Bronchoscopic Indocyanine Green Fluorescence Imaging of the Anastomotic Perfusion After Tracheal Surgery

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Background. **Anastomotic failure is a rare but severe complication after airway surgery. A sufficient blood supply is crucial for the healing of the anastomosis. Currently, judging the appearance of the mucosa by conventional bronchoscopy is the only available technique to monitor the anastomosis. Near-infrared imaging using indocyanine green (ICG) as an intravasal fluorescent can be used to directly assess tissue perfusion. For technical reasons, bronchoscopic ICG angiography to evaluate blood supply of airway anastomosis was unavailable in the past. We sought to investigate the technical feasibility of ICG perfusion using a newly developed bronchoscopy unit with an integrated near-infrared filter to monitor perfusion during the healing of tracheal anastomosis.**

Methods. **Twelve patients who underwent elective airway surgery were included in this prospective, single-center feasibility study. The ICG was administered intravenously at 0.2 mg/kg body weight at three time-points: at the end of surgery; 3 to 5 days postoperatively; and 2 months postoperatively. A custom-made bronchoscopy unit (Karl Storz, Tuttlingen, Germany) was used to assess the anastomosis with white light and additionally with near-infrared light to monitor the distribution and intensity of the fluorescence signal.**

Results. **A total of 32 ICG fluorescence bronchoscopies were performed in our study cohort. In all measurements, a sufficient fluorescence signal was detected. A lack of perfusion was detected in all patients confined to the anastomotic suture line immediately after the operation. This malperfusion resolved gradually after 3 to 5 days and disappeared completely after 2 months. No anastomotic complication developed in our series of patients during follow-up (median 7 months).**

Conclusions. **To the best of our knowledge, this is the first report on ICG fluorescence bronchoscopy in the literature. It is an easy and effective method to evaluate the perfusion at the tracheal anastomosis. In the future, it might contribute to an early detection of anastomotic failure and reduce morbidity and mortality after airway surgery.**

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Anastomotic complications are a rare but serious problem in surgery of the central airways. They occur in approximately 4% to 9% of cases after tracheal resection [1–5]. Grillo and colleagues [6] described several anatomic characteristics that make tracheal resection and reanastomosis challenging, including the limited longitudinal elasticity and the largely segmental blood supply. In addition, several clinical risk factors associated with postoperative anastomotic failure were identified, including resection length 4 cm or greater, preoperative tracheostomy, age 17 years or more, diabetes mellitus, reoperation, and laryngotracheal resection [1]. Circumferential dissection of the trachea can lead to malperfusion of the tracheal tissue at the anastomotic site [6]. As a result of this malperfusion, infection, leakage, dehiscence, or complete separation of the anastomosis may follow later. Long-term sequelae of an impaired perfusion, such as malacia or restenosis by extensive scar formation, limit the functional long-term outcome after surgery. Thus, a sufficient postoperative blood supply of the remaining trachea is crucial for a successful procedure. Currently, conventional bronchoscopy is the only available imaging modality to judge on the viability of the mucosa at the anastomotic site. It is limited by a difficult interpretation dependent on the experience of the surgeon and is therefore subjective until obvious tissue damage occurs.

Indocyanine green (ICG) is a fluorescent dye with various applications and is widely used in medicine. It is mainly applied for noninvasive angiography in

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ophthalmology and the evaluation of tissue perfusion [7–10]. Indocyanine green was approved by the Food and Drug Administration as a diagnostic substance in the late 1950s. It is plasma protein bound after intravenous injection with rapid biliary excretion [11]. The half-life is approximately 150 to 180 seconds. ICG absorbs between 600 nm to 900 nm and emits between 750 nm to 950 nm with a maximum at 800 nm, which allows a very specific measurement of the emitted near-infrared light with special optical devices. Owing to the highly plasma-bound state of ICG after injection and strong fluorescence, perfused tissue can be visualized and clearly distinguished from tissue with no blood flow. To the best of our knowledge, near-infrared imaging has never been used to assess the anastomotic perfusion in patients undergoing tracheal resection. Therefore, we aimed to assess the feasibility of ICG bronchoscopy to monitor the blood supply of the anastomosis in airway surgery.

Material and Methods

Study Cohort

From January 2014 to July 2015, 12 consecutive eligible patients receiving airway surgery at the Medical University of Vienna were included in this study. Inclusion criteria were age 18 years or more, written informed consent, and elective laryngotracheal surgery at the Division of Thoracic Surgery, Medical University of Vienna. Exclusion criteria were age greater than 80, pregnancy, renal or hepatic failure, previous tracheal surgery, known allergy (ICG or iodide), hyperthyroidism/hypothyroidism, active hematologic disease, significant comorbidities, and participation in other clinical studies. The study was approved by the Institutional Ethics Committee (EK 1250/2013) and by national authorities. Written informed consent was obtained from all patients before study participation. The study was registered at EUDRACT (#2013-001725-10) and EUDAMED (#CIV-AT-15-06-013636).

Preoperative Evaluation and Surgical Technique

All patients were referred to a dedicated, interdisciplinary team consisting of thoracic surgeons, otolaryngologist, speech therapists, and anesthesiologists. Preoperatively, all patients underwent flexible tracheoscopy under general anesthesia. By variation of the depth of anesthesia, dynamic obstructions were documented. Total length of the trachea, height and precise dimensions, and type and extension of the airway problem were documented. Functional assessment included spirometry, transnasal flexible laryngoscopy, and evaluation of respiration, swallowing, and phonation. The majority of patients had a cricotracheal stenosis (n = 7), 4 patients were operated on for an airway tumor, and 1 patient had a symptomatic retrotracheal cyst. We performed a cervical tracheal resection with an end-to-end anastomosis in 5 cases. In 4 patients, a classical cricotracheal resection (Grillo technique) with a thyreotracheal anastomosis was utilized. In 1 patient, an intrathoracic tracheal resection was performed through a right posterolateral thoracotomy; the remaining 2 patients underwent carinal resection and reconstruction for tumors involving the carina. The mean length of the resected airway was 31 mm (range, 20 to 55 mm). Anastomosis was performed using a running 4-0 polydioxanone suture for intrathoracic resections/reconstructions. For cervical resections, the posterior airway was anastomosed using a 5-0 polydioxanone running suture and interrupted 4-0 and 3-0 polydioxanone stitches for the cartilaginous parts. Complications were recorded in 2 patients. One patient had dysphagia with aspiration and transient acute renal failure during his prolonged postoperative course. After intensive swallowing training he completely recovered. One patient had new-onset atrial fibrillation postoperatively, which was successfully treated with amiodarone.

ICG Bronchoscopy

The ICG bronchoscopy unit (Karl Storz Endoscopy, Tuttlingen, Germany) comprised a cold light fountain D-LIGHT P (#20133720-1), fluid light cable (495FR), full HD camera head (#22220085-3), a custom made near-infrared filter, and a bronchofiberscope (#11009BC1). For video documentation, a media hub was connected to the bronchoscopy unit (#22201020-112; Karl Storz Endoscopy).

The patients were assessed at three timepoints. The baseline assessment was immediately after finishing the anastomosis (postoperative day 0), the second assessment was before discharge from hospital (postoperative days 3 to 5), and the last measurement was during a follow-up examination 2 months after surgery. Before bronchoscopy, monitoring devices of the vital parameters were attached, patients received sedation with propofol, and a laryngeal mask was inserted. At each session, the anastomosis was documented with standard white light and also in the ICG fluorescence mode. The ICG (ICG Pulsion; Pulsion Medical Systems, Munich, Germany), 0.2 mg/kg body weight, was injected intravenously. The light source was then switched to ICG mode, and the dynamic distribution of the dye at the anastomotic site was recorded.

Image Analysis

The obtained images and videos were processed using ImageJ (National Institutes of Health, Bethesda, MD) [12]. Heatmaps illustrating the fluorescence intensities were generated by conversion of the fluorescence images into 32-bit gray scale images. These gray scale images were then translated into heatmaps using a preset lookup-table (fire).

Fluorescence intensities were measured by comparing regions of interests (ROIs) in the area of anastomosis immediately after the perfusion reached the peak fluorescence in 32-bit gray scale images. An aspect of the anastomosis with a circumferential ring of healthy mucosa (reference ROI) proximal to the anastomosis was used for the comparison of the fluorescence intensities. The ROI of the anastomosis was defined as the circumferential area between the suture line. We calculated the mean fluorescence intensity in the ROIs using ImageJ.

The signal intensity in the control ROI was the reference intensity in each examination and therefore corresponded to 100% relative fluorescence intensity. Fluorescence intensity at the level of the anastomosis was expressed as percent of the reference fluorescence intensity in each examination.

The dynamic changes were assessed and included 11 examinations (3 at postoperative day 0, 4 at postoperative days 3 to 5, and 4 examinations 2 months after surgery) by transducing the obtained videos into 32-bit gray scale image stacks and measuring of ROIs at areas of healthy airway mucosa as described above.

Results

Twelve patients were included in this prospective, single-center feasibility study. Median age was 57 years (range, 45 to 74). A detailed description of the study cohort is provided in Table 1. As the authors had no experience with this novel method, the first measurement was carried out in a patient at the last timepoint with an already well-healed anastomosis. One patient had to be excluded from the study before the last measurement owing to acute renal failure. One patient died 2 months after surgery because of sudden cardiac arrest at home, which was unrelated to the surgery. Patient characteristics are summarized in Table 1. In total, 32 examinations were performed using a novel near-infrared bronchoscopy unit (Fig 1). The blood pressure (RR) was monitored during the procedures and did not differ significantly among the three timepoints. For postoperative day 0, days 3 to 5, and 2 months after surgery, respectively: $RR_{systolic}$ mean ± SD/$RR_{diastolic}$ mean ± SD was 118.2 ± 19.9/66.4 ± 14.8 mm Hg; 117.4 ± 12.7/66.6 ± 9.8 mm Hg; and 106.3 ± 16.5/60.7 ± 10.4 mm Hg (analysis of variance $p = 0.226$ for $RR_{systolic}$ and $p = 0.275$ for $RR_{diastolic}$).

Severe adverse events related to the ICG injection were not observed. The fluorescence signal appeared 10 to 15 seconds after injection, and the intensity gradually increased at the airway mucosa until it peaked after a further 7 to 13 seconds (Fig 2A). Fifty percent fluorescence intensity was reached after 5.72 seconds (95% CI: 4.92 to 6.52). After the peak intensity, the fluorescence signal slowly decreased and was detectable for more than 5 minutes (Fig 2B). Image resolution was sufficient to demonstrate perfusion of the transverse intercartilaginous arteries branching into the submucous capillary plexus (Fig 3).

Immediately after surgery, anastomoses presented as a dark ring in the fluorescence mode, whereas the mucosa looked healthy in the standard bronchoscopy (Fig 4 and Supplementary Video). This circumferential decrease of fluorescence signal was still evident at the second timepoint (3 to 5 days after surgery). Moreover, the mucosa next to the anastomosis appeared hyperperfused. Two months after surgery, anastomoses were well healed as observed by conventional bronchoscopy. Also in the ICG fluorescence mode, the anastomoses appeared well perfused. Fluorescence intensities were measured using ImageJ. The fluorescence intensity at the anastomosis was 66.2% ± 10.0% immediately after surgery, which increased to 82.3% ± 7.4% on postoperative days 3 to 5, and finally reached 107.4% ± 6.0% after 2 months, which corresponds to a hypervascularized mucosa confined to the anastomosis (Fig 2C). We did not observe any anastomotic complications in our study cohort during the follow-up (median 7 months; range, 1 to 19).

Comment

Herein, we report our initial experience with ICG fluorescence bronchoscopy in patients undergoing tracheal

Table 1. Clinical Characteristics of Included Patients (n = 12)

Pt. No.	Sex	Age (years)	Diagnosis	Type of Resection	Resection Length (mm)	Examination			Complications
						First	Second	Third	
01	M	49	Idiopathic stenosis	TR	25	…	…	x	None
02	F	45	Idiopathic stenosis	TR	25	x	x	x	None
03	M	75	PT stenosis	CTR	40	x	x	…	Dysphagia, tracheostomy, pleural effusions, acute renal failure
04	F	52	ACC	TR	32	x	x	x	None
05	M	74	ADC	CR	NA	x	x	x	None
06	M	68	SCC	SP	20	x	x	…	None (died of cardiac arrest 2 months after surgery)
07	F	47	RT cyst/malacia	TR	22	x	x	x	None
08	M	61	SCC	TR	30	x	x	x	None
09	F	38	Postintubation stenosis	LTR	NA	x	x	x	None
10	F	65	Idiopathic stenosis	CTR	30	x	x	x	None
11	M	29	PT stenosis	CTR	55	x	x	x	None
12	M	67	PT stenosis	TR	30	x	x	x	None

ACC = adenoid cystic carcinoma; ADC = adenocarcinoma; CR = carina resection; CTR = cricotracheal resection; F = female; LTR = laryngotracheal resection; M = male; PT = posttracheostomy; Pt. No. = patient number; RT = retrotracheal; SCC = squamous cell carcinoma; SP = sleeve pneumonectomy; TR = tracheal resection.

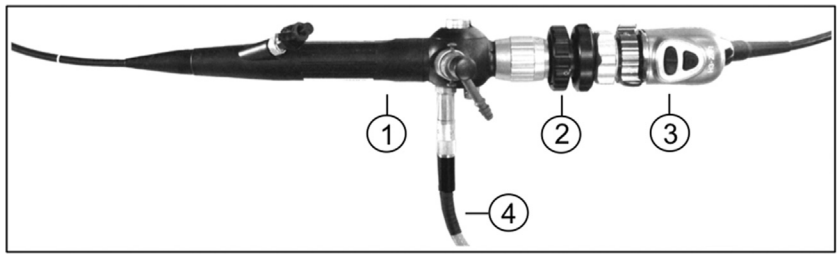

Fig 1. The used indocyanine green bronchoscopy unit comprising (1) a flexible bronchofiberscope, (2) a near-infrared filter, (3) a high- definition camera head, and (4) a fluid light cable connected to standard white light/near-infrared light source.

surgery. The rather complex vascular supply of the trachea makes tracheal surgery challenging. Arteries mainly originate from the inferior thyroid arteries, and the internal thoracic arteries and bronchial arteries anastomose longitudinally in the lateral tracheoesophageal groove. Transverse intercartilaginous artery branches provide the segmental blood supply to the submucous plexus, which is crucial for the viability of the cartilage [13]. Therefore, care should be taken to preserve airway perfusion during dissection of the trachea. A denudation of the trachea should be avoided and lateral dissection should be performed with great care to spare the blood vessels running in the tracheoesophageal groove. Impaired blood supply and subsequent tissue ischemia are the basis for anastomotic complications. Therefore, a quantification of the tissue perfusion at the level of the anastomosis is valuable information in airway surgery. Currently, the anastomoses are judged by white-light bronchoscopy. Perfusion can only be indirectly assessed by evaluating the quality of the mucosa. Often only late consequences of a lack of perfusion can be found: necrosis at the site of the anastomosis and partial or complete dehiscence. Diagnostic tests or imaging modalities, which allow early detection of anastomotic malperfusion, are currently lacking.

An ICG-based technique similar to the one reported in this study has previously been used to investigate the local anastomotic microcirculation in patients after colorectal surgery [10, 14, 15]. Jafari and colleagues [10] reported, in a retrospective analysis of patients receiving low anterior resection of the rectum, anastomotic failure of 18% in the control group with conventional assessment. In the other patient subgroup, the planned transection line was assessed with ICG perfusion and corrected according to the findings during ICG measurement, which led to a failure rate of only 6% [10]. The findings of this initial report were recently confirmed by a multiinstitutional feasibility trial with 139 eligible patients. Anastomotic complications occurred in only 2 patients (1.4%). The ICG fluorescence angiography was technically successful in 99% and safe in 100%, which underlines the minimal learning curve to use these devices [16]. The results are comparable to our work with 100% successful ICG assessments and no severe adverse events. In patients receiving resection of the colon, anastomotic leakage was observed in 3.5% of patients undergoing additional intraoperative ICG perfusion measurement compared with 7.5% of the patients receiving standard treatment. Most strikingly, especially the subgroup of patients receiving hand-sewn anastomoses had a benefit of the additional perfusion measurement (revision rate 1.2% versus 8.5%) [15]. Various other applications of ICG fluorescence measurement

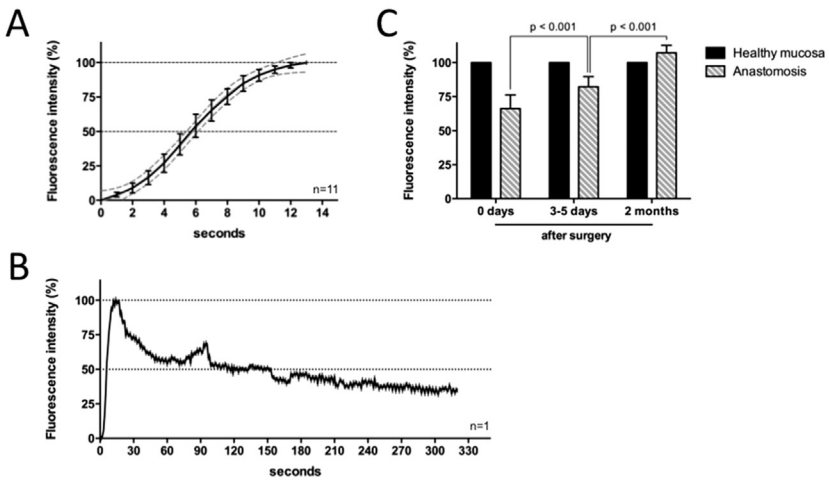

Fig 2. (A) Dynamic changes of the fluorescence intensity (n = 11). (B) After reaching the peak fluorescence, the airway can be assessed for several minutes with slowly decreasing levels of fluorescence intensity. (C) Temporal changes of the fluorescence intensity at the anastomosis (hatched bars) in relation to the healthy mucosa (solid bars [control]) immediately after surgery (n = 11), 3 to 5 days (n = 11), and 2 months (n = 10) after the surgical procedure.

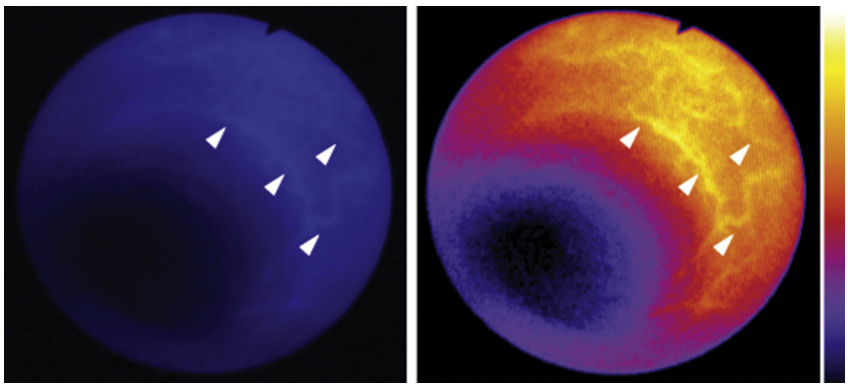

Fig 3. Imaging of the submucousal capillary plexus (arrowheads). The resolution of the bronchoscopy unit is sufficient to detect single perfused capillaries (left). After translating the fluorescence intensities to a heatmap, the perfusion of the submucousal plexus is clearly visible (right).

have been described in the literature. First experiences in cardiothoracic surgery with this method have been previously made [17–20]. For example, Anayama and colleagues [20] used ICG injected bronchoscopically into pulmonary nodules as a localization technique to identify these nodules afterwards during video-assisted thoracic surgery.

Regarding tracheal anastomoses, Iga and associates [21] aimed to assess tissue ischemia by another bronchoscopic technique. The investigators measured the autofluorescence in the central airways of tracheal autografts in a pig model. The autofluorescence signal was increased in the transplanted grafts. This phenomenon was explained by the autofluorescence of elastin fibers in the submucosa, which became more exposed owing to the detachment of the epithelial lining [21]. An obvious limitation of this method is that it measures the change in tissue quality, which is the delayed result of the perfusion deficiency. The clinical value of autofluorescence in the detection of ischemia of central airway anastomoses needs further clarification in human studies.

This work is the first description of ICG fluorescence imaging using a flexible endoscope. Repeated measurements after tracheal resection were performed. We could demonstrate a perfusion deficiency confined to the anastomotic suture line, which gradually decreased after surgery. As this localized malperfusion was observed in all patients and anastomotic complications did not occur in our study cohort, a limited degree of malperfusion does not seem to have a negative impact on the outcome after tracheal surgery. A meticulous preservation of the tracheal blood supply was performed in all of our patients. We believe this is the main reason why no healing disorders were observed in our patients. Moreover, our study cohort consisted of mainly healthy individuals with no severe comorbidities owing to the exclusion criteria defined in the study protocol.

There are several limitations to our study. As discussed, no anastomotic complications occurred in our cohort but the value of this novel technique to predict anastomotic failure needs to be clarified in studies with larger patient cohorts. Next, the analysis of the obtained images and videos needs to be further standardized with software tailored to this novel application of fluorescence imaging to make the results comparable between different studies. Furthermore, subsequent studies are warranted to clarify whether this method can distinguish between malperfusion confined to the mucosa versus full-thickness perfusion defects of the tracheal wall.

Noteworthy, already at postoperative days 3 to 5, correlating with the inflammatory phase of wound healing, a hyperperfused area surrounding the anastomosis became apparent in our patients. This finding is in line with observations in wound healing of injured skin. From day 3 to day 10 after skin injuries, an increased blood flow in the surrounding area can be observed. This increased blood flow is already accompanied by an upregulation of the proangiogenic factors vascular endothelial growth factor A and placental growth factor. These cytokines, which are key mediators of the revascularization during the proliferative phase of wound healing, further increase until day 14 after the initial damage [22].

During bronchoscopic evaluations, we had to switch between white light and near-infrared filtered light. The newest generation of near-infrared endoscopes will provide simultaneous cold light and fluorescence visualization. That makes the application of this novel technique even more attractive. We expect to assess potential improvements (eg, time efficiency, more precise spatial distribution of perfusion defects) in the near future in a subsequent study.

In our cohort, a sufficient fluorescence signal with an analyzable image quality was obtained already at the first attempt. The injected ICG dose of 0.2mg/kg body weight, which is also used for perfusion measurements in other organs, allowed excellent imaging of the central airway perfusion. As ICG fluorescence imaging is easy to conduct and can be combined with standard bronchoscopy, an application of this technique in the daily clinical routine seems possible in the near future. Even before necrosis of the mucosa becomes evident, malperfusion could be treated by drugs improving the microcirculation (rheologicals). Most recently hyperbaric oxygen therapy was found to be a promising technique to treat anastomotic dehiscence after airway surgery [23]. The detection of a significant malperfusion could lead to an initiation of hyperbaric oxygen therapy before a dehiscence

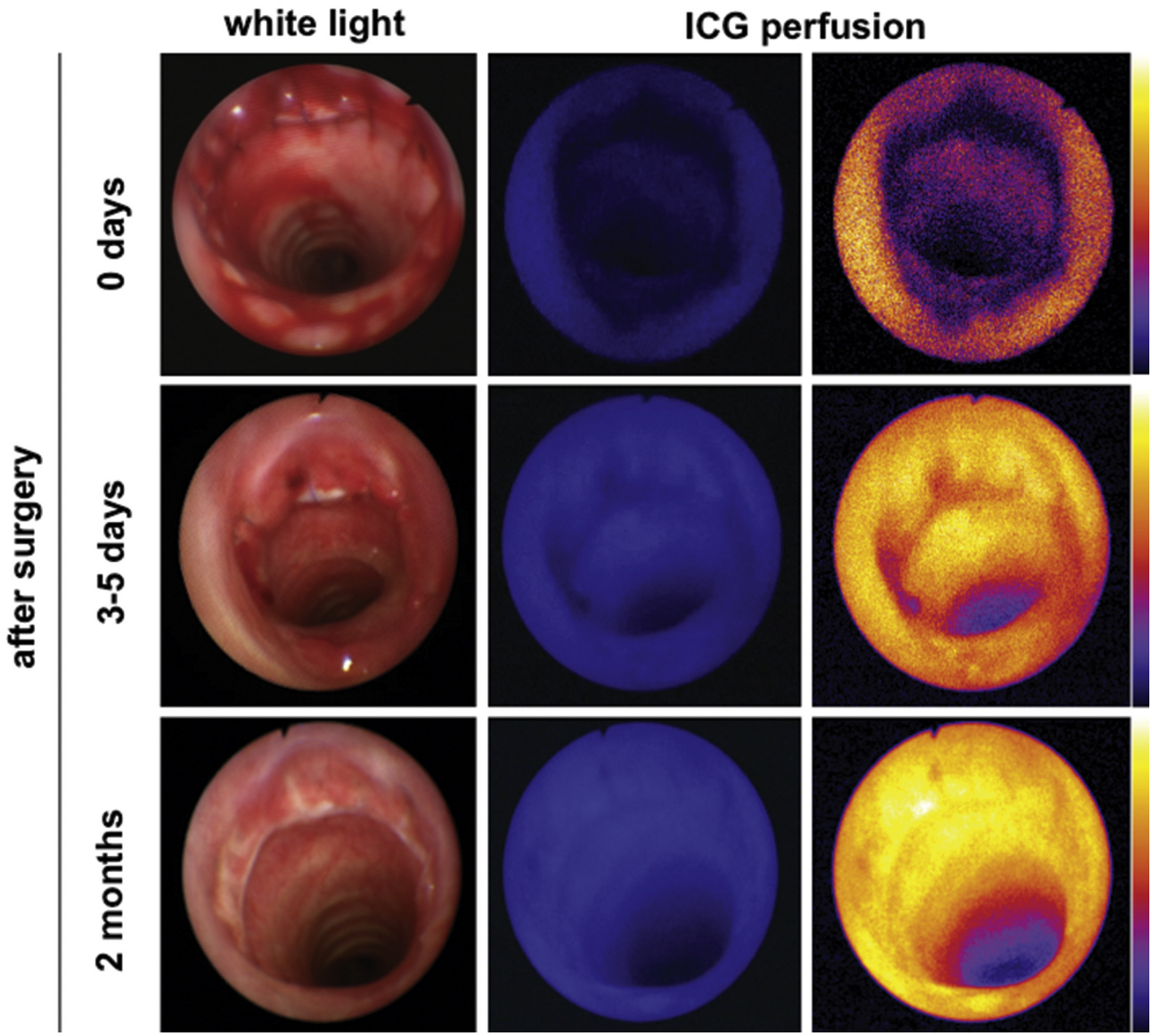

Fig 4. Temporal changes after central airway anastomoses in a representative patient undergoing cervical tracheal resection and end-to-end anastomosis. The mucosa at the suture line appears to be healthy at all timepoint during conventional bronchoscopy (left column). Assessing the anastomosis using the indocyanine green (ICG) bronchoscope shows a perfusion deficiency confined to the suture line, decreasing by time (middle and right columns).

becomes evident. Other possible surgical techniques to minimize the risk of an expected anastomotic insufficiency include the reinforcement of the anastomosis by covering it with healthy tissue (eg, muscle or omental flap) and release maneuvers to decrease the tension on the anastomosis. An intraoperatively detected malperfusion might be a decisive factor for such additional procedures.

Further investigations are needed to clarify how the detected differences of fluorescence intensities after tracheal surgery should be interpreted and whether this novel bronchoscopic technique has further applications in the diagnosis of diseases of the respiratory system.

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