Anaesthesia in patients with cystic fibrosis
Giorgio Della Rocca

Cystic fibrosis is an autosomal-recessive disorder. In 1989 the gene mutation that causes cystic fibrosis was localized on the long arm of chromosome 7. Cystic fibrosis occurs in 1/2000 children and the majority now reach adulthood. In view of numerous clinical manifestations of cystic fibrosis, these patients frequently require surgery. Cystic fibrosis is therefore of increasing interest to anaesthesiologists. Preoperative assessment is reviewed. Pre-, intra- and postoperative care must be directed toward optimal clearance of viscous respiratory secretions, and should minimize the risk of postoperative respiratory complications. All procedures should be planned but it is very important to prepare patients for surgery, with daily physiotherapy, administration of therapeutic agents using aerosols, management of nutrition and pancreatic enzymes, and administration of vitamins and antibiotics if indicated. Currently, anaesthesia can safely be carried out in cystic fibrosis patients undergoing minor surgery, with very low incidence of postoperative respiratory complications. Finally, organ transplantation, and in particular lung transplantation, with all its attendant anaesthesiological implications, has improved the outcome for many patients with cystic fibrosis. Curr Opin Anaesthesiol 15:95–101. © 2002 Lippincott Williams & Wilkins.

Introduction
Cystic fibrosis (CF) is the commonest fatal inherited disease of Caucasians, with an incidence of 1 in 2000 births [1]. The CF gene is carried by 5% of the populations of Europe and North America [2] and the disease is transmitted in an autosomal-recessive manner.

When the disease was initially described in the 1930s, 80% of affected infants died during the first year of life [3]. Since then, survival and longevity have improved considerably, particularly during the past 20 years [4]. With improved longevity, more anaesthetists are likely to encounter patients with CF, presenting either with complications of the disease or for unrelated surgery (Table 1). Although the disease has been likened to chronic bronchitis [5], it is a complex multisystem disorder with several implications for the anaesthesiologist.

Cystic fibrosis
In 1989, the gene mutation that causes CF was localized to a specific locus on the long arm of chromosome 7 [6]. During the past 6 years we have gained considerable insight into the origin and evolution of the cystic fibrosis transmembrane conductance regulator gene [7] and CF alleles. Most of the questions we had before the cloning of the gene have now been answered [8–18].

The disease manifests as a clinical spectrum of differing severity and patterns of organ involvement. Daily management of patients plays the most important role. During the first stage of disease, good nutrition, administration of pancreatic enzymes and continuous physiotherapy are sufficient. In the early stages of CF, infections are avoided by clearance of secretions and careful toilet of the bronchial tree. Management of infections is based on regular sputum culture and direct use of antimicrobial agents, based on the pathogen-specific sensitivity.

In clinical practice, aggressive management and the introduction of new symptomatic treatments may account for the dramatic increase in survival of patients with CF [19]. The cornerstones of treatment include chest physiotherapy and exercise to optimize sputum clearance, adequate nutrition to promote normal growth, and aggressive antibiotic treatment of infections [20].

At the beginning of disease, most patients should have regular pulmonary function tests. Forced expiratory volume in 1 s (FEV₁) is used to determine whether
prior anaesthesia and surgery had any deleterious effects. FEV\(_1\) has also been used to compare the effects of treatments [21]; the change in FEV\(_1\) between successive pulmonary function tests was calculated for each patient from 3 months before the study period to 3 months after. A blood gas sample is often necessary to quantify the severity of pulmonary disease in CF patients.

**Anaesthetic management**

Surgical procedures that are commonly conducted in patients with CF include nasal polypectomy, venous access, bronchoscopy, pleural stripping, lung transplantation, laparotomy for bowel obstruction and enteral feeding procedures. Few studies have addressed anaesthesia in the context of CF. Most of those that have been published are retrospective and were conducted after 1964, when Salanitre et al. [22] reviewed 133 anaesthetic procedures in 93 patients over the preceding 18 years. In that study the perioperative mortality was 27%, with a high incidence of pulmonary complications (42%).

In 1972 Doershuk et al. [23] reviewed 144 anaesthetic procedures conducted over 11 years, and noted a perioperative mortality of 4%. A review by Lamberty and Rubin [24] examined 126 anaesthetic procedures over a 3-year period. The complication rate was 9%, and most complications were pulmonary; no patients died during the perioperative period. A retrospective analysis of pulmonary function tests in those patients suggested that anaesthesia had no long-term detrimental effects on the course of pulmonary disease. A small, prospective, controlled study of CF patients undergoing general anaesthesia for injection sclerotherapy of varices [25] showed a significant decline in pulmonary function tests 48 h after surgery, but no longer term follow up was undertaken.

In patients with CF undergoing minor ear, nose and throat surgery, only 5% of patients showed minor postoperative respiratory complications [26*]; thus, anaesthesia can safely be carried out in such cases.

It is unclear whether general anaesthesia per se has any effect on the long-term course of pulmonary disease, but it appears logical to avoid it by using local anaesthesia or nonsurgical management whenever possible.

**Preoperative period**

Suggested preoperative investigations are summarized in Table 2. Efforts should be made to quantify the level of disability and extent of cardiopulmonary disease preoperatively.

Preoperative pulmonary function studies commonly reveal an obstructive pattern of disease: increased functional residual capacity, decreased FEV\(_1\), decreased peak expiratory flow rate and decreased vital capacity. Pulmonary fibrosis, bronchospasm and intraluminal secretions cause low ventilation: perfusion ratios, leading to increased alveolar–arterial oxygen tension differences and lowered arterial oxygen tension. Arterial carbon dioxide tension is usually low or normal; the presence of an elevated arterial carbon dioxide tension often indicates advanced disease.

Decreased synthesis of clotting factors by diseased liver and impaired absorption of vitamin K are indicated by prolonged prothrombin time and partial thromboplastin time. These parameters should therefore be evaluated.

If preoperative sedation is required, and can be tolerated by the patient, then midazolam (0.4 ± 0.07 mg/kg) can safely be used, as indicated by Kumble et al. [26*]. Avoidance of postoperative constipation is of major importance, and represents a further reason to avoid the use of opioids since the preoperative period. Prophylactic use of osmotically active laxatives will

<table>
<thead>
<tr>
<th>Table 2. Preoperative evaluation</th>
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<tr>
<td><strong>All patients</strong></td>
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<tr>
<td>Full blood count</td>
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<td>Urea and electrolytes</td>
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<td>Liver function tests</td>
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<td>Chest X-ray</td>
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<td>Sputum culture and sensitivity</td>
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<td>Respiratory function tests</td>
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Shown are the investigations that are necessary for all cases and those that should be reserved for selected patients (when indicated).

**Table 1. The most frequent indications for anaesthesia in cystic fibrosis**

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<th>Neonates</th>
<th>Children/teenagers</th>
<th>Adults</th>
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<tr>
<td>Meconium ileus</td>
<td>Nasal polypectomy</td>
<td>Oesophageal varices</td>
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<td>Meconium peritonitis</td>
<td>Intravenous access</td>
<td>Recurrent pneumothorax</td>
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<td>Intestinal atresia</td>
<td>Ear/nose/throat surgery</td>
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<td>Lung (liver) transplantation</td>
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prevent constipation and obstruction during the postoperative period. Use of histamine-2 receptor antagonists and antacid premedication is recommended, because the incidence of gastroesophageal reflux is high [20]. The patient’s routine medications, particularly bronchodilators, corticosteroids and cardiotonic drugs, are continued into the perioperative period, including the morning of surgery [27].

Sputum clearance and chest physiotherapy should continue until the patient arrives at the operating room. Some patients require a considerable period in the morning to clear secretions that accumulate during sleep. Procedures are therefore best delayed until mid-morning, so that clearance of secretions is completed before induction of anaesthesia.

**Intraoperative period**

Advanced haemodynamic monitoring may be indicated, depending on the patient’s condition and the surgical procedure. A central venous line (through the internal jugular vein), an arterial line and, if indicated, a pulmonary artery catheter or a femoral artery line for the PiCCO System (Pulsion Medical System, Munich, Germany) may be introduced. Transoesophageal echocardiography should be available in case of pulmonary hypertension and/or right heart dysfunction. Also, arterial blood gas determinations are indicated for patients with severe disease.

Because the risk of pneumothorax is high in patients with severe disease, nitrous oxide should be omitted in favour of an air–oxygen mixture.

A patient history of clinically significant gastroesophageal reflux will mandate a rapid sequence induction; otherwise, standard intravenous or inhalational induction is acceptable [20]. The rapid recovery characteristics of propofol make it a rational selection. High functional residual capacity, small tidal volume and ventilation–perfusion mismatch lengthen inhalation induction time. Ketamine is relatively contraindicated because of its propensity to increase bronchial secretions and bronchoostrahea. Agents that irritate the respiratory tract, such as isoflurane or desflurane, should be avoided during the induction of anaesthesia; sevoflurane may be the most appropriate choice.

Local and regional blocks with maintenance of spontaneous ventilation are favoured techniques if the nature of the surgical procedure allows it. Continuous epidural anaesthesia without endotracheal intubation was used successfully in one study [28], but that report is not enough, as it is only a case report, for the assertion that such an approach is safe; however, it may be considered in patients with severe pulmonary disease. If a general anaesthesia is required, then maintenance of anaesthesia with one of the volatile agents is advantageous because they permit administration of high inspired concentrations of oxygen. Bronchodilatation, decreased muscle relaxant dosage and reduced airways hyperactivity are further advantages of inhalational agents.

A single-lumen endobronchial tube is commonly used, but in case of thoracic anaesthesia endobronchial intubation is usually performed with a left-sided double-lumen tube. If nasal intubation is indicated, then the turbinate should be examined preoperatively for polyps [29]; nevertheless, nasal intubation should usually be avoided because it may carry infections from the nasal cavity to the trachea. If tracheal intubation is to be performed, then it is recommended that a large size single-lumen tube (introduced using fibreoptic bronchoscopy) be used after induction of anaesthesia for endobronchial toilet and, if necessary, bronchoalveolar lavage. The laryngeal mask airway has been found to be well tolerated by many patients with CF [20]. However, such airway management tools carry a risk for aspiration and airways obstruction from secretions. Ventilation through a tracheal tube is usually satisfactory, although it could be argued that passage of a double-lumen tube is preferable in case the air leak is of such magnitude that ventilation has to be restricted to one lung. One-lung anaesthesia should be avoided as far as possible in such patients, because oxygenation cannot always be ensured if only one lung is ventilated, even with high concentrations of oxygen, and delivery of the entire tidal volume to one side increases the inflation pressure and hence the risk for pneumothorax on the nondependent side.

Muscle relaxants such as vecuronium, rocuronium or cisatracurium may be particularly appropriate because of their clearance and safety characteristics. Aminoglycoside antibiotics used to treat infections may prolong the neuromuscular blocking effect. Relaxants should be administered when necessary and only at minimum doses, and a nerve stimulator should routinely be used to guide administration and assess recovery of muscle function.

At the end of surgery all patients should be placed in a 30–40° sitting position, which is ideal for CF patients, as well as patients with chronic obstructive pulmonary disease.

All of the benefits of ambulatory surgery may be enjoyed by patients with CF, including minimizing time spent in hospital, reduced disruption to schedule and decreased exposure to nosocomial infections. The patient with CF alternates dramatically between periods of clinical stability and deterioration. Ambulatory surgery should be performed only during times of clinical
stability and optimal pulmonary function [20]. Nasal polypectomy, sinus endoscopy, sinus lavage and bronchoscopy are common outpatient surgical procedures in patients with CF.

**Postoperative period**

Because active respiratory physiotherapy should be performed as soon as possible after surgical procedures, anaesthesia should be tailored for rapid postoperative resumption of the ability to cough, breathe deeply and clear secretions actively. Provision of postoperative analgesia with nonsteroidal anti-inflammatory agents and/or carefully administered opioids is mandatory, and should be initiated preoperatively (pre-emptive analgesia).

Postoperative analgesia for both spontaneously breathing and mechanically ventilated patients usually consists of small doses of narcotic analgesics, because nonsteroidal anti-inflammatory agents may interfere with coagulation in case of decreasing prothrombin time. Local wound infiltration with longer acting local anaesthetics (ropivacaine/levobupivacaine) reduces the need for opioids for postoperative analgesia. Regional analgesia and anaesthesia techniques (epidural opioids and intercostal nerve blocks) are also effective in preserving pulmonary function while adequately treating postoperative pain [29]. However, epidural analgesia with bupivacaine/ropivacaine and fentanyl/sufentanil is indicated in major surgery.

Throughout the postoperative period, the patient with CF continues to be at risk for respiratory depression, pneumothorax, pneumonia, atelectasis and airways obstruction [30]. Therefore, patients with mild to severe respiratory failure should be continuously monitored in a postanaesthesia care unit and/or intensive care unit.

Effective humidification is essential if viscid sputum is to be expectorated as easily as possible, and the inspired gas should be humidified during anaesthesia. Humidified oxygen is used postoperatively, and additional humidification can be provided using an ultrasonic nebulizer. Inhalation of nebulized hypertonic saline may help to loosen tenacious sputum.

**Organ transplantation**

Until the advent of organ transplantation for patients with CF in 1984, for the majority the inevitable outcome was death from overwhelming pulmonary sepsis. The availability of transplantation has profoundly altered the emphasis of care and, following the procedure itself, the quality of life for CF patients [31–33].

When medical treatment is failing and a patient is listed for transplantation, there is a need not only to keep the patient alive, but also to maintain them in optimal clinical condition. A poorly nourished, bed-bound, demoralized patient is unlikely to survive the rigours of transplantation. It is a paradox that CF patients are listed for transplantation because they are unlikely to live for longer than 2 years, but they must be presented for a life-saving or life-threatening operation in the best possible health.

**Liver transplantation**

A significant number of adults with CF have palpable hepatosplenomegaly, with normal liver function tests. The basic defect in CF affects the biliary tree, with epithelial cell loss and mural fibrosis [34]. Intrahepatic and extrahepatic narrowing of the biliary tree may be localized or diffuse. Assessing the severity of liver disease when ascites and portal hypertension are absent is difficult. Severe progressive liver disease with good lung function is an indication for single-liver transplantation. Considerable success has been achieved in this field [35,36].

Liver transplantation should be considered in patients with CF that is complicated by hepatic cirrhosis and portal hypertension, but with mild to moderate pulmonary function abnormalities. These patients are at constant risk for variceal bleeding, and worsening of nutritional and respiratory status may lead to premature death from pulmonary complications. Close co-operation among clinicians and specialists is of utmost importance in determining which patients with CF and associated lung or liver diseases should be referred and accepted for combined lung and liver transplantation, and sometimes for isolated liver transplantation. With a good graft, portal hypertension is relieved, and absorption, nutrition and respiratory function are all improved. The improved quality of life in these patients (including respiratory function) after liver transplantation is remarkable.

**Lung transplantation**

Most CF patients who undergo a transplantation procedure receive a lung transplantation, even though the availability of donors continues to be limited, particularly for children [37]. Pulmonary haemodynamics are worst in patients dying on the waiting list and deteriorate significantly while they await transplantation. Increased pulmonary arterial pressure, cardiac index, pulmonary arterial occlusion pressure and shunt indicate a low life expectancy and increased risk for death within 6–8 months; such patients should be considered to be in the descending phase of the ‘transplant window’ and should receive priority for organ allocation. The cardiopulmonary characteristics of CF patients may therefore help to establish them as high-priority candidates for lung transplantation [38*].
With regard to intraoperative management, after induction of anaesthesia a large size, single-lumen tube is used for fibreoptic bronchoscopy in order to allow endobronchial toilet and bronchoalveolar lavage. The appropriate left endobronchial tube (37–39 Fr) is then positioned.

During lung implantation, drug support consists of dobutamine (5–10 μg/kg per min), noradrenaline (norepinephrine; 0.05–3 μg/kg per min), ephedrine (5–10 mg boluses when necessary) and, if necessary, epinephrine, enoximone or isoprenaline. Prostaglandin E1 (20–100 ng/kg per min) and inhaled nitric oxide (NO) (10–40 parts per million) and, rarely, nitroglycerine or sodium nitroprusside are used as pulmonary vasodilators. It has been shown that the vasodilator properties of inhaled NO are mainly restricted to the pulmonary circulation [39,40], and this makes NO an attractive agent for use in several clinical conditions associated with pulmonary hypertension [41–47], including conventional thoracic surgery [48]. In patients undergoing lung transplantation, its efficacy may be increased by the simultaneous administration of inhaled aerosolized prostacyclin [49*].

Another innovative advance in modern anaesthesia is volumetric monitoring, which is indicated in CF patients undergoing solid organ transplantation [50**]. Intrathoracic blood volume (measured using a transpulmonary thermodilution technique) [51], when compared with central venous pressure and pulmonary artery occlusion pressure, more accurately reflects cardiac preload [52,53]. The evaluation of a measure of pulmonary oedema such as extravascular lung water make this new system very useful not only in the intraoperative period but also in the postoperative period in critically ill patients.

**Conclusion**

Although CF is not yet curable, the good news is that the situation is not hopeless. The improvement in prognosis is encouraging; in the 1960s children struck by the disease were not expected to reach their eighth birthday, but today most have an average lifespan of 30 years.

In addition to liver or lung transplantation, it is not uncommon for a CF patient to require general anaesthesia for surgical treatment of other pathologies. Because of their pathologies, care must be taken with
airway management. Use of fibroptic bronchoscopy to position accurately a tube for endobronchial toilet is mandatory in these patients before and at the end of the surgical procedure. Extended monitoring, including transoesophageal echocardiography, pulmonary artery catheterization and/or use of a PiCCO system, may be necessary in case of pulmonary hypertension and/or right heart dysfunction.

Short-acting anaesthetics are recommended because they allow rapid recovery; propofol and sevoflurane are the most appropriate agents for induction of anaesthesia. An algorithm for management of anaesthesia is provided in Figure 1. Postoperative analgesia is mandatory, because chest physiotherapy has to be performed as soon after the procedure as possible in order to remove viscous secretions and therefore avoid pulmonary infection. When medical treatment fails in patients with CF, they can be referred for liver or lung transplantation. These procedures improve the quality of life of CF patients and increase their average lifespan.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest


