

Postoperative Care of Patients Undergoing Lung Resection

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Abstract

Due to frequent pre-existing comorbidities and variable impairment of postoperative respiratory function thoracic surgical patients still encounter various complications which in high risk individuals may contribute to poor outcome.

Postoperative management of patients undergoing lung resection may vary from simple and transient monitoring of vital functions in the recovery room to the highly specialized therapeutic approach that requires direct admission to the ICU.

Proper care of these patients focuses on obtaining an early recovery from anesthesia and mechanical ventilation, achieving optimal pain control, preventing postoperative pulmonary complications, and facilitating early mobilization.

The early post-operative period following extensive surgical resection is a crucial time when major cardiac and respiratory adverse events may significantly affect both the hemodynamic response and "residual" lung performance.

Among the worst complications an early onset of acute hypoxemia, usually identified as post-resectional ALI or ARDS, has always been considered an ominous sign. This severe pulmonary edema, unrelated to cardiac failure and accompanied with endothelial damage and radiographic pulmonary infiltrates, has been shown to be the leading cause of death in patients undergoing lung surgery. In severe postoperative lung dysfunction conventional mechanical ventilation with protective ventilatory settings is needed to improve gas exchange; in less serious disease noninvasive ventilatory strategies may be safe and effective.

Other potentially useful treatments for unresponsive hypoxia include the administration of inhaled pulmonary vasodilators, ventilatory support in the prone position, and the application of extracorporeal membrane oxygenation (ECMO).

A multidisciplinary management of high risk patients undergoing lung surgery, focused on adequate preoperative "pulmonary rehabilitation", intraoperative lung protective strategies, postoperative optimization of analgesia and incentivization of cough effectiveness, is essential for a positive outcome.

Keywords: Lung surgery; Postresectional edema; Postoperative lung dysfunction; Postresectional hypoxia

Despite the advances in surgical technique, anesthesia management, and perioperative care, patients undergoing thoracotomy may still experience postoperative lung dysfunction and other complications which contribute to an increased overall perioperative risk. Optimized postoperative care is very important in achieving a successful outcome after thoracic surgery. Respiratory function following lung resection may be affected by various factors including phrenic nerve dysfunction, disruption of normal activity of respiratory muscles starting at induction of anesthesia and continuing into the postoperative period, sputum retention, incomplete relief of surgical pain, and inadequate physical therapy [1].

In relatively healthy patients not submitted to extensive surgical procedures, the common care at the emergence of anesthesia and after tracheal extubation can be sufficiently provided in the recovery room. Continuous monitoring of consciousness recovery, spontaneous breathing pattern, arterial oxygen saturation, body temperature, urinary output, pain intensity, along with encouragement to breathe deeply are the essential aspects of routine postoperative assistance. These patients are then discharged to the general ward once they meet the following criteria: the ability to maintain adequate oxygenation with minimal oxygen enrichment, hemodynamic stability, sufficient spontaneous clearance of bronchial secretion, reduced work of breathing, and almost total absence of postoperative pain.

However, often due to advanced age, poor preoperative pulmonary function, cardiovascular comorbidity or surgical invasiveness, postoperative care of high risk patients undergoing thoracotomy

may be challenging and almost always necessitates intensive care and multidisciplinary therapeutic approach. Some pre-existing cardiopulmonary diseases and other medical conditions may in fact become exacerbated by the operative procedure thus leading to several postoperative complications. Major respiratory and cardiac complications continue to present an important source of morbidity and mortality after lung surgery.

The early post-operative period following extensive surgical resection is a crucial time when strict monitoring and support of cardiorespiratory function, frequent assessment of residual lung performance, timely recognition of severe complications, and prompt treatment of extralung organ system dysfunction are mandatory. Postoperative care of these patients mainly centers on rapid hemodynamic stabilization, early weaning from mechanical ventilation, complete relief of postoperative pain, proper fluid administration, and facilitation of specific maneuvers designed to increase lung volumes.

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Intensive Care Unit (ICU) Admission after Thoracic Surgery

Although current practice in thoracic surgery recommends routine extubation immediately after surgery, a number of patients will still suffer postoperative complications that can only be managed in an ICU setting. Direct admission to the ICU following surgery without planning for extubation in the operating room or recovery room should be considered in patients undergoing extensive resections or in individuals with preoperative comorbidities and/or limited functional reserve.

Thoracic surgery is one of the specialties that frequently uses ICU resources either electively for monitoring high-risk patients in the early postoperative period or emergently for major cardiorespiratory complications requiring active life-supporting treatments [2]. Brunelli et al. [3], in a multicenter investigation looking at validating a risk score capable of predicting the need for ICU admission after major lung resection, demonstrated that the highest predictive variables were: pneumonectomy, age older than 65, predicted postoperative forced expiratory volume in 1 second below 65%, predicted postoperative carbon monoxide lung diffusion capacity below 50%, and cardiac comorbidity. ICU admission is mostly required to continue postoperative ventilatory assistance in a patient who is not suitable for early weaning from mechanical ventilation, or to implement a more invasive monitoring in case of hemodynamic or metabolic disturbances. It is also required for those patients who after the emergence from anesthesia still suffer from respiratory fatigue or gas exchange abnormalities and are candidates for non-invasive ventilatory support.

Post-resectional lung injury, a specific disease defined as acute hypoxemia accompanied by radiographic pulmonary infiltrates developing early after major pulmonary resection, or at any time in the postoperative course, requires an immediate admission to the ICU. Patients at risk for hypertensive crisis, severe arrhythmia, or cardiac failure should also be prophylactically admitted to a high dependency unit or an ICU.

Postoperative Ventilatory Assistance

Even though the great majority of patients undergo successful tracheal extubation soon after the end of the procedure or within the first hours, some individuals with marginal cardiopulmonary reserve or undergoing invasive and prolonged surgery inevitably require postoperative mechanical ventilation. However, mechanical ventilation is not devoid of adverse effects; thoracic surgery patients represent a particular group in whom ventilation-induced cytokine upregulation produces a proinflammatory state that renders the host more vulnerable to subsequent hit(s) such as hypoxia–reoxygenation and direct tissue trauma [4]. In addition, mechanical ventilation may increase the risk of bronchial stump disruption, bronchopleural fistula, persistent air leakage, and pulmonary infection [5].

Protective ventilatory settings with small tidal volumes (Vts) and positive end-expiratory pressure (PEEP) should be applied to reduce the risk of ventilator-induced lung injury. Using predicted rather than actual body weight for calculating the Vt per kilogram of body weight is a useful strategy to avoid lung hyperinflation and to reduce the risk of barotrauma [6]. As prolonged mechanical ventilation may be associated with a significant risk for pneumonia every effort should be made to promote fast weaning from invasive airways [7].

Noninvasive ventilation (NIV) has been proposed to assist the patient's spontaneous ventilation soon after early removal of the endotracheal tube, to prevent the occurrence of acute respiratory failure after surgery or to treat it [8]. One of the first studies on NIV after thoracic surgery was reported by Aguiló et al. [9]. The Author in a prospective, randomized, controlled and parallel trial investigated the short-term effects of NIV on pulmonary gas exchange, ventilatory pattern, systemic hemodynamics and pleural air leaks in 19 patients submitted to elective lung resection. Compared to medical therapy alone, the 10 subjects who received NIV therapy experienced a significant increase in PaO₂ and also a significant decrease in alveolar to arterial oxygen pressure gradient. However, this study added only limited information on surgical outcome as the duration of NIV was very short (60 min.) and post-resectional pulmonary complications were not recorded. Perrin et al. [10] investigated whether a perioperative prophylactic use of NIV in patients with a forced expiratory volume (FEV) lower than 70% of the predicted produced an improvement in pulmonary function after lung resection compared to oxygen therapy alone. In NIV group forced vital capacity and FEV1 improved on day 1, while PaO₂ was significantly improved on day 1, 2 and 3. The authors concluded that preventive NIV therapy used in patients submitted to elective lung resection improved the overall perioperative evolution of arterial blood gas values and pulmonary function parameters. At present, even though the early administration of NIV has been claimed a prophylactic and therapeutic tool for improving gas exchange in different surgical settings [8], no large randomised controlled studies support the routine prophylactic use of a non invasive approach as a means to facilitate early weaning from mechanical ventilation following lung surgery or to help in obtaining a persistent improvement of lung function.

Postoperative Analgesia

Postoperative pain is a major cause of shallow breathing and impaired coughing resulting in retention of secretions, atelectasis, hypoxaemia, hypercapnia and respiratory failure, especially in patients with pre-existing lung disease. Other adverse effects of incomplete pain relief include increased sympathetic tone, increased myocardial oxygen demand, increased afterload, myocardial dysfunction, and arrhythmias. Pain relief enhances restoration of pulmonary function, enables the patient to breathe and move about more easily, and facilitates active rehabilitation [11,12].

Infusion and patient-controlled analgesia (PCA) or regional techniques that mainly rely on epidural, intrathecal, or paravertebral blocks, along with intercostal nerve block or cryoprobe neurolysis are the most used techniques for postoperative pain control. Satisfactory analgesia can be achieved with i.v. opioids; however, their beneficial effects might be counterbalanced by the risk of respiratory depression, mild attenuation of the cough reflex, and diaphragm elevation due to bowel distension. Nonsteroidal antiinflammatory drugs, especially ketorolac tromethamine, are also used to supplement opioid analgesia. These drugs work synergistically with opioids and have no respiratory depressive effects. Disadvantages include platelet and renal dysfunction. Paracetamol at recommended doses, along with rescue doses of tramadol, may be proposed as a valid analgesic regimen [13]. This association is devoid of outright sedation and it is generally applied without strict respiratory monitoring. Respiratory depression is less common and less pronounced with tramadol than with other opioids [14].

Epidural analgesia is a well accepted method of postoperative pain

control after thoracic surgery. The opioid-sparing effect of a neuraxial technique and avoidance of possible side effects of systemic analgesics may be advantageous in increasing tidal volume and vital capacity, and improving diaphragm activity [15].

No large randomized study has yet examined whether epidural analgesia reduces complications and improves outcome after thoracotomy. A meta-analysis that included both postabdominal and postthoracotomy patients concluded that, compared with systemic opioids, epidural opioids reduce the incidence of atelectasis, pulmonary infections, and pulmonary complications [16].

Epidural local anesthetics alone or in association with low-dose opioids appear to be superior to patient controlled intravenous opioid-based analgesia [17]. However, as local anesthetics can also paralyze the intercostal respiratory muscles, a low concentration of local anesthetic should be used, especially in patients who already have a low FEV1. Local anesthetics even in relatively low concentrations are very effective in dynamic pain control thus allowing the patient to exercise [18]. Side effects of postoperative epidural infusions almost always come from bilateral sympathetic blockade, which frequently causes hypotension, especially if these patients are managed in a relatively hypovolaemic state for reasons of pulmonary function.

The use of thoracic epidural analgesia has been demonstrated highly satisfactory in terms of alleviating pain as judged by VAS evaluation [19]. Single intrathecal injection of morphine has also been shown to offer 12–24 h of postoperative pain relief [20]. However, single intrathecal opioid has limited duration of action and it needs to be followed by some other form of analgesia. Additionally, there is a significant delay between administration of intrathecal morphine and the onset of analgesia (usually 1–2 h) [20]. Continuous intrathecal infusion of morphine has been introduced into clinical practice, however, it is nowadays almost abandoned due to the associated significant adverse effects, such as the development of delayed sedation and respiratory depression caused by excessive rostral spread [21].

Thoracic paravertebral blockade for post-thoracotomy analgesia had a recent resurgence. This technique has been refined to give optimal pain relief with better safety profile when compared to intravenous drugs and thoracic epidural [22]. Vila et al. [23] reported that paravertebral block is equal to thoracic epidural analgesia and superior to intravenous analgesia in providing pain control and preserving postoperative pulmonary function. Placement of a catheter in the paravertebral space facilitates continuous infusion of a local anesthetic throughout the postoperative period; plain local anaesthetic solutions (e.g. L-bupivacaine, ropivacaine, 0.15–0.25%) or equivalents are generally used at a rate of 10–15 ml h⁻¹ [24].

Since the severity of acute postoperative pain is also a predictor of long-term pain after thoracotomy, optimization of perioperative pain control may help to reduce the currently high frequency of the post thoracotomy chronic pain syndrome [25].

Perioperative Fluid Management

Even though there is very little evidence regarding the proper amount of fluid to administer during and following thoracic surgery, concerns about the potential risk of postoperative lung injury recommend caution with liberal fluid administration. Elimination of infused crystalloids is significantly decreased during anesthesia and surgery [26]. Pulmonary function may be impaired by accumulation of interstitial fluids which may contribute to the development of pulmonary oedema, atelectasis, pneumonia or respiratory failure. The

resulting decreased tissue oxygenation may lead to impaired wound healing [27]. Because crystalloids distribute freely between interstitial and intravascular space they might not be suitable for volume resuscitation in acute hypovolemia or in acute lung injury (ALI). A strategy to limit fluid administration while still maintaining sufficient intravascular volume to prevent hypotension and renal complications may be the use of colloids such as starches [28]. However, volume resuscitation with colloids requires careful titration to current losses to avoid a remarkable protein shift toward the interstitial space [29]. In case of lung injury hypoproteinemia intensifies the vascular barrier dysfunction and promotes tissue edema formation. This is likely due to the increased capillary permeability of the nonoperative lung after pneumonectomy [30]. Studies have shown that early onset ALI can be partially prevented by careful perioperative fluid management. According to Moller et al. [31], administration of less than 3 liters of fluids in the first 24 hours or lower positive fluid balance over the first 3 days have been associated with reduced incidence of ALI. Perioperative generous fluid replacement is particularly deleterious once extubation and spontaneous ventilation have been regained because the increase in venous return at withdrawal of mechanical ventilation may determine interstitial congestion in the residual lung parenchyma [32].

Preventing Postoperative Pulmonary Complications (PPC)

As previously mentioned, severe pulmonary complications which lead to respiratory failure requiring artificial ventilation are associated with high morbidity, increased length of ICU stay, and mortality. Besides some life-threatening adverse events such as herniation of the heart, major hemorrhage, bronchial disruption and thromboembolism, several types of lung injury may affect these patients. These include atelectasis, pneumonia, pneumothorax, prolonged air leak and pleural effusion, ALI and acute respiratory distress syndrome (ARDS). ALI and ARDS are responsible for the vast majority of respiratory-related deaths [33]. There is a significant risk for postoperative lung dysfunction following resection surgery as a result of several factors such as inhibition of the phrenic nerve, pain, reduced muscle tone due to general anaesthesia, and loss of functioning lung parenchyma. These can lead to sputum retention, lobar atelectasis, pneumonia and respiratory failure. In addition, anesthesia and aggressive surgery may impair the function of lung inflammatory cells, which could increase the susceptibility to post-operative infections. The overall incidence of PPC following thoracic surgery has been reported to vary from 15% to 37.5%, primarily due to the type of pulmonary complications studied, the clinical criteria used in the definition, and the type of lung surgery included [34]. Recent studies have reported a much lower incidence, ranging from 3.9% in the study by Reeve et al. [35] to 12% in the Agostini et al. study [36] (where PPC were defined as clinical or microbiological evidence of pulmonary infection requiring antibiotic therapy, or clinically significant atelectasis requiring bronchoscopy) to 15.5% and 4.7% respectively before and after implementing intensive physiotherapy in the report by Novoa et al. [37]. Minor PPC are quite common and include unexplained fever, excessive bronchial secretions, abnormal breath sounds, and productive cough. On the contrary, severe PPC are less frequent but consistently impact perioperative mortality. In the recent study by Amar et al. [38] severe PPC, defined as respiratory failure requiring intensive care unit admission or intubation, pneumonia, atelectasis requiring bronchoscopy, pulmonary embolism, and need for supplemental oxygen at hospital discharge, occurred in approximately 13% of patients. Recognised risk factors include age, preoperative

pulmonary function tests, cardiovascular comorbidity, smoking status and chronic obstructive pulmonary disease (COPD). Operating time > 80 minutes and the need for postoperative mechanical ventilation have been proven to be two independent risk factors for the development of any kind of complication [39]. Various procedures have been adopted to decrease the incidence of PPC. Muehling et al. [40] implemented a multimodal therapeutic approach, the so called fast track clinical pathway, to reduce morbidity and mortality after major lung surgery. It consisted in preoperative patient education about postoperative care, preoperative fasting limited to 2 h preoperatively, pain control with thoracic epidural catheter between T5 and T9 accompanied by NSAIDs, and enteral feeding and ambulation started on the evening of the operation. In this optimized patient care program using a fast track regimen the rate of pulmonary complications was significantly decreased as compared to a conservative treatment protocol. However, the current practice demonstrates that fast-track surgery alone may not always decrease the incidence of PPC and several other measures have been recommended as part of a multimodal and multidisciplinary perioperative approach aiming at preventing their occurrence. Even though many of the procedures believed to reduce the risk of PPC are supported by a conventional "traditional" consensus, no clear evidence recommends their routine application. For example to date no reports attest to the effectiveness of preoperative incentive spirometry, active breathing, and forced expiration techniques in preventing complications in the specific setting of thoracic surgery. A significant benefit was only demonstrated by Perrin et al. [10] who prophylactically implemented trials of NIV 7 days before surgery and, as previously stated, observed a significant postoperative improvement of both gas exchange and pulmonary volumes. In their study the incidence of major atelectasis was 14.2% in the NIV group and 38.9% in the control group. The hospital stay was significantly longer in the latter group. Intraoperative protective ventilatory strategies during one lung ventilation have been shown to reduce the incidence of PPC. Yang et al. [41] demonstrated that a protective ventilation strategy consisting of FiO₂ 0.5, Vt 6 mL/kg, PEEP 5 cm H₂O, and pressure controlled ventilation provided beneficial effects in terms of fewer pulmonary complications and improved oxygenation indices as opposed to the conventional ventilation strategy. In patients who received low Vt (5 mL/kg) with a PEEP level of 5 cmH₂O, as compared to a Vt of 10 mL/kg and no PEEP, Michelet and coworkers [42] reported an attenuated systemic proinflammatory response, reduced extravascular lung water index, and improved PaO₂ /FiO₂ that allowed earlier extubation. Even though early postoperative use of continuous positive airway pressure (CPAP) or NIV with pressure support may result in faster improvement of arterial hypoxemia, their advantage in reducing the risk of PPC has been reported only in a few trials, and particularly when non invasive ventilatory support was associated with chest physiotherapy [43]. Besides Perrin's study [10] where NIV showed an improvement of oxygenation and a reduction in atelectasis, the benefits from non invasive ventilatory support are mainly reported in the treatment of rather than in prevention of postoperative acute respiratory failure [44,45]. Some authors have underlined the role of prophylactic minitracheostomy (MT) to aid postoperative sputum clearance in high-risk patients undergoing lung resection [46,47]. It is well-known that minitracheostomy facilitates early and regular suctioning of the tracheobronchial tree and may be beneficial in preventing complications associated with bronchial secretions retention. Two old randomized controlled studies conducted by Isssa et al. [47] and Randell et al. [48] were able to demonstrate a significant reduction in the rate of pneumonia and postoperative atelectasis, and in the need for bronchoscopy in the prophylactic MT group. In Issa's study 56 to

86% of individuals were at high risk of pulmonary complications due to heavy smoking or obstructive or infectious lung disease. Bonde et al. [46] randomised 102 patients to receive physiotherapy at least twice daily for five days (n = 52) or a minitracheostomy (n = 50) with tracheal cannula suctions at least twice daily in addition to physiotherapy. In their report the prophylactic MT group had a significant reduction in sputum retention and postoperative atelectasis, along with a reduction (not significant) in the incidence of pneumonia and toilet bronchoscopy. A recent report by Abdelaziz et al. [49] underlines that prophylactic MT facilitates early and regular suctioning of the tracheobronchial tree, and that for high-risk patients it may be beneficial during the critical postoperative period in preventing complications associated with sputum retention. However, they reported that no studies have demonstrated a significant reduction in mortality, intensive care unit or hospital length of stay following MT. Complications from MT insertion are mostly minor and self-limiting, but serious adverse events have also been reported [50].

Incentive spirometry, "lung expansion" exercises, chest physiotherapy and early mobilization have for years been recommended to prevent the reduction in lung volumes and function, and the decrease in expiratory flow after thoracic surgery [51]. Deep breathing and early upright position in the immediate postoperative period were considered the best way to facilitate rapid recovery and minimize respiratory and other serious complications (such as deep venous thrombosis/pulmonary embolism) [52]. Agostini et al. [53] demonstrated that physiotherapy either with or without incentive spirometry may reduce the incidence of PPC and improve lung function. Novoa et al. [37] evaluated the role of perioperative chest physiotherapy in modifying the risk of pulmonary morbidity after lobectomy in 784 lung cancer patients (361 operated after implementing a new physiotherapy program). They reported that chest physiotherapy performed by specialized therapists reduced the overall pulmonary morbidity after lobectomy for lung cancer. However, in recent years the evidence for the use of incentive spirometry and chest physiotherapy following thoracic surgery has been reviewed and their effectiveness reevaluated. A recent summary of MEDLINE, CINAHL, and Cochrane Library databases for articles published between January 1995 and April 2011, and reporting the results of 54 clinical trials and systematic reviews on incentive spirometry [54] reports as following: Incentive spirometry alone is not recommended for routine use in the preoperative and postoperative setting to prevent PPC; it should be used in association with deep breathing techniques, directed coughing, early mobilization, and optimal analgesia; it is suggested that deep breathing exercises provide the same benefit as incentive spirometry in the preoperative and postoperative setting. The traditional recommendations on implementing preoperative rehabilitation, lung expansion maneuvers, and postoperative physiotherapy following thoracic surgery are losing ground since the supposed advantages of these regimens have met little evidence in recent reports. According to the clinical practice guidelines developed by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS), [55] even though early pre- and post-operative rehabilitation should still be recommended since it may produce functional benefits in resectable lung cancer patients, factors such as candidate selection, late outcomes (i.e. post-operative complications and death), and programme content and duration need to be further investigated. A recent study by Ludwig et al. [56] prospectively evaluated the effectiveness of intermittent positive-pressure breathing on the prevention of PPC in 55 patients undergoing major lung resection. PPC occurred in 19% of patients without intermittent positive-pressure breathing and in 27% of the treatment

group. In the treatment group the incidence of pneumonia was slightly higher. The authors were unable to find evidence of an additional improvement in postoperative pulmonary function when intermittent positive-pressure breathing was added to the standard physical therapy. Reeve et al. [35] conducted a prospective, single-blind, parallel-group, randomised trial aimed at investigating whether targeted postoperative respiratory physiotherapy decreased the incidence of PPC and length of stay in 76 patients undergoing elective pulmonary resection via open thoracotomy. Daily respiratory physiotherapy until discharge was provided in the treatment group whereas the control group received standard medical/nursing care. PPC developed in two participants (4.8%) in the treatment group and in one participant (2.9%) in the control group. The authors concluded that targeted respiratory physiotherapy may not be required in addition to standard nursing care. In their report the outcome of patients who were managed with an early sitting out of bed and ambulation was good and not further improved by the addition of targeted respiratory physiotherapy. Given the relatively low incidence of PPC in more recent observations, and the conflicting results reported in various studies, further trials on the benefit of physical therapy are needed, particularly in high respiratory risk patients. In this patient group trials should be focusing not only on the prevention of PPC but also on the time to return to pre-surgery lung function.

Postoperative Arrhythmias

Cardiovascular complications are not infrequent after lung surgery and result in increased morbidity, a longer ICU and hospital stay, and higher costs [57]. Despite extensive and aggressive perioperative management different types of arrhythmias may still occur in the postoperative course. Cardiac arrhythmias are associated both with hemodynamic impairment and an increased risk of thromboembolism, stroke, myocardial infarction, and heart failure. Atrial arrhythmia occurs after 10% to 20% of major noncardiac thoracic operations, even though it is often underreported because it is generally self-limited. According to the American Society of Thoracic Surgeons (ASTS) database, five variables are highly predictive of postoperative atrial fibrillation (AF): increasing age, increasing extent of operation, male sex, nonblack race, and clinical stage II or greater tumors [58]. Right-sided pneumonectomy is burdened by a high incidence of AF, which has been shown to be independently associated with ventricular tachycardia [59]. Two major causes of supraventricular arrhythmias have been recognized: a relatively high sympathetic status caused by injury to the cardiac parasympathetic nerves by surgical manipulation, and right-sided heart pressures increase due to a reduction in pulmonary vascular bed volume and reactive pulmonary vasoconstriction [60,61].

Given the frequency and significance of supraventricular arrhythmias (SVA) after thoracic surgery different drugs have been investigated. Prophylactic treatment with digoxin was used for rate control in patients with AF, but it failed to control dysrhythmia or it was associated with increased SVA in the digoxin treated arm [62]. Magnesium sulphate is often used as an anti-arrhythmic agent in the perioperative setting as it reduces the rate of the sino-atrial node impulses and increases the refractory period of the atrioventricular node [63]. Data on magnesium effectiveness are still conflicting. While Terzi et al. [64] in a prospective, randomized, open, placebo controlled trial showed a statistically significant reduction in the incidence of SVA from 26.7% in the control group to 10.7% in the magnesium group, Saran et al. [65] observed no reduction in the incidence of SVA with prophylactic magnesium, even though it reduced their incidence in the high risk cohort of patients undergoing pneumonectomy. Statin

drugs, which have anti-inflammatory properties, have also been shown to be associated with a reduction in the incidence of post-pulmonary resection AF [66] but their use is not supported by clear evidence. Beta blockers should not be recommended because of their limited capacity to convert arrhythmias to sinus rhythm and their potential to cause hemodynamic derangement [67]. Amiodarone is one of the preferred drugs for treating both supraventricular and ventricular arrhythmias. Due to potential development of ARDS after amiodarone in pneumonectomy [68] its use in the perioperative period has long been debated. Recent reports, however, attest to the efficacy and high safety of amiodarone in thoracic surgery. In the study by Lanza et al. [69] the amiodarone-treated patients (200 mg orally every 8 hours continued until hospital discharge) showed an incidence of AF of 9.7%, compared with 33% in the control group. Tisdale et al. [70] demonstrated that Amiodarone prophylaxis significantly reduced the incidence of AF after anatomic pulmonary resection. In the 65 patients randomly assigned to receive amiodarone (1,050 mg by continuous intravenous infusion over 24 hours, initiated at the time of anesthesia induction, followed by 400 mg orally twice daily until hospital discharge or for a maximum of 6 days) the incidence of AF was lower in the amiodarone group than in the control group (13.8% versus 32.3%, p = 0.02). Median length of intensive care unit stay was shorter in the amiodarone group (46 versus 84 hours, p = 0.03). There was no significant difference between the amiodarone and control groups in the incidence of pulmonary complications. Recently eighty patients undergoing transthoracic esophagectomy were randomly, prospectively assigned to receive amiodarone or no prophylaxis [71]. The incidence of atrial fibrillation requiring treatment was lower in the amiodarone group than in the control group (15% vs 40%). According to the evidence available amiodarone, and to a lesser extent magnesium, appear now the drugs associated with greatest benefit in the prevention/treatment of SVA following lung resection. Pulmonary fibrosis as a consequence of amiodarone therapy has been variably reported. Its overall incidence is less than 3%, it occurs in association with long-term oral therapy, and is most likely related to large cumulative doses [72].

Post-resectional ALI/ARDS and Ventilatory Management

Acute hypoxemia associated with radiographic pulmonary infiltrates without a clearly identifiable cause, previously coined postpneumonectomy pulmonary edema, low pressure edema or permeability pulmonary edema, is nowadays identified as post-thoracotomy ALI or ARDS, depending on the severity of gas exchange impairment. The reported incidence of post-resectional ALI and ARDS varies from 2% to 8% [73,74]. It remains among the worst complications and it is still the leading cause of death in patients undergoing lung resection [75]. Post-pneumonectomy ALI has been described with a bimodal time of onset. Late cases present 3–10 days after operation and are secondary to obvious causes such as bronchopneumonia, bronchial rupture, bronchopulmonary fistula or gastric aspiration. Early or “primary” ALI presents on postoperative days 0–3. Sen et al. [74] demonstrated that the most important predictive factors for ALI and ARDS were alcohol abuse, higher ASA score classification, pulmonary resection type and the transfusion of fresh frozen plasma during intraoperative period. In the report by Licker et al. [76] four factors were independent significant predictors of primary ALI: high intraoperative ventilation pressures, excessive i.v. volume replacement, pneumonectomy, and preoperative alcohol abuse. Surgical trauma, lymphatic disruption, hyperinflation, capillary endothelial injury, and increased permeability can all contribute to the developing of post-

pneumonectomy lung injury [77]. Although there is an association between postoperative ALI and fluid overload, the noncardiogenic nature of the pulmonary oedema and the protein-rich oedema fluid is more consistent with an ARDS-type mechanism, with endothelial damage playing a key role. Preventive strategies to reduce the risk of post-resectional ALI or ARDS mainly include the avoidance of intraoperative overhydration and lung hyperinflation during one-lung ventilation. In two retrospective observational studies a large V_t and an elevated inspiratory pressure during one lung ventilation have been identified as strong predictors of ALI [77,78]. Both non-invasive and invasive ventilatory strategies have been adopted to support the patients with post-resectional lung injury. A first attempt with NIV appears reasonable in the presence of non severe hypoxemia or respiratory fatigue. Auriant et al. [44] in a randomized trial evaluated the efficacy of bilevel non invasive ventilation compared with standard therapy in 48 patients with acute hypoxic respiratory insufficiency after lung resection. In the NIV group the arterial oxygenation and respiratory rate significantly improved just after 2 hours of treatment. Twelve of the 24 patients (50%) in the standard treatment group required invasive mechanical ventilation versus only 5 (20.8%) in the NIV group. Mortality rates were significantly lower in the NIV group (12.5% vs 37.5% in the standard group). In the report by Lefebvre et al. [45], among the 690 patients admitted to intensive care following lung resection 89 underwent NIV support, 59 patients due to hypoxic acute respiratory failure and 30 due to hypercapnic acute respiratory failure. The overall success rate of NIV was 85.3%, while NIV failure occurred in 13 patients (14%). The mortality rate of patients who did not benefit from NIV and required intubation was 46.1%. The presence of cardiac co-morbidities and lack of initial response to NIV were found to be independently associated with NIV failure. Although NIV may increase lung volumes, improve gas exchange and reduce the work of breathing, in case of full blown ARDS it will no longer be sufficient and conventional invasive ventilation should be instituted. However, post-resectional ARDS requiring invasive ventilation is associated with significant morbidity, and mortality rates in the range of 40%-60% have been reported [79]. Under mechanical ventilation, given the dishomogeneous distribution of lung injury, the regions that are relatively unaffected receive a disproportionate amount of the delivered tidal volume and are therefore at risk of overdistension (volutrauma). For this reason, to prevent further ventilator-induced lung damage, lung-protective ventilatory strategies, similar to those associated with the greater benefits in critically ill patients with ALI/ ARDS, should be implemented [80,81]. Even though clear evidence on the best ventilatory technique in the specific setting of post-resectional ARDS is lacking, using low tidal volumes combined with lung recruitment maneuvers and moderate to high PEEP may ensure satisfactory gas exchange. The pressure-controlled mode of ventilation (vs. volume controlled mode) may also be useful to lower peak airway pressure and provide similar blood oxygenation indices [41]. Additional treatment suggested for ARDS-induced severe hypoxemia, refractory to "maximal" ventilatory treatment, includes the use of two selective inhaled pulmonary vasodilators, nitric oxide (NO) and prostacyclins. They have been proposed for their capacitance of increasing the remaining pulmonary vasculature and improving ventilation/perfusion matching. NO is a selective pulmonary vasodilator capable of increasing the perfusion of well-ventilated portions of the lung and decreasing extravasation of fluid from the pulmonary vasculature [82]. Besides its theoretical advantages and the ability to temporarily improve oxygenation in ALI or ARDS, it has shown no mortality benefit. In a recent meta-analysis its routine use has been strongly debated or not recommended [83]. Observational studies confirmed that inhaled prostacyclins, such as aerosolized

PG I2, and PG E1, determined an improvement in oxygenation and lung compliance, and a reduction in ventilator dependency but no difference in mortality [84,85]. Mechanical ventilation in the prone position has also been applied in case of serious impairment of gas exchange associated with ARDS [86]. It may result in an improvement in oxygenation due to various possible mechanisms: recruitment of dependent lung units, redistribution of blood flow to the more unaffected lung regions, reducing ventilation perfusion mismatch, and facilitation of respiratory secretion clearance [87]. To date neither large studies nor recommendations have been provided on the effectiveness of the prone position in the ventilatory management of patients with severe post-resectional injury. However, in our opinion, the redistribution of inspiratory gas flow and pulmonary blood flow, along with the potential re-inflation of the dependent dorsal lung regions induced by prone ventilation may be of some benefit for significant hypoxemia despite full ventilator support. In addition to protective ventilation the interventional lung-assist membrane ventilator (iLA, Novalung, Hechingen, Germany) [88] has also been proposed to facilitate the healing of postoperative ARDS. It is a pumpless device that provides passive complete carbon dioxide removal by means of a peripheral arteriovenous shunt using only the heart as the driving force. Since it allows the reduction of mechanical ventilator settings to such an extent as to achieve nondamaging ventilation, it may further prevent the potentially damaging lung stretching and release of inflammatory mediators induced by the conventional protective ventilation. In the occurrence of a life-threatening impairment of gas exchange under full ventilatory assistance the application of extracorporeal membrane oxygenation (ECMO) can provide temporary life-saving support in anticipation of recovery of residual diseased lung. As ECMO permits the removal of carbon dioxide and the reduction of fraction of inspired oxygen it allows minimizing mechanical stress injury on the alveoli from the ventilator [89].

Conclusions

The period following thoracic surgery is marked by variable changes in the structure and function of the respiratory system which can affect both the relatively healthy patients and those with pre-existing respiratory disease. Even though significant advances have been made in perioperative pain relief, non-invasive and invasive assisted ventilation, hemodynamic and fluid management, and heart rate control, many questions remain unexplained on the measures to adopt for preventing PPC, the mechanisms of ALI or ARDS development, and their proper treatment.

Current management of high-risk patients undergoing lung resection should be focused on preoperative pulmonary rehabilitation [90], intraoperative lung protective strategies, surgical skill aiming at preventing lung air leaks, optimal analgesia, and improvement of coughing effectiveness.

Recently the value of pulmonary rehabilitation prior to lung resection has come under closer scrutiny as the short period between diagnosis and surgery has often been considered insufficient to impact upon exercise capacity and thus be unlikely to reduce pre/post operative risk [91]. In the postoperative multimodal approach aiming at preventing PPC and facilitating prompt recovery an accumulating body of evidence seems also to demonstrate that prophylactic postoperative physiotherapy beyond early mobilisation may be unnecessary. High risk patients with "marginal" preoperative cardiac and pulmonary parameters should be admitted to appropriate high-dependency units following thoracotomy; ICU stay should instead be

recommended following complex pulmonary resections, or for lung resection candidates who need ventilatory support or with significant inability due to concomitant incapacitating co-morbidities.

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