Experimental lung collapse following deployment of a self-expandable bronchial occluder in a rabbit model

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Objectives: Closure of a bronchopleural fistula is required to prevent fatal empyema or aspiration pneumonia. The purpose of this study was to determine the feasibility and efficacy of bronchial occlusion with a self-expandable occluder to induce experimental lung collapse in a rabbit model.

Methods: 10 bronchial occluders (wine glass appearance; 8 mm in diameter and 15 mm in length) were implanted in the native left main bronchi of 10 rabbits via an endotracheal route. We analysed the following: (1) diameters and morphological changes of the bronchial occluders during follow-up; (2) percentage volume of the collapsed lung during follow-up; and (3) complications and gross pathology. 1-day and 2-week follow-up CT scans were routinely obtained. Rabbits were sacrificed 4 weeks after the experiment.

Results: In all 10 rabbits, the bronchial occluders were successfully implanted and were completely expanded within 2 weeks. Complete collapse of the left lung occurred in three rabbits on day 1 and in an additional two rabbits 2 weeks following implantation. Two other rabbits maintained the percentage volume of the collapsed lung between 51% and 99% during follow-up; the other three rabbits had <50% during follow-up. Pneumothoraces occurred in nine rabbits, but completely resolved at the 2-week follow-up. Right lung herniation across the midline progressed 2 weeks after occluder implantation.

Conclusion: Placement of self-expandable occluders in a rabbit bronchus model was feasible and showed a potential to induce artificial lung collapse. While pneumothoraces were common, they resolved during follow-up.

Received 23 July 2010
Revised 27 October 2010
Accepted 27 October 2010

DOI: 10.1259/bjr/40247893

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Radiology

Bronchopleural fistulas (BPFs) are rare pathological conditions which may be life-threatening complications with a mortality rate ranging between 11% and 15% [1–5]. BPFs are among the most serious complications after pneumonectomy, the surgical repair of which may be difficult [6]. Many interventional and endoscopic options proposed to close the fistula include injection of tissue adhesives, insertion of modified Dumon stents, and embolisation with vascular occluding coils and glue [2–5].

Recently, there have been a few case series regarding successful interventional treatments using covered endobronchial stents for patients with BPFs [6–10]; however, there have been no reported experimental studies using metallic endobronchial occluder combined with covered materials to occlude the bronchus and induce experimental lung collapse in an animal bronchial model. Such an experiment can provide a firm basis for the occlusion of

BPFs using metallic endobronchial occluders. The purpose of this study was to determine the feasibility and efficacy of bronchial occlusion using self-expandable occluders to induce experimental lung collapse in a rabbit bronchus model using three-dimensional (3D) CT follow-up.

Methods

Animal preparation

All 10 animals used in this study were 2.5–3 kg New Zealand white rabbits. The left main rabbit bronchus was chosen for the experimental model because the left main rabbit bronchus has a shorter and straighter course than the right main bronchus, thus allowing interventional procedures to be performed more easily via the endotracheal route [11,12].

All experimental procedures were performed in accordance with the National Institutes of Health guidelines for humane handling of animals and were approved by our institutional review board on animal research.

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For pre-procedural evaluation of the native main bronchus in rabbits, CT scans were performed to measure the mean diameter of the left main bronchus; we then observed the anatomic features of the tracheobronchial tree using 3D reconstruction. The CT examinations were performed on a HiSpeed scanner (GE Medical Systems, Milwaukee, WI). Rapidia software was used as a 3D reconstruction method (Infinity Co., Seoul, Republic of Korea).

Occluder construction and placement technique

The tracheobronchial stent was woven from a single thread of 0.016 inch nitinol wire into a tubular configuration. The occluder (8 mm in diameter and 15 mm in length) was designed to have a typical wine glass configuration after constriction with nylon strings in the distal three-quarter portion of the stent for this study, and manufactured by the local company according to our specifications (Figure 1). Both sides of the occluders were then coated with silicone, so they would be air and waterproof. Finally, an additional silicone coating was applied to the inner lumen of the bronchial occluders in order to increase their occluding capacity (Figure 1). Both ends of the occluders were left covered with silicone. The radio-opaque markers, using gold components, were attached at the proximal and distal ends and at the constricted portion of the occluders in order to allow an easier implantation procedure (Figure 1). We assured the radial force of the bronchial occluder by confirming its integrity with additional examination using UTM (Universal Testing machine®; LLOYD, London, UK). The appropriate diameter of an occluder was made approximately 3 mm larger than that for the targeted left main bronchus.

Anaesthesia was induced with intramuscular administration of ketamine hydrochloride and xylazine

hydrochloride, each at a dose of 5 mg kg^{-1} . Intubation was not performed because the procedure of occluder deployment was simple and could be tolerable with intramuscular anaesthesia. The deployment process is shown in Figure 2 in detail. After supine positioning of each rabbit, we first inserted a 0.035 inch guidewire (Radifocus M®; Terumo, Tokyo, Japan) through the trachea into the left main bronchus under fluoroscopy. A 9-Fr braided sheath and its dilator (Hyperflex II®; Cook, Bloomington, IN) was then advanced over the wire into the distal portion of the left main bronchus. After we removed the sheath dilator and guidewire from the 9-Fr braided sheath, we loaded the bronchial occluder from the loader catheter into the 9-Fr braided sheath and pushed the occluder into the end portion of a 9-Fr braided sheath using a pusher catheter. The bronchial occluder was implanted by withdrawing the 9-Fr braided sheath while the pusher catheter was held immobile. Post-procedural plain radiography was obtained immediately after occluder placement in order to verify the position, expansion, and shape of the implanted bronchial occluder.

Follow-up and analysis

During follow-up, chest CT was performed 1 day and 2 weeks after the procedure on all 10 rabbits. We compared the maximum inner diameters and morphological changes, such as the position and shape of the implanted occluders, on the 1-day and 2-week follow-up 3D reconstructed CT images.

We estimated the efficacy of the bronchial occluders by quantifying lung collapse as the percentage volume of the collapsed lung (non-aerated lung volume/left total lung volume) using a technique known as the "ROI drawing in 2D slice method" on Rapidia software. That is, we manually traced the contours of all lung sections

Figure 1. Photographs of a self-expandable bronchial occluder. (a) The constricting point (arrow) is at the distal three-quarter point of the stent which is tied with nylon string and functions to occlude the stent. (b) The inner lumen of the occluder is reinforced with an additional silicone coating to enhance the occluding capacity.

Figure 2. Deployment process of the bronchial occluder. (a) A 0.035-inch guidewire (arrows) is inserted through the trachea into the left main bronchus. (b) 9-Fr braided sheath (arrows) is inserted with the tip located in the left main bronchus. Sheath dilator and guidewire was removed (not shown). Radiopaque marker (arrowheads) is shown to indicate the location of carina. (c) Bronchial occluder (arrows) is loaded into the end portion of the 9-Fr braided sheath using a pusher catheter. The radiopaque end (arrowhead) of the pusher catheter is seen just proximal to the collapsed occluder. (d) Bronchial occluder is deployed by withdrawing the 9-Fr braided sheath while the pusher catheter is held immobile.

from apex to diaphragm by using the cursor of the computer. The circumscribed areas in all scanned lung sections were summed and then multiplied by the slice thickness to give the total volume of involved lung [13,14]. An additional 3-week follow-up CT was obtained if the percentage volume of the collapsed lung was <50% during the 2 weeks. Finally, possible post-procedure complications, such as stent migration, procedure-related airway injury, pneumothorax or lung herniation, were evaluated. A pneumothorax was defined as severe, moderate and mild when more than two-thirds, between one- and two-thirds and less than one-third of the ipsilateral lung volume was involved, respectively. Lung herniation was defined as protrusion of the opposite lung across the midline toward the collapsed lung.

Rabbits were sacrificed with an overdose of ketamine hydrochloride 4 weeks after the experiment. Surgical exploration of the tracheobronchial tree was performed and possible complications, such as bronchial perforation or laceration of the extracted tracheobronchial tree, and the presence of migration or morphological abnormality of the implanted occluders, were evaluated.

Results

Diameters and morphological changes of the bronchial occluders

According to the pre-procedural CT scans, the average diameter of the proximal left main bronchus was 5.01 mm (range: 4.74–5.5 mm; median: 5.12 mm).

All bronchial occluders were successfully placed without deployment failure or stent migration in the proximal left main bronchus. In eight rabbits, the proximal margin of the bronchial occluders was exactly at the proximal end of the left main bronchus (Figure 3), while in two rabbits (numbers 5 and 8), it was a few millimeters from the proximal end of the left main bronchus. In eight rabbits, full expansion and the proper shape of the occluders were observed immediately after stent placement. There were two cases (numbers 3 and 9) of focal incomplete occluder expansion due to partial inward folding of the proximal portion of the occluders. On the 2-week follow-up, complete expansion of the occluders without inward folding was also observed in those two rabbits. The mean ($\pm$ standard deviation)

Figure 3. Complete collapse of the left lung after bronchial occluder implantation (number 4). (a) A plain radiograph immediately after occluder deployment shows well-expansion of the occluder in the left main bronchus. (b) The axial image on the day 1 follow-up CT scan shows the well-expanded bronchial occluder, complete collapse of the left lung and bilateral pneumothorax (asterisks). The axial image (c) and its matched three-dimensional reconstructed image (d) of the 2-week follow-up CT scans show complete collapse of the left lung (black arrows) and right lung herniation (white arrows). Pneumothorax seen on the day 1 follow-CT scans resolved.

diameter of the occluders changed from 3.82 ± 0.59 mm on the day 1 follow-up CT to 5.74 ± 0.4 mm on the 2-week follow-up CT.

Change of percentage volume of collapsed lung during follow-up

On the day 1 follow-up chest CT scans, complete collapse of the entire left lung occurred in three rabbits (numbers 4, 5 and 10; Figure 3) and 51–99% collapse occurred in an additional five rabbits (Table 1). The remaining 2 rabbits (numbers 6 and 7) showed <50% collapse (Figure 4). On the 2-week follow-up CT scans, complete collapse persisted in three rabbits with initial complete collapse and occurred in an additional two rabbits (numbers 1 and 9). Two rabbits had 51–99% collapse (numbers 2 and 3), while there was <50% collapse (35%, 32% and 19%, respectively) in three rabbits (numbers 6, 7 and 8). These three rabbits had a greater decreased lung collapse percentage (24%, 24% and 16%, respectively) on the 3-week follow-up CT scans.

Complications and gross pathology results

Nine rabbits had pneumothoraces in one or two lungs on the day 1 follow-up CT (Figures 3 and 4;

Table 2). The distribution and severity of pneumothorax are shown in Table 2. The pneumothoraces resolved completely during the 2-week follow-up in all nine rabbits. Contralateral right lung herniation was observed on the day 1 follow-up CT in eight rabbits and had increased by the time of the 2-week follow-up CT (Table 2). Lung herniation was noted on the 2-week follow-up in two rabbits that initially had no right lung herniation.

Upon gross examination on the 10 extracted tracheo-bronchial trees from all of the rabbits, there were no lung lacerations, perforation or migration or any morphological abnormalities in the implanted occluders.

Discussion

Two recent studies that used interventional treatment for BPFs have reported encouraging results [6, 7]. Kim et al [6] reported two cases using specially designed bronchial stents known as “stent-graft occluders” with covering material consisting of a Dacron graft, which were placed via a transthoracic route. Han et al [7] reported six cases using hinged tracheobronchial stents consisting of two parts, *i.e.* the tubular tracheal part and the bullet-shaped bronchial limbs. Even though those two studies reported successful treatments, they were case series and lacked animal experiments. Normal rabbit bronchial models were used in this study to

Table 1. Measurement of lung volume on follow-up CT scans

Number	1-day CT		2-week CT	
	Collapsed/Total left lung volume (mm ³)	Percentage volume of collapsed lung (%)	Collapsed/Total left lung volume (mm ³)	Percentage volume of collapsed lung (%)
1	8097.1/13119.0	61	6717.0/6717.0	100
2	8906.1/16219.9	54	10540.2/14639.2	72
3	6250.6/8683.2	71	6901.5/11293.0	83
4	6934.3/6934.3	100	3634.3/3634.3	100
5	10690.1/10690.1	100	10696.0/10696.0	100
6	3780.4/9254.9	40	3303.1/12132.0	35
7	5560.7/12681.5	43	4428.4/13543.8	32
8	4129.8/7059.9	58	3712.2/19169.2	19
9	7074.8/11237.5	62	4503.0/4503.0	100
10	4241.5/4241.5	100	3602.2/3602.2	100
Mean $\pm$ SD	6566.54 $\pm$ 2246.75 / 10012.18 $\pm$ 3513.53	68.90 $\pm$ 23.24	5803.79 $\pm$ 2831.80 / 9992.97 $\pm$ 5241.98	74.10 $\pm$ 32.96

SD, standard deviation.

Total left lung volume includes both aerated and collapsed left lung volumes.

induce experimental lung collapse. It would be difficult to make a reproducible BPF model.

In our study, the self-expandable bronchial occluders showed delayed expansion in all rabbits. Delayed expansion is very important as proper oversizing of the bronchial occluders is essential, not only to achieve complete lung collapse, but also to prevent occluder migration. Including the two cases with initial incomplete expansion, all occluders showed complete delayed expansion with an increase in diameter in the current study. These self-expandable characteristics may contribute to perfect fistula sealing in a clinical setting if the expansile force is not excessive. Excessive expansile force could enlarge or disrupt the fistula.

In this study, the self-expandable bronchial occluders showed the potential to induce artificial lung collapse by causing >50% of the lung collapse in 7 of the 10 rabbits, as noted on the 2-week follow-up CT. The lung collapse percentage was similar or increased in seven cases during follow-up. Theoretically, the lung collapse percentage should increase as the collapsed volume increases.

However, in three rabbits, the lung collapse decreased during follow-up. We presume that the degree of lung collapse is affected by the collateral ventilation, coexisting pneumothorax, and the degree of contralateral lung herniation [15–17]. Considering that the percentage volume of the collapsed lung on day 1 CT was low in those three rabbits, collateral ventilation of the collapsed lung with the adjacent aerated lung seems to be the most important. In the clinical setting of a BPF after pneumonectomy, however, secure occlusion of the fistula would be the single most important factor determining treatment success, thus greater lung collapse percentage is expected.

Compared with the modified Y-shaped Dumon stent (with the ipsilateral arm shortened and closed) [5, 18, 19], the bronchial occluders used in this study have the advantages of a smaller occluder introducer system, less patient discomfort, and no need for a rigid bronchoscope. In addition, the risk of sputum retention or infection could be reduced as the trachea and contralateral bronchus were not affected by the bronchial occluder and the occluder

Figure 4. Incomplete collapse after bronchial occluder implantation (number 7). The axial image (a) and its matched three-dimensional reconstructed image (b) of the day 1 follow-up CT scans show incomplete collapse of the left lung (arrows), severe ipsilateral pneumothorax (asterisks) and contralateral lung herniation. Ipsilateral pneumothorax resolved on 2-week follow-up CT images (not shown).

Table 2. Pneumothorax and lung herniation on follow-up CT scans

Number	1-day CT		2-week CT	
	Pneumothorax in left /right lung	Right lung herniation	Pneumothorax	Right lung herniation
1	Severe / (–)	(+)	Resolved	Increase
2	(–) / (–)	(+)	(–)	Increase
3	Severe / (–)	(–)	Resolved	(+)
4	Severe / mild	(+)	Resolved	Increase
5	Mild / (–)	(+)	Resolved	Increase
6	(–) / mild	(+)	Resolved	Increase
7	Severe / (–)	(+)	Resolved	Increase
8	Severe / (–)	(–)	Resolved	(+)
9	Severe / severe	(+)	Resolved	Increase
10	Severe / severe	(+)	Resolved	Increase

–, negative; +, positive.

used in this study was placed via the endotracheal route instead of transthoracic route.

A self-expandable occluder used in our study could be used for patients with BPF and a residual bronchial stump. It may occlude the BPF non-surgically, help to obliterate the pneumonectomy space and prevent further spread of possible infection to the contralateral lung. A sufficient portion of the bronchial stump should remain after surgery for secure implantation of the bronchial occluder. Without this, the proximal end of the occluder can protrude into the carina and cause subsequent dyspnoea. One recent report described the use of an hourglass-shaped covered stents in three patients with BPF [10], which were placed in the bronchial stump using a combination of rigid bronchoscopy and thoracoscopy or thoracostomy. This report showed a great potential of an occluder to seal off the BPF [10]. Although re-amputation of the long bronchial stump could be performed, non-surgical stent placement could be considered first. In addition, this kind of bronchial occluder could be used for volume reduction procedure in patients with emphysema.

In our study, pneumothorax was observed in nine rabbits on the day 1 follow-up CT. Pneumothorax in the ipsilateral lung is speculated to be a procedure-related trauma or pneumothorax *ex vacuo* after acute lobar collapse from acute bronchial obstruction [15–17]. Pneumothorax *ex vacuo* is a kind of “vacuum phenomenon” due to sudden increase of negative pressure in the ipsilateral pleural cavity, which usually occurs as a meniscus-appearing air collection in the pleural cavity [15–17]. In this study, the pneumothorax *ex vacuo* can be evidence of the excellent occluding capacity of the occluder. Pneumothorax in the contralateral lung could be explained as follows. First, a sudden increased pressure in the contralateral lung during occluder deployment procedure (reinforced by decrease of airflow through the ipsilateral lung) could cause a defect in the visceral pleura and result in a pneumothorax [20]. Second, possible procedure-related trauma such as airway injury by the occluder introducer system or inadvertent guidewire traversing through the lung parenchyma, could result in pneumothorax in the contralateral lung [20]. Fortunately, the pneumothorax completely resolved during the 2-week follow-up in all rabbits. In a clinical setting, however, such pneumothorax in the ipsilateral lung could not be expected to occur as BPF follows pneumonectomy. Use of bronchoscopic guidance

during the procedure and gentle manipulation of the devices could prevent possible device-related pneumothorax. Contralateral right lung herniation became worse during follow-up and seems to be inevitable as it is a natural phenomenon secondary to the volume decrease of the left lung.

Before clinical application, the diameter of the bronchial occluder could be adjusted to that of the human bronchus. Considering possible shortness and the blunt end of the bronchial stump, the occluder length should be tailored, and the flare distal to the constricting point could be shortened or removed. To prevent possible migration, barbs could be attached to the external part of the occluder. In addition, airway maintenance is important during human application. Bronchoscopic assistance will be of great help to evaluate airway status and tackle emergent situations during the procedure in humans.

This study had several limitations. First, as the animal model was a normal rabbit model, it cannot mimic the clinical state of BPF after pneumonectomy. Second, bronchoscopic guidance and confirmation could prevent possible device-related complications and enable better evaluation of apposition of the stent and bronchial wall. Third, the number of rabbits used was small, and the follow-up period was somewhat short. Fourth, no microscopic histology was obtained because we focused on radiological and gross histological findings.

In conclusion, placement of self-expandable occluders in a rabbit bronchus model is feasible and shows a potential to induce artificial lung collapse. While pneumothoraces were common, they resolved during follow-up.

Acknowledgments

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (A060603), National Research Foundation of Korea Grant by the Korean Government (KRF-2005-206-E00015), a grant (2008-312) from the Asan Institute for Life Sciences, Seoul, Republic of Korea, and a 2009 research grant from the Korean Society of Radiology provided by Bayer Schering Pharma, Republic of Korea. We thank Bonnie Hami, MA, Department of Radiology, University Hospitals of Cleveland, OH, USA for her editorial assistance in the preparation of the manuscript.

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