Cardiovascular Adaptations and Complications

56

Alessia Pedoto and David Amar

Key Points

- Changes in *right ventricular anatomy and function* can occur at several stages of lung resection, starting after induction of general anesthesia and positioning, followed by one-lung ventilation and surgical dissection. Compensatory mechanisms may not occur in patients with advanced COPD who are at risk of developing long-term complications. Several tests are available during the intraoperative period to evaluate right heart function, and their merits are reviewed.
- *Supraventricular arrhythmias* are a common complication after thoracic surgery, depending on the extent of the dissection. Atrial fibrillation is the most common postoperative rhythm disturbance after lung resection. Several pathophysiologic mechanisms as well as prophylactic and/or therapeutic maneuvers have been proposed. Older age and intrapericardial procedures are among the risk factors that strongly correlate with this condition.
- *Acute coronary syndrome* after thoracic surgery is rare but is associated with a high risk of death. Patients at risk are the ones with preoperative coronary artery disease and abnormal exercise testing. There are no clear recommendations on the role of preoperative cardiac catheterization and coronary revascularization.
- *Cardiac failure* can result from either right or left heart dysfunction and can be transient or long standing. Symptoms may be subtle at rest and become evident during exertion. *Cardiac herniation* is a rare complication that may occur after intrapericardial pneumonectomy and is associated with a high mortality rate. Clinical and electrocardiographic signs are very nonspecific, and treatment is surgical.
- *Mediastinal shift* is the result of changes in the post-pneumonectomy space. A high index of suspicion is needed for the diagnosis, which can present with severe hemodynamic compromise or respiratory symptoms. *Post-pneumonectomy syndrome* may occur in the late postoperative period. It is characterized by an extreme mediastinal shift which causes dynamic compression of the distal airway and respiratory insufficiency. Treatment is surgical.

Introduction

Lung resection, especially if extensive, can cause acute and chronic changes in the anatomy and function of the right heart. This can be the result of either transient or sustained pressure or volume overload, reduction in contractility, cardiomyopathy, or arrhythmias [1], especially in the presence of pre-existing abnormalities [2]. The right heart is very sensitive to increases in afterload [3]. Acute increase in pulmonary arterial pressures (PAP) can lead to a significant decrease in right ventricular (RV) output with subsequent RV failure. Secondary left ventricular (LV) compression can cause systemic hypotension, with right coronary artery (RCA) hypoperfusion and possible right myocardial ischemia [4]. The right heart has recently been recognized as an active mediator, rather than a passive conduit, that can contribute to perioperative morbidity [5]. Any pathology associated with pulmonary hypertension and chronic hypoxia (such as end-stage COPD or connective tissue interstitial lung disease) can cause baseline right

A. Pedoto (✉) · D. Amar
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: pedotoa@mskcc.org

P. Slinger (ed.), *Principles and Practice of Anesthesia for Thoracic Surgery*, https://doi.org/10.1007/978-3-030-00859-8_56

Table 56.1 Causes of right ventricular failure [6]

Pressure overload	Left heart failure (most common)
	Pulmonary embolus (common)
	Pulmonary hypertension
	Right ventricular outflow tract obstruction
	Peripheral pulmonary stenosis
	Double chamber right ventricle
	Systemic right ventricle
Volume overload	Tricuspid regurgitation
	Pulmonary regurgitation
	Atrial septal defect
	Anomalous pulmonary venous return
	Sinus of Valsalva rupture in the right atrium
	Coronary artery fistula in the right atrium or right ventricle
	Carcinoid syndrome
	Rheumatic valvulitis
Ischemia/infarction	Right ventricular myocardial ischemia
Intrinsic myocardial processes	Cardiomyopathy and heart failure
	Arrhythmogenic right ventricular dysplasia
	Sepsis
Inflow limitation	Tricuspid stenosis
	Superior vena cava stenosis
Congenital defects	Ebstein's anomaly
	Tetralogy of Fallot
	Transposition of the great vessels
	Double outlet right ventricle with mitral atresia
Pericardial disease	Constrictive pericarditis

ventricular dysfunction (see Table 56.1) [6]. Known etiology includes induction of general anesthesia, institution of one-lung ventilation and lateral decubitus, manipulation of the pulmonary circulation, or triggering of the inflammatory response [7]. While cardiac adaptations occur with time after lung resection, cardiac complications, especially arrhythmias, are commonly seen in the immediate postoperative period before patient discharge.

Cardiac Adaptation

Cardiac adaptation can occur in the immediate intraoperative period, after induction of general anesthesia and positioning or in the postoperative phase.

Intraoperative Changes in Right Ventricular Function and Anatomy Related to One-Lung Ventilation and Positioning

Pulmonary arterial pressures can increase after induction of general anesthesia, as a consequence of positive pressure ventilation, placement of the patient in the lateral decubitus, opening of the chest, and initiation of one-lung ventilation (OLV) [8, 9]. Mediastinal shift and gravity-related changes in pulmonary perfusion and hypoxic vasoconstriction can also contribute to higher pulmonary arterial pressure. In patients with normal pulmonary vascular compliance, an increase in right cardiac output can compensate for the higher afterload without significant changes in pulmonary arterial pressures. This may not occur in patients with advanced COPD, or obstructive sleep apnea, even in the presence of baseline right ventricular hypertrophy [7], theoretically making this population at higher risk for intra- and postoperative cardiac complications. Preexisting significant pulmonary hypertension can worsen during OLV or clamping of the pulmonary artery. Ligation of the main pulmonary artery during pneumonectomy (right more than left) or lung transplantation in patients with severe COPD can cause acute right heart overload and consequent dilation followed by ischemia or arrhythmias, either intra- or postoperatively [10, 11]. A temporary slow "clamp test" of the pulmonary artery can be done intraoperatively to evaluate the clinical and echocardiographic response of the right heart to acute shifting of blood to the remaining pulmonary circulation [12]. However, this maneuver rarely changes the intraoperative management, since the results may be difficult to observe or interpret as soon as the clamp is applied.

If there are any intraoperative concerns of potential hemodynamic instability or right heart dysfunction, transesophageal echocardiography (TEE) has become a first-line diagnostic tool, replacing *pulmonary arterial catheter data* [13]. This information may influence the clinical decision in patients undergoing lung transplantation on when to initiate cardiopulmonary bypass or help evaluate the response to fluid or vasoactive treatment [14]. While TEE is a valuable "real-time" tool to assess left ventricular function, its role in investigating the right ventricular function is less clear. Despite the superficial location of the right heart, its irregular and asymmetric shape makes the motion and volume calculations much more difficult and less detailed than the left side when 2-D echo is used [5]. The advent of 3-D imaging has improved the quality of the right heart exam, in assessing structural changes and hemodynamic parameters [5, 15]. 3-D techniques have demonstrated a good resolution for the study of RV volumes and a good correlation with thermodilution data [15]. The main disadvantage still remains the costs and need for vendor-specific software. In case of high suspicion for perioperative right heart dysfunction, such as in patients with a predicted postoperative FEV_1 less than 40%, detailed preoperative testing becomes extremely important and is highly recommended [16]. In non-transplant patients, there is little evidence that routine TEE influences outcome [14].

Acute and Late Phase Changes in Right Ventricular Anatomy After Lung Resection

Intraoperative increases in resting pulmonary arterial pressure and pulmonary vascular resistance are usually proportional to the extent of the resection [17] and tend to normalize in the immediate postoperative period. However, aging is associated with a slow decline in right ventricular function, suggesting adaptive or reactive processes that can lead to right ventricular hypertrophy [8]. Changes in right ventricular ejection fraction have been described during exercise and depend on the level of exertion [18]. Compensatory mechanisms are more efficient during moderate exercise, with a fixed right ventricular stroke volume at maximal exertion which is independent from the increase in the workload and the time from surgery [8]. The extent of the resection and the compensatory volume expansion of the remaining lung can cause changes in the mediastinal anatomy with a rotation of the heart in the chest cavity, affecting the left ventricular function. Changes in filling and contraction have been observed. The degree of compensation after lung resection seems to be age dependent [8].

Lung surgery is currently the most common treatment for nonmetastatic resectable lung cancer and is part of a multimodal approach with chemotherapy and radiation [19]. Currently, surgical candidates are much older and with more extensive comorbidities, perhaps due to the combination of an aging population and improvement in surgical and anesthesia techniques [20]. Pre-existing cardiac and pulmonary diseases are common factors that may significantly influence the postoperative course and increase mortality rates [20]. The use of minimally invasive techniques, often relying on pneumo-capnothorax to expedite lung collapse, may cause acute changes in pulmonary pressures and right heart function. Severe pulmonary hypertension (mean pulmonary arterial pressure >45 mmHg) has been demonstrated only in 3.7% of patients with lung disease [21], despite a long smoking history and the presence of variable degrees of COPD in some patients. Ninety percent of patients with FEV_1 less than 50% have mean pulmonary arterial pressures of about 20 mmHg, and only 5% may have values greater than 35 mmHg [22].

Several studies have investigated postoperative right ventricular function (see Table 56.2 [7]), but the results are difficult to compare due to small sample sizes and extremely variable methodology. Some agreement exists among studies in patients after pneumonectomy that show a mild increase in pulmonary arterial systolic pressure, right ventricular diastolic volume or systolic pressure on transthoracic echocardiography [7], and CT scan exams [17]. These changes occurred in the second postoperative day and may persist after 4 years [7], suggesting an evolution of the cardiovascular response over time [8]. An increase in both afterload and catecholamine tone after clamping the pulmonary artery may lead to an increase in diastolic volume, pulmonary arterial systolic pressure, and mild tricuspid regurgitation which is observed on 2-D echocardiography. Most of the studies showed an increased incidence of tachyarrhythmias after pneumonectomy, which was transient in most cases and not associated with either heart failure or long-term complications [7]. Despite all these observed changes, there was no effect on 30-day mortality rates.

Cardiac Complications

Supraventricular Tachyarrhythmias (Atrial Fibrillation, Atrial Flutter, and Supraventricular Tachycardia)

Supraventricular tachyarrhythmias occur in approximately 4–25% of patients undergoing noncardiac thoracic surgery [28, 29]. Age of 60 years and older [30] and intrapericardial pneumonectomy [31] remain the most important risk factors. An elevated white blood cell count on postoperative day 1 [32] and an elevated perioperative N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) [33] and BNP [33–35] have also been suggested as possible predicting biomarkers, with a higher sensitivity when associated with older age [36]. Male gender, extent of surgical resection but not surgical approach or laterality, left ventricular early transmitral velocity/mitral annular early diastolic velocity (E/e') [36], increased trans mitral flow deceleration time, and left diastolic volume index [37] on echocardiography were also reported as potential risk factors for POAF. The combination of multiple risk factors such as gender, age, BNP, and extent of lung volume to be resected can be used as criteria to select high-risk patients who would benefit from a preoperative echocardiographic exam [36] and postoperative arrhythmia prophylaxis [38–41].

Atrial fibrillation (AF) is the most common rhythm disturbance, followed by supraventricular tachycardia (SVT), atrial flutter, and premature ventricular contractions (PVCs). The diagnosis is usually made on the second postoperative day (with a range of 1–7 days), and its duration is usually self-limited. Postoperative atrial fibrillation (POAF) has a good response to pharmacological cardioversion with approximately 85% resolved within 24 h from onset [30, 42–44].

Sustained ventricular tachyarrhythmias are quite rare after lung resection [28, 45]. Non-sustained ventricular tachycardia (more than three consecutive beats but <30 s) has an incidence of 0.5–1.5% and can occur in the first 96 h after lung resection, especially in patients with preoperative

Table 56.2 Summary of the literature analyzing right ventricular changes after lung surgery. All the studies listed are prospective in nature

Study	Time of the study	Type of surgery	Study	Results Lobectomy pneumonectomy		Exclusion	Comments
Venuta [23]	4 years	Lobe (*N* = 36) Pneumonectomy (*N* = 15)	TTE	No changes.	↑RVDD ↑PASP moderate TVI	FEV_1 < 60%, h/o MI, angina, valvular ds, AF, cardiac surgery	Mild increase in PASP and RVDV not clinically significant to cause RVH
Foroulis [24]	6 months	Lobe (*N* = 17) Pneumonectomy (*N* = 35)	TTE	↑PASP, ↑RVDD ↑TR	↑↑PASP ↑↑RVDD ↑↑TR	Postoperative BPF, empyema, respiratory failure, MI	Small study, higher PASP in pneumonectomy patients at 6 months (R > L cases), with higher incidence of postoperative AF and SVT requiring treatment, attributed to RV dilatation
Amar [25]	1 month	Pneumonectomy (*N* = 70)	TTE		No changes in R and L atrial diameter, EF, TR and RVSP	AF, lung resection, lesser operations, unresectable	Study to evaluate role of diltiazem and digoxin on AF Echo done as part of their follow-up
Amar [26]	1 week	Lobe (*N* = 47) Pneumonectomy (*N* = 39)	TTE	↑HR	↑RSVP ↑HR	Wedge, prior thoracic surgery Non-sinus rhythm	RVSP of 31, not affecting RV systolic function unless respiratory failure occurs
Kowalewski [10]	2 days	Lobe (*N* = 9) Pneumonectomy (*N* = 22)	TTE	No changes	↑RVEDV ↓RVEF ↑ SVT		Not very accurate and nonstandard right heart volumes calculations which can underestimate large volumes. RVEF usually underestimates the true value by echo due to RV geometry
Smulders [27]	5 years	Pneumonectomy (*N* = 15)	MRI		*R side* = cardiac lateral shift. ↓RVEDV, nl LV function *L side* = rotation, nl RVEDV, ↓LVEF ↑HR, ↓SV		No signs of RVH at 5 years
Katz [11]	Intraoperative	Lung transplantation (*N* = 32)	TEE	Immediate ↓PAP (systolic+mean), and ↓RV size post transplantation, normalization of septal geometry in severe pulmonary HTN (↓RVED area)			CPB used in all cases of severe pulmonary HTN

Abbreviations: *N* number of cases, *TTE* transthoracic echocardiography, *RVDD* right midventricular diastolic diameter, *PASP* pulmonary arterial systolic pressures, *TVI* tricuspid valve insufficiency, FEV_1 forced expiratory volume at 1 s, *MI* myocardial infarction, *AF* atrial fibrillation, *RVDV* right ventricular diastolic volume, *RVH* right ventricular hypertrophy, *TR* tricuspid regurgitation, *BPF* bronchopleural fistula, *SVT* supraventricular tachycardia, *RV* right ventricle, *R* right, *L* left, *EF* ejection fraction, *RVSP* right ventricular systolic pressure, *RVEDV* right ventricular end-diastolic volume, *RVEF* right ventricular ejection fraction, *MRI* magnetic resonance imaging, *LV* left ventricle, *SV* stroke volume, *TEE* transesophageal echocardiography, *PAP* pulmonary arterial pressure, *HR* heart rate, *HTN* hypertension, *CPB* cardiopulmonary bypass

left bundle branch block [46]. It is rarely associated with hemodynamic instability requiring treatment at any time. There is no association with age, other clinical factors, or core temperature upon arrival to PACU. On multivariate analysis, an independent association seems to exist between non-sustained ventricular tachycardia and POAF, possibly due to vagal withdrawal or irritation and/or a surge in sympathetic activity. These findings differ from the cardiac surgical literature, where the presence of postoperative ventricular tachycardia often leads to poor outcome [28].

POAF can be an isolated complication within the first week after surgery or associated with respiratory or infectious disease [30]. It is typically transient and reversible and seems to affect individuals with an electrophysiologic substrate for arrhythmias present before or as a result of surgery [29, 47]. Despite the good prognosis, POAF is associated with a 1.7% risk of developing cerebrovascular accidents if persistent [38, 48]. Thromboembolic events can occur within 24–48 h from the onset of sustained POAF and may have devastating sequelae. If sinus rhythm fails to be restored

within this time frame, anticoagulation should be considered weighing the risk of postoperative bleeding [28]. The most recent American Heart Association (AHA) guidelines on management of AF unrelated to surgery provide similar recommendations for which antithrombotic medications one should employ in postoperative patients depending on the patient's risk (i.e., presence of a prosthetic valve, etc., prior cerebrovascular accidents, or no risk factors) [49].

Several mechanisms have been proposed to explain POAF, but the most consistent factors other than age have been prior history of paroxysmal AF and extent of resection. Aging per se has been associated with loss of about 90% of normal sinus nodal fibers and remodeling of the atrial myocardium, with changes in the sinoatrial and atrioventricular nodal conduction, as well as an increased sensitivity to catecholamine activity, especially after surgical trauma in the area [38, 45]. Triggering of an inflammatory response with activation of the complement system and several pro-inflammatory cytokines has also been suggested as a contributing factor for POAF in this age population [50]. This thought is supported by a doubling in white blood cell (WBC) count observed in patients older than 60 years of age on postoperative day 1, which is associated with a threefold increase in the odds of developing POAF [32]. Catecholamine-induced leukocytosis via α- and β_2-receptor activation is a known phenomenon which could in part explain this finding. The use of thoracic epidural analgesia as a modality to cause sympathectomy and prevent POAF has led to disappointing results [51], maybe due to the high individual variability of sympathetic blockade. Stretching or inflammation of the pulmonary veins, hilar manipulation, and mediastinal shift may be additional contributing factors [47]. Positive inotropic agents, i.e., dopamine, as well as anemia, fever, hypoglycemia, postoperative ischemia, and surgical complications, are all aggravating factors [42, 52].

Presenting symptoms of rapid POAF include dyspnea, palpitations, dizziness, syncope, respiratory distress, and hypotension [38, 45]. Although pulmonary embolism or myocardial ischemia and electrolyte abnormality are commonly included in the differential diagnosis they are rarely proven [53]. According to the AHA guidelines, transthoracic echocardiography should be part of the workup for new-onset POAF to rule out any structural disease, if such information is not already available [40]. Similarly, the AHA guidelines do not recommend "ruling out" pulmonary embolism, thyrotoxicosis, or myocardial ischemia if there are no accompanying clinical signs or symptoms.

Postoperative arrhythmia is indirectly associated with higher morbidity [45]. It also can be a direct cause of death in the presence of heart failure or prolonged hypotension [40, 54]. Length of hospital stay and costs are increased in patients with arrhythmias, highlighting the importance of prevention when possible [36, 45, 54]. In most cases, POAF resolves prior to hospital discharge with a complete resolution at 6 weeks from surgery [38, 45]. Patients are considered at risk for postoperative supraventricular arrhythmias if they have two or more of the risk factors listed in Table 56.3, and, if so, they may be started on pharmacological prophylaxis either preoperatively or in the immediate postoperative period. Several regimens are available to prevent or treat atrial tachyarrhythmias.

Table 56.3 Proposed risk factors for supraventricular tachyarrhythmias [28, 30, 43, 45, 47]

Age > 60
Male gender
History of paroxysmal atrial fibrillation
Prolonged P wave duration
Preoperative HR > 72 bpm
Elevated BNP level
Increased WBC count on POD 1
Intrapericardial procedure

Abbreviations: *HR* heart rate, *bpm* beats per minute, *BNP* brain natriuretic peptide, *WBC* white blood cell count, *POD* postoperative day

Role of Medications Used for Treatment and Prevention

Rate Control Agents

β-blockers are antiarrhythmic agents with cardioprotective effects. As prophylactic agents, they counteract the effects of the high sympathetic tone that occurs after surgery, which may enhance patient susceptibility to dysrhythmias. β-Blockers inhibit intracellular calcium influx via a second messenger have a membrane stabilizing effect and inhibit the renin-angiotensin-aldosterone system [40, 55]. Their respiratory side effects become particularly important after lung resection since nonselective β-blocker can cause bronchospasm and worsen pulmonary function in the postoperative period. Pulmonary edema has been described as a potential side effect [56], as well as hypotension and bradycardia. Moreover, in patients on chronic β-blockers, withdrawal may lead to rebound tachycardia and related complications due to an upregulation of the β receptors [57]. The β-blocker length of stay study (BLOS) analyzed the effects of β-blockers after cardiac surgery used as prophylactic agents in patients both naïve and already taking β-blockers [58]. The goal was to prevent POAF and possibly decrease the length of stay in the hospital and ICU. Patients already on a β-blocker had a small decrease in the incidence of POAF, but their hospital length of stay was increased. This was attributed to the development of adverse cardiac and pulmonary effects. The Perioperative Ischemic Evaluation (POISE) trial showed that aggressive β-blockade in patients at risk or with atherosclerotic disease can reduce postoperative myocardial infarction and even POAF but at the cost of an increase in mortality related to

cerebrovascular events in patients who had hypotension and decreased cerebral perfusion [59]. These findings have been consistent with other trials using lower doses of β-blockers, which questioned the safety of this strategy [60]. The AATS 2014 guidelines do not recommend the use of β-blockers in patients who are not already taking the medication [40].

The *calcium channel blockers* verapamil and diltiazem are both prophylactic and therapeutic agents for the treatment of POAF. They decrease intracellular calcium entry by directly blocking the L-type calcium channel and slowing the sinoatrial automaticity and atrioventricular nodal conduction [55]. This class of drugs seems to reduce pulmonary vascular resistance and right ventricular pressure as well, making this an attractive option after major lung resection [56]. Hypotension is one of the major side effects, especially with verapamil, and one of the most common reasons to stop these medications. Calcium channel blockers cause a 40% decrease of postoperative myocardial infarction rates and a 45% reduction of ischemia when used in the cardiac surgical population [56]. Diltiazem is superior to digoxin when used to prevent POAF after intrapericardial or standard pneumonectomy [25]. However, both drugs have equal effect on postoperative ventricular ectopy, echocardiographic changes in right ventricular function, and hospital length of stay. In the largest study to prevent POAF in thoracic surgical patients, diltiazem was safe and effective in reducing the rate of POAF of almost 50% [61]. When administered as a bolus followed by a continuous infusion, diltiazem controls the ventricular rate in about 90% of patients with recent onset of POAF, with an onset of action of 2–7 min [40].

Amiodarone is a sodium-potassium-calcium channel blocker and a β-adrenergic inhibitor. It has been demonstrated to be the most effective prophylactic agent after major lung resection when started in the immediate postoperative period [41]. It is often used to maintain sinus rhythm after electrical cardioversion in the general population. An intravenous bolus followed by a continuous infusion has a similar effect to intravenous diltiazem and digoxin. Its onset is of about 4 h with a 24 h duration of the effect [40]. As a prophylactic agent, it works best when administered 1 week prior to cardiac surgery [62]; however the precise mechanism of action is unknown [63]. The sodium-calcium-potassium channel blockade causes an increase in the duration of the action potential and the refractory period in the cardiac tissue. As a result, hypotension, bradycardia, and QT prolongation can be significant, especially in patients with congestive heart failure and left ventricular dysfunction [52]. Other side effects seen with prolonged oral use include hypo- or hyperthyroidism, hepatic and neurotoxicity, and prolongation of warfarin half-life [63]. However, pulmonary toxicity remains the main concern of amiodarone therapy after lung resection [40, 56]. It can occur at lower dosages and can manifest as chronic interstitial pneumonitis, bronchiolitis obliterans, adult respiratory distress syndrome (ARDS), or a solitary lung mass [52]. In a very small prospective randomized study, Van Mieghem et al. [64] examined the role of amiodarone prophylaxis on POAF after lung resection. When compared to verapamil, there was no difference in the rate of POAF at the interim analysis. However the study was stopped prematurely due to an increased incidence of ARDS in the amiodarone group, which was 7.4% in the patients who had a right pneumonectomy versus 1.6% for other types of lung resections. This was associated with higher mortality rates and occurred despite using standard intravenous regimens and having therapeutic plasma concentrations. Two mechanisms were proposed: an indirect one, by increasing inflammatory mediators, and a direct one, by causing direct damage to the cells and subsequent fibrosis. Independently from the etiology, their recommendation was to avoid amiodarone after lung resection. By surgically decreasing the amount of lung parenchyma available, standard doses of amiodarone can account for higher pulmonary concentrations of the drug which may reach toxic levels. These results were not confirmed by later studies, when amiodarone was used for a short time period [28]. Tisdale et al. [65] randomized 130 patients undergoing anatomical lung resection, demonstrating a decreased incidence of AF in the amiodarone group (13.8% versus 32.3% in the control), with no difference in respiratory or cardiac complications. The lack of double blinding and the selection bias represented by a high rate of exclusion of cases of intraoperative AF were the main limitations for this study. Riber et al. [66] confirmed these results in a similar patient population. Amiodarone significantly decreased the incidence of POAF, with a good rate control and lack of symptoms in patients who developed POAF while receiving the medication. Overall, amiodarone and diltiazem seem to have similar efficacy in preventing POAF after major lung resection [28]. The main indication for amiodarone use still remains as a second-tier drug for POAF refractory to rate control drugs or as a therapeutic agent for POAF coupled with preexcitation conduction abnormalities, such as Wolff-Parkinson-White syndrome [40]. Monitoring serum concentrations is not necessary; however it is recommended to maintain the total cumulative dose less than 2150 mg given over 48–72 h [40].

Prophylactic *digitalization* to prevent POAF is not recommended any longer since there are no proven benefits but potential side effects [67]. The main mechanism of action is by enhancing vagal stimulation at the atrioventricular node, thus decreasing ventricular response during atrial arrhythmias [57]. There is also an inhibition of the sympathetic response which is unrelated to the increase in cardiac output and a binding of the myocardial sodium-potassium ATPase channel, blocking its transport [68]. The increase in intracellular sodium and subsequent calcium concentrations promote cardiac contractility. Digoxin does not seem to restore

normal sinus rhythm in patients with chronic atrial fibrillation, and as a single agent it does not adequately control the ventricular response unless given at very high doses [67] or when combined with β-blockers or calcium channel blockers [68]. Calcium channel blockers have demonstrated to have better results in preventing POAF with fewer side effects [25]. Superior results are seen when digoxin is used in patients with chronic atrial fibrillation and heart failure with systolic dysfunction [67]. The onset after intravenous administration of 0.5–0.75 mg bolus is between 30 min and 2 h. AF rate control is usually achieved with further doses of 0.25 mg iv every 2–6 h to a maximum of 1.25–1.75 mg [40]. Digitalis toxicity and the difficulty in assessing proper plasma levels remain the main limiting factors for its use [43]. However, no difference in mortality was reported when chronic digoxin was compared with beta-blocker or calcium channel blockers [69]. Digoxin should be avoided in patients with renal insufficiency, electrolyte disturbances (hypokalemia, hypomagnesemia, and hypercalcemia), acute coronary syndromes, and thyroid disorders.

Rhythm Control Medications

Sotalol is a class III antiarrhythmic medication with significant activity as a nonselective β-blocker and a potassium channel blocker. Potassium current blockade prolongs both the action potential and the QT interval, predisposing to ventricular dysrhythmias such as torsades de pointes [57]. This can occur at both therapeutic and toxic dosages [55]. Due to the renal excretion, its use is contraindicated in patients with a creatinine clearance less than 46 ml/min. As with other β-blockers, sotalol is effective in decreasing POAF but does not reduce hospital length of stay or postoperative morbidity. Bradycardia can be significant enough to warrant discontinuation [47]. According to the American College of Cardiology recommendations, sotalol may be harmful if used to pharmacologically cardiovert atrial fibrillation [40]. Unfortunately, most of the data on this medication come from the cardiac surgical population [53], with no studies in the noncardiac population [40].

Magnesium is indicated in case of hypomagnesemia. The data on the use of magnesium are mainly from the cardiac surgical literature and are conflicting. One randomized controlled study done in 200 patients undergoing cardiopulmonary bypass surgery showed a decreased incidence of POAF when magnesium sulfate was administered for prophylaxis [70]. However, several other trials in similar surgical populations have given conflicting results on the benefits of magnesium and POAF prophylaxis, with the only agreement to maintain magnesium levels within normal values [57]. Compared to β-blockers and amiodarone, magnesium is inferior in preventing POAF [71]. Except in patients with acute renal failure, magnesium has a relatively safe profile.

Statins (3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors) have been shown to suppress electrical remodeling and prevent POAF in animal models [52]. They are powerful lipid lowering drugs highly effective in preventing coronary artery disease [40]. Studies conducted in hypercholesterolemic patients on statins undergoing coronary artery bypass grafting (CAGB) showed a decrease in postoperative major cardiac events [72]. This effect was potentiated by simultaneously taking β-blockers [73]. The main benefits of statins seem to occur when these drugs are started in the preoperative period. When administered 1 week prior to on pump CABG, they decreased the incidence of POAF, as well as hospital length stay [47, 73]. After major lung resection, patients already on statins prior to surgery showed a threefold decrease probability of developing POAF [74] and overall complications [75]. One possible explanation seems to be related to their anti-inflammatory or antioxidant mechanism. Observational studies conducted in patients undergoing major lung resection have reported an increase in C-reactive protein and interleukin 6 in the postoperative period [76]. Atorvastatin (40 mg PO) started 7 days prior to lung resection and continued for 7 postoperative days in statin-naïve patients undergoing elective anatomical lung resection was associated with a decrease in hospital complications [75].

Angiotensin-converting enzyme inhibitors (*ACEIs*) and *angiotensin receptor blockers* (*ARBs*) have been suggested to reduce the incidence of POAF in patients with coexisting heart failure and systolic left ventricular dysfunction, but not in cases associated with systemic hypertension [77]. They may also play a role in maintaining sinus rhythm after electrical cardioversion. The data in the literature has focused on the role of these drugs on the outcome in chronic AF patients. The prophylactic use of ACEIs/ARBs to prevent POAF remains quite controversial. Losartan prevented POAF better than metoprolol when used in the postoperative period after major lung resection (6% vs 12%) [39]. Inhibition of the renin-angiotensin-aldosterone system seems to attenuate left atrial dilatation and atrial fibrosis and contributes in slowing conduction in animal studies, all factors that can trigger and maintain reentry circuits. These effects seem to be potentiated in patients with chronic heart failure when β-blockers are added [47].

Novel Medications

N-Acetylcysteine has successfully been used to decrease POAF and all-cause mortality after cardiac surgery alone or in combination with other agents [78, 79]. The mechanism of action seems to be related to its antioxidant properties, by stimulating glutathione production. Inclusion of cysteine in the perfusate of isolated rat hearts has been shown to confer significant cardioprotection and improved preservation of ATP and glutathione [80]. Other proposed mechanisms include inhibition of the renin-angiotensin system and/or

atrial remodeling [78]. There are no current studies in the literature on the role of NAC in thoracic noncardiac surgery.

Vernakalant is an atrial-selective sodium-potassium channel blocker approved for pharmacological cardioversion of recent onset AF. Vernakalant has a better conversion rates than amiodarone but similar to propafenone and flecainide with less side effects [81]. Its main advantage is the rapid onset (10–15 min) and the high success rate after one dose [81]. Hypotension, especially in patients with heart failure, bradycardia, QT prolongation, and torsade de pointes are the most common side effects. Vernakalant is not effective in cardioverting atrial flutter or AF lasting more than 7 days [81]. While it is approved for clinical use in Europe, it is still under FDA investigation in the USA.

Olprinone is a specific phosphodiesterase III inhibitor with inotropic and vasodilating effects, commonly used to treat heart failure. It is also a bronchodilator. When administered prophylactically in patients after lung resection [82], it decreased the incidence of POAF, lowering the BNP and WBC levels without affecting the hemodynamics. It is usually given as a continuous infusion for 1 day, with duration of action up to 7 days. Suggested mechanisms include pulmonary vasodilatation with unloading of the right ventricle, positive chronotropism, and inhibition of the inflammatory response. In the USA this medication is approved for research use only.

Human atrial natriuretic peptide is a peptide hormone synthesized by the atria and available as treatment option for heart failure. It inhibits the sympathetic nervous system and the renin-angiotensin-aldosterone axis, leading to cardioprotective effects. A prophylactic 3-day infusion has been associated with a decrease in POAF**,** WBC, and CRP but no significant changes in blood pressures in patients with COPD undergoing lung resection [83]. The effect seems to be lasting up to a month after the infusion is stopped. This medication is routinely used in Japan.

Role of Postoperative Chemical and Electrical Cardioversion

Chemical and electrical cardioversion: restoration of sinus rhythm is recommended in patients who have stable AF but are symptomatic, when the duration is longer than 24 h and when anticoagulation may cause postoperative bleeding [84]. Several medications are available for cardioversion, with the greatest success rate when started within 7 days from the onset [85]. Drugs commonly used for chemical cardioversion of POAF include flecainide, dofetilide, propafenone, and ibutilide [28]. Ibutilide is available in the iv form, and it has been shown to have modest success in converting acute AF after cardiac surgery. However, it is associated with polymorphic ventricular tachycardia in up to 2% of patients, especially in the presence of electrolyte abnormality [85]. In the presence of QT prolongation, hypokalemia and low ejection fraction can trigger ventricular tachycardia. Single oral doses of flecainide (300 mg) or propafenone (600 mg) seem to be safe, cardioverting 91% and 76% of cases, respectively, within 8 h from the onset of AF. To be eligible for this class of medications, patients must be free from cardiac structural disease, such as left ventricular hypertrophy, mitral valve disease, coronary artery disease, or heart failure [86]. Potential side effects include ventricular tachycardia, heart failure, and conversion to atrial flutter with rapid ventricular response [85].

Electrical cardioversion is used to treat AF in case of hemodynamic instability, including symptomatic profound hypotension, myocardial ischemia or infarction, and/or heart failure [40]. The success rate is about 67–94% [52]. Biphasic DC cardioversion has higher success rates than monophasic, using a current around 100–200 J and in a synchronized mode. Higher energy can be used for patients with high body mass index, prolonged AF, or left atrial enlargement. Deep sedation is recommended. Bradycardia (more common in patients on antiarrhythmics prior to cardioversion), ventricular tachyarrhythmias (when the shock is applied during repolarization), hypotension, pulmonary edema (probably due to myocardial stunning), and embolism are all potential complications. Electrolytes should be checked and normalized before cardioversion. In case of digitalis toxicity and hypokalemia, cardioversion should be avoided due to the high incidence of ventricular fibrillation. In this setting, low currents and prophylactic lidocaine should be used. Pacing capabilities should be readily availbale, since bradycardia can be profound to the point of asystole [52]. If the duration of the AF is less than 48 h, cardioversion can be done prior to anticoagulation [40]. After the 48 h mark, anticoagulation is recommended if not contraindicated by the surgical procedure. Whether intravenous heparin should be started and then followed by a 4 weeks cycle of oral anticoagulants is unclear. Common practice is to start patients on oral anticoagulants such as warfarin or the novel anticoagulant drugs [10].

Acute Coronary Syndrome

Myocardial ischemia may occur transiently after lung resection and present as an electrocardiographic finding in 3.8% of patients, while infarction can occur in 0.2–0.9% of the cases [29, 87–89]. The diagnosis of symptomatic perioperative myocardial infarct is associated with a 30–50% risk of death [90]. The incidence increases in the presence of preoperative coronary artery disease and abnormal exercise testing. Patients are at the highest risk during the first 3 postoperative days, when a high degree of monitoring is suggested.

Nonspecific diffuse ST segment changes may be present after intrapericardial resection due to direct mechanical injury [91]. Mediastinal shift can also cause dynamic EKG abnormalities in the postoperative period. An increase in troponin may be observed in all these scenarios.

There are no definite recommendations for preoperative invasive testing or interventions. Most of the decision-making should be based on the clinical presentation [92]. In patients at high risk (such as the ones with unstable angina, uncompensated chronic heart failure, arrhythmias, and severe valvular disease), cardiac catheterization is highly recommended if followed by coronary artery revascularization, when necessary [53, 93]. Patients with and without preexisting cardiac disease have a similar incidence of postoperative major adverse cardiac events (MACE) after thoracoscopic lung resection [94]. However the former have higher incidence of atrial fibrillation and 30-day postoperative mortality. Preoperative angina is associated with a higher incidence of postoperative adverse cardiac events (such as MI or cardiac arrest) [95]. According to the latest AHA-ACC recommendations [90], if the risk of reinfarction is high for at least 2 months after an MI, CABG but not percutaneous coronary intervention (PCI) may decrease that risk. If patients require revascularization, elective surgery needs to be postponed, with the dilemma of how long to wait, as in the case of cancer where there is potential disease progression [96]. Cardiac stents, especially drug-eluting ones, represent a significant problem due to the prolonged need for anticoagulation. Stopping dual antiplatelet therapy (aspirin and clopidogrel) is associated with a high risk of stent thrombosis, while continuing it leads to an increased risk of intra and postoperative bleeding and precludes regional anesthetic techniques [97]. The duration of the anticoagulation is usually based upon the type of stent: bare-metal stents commonly require 4–6 weeks, while in the presence of drug-eluting stent 12 months are recommended for elective procedures and 6 for urgent cases [90]. The risk of stent thrombosis is higher for drug-eluting stents, especially if the stent is long, at a bifurcation, if the revascularization is incomplete, or if the patient has history of diabetes or heart failure [98]. A non-randomized observational prospective study done in noncardiac surgery patients who had cardiac stents placed within a year from surgery found a 44.7% rate of postoperative cardiac complications and a 4.7% mortality rate [99]. Dual antiplatelet therapy was stopped on average 3 days prior to surgery and substituted with intravenous unfractionated heparin or subcutaneous enoxaparin. Most of the complications occurred within the first 35 days from the stent placement and were cardiac in nature. Bleeding was not a significant variable. This data was not confirmed by another small prospective observational study done in 16 patients undergoing major lung resection 4 weeks after coronary angioplasty or PCI [100]. Dual antiplatelet therapy was given for 4 weeks and interrupted 5 days prior to surgery when it was bridged with low molecular weight heparin. No MI or deaths were reported. Despite the absence of randomization, these studies stress several important points. Once the antiplatelet treatment is stopped, low molecular weight heparin should be used (heparin alone is insufficient); all non-life-saving procedures should be postponed at least for 6–12 weeks from the stent placement, and aspirin should be continued up to the day of surgery [101, 102]. The protective effects against MACE in the immediate postoperative period outweigh the lower risk of postoperative bleeding [101]. Prophylactic revascularization (CABG versus PCI) does not seem to add further benefits over optimal medical treatment in patients with cardiac risk undergoing elective major vascular surgery [90, 96]. Long-term survival as well as myocardial infarction, death, and hospital length of stay seems to be unchanged. However, CABG is associated with less postoperative myocardial infarctions and decreased hospital length of stay when compared to PCI, probably because of better revascularization [103]. According to the American College of Cardiology, revascularization should be reserved for patients with unstable angina or advanced coronary artery disease [90]. If revascularization is needed before surgery, bare-metal stents [90] or balloon angioplasty [102] are the preferred options due to their lower risk of thrombosis. In both cases, elective surgery needs to be appropriately delayed to prevent graft or stent thrombosis.

Heart Failure and Cardiac Herniation

Heart failure can occur after major lung resection as a result of right- or left-sided dysfunction. *Right heart failure* can result from changes either in contractility or afterload. Unfortunately, most of the studies investigating the changes in right ventricular function after lung resection are small and found minor and transient differences when compared to the preoperative period. In the first 2 postoperative days, there is a reversible increase in right ventricular end-diastolic volume [53], as well as a mild increase in pulmonary arterial pressures and pulmonary vascular resistance [104]. While postoperative changes in pulmonary arterial pressures, central venous pressures, and pulmonary vascular resistance seem to be subtle at rest, they may become significant during exercise. Changes in right ventricular function are usually able to compensate at rest, but they may fail during exercise, leading to pulmonary hypertension [53]. When transthoracic echocardiography has been used to evaluate right ventricular function after pneumonectomy, it has shown only a mild increase in pulmonary arterial pressure which is not associated with ventricular dysfunction [26]. Other possible causes of right ventricular failure, although rare, include pulmonary embolism and cardiac

herniation. *Left side heart failure* is usually a consequence of right heart dysfunction, either by decreasing left ventricular preload or shifting the interventricular septum [3, 53]. Acute ischemia and valvular disease may also be contributing factors. *Cardiac herniation*, a rare complication after pneumonectomy, may be responsible for both right and left heart failure. It occurs more commonly after intrapericardial pneumonectomy, right more than left, and leads to a 50% mortality rate [53]. Herniation can be secondary to an incomplete surgical closure of the pericardium or the breakdown of a pericardial patch [105]. One main contributing factor includes an increase in intrathoracic pressure, such as with coughing or sudden increase in peak airway pressures during mechanical ventilation [29]. Changes in position, with the operative side being dependent, positive pressure ventilation, rapid lung re-expansion, or suction on the chest tube are all other possible causes. Symptoms depend on the side of the herniation. Right-sided cases present with superior vena cava syndrome, due to kinking of the superior vena cava and decreased right ventricular filling, with subsequent hypotension, tachycardia, and shock. Left-sided cases present with arrhythmias and ischemia, causing myocardial infarction, hypotension, and ventricular fibrillation if left untreated [106]. This appears to be related to less cardiac rotation, with subsequent pericardial compression on the myocardium. Clinical presentation and electrocardiographic findings are fairly nonspecific in suggesting the diagnosis, stressing the role of chest radiography and a high index of suspicion. Treatment is surgical, with repositioning of the heart and placement of a patch. In order to minimize hemodynamic instability, the patient should be kept on the lateral decubitus with the operative side up [105].

Mediastinal Shift and Post-pneumonectomy Syndrome

Mediastinal shift can occur intraoperatively or in the postoperative period as a result of changes in the post-pneumonectomy space. At the end of surgery, once the chest is closed, some surgeons evacuate the air and fluid that fill the empty space aiming to bring the mediastinum back to midline. Excessive fluid drainage can lead to ipsilateral mediastinal shift and contralateral lung expansion, with decreased venous return and significant hypotension [107]. Rapid accumulation of fluid in the pneumonectomy space (such as hemo- or chylothorax) can cause contralateral shift, with secondary compression of the remaining lung [29]. A high index of clinical suspicion, careful monitoring of the hemodynamics, and communication with the surgical team are needed to prevent hemodynamic collapse. When excessive fluid accumulates in this space, contralateral mediastinal shift occurs, leading to compression of the remaining lung and secondary respiratory insufficiency. This is seen more often in the postoperative period, and the use of intracavitary pressures monitoring can guide the drainage of the excess fluid if needed [107]. CT scan studies have shown obliteration of the post-pneumonectomy space with fluid over time, elevation of the hemidiaphragm, and expansion of the contralateral lung [108]. In case of extreme mediastinal shift, dynamic compression of the distal airway can occur, leading to the so-called post-pneumonectomy syndrome [29, 109, 110]. This is a rare and late complication, which can occur at a median of 7 years from surgery. It is more common in females and children and with right-sided procedures (even though it has been described for left cases as well) [111]. It manifests with decreased exercise tolerance, exertional respiratory insufficiency, stridor, and recurrent infections. Respiratory symptoms are caused by dynamic compression of the distal trachea and left mainstem bronchus against the spinal column and the left pulmonary artery, secondary to the severe mediastinal shift to the right. Treatment involves the use of airway stents as a temporary measure or thoracotomy and repositioning of the mediastinum via Lucite plastic balls, Silastic implants, or saline-filled prosthesis [111] (see also Chap. 41). In the rare event of *cardiac arrest* (3–7%), close chest compression is ineffective [29]. As a result of the mediastinal shift, the heart cannot be compressed between the sternum and the vertebral bodies, requiring an emergency thoracotomy and open cardiac massage. In the case of intrapericardial dissection, chest compression can cause cardiac herniation.

Conclusion

In the last few decades, a significant improvement in the surgical and anesthetic techniques has made pneumonectomy and anatomical lung resection safer. The introduction of enhanced recovery pathways, minimally invasive surgical techniques, the use of short-acting anesthetics, and a multimodal analgesic approach have all contributed to decrease the incidence of postoperative complications. Fast-track strategies and careful selection of patients undergoing lung resection procedures have also played an important role in postoperative and long-term outcome. Better utilization of step down and acute postoperative care units have decreased the rate of ICU admissions, saving costs. Since the average age of patients requiring lung resection is increasing, anesthesiologists and surgeons will be facing more complex cases, due to the presence of multiple comorbidities. Careful preoperative workup customizing the type of surgery as well as planning for in-hospital and post discharge rehabilitation options will prove to be essential for decreasing even further the possible complications and improving the overall care.

Clinical Case Discussion

A 65-year-old-man with squamous cell cancer of the right upper lobe underwent a right intrapericardial pneumonectomy. Surgery was 150 min and uneventful. Estimated blood loss was 700 cc, and 700 cc of ringer's lactate was used during the case. Urinary output was 100 cc. The patient was extubated in the operating room at the end of the case. A thoracic epidural was used intraoperatively, and the patient was comfortable in PACU. As part of the postoperative blood work, troponin levels were checked, and the first set was 1.66 (1.07 and 0.52 the second and the third one). ST segment elevations transiently occurred on POD 1 in correspondence to a fourth troponin of 1.55.

On POD 2, subcutaneous emphysema was noted on the right chest wall, neck, and eye. While walking, he had an episode of desaturation and tachycardia. Chest X-ray is shown (see Fig. 56.1). Electrocardiogram showed rapid SVT, with hypotension (HR = 128, BP = 88/45). The patient was transferred to the ICU where he was intubated. He slowly became hemodynamically unstable, requiring multiple pressors.

Questions

What are common cardiac complications after lung resection?

1. Arrhythmias (atrial fibrillation, atrial flutter, and supraventricular tachycardia (SVT))
2. Ischemia and acute coronary syndrome
3. Heart failure and cardiac herniation
4. Mediastinal shift and post-pneumonectomy syndrome

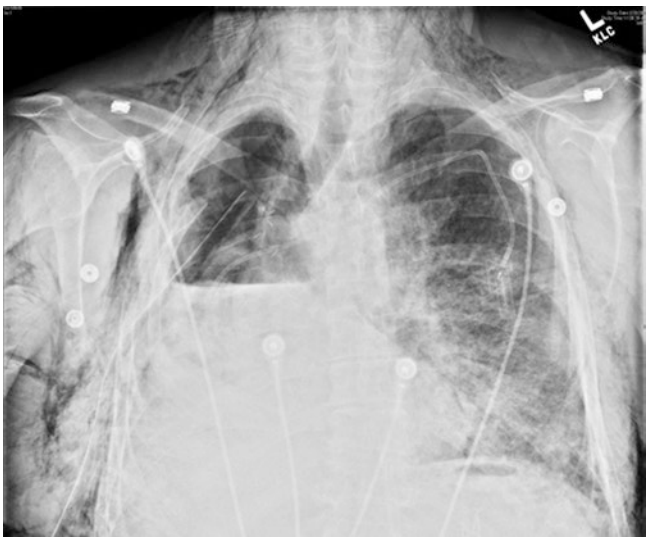

Fig. 56.1 Radiographic changes on postoperative day 2

Specifically

1. *Arrhythmias*: Who is at risk (suggested pathophysiology, role of WBC and inflammatory response, BNP levels)? What we can do to prevent it (rate or rhythm control? Preoperative medications?)? How do we treat postoperatively (medications vs cardioversion)? Risks/side effects of the treatment.
2. *Acute coronary syndrome*: What are known risk factors? Is preoperative stenting better than medical treatment in a patient with a positive stress test? What is the treatment? How does it affect mortality?
3. *Cardiomegaly/ cardiac failure*: Who is at risk (role of the extent of dissection, preoperative risk factors)? How does it affect mortality?
4. *Mediastinal shift*: Why does this happen (extent of dissection)? How common is cardiac herniation? What is the pathophysiology and the diagnosis?

Back to the Case

The intraoperative course was uneventful, despite a more extensive procedure than scheduled. The patient suffered transient ischemia in the PACU (ST changes on EKG and elevated troponin) that was managed medically and resolved. On POD 2, he had both respiratory and hemodynamic symptoms while ambulating.

The CXR at that time showed massive subcutaneous emphysema on the side of surgery, extending to the neck; a post-pneumonectomy cavity filled with fluid and a mediastinal shift toward the operative side; and an opacification of the left lung base. These are all surgical complications that may not be easily preventable, despite a high degree of alertness and aggressive postoperative physical therapy and pulmonary toileting.

In most cases isolated cardiac complications after pneumonectomy can be successfully treated with medications or invasive procedures. Respiratory complications are more difficult to prevent and manage, especially if the onset is quick. In this case scenario, hypoxemia developed very quickly and was so severe to require reintubation and transfer to the ICU for further care. A repeat CXR (Fig. 56.2) after intubation shows a significant worsening of the left base opacification. Ideally treatment should follow a diagnosis. However, in practice, patients may be clinically too unstable for transport to the imaging suite. Supportive measures become the mainstay of therapy. In this case, the need for vasopressor continued to increase and the degree of hypoxia to worsen. The patient suffered a secondary cardiac arrest and expired on POD 2.

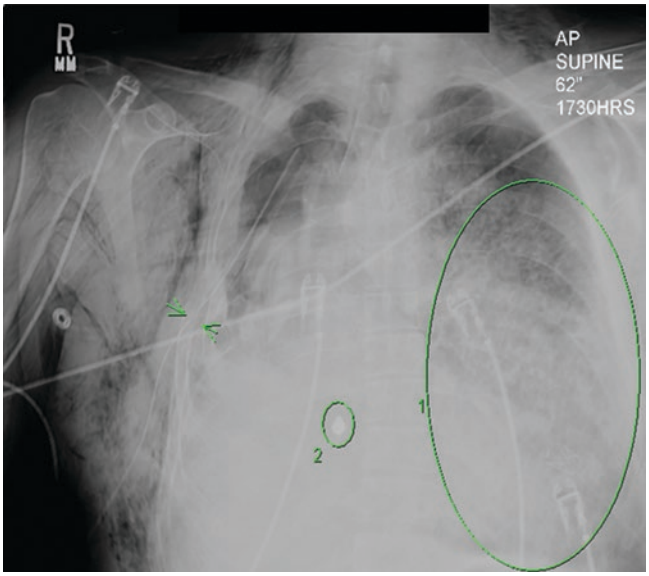

Fig. 56.2 Worsening of the left base opacification

References

1. Harjola VP, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail. 2016;18(3):226–41.
2. Ho SY, Nihoyannopoulos P. Anatomy, echocardiography, and normal right ventricular dimensions. Heart. 2006;92(Suppl 1):i2–13.
3. Gordon C, Collard CD, Pan W. Intraoperative management of pulmonary hypertension and associated right heart failure. Curr Opin Anaesthesiol. 2010;23(1):49–56.
4. Szabo G, et al. Adaptation of the right ventricle to an increased afterload in the chronically volume overloaded heart. Ann Thorac Surg. 2006;82(3):989–95.
5. Bartels K, et al. Update on perioperative right heart assessment using transesophageal echocardiography. Semin Cardiothorac Vasc Anesth. 2014;18(4):341–51.
6. Haddad F, et al. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation. 2008;117(13):1717–31.
7. Pedoto A, Amar D. Right heart function in thoracic surgery: role of echocardiography. Curr Opin Anaesthesiol. 2009;22(1):44–9.
8. Heerdt PM, Malhotra J. The right ventricular response to lung resection. In: Slinger PD, editor. Progress in thoracic anesthesiology. Baltimore: Lippincott Williams & Wilkins; 2004. p. 221–46.
9. Xu WY, et al. Effects of sevoflurane and propofol on right ventricular function and pulmonary circulation in patients undergone esophagectomy. Int J Clin Exp Pathol. 2014;7(1):272–9.
10. Kowalewski J, et al. Right ventricular morphology and function after pulmonary resection. Eur J Cardiothorac Surg. 1999;15(4):444–8.
11. Katz WE, et al. Immediate effects of lung transplantation on right ventricular morphology and function in patients with variable degrees of pulmonary hypertension. J Am Coll Cardiol. 1996;27(2):384–91.
12. Sugarbaker DJ, Haywood-Watson RJ, Wald O. Pneumonectomy for non–small cell lung cancer. Surg Oncol Clin N Am. 2016;25(3):533–51.
13. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. Ann Intensive Care. 2013;3(1):38.
14. Ashes C, Roscoe A. Transesophageal echocardiography in thoracic anesthesia: pulmonary hypertension and right ventricular function. Curr Opin Anesthesiol. 2015;28(1):38–44.
15. Tan CO, Harley I. Perioperative transesophageal echocardiographic assessment of the right heart and associated structures: a comprehensive update and technical report. J Cardiothorac Vasc Anesth. 2014;28(4):1100–21.
16. Slinger PD, Johnston MR. Preoperative assessment: an anesthesiologist's perspective. Thorac Surg Clin. 2005;15(1):11–25.
17. Rauch M, et al. Cardiovascular computed tomography findings after pneumonectomy: comparison to lobectomy. Acad Radiol. 2017;24(7):860–6.
18. D'Ascenzi F, et al. Right ventricular remodelling induced by exercise training in competitive athletes. Eur Heart J Cardiovasc Imaging. 2016;17(3):301–7.
19. Tam K, Daly M, Kelly K. Treatment of locally advanced non–small cell lung cancer. Hematol Oncol Clin North Am. 2017;31(1):45–57.
20. Pedoto A, Heerdt PM. Postoperative care after pulmonary resection: postanesthesia care unit versus intensive care unit. Curr Opin Anaesthesiol. 2009;22(1):50–5.
21. Galiè N, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.
22. Zangiabadi A, De Pasquale CG, Sajkov D. Pulmonary hypertension and right heart dysfunction in chronic lung disease. Biomed Res Int. 2014;2014:739674.
23. Venuta F, et al. Long-term Doppler echocardiographic evaluation of the right heart after major lung resections. Eur J Cardiothorac Surg. 2007;32(5):787–90.
24. Foroulis CN, et al. Study on the late effect of pneumonectomy on right heart pressures using Doppler echocardiography. Eur J Cardiothorac Surg. 2004;26(3):508–14.
25. Amar D, et al. Effects of diltiazem versus digoxin on dysrhythmias and cardiac function after pneumonectomy. Ann Thorac Surg. 1997;63(5):1374–81; discussion 1381–2.
26. Amar D, et al. Value of perioperative Doppler echocardiography in patients undergoing major lung resection. Ann Thorac Surg. 1996;61(2):516–20.
27. Smulders SA, et al. Cardiac function and position more than 5 years after pneumonectomy. Ann Thorac Surg. 2007;83(6):1986–92.
28. Amar D. Prevention and management of perioperative arrhythmias in the thoracic surgical population. Anesthesiol Clin. 2008;26(2):325–35, vii.
29. Groth SS, Burt BM, Sugarbaker DJ. Management of complications after pneumonectomy. Thorac Surg Clin. 2015;25(3):335–48.
30. Roselli EE, et al. Atrial fibrillation complicating lung cancer resection. J Thorac Cardiovasc Surg. 2005;130(2):438–44.
31. Dancewicz M, Kowalewski J, Peplinski J. Factors associated with perioperative complications after pneumonectomy for primary carcinoma of the lung. Interact Cardiovasc Thorac Surg. 2006;5(2):97–100.
32. Amar D, et al. Leukocytosis and increased risk of atrial fibrillation after general thoracic surgery. Ann Thorac Surg. 2006;82(3):1057–61.
33. Cardinale D, et al. Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. Circulation. 2007;115(11):1339–44.
34. Nojiri T, et al. Predictive value of B-type natriuretic peptide for postoperative atrial fibrillation following pulmonary resection for lung cancer. Eur J Cardiothorac Surg. 2010;37(4):787–91.

35. Amar D, et al. Brain natriuretic peptide and risk of atrial fibrillation after thoracic surgery. J Thorac Cardiovasc Surg. 2012;144(5):1249–53.
36. Iwata T, et al. Risk factors predictive of atrial fibrillation after lung cancer surgery. Surg Today. 2016;46(8):877–86.
37. Brecher O, et al. Preoperative echocardiographic indices of diastolic dysfunction and brain natriuretic peptide in predicting postoperative atrial fibrillation after noncardiac surgery. Anesth Analg. 2017;124(4):1099–104.
38. Amar D. Postoperative atrial fibrillation: is there a need for prevention? J Thorac Cardiovasc Surg. 2016;151(4):913–5.
39. Cardinale D, et al. Prevention of atrial fibrillation in high-risk patients undergoing lung cancer surgery: the PRESAGE trial. Ann Surg. 2016;264(2):244–51.
40. Frendl G, et al. 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. Executive summary. J Thorac Cardiovasc Surg. 2014;148(3):772–91.
41. Riber LP, Larsen TB, Christensen TD. Postoperative atrial fibrillation prophylaxis after lung surgery: systematic review and meta-analysis. Ann Thorac Surg. 2014;98(6):1989–97.
42. Vaporciyan AA, et al. Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: analysis of 2588 patients. J Thorac Cardiovasc Surg. 2004;127(3):779–86.
43. Foroulis CN, et al. Factors associated with cardiac rhythm disturbances in the early post-pneumonectomy period: a study on 259 pneumonectomies. Eur J Cardiothorac Surg. 2003;23(3):384–9.
44. Bobbio A, et al. Postoperative outcome of patients undergoing lung resection presenting with new-onset atrial fibrillation managed by amiodarone or diltiazem. Eur J Cardiothorac Surg. 2007;31(1):70–4.
45. Haverkamp WW. Post-thoracotomy dysrhythmia. Curr Opin Anaesthesiol. 2016;29(1):26–33.
46. Amar D, Zhang H, Roistacher N. The incidence and outcome of ventricular arrhythmias after noncardiac thoracic surgery. Anesth Analg. 2002;95(3):537–43, table of contents.
47. Mayson SE, et al. The changing face of postoperative atrial fibrillation prevention: a review of current medical therapy. Cardiol Rev. 2007;15(5):231–41.
48. Gialdini G, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. JAMA. 2014;312(6):616–22.
49. Wijeysundera DN, et al. Perioperative Beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2014;130:1–37.
50. Amar D. Post-thoracotomy atrial fibrillation. Curr Opin Anesthesiol. 2007;20(1):43.
51. Ahn HJ, et al. Thoracic epidural anesthesia does not improve the incidence of arrhythmias after transthoracic esophagectomy. Eur J Cardiothorac Surg. 2005;28(1):19–21.
52. Crawford TC, Oral H. Cardiac arrhythmias: management of atrial fibrillation in the critically ill patient. Crit Care Clin. 2007;23(4):855–72. vii
53. Karamichalis JM, Putnam JB Jr, Lambright ES. Cardiovascular complications after lung surgery. Thorac Surg Clin. 2006;16(3):253–60.
54. Ivanovic J, et al. Incidence, severity and perioperative risk factors for atrial fibrillation following pulmonary resection. Interact Cardiovasc Thorac Surg. 2014;18(3):340–6.
55. DeWitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev. 2004;23(4):223–38.
56. Sedrakyan A, et al. Pharmacologic prophylaxis for postoperative atrial tachyarrhythmia in general thoracic surgery: evidence from randomized clinical trials. J Thorac Cardiovasc Surg. 2005;129(5):997–1005.
57. Bradley D, et al. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest. 2005;128(2 Suppl):39S–47S.
58. Connolly SJ, et al. Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: the Beta-Blocker Length of Stay (BLOS) study. Am Heart J. 2003;145(2):226–32.
59. Group, P.S., et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008;371(9627):1839–47.
60. Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? Lancet. 2008;371(9627):1813–4.
61. Amar D, et al. Effects of diltiazem prophylaxis on the incidence and clinical outcome of atrial arrhythmias after thoracic surgery. J Thorac Cardiovasc Surg. 2000;120(4):790–8.
62. Mitchell LB, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: a randomized controlled trial. JAMA. 2005;294(24):3093–100.
63. Zimetbaum P. Amiodarone for atrial fibrillation. N Engl J Med. 2007;356(9):935–41.
64. Van Mieghem W, et al. Amiodarone and the development of ARDS after lung surgery. Chest. 1994;105(6):1642–5.
65. Tisdale JE, et al. A randomized trial evaluating amiodarone for prevention of atrial fibrillation after pulmonary resection. Ann Thorac Surg. 2009;88(3):886–93; discussion 894–5.
66. Riber LP, et al. Amiodarone significantly decreases atrial fibrillation in patients undergoing surgery for lung cancer. Ann Thorac Surg. 2012;94(2):339–44; discussion 345–6.
67. Tamargo J, Delpon E, Caballero R. The safety of digoxin as a pharmacological treatment of atrial fibrillation. Expert Opin Drug Saf. 2006;5(3):453–67.
68. Gheorghiade M, Adams KF Jr, Colucci WS. Digoxin in the management of cardiovascular disorders. Circulation. 2004;109(24):2959–64.
69. Gheorghiade M, et al. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. Eur Heart J. 2013;34(20):1489–97.
70. Toraman F, et al. Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting. Ann Thorac Surg. 2001;72(4):1256–61; discussion 1261–2.
71. Zhao B-C, et al. Prophylaxis against atrial fibrillation after general thoracic surgery: trial sequential analysis and network meta-analysis. Chest. 2017;151(1):149–59.
72. Thielmann M, et al. Lipid-lowering effect of preoperative statin therapy on postoperative major adverse cardiac events after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2007;134(5):1143–9.
73. Patti G, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation. 2006;114(14):1455–61.
74. Amar D, et al. Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery independent of C-reactive protein. Chest. 2005;128(5):3421–7.
75. Amar D, et al. Beneficial effects of perioperative statins for major pulmonary resection. J Thorac Cardiovasc Surg. 2015;149(6):1532–8.
76. Amar D, et al. Inflammation and outcome after general thoracic surgery. Eur J Cardiothorac Surg. 2007;32(3):431–4.
77. Healey JS, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol. 2005;45(11):1832–9.

78. Liu XH, Xu CY, Fan GH. Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials. BMC Cardiovasc Disord. 2014;14:52.
79. Ozaydin M, et al. Metoprolol vs. carvedilol or carvedilol plus N-acetyl cysteine on post-operative atrial fibrillation: a randomized, double-blind, placebo-controlled study. Eur Heart J. 2013;34(8):597–604.
80. Shackebaei D, et al. Mechanisms underlying the cardioprotective effect of L-cysteine. Mol Cell Biochem. 2005;277(1–2):27–31.
81. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC guidelines. Europace. 2014;16(2):162–73.
82. Nojiri T, et al. A double-blind placebo-controlled study of the effects of olprinone, a specific phosphodiesterase III inhibitor, for preventing postoperative atrial fibrillation in patients undergoing pulmonary resection for lung cancer. Chest. 2015;148(5):1285–92.
83. Nojiri T, et al. Low-dose human atrial natriuretic peptide for the prevention of postoperative cardiopulmonary complications in chronic obstructive pulmonary disease patients undergoing lung cancer surgery. Eur J Cardiothorac Surg. 2013;44(1):98–103.
84. Lomivorotov VV, et al. New-onset atrial fibrillation after cardiac surgery: pathophysiology, prophylaxis, and treatment. J Cardiothorac Vasc Anesth. 2016;30(1):200–16.
85. January CT. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation (New York, NY). 2014;130(23):e199–267.
86. Amar D. Postthoracotomy atrial fibrillation. Curr Opin Anaesthesiol. 2007;20(1):43–7.
87. Martin J, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. Ann Thorac Surg. 2001;72(4):1149–54.
88. Boffa DJ, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg. 2008;135(2):247–54.
89. Allen MS, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg. 2006;81(3):1013–9; discussion 1019–20.
90. Fleisher LA. ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non cardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation (New York, NY). 2014;130(24):e278–333.
91. Vasic N, et al. Acute "Pseudoischemic" ECG abnormalities after right pneumonectomy. Case Rep Surg. 2017;2017:4.
92. Jaroszewski DE, et al. Utility of detailed preoperative cardiac testing and incidence of post-thoracotomy myocardial infarction. J Thorac Cardiovasc Surg. 2008;135(3):648–55.
93. Kristensen SD, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014;35(35):2383–431.
94. Sandri A, et al. Coronary artery disease is associated with an increased mortality rate following video-assisted thoracoscopic lobectomy. J Thorac Cardiovasc Surg. 2017;154(1):352–7.
95. Pandey A, et al. Effect of preoperative angina pectoris on cardiac outcomes in patients with previous myocardial infarction undergoing major noncardiac surgery (Data from ACS-NSQIP). Am J Cardiol. 2015;115(8):1080–4.
96. McFalls EO, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004;351(27):2795–804.
97. Spahn DR, et al. Coronary stents and perioperative anti-platelet regimen: dilemma of bleeding and stent thrombosis. Br J Anaesth. 2006;96(6):675–7.
98. Albaladejo P, et al. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. Br J Anaesth. 2006;97(4):580–2.
99. Vicenzi MN, et al. Coronary artery stenting and non-cardiac surgery--a prospective outcome study. Br J Anaesth. 2006;96(6):686–93.
100. Voltolini L, et al. Lung resection for non-small cell lung cancer after prophylactic coronary angioplasty and stenting: short- and long-term results. Minerva Chir. 2012;67(1):77–85.
101. Oscarsson A, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. BJA: Br J Anaesth. 2010;104(3):305–12.
102. Banerjee S, et al. Use of antiplatelet therapy/DAPT for post-PCI patients undergoing noncardiac surgery. J Am Coll Cardiol. 2017;69(14):1861–70.
103. Ward HB, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during subsequent vascular surgery. Ann Thorac Surg. 2006;82(3):795–800; discussion 800–1.
104. Reed CE, Spinale FG, Crawford FA Jr. Effect of pulmonary resection on right ventricular function. Ann Thorac Surg. 1992;53(4):578–82.
105. Slinger P. Update on anesthetic management for pneumonectomy. Curr Opin Anaesthesiol. 2009;22(1):31–7.
106. Mehanna MJ, et al. Cardiac herniation after right pneumonectomy: case report and review of the literature. J Thorac Imaging. 2007;22(3):280–2.
107. Wolf AS, et al. Managing the pneumonectomy space after extrapleural pneumonectomy: postoperative intrathoracic pressure monitoring. Eur J Cardiothorac Surg. 2010;37(4):770–5.
108. Biondetti PR, et al. Evaluation of post-pneumonectomy space by computed tomography. J Comput Assist Tomogr. 1982;6(2):238–42.
109. Bedard EL, Uy K, Keshavjee S. Postpneumonectomy syndrome: a spectrum of clinical presentations. Ann Thorac Surg. 2007;83(3):1185–8.
110. Shen KR, et al. Postpneumonectomy syndrome: surgical management and long-term results. J Thorac Cardiovasc Surg. 2008;135(6):1210–6; discussion 1216–9.
111. Jung JJ, et al. Management of post-pneumonectomy syndrome using tissue expanders. Thorac Cancer. 2016;7(1):88–93.