The anesthetic management and the role of extracorporeal membrane oxygenation for giant mediastinal tumor surgery

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Abstract: Mediastinal tumors are a remarkably diverse category. They include malignant and benign forms with different rates of disease progression and tissue invasion. Anesthesiologists may encounter significant difficulties in managing patients with giant mediastinal tumors due to the non-negligible occurrence of severe cardiorespiratory collapse. Respiratory complications ensue from the compression of the airways induced by the mediastinal mass: the compressive effects may be exacerbated by positioning or anesthesia induction. Furthermore, the compression or invasion of major vessels may elicit acute cardiovascular collapse. The specter of sudden cardiorespiratory deterioration should lead the anesthesiologist to careful planning: acknowledging clinical and radiological signs that may presage an increased risk of life-threatening complications is of pivotal importance. This review aims to present a strategy for treating patients with mediastinal masses, starting with the pathophysiological elements and moving through preoperative care, intraoperative behavior, and the recovery period. We will also focus on respiratory and cardiovascular issues, emphasizing the need for extracorporeal membrane oxygenation (ECMO) as a rescue and crucial component of the anesthesia strategy. Understanding the physiological alterations after anesthesia induction can aid in identifying and treating potential problems. In addition, we attempted to offer insight into multimodal anesthesia and analgesia management: we emphasize the importance of a thorough preoperative assessment and the need for reviewing extracorporeal support not just a resuscitative strategy but as an integrated component of the perioperative care.

Keywords: Thoracic anesthesia; mediastinum; mediastinal tumor; extracorporeal membrane oxygenation (ECMO)

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Introduction

Mediastinal tumors are uncommon and represent a very heterogeneous group as they are populated by benign and malignant forms. Moreover, the histological variants of tumors vary widely between the adult and pediatric populations.

The anesthetic management of patients with giant mediastinal tumors is challenging due to the non-negligible incidence of severe cardiorespiratory adverse events. In a retrospective analysis of 117 pediatric patients with mediastinal masses, the rate of anesthesia-related complications was 9.4% (1). Adult patients have a similar incidence of perioperative adverse events. Béchard and colleagues demonstrated 3.8% intraoperative cardiorespiratory complications and 10.5% postoperative respiratory complications in their analysis of 105 patients (2).

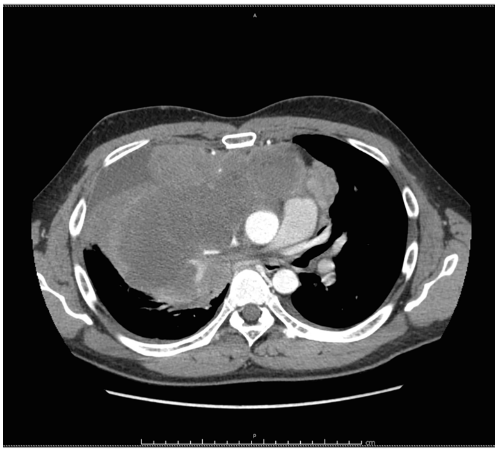

Figure 1 CT image of a 36-year-old male with non-Hodgkin's lymphoma adhered to the pleura and pericardium and with signs of bronchial and vascular compression. CT, computed tomography.

In addition, general anesthesia causes physiological changes that can exacerbate cardiorespiratory collapse. Therefore, a multidisciplinary approach is mandatory from the preoperative to the postoperative phase to avoid life-threatening situations.

This review aims to provide an approach to the patient with mediastinal mass starting from the pathophysiological aspects, passing through the preoperative management, the intraoperative conduct, and the postoperative phase. In addition, we will focus on respiratory and cardiovascular complications, highlighting the role of extracorporeal membrane oxygenation (ECMO) as an integrated part of the perioperative management.

The anesthesiologist's approach varies according to the type of planned surgical procedure. Therefore, our review aims to provide insight into the perioperative planning of patients undergoing major mediastinal surgery, leaving aside minor procedures.

Mediastinal Mass Syndrome (MMS) pathophysiology

MMS is the clinical expression of cardiorespiratory effects induced by mediastinal masses (3). These effects are enhanced by general anesthesia, which can be by itself the element of decompensation.

Respiratory complications

Respiratory complications are due to mechanical compression and/or tumor infiltration at the level of the tracheobronchial tree. Airway compression is responsible for specific signs and symptoms: cough, dyspnea, stridor, and hoarseness. The display of these symptoms is undoubtedly a warning sign for the anesthesiologist. Nevertheless, paucisymptomatic or asymptomatic patients may experience acute decompensation due to anesthesia induction as well (4). Therefore, the absence of preoperative symptoms does not exclude the risk of catastrophic intraoperative events (5). Anesthesia can exacerbate the compressive effects induced by mediastinal tumors through several mechanisms. A supine position is often required for induction of anesthesia or during surgery. It raises the compression of mediastinal structures by the gravitational effect. It also causes a cephalic displacement of the diaphragmatic dome, increasing intrathoracic pressure promoting airway compression, and impairing ventilation. Finally, the supine position increases the central blood volume, which may facilitate the volumetric increase of highly vascularised tumors. The induction of anesthesia is another critical point. The reduction of muscle tone favors the cephalad movement of the diaphragm and airway smooth muscle relaxation. This increases the risk of airway compression, mainly in the pediatric population, due to the more collapsible tissues (6).

The loss of spontaneous breathing can promote the onset of respiratory complications. Positive pressure ventilation increases pleural pressure, strengthening the compression of mediastinal structures. Poiseuille's law states that the flow resistance is directly proportional to the fourth power of the radius when the cross-section of the airway is reduced. In this case, post-stenotic turbulent flow is produced via positive pressure ventilation. Although air can overcome the stenotic airway due to the positive pressure, it cannot be completely flushed out during the expiratory phase due to the obstruction and the lack of laminar flow, which impede gas exchange and encourage the genesis of air trapping phenomena.

Hemodynamic complications

The hemodynamic imbalance is due to compression or infiltration of the heart or major vessels (*Figure 1*). The compression of the pulmonary artery is uncommon, thanks to the protection provided by the tracheobronchial tree. Patients are often paucisymptomatic, sometimes presenting only exertional dyspnea. The induction of anesthesia with reduced venous return, increased pleural pressure (due to

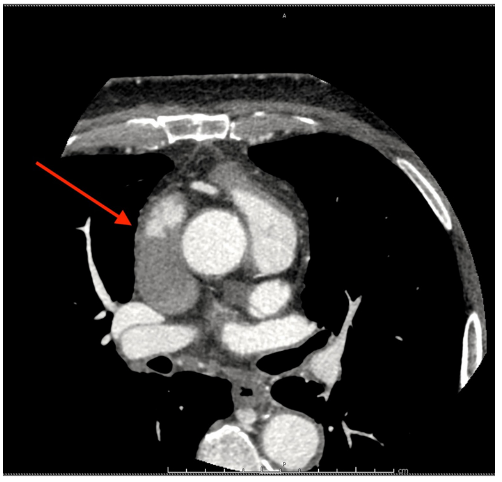

Figure 2 CT image of invasion and occlusion of superior vena cava extending up to the right atrium in a 72-year-old patient with malignant thymoma (red arrow). CT, computed tomography.

positive pressure ventilation), and the supine position may exacerbate right ventricular failure. Conversely, the superior vena cava (SVC) is more easily affected due to its location and low intravascular pressure. The obstruction of venous return from SVC generates superior vena cava syndrome (SVCS). The increased venous pressure in the upper body can result in edema of the pharynx and larynx with the onset of coughing, stridor, dyspnea, and dysphagia up to cerebral edema with headaches and mental confusion. Obstruction of venous return generates jugular turgor and in chronic forms the development of vascular networks allowing blood drainage into the inferior vena cava. SVCS occurs annually in about 15,000 people in the United States (7). Mediastinal tumors represent the most frequent malignant cause after non-small-cell and small-cell lung cancer (7). An Italian retrospective analysis of patients with stage III thymic tumors showed 24.1% involvement of major vessels with 12.4% involvement of the SVC (8). The induction of anesthesia is once again a possible cause of decompensation. Lowering the patient's head increases hydrostatic pressure, magnifying cerebral edema. Furthermore, reducing systemic vascular resistance induced by anesthetic drugs may induce acute central hypovolemia, given the existing impairment of blood return from the SVC, which carries approximately one-third of the venous return to the heart (7).

Preoperative assessment

Clinical examination is the first step in evaluating a patient with mediastinal tumors. It is important to recognize signs and symptoms of cardio-respiratory involvement: dyspnea, coughing, stridor, hoarseness, syncope, and the patient's upper-body edema. Furthermore, it is essential to evaluate the variation of symptoms with the patient's position and to collect a detailed history of the patient's preferred and non-tolerated positions. A "rescue position" should be reported during the anesthetic assessment. Patient positioning may be the simplest and most effective intraoperative maneuver to resolve life-threatening cardio-pulmonary complications. This primary assessment provides an initial grading of anesthesia risk: Anghelescu and colleagues demonstrated that orthopnea and upper body edema were significantly associated with anesthetic complications (1). Béchard and colleagues obtained similar results in adults: severe cardiorespiratory signs and symptoms were strongly associated with perioperative complications (2).

Radiological imaging is an essential adjunct in the preoperative evaluation of patients with giant mediastinal tumors. Computed tomography (CT) is the standard imaging technique. It is a rapid examination, possible to perform even in patients with poor supine tolerance. CT scan has a high sensitivity in assessing airway diameter, and the administration of contrast material allows accurate assessment of compression or thrombosis of the SVC (*Figure 2*). Reduction of the tracheal cross-sectional area (CSA) is a strong predictor of perioperative respiratory complications. An airway CSA, less than 50% of the standard diameter, seems to be associated with an increased risk of postoperative severe respiratory complications (2). A retrospective analysis of children with anterior mediastinal masses demonstrated a high risk of intraoperative respiratory complications in patients with either an isolated tracheal CSA less than 30% of normal or a tracheal CSA less than 70% associated with carinal or bronchial compression (9). Fiberoptic tracheobronchoscopy is another effective technique to assess airway compression or infiltration but, it should be performed in selected cases as the airway partial occlusion caused by the instrument might be itself a cause of clinical derangement. Pulmonary function tests have been extensively used in the preoperative phase, though they demonstrated a low sensitivity in the prediction of intraoperative respiratory complication. Nevertheless, Béchard and colleagues demonstrated that a peak expiratory flow of less than 40% was associated with a more than 10-fold increase in the risk of postoperative respiratory complications (2).

A comprehensive echocardiographic examination should be performed in all patients with signs or symptoms of SVCS or suggestive CT scan imaging. Echocardiographic evaluation may help excluding signs of pericardial effusion and providing information on biventricular systolic and diastolic function: good biventricular function ensures greater functional reserve in case of sudden hemodynamic changes (10). The preoperative assessment should ultimately provide a classification of anesthesia risk. We can classify patients into risk classes: *safe*, *uncertain*, and *unsafe* (3).

Preoperative planning is the cornerstone in managing patients with giant mediastinal masses. Perioperative discussion should involve anesthesiologists, surgeons and oncologists. All professionals should agree on the proposed treatment and alternative strategies in case of intraoperative drawbacks. Creating a multidisciplinary discussion may reduce the risk of life-threatening complications (11).

ECMO prediction

ECMO is used to treat severe cardiopulmonary failure, but it is not yet known whether it is also appropriate for use in patients with cancer. Thoracic neoplasms are distinct from other malignant tumors because they may have a direct effect on cardiopulmonary function, nevertheless as observational and registry analysis could not provide a clear recommendation pro or contra ECMO application, focus on tailored patient selection should pursued to achieve optimal results (12-14).

The preoperative phase should also identify patients at high risk of respiratory or hemodynamic collapse who could benefit from extracorporeal support. In recent years, many case reports have been published on the use of intraoperative ECMO in patients with mediastinal tumors (15,16). In addition, extracorporeal support has also been used to ensure the initial stages of chemotherapy in selected patients (17-19). The feasibility of ECMO support in cancer surgery is acknowledged (20). However, extracorporeal support is often started in emergency conditions as a rescue therapy. In 2011 a systematic review of lung resections for non–small cell lung cancer under extracorporeal support demonstrated that survival was significantly higher when placement on bypass was planned as opposed to unplanned or emergency placement (21). These data confirm the need for preoperative planning to identify patients who may benefit from extracorporeal support. Recently, Leow *et al.* (16) and Ramanathan and colleagues (22) proposed an algorithm to identify patients with mediastinal masses potentially eligible for ECMO. They individuated high-risk patients in the case of:

- (I) Acute SVCS;
- (II) Pulmonary artery or right ventricular outflow tract obstruction;
- (III) Airway compression >50%;
- (IV) Cardiac or great vessel involvement/invasion with possible need for cardiac or vascular excision or reconstruction.

However, identifying patients with acutely decompensated SVCS who could benefit from ECMO support is not straightforward. Recently, Potere and colleagues evaluated the possible creation of a scoring system to assess the use of ECMO in patients with SVCS (23). Patients with a radiological score of II or higher (according to the classification of Qanadli *et al.* (24) and a grade II or higher in the symptoms classification of Yu *et al.* (25) should be considered candidates for ECMO (*Tables 1,2*).

Moreover, high-risk patients should receive multidisciplinary planning to decide between a veno-venous or veno-arterial ECMO approach. Veno-arterial ECMO should be preferred in compromised patients with giant mediastinal masses and high risk of respiratory and hemodynamic collapse. Therefore, veno-venous ECMO should be applied in selected cases of patients with isolated respiratory symptoms and airway compression.

In all patients with at least one of the former risk factors, femoral vein/femoral artery sheaths should be inserted (depending on the type of ECMO setup chosen) before the induction of anesthesia. Perfusionists should be available in the operating room for the whole duration of surgery with a primed ECMO machine. Conversely, in patients with more than one risk factor, preoperative cannulation with the start of extracorporeal circulation before anesthetic induction should be strongly advocated.

Intraoperative management

Patients with giant mediastinal tumors need an endorsed multidisciplinary approach to achieve the best intraoperative conduct. The anesthetic approach should be tailored to the patient's risk class and the need for possible ECMO support. Patients classified as *safe* should receive the same care dedicated to major thoracic surgery. Nonetheless, as already pointed out, anesthesia induction and intrathoracic pressure changes may exacerbate a cardiorespiratory collapse even in asymptomatic patients.

The anesthesiologist should escort all *unsafe* patients to the operating theatre. Before induction of anesthesia, a

Table 1 Radiological classification of superior vena cava obstruction according to Qanadli *et al.* (24)

Types	Degree of SVC obstruction
Type I	Stenosis of SVC up to 90%
Type II	90–99% of SVC stenosis
Type III	Complete obstruction of SVC
Type IV	Complete obstruction of SVC and at least one major tributary

SVC, superior vena cava.

Table 2 Symptomatic classification of superior vena cava obstruction according to Yu *et al.* (25)

Grade	Category	Definition
0	Asymptomatic	Radiographic signs of SVC obstruction, but no symptoms
1	Mild	Mild edema in head or neck, cyanosis or plethora
2	Moderate	Edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema)
3	Severe	Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	Significant cerebral edema (confusion, obtundation) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)
5	Fatal	Death

SVC, superior vena cava.

safety checklist should be follow:

(I) Vascular access: in all cases of SVCS, the placement of vascular accesses in tributary vessels of the SVC should be avoided to reduce thrombosis risk and to ensure the proper onset of administered drugs. The insertion of a large-bore femoral vein catheter and a femoral artery catheter should be achieved. The femoral venous catheter should be inserted distally when placing a femoral vein sheath or cannulation for ECMO or on the other limb. The risk of significant hemorrhages during mediastinal surgery dramatically increases in patients with SVCS (7,26). For this reason, the placement of a rapid infusion catheter (RIC) in a lower limb vessel is recommended.

(II) Airway management is always a challenge. Indeed, even without symptoms or radiological signs of airway compression, supine positioning and anesthesia induction can lead to critical airway stenosis. Therefore, the availability of various airway management devices is obliged: video laryngoscope, flexible fiberscope, rigid bronchoscope, and reinforced and double-lumen endotracheal tubes. In our opinion, well-trained thoracic anesthesiologists and experienced bronchoscopists should be available for the duration of the surgery. Moreover, perfusionists and a primed ECMO machine should always be accessible, even in unexpected cases.

(III) Anesthetic monitoring:

  (i) Hemodynamic monitoring: transpulmonary thermodilution systems or pulse-contour analysis to monitor cardiac function continuously should be applied;

  (ii) Transesophageal echocardiography (TEE) should be used when available especially in previously evaluated patients with systolic or diastolic dysfunction, pericardial effusion, signs of heart compression or masses (*Figure 3*);

  (iii) Near infrared spectroscopy (NIRS) monitoring to assess any worsening of the SVCS-induced cerebral edema;

  (iv) Right arm pulse oximetry to evaluate possible injuries to the brachiocephalic trunk.

Induction of anesthesia requires a stepwise approach. Depending on local protocols and anesthesiologist's

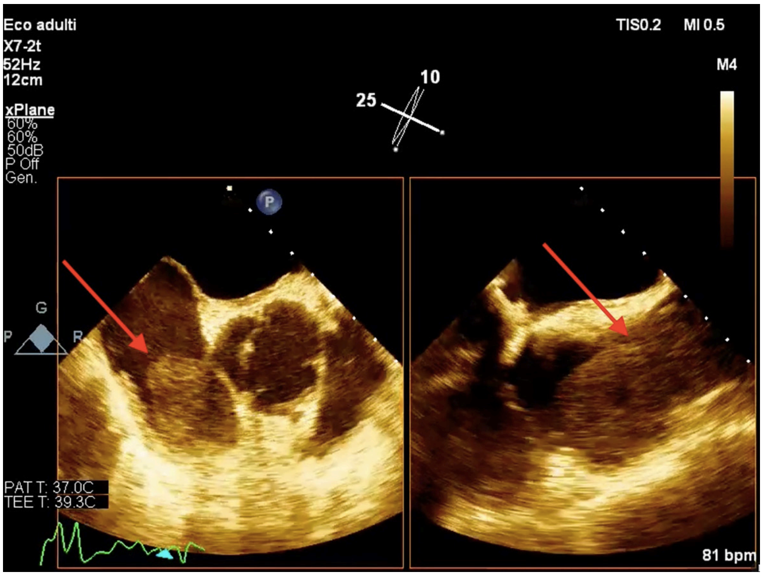

Figure 3 Transesophageal echocardiography image of tumoral invasion of superior vena cava and right atrium in a 72-year-old patient with malignant thymoma (red arrows). PAT T, patient's temperature; TEE T, transesophageal echocardiography probe temperature; TIS, Soft Tissue Thermal Index; MI, Mechanical Index.

experience, an effective way to secure the airways is awake fiberoptic intubation with the patient in spontaneous breathing. Topic anesthesia and intravenous drugs with a short half-life (remifentanil, dexmedetomidine, ketamine) guarantee the achievement of oro-tracheal intubation with an excellent level of security. Remifentanil boluses that could exacerbate stiffness, compromising patient ventilation and subsequent intubation should be avoided.

The endotracheal tube should be the largest possible to resist extrinsic compressions. We may use spiral-reinforced endotracheal or dual-lumen tubes if the surgeon requires them. Subsequently, the anesthetic plan should be deepened gradually to keep the patient breathing spontaneously. The maintenance of spontaneous breathing or pressure support ventilation avoids a significant increase in pleural pressure, decreasing the compressing effects of the mediastinal mass.

Nevertheless, as surgery often requires neuromuscular blockade, using short-acting paralyzers, such as succinylcholine or rocuronium, as its antidote; sugammadex is currently available seems a convenient choice to return to spontaneous ventilation in case of severe airway collapse or hemodynamic instability.

Recently, Hartigan and colleagues demonstrated that neuromuscular blockade did not induce airway collapse or difficult ventilation in patients with mediastinal masses presenting different grades of airway stenosis (27). Nevertheless, the study included only seventeen patients. Furthermore, patients could be excluded from the study according to the attending anesthesiologists' choice, maybe creating a selection bias.

If the loss of spontaneous breathing exacerbates cardiorespiratory collapse in fact, the first step should be the rapid reversal of neuromuscular blockade. Meanwhile, the patient should be placed in her/his "rescue position" (if there is one), and ventilation should be attempted using a rigid bronchoscope. Unfortunately, a rigid bronchoscope can overcome tracheal compression but it hardly restores adequate ventilation in case of compression at the level of the bronchial branches.

Cardiorespiratory collapse may appear even in spontaneous breathing patients placed in their safety position. In this case, excluding a displacement of the endotracheal tube, an anesthetic plane too deep, or intraoperative bleeding, a common complication in patients with SVCS, is mandatory. Therefore, when all the reversible causes have been ruled out and treated, only two rescue therapies remain for the clinicians: the elevation of the mediastinal mass by the surgeon (sometimes with emergent sternotomy) or the extracorporeal support (veno-venous ECMO or veno-arterial ECMO). However, as already pointed out, ECMO support should be planned in the preoperative phase and not considered the last resource.

Postoperative management

Safe patients should be promptly extubated at the end of surgery and require sub-intensive care monitoring for at least 24 hours in case of no intraoperative complications.

Patients classified as *unsafe* or *uncertain* should be monitored in the intensive care unit after surgery. Achieving rapid postoperative extubation to avoid complications related to invasive ventilation (i.e., ventilator-associated pneumonia) and ensure rapid access to the rehabilitation phase or the start of chemo-radiotherapy should be pursued. Nevertheless, adequate pain management is essential to ensure rapid extubation and rehabilitation. One of the most effective approaches is multimodal and opioid-sparing analgesia (28). Several medications in combination with local anesthetics seem to have a good profile in reducing the opioids needed after thoracic surgery: ketoprofen, ketorolac, paracetamol, pethidine, flurbiprofen, dexmedetomidine (29). Among others, ketamine demonstrated a statistically significant reduction in acute post-thoracotomy pain but low power as a preventative agent for chronic post-thoracotomy pain (30) as well as pregabalin significantly reduced pain scores, decreasing postoperative neuropathic pain and morphine consumption (31).

The multimodal approach to analgesia involves regional anesthesia techniques. Thoracic epidural analgesia has been the gold standard for perioperative post-thoracotomy pain management (32). However, it is burdened by the risk of hypotension and the inability to place the epidural catheter in patients with impaired coagulation status. The search for less invasive and safer techniques is then advocated. The erector spinae plane (ESP) block might be the regional anesthesia technique of choice for the patient. It carries a low-risk profile, far from the pleura, spinal cord, and major blood vessels (32). It can be performed with high safety even in patients with impaired coagulation, and it demonstrated similar pain relief effects compared to thoracic paravertebral block (33). In a randomized controlled trial conducted on sixty patients, ultrasound-guided ESP block exhibited a significant analgesic and opioid-sparing effect in patients undergoing thoracotomy surgery (34).

Conclusions

We aimed to provide a pathophysiological view of anesthesia-induced changes in patients with giant mediastinal tumors. Understanding the physiological changes induced by anesthesia can help prevent and treat possible complications. In addition, we tried to provide an insight into different and multimodal approaches, stressing the need for a detailed preoperative phase and the need to consider extracorporeal support not as a rescue therapy but as an incorporated part of perioperative management.

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Footnote

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