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Endobronchial Valve Treatment Does Not Cause Significant Nickel Deposition in Lung Tissue

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Established Facts

- Endobronchial valves can release nickel in vitro.
- Other nitinol-containing medical implants have shown to release nickel both in vitro and in vivo.

Novel Insights

- No deposition of nickel was found in lung tissue after endobronchial valve treatment.

Keywords
COPD · Bronchoscopy · Endobronchial valve · Nickel release

Abstract
Bronchoscopic lung volume reduction using endobronchial valves (EBVs) is a treatment option for patients with severe emphysema. These EBVs are made out of a nitinol mesh covered by a silicone layer. Nitinol is an alloy of nickel and titanium and is commonly used in implantable medical devices because of its biocompatibility and memory-shape properties. However, there are some concerns that nickel ions can be released from nitinol-containing devices which might cause adverse health effects, especially in patients with a known nickel hypersensitivity. In vitro, it was found that EBV release significant amounts of nickel in the first hours. Our aim was to assess the nickel concentration in lung tissue from a patient who previously underwent EBV treatment but, due to treatment failure, underwent lung volume reduction surgery and to compare this to a reference

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sample. We found no significant difference in the median nickel concentration between the EBV-treated patient and the non-EBV-treated patient (0.270 vs. 0.328 μg/g, respectively, $p = 0.693$) and these concentrations were also comparable to previously published nickel concentrations in human lung tissue samples not having any medically implanted devices in the lung. Our results suggest that there is no significant long-term nickel deposition in lung tissue after EBV treatment.

Introduction

Bronchoscopic lung volume reduction with endobronchial valves (EBVs) is a treatment option for a selected group of patients with severe emphysema. Clinically meaningful improvements in pulmonary function, exercise capacity, and quality of life are reported after treatment [1]. The most frequently used EBV is the Zephyr EBV (PulmonX Inc., Redwood, CA, USA) which consists of a circular mesh made of nitinol, a metal alloy of nickel and titanium, covered with a thin silicone layer.

Because of its biocompatibility, corrosion resistance, and memory-shape properties, nitinol is a commonly used compound in implantable medical devices [2]. Nitinol is composed of approximately 54.5–57% nickel by weight percent [2, 3]. Nickel is known as the most common metal sensitizer, and therefore, the use of nitinol in medical implantable devices raises the concern of nickel ion release which might lead to adverse health effects, especially in nickel-sensitized individuals [3].

Release of nickel ions from nitinol implants has been studied with Amplatzer septal occluders, cardiac implants used to close atrial septal defects. Several studies, both in vitro and in vivo, have shown that these implants release nickel ions [4–6]. However, it remains unclear if there is a cause-effect relation between this release and the occurrence of complications, or if this release has any clinical relevance in general. The amount of nickel ions that are released from EBVs might be different from other nitinol-containing devices as the amount of nickel that leaches from a device is dependent on multiple factors related to the manufacturing process and the environment in which the device is implanted [2, 3]. Furthermore, the nitinol frame of EBVs is mostly covered by silicone, preventing nickel ion release, which is not the case with Amplatzer septal occluders. However, it has been shown that the surface area of the EBV is not always completely covered with silicone [7, 8].

To date, only one in vitro study has assessed the release of nickel ions from EBVs. This study found a significant release of nickel in the first 48 hours, which did remain below the toxic level (for oral intake of nickel) [7]. However, it remains unknown if these results resemble the in vivo situation, especially because the implantation environment can influence the amount of nickel that can leach from nitinol devices. Therefore, we assessed the nickel concentration in surgically removed lung tissue from a patient previously treated with EBVs and compared this to the nickel concentration in lung tissue from a control sample (non-EBV patient) and nickel concentrations in lung tissue reported in the literature.

Case Report

Our EBV lung tissue sample was retrieved from a 63-year-old female COPD patient with predominately lower lobe emphysema. She had a pre-treatment FEV_1 of 29% of predicted, residual volume (RV) of 230% of predicted, and 6-min walk distance of 404 m and was treated with EBVs in the right lower lobe. After treatment, she developed a complete lobar atelectasis and showed clinical meaningful improvement in pulmonary function and exercise capacity (FEV_1 +250 mL, RV −830 mL, and +61 m on the 6-min walk test). One year after the initial treatment, a revision bronchoscopy was performed due to loss of treatment effect. Severe granulation tissue formation was observed, and all valves were temporarily removed to allow the airways to recover. After 3 months, EBVs were replaced, which again resulted in a clinical meaningful benefit. One and a half years after the second EBV placement, the patient reported repeated episodes of hemoptysis. A bronchoscopy showed that this was caused by new granulation tissue formation, and after a few months, it was decided to permanently remove all EBVs. Subsequently, the patient underwent lung volume reduction surgery by performing a right lower lobe lobectomy via video-assisted thoracoscopy surgery with again good outcomes.

Out of the removed lung lobe, four tissue samples from two different anatomical locations (both in the exact area where EBVs were previously implanted) were selected. The samples were deparaffinized, weighed, solved in 0.5 mL 65% HNO_3, and diluted with H_2O to a total volume of 1.5 mL. The nickel concentration in all four tissue samples was measured in fourfold: two baseline replicates, one replicate enriched with 10 μg/L nickel, and one replicate enriched with 20 μg/L nickel. Inductively coupled plasma mass spectrometry (ICP-MS) was used to measure the nickel concentration in each of the samples. For the reference sample, three lung tissue samples were used from a patient who was never treated with EBVs or any other lung implant and analyzed in the same manner. The median nickel concentration in the EBV samples (0.270 μg/g, range 0.000–0.905) was not significantly different from the median concentration found in the reference samples (0.328 μg/g, range 0.148–0.542, $p = 0.693$ [Mann-Whitney U test]) (Fig. 1).

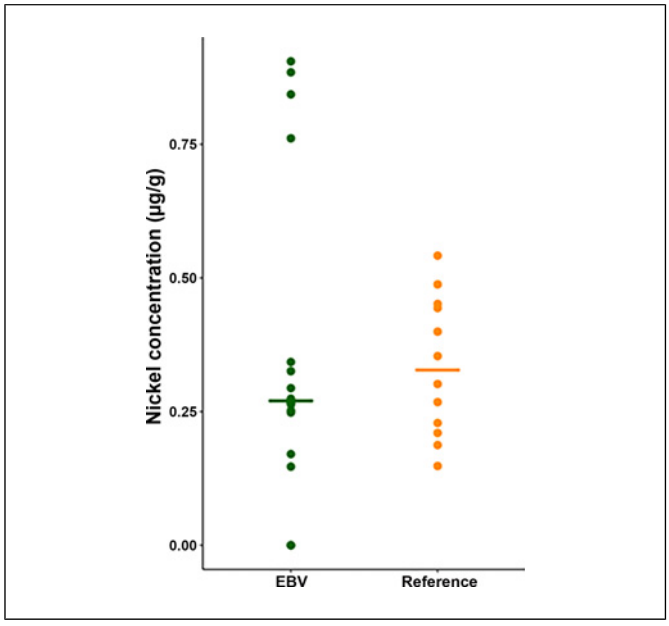

Fig. 1. Nickel concentrations in the lung tissue samples of the patient treated with EBV and the reference patient. Data are shown as individual measurements (points) and median (line). There was no significant difference in the median between both samples (p = 0.688; Mann-Whitney U test).

Discussion

In this case report, we identified that the nickel concentration in lung tissue was similar between a patient that was previously treated with EBVs and a patient never treated with any lung implant. Furthermore, the concentrations in our study were comparable to previously published nickel concentrations in lung tissue from both cancerous and noncancerous individuals never treated with lung implants, which ranged from 0.221 to 1.77 µg/g [9, 10]. In our analysis, one of the samples showed a substantial higher nickel concentration compared to all other samples. Most likely, this is due to normal variability of the nickel concentration in the lungs since the values were within the "normal ranges" reported in the literature.

A previous in vitro study found that EBVs only released a significant amount of nickel in the first 48 h after immersion in artificial saliva [6]. If this is representative for the in vivo situation, it is possible that the release of nickel was already "completed" in the patient from whom the lung tissue samples were taken and that nickel was already cleared by the immune system. However, it is likely that the in vitro finding is related to saturation of the used medium by nickel ions since there is no good physiological explanation for why nickel release will end after 48 h. Furthermore, if nickel release from EBVs does in fact stop after 48 h of implantation, the results would have been different for new and explanted EBVs. However, if EBVs do release a substantial amount of nickel ions and saturation of the medium was the problem with the in vitro experiment, nickel release will continue for a longer period of time within the lungs of a patient.

Studies testing the serum nickel concentration in patients treated with an Amplatzer septal occluder found a significant increase in the nickel concentration in the serum which returned to baseline values within 3–6 months after treatment [4, 5]. It is thought that this "normalisation" of the serum nickel concentration is associated with the endothelization of the device because this also takes around 3–6 months. EBVs, however, are not or barely endothelialized, which will probably affect the amount of nickel released and the duration of the release. Nevertheless, it is still possible that in the first weeks or months after treatment, the nickel concentration was significantly higher in lung tissue of the EBV-treated patient, which was not assessed in our study since the time between the last EBV procedure and LVRS was 27 months. It might, therefore, be interesting to repeat the analysis with lung tissue samples from patients in whom time between the last EBV implantation and surgery is only several weeks or months; however, this situation is not common in clinical practice; or to determine the (serum) nickel concentration at multiple timepoints after EBV treatment.

In conclusion, no evidence was found for significant nickel deposition in lung tissue more than 2 years after treatment with EBVs. This could suggest that EBVs do not release significant amounts of nickel in vivo and that patients with known nickel hypersensitivity can probably safely undergo treatment with EBVs. However, it could also be that EBVs only release nickel ions in the first period after implantation, of which the duration is unknown. It might, therefore, be of interest to perform a prospective study to assess the nickel release from EBVs in a larger cohort using serum, sputum, bronchoalveolar lavage fluid, or local biopsies to get a deeper understanding of the nickel release from implanted EBVs.

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Statement of Ethics

The patient described in this case report has given written informed consent for the usage of their tissue for the performed analysis, publication of this case report, and any accompanying images. The published research complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. Research on human tissue does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO), and therefore, formal ethics approval was not obtained.

Conflict of Interest Statement

Dirk-Jan Slebos, Simon D. Pouwels, and Karin Klooster have received financial support from PulmonX, outside the context of the current analysis. Sharyn A. Roodenburg and Daan J. Touw have no conflicts of interest to disclose.

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Author Contributions

Sharyn A. Roodenburg was responsible for conceptualization of the case report, data collection and analysis, and drafting of the manuscript. Simon D. Pouwels, Karin Klooster, and Dirk-Jan Slebos were responsible for conceptualization of the case report, assistance with data collection and analysis, and review of the manuscript. Daan J. Touw was responsible for the ICP-MS measurements and review of the manuscript.

Data Availability Statement

All data collected in the context of this study are reported in this case report. Additional requests for data can be directed at the corresponding author.

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