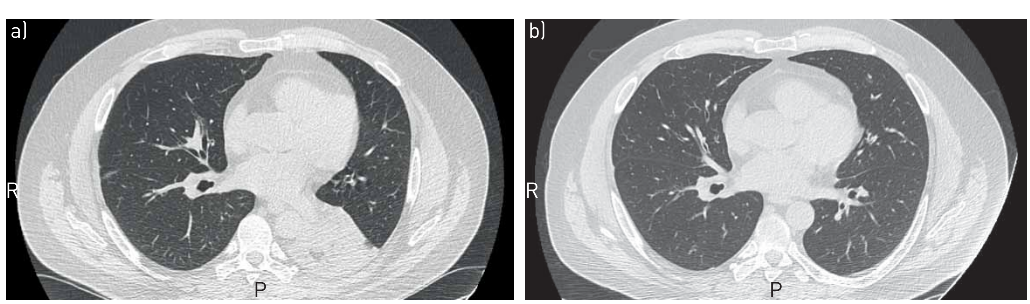

FIGURE 3 Chest computed tomography scans in the axial plane the day after bronchial thermoplasty in a) the left lower lobe, showing complete collapse of the treated lobe. b) The collapse has spontaneously resolved 1 month later.

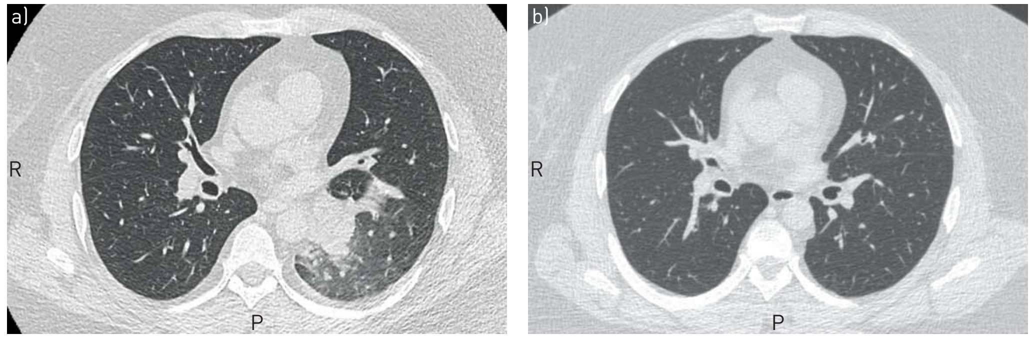

FIGURE 4 Chest computed tomography scans in the axial plane the day after bronchial thermoplasty in a) the left lower lobe and b) 1 week later showing the rapid disappearance of opacities.

except three patients who remained at the hospital 48 h after BT because of asthma exacerbation (two cases) and transient fever (one case). No patient required bronchoscopy.

Discussion

The current study illustrates for the first time an imaging series of early CT observations following BT in patients with severe asthma. We found that pulmonary consolidations, predominantly of peribronchial origin or, more rarely, related to complete lobar collapse, were a consistent event in the BT-treated lung lobes on the day after each session. These alterations rapidly decreased, without antibiotics, and they disappeared at 1 month in two-thirds of cases. CT abnormalities extended beyond the BT-treated zones with involvement of the adjacent untreated lung lobe in one-third of cases.

BT is a usually well-tolerated treatment of severe asthma, although patients can experience adverse events during the first days following the procedure. These effects are mainly related to bronchial irritation, including worsening of asthma symptoms and upper respiratory tract infection. A few cases of lower respiratory tract infection, partial lobar collapse and haemoptysis have also been reported in clinical trials [5–7]. Recently, a case of recurrent lobar collapse occurring a few hours after two BT sessions was described [11]. This manifested as acute respiratory failure and required bronchoscopic removal of hard endobronchial plugs, composed of fibrin and mucous debris. The three cases of complete lobar collapse we report did not manifest any respiratory failure and they spontaneously resolved after 1 month. As previously reported [11], this collapse could result from filling of the bronchial wall by different inflammatory components, although fibroscopy with bronchial aspiration was not performed in these patients.

Lower respiratory tract infection is usually characterised by alveolar opacity on chest radiography and consolidation with or without ground-glass opacities and bronchiolar type micronodules on chest CT. Post-procedural pulmonary opacities were consistently observed the day after the BT session and could be misinterpreted as pneumonia, especially on chest radiography, as was the case for the first patient included in our series. However, these alterations showed particular characteristics on CT, with consistent peribronchial predominance, associated with septal line thickening, in the absence of micronodules. Chest radiography could not identify these opacities in up to 25% of cases and failed to correctly analyse their particular features. Such features, associated with the absence of any clinical symptom of infection, refute the presence of pneumonia and thereby preclude antibiotic use. Superimposed small bubble-like lucencies, which were present in two-thirds of cases, cannot be considered as cavitations because they had disappeared without parenchymal sequelae at 1 month. We suggest that these lucencies represent small residual aerated bronchial segments in filled bronchial lumen, resulting from some gas generated by the BT procedure. Nevertheless, in the absence of a careful histologic examination, the nature of these pulmonary opacities remains speculative. Given the particular imaging features of these elements, combining consolidations, ground-glass opacities, septal lines and minimal pleural effusion, as well as their rapid decrease, we hypothesise that these elements reflect alveolar inflammation and oedema secondary to heat-shock induced by BT. Previous histologic studies performed several days or weeks after BT in dogs [12] and in humans [13] reported microscopic alterations principally involving the airway wall. Small areas of inflammatory pneumonitis or coagulative necrosis were limited to the immediate peribronchial region in a few patients [13]. In our study, pulmonary opacities observed immediately after BT extended far beyond the immediate peribronchial area, although their rapid decrease does not support significant parenchymal necrosis.

Although our study focused on early post procedural changes, we noticed mild focal bronchial dilatations a few months later in three treated lobes. The mechanism and clinical significance of such dilatations deserve further evaluation. These observations differ from those obtained upon pulmonary radiofrequency ablation (RFA) of tumours, a technique that uses the same radiofrequency technology but that involves a higher energy deposit to promote whole tissue necrosis. Contrary to RFA, which delivers energy for several minutes, radiofrequency energy in BT is distributed at each site for only a few seconds. In addition, in contrast to the concentration of energy in the tumour during RFA provided by the insulating effect of surrounding pulmonary air [14], the energy deposited during BT can diffuse along the bronchial wall and rapidly decrease at the treated site.

The diffusion of energy along the bronchial wall could explain the recently reported decrease in airway smooth muscle area in BT-untreated middle lung lobes [10]. This diffusion could also participate in the induction of opacities in the adjacent lobe to the BT-treated lobe that was observed in one-third of cases in our series. However, because the involvement of the BT-untreated lobe was always minimal, any peribronchial predominance that would have supported this hypothesis was difficult to appreciate. Another mechanism to explain the involvement of adjacent lung lobes could be an extension of parenchymal oedema, or inflammation through incomplete fissures.

The limitations of our current study include 1) the low number of patients with severe asthma examined, 2) the lack of histologic correlation to explain the nature of pulmonary opacities, and 3) the short duration of the follow-up. Despite these limitations, we believe that knowledge of imaging effects of BT will be useful in clinical practice to ensure a proper follow-up of these patients.

In conclusion, we report the first imaging series of early CT findings following BT. We show a transient and predominant peribronchial consolidation, suggestive of pulmonary inflammation or oedema, as a consistent event in the BT-treated lung lobes the day after the procedure. These opacities should not be misinterpreted as infectious pneumonia and, therefore, should not lead to antibiotic use. Pulmonary opacities can extend to an adjacent untreated lobe in up to one-third of cases, possibly as a result of heat diffusion along the bronchial tree or along parenchymal pathways through incomplete fissures.

Whatever the mechanisms underlying these CT imaging alterations following BT, our findings suggest that an pulmonary area much larger than the proximal airways is impacted by the heat shock is and that this can contribute to the clinical benefit of this procedure.

References

1 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.

2 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; 18: 716–725.

3 Chung KF, Adcock IM. How variability in clinical phenotypes should guide research into disease mechanisms in asthma. *Ann Am Thorac Soc* 2013; 10: Suppl., S109–S117.

4 Dombret MC, Alagha K, Boulet LP, *et al.* Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. *Eur Respir Rev* 2014; 23: 510–518.

5 Pavord ID, Cox G, Thomson NC, *et al.* Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007; 176: 1185–1191.

6 Cox G, Thomson NC, Rubin AS, *et al.* Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007; 356: 1327–1337.

7 Castro M, Rubin AS, Laviolette M, *et al.* Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010; 181: 116–124.

8 Wechsler ME, Laviolette M, Rubin AS, *et al.* Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013; 132: 1295–1302.

9 Cox G, Miller JD, McWilliams A, *et al.* Bronchial thermoplasty for asthma. *Am J Respir Crit Care Med* 2006; 173: 965–969.

10 Pretolani M, Dombret MC, Thabut G, *et al.* Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Crit Care Med* 2014; 190: 1452–1454.

11 Facciolongo N, Menzella F, Lusuardi M, *et al.* Recurrent lung atelectasis from fibrin plugs as a very early complication of bronchial thermoplasty: a case report. *Multidiscip Respir Med* 2015; 10: 9.

12 Brown RH, Wizeman W, Danek C, *et al.* In vivo evaluation of the effectiveness of bronchial thermoplasty with computed tomography. *J Appl Physiol* 2005; 98: 1603–1606.

13 Miller JD, Cox G, Vincic L, *et al.* A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest* 2005; 127: 1999–2006.

14 Dupuy DE, Mayo-Smith WW, Abbott GF, *et al.* Clinical applications of radio-frequency tumor ablation in the thorax. *Radiographics* 2002; 22: Spec No., S259–S269.