The role of extracorporeal life support in extended lung resections for non-small cell lung cancer: a narrative review

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Background and Objective: Extracorporeal membrane oxygenation (ECMO) may be used as a substitute of traditional cardiopulmonary bypass (CPB) in thoracic surgeries. Extended resections for the treatment of non-small cell lung cancer (NSCLC) occasionally require extracorporeal life support. We present a narrative review of the current clinical uses of extracorporeal devices in this setting of patients.

Methods: We searched Medline database/PubMed for "extra-corporeal membrane oxygenation" and "non-small cell lung carcinoma" in the English language literature between the years 2000 and 2022.

Key Content and Findings: As opposed to CPB, ECMO is simple, requires minimal or no anticoagulation and elicits fewer complications. T4 lung cancers are frequently considered for surgery in marginally operable patients. ECMO may provide the means to achieve these resections. There are case series of carinal extended resections safely performed under venovenous (VV) or venoarterial (VA) support. The main advantages are a clear surgical field, certainty of proper oxygenation and avoidance of ventilator induced trauma. Left atrial resections have been described with VA ECMO, but the standard of care is still CPB. Descending thoracic aorta resections can also benefit from extracorporeal support, making sure that abdominal organs and lower limbs are well perfused, the heart is not overloaded, and cross clamping is safe.

Conclusions: Surgeons performing extended lung cancer resections should be familiar with ECMO and are encouraged to report their experience.

Keywords: Extracorporeal life support; extracorporeal membrane oxygenation (ECMO); non-small cell lung cancer (NSCLC); extended pulmonary resection

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Introduction

Background

Extracorporeal membrane oxygenation (ECMO) has gained wide acceptance in the past 20 years for its therapeutic use in several clinical scenarios (1). In lung transplantation, for instance, this technology has largely replaced traditional cardiopulmonary bypass (CPB) considering the decrease of blood product needs, the lower intensive care unit (ICU) and hospital stay (2,3).

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Table 1 Search strategy summary

Items	Specification
Date of search	30/06/2022–01/08/2022
Databases and other sources searched	Medline database/PubMed
Search terms used	"Extra-corporeal membrane oxygenation" and "non-small cell lung carcinoma"
Timeframe	01/01/2000–30/06/2022
Inclusion criteria	Research articles on extended NSCLC resection written in English were considered excluding other NSCLC-related uses of ECMO, such as in patients with poor lung function and impossible one-lung ventilation
Selection process	Two authors conducted independently the selection of the relevant literature and reached consensus

NSCLC, non-small cell lung cancer; ECMO, extracorporeal membrane oxygenation.

Rationale and knowledge gap

The question of whether, and to what extent, should ECMO replace CPB in thoracic oncological cases is still open. Indeed, lung cancer surgical treatment may need extended resections which could cause some technical issues for the use of ECMO rather than CPB.

Objective

We present a narrative review of the current possible uses of ECMO in extended surgical resection of non-small cell lung cancer (NSCLC). We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1213/rc).

Methods

The search strategy (*Table 1*) was performed using a combination of relevant keywords in the Medline database using the entry terms for "extra-corporeal membrane oxygenation" and "non-small cell lung carcinoma", which are the Mesh terms for ECMO and NSCLC, respectively. Other NSCLC-related uses of ECMO, such as in patients with poor lung function and impossible one-lung ventilation during minimal invasive surgery, will be addressed elsewhere in this issue of the *JTD*, and therefore were excluded from our search. Search was limited to the English language literature between the years 2000 and 2022. We initially found 165 articles and considered 22 articles for the present review.

Findings and discussion

CPB versus ECMO

In comparison to CPB, ECMO allows longer courses of treatment, peripheral cannulation, limited systemic anticoagulation, and less important activation of inflammatory pathways (4). The possibility of low levels of anticoagulation, or even no anticoagulation at all, is an obvious advantage of ECMO over CPB for non-cardiac thoracic surgeries.

On the other hand, there are some extended resections that can only be carried out under CPB, since it allows for aortic clamping, cardiac arrest and suction of blood from the surgical field. Open left atrial resections are made possible by bypassing the left heart and avoiding massive systemic air embolism by cross clamping the aorta. Opening the left atrium (LA) is obligatory when there is an intra-atrial thrombus, the tumor itself invades the atrial wall or clamping of the atrium results in unacceptable instability or arrhythmia (5). For resections involving the pulmonary trunk, CPB will divert blood from the pulmonary circulation and the resections can be done without cardioplegia. Blood will still be ejected from the right ventricle (RV) and suctioned back to the CPB reservoir, since the coronary output will continue to drain into the right atrium (RA). Limited aortic arch resections can be performed by side clamping or temporarily cross clamping distal to the left carotid artery (6). Actual aortic arch resections for NSCLC are rare occurrences of questionable oncologic benefit and would, in many cases, require deep hypothermic circulatory arrest for the reconstruction of the arch.

NSCLC operability

Surgical resectability refers to the purely technical possibility of surgery; operability, on the other hand, concerns tolerability to surgical trauma, center expertise and patient's preferences. Surgical treatment or multimodality treatments that include surgery for NSCLC are those most likely to result in long term survival. However, NSCLC is only resectable in 9–22% of cases (7), and around 20% of those are considered very high-risk patients, not operable due to comorbidities such as poor lung reserve or heart disease (8). Another group of patients are denied of surgery due to concerns over the actual benefit of extended resection when balanced against surgical risk.

Extended surgical resection for centrally located T4 NSCLC is always challenging. Despite that, ECMO has been an infrequent necessity. Among 201 patients operated for invasion of the superior vena cava, carina, thoracic aorta, LA or pulmonary artery trunk in a high-volume French center over 30 years, only 13 required CPB, indicating that extracorporeal support was an infrequent occurrence (9). In general thoracic (non-cardiac) surgery, only a very small percentage (about 0.5%) of patients were reported to require ECMO (10).

ECMO allows marginal risk patients to receive the best possible treatment from the oncological point of view while still been able to endure through the surgical process.

Monitoring

Intraoperative monitoring for patient on ECMO is not particularly different from other major thoracic surgeries. Nonetheless, the unique physiology of ECMO must be considered while interpreting data, which will be adapted to type of circuit and site of cannulation (11).

During venoarterial (VA) ECMO, pulse oximetry is often unreliable if the ECMO flow is too high and there is no pulsatility, making arterial blood gas (ABG) analysis compulsory to access oxygenation parameters. In femoral VA ECMO, attention must be paid to differential oxygenation and the site of watershed, since the coronary arteries and the brain might not be properly oxygenated. For that reason, pulse oximetry and ABG should be obtained from the right arm, which is the site farthest from the arterial cannula and most likely to reflect brain, and conceivably, coronary perfusion (12). A validated alternative is the use of near-infrared spectroscopy to directly assess regional brain saturation of oxygen, which predicts mortality in VA ECMO patients (13). The absence of left ventricular distention and thrombus formation should be monitored by transesophageal echocardiography, since most surgical patients will not be anticoagulated throughout the procedure. Of note, the mere presence of a pulsatile waveform is not guarantee of proper left ventricle (LV) unloading.

Venovenous (VV) ECMO monitoring also has its particularities, due to the *in series* nature of the circuit. Central venous saturation of oxygen (SvO_2) must be interpreted with caution because recirculation within the circuit may falsely elevate readings; conversely, low SvO_2 may be related to low arterial saturation instead of excessive peripheral consumption. Estimating the cardiac output (CO) based on thermodilution methods is difficult, if not impossible, under VV ECMO; other methods such as arterial waveform analysis are recommended. Expertise in transesophageal echocardiography may prove invaluable to establish proper preload by measuring the inferior vena cava, while making sure the drainage cannula is well positioned. Also, echographic evidence of RV dysfunction would be an indication of conversion to a VA ECMO.

The issue of anticoagulation is most relevant to surgeons, especially when extensive dissection is performed. There is no consensus in the literature to which level of anticoagulation or monitoring method is preferred. Activated clotting times (ACTs) between 160 and 200 s, activated partial thromboplastin time (APTT) of 1.5× the control, or anti-Xa between 0.3 and 0.7 IU/mL are commonly used targets, but it is not clear whether or not these levels are necessary for exclusively intraoperative support. Currently used heparin-coated circuits, polymethylpentene membranes and centrifugal pumps are of low thrombogenic potential and can operate safely in the trans- and post-operative periods after a single low dose of heparin (50–70 UI/kg) before cannulation (14). Manufacturers do not recommend priming with heparinized solutions. At the limit, patients who are considered at extremely high-risk of bleeding (e.g., intrapleural adherences or reoperations) may undergo ECMO without any doses of heparin, by simply flushing the cannulas with saline immediately after cannulation (15).

Intraoperative ECMO

Choice of incision is of utmost importance in thoracic surgery. *Table 2* summarizes cannulation sites according to multiple approaches. Since ECMO can be viewed as a

Table 2 Cannulation sites according to the incision

Incision	Venous cannulation[§]	Arterial cannulation
Sternotomy	Right atrium	Ascending aorta
	Femoral veins	Femoral arteries
	Jugular/subclavian veins	Axillary arteries
Right thoracotomy	Right atrium	Ascending aorta
	Femoral veins	Femoral arteries
	Jugular/subclavian veins[†]	Axillary arteries[†]
Left thoracotomy	Femoral veins	Descending aorta
	Pulmonary artery trunk	Femoral arteries
	Jugular/subclavian veins[†]	Axillary arteries[†]
	Right atrium[†]	Ascending aorta[†]
Clamshell	Right atrium	Ascending aorta
	Femoral veins	Femoral arteries
	Jugular/subclavian veins	Descending aorta
	Any pulmonary artery or trunk	Axillary arteries
Right hemiclamshell	Right atrium	Ascending aorta
	Femoral veins	Femoral arteries
	Jugular/subclavian veins	Axillary arteries
	Right pulmonary artery or trunk	
Left hemiclamshell	Right atrium	Ascending aorta
	Femoral veins	Descending aorta
	Jugular/subclavian veins	Femoral arteries
	Any pulmonary artery or trunk	Axillary arteries

[§], venous cannulation sites apply for both drainage and reinfusion cannulas in VV ECMO; [†], if anterior thoracotomy on dorsal decubitus. VV ECMO, venovenous extracorporeal membrane oxygenation.

partial bypass circuit running with less than the full CO, multiple choices are available.

Indications of intraoperative ECMO are as follows.

Carinal resections

Surgery involving the trachea and/or the main carina is probably the most well-established indication of ECMO for the resection of NSCLC. In our opinion, there is no advantage of a VA circuit over a VV one in these scenarios, as hemodynamic derangements are not an issue and surgical exposure is not improved by VA ECMO. Central VA ECMO, nonetheless, has been the preference of other groups (16).

To completely stop ventilation while on VV ECMO and still maintain pulse oximetry above 90%, a flow of 75% of the CO, or around 50 mL/kg, is usually enough. If the patient's CO is too high, beta-blockers and alfa-agonists can cautiously be used intravenously to reduce the CO and therefore increase the proportional contribution of ECMO oxygenated blood.

As a rule, we prefer to approach the right carinal pneumonectomies and the right upper lobe sleeve lobectomies with carinectomy though a right 5^{th} intercostal space posterolateral thoracotomy. It allows an excellent view of the left main bronchus for the tracheobronchial anastomosis and at the same time to safely enlarge the tracheal part of the resection and/or to resect the superior vena cava. If in need, ECMO can be established before turning the patient to the side, in a femoral-jugular fashion. Both cannulas should be properly secured before changing the decubitus. Through the right thoracotomy, opening of the pericardium anteriorly to the phrenic nerve gives the surgeon access to both the RA and the ascending aorta. Pericardial stay sutures sutured to the retrosternal tissues are a formidable resource to expose this cannulation sites if the choice is central cannulation through thoracotomy. We have also run central VV ECMO by placing both cannulas in the RA, with the reinfusion directed towards the tricuspid valve. Advancing a femoral cannula while on lateral decubitus can be tricky, therefore we would recommend, if that is the case, to place a small femoral catheter before the thoracotomy, while the patient is still in dorsal position.

On the other hand, isolated carinal resections, limited left main bronchus resections and left carinal pneumonectomies are usually approached transsternaly. That allows us to cannulate the femoral and neck vessels, as well as the RA and aorta, according to the surgeon's preferences and skills. In most cases, a VV ECMO will allow the surgery to be performed without any ventilation of the remaining parenchyma, no cross-field tubes or even jet ventilation. ECMO not only clears the surgical field and allows a quicker surgery, but it also prevents ventilator-induced trauma (17), which can be especially deleterious for pneumonectomy patients.

Results following ECMO-supported carinal resections are unclear since only small case series and case reports have been published so far (16,18,19).

Atrial resections

T4 NSCLC tumors with limited invasion of the LA are amenable to surgical resection if there is no N2 or M1 disease, or even after neoadjuvant downstaging. As previously stated, open left atrial resections are typically done under CPB and cardiac arrest. Recently, a German group has published a series of 8 patients who underwent left atrial resection and lobectomy/bilobectomy for NSCLC under peripheral V(femoral)V(jugular)-A(femoral) ECMO without aortic cross clamping, of which 6 were R0 resections. They reported acceptable bleeding and sufficient time to resect the polypoid tumor abutting the atrium, and even to patch reconstruct the atrial wall, after cross clamping both vena cava. While encircling the vena cava is commonplace from a right thoracotomy, it is not readily evident from the left. The authors stated that the cava can be approached through an anterolateral left thoracotomy after running the VA ECMO and unloading the heart (16). Concerns should be raised on the potential for air embolism while opening a left sided chamber on a beating heart. The LV must be well unloaded, and the aortic valve should be closed at all times, under echocardiographic control; carbon dioxide field insufflation and aortic root continuous aspiration could also help reduce this risk (20). Despite Koryllos *et al.* report of no neurological complications due to air embolism, it doesn't seem to be as safe as CPB in our opinion (16).

Descending thoracic aorta resections

Descending aorta resections are infrequent, as the adventitial layer offers protection from direct invasion. However, once the decision to replace the aorta is made, clamping of the aorta may profoundly affect the patient's hemodynamic status by increasing the afterload, potentially leading to acute LV distention. Also, the abdominal organs and lower limbs would be under warm ischemia during the aortic reconstruction. Of note, before surgery of the descending aorta or lower thoracic spine, we favor preoperative identification of the origin of the Adamkiewicz artery by arteriography in order to avoid its inadvertent ligation.

Peripheral VA ECMO provides appropriate unloading of the LV and perfusion of the lower body, and at the same time does not interfere with the surgical exposure, leaving the choice of incision to the surgeon's discretion. The heart and lung will continue to perfuse the upper body. Adequate monitoring of perfusion and oxygenation of both the upper and lower body is mandatory. Too much ECMO flow will excessively unload the heart, leading to coronary and cerebral malperfusion, and, very rarely, pulmonary ischemia—if the bronchial arteries are ligated during the aortic resection. Insufficient ECMO flow will overload the heart with volume and malperfuse the lower body. As a rule of thumb, in this scenario VA ECMO flow can be set at 50% of the patients measured CO, and small adjustments can be made after cross clamping.

Modernly, a hybrid approach to the descending aorta is also possible. Before the surgery, an aortic endograft is deployed, making sure there are no endoleaks. During surgery, the aortic wall may be incised safely down to the graft, avoiding circumferential resections, cross clamping or any kind of bypass (21).

Post-operative ECMO

NSCLC patients frequently have poor lung status and therefore are prone to complications such as pneumonia, aspiration of gastric contents and acute pulmonary embolism, which may impair gas exchange on a temporary basis. ECMO may be used as a rescue measure for patients who require non-protective mechanical ventilation in the postoperative period and will be dealt with in a different article of this issue of the *JTD*.

From a general perspective, post-operative ECMO is infrequently needed. As an example, in a retrospective review of 10,434 pulmonary resections in South Korea, 29 patients (0.28%) required ECMO in the postoperative period, including 13 lobectomies, 11 pneumonectomies and 5 bilobectomies (22). Of those, 10 patients were decannulated and only 7 were discharged from the hospital, indicating that the need of ECMO is on itself a marker of dismal prognosis. However, the proportion of patients who undergo extended resections and require ECMO in the post-operative setting is unknown, and so are the outcomes.

Limitations and future perspectives

We have only been able to find small series and case reports of ECMO in the setting of NSCLC extended resections, reflecting the experience of some large-volume centers. As more groups report their experiences, more robust data will be available, maybe even comparative data with historical controls, although randomized trials seem unlikely. Growing availability and familiarity with the method may render it more frequently the first choice for intraoperative support in the future, replacing CPB to a considerable extend.

Rarely, patients with resectable locally advanced NSCLC are deemed inoperable due to respiratory distress related to local factors, such as bronchial obstruction and atelectasis or vascular invasion. These factors may contribute to a temporary and potentially reversible loss of pulmonary function, which could theoretically be surpassed with the aid of ECMO. This hypothesis is yet to be explored.

Oncological impact of ECMO use during extended lung cancer resection has not been evaluated yet. The role of perioperative inflammation and molecular residual disease needs to be assessed and compared during surgeries with and without ECMO. One should emphasize that, in the near future, ECMO circuit could be implemented by several type of filters which could clean circulation from molecular residual disease or inflammatory cytokines in the goal of improving results of extended surgeries for NSCLC.

Conclusions

ECMO can be performed safely in the perioperative period and allows marginal patients to be operated. Although a rare indication, ECMO should be part of the surgical armamentarium for teams who deal frequently with extended resections for the treatment of NSCLC.

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