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Article

Autofluorescence bronchoscopy

Avtofluorescenčna bronhoskopija

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Abstract

Autofluorescence is a form of emission of light of longer wave length occurring after a light of a specific wavelength has been applied to bronchial mucosa. The response of malignant and premalignant tissues differs from that of healthy bronchial mucosa. Dysplasia and carcinoma in situ, which are only a few unit cells thick and a few milimeters in diameter, have different fluorophore concentrations and show pathological vascularisation. Early malignant changes, dysplasia and carcinoma in situ are difficult to detect with conventional white light bronchoscopy even by experienced bronchoscopists. Autofluorescence bronchoscopy (AFB) is a very sensitive tool for detecting preneoplastic changes and carcinoma in situ, and yields up to three times more accurate results than light bronchoscopy. The method is performed under topical anaesthesia and prolongs the procedure time by five to ten minutes. The complication rate is similar to that reported for white light bronchoscopy. New techniques have been clinically evaluated with the aim to improve sensitivity and specificity of the method, to simplify the procedure and to objectify the results. AFB facilitates the diagnosis of premalignant changes of bronchial mucosa and early bronchial carcinoma in high-risk patients, and enables clinicians to study carcinogenesis. The method will offer the possibility for treating patients by the endoscopic approach, and promises to improve prognosis in patients with lung cancer. AFB is not used in everyday diagnosis of primary and secondary invasive bronchial carcinoma. Its future use should be restricted to the detection of preneoplastic changes and carcinoma in situ in groups at high risk for the development of lung cancer

Key words. *Autofluorescence bronchoscopy, preneoplastic changes, early bronchial carcinoma, carcinogenesis, endoscopic treatment.*

Izvleček

Avtofluorescenca je oddajanje svetlobe daljše valovne dolžine po osvetlitvi bronhialne sluznice s svetlobo ozko določene valovne dolžine. Maligno in premaligno tkivo se odzove drugače kot zdrava bronhialna sluznica. Displazija in t.i. karcinom in situ sta debela le nekaj celic in merita nekaj milimetrov v premeru, imata pa drugačno koncentracijo fluorofer in patološko žilje. Z običajno bronhoskopijo z belo svetlobo celo izkušeni preiskovalec težko opazi zgodnje maligne spremembe, displazijo in t.i. karcinom in situ.

Avtofluorescenčna bronhoskopija (AFB) z visoko občutljivostjo zazna predneoplastične spremembe in t.i. karcinom in situ. Rezultate bronhoskopije z belo svetlobo izboljša do trikrat. AFB naredimo v lokalni anesteziji, samo preiskavo pa podaljša za 5 do 10 minut. Zapleti so podobni kot pri običajni bronhoskopiji z belo svetlobo. AFB ima nizko specifičnost in je odvisna od osebne izkušenosti bronhoskopista. Zaradi nizke specifičnosti AFB se v kliničnem preizkušanju uveljavljajo nekatere nove tehnike z namenom izboljšati občutljivost in specifičnost ter samo preiskavo in bolje objektivizirali ugotovke.

AFB izboljša sposobnost prepoznavanja predmalignih sprememb bronhialne sluznice in zgodnjega bronhialnega karcinoma pri skupinah bolnikov z visokim tveganjem in omogoča proučevanje nastajanja raka. Ta metoda bo omogočila bolnikom endoskopsko zdravljenje in morda izboljšala napoved izida pri bolnikih s pljučnim rakom.

AFB v vsakdanji diagnostiki primarnega in sekundarnega invazivnega bronhialnega karcinoma ni potrebna. V prihodnje bi jo morali uporabiti samo v raziskavah za ugotavljanje predneoplastičnih sprememb ter t.i. karcinoma in situ pri skupinah prebivalstva z visokim tveganjem za razvoj pljučnega raka.

Ključne besede. Avtofluorescenčna bronhoskopija, predneoplastične spremembe, zgodnji bronhialni karcinom, karcinogeneza, endoskopsko zdravljenje.

Introduction

AFB has proved effective in the detection of dysplastic and preneoplastic changes of the bronchial mucosa, as well as of carcinoma in situ and early invasive bronchial carcinoma in the central bronchi.

AFB exhibits very high sensitivity and low specificity, yet it is not suitable for screening the entire population. None of the currently available lung cancer screening methods has yet succeeded in reducing mortality rates. AFB has not been incorporated into the population screening programs (1).

AFB is a method for screening high-risk population groups with an increased incidence of lung cancer, i.e. individuals smoking for more than 40 years with a cigarette index of > 20; patients after successful resection of lung and upper respiratory tract cancers; persons exposed to radioactive radiation; those with X-ray occult lung cancer T0 (with malignant cells in sputum), patients with suspected lung cancer (2), and patients with bronchial cancer who are suspected of having secondary malignancy (3). In addition, AFB is used for the study of carcinogenesis (4).

Carcinogenesis

Experimental animals developed dysplasia in three to four years, and in the next six months dysplasia progressed to carcinoma in situ (5). The transformation of carcinoma in situ into microinvasive carcinoma in three to four months was observed in a patient evaluated by both conventional bronchoscopy and AFB (6). Other researchers reported on the development of invasive carcinoma in 23% of patients (7).

AFB indicates the site in the changed bronchial mucosa from which bronchial biopsies should be taken.

Pathological classification is as follows: normal mucosa; reserve cell hyperplasia; metaplasia; slight,

moderate, and severe dysplasia; carcinoma in situ; and invasive carcinoma (7). Pathological classification of biopsies taken from preneoplastic changes in the bronchial mucosa is a difficult task, and shows significant interobserver differences.
Conventional white light bronchoscopy is a less sensitive tool than AFB for the detection of premalignant lesions in the bronchial mucosa. Even when performed by an experienced endoscopist its diagnostic yield in carcinoma in situ in only 29% (8).

Technique

AFB was developed from fluorescence bronchoscopy. Fluorescence bronchoscopy utilizes different photosensitizers, such as a hematoporphyrin derivative, dihematoporphyrin ether, and delta-aminolevulinic acid (ALA), to enhance the fluorescence of premalignant and malignant changes of the bronchial mucosa. The main disadvantage of systemic application of these substances is that skin is more sensitive to light. Fluorescence bronchoscopy has not yet been used clinically to a considerable extent.
AFB does not require the application of photosensitizers. Autofluorescence of premalignant lesions or carcinoma in situ differs from fluorescence of normal bronchial mucosa. This difference is probably due to different thicknesses of premalignant and malignant tissues, as well as to enhanced vascularisation and lower fluorophore concentrations in the changed bronchial mucosa (9). The average thickness of carcinoma in situ is only five cells (4 to 38). In smokers, carcinoma in situ was found in 4.3% and in 11.4% of moderate and heavy smokers, respectively (10).
AFB is based on a reduction of fluorescent light within premalignant and malignant bronchial mucosa occurring illumination with a light of specific wavelength.

AFB systems

The largest experience has been reported with laser imaging fluorescence endoscopy (LIFE) (Xillix Technologies, Vancouver, Canada) (11) and the D-light Storz system (12).
The LIFE system is comprised of a helium-cadmium laser light, two image-intensifier CCD cameras, and a colour video monitor (11). Bronchial mucosa is illuminated with a helium-cadmium laser light with wavelengths close to the ultraviolet range up to blue light (250-500 nm). Malignant areas appear bluish-reddish and darkened and normal mucosa is dominated by green fluorescence. For conventional bronchoscopy, a separate source of white light is necessary. The system allows a simple change between white light bronchoscopy and AFB.
The main disadvantages of the system include high costs and a rather complex technical equipment required.
Experience with the system was first reported by Lam in 1998. It was used in 700 bronchial biopsies performed in 173 patients, diagnosed with 142 dysplasias, carcinomas in situ, and invasive carcinomas. Compared to conventional white light bronchoscopy, AFB was found to have a relative sensitivity of 2.7 (11).
Other authors using LIFE reported no improved sensitivity of AFB for the detection of preneoplastic changes, dysplasia, and carcinoma in situ of the bronchial mucosa (13).

D-light system (Storz, Tuttlingen, Germany)

A xenon lamp is the light source with a wavelength of 380-460 nm in the ultraviolet to blue spectrum. The system utilizes one camera that can be used for both AFB and conventional bronchoscopy. It is possible to simply switch between the two kinds of bronchoscopy. Normal mucosa appears green, and preneoplastic changes and malignant tissue are shown with a dark, even red color. The accuracy of the results largely depend on the endoscopist's experience.
The first reports on the use of this AFB system were published in 1999 (12). The authors examined 60 patients with suspected bronchial cancer and performed 264 bronchial biopsies. AFB exhibited improved sensitivity for the detection of preneoplastic changes in the bronchial mucosa and of carcinoma in situ. Relative sensitivity was found to be 2.8 times higher than that of white light bronchoscopy.
The pilot research conducted at the Department of Respiratory and Allergic Diseases Golnik in

2002 included 31 patients with suspected lung cancer who had smoked for more than 40 years and had had a successful therapy of the respiratory tract. They had three to five biopsies taken from 52 sites in the bronchial mucosa. The sensitivity of AFB for preneoplastic changes and carcinoma in situ was 0.95 and the specificity was 0.44. AFB did not improve the sensitivity of white light bronchoscopy. The relative sensitivity of AFB was 1.07 (14).

Storz D-light/AF autofluorescent, video and flexible bronchoscopy were compared in a group of 101 patients with suspected lung cancer Fifty patients were examined by video and 51 using flexible and autofluorescent bronchoscopy. A total of 979 bronchial biopsies were taken from 252 sites. Primary invasive carcinoma was histologically confirmed in 91 patients. Synchronous bronchial carcinoma was found in five patients, proximal progression of carcinoma in 12, and pre-neoplastic changes in 11 patients.

Autofluorescence bronchoscopy video bronchoscopy and flexible bronchoscopy were found to have equal sensitivity for the detection of invasive carcinoma (0.92,0.91 and 0.84, respectively) Auto fluorescence bronchoscopy was less specific for the detection of invasive bronchial carcinoma (0.69; $p>0.05$) than videobronchoscopy (0.88) or flexible bronchoscopy (0.75).

Autofluorescence bronchoscopy proved more sensitive for the diagnosis of pre-neoplastic lesions than flexible and video bronchoscopy (0.89 versus 0.45).

We found that autofluorescence bronchoscopy does not improve the diagnosis of primary and synchronous invasive carcinoma, but provides more accurate detection results of pre-neoplastic changes (15).

The use of SAFE 1000 system (Pentax, Asahi optical Tokyo, Japan) was first described by Japanese authors in 1999 (16).

The Wolf AF system was first presented in 2003, but experience with this system is scarce.

The AFB LIFE and D-light Storz systems were found to have comparable sensitivity and specificity, and that they yield comparable results. The D-light system, however, is cheaper and easier to use (17).

In order to improve sensitivity and specificity, and to simplify the procedure and objectify the results, the following new systems of detection of premalignant changes and early bronchial carcinoma of bronchial mucosa have been developed: reflectance spectroscopy showing different spectrograms in premalignant and malignant changes (18); optical coherence tomography which is similar to ultrasound, but uses light rather than acoustical waves (19); dual video and autofluorescence bronchoscopy (20); colour autofluorescence for objective measuring of the red/green intensity ratio (21); and narrow-band imaging for visualisation of pathological blood vessels (22).

Treatment of early stage bronchial carcinoma

The prognosis of invasive lung cancer is dismal. Our primary aim is to make an early diagnosis of preneoplastic changes, carcinoma in situ, and early stage invasive bronchial carcinoma, to start treatment as early as possible, and to increase the chance of longer survival in these patients.

The prognosis of X-ray occult lung cancer is much better: a relative five-year survival of up to 90% has been reported (23).

Patients in the earlier stages of the disease have a significantly better prognosis (24). The relative five-year survival for stage I A is 61% and for stage I B, 38%. It declines with each successively higher stage, and is only 1% in stage IV patients.

Patients with early-stage lung cancer are treated surgically using a conservative approach in order to preserve as much lung parenchyma as possible. Patients with functionally inoperable lung cancer are treated endoscopically (25).

Comorbidities related to smoking and old age include COPD, vascular disease, and heart disease. These patients are often functionally inoperable. Synchronous or metachronous multiple lung cancers cannot be treated surgically.

Small intraluminal central bronchial carcinoma is manageable by endoscopic procedures, such as electrocautery (26,27), laser, argon plasma coagulation, cryotherapy, mechanical tumor removal (25), or photodynamic therapy (28).

Using endoscopic therapy, complete remission of in situ bronchial carcinoma was achieved in up to 93% of patients (29).

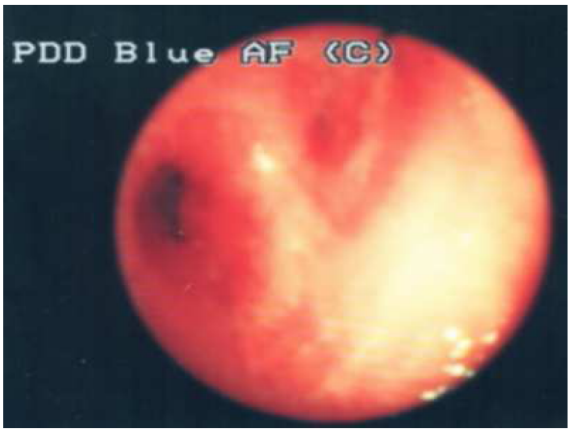

Figure 1
Carina of the right upper lobe bronchus. Conventional bronchoscopy: without definitive pathology.

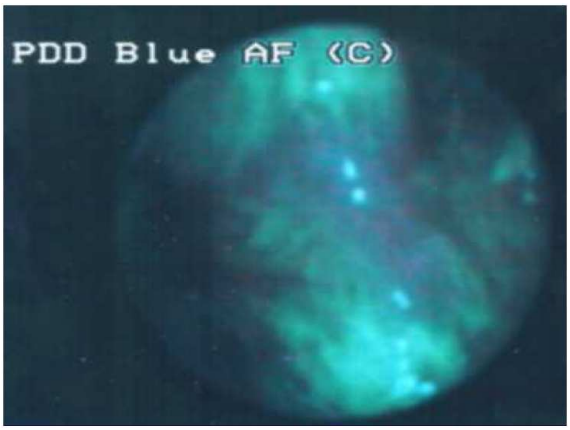

Figure 2
Autofluorescence bronchoscopy; the same patient: darkened bluish colour of the mucosa on the carina. Histology: moderate dysplasia.

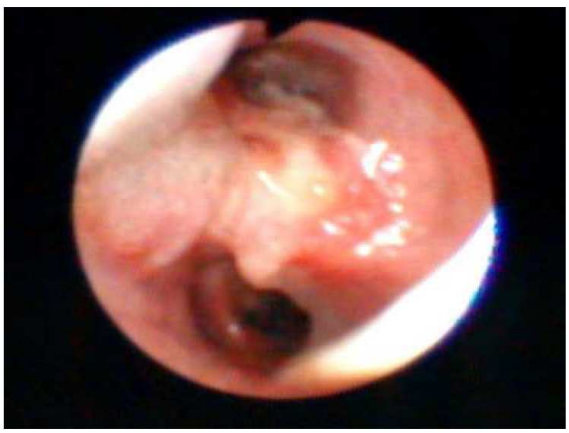

Figure 3
Conventional bronchoscopy; histology: invasive epidermoid cancer of the left upper lobe carina.

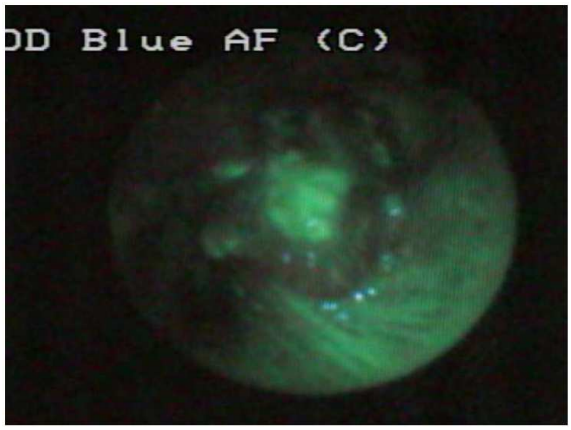

Figure 4
The same patient. Autofluorescent bronchoscopy: dark reddish colour of malignant changes of bronchial mucosa.

References

1. Mandel J, Weinberger SE. Screening for lung cancer. Up to date 2003; (800) 998-6374, (781) 237-4788.
2. Early Lung Cancer Cooperative StudY: Early lung cancer detection: Summary and conclusions. Am Rev Respir Dis 1984; 130:565-70.
3. Pierard P, Vermylen P, Bosschaerts T et al. Synchronus rentgenographically occult lung carcinoma in patients with resectable primary lung cancer. Chest 2000; 117: 779-85.
4. Sacomano G, Archer VE, Auerbach O. Development of carcinoma of the lungs as reflected in exfolliative cells. Cancer 1974; 33: 256-70.
5. Sacomano G. Carcinoma in situ of tehe lung: Its development, detection, and treatment. Semin Respir Med 1982; 4: 156-60.
6. Sutedja TG, Venmans BJ, Smit EF, Postmus PE. Fluorescence bronchoscopy for early detection of lung cancer. A clinical perspective. Lung cancer 2001;34: 157-68.
7. Thiberville L, Metayer J, Raspaud C, Nouvet G. A prospective, short term follow-up study of 59 severe dysplasias and carcinoma in situ of the bronchus using autofluorescence endoscopy. Eur Resp J 1997; 10, suppl 25: 425S.
8. Woolner LB, Fontana RS, Cortese DA. Roentgenographically occult lung cancer. Pathologic findings and frequency of multicentricity during a 10-years period. Mayo Clin Proc 1984; 59: 453-66.
9. Qu J, MacAulay C, Lam S, et al: Laser induced fluorescence spectroscopy at endoscopy: Tissue optics, Monte Carlo modeling, and in vivo measurement. Optical Eng 1995; 34: 3334-43.

10. Auerbach O, Stout AP, Hammond C, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. New Engl J Med 1961; 265: 253-68.
11. Lam S, Kennedy T, Unger M et al. Localisation of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998; 113: 696-702.
12. Häussinger K, Stanzel F, Huber RM, Pichler J, Stepp H. Autofluorescence detection of bronchial tumors with the D-Light/AF. Diagn Ther Endosc 1999; 5: 113-8.
13. Kurie JM, Lee JS, Morice RC et al. Autofluorescence bronchoscopy in the detection of squamous metaplasia and dysplasia in current and former smokers. J Nat Cancer Inst 1998; 90: 991-5.
14. Debeljak A, Triller N, Kecelj p, Kern I. Avtofluorescenčna bronhoskopija v diagnostiki preneoplastičnih sprememb in bronhialnega karcinoma. Zdrav Vestn 2002; 71: 449-52.
15. Debeljak A. The role of autofluorescent bronchoscopy in the diagnosis of synchronous bronchial carcinomas. In Rott T, Luzar B eds.: Lung Cancer. Inštitut za patologijo Medicinske fakultete Univerze v Ljubljani, Ljubljana, december 2007: 313-326.
16. Kakihana M, Kim KI, Okunaka et al. Early detection of bronchial lesions using system of autofluorescence endoscopy (SAFE) 1000. Diag Ther Endosc 1999; 5: 99-104.
17. Herth FJF, Ernst A, Becker HD. Autofluorescence bronchoscopy – a comparison of two systems (LIFE and D-Light). Respiration 2003; 70: 395-8.
18. Tercelj M, Zeng H, Petek M, Rott T, Palcic B. Acquisition of fluorescence and reflectance spectra during routine bronchoscopy examinations using ClearVu Elite™ device: Pilot Study. Lung Cancer 2005; 50:35-42.
19. Tsuboi M, Hayashi A, Ikeda N, Honda H, Kato Y, Ichinose S, Kato H. Optical coherence tomography in the diagnosis of bronchial lesions. Lung Cancer 2005; 49: 387-94.
20. Lee P, Brokx HAP, Postmus PE, Sutedja TG. Dual digital video-autofluorescence imaging for detection of pre-neoplastic lesions. Lung Cancer 2007; 58: 44-49.
21. Nakanishi K, Ohsaki Y, Kurihara M, Nakao S, Fujita Y, Takeyama K, Osanai S, Miyokawa N, Nakajima S. Color auto-fluorescence from cancer lesions: Improved detection of central type lung cancer. Lung cancer 2007; 49: 387-94.
22. Vincent BD, Fraig M, Silvestri GA. A pilot study of narrow-band imaging compared to white light bronchoscopy for evaluation of normal airways and premalignant and malignant airways disease. Chest 2007; 131: 1794-9.
23. Cortese DA, Pairolero PD, Bergstralh EJB, et al.: Roentgenographically occult lung cancer: A ten year experience. J Thorac Cardiovasc Surg 1983; 86: 373-80.
24. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997; 111: 1710-7.
25. Freitag L, Macha HN, Loddenkemper R. Interventional bronchoscopic procedures. In Spiro SG ed. Lung cancer. ERS monograph 2001; 6: 272-304.
26. van Boxem TJ, Venmans BJ, SChramel FM, et al. Radiographically occult cancer treated with fiberoptic bronchoscopic electrocautery: a pilot study of a simple and inexpensive technique. Eur Respir J 1998: 11: 169-72.
27. Sutedja G, Schramel FMNH, Smith HJF, Postmus PE: Bronchoscopic electrocautery has a curative potential for small intraluminal lung tumors. Eur Resp J 1996; 9: 374S.
28. Hayata Y, Kato H, Furuse K, Kusunoki Y, Suzuki S, Mimura S. Photodynamic therapy of 169 early stage cancers of the lung and oesophagus: a Japanese multi-centre study. Lasers Med Sci 1966; 11: 105-12.
29. Venmans BJ, van Boxem TJ, Smit EF, Postmus PE, Sutedja TG. Outcome of bronchial carcinoma in situ. Chest 2000; 117: 1472-6.