Reaction Patterns of the Tracheobronchial Wall to Implanted Noncovered Metal Stents*

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Background: Endoluminal implantation of stents has evolved as a nonsurgical treatment option for stenosis of the central airways. Based on the favorable results in treatment of tumorous tracheobronchial stenosis, stenting has been introduced into the therapy of nonmalignant stenosis.

Aim: To study the long-term biocompatibility and incorporation of implanted bronchial stents based on the pathoanatomic reaction of the tracheobronchial system in humans. The incorporation of bronchial stents was documented, with specific interest in transformation or induction of dysplasia in the implantation zone.

Methods: The tracheobronchial reaction was studied in 18 patients 2 days to 18 months after implantation of 24 noncovered metal stents (Wallstent; Schneider; Bülach, Switzerland; n = 8; and Ultraflex; Boston Scientific; Natick, MA; n = 16).

Results: Stenting produced slow papillomatous growth of granulative tissue through the interfilamentary space of the stents. A nonspecific inflammatory response of nontumorous tissue could be documented. Sparse spots of superficial squamous cells occurred. No epithelial dysplasia or giant cells were detected within the stented region. The number of superficial ciliated cells in the implantation zone was markedly reduced.

Conclusion: After stent insertion in the upper airways, no malignant transformation of initially nontumorous tissue occurs. Stenting seems to be a safe therapy option when considered even for nonmalignant airway stenoses.

Key words: dysplasia; stenosis; stent; upper airways

Abbreviations: EVG = Elastica-von-Gieson; HE = hematoxylin-eosin; HEA = human epithelial antigen; KL-1 = cytokeratin protein keratin

Endoscopically implantable bronchial endoprostheses (bronchial stents) have evolved as a non-surgical, minimally invasive treatment option of stenoses of the upper airway tract.1,2 Bronchial stents were implemented successfully as palliative therapy for malignant obstructions of the central airways.3 Previous studies1–5 suggest that implanted stents not only reduce the extent of bronchial malignant stenosis but also suppress growth of local tumors. The first analysis of the morphologic reactions of tumorous bronchial tissue after stenting was recently communicated by Hauck et al4 in 2002. In this study, a significant reduction of vital tumor cells after stenting of tumorous stenoses was observed 1 week after implantation of covered metal stents.

Based on the good clinical results in malignant bronchial stenoses, the concept of intraluminal stenting has been transferred to treating benign upper airways stenoses. In this setting, stenting has been used for children with primary tracheobronchomalacia, but also in patients with secondary tracheobronchomalacia to prevent airway collapse.5,6 In addition, the alleviation of posttransplantation airway strictures, post-upper lobectomy bronchial obstruction or bronchial compression in patients with tetralogy of Fallot, has been documented in a single case report.7

The reaction of normal (nontumorous) bronchial
tissue on implanted endoprostheses has not been studied in a larger series of patients. We studied the histomorphologic effects of metal stents on nontumorous bronchial tissue. We were particularly interested in determining whether a relation to epithelial dysplasia or secondary malignant transformation can be detected.

**MATERIALS AND METHODS**

In 18 patients (mean ± SD age, 59 ± 10 years), the implantation zones after bronchial stenting were analyzed. Eleven patients (patients 1 through 11; Table 1) had malignant central airway stenosis (primary lung adenoid carcinoma, n = 7; squamous cell carcinoma of the lung, n = 1; thyroid carcinoma, n = 1; breast cancer, n = 1; laryngeal carcinoma, n = 1). To document the histomorphologic reaction of nontumorous parts of the tracheobronchial wall, samples were gathered from regions macroscopically free from tumorous infiltration (as identified during bronchoscopy). Thirty-nine biopsy specimens were obtained during bronchoscopy 2 days to 18 months after stent implantation (when considered relevant for the clinical course). Autopsy was performed in four patients who died during follow-up (3 to 18 months) [Table 1].

Seven patients were studied (patients 12 through 18; Table 1) after stenting for benign tracheal stenosis (postintubation stenosis, n = 2; tracheomalacia, n = 4, after transplant, n = 1). In 8 patients, Wallstents were implanted (n = 8; Schneider; Büllach, Switzerland); in 10 patients noncovered Ultraflex stents (n = 16; Boston Scientific;Natick, MA).

In the autopsy cases, analysis of the histomorphologic reaction pattern of deeper bronchial wall segments preparation was performed using cut-and-grinding technique. This technique allows artifact-free microscopic analysis of the stented bronchial wall. Probes were embedded in methacrylate plastic (Technovit 9100; Heraeus Kulzer; Wehrheim, Germany). Sectioning was performed using a rotating cutting microtome (Accutom-5; Struers; Düsseldorf, Germany) to obtain samples 15 to 20 μm in thickness. After grinding and polishing (precision grinding), samples were stained using hematoxylin–eosin (HE) and Elastica-von-Gieson (EvG) staining for microscopy. A second part of the stented segment was processed after excision of the stent struts for paraffin embedding and HE and EvG staining. Bronchoscopically acquired probes were processed for paraffin embedding and stained using HE and EvG methods (standard procedure).

**Immunohistochemistry**

Characterization of the epithelium via immunohistochemical staining was performed: cytoskeleton protein keratin (KL-1) and human epithelial antigen (HEA)-125 (DACO; Hamburg, Germany). KL-1 is a broad-spectrum antikeratin reagent reacting with intermediate and low-molecular-weight keratins. Thus, it stains epithelial tissue from simple glandular to stratified squamous epithelium. Therefore, it stains nonkeratinizing layers of epidermis as well as esophageal mucosa. HEA-125 labeling most epithelial cells is useful as a discriminant in the differential diagnosis of basal and squamous cell carcinoma. To quantify local inflammatory response, cells of the mononuclear/macrophagous system were labeled using DC-68 (DACO).

**RESULTS**

Thirty-nine bronchoscopic biopsies were performed in 18 patients from 2 days to 18 months after stent implantation (Table 1). During the follow-up period, four patients (36%) with malignant disease died from 3 to 18 months of follow-up. Eighteen biopsies were performed within 21 days (mean, 13 ± 7 days), and 17 biopsy samples were obtained from 1 to 12 months after stenting (mean, 6 ± 4 months) [Table 1].

**Macroscopic/Bronchoscopic Evaluation**

The bronchial epithelium appeared pale and swollen in the acute phase after stenting (up to 21 days). After maximal expansion of the stent struts, only cobblestone-like mucosa can be seen in the implantation zone. This relief is due to protrusion of mucosa through the interfilamentary space of the metal stent. From 2 days to 3 weeks, the endoprostheses were completely covered by ingrowing tissue almost invisible during bronchoscopy. During later follow-up, a polypoid tissue hyperproliferation was seen in the stented regions that led to partial restenosis in four patients (22%) [without the need for invasive therapy; Fig 1].

**Histomorphologic Evaluation**

Implanted stents led to compression of mucosa segments down to the lumbar muscularis propria but

<table>
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<th>Patient No.</th>
<th>Biopsies Within 21 Days*</th>
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<tr>
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<td>3†</td>
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<td>11</td>
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<td>20</td>
</tr>
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*Data are presented as No. of days.
† Data are presented as No. of months.
‡ Autopsy.
without affecting (compressing) the tunica muscularis or fibrocartilaginosa. Typically, the stent struts led to deep impressions of the ciliated epitheloid cell layer including mechanical destruction of the superficial cells. No tissue hematoma or intramural hemorrhage was noted, and no alteration of microvessels within the submucosa tissue was detected.

In the acute phase, edema of the mucosa but still preserved covering cell layers were visible. Epithelial cells impressed into deeper layers of the bronchial wall can be detected under the stent filaments (Fig 2). Seven days after stenting, dense infiltrations of macrophages were seen in the zones of superficial necrosis under the stent filaments. Three weeks after stent insertion, cellular granulation tissue spots extending polypoid-like into the bronchial lumen can be detected. Stent filaments were completely covered by confluent granulation tissue polyps. Later integration of the stents was characterized by growing amounts of fibrosis.

In bioptic material 3 months after stenting, epithelial differentiation from respiratory to squamous epithelium was seen. Epithelial cells were found to have a more cubic polygonal configuration. Twelve months after stent insertion, less inflammatory cells were detected within the spots of sclerosed granulation tissue covered by squamous cell metaplasia.

No cellular dysplasia was seen in the studied samples. No specific inflammatory removal reaction including giant cell invasion or increased eosinophilic reaction was detected. No foreign body giant cells could be found.

**Immunohistochemistry**

**Early Phase (Up to 3 Weeks):** CD-68–positive cells (monocytes/macrophages) invading the stented region were detected in the superficial regions of granulation tissue polyps. No increased expressions of KL-1–positive or HEA-125–positive cells were spotted in this early phase, indicating the absence of squamous cells.

**Late Phase (> 1 Month):** The immunohistochemical expression pattern of the tissue incorporation the endoprostheses was found to be completely different when compared to the early phase: CD-68–positive cells were rarely detected in the deeper layers of the granulation tissue cover. An intact basal membrane separated superficial cells from deeper tissue layers. The superficial cells labeled positive for KL-1 but negative for HEA-125. This expression pattern strongly suggests benign squamous cell metaplasia (Fig 3).
In this study, the effects of permanently implanted metal stents to treat malignant bronchial stenoses on nontumorous wall segments were studied. The main observation is that no epithelial dysplasia or tumorous transformation occurred in response to implanted bronchial stents. In selected patients, intraluminal stenting of stenotic central airways has been shown to be an effective addition to the treatment regimen.\(^5\)\(^8\)\(^\text{–}11\) Whereas stenting was initially used only as palliative therapy in patients with end-stage malignant disease and tumorous bronchial stenosis, the indications have been extended to patients with nonmalignant obstructions.\(^3\)\(^5\)\(^9\)\(^12\)\(^\text{–}14\)

This therapeutic concept implies years of contact between airway tissue and endoprosthetic material. On this behalf, tissue compatibility of implanted stents became a significant factor for long-term success.\(^8\) Biocompatibility of bronchial stents has been deducted from experience in other parts of the human body (eg, coronary arteries).\(^15\)\(^16\) So far, knowledge of the effects of bronchial metal stents on the central airway tissue has only been documented in bronchoscopically acquired probes focusing on the reaction pattern of superficial tissue.\(^4\)

By analyzing biopsy and autoptic material, the present study reveals new insights on transmural effects of bronchial stenting. In the acute phase, stents were covered by acellular detritus, mucus, and fibrinous material. The basal membrane was regionally destroyed by stent filaments migrating into deeper tissue layers. Microvessels in the submucosa were found to be eroded, but no larger intramural hematoma was documented. A few days after stenting, the filaments became incorporated by granulation tissue consisting of matrix proteins and nonspe-

**Figure 2.** Hard cut-and-grinding preparation of the trachea after stenting, showing histology of the mucosa lining after stent insertion. One stent filament is not embedded into the mucosa. Unaltered epithelium (→) is seen under the metal stent; the region between stent and ciliated epithelium is filled with mucus (magnification, 60×).

**Figure 3.** Histology of a biopsy sample from a stent margin 12 months after implantation, showing cells on an intact basal membrane (KL-1 positive, left, A; HEA-125 negative, right, B) indicating transformation from ciliated to squamous cell epithelium.
specific granulocytic inflammatory reaction. The last phase of incorporation is characterized by tissue polyps consisting of reactive squamous cells proliferating through the interfilamentary space of the stents. The submucosa consisted of aggregated monocytes and macrophages without giant "foreign body" cells.

The most severe complication in the late phase of stent incorporation was restenosis due to transprosthetic exophytic growth of granulation tissue. Immunohistochemistry reveals metaplastic differentiation to be the cause for reactive alterations of superficial epithelial cells. Up to 18 months after stenting, no cellular dysplasia or tumorous transformation including invasion of the basal membrane was detected. These morphologic findings support clinical data indicating that noncovered metal stents may be used for long-term therapy of bronchial stenoses even in patients with nonmalignant obstructive disease.

REFERENCES