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An endomicroscopic OCT for clinical trials in the field of ENT

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ABSTRACT

Changes in the structure of the nasal mucosa can be a morphological biomarker and therefore helpful for diagnosis and follow-up of various pulmonary diseases such as asthma, cystic fibrosis and primary ciliary dyskinesia. In order to verify that microscopic optical coherence tomography (mOCT) is a valuable instrument for the investigation of those changes, an endoscopic OCT system with microscopic resolution (emOCT) was developed and built for clinical testing. The endoscope is based on a graded-index (GRIN) lens optic and provides a calculated lateral resolution of 0.7 µm and an axial resolution of 1.25 µm. The imaging depth was up to 500 µm in tissue; axially, a lateral range of approximate 250 µm could be covered. B-scans were acquired at 80 Hz with 512 pixels in lateral and 1024 pixels in depth-direction. The diameter of the endoscope decreases over a length of 8 cm from 8 mm at the beginning to 1.4 mm at the end and is small enough to observe the mucous membrane in the human *nasal concha media and inferior* down to the nasopharynx. The emOCT workstation was designed to meet German electrical, optical and biological safety standards. The applicability of the endoscope could be demonstrated *in vivo*. Mucus transport, glands, blood and lymphatic vessels could be visualized.

Keywords: OCT, endoscope, microscope, mucus-transport, nasal concha, in vivo, clinical study

1. INTRODUCTION

Pulmonary diseases such as asthma, cystic fibrosis and primary ciliary dyskinesia significantly reduce the quality of life and also reduce life expectancy. Indicators for these diseases are changes in the mucus membrane in the respiratory tract and of the mucus itself. Besides the microbiological examination of the mucus membrane, the examination of the transport of the mucous and the movement of the cilia are of interest. In previous works, the cilia movement and mucus transport were examined on excised prepared mouse trachea [1], *in vivo* on mouse trachea [2] and *in vivo* on swine trachea [3]. Recently, we present first *in vivo* measurements on humans[4]. Now, as part of the research community *Deutsche Zentrum für Lungenforschung* (DZL), a device for a clinical study was built. The aim of the study is the *in vivo* observation and investigation of cilia movement and mucus transport in the human nasal concha. The design of the endoscope presented in [4] has been modified to fit to a commercial OCT hand probe. The endoscope was extended with a 4f-optic to be long enough for the human *nasal concha* including the nasopharynx. To meet technical standards for the electrical, optical and biological safety of the volunteers, a custom measurement setup including an emOCT system, a measurement PC and safety circuits were designed and built up. Mucus transport, glands, blood and lymphatic vessels have been observed in the inferior and middle *nasal concha*.

2. MATERIAL AND METHODS

2.1 OCT-System

The emOCT system (see Figure 1) uses a supercontinuum white light source (SuperK Extreme-OCT, NKT Photonics, Denmark) equipped with a spectral splitting filter (SuperK SPLIT, NKT Photonics, Denmark). A 75:25 beam splitter connects the light source and the camera/spectrometer unit on the left hand and the reference as well as the probe arm on the right hand. A customized 400 nm bandwidth spectrometer (Thorlabs GmbH, Germany) including a CMOS line scan camera (Piranha4, Teledyne DALSA Inc., Canada) with a resolution of 2048 pixels and a maximum line rate of 100 kHz detects the interference spectrum. In the reference arm, the light was collimated and guided through a variable iris for

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adjusting the reference intensity and customized dispersion compensating SF57 substrate (Casix Inc., China) onto a retroreflector. For reasons of laser safety, one percent of the light in the sample arm is decoupled into a safety circuit via a fiber coupler. The safety circuit consisting of an amplified silicon detector (PDA36A-EC, Thorlabs Inc., USA) and a limit switch (GW4, LEG Industrie-Elektronik GmbH, Germany) which was connected to the interlock switch of the light source. The OCT scanner is a customized MEMS hand probe (OCTH-900, Thorlabs GmbH, Lübeck, Germany) assembled with a custom build endoscope. The endoscope optic was simulated with OpticStudio (Zemax, U.S.) and consists of a relay optic (4f-optic) (#49-315, Edmund Optics, U.S.), a scan lens (#49-305, Edmund Optics, U.S.) which focused into a low NA relay GRIN lens followed by the collimating GRIN rod lens. The GRIN lenses are custom made (Grintech GmbH, Germany). The GRIN lens was glued into a rigid steel tube with an outer diameter of 1.4 mm. In order to reduce parasitic reflections, the outer surface of the lens was 4° polished. Driving voltage of the MEMS mirror was controlled by a data acquisition box (NI-USB- 6251, National Instruments, Germany), triggering and acquisition were done by a frame grabber card (PCIe-1433, National Instruments, Germany).

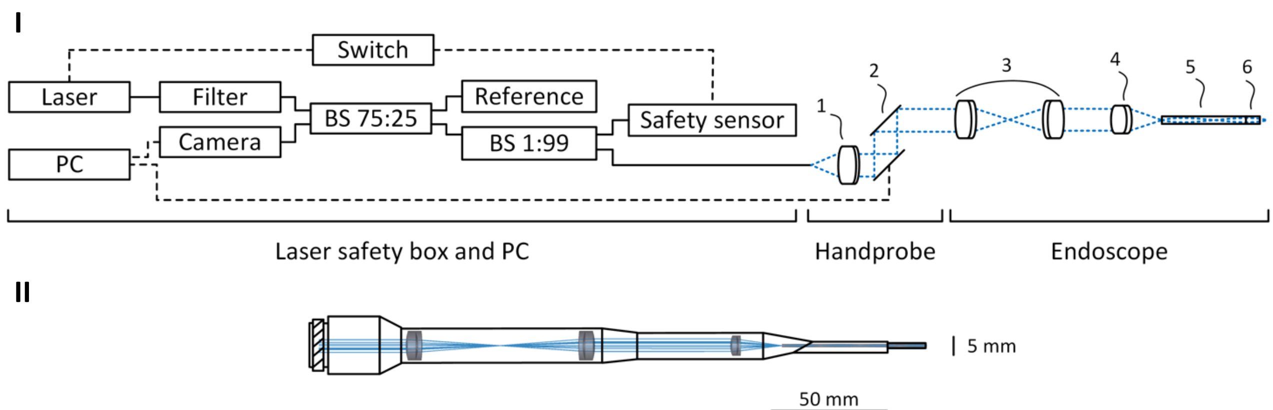

Figure 1: I - Electro-optical scheme of the relevant set-up components. Solid lines: optical fiber, dotted lines: beam optics, dashed lines: electrical wires, furthermore: 1 – collimator, 2 – MEMS-mirror and deflecting mirror, 3 – relay-optic, 4 – scan lens, 5 – low NA relay GRIN lens, 6 – collimating GRIN rod lens. II – Beamline and cross section sketch of the endoscope, lengths in mm.

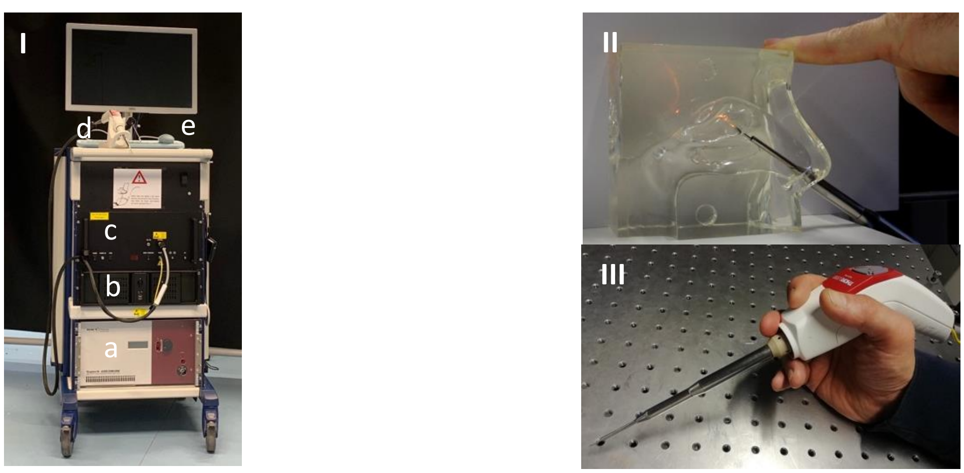

Figure 2: I - Image of the complete clinical set-up including the light source (a), the PC (b), the laser safety box (c), the hand probe (d) and the peripheral equipment (e). II – Image of the endoscope tip in a model nose. III – Image of the MEMS hand probe and the endoscope.

The calculated optical resolution was 0.7 µm in lateral and 1.25 µm in axial direction. B-scans were acquired at a rate of 80 Hz with a resolution of 512 in x and 1024 pixel in z direction. OCT images were processed and visualized by the ThorImage software (Thorlabs GmbH, Germany). The whole system, except the hand probe was mounted on a moveable rack. Electrical safety was covered according to the IEC 60601-1[5] and optical safety according to the 60825-1 [6]. The system meets the requirements for a Group 1 product according to MPG and Class 1M according to the 60825-1.

The diameter of the endoscope tip decreases over a length of 8 cm from 8 mm at the beginning to 1.4 mm at the end and is small enough to observe the mucous membrane in the inferior and middle *nasal concha* (proximal and distal), as well as in the pharynx. This was tested in an anatomically correct model, see Figure 2 – II. Figure 2 – III shows the OCT hand probe including the endoscope.

3. RESULTS AND DISCUSSION

3.1 Ex-vivo measurements

Prior to in-vivo measurements, measurements were done using freshly excised mouse trachea. For this, female C57BL/6 mice were used (Charles River Laboratories, Sulzfeld, Germany); the preparation and use of trachea was well described in [7].

Figure **3**-A shows a single B-scan which includes the epithelia layer, connective tissue, cartilage and lymphatic and/or blood vessels.

Figure **3**-B shows a z-projection (Fiji [8], 100 images, max intensity) of a part of the epithelia layer. The blurred area on the top of the epithelia layer indicated cilia movement.

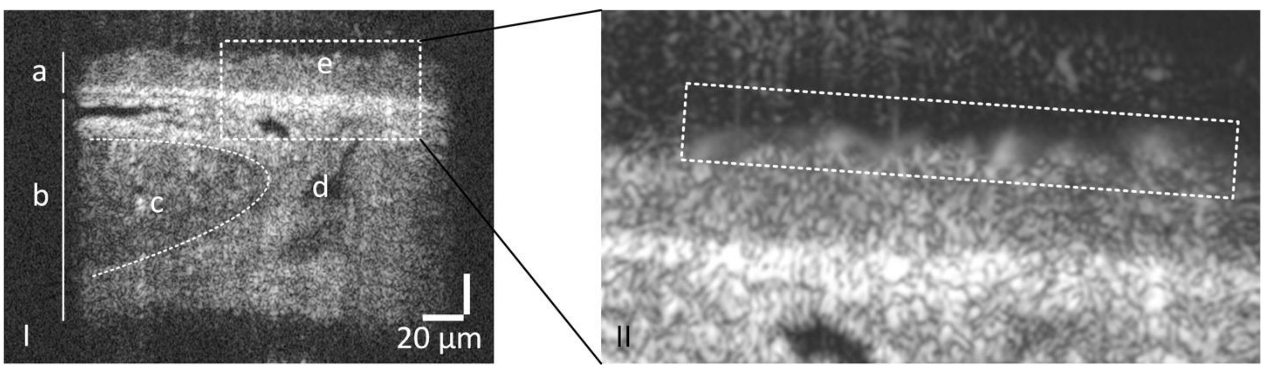

Figure 3: Mouse trachea. I: Lumen of trachea: a - epithelia, b - connective tissue, c - cartilages, d - lymphatic and/or blood vessels, e - cilia. II: In the upper area cilia movement.

3.2 In vivo measurements

First *in vivo* measurements were done by a physician on a volunteer in the ENT clinic of the Universitätsklinikum Schleswig-Holstein. During this trial, the vestibule of the nose, the inferior *nasal concha* and the middle *nasal concha* were imaged; the pharynx was not reached at all volunteers due to anatomical conditions. The measurements were carried out without further aids, such as a video endoscope.

A nasal speculum helps the physician to guide the endoscope and to reduce the tremor.
Figure 4 shows results of the measurement in the inferior and middle *nasal concha*; here, mucus, glands and lymphatic vessels could be shown. The bright line at the top of the images is the end face or GRIN lens; to the left and right of the visible tissue are shadings due to construction.

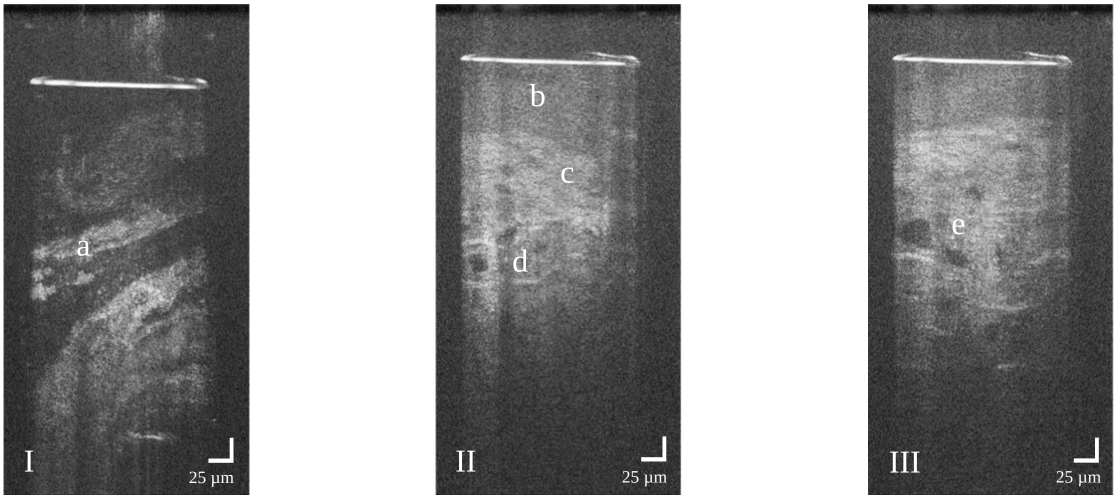

Figure 4: I - mucus, II - glands, both in the inferior *nasal concha*, III - lymphatic vessels, in the middle nasal concha; a – mucus, b – epithelia tissue, c – connective tissue, d - glands, e - lymphatics vessels.

4. CONCLUSION

The emOCT presented in this paper is applicable for *in vivo* measurements in the inferior and middle nasal concha. The axial and lateral resolution are sufficient to show mucus transport, details of the epithelium (glands, blood and lymph vessels) are visible. In case of a fixed probe it is possible to observe cilia movement. The system meets the technical standards for the electrical, optical and biological safety, the approval process as a research device in the clinical environment will begin soon.

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