Flexible Fiberoptic Bronchoscopy

Studies on Methods for the Diagnosis of Carcinoma of the Lung, Bronchial Mucosal Damage and Haemodynamic Effects.

by

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ABSTRACT

The diagnostic accuracy attained with the use of transbronchial fine needle aspiration biopsy, aspiration of bronchial secretion, bronchial washing, brush biopsy and forceps biopsy via a flexible fiberoptic bronchoscope was compared in patients with carcinoma of the lung. In endoscopic visible tumours the sensitivity of forceps biopsy was higher than that of the other methods. When forceps biopsy was combined with bronchial washing the overall diagnostic accuracy was significantly higher than that of any of the single methods, while no appreciable increase was obtained by adding additional methods.

Selective brush biopsy from every segment bronchus has been established as a method in the search for occult bronchial carcinoma. The extent of respiratory mucosal damage and wound healing after brush biopsy was therefore studied in rabbits. Large differences in the extension and depth of the damage was observed. The basement membrane was often penetrated. Regeneration started during the first day after brush biopsy and a normal ciliated epithelium was restored within three weeks.

To determine if the bronchoscope itself damaged the respiratory epithelium, bronchial mucosa was studied in the pig after examination with a flexible fiberoptic bronchoscope. The columnar epithelial cells were torn off in areas where the bronchoscope had rubbed against the airway wall but the basement membrane was not damaged. Since the function of the respiratory epithelium is to remove inhaled particles from the airways, mucociliary clearance was studied in man after fiberoptic bronchoscopy. The study suggests that the tracheobronchial clearance system has a large reserve for mechanical trauma. Mucociliary clearance can however be decreased after fiberoptic bronchoscopy in some patients.

An increasing number of patients with impaired cardiopulmonary function are today subjected to examination with flexible fiberoptic bronchoscopy. The haemodynamic effects of fiberoptic bronchoscopy performed under topical anaesthesia were therefore studied in patients with restrictive lung disease. The procedure induced marked haemodynamic changes during passage of the larynx and during suctioning. A slight fall in arterial oxygen tension was observed during bronchial suctioning and in the post-bronchoscopic period. Three of ten patients developed ST-T-segment changes during bronchial suctioning.

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Key words

To Margaretha
Anna
Ulrika
"In case of doubt as to whether bronchoscopy should be done or not, bronchoscopy should always be done".

Chevalier Jackson 1915.
This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


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RESPIRATORY MUCOSAL DAMAGE AFTER BRUSH BIOPSY. An experimental study in rabbits (II).

RESPIRATORY MUCOSAL DAMAGE BY FLEXIBLE FIBEROPTIC BRONCHOSCOPY IN PIGS (III).

TRACHEOBRONCHIAL CLEARANCE AFTER FLEXIBLE FIBEROPTIC BRONCHOSCOPY (IV).

HEMODYNAMIC EFFECTS OF FLEXIBLE FIBEROPTIC BRONCHOSCOPY PERFORMED UNDER TOPICAL ANESTHESIA (V).
INTRODUCTION

History of bronchoscopy
When Green in 1847 reported on his method of catheterizing the larynx and bronchi to the Medical and Surgical Society of New York his claims were promptly condemned as "an anatomical impossibility and an unwarrantable innovation in practical medicine" and he was asked to withdraw from membership (Patterson 1926).

Killian was the first who succeeded in extracting a foreign body from the bronchus by the translaryngeal route, and this first "direct bronchoscopy" was performed in 1897 (Zöllner 1965). The bronchoscope was improved by Jackson, who incorporated a suctioning tube and tip illumination, and since then the Killian or Jackson type of bronchoscope or modifications of these instruments have been used. Development of the illumination and the optical system improved the diagnostic value of bronchoscopy, and different techniques of performing the examination under general anaesthesia were developed.

When Ikeda in 1966 demonstrated the prototype of a flexible fiberoptic bronchoscope he started a new chapter in the history of bronchoscopy. According to Sackner (1975) "probably no other diagnostic or therapeutic technique has revolutionized pulmonary medical practice in so short a time".

Diagnostic flexible fiberoptic bronchoscopy

In patient with malignant cells in expectorated sputum but without roentgenological visible tumour - occult bronchial carcinoma - selective brushing from every segment bronchus may be necessary to detect the tumour (Sanderson et al 1974, Tyers & McCavran 1976, Marsh et al 1978). From studies in different animal species it has been shown that the respiratory mucosa is vulnerable to mechanical trauma (Hilding & Hilding 1962, Hilding 1964, Hilding 1965, Way & Sooy 1965, Hilding 1968, Sackner et al 1973, Klainer et al 1975, Bleeker & Edens 1977, Nordin 1977, Schmidt et al 1979) but there is little information available about the respiratory mucosal damage caused by brush biopsy.


When using the flexible fiberoptic bronchoscope for taking material for bacteriological culture, contamination by oropharyngeal bacteria is a problem (Bartlett et al 1977, Fossieck Jr et al 1977). Wimberley et al (1979) have reported a technique to obtain uncontaminated lower airway secretion for bacteriological culture by using a special brush catheter.

The fiberoptic bronchoscope has been adopted for bronchioalveolar lavage of the lower respiratory tract as a new approach to the evaluation of patients with interstitial lung disease (Reynolds et al 1977, Hunninghake et al 1979, Strumpf et al 1981). Among the advantages of the flexible fiberoptic bronchoscope compared with the rigid bronchoscope are increased visual and biopsy range, minimal discomfort to the patient and increased diagnostic accuracy, and this has increased the possibility of diagnosing unusual bronchial diseases, such as bronchial stenosis due to sarcoidosis (Olsson et al 1980) and tracheobronchopathia osteochondroplastica (Lundgren & Stjernberg 1981). The bronchoscope can also be used for selective bronchography (Lundgren et al 1982).

**Therapeutic flexible fiberoptic bronchoscopy**

The flexible fiberoptic bronchoscope was introduced mainly as a diagnostic tool but has also become useful for therapeutical purposes. To remove foreign bodies most bronchoscopists use the rigid tube bronchoscope but the flexible fiberoptic bronchoscope has also been used (Cunanan 1978, Oho & Amemiya 1981). The fiberoptic bronchoscope has been used successfully for resection of endobronchial chondroma (Lundgren & Winblad 1980), as well as for laser treatment of endobronchial lesions (Dumon et al 1981).

In critical care medicine the efficiency of the fiberoptic bronchoscope has been well established for the management of airway problems that occur during acute respiratory failure. The instrument can be helpful for assessing airway damage, for management of atelectasis and to remove retained secretion, as well as for intubation in selected patients (Lindholm 1974, Lindholm et al 1974, Barrett Jr et al 1974, Barrett Jr 1978, Davidson et al 1975, Vigneswaran & Whitfield 1981). Fiberoptic bronchoscopy has also been used for therapeutic bronchial lavage e.g. in alveolar proteinosis (Brach et al 1976), cystic fibrosis (Ewing 1978) and for removal of retained bronchial secretions in
patients with respiratory failure (Weinstein et al 1977). Repeated endotracheal suctioning has been shown to damage mucociliary transport in sheep (Landa et al 1980) however little is known about the effect of fiberoptic bronchoscopy on the respiratory epithelium and mucociliary transport system.

Complications
Flexible fiberoptic bronchoscopy is considered to be a safe procedure, easy to perform under topical anaesthesia and usually well tolerated by the patient (Sackner 1975, Donland Jr et al 1978, Zavala 1978, Oho & Amemiya 1981). Consequently, an increasing number of patients, including patients with impaired cardiopulmonary function, are subjected to examination by this method. Severe complications have, however, been reported in association with fiberoptic bronchoscopy (Credle et al 1974, Suratt et al 1976, Sahn & Scoggin 1976, Dresin et al 1978, Pereira Jr et al 1978, Herf et al 1979, Lukomsky et al 1981). Premedication and topical anaesthesia, especially tetracaine, can give adverse reactions (Credle et al 1974). The bronchoscope can obstruct the airways if it is passed via small endotracheal tubes (Månsson 1977, Lindholm et al 1978) and the bronchoscopic procedure can also induce laryngospasm, bronchospasm, hypoxemia, pneumonia and life-threatening endobronchial bleeding (Credle et al 1974, Albertini et al 1974, Dubrawsky et al 1975, Sahn & Scoggin 1976, Suratt et al 1976, Randazzo & Wilson 1976, Pereira Jr et al 1978, Shrader & Lakshminarayan 1978, Luck et al 1978). In addition to endobronchial bleeding, pneumothorax is the complication most usually associated with transbronchial lung biopsy (Zavala 1976, Herf et al 1977). Cardiovascular complications are responsible for many of the deaths reported in association with flexible fiberoptic bronchoscopy (Suratt et al 1976), but, apart from studies on cardiac rhythm and hypoxemia, there are no reported investigations elucidating the effects of fiberoptic bronchoscopy performed under topical anaesthesia on the cardiovascular system.
THE AIM OF THE PRESENT INVESTIGATION

In the diagnosis of carcinoma of the lung flexible fiberoptic bronchoscopy has been established as a useful tool. Opinions differ about which of the several methods available should be used for collecting material for histologic and/or cytologic examination. When deciding which device or method to use the diagnostic accuracy but also the adverse effects should be considered. Brush biopsy is one of the methods most frequently used in the diagnosis of carcinoma of the lung, and in occult bronchial carcinoma selective brushing from every single segment bronchus is often the only way to localize the tumour. It is therefore important to examine the extent of respiratory mucosal damage and wound healing after brush biopsy. It is also important to establish if the flexible fiberoptic bronchoscope itself damages the respiratory mucosa and impairs mucociliary transport. An increasing number of patients with impaired cardiopulmonary function are subjected to examination with flexible fiberoptic bronchoscopy. This makes it important to determine the haemodynamic effects of flexible fiberoptic bronchoscopy performed under topical anaesthesia.

Thus, the aim of the present study was
1. to compare the diagnostic accuracy of transbronchial thin needle aspiration biopsy, aspiration of bronchial secretion, bronchial washing, brush biopsy and forceps biopsy in the diagnosis of carcinoma of the lung.
2. to examine the extent of respiratory mucosal damage and wound healing after brush biopsy.
3. to determine if the flexible fiberoptic bronchoscope itself damages the respiratory mucosa.
4. to determine if flexible fiberoptic bronchoscopy has any influence on tracheobronchial clearance.
5. to determine if flexible fiberoptic bronchoscopy performed under topical anaesthesia has any influence on central haemodynamics, ECG and blood gases.
MATERIAL AND METHODS

Clinical Studies (I, IV, V)

Material
Study I: To compare different sampling techniques in the diagnosis of carcinoma of the lung, transbronchial fine needle aspiration biopsy, aspiration of bronchial secretion, bronchial washing, brush biopsy and forceps biopsy were performed on 60 tumours in 59 patients (48 male and 11 female with a mean age of 65 years). Three sputum cytology samples were obtained from 52 of the patients. All patients were examined by the same bronchoscopist and all samples for histopathology and cytology, including operation and autopsy specimens were re-examined by one pathologist and one cytologist, respectively. The histologic type of the lung tumours was classified according to the WHO classification (Kreyberg et al 1967).

Study IV: To study the influence of flexible fiberoptic bronchoscopy on mucociliary clearance, 12 persons were examined. Eleven were patients on whom bronchoscopy was performed on diagnostic criteria and one was a healthy volunteer.

Study V: To investigate the influence of flexible fiberoptic bronchoscopy, performed under topical anaesthesia, on central haemodynamics, ECG and blood gases in patients with impaired pulmonary function, 10 patients with restrictive lung disease were studied. In one patient there was also an obstructive impairment of lung function. All patients were in medically optimal conditions, haemodynamically stable and in sinus rhythm.

The studies were approved by the Ethics Committees of the University of Umeå and the Karolinska Institute, Stockholm.

Bronchoscopic procedures (I, IV, V)
All examinations in man were performed under topical anaesthesia using lidocaine (Xylocain\textsuperscript{R}, Astra, Sweden). The patients were premedicated
with morphine-scopolamine (Morfin-skopolaminR, ACO, Sweden). For topical anaesthesia of the mouth and pharynx lidocaine spray was used and for anaesthesia of the larynx, trachea and bronchi lidocaine (4 mg/ml) was applied through a laryngeal syringe with the patient sitting in a chair (I, IV). If needed, additional lidocaine (2 mg/ml) was given via the bronchoscope. The total amount of lidocaine given was about 250 mg. In study V the procedure of topical anaesthesia was performed with the patient in the supine position and the larynx, trachea and bronchi were anaesthetized (lidocaine 2 mg/ml) via the bronchoscope. All examinations were performed with the patients in the supine position and the bronchoscope (BF-B3, BF-4C or BF-1T, Olympus Optical Co Ltd, Japan) was inserted through the mouth without an endotracheal tube. After careful visual examination, samples were taken for cytologic, histopathologic and/or bacteriologic examinations. In study I, bronchial washing was performed with about 10 ml of physiological saline. In study V, 40 ml of physiological saline was used for bronchioalveolar lavage. Transbronchial lung biopsy was performed under fluoroscopic guidance (I, V).

Tracheobronchial clearance measurements (IV)

Six um teflon particles were produced by a spinning disc technique and tagged with $^{99m}$Tc (Camner 1971, Philipson 1977). Before use the particles were suspended in 0.2% tergitol solution in water and after leaching for 2 hours they were allowed to sediment. 0.2 ml (2 mg particles/ml) was sprayed twice into a 25 liter glass tower. The subjects performed 10-20 deep inhalations for about 3 minutes from a short nozzle attached to the tower at a rate of about 1.2 liter/second. Radioactivity in the lungs was repeatedly measured by profile scanning over the thorax of the supine subjects, using two 3 x 2 inch NaI crystals provided with collimators (Camner 1971).

Haemodynamic and blood gas measurements (V)

For catheterization a 7F balloon-tipped pulmonary artery thermodilution catheter (Cardiovascular Instruments, USA) was inserted via the right internal jugular vein and wedged in the right lower lobe pulmonary artery under fluoroscopic control. A catheter for arterial
pressure monitoring was inserted into the right femoral artery and a Chemetron\textsuperscript{R} (Chemetron Corp, USA) heparinized silastic catheter for continuous mass spectrometric blood gas analysis was inserted through it. All intravascular catheters were flushed with normal saline using the Intraflo CFS\textsuperscript{R} (Sorensen, USA) at 6 ml/h. ECG (lead V5) arterial, pulmonary arterial and right atrial pressures were recorded continuously throughout the procedure on a Mingograph 82 (Siemens-Elema, FRG) recorder using Siemens-Elema's pressure transducers 746/51 positioned at mid chest (0-level). Cardiac output was determined by the thermodilution method (CVI 600, Cardiovascular Instruments, USA) described by Ganz et al 1971. The arterial oxygen and carbon dioxide tensions were recorded continuously from the mass spectrometer (MS2, Medshield Corp Ltd, U K). Arterial blood samples were analyzed (ABL-2, Radiometer Instr. Denmark) before, during and after fiberoptic bronchoscopy to check the linearity of the blood gas catheter.

Animal studies (II, III)

Material
Study II: Thirty-seven adult rabbits (19 male and 18 female, mean weight 4 kg) were used in the study of respiratory epithelial damage and wound healing after brush biopsy. The rabbit was chosen as experimental animal for budget reasons and because the rabbit trachea was large enough to allow brushing with a standard brush. Lower respiratory tract infections are difficult to exclude in the rabbit, thus no animal was eliminated from the study even if there were clinical signs of upper airway infection.

Study III: To establish whether the flexible fiberoptic bronchoscope itself damaged the respiratory epithelium, 11 pigs (2 male and 9 female) about 25 kg of weight were used. The pig was chosen as experimental animal because its respiratory mucosa is similar to that of man (Baskerville 1970) and its airways are large enough to allow examination with a standard flexible fiberoptic bronchoscope. Only animals with a normal respiratory epithelium in the right (control) bronchus were used.
Operation procedures (II, III)

Study II: The rabbits were anaesthetized with intravenous injected sodium pentobarbital (Mebumal vet<sup>®</sup> ACO, Sweden) and the tip of a flexible fiberoptic bronchoscope (Olympus BF-5B2) was placed about 0.5 cm above the vocal cords. The brush (BC-1B, Olympus Optical Co Ltd, Japan) was passed into the trachea which was brushed five times. The animals were sacrificed at different time intervals up to four weeks after brushing. The trachea was removed and prepared for scanning electron microscopy and light microscopy.

Study III: All animals were tracheotomized under general anaesthesia with sodium pentobarbital (Mebumal vet<sup>®</sup>) and a flexible fiberoptic bronchoscope (Olympus BF-5B2) was inserted through the tracheostoma. In five animals the bronchoscopy was performed during spontaneous ventilation without endotracheal intubation and in six animals via an endotracheal tube during artificial ventilation. The left bronchial tree was examined with the bronchoscope without suctioning or brushing and the right bronchial tree was used as a control. Nine animals were sacrificed immediately after bronchoscopy while two animals were allowed to revive and were sacrificed 24 hours after bronchoscopy. Trachea and bronchi were removed and prepared for scanning electron microscopy and light microscopy.

Scanning electron microscopy and light microscopy (II, III)
The specimens were prepared for scanning electron microscopy and after completed examination sectioned for light microscopy to enable study of the same area by both methods. After washing with physiological saline to remove mucus covering the epithelium, the specimens were fixed in 2.5% glutaraldehyde in 0.1 M sodium phosphate buffer, pH 7.2, 350 mOsm, for 24 to 48 hours. After dehydration in ethanol and ethanol-isoamylacetate, the specimens were dried from liquid carbon dioxide by critical point drying in a Polaron E-3000 critical point drying apparatus (Polaron Equipment Ltd U K). The dried specimens were mounted on stubs and coated with an approximately 300 Å thick film of gold under continuos rotating and tilting in a modified Edwards Vacuum Coating Unit E12E14 (Edwards High Vacuum U K).
at $10^{-5}$ T. The specimens were studied in a Cambridge Stereoscan S4 scanning electron microscope (Cambridge Scientific Instruments Ltd UK). After scanning electron microscopic examination, the gold-coated specimens were embedded in paraplast (Lancer-Brunswick, USA) and/or in plastic (JB-4, Sorvall, USA). The specimens were cut into sections and stained with hematoxylin-eosin.
RESULTS

Comparison of methods used via the flexible fiberoptic bronchoscope in the diagnosis of carcinoma of the lung (I).

Flexible fiberoptic bronchoscopy confirmed the diagnosis of carcinoma of the lung in 88% (53/60) of the tumours examined with all five diagnostic methods. The diagnostic accuracy of the different cytologic and histologic methods in relation to the bronchoscopic findings is shown in Fig. 1.

![Graph showing diagnostic accuracy of different methods](image)

Fig. 1. Diagnostic accuracy of different methods used via the flexible fiberoptic bronchoscope in 60 malignant lung tumours. BS = aspiration of bronchial secretion, BW = bronchial washing, TBN = transbronchial fine needle aspiration biopsy, BB = bronchial brushing FB = forceps biopsy.

■ = positive samples in visible tumours.
□ = positive samples in patients with secondary signs of tumours.
■■ = positive samples in non-visible tumours.
■■■ = suspicion of malignancy.
□□ = negative.
In visible tumours the best results were obtained with forceps biopsy (85%) while transbronchial thin needle aspiration biopsy was positive in 65%. In cases where bronchoscopy only showed secondary signs of tumour, the sensitivity of forceps biopsy, brush biopsy and transbronchial thin needle aspiration biopsy was higher than that of bronchial washing and aspiration of bronchial secretion. In tumours not visible through the bronchoscope, the diagnostic accuracy of brush biopsy, bronchial washing and aspiration of bronchial secretion was higher than that of forceps biopsy and transbronchial needle aspiration biopsy.

The diagnostic yield increased when combining forceps biopsy with one of the cytologic methods. The highest sensitivity was obtained by a combination of forceps biopsy and bronchial washing, and only two additional tumours were diagnosed by using three, four or all five diagnostic methods. In epidermoid carcinomas forceps biopsy and brush biopsy were somewhat more sensitive than the other methods. In small cell anaplastic carcinomas the sensitivity with forceps biopsy was higher than with other methods.

Cytologic examination of sputum was positive in 33 (63%) of the 52 patients examined with three representative samples.

**Respiratory mucosal damage after brush biopsy (II)**

The rabbit respiratory epithelium is of the pseudostratified type, built up mainly of basal cells which do not reach to the lumen together with ciliated cells and secretory cells which extend from the basement membrane to the lumen. The connective tissue beneath the basement membrane contains a lot of small blood vessels.

Large differences were observed in the extension and depth of the trauma caused by brush biopsy in the rabbit trachea. In 12 of the 19 animals examined within five days after brushing, the brush had penetrated through the basement membrane. Within a few hours after brushing, the deep damaged areas, which penetrated basement
membrane, were covered by a fibrin clot containing erythrocytes and granulocytes. The clot was attached to the wound during the first days after brushing. The protruding part of the clot was generally rejected two to three days after brushing. Cell regeneration after brushing seemed to start already during the first day after the damage. In areas with an undamaged basement membrane there was a covering cell layer within one to two days. The deep ulcerated areas were covered by an epithelium within about five days after brushing and a normal ciliated respiratory epithelium was restored within three weeks after brushing.

Respiratory mucosal damage after flexible fiberoptic bronchoscopy (III)
The pig respiratory epithelium is of the pseudostratified type, with a lot of mucous glands in the connective tissue beneath the basement membrane. The gland orifices are often located in longitudinal lines.

Respiratory mucosal damage could be identified in the trachea and in the left bronchial tree in all animals examined after flexible fiberoptic bronchoscopy. The right bronchial tree, which was used as control, was normal. In most animals, large areas of the epithelium were grazed off but there were interspersed areas of undamaged epithelium, especially around the gland orifices. Usually there was a marked borderline between damaged and undamaged epithelium. The columnar epithelial cells were torn off leaving a single layer of basal cells or a bare basement membrane but no parts of the basement membrane were found to be penetrated by the fiberoptic bronchoscope. In the two animals examined 24 hours after bronchoscopy, the damaged areas were covered by a flattened non-ciliated epithelium.

Tracheobronchial clearance after flexible fiberoptic bronchoscopy (IV)
Most of the patients had a fairly similar tracheobronchial clearance the day before and the day after flexible fiberoptic bronchoscopy. A markedly reduced clearance after bronchoscopy was only observed in one patient. One patient, number 3, had no clearance.
During the bronchoscopic examination of the patients in study IV, forceps biopsies were taken from patients numbers 2, 3, 5, 6, 9, 10 and 12, and these biopsies have later been examined in the scanning electron microscope. In the biopsy taken from patient number 3, there were no normal ciliated epithelial cells. In patient number 2 only few ciliated cells could be seen and in patient number 5 a slight increase in non-ciliated cells were observed while, the biopsies from the other patients showed a normal ciliated epithelium.

Haemodynamic effects of flexible fiberoptic bronchoscopy performed under topical anaesthesia (V)

During topical anaesthesia and passage of the larynx with the bronchoscope there were marked increases in heart rate, mean arterial pressure, mean pulmonary arteriolar occlusion pressure and cardiac index (Figs. 2, 3). The rise in heart rate, mean arterial pressure and cardiac index seen during passage through the larynx had fallen slightly after completed topical anaesthesia and decreased further during bronchial lavage, which was performed after completed topical anaesthesia (Figs. 2, 3). There was no decrease in the continuously measured arterial oxygen tension during segmental lavage performed with 50 ml physiological saline (Fig. 4). Five minutes of intermittent suctioning through the flexible fiberoptic bronchoscope increased mean arterial pressure, heart rate, mean pulmonary arteriolar occlusion pressure and cardiac index (Figs. 2, 3) and there was a significant decrease in arterial oxygen tension (Fig. 4). Rate pressure product reached it's highest value during suctioning (Fig. 5). In three patients, ST-T-segment depression was recorded on ECG during suctioning. In these patients arterial oxygen tension had decreased 1 kPa or more and rate pressure product was approximately 2.5 times the control value. Fifteen minutes after completed examination all values except heart rate and arterial oxygen tension had returned to baseline (Figs. 2-5).
Fig. 2. Effects of flexible fiberoptic bronchoscopy (FFB) on mean arterial pressure (MAP), heart rate (HR) and mean pulmonary arteriolar occlusion pressure (MPAOP). A = baseline value before FFB. B = anaesthesia and passage of larynx with FFB. C = completed topical anaesthesia. D = bronchioalveolar lavage. E = suctioning. F = seven minutes after completed FFB. G = fifteen minutes after completed FFB. Results are expressed as means + SEM, n = 10. For the statistical analysis of the difference between the baseline values (A) and the following values (B-G) the Wilcoxon's matched-pair signed-rank test was used. * = p < 0.05, ** = p < 0.01.
Fig. 3. Effects of FFB on cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Results are expressed as means ± SEM, n = 10, * p < 0.05, ** p < 0.01.
Fig. 4. Effects of flexible fiberoptic bronchoscopy on arterial oxygen tension ($P_aO_2$) and arterial carbon dioxide tension ($P_aCO_2$). Results are presented as means ± SEM, $n = 10$, * $p < 0.05$, ** $p < 0.01$.

Fig. 5. Changes in rate pressure product (RPP = systemic blood pressure x heart rate) during FFB. Results are presented as means ± SEM, $n = 10$, * $p < 0.05$, ** $p < 0.01$. 
DISCUSSION

The flexible fiberoptic bronchoscope is increasingly being used as a multipurpose instrument in the diagnosis and treatment of airway and pulmonary diseases. The number of patients examined by this method has increased, including patients with rather slight symptoms as well as critically ill patients. When deciding to perform a flexible fiberoptic bronchoscopy not only the diagnostic or therapeutic gain but also the adverse effects of the procedure should be taken into consideration and attempts should be made to avoid these effects.

Flexible fiberoptic bronchoscopy in the diagnosis of carcinoma of the lung: methodological aspects

Flexible fiberoptic bronchoscopy is a valuable tool in the diagnosis of carcinoma of the lung (Ikeda 1974, Zavala 1975, Kvale et al 1976) and this was confirmed in study I. Cytologic examination of sputum is valuable in the diagnosis of carcinoma of the lung (Wiman 1964), however, in our study the diagnostic accuracy by flexible fiberoptic bronchoscopy was superior to that of sputum cytology.

The overall diagnostic yield by using the flexible fiberoptic bronchoscope in the diagnosis of carcinoma of the lung correlates well with those of other reports (Richardson et al 1974, Solomon et al 1974, Zavala 1975, Kvale et al 1976, Funahashi et al 1979). Higher diagnostic accuracy of the different methods than those obtained in study I has been reported (Zavala 1975, Kvale et al 1976, Chopra et al 1977, Augusseau et al 1978, Funahashi et al 1979). Only cases were all five diagnostic methods were used were included in our study, although there were no obvious methodological reasons not to perform a complete examination in the patients excluded. In most other studies the different diagnostic methods have been used in only some of the patients examined. In such studies there is a possibility that the choice of diagnostic methods can have been influenced by the bronchoscopic findings, thus giving a too high diagnostic accuracy for the different methods. Differences in the technique of performing the diagnostic procedures as well as in the methods of dealing with the
specimens may have an influence on the diagnostic accuracy. The sequence of diagnostic procedures may also influence the diagnostic yield of the different methods.

The results from study I indicates that a combination of two methods, including forceps biopsy and one of the cytologic methods, should be used. The decision of which combination of methods to use should be adapted to the circumstances during the examination. Not only the diagnostic yield, but also possible adverse effects of the different instruments and methods should be considered (II, V).

In visible tumours a high diagnostic accuracy can be obtained by using forceps biopsy (I). The major risk in using this method is bleeding after biopsy (Zavala 1975, Suratt et al 1976). To decrease the risk of bleeding local application of epinephrine to the tumour has been recommended and to control haemorrhage after transbronchial lung biopsy a wedge technique has been described by Zavala (1978). Pulmonary hypertension is considered a relative contraindication for transbronchial lung biopsy (Zavala 1976). In patients with impaired pulmonary function, passage of the larynx and intermittent suctioning induced an increase in mean pulmonary arterial pressure and mean pulmonary arteriolar occlusion pressure (V).

A high diagnostic accuracy (85 %) was received by combining forceps biopsy and bronchial washing in the diagnosis of carcinoma of the lung (I). Dubrawsky et al (1975) reported a significant decrease in arterial oxygen tension following bronchial washing with 30 to 40 ml saline, but this could not be verified in our study, where bronchi-alveolar lavage, performed with 50 ml of normal saline, seemed to be a rather safe procedure (V). Furthermore, for the diagnosis of bronchial carcinoma usually only smaller amounts of saline are used.

Flexible thin needle aspiration biopsy is useful in the diagnosis of endoscopically visible tumours and tumours covered by an intact bronchial mucosa, and in one patient with a carcinoid tumour transbronchial needle aspiration biopsy was the only positive method
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(I). Carcinoid tumours may bleed briskly, thus surgery without forceps biopsy has been recommended (Zavala 1978). Bleeding may occur after transbronchial needle aspiration biopsy, especially if a vessel is punctured, but the small needle diameter decreases the risk of bleeding (Lundgren 1980).

Aspiration of bronchial secretion is an easy way to obtain material for cytologic examination. Long-time intermittent suctioning through the flexible fiberoptic bronchoscope, however, induced hypoxemia and considerable haemodynamic changes in patients with restrictive lung disease (V).

Brush biopsy, one of the first devices introduced for use via the flexible fiberoptic bronchoscope, is valuable in the diagnosis of carcinoma of the lung (Solomon et al 1974, Teirstein et al 1978). The number of tumours beyond the visual range of the bronchoscope was small in our study (I), which makes a comparison between the methods uncertain. However, the diagnostic accuracy of brush biopsy seemed to be better than that of forceps biopsy and transbronchial needle aspiration biopsy in endoscopically non-visible tumours (I). In endoscopical or roentgenological visible tumours the brushing procedure can be restricted to the tumour area. In patients with malignant cells in expectorated sputum without roentgenologically visible tumour-occult bronchial carcinoma-selective brushing from every segment bronchus is often the only way to localize the tumour (Sanderson et al 1974).

In the study in rabbits (II) brush biopsy damaged the normal respiratory epithelium and the basement membrane was often penetrated, however, a normal ciliated epithelium was restored within three weeks after brushing. As brush biopsy in the rabbit trachea did not give any lasting respiratory mucosal damage, it seems reasonable to consider, although yet not proved, that brush biopsy also could be performed in man without permanent bronchial mucosal damage. From this point of view, selective bronchial brushing in the search for occult bronchial carcinoma can be justified.
Effects on respiratory mucosa and mucociliary clearance by flexible fiberoptic bronchoscopy and brush biopsy

In conformity with man (McDowell et al 1978) and other mammalian species (Breeze & Wheeldon 1977, Reid & Jones 1979) the rabbit and pig respiratory epithelium is of the pseudostratified type and this epithelium is vulnerable to mechanical trauma such as endotracheal intubation (Klainer et al 1975, Nordin 1977, Schmidt et al 1979), suctioning catheters (Sackner et al 1973, Landa et al 1980) and rigid tube bronchoscopy (Hilding 1968, Bleeker & Edens 1977). In all animals examined in study III the flexible fiberoptic bronchoscope had damaged the respiratory epithelium in the trachea and in the left bronchial tree, even without suctioning or brushing. The columnar epithelial cells were torn off along the path of the bronchoscope and a mechanical mode of injury was most likely responsible for the respiratory mucosal damage seen after flexible fiberoptic bronchoscopy. In contrast, the damage observed after endotracheal intubation is considered to be due to ischemia caused by the cuff pressure (Nordin 1977, Arola & Anttilen 1979). After rigid tube bronchoscopy in calves, Hilding (1968) noticed mucosal damage ranging from removal of only the superficial cells to abrasions extending through the basement membrane. In our study on pigs (III), the flexible fiberoptic bronchoscope had not penetrated the basement membrane and this is of importance for the regeneration of the epithelium (II).

Biopsy brushes are designed to tear off malignant cells from the tumour surface. Brush biopsy in the rabbit trachea damaged the normal respiratory epithelium, but large differences were observed in extension and depth of the trauma caused by brushing. In a majority of animals the basement membrane was penetrated but also superficial damage could be seen. Variations in pressure and movement of the brush may explain the differences in extension and depth of the trauma caused by brushing. Even a superficial damage, which only removes the cilia and the top of the cells, may, however, result in exfoliation of the damaged cells (Hilding 1965).
Regeneration of the damaged respiratory epithelium started already during the first day after brush biopsy. In areas with an undamaged basement membrane there was a covering cell layer within one to two days in the rabbit trachea (II). In the two pigs examined 24 hours after flexible fiberoptic bronchoscopy, the damaged areas were covered by a flattened non-ciliated epithelium (III). Gordon & Lane (1976) observed that the basal cells became flattened and within six hours covered small superficially damaged areas in the rat trachea. They also observed a peak of mitotic activity from the 26th to 30th hour following trauma (Lane & Gordon 1974). In our study (II), damaged areas with penetrated basement membrane were covered by a fibrin clot containing erythrocytes and granulocytes within a few hours after brushing. The clot which was attached to the wound during the first days after brushing, was generally rejected two to three days after brush biopsy and similar observations have been reported by Wilhelm (1953) and Hilding (1968). Within about five days after brushing, the deep ulcerated areas were covered by an epithelium and a normal ciliated respiratory epithelium was restored in the rabbit trachea within three weeks after brush biopsy (II).

Large differences have been reported in the time required for wound healing after different types of respiratory mucosal damage in several animal species. Hilding (1965) reported that a superficial respiratory mucosal damage in calf trachea, not penetrating the basement membrane, was restored within seven to ten days, and according to Ramphal et al (1979) similar damage caused by influenza virus in the mouse trachea was regenerated within two weeks. Regeneration after endotracheal intubation damage in the dog was nearly complete after seven days (Klainer et al 1975), and both normal morphology and ciliary function was restored within 29 days in the chicken trachea after brushing (Battista et al 1972), while six weeks were required for wound healing after curettage of rat trachea (Wilhelm 1953). Differences in extension and depth of trauma, different animal species, age of animal and level of the airway affected may explain the differences reported in the time required for wound healing in the airways.
From a clinical point of view the most important finding in study II was that no lasting respiratory mucosal damage could be seen in the rabbit trachea after brush biopsy. There are no studies available on wound healing in the human respiratory mucosa after brush biopsy, and great care must always be taken when applying results found in animal studies to man. It is, however, tempting to suggest that a damage similar to that observed in the rabbit trachea is also restored with a normal ciliated epithelium in man.

Brush biopsy (II) and even the flexible fiberoptic bronchoscope itself (III) induced considerable respiratory mucosal damage in experimental animals. The pig respiratory mucosa is similar to that of man (Baskerville 1970) and it is therefore tempting to suggest that damage similar to that observed in study III may also occur in man after examination with flexible fiberoptic bronchoscopy. Since the function of the ciliated epithelium is to clear the airways from inhaled particles, mucociliary clearance was measured in 12 persons one day before and one day after examination with fiberoptic bronchoscopy. With the clearance methods used in study IV, test particles are deposited mainly in larger airways (Camner 1971), which are easily reached by the fiberoptic bronchoscope. Landa et al (1980) reported decreased mucociliary transport after repeated endotracheal suctioning in sheep. On the other hand, inhalations of irritants such as tobacco smoke, carbon dust and sulphur dioxide produced an increased mucociliary clearance (Camner et al 1971, Camner et al 1973, Albert et al 1975, Wolff et al 1975, Newhouse et al 1978). In a study on dogs, Landa et al (1980) observed an increased mucociliary transport six hours after flexible fiberoptic bronchoscopy and suggested that this increase might represent a mild mucosal stimulation. They could not, however, observe any impaired mucociliary transport in dogs after examination with a rigid tube bronchoscope. In our study in man, the differences in tracheobronchial clearance before and after fiberoptic bronchoscopy were small when compared with variations in clearance between the patients. A markedly reduced clearance after bronchoscopy was only observed in one patient. Some patients coughed during the measurements, and in these patients it was not known whether or not muco-
ciliary clearance had been affected. However, overall clearance, that is the sum of mucociliary clearance and cough, was fairly similar on the two days also in these patients.

Our study in man (IV) as well as a study in anaesthetized dogs (Landa et al 1980) suggests that the mucociliary transport system has a large reserve for mechanical trauma. One reason could be that the respiratory mucosal damage induced by the flexible fiberoptic bronchoscope seldom involved the whole circumference of the bronchi (III). In one of our patients a marked decreased clearance was nevertheless observed after bronchoscopy (IV). Decreased mucociliary clearance can be compensated for, at least partly, by coughing (Mossberg et al 1981, Camner 1981). Consequently, respiratory mucosal damage and possible impairment of tracheobronchial clearance should be taken into consideration, especially under certain circumstances, for example, in patients who can not cough.

Scanning electron microscopy is the most suitable method to study the surface area in bronchial mucosal biopsies (Regland et al 1976), and biopsies from some of the patients in study IV were examined with this technique. In the biopsy taken from patient number 3, a heavy smoker with chronic bronchitis, a disease associated with decreased mucociliary transport (Camner et al 1973, Mossberg et al 1976), there were no normal ciliated epithelial cells. This may explain why he did not have any clearance. The biopsies examined only represent a very small area of the bronchial epithelium. The morphological findings in the biopsies correlated however rather well with the clearance patterns in the patients examined.

Haemodynamic effects of flexible fiberoptic bronchoscopy performed under topical anaesthesia

the cardiovascular effects of flexible fiberoptic bronchoscopy performed under topical anaesthesia. In patients with restrictive lung disease flexible fiberoptic bronchoscopy performed under topical anaesthesia induced substantial haemodynamic changes with marked increases in heart rate, mean arterial pressure, mean pulmonary arterial pressure, mean pulmonary arteriolar occlusion pressure and cardiac index (V).

Endotracheal intubation and laryngoscopy under general anaesthesia is associated with a rise in heart rate and arterial pressure (King et al. 1951, Stoelting 1977, Sørensen C Hjort et al. 1981), probably due to a sympathetic stimulation (Tomori & Widdicombe 1969, Siedlecki 1975, Russell et al. 1981). It is therefore tempting to consider that passage of the larynx and repeated irritation of the larynx by movement of the flexible fiberoptic bronchoscope during suctioning is also associated with sympathetic stimulation. It seems likely that part of the haemodynamic changes might be reduced by improved anaesthetic technique. Intravenous injected lidocaine and mouth wash and gargling with viscous lidocaine can attenuate the blood pressure response to laryngoscopy (Stoelting 1977). Although effective against tachycardia, beta-blocking agents do not effectively counteract the hypertensive response to laryngoscopy (Werner et al. 1980).

Hypoxemia during flexible fiberoptic bronchoscopy has been reported (Albertini et al. 1974, Randazzo & Wilson 1976, Shrader & Lakshmimaran 1978, Elguindi et al. 1979), and Dubrawsky et al. (1975) reported a significant decrease in arterial oxygen tension following bronchial washing and aspiration of 30 to 40 ml saline in the main bronchus. They suggested an altered ventilation-perfusion ratio following bronchial washing. A decreased ventilation-perfusion ratio after segmental lavage could however not be verified by Brash et al. (1976). In our study (V) arterial oxygen tension was continuously measured. Segmental lavage performed with 50 ml of normal saline did not induce hypoxemia. However, hypoxemia was induced during suctioning (V). A dramatically decreased arterial oxygen tension together with decreased tidal volume, increased arterial carbon dioxide tension and
increased cardiac output, was measured during intermittent suctioning through a flexible fiberoptic bronchoscope in six critically ill patients examined under ongoing controlled mechanical ventilation (Lindholm et al 1978). Fifteen minutes after bronchoscopy the values had returned to the pre-bronchoscopic recorded level in their study. The decrease in arterial oxygen tension induced during intermittent suctioning persisted 15 minutes after completed bronchoscopy in our study (V) and similar observations have been reported by Albertini et al (1974) and Randazzo & Wilson (1976) while Larsson et al (1981) did not observe hypoxemia after flexible fiberoptic bronchoscopy performed under topical anaesthesia. Altered ventilation-perfusion ratio due to suctioning and bronchoconstriction by mechanical stimulation of vagal receptors in the bronchial mucosa might explain hypoxemia during and after suctioning. The reflex-induced bronchoconstriction can be abolished by administration of atropine (Simonsson et al 1967, Belen et al 1981). As atropine also reduces bronchial secretion and prevents possible bradycardia due to vagal stimulation, it is reasonable to use atropine for premedication before bronchoscopy.

During flexible fiberoptic bronchoscopy cardiac arrhythmias have been reported as a complication associated with hypoxemia (Schrader & Lakshminarayan 1978). We did not observe any increase in cardiac arrhythmias in our study (V) and Luck et al (1978) suggested that the main determinant of arrhythmia appears not to be the procedure itself but rather the underlying cardiopulmonary status. Elguindi et al (1979) suggested that careful use of large dosages of topical lidocaine may prevent or ameliorate major cardiac arrhythmias during fiberoptic bronchoscopy. In our study (V) ST-T-segment depression was observed in three of ten patients during suctioning. A mismatching between myocardial oxygen demand and supply might explain this ST-T-segment depression. Increase in rate pressure product indicates increased myocardial oxygen consumption (Gobel et al 1978). During suctioning when myocardial oxygen availability was decreased because of decreased arterial oxygen tension and shortening of the diastolic coronary perfusion time, rate pressure product reached it's highest value.
The increase in arterial pressure and heart rate during flexible fiberoptic bronchoscopy may be dangerous for patients with cardiac disease, especially in combination with hypoxemia. Supplementary oxygen should be given during bronchoscopy, and for monitoring purposes the ECG V5-lead can be of value to detect myocardial hypoxemia (Kaplan 1979).
CONCLUSIONS

1. In the diagnosis of carcinoma of the lung the diagnostic accuracy of combining forceps biopsy and one cytologic method (bronchial washing) was higher than that of any of the single methods, while no appreciable increase was received by using three, four or five diagnostic methods.

2. Brush biopsy damaged the rabbit respiratory mucosa and often penetrated the basement membrane. Regeneration started within the first day after brushing and a normal ciliated epithelium was re-generated within three weeks.

3. Flexible fiberoptic bronchoscopy in the pig induced respiratory mucosal damage even without brushing or suctioning. The columnal epithelial cells were torn off in areas where the bronchoscope had rubbed against the airway wall but the basement membrane was not damaged.

4. The tracheobronchial clearance system has a large reserve for mechanical trauma. Flexible fiberoptic bronchoscopy can, however, damage tracheobronchial clearance in some patients.

5. Flexible fiberoptic bronchoscopy induced marked haemodynamic changes, which were at maximum and of similar magnitude during passage through the larynx and during suctioning, while the haemodynamic effects of segmental lavage with 50 ml of normal saline were less prominent. A slight fall in arterial oxygen tension was measured during bronchial suctioning and in the postbronchoscopic period. During bronchial suctioning three of 10 patients developed ST-T-segment changes.
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