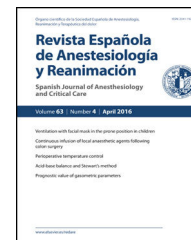




Revista Española de Anestesiología y Reanimación

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REVIEW

Review of difficult airway management in thoracic surgery☆☆



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Received 29 August 2017; accepted 30 August 2017

KEYWORDS

Difficult intubation;
Thoracic surgery;
Lung isolation;
Lung separation

Abstract The management of difficult airway (DA) in thoracic surgery is more difficult due to the need for lung separation or isolation and frequent presence of associated upper and lower airway problems. We performed an article review analysing 818 papers published with clinical evidence indexed in Pubmed that allowed us to develop an algorithm.

The best airway management in predicted DA is tracheal intubation and independent bronchial blockers guided by fibroscopy maintaining spontaneous ventilation. For unpredicted DA, the use of videolaryngoscopes is recommended initially, and adequate neuromuscular relaxation (rocuronium/sugammadex), among other manoeuvres. In both cases, double lumen tubes should be reserved for when lung separation is absolutely indicated.

Finally, extubation should be a time of maximum care and be performed according to the safety measures of the Difficult Airway Society.

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☆ Please cite this article as: Granell M, Parra MJ, Jiménez MJ, Gallart L, Villalonga A, Valencia O, et al. Revisión del manejo de la vía aérea difícil en cirugía torácica. Rev Esp Anestesiol Reanim. 2018;65:31–40.

☆☆ This article is part of the Anaesthesiology and Resuscitation Continuing Medical Education Program. An evaluation of the questions on this article can be made through the Internet by accessing the Education Section of the following web page: www.elsevier.es/redar

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PALABRAS CLAVE

Intubación difícil;
Cirugía torácica;
Aislamiento
pulmonar;
Separación pulmonar

Revisión del manejo de la vía aérea difícil en cirugía torácica

Resumen El manejo de la vía aérea difícil (VAD) en cirugía torácica es muy específico y más complejo que en otras especialidades debido a la exigencia de separación o aislamiento pulmonar y a una mayor presencia de anomalías asociadas a la vía aérea superior e inferior.

Basándonos en el análisis de las evidencias clínicas de 818 artículos indexados en PubMed, presentamos una revisión actualizada y un algoritmo específico del manejo de la VAD en cirugía torácica.

Recomendamos: para la VAD prevista la intubación traqueal con fibronoscopio en ventilación espontánea y el uso de bloqueador bronquial. Para la VAD imprevista, el uso inicial de video-laringoscopios y un adecuado nivel de relajación neuromuscular (rocuronio/sugammadex). Solo se recomienda el uso de tubos de doble luz si hay indicación absoluta de aislamiento pulmonar.

Finalmente, la extubación en este contexto debe ejecutarse con la máxima atención y realizarse según las normas de la Difficult Airway Society.

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Introduction

Difficult airway (DA) is one of the main causes of anaesthesia-related morbidity and mortality. The most serious complications in airway management are bronchoaspiration, failure of tracheal intubation, and extubation problems. Although these complications are uncommon, they are estimated to lead to 5.6 patient deaths per million general anaesthetics, and inadequate airway management occurs in up to 84% of severely ill patients.¹

A turning point in DA management came with the publication of the American Society of Anesthesiology algorithm, which defines DA as the difficulty to ventilate or intubate, promotes the use of tests to predict DA, recommends awake intubation as the first option in patients with DA, encourages anaesthesiologists to ask for help, limits the number of airway manipulations, and prioritises oxygenation.

Although DA management in tracheal intubation has been extensively analysed in the medical literature, the evidence cannot be extrapolated to airway management in thoracic surgery for 2 reasons: First, the need for lung isolation or separation, according to the patient's situation and surgical requirements (single-lung ventilation) and, second, because the anatomy of the upper and lower airway can be altered by the presence of a concomitant oropharyngeal or laryngeal tumour, by previous surgery, by radiotherapy, and by tracheal or bronchial anomalies, and these can complicate intubation. Furthermore, intubation using double lumen tubes (DLT) is more complex and can be difficult even in patients in whom standard intubation would be straightforward.²

Finally, the increased efficacy of video laryngoscopy (VL) in resolving cases of DA has prompted the American Society of Anesthesiology³ and the Difficult Airway Society (DAS) to include these devices at Plan A of their algorithms⁴; therefore, VL can also be considered useful in thoracic surgery.

For all the above reasons, we considered it important to perform a literature review to update the state of the knowledge on the safest and most effective clinical practices in DA management in thoracic surgery. To this end, a search was made of Pubmed using the terms "difficult intubation and thoracic surgery" (822 articles), "difficult intubation and lung isolation" (21 articles) and "difficult intubation and lung separation" (15 articles).

Difficult airway management in lung isolation or separation

The few absolute (life-threatening) indications for lung separation and isolation with TDL are shown in Table 1. However, the absolute priority in difficult-to-intubate patients is to ensure adequate oxygenation and ventilation. In this scenario, lung isolation is a secondary objective whose risks and benefits should be considered. In the context of thoracic surgery, patients with DA who require lung separation generally fall into 4 clinical categories⁵: predicted DA, unanticipated DA, patients with a previous patent tracheostomy,

Table 1 Absolute (life-threatening) indications for lung separation with double-lumen tube.

<i>Lung isolation due to bleeding or infection in the contralateral lung</i>
<i>Control of ventilation distribution</i>
Solution of continuity in the airway (fistula, rupture, or tracheal opening)
Blisters or giant cysts
Severe hypoxaemia due to unilateral lung disease
Lung transplantation
<i>Unilateral bronchoalveolar lavage due to alveolar proteinosis</i>
<i>Need for one-lung ventilation</i>

or patients already intubated with a conventional tracheal tube.

These scenarios can occur in both scheduled or urgent procedures, and call for DA management to be adjusted accordingly.⁶

Predicted difficult airway

Predicted DA occurs in patients with a known history of DA or who present predictors of difficult intubation.

Scheduled surgery

In patients with predicted DA and no absolute indication for lung separation, the technique of choice would be fibreoptic-guided intubation (FI) using a standard endotracheal tube (ETT) in an awake or sedated patient with spontaneous ventilation, followed by placement of a bronchial blocker (BB) under fibreoptic bronchoscopy (FB) guidance. Although some guidelines still recommend the Univent tube, we believe it has several drawbacks, such as greater rigidity, excessively large external diameter in relation to the internal lumen, high pressure and high volume cuff, and higher price compared to other devices.⁶

In cases of predicted DA with absolute indication for lung separation (mandatory use of a DLT), the first option would be tracheal intubation, as in the previous situation, after which the ETT is replaced with a DLT. This is done using an airway exchange catheter (AEC) with a flexible tip inserted using traditional laryngoscopy or VL. Some studies have also reported good results with direct DLT insertion using VL (e.g. Airtraq, Glidescope or Pentax AWS)⁷⁻¹⁰; however, more evidence is needed before this can be recommended.

In patients that cannot be intubated by mouth, a nasal ETT and BB can be used (taking into account that the 9 Fr BB requires an ETT with an internal diameter of at least 8 mm, thus increasing the risk of injury to the nasal conchae).

Emergency procedures

When surgery can be delayed, the same approach as described above can be used for patient with DA. In urgent surgery, the final decision will depend on the patient's status: their capacity to collaborate during fibre-optic bronchoscopy, their state of awareness (conscious or unconscious), the presence of blood in the airway, a full stomach, or other relevant factors.

In urgent surgery that cannot be delayed, or in emergency situations, the possibility of performing FI will also depend on the foregoing factors. If FI is impossible, the final decision will depend on the ventilation options:

if ventilation is impossible, a cricothyrotomy will be needed;

if ventilation is adequate, tracheal intubation (aided by VL, introducers, etc.) can be attempted, followed by placement of a BB; if ventilation is adequate but tracheal intubation fails, a tracheostomy can be performed, maintaining ventilation by means of a face mask or supraglottic airway.⁶

Unforeseen difficult airway

An unforeseen DA occurs in patients with no known history of DA or no predictors of difficult intubation.

Scheduled surgery

In the event of an unforeseen DA, the approach taken will depend on the ventilation options:

If ventilation is effective, tracheal intubation can be attempted using adjuncts (intubating introducers, supra-glottic devices, VL, luminous stylet, etc.). If intubation is successful, proceed as described in predicted DA. If ventilation is effective, but intubation is unsuccessful, the option of reversing neuromuscular blockade and awakening the patient must be considered, after which FI can be performed. However, if ventilation is insufficient and neuromuscular blockade cannot be reversed in the context of unforeseen DA, a cricothyrotomy would be required.^{5,6}

Emergency procedures

In cases of unforeseen DA in surgery that can be delayed, the same procedure for scheduled surgery is used. In surgery cannot be delayed, or in emergency situations, the approach will depend on the ventilation options:

If the patient cannot be intubated despite intubation adjuncts but can be effectively ventilated, a tracheostomy should be considered.

If effective ventilation is impossible, a cricothyrotomy will be required.⁶

Difficult airway in a patient with a tracheostomy

In patients with a tracheostomy requiring one-lung ventilation, the use of a standard DLT is complex, so other alternatives are recommended, such insertion of an ETT with a BB, a disposable tracheostomy cannula plus a BB, or a specially designed DLT for patients with a tracheostomy.⁵

Predicted difficult airway in an intubated patient

In a patient with a known DA that has already been intubated with a conventional ETT, the simplest option to achieve lung isolation is FB-guided placement of a BB; if this is impossible due to the interior diameter of the ETT, it must be replaced with a larger calibre ETT using a 14 Fr AEC under direct vision with a VL or laryngoscope.⁵ If lung separation is an absolute indication in an already intubated patients, the ETT must be replaced by a DLT using an 11 Fr AEC under direct vision or with a laryngoscope.¹¹

Devices and techniques for lung isolation or separation in patients with difficult airway

Standard endotracheal tubes

Lung separation with an ETT is achieved by advancing the tube from the trachea to the main bronchus of the lung to be ventilated. This technique is only recommended in

young children, in cases where a DLT cannot be used, when a BB is not available, and in some emergency situations (e.g. airway bleeding, tension pneumothorax, etc.). FI is the safest and most reliable method of placing the ETT in the chosen bronchus. The disadvantages of this technique include: the inability to aspirate in the non-ventilated lung, the impossibility of using CPAP in the case of hypoxaemia, and the insufficient length of the tube in nasally intubated patients.¹²

Double lumen tubes

Today's DLTs are made of transparent, thermosensitive PVC, and are equipped with low pressure cuffs.¹³ Despite these characteristics, insertion of a DLT is more complex than an ETT due to its greater external diameter, rigidity and concavity, and in patients with DA, DLTs should only be used after initial single lumen intubation.¹⁴

A few cases of FI through a DLT have been describe in awake or anaesthetised patients.¹⁵ Due to their rigidity, these tubes should be softened by immersing them in a container of warm water. As the fiberoptic bronchoscope must be inserted through the bronchial lumen, there is lit-

tle length left for manoeuvre. This can be overcome by cutting the proximal portions of the tube, making sure to leave sufficient distance for the 15 mm connectors. A conventional or video laryngoscope can often help guide the tube through the glottis. The suitability of the DLT and fiberoptic bronchoscope should be verified prior to the procedure (Table 2). When mouth opening is less than 3 cm, some authors have recommended nasal intubation with a DLT (28 and 32 Fr¹⁶); in our opinion, this is a hazardous technique, so we only recommend oral or nasal FI with a single lumen ETT.

Insertion of standard or double lumen tubes with the help of optical devices

Various devices can now be used to facilitate the insertion of different tubes that are specific for thoracic surgery (Table 3).

VL has revolutionised DA management. The following is a summary of the devices currently available:

The GlideScope, which improves visualisation of the vocal cords and of the passage of the ETT/DLT through them, has been used successfully for the insertion of ETTs and DLTs in awake or anaesthetised patients with DA. Disadvantages of this device include large blade size and difficulty in manipulating the tube past the vocal cords,¹⁷ so it is advisable to insert a stylet with a 60° angle at the distal end in the DLT; the stylet must always be removed when the tube has passed through the vocal cords.¹⁸ The Airtraq has one blade for the ETT and another blade with a wider channel for the DLT. The intubation technique is similar in both cases. The DLT is lubricated and mounted in the lateral channel, without requiring the use of a stylet or introducer.⁹ Some authors, however, recommend using an intubating introducer (e.g. Frova) or an exchanger in the bronchial lumen of the DLT or the ETT to facilitate insertion. Awake intubation has also been described in patients with predicted DA, although this is associated with a higher incidence of postoperative sore throat.¹⁹

Table 2 Compatibility of DLT and FB.

DLT (ID in mm)	FB (ED in mm)				
	<5	4.2–4.7	3.5–3.9	2.8–3.2	1.8–2.5
41 Fr (ID 5.5)	No	Yes	Yes	Yes	Yes
39 Fr (ID 4.9)	No	Dif	Yes	Yes	Yes
37 Fr (ID 4.5)	No	Dif	Yes	Yes	Yes
35 Fr (ID 4.3)	No	No	Dif	Yes	Yes
32 Fr (ID 3.5)	No	No	No	Yes	Yes
28 Fr (ID 3.4)	No	No	No	Dif	Yes
26 Fr (ID 3.2)	No	No	No	Dif	Yes

DLT: double lumen tube; ED: external diameter; FB: fiberbronchoscope; ID: internal diameter.

DLT and FB diameter compatibility: Dif (difficult); No (impossible); Yes (easy).

Table 3 Video laryngoscope characteristics.

VL (type)	Intubation channel	Optical system	Screen	Video output	Portable	Disposable	Paediatric
Glidescope	No	Video camera, anti-fog system	External, LCD	Yes	No/yes	No/yes	Yes
AirTraq	Yes	Lens + anti-fog system	External, optional	Yes	Yes	Yes	Yes
McGrath	No	Video camera	Built-in	No	Yes	Yes	No
C-MAC	No	Video camera, anti-fog system, direct vision	External, LCD	Yes	No	No	Yes
King vision	Yes/no	Direct vision camera, anti-fog system	LED	Yes	Yes	Yes	No
Total track	Yes	Video camera, anti-fog system	Built-in	No	Yes	Yes	No

VL: video laryngoscope.

The McGrath can be potentially beneficial in patients with DA who require lung isolation, since it can be used with either an ETT or DLT.²⁰

The C-MAC has the great advantage of incorporating an improved conventional laryngoscopy blade that occupies little intraoral space and facilitates the introduction of large gauge tubes (TDL or Univent).²¹

The King Vision has both channelled and non-channelled blades. Experiences of awake DLT insertion in patients with DA²² using this device have also been published.

The Pentax Airway Scope® is an indirect rigid VL with a disposable channelled blade.

The Totaltrack is a hybrid between a supraglottic device and a VL. It gives fibre optic visualisation of the larynx, which facilitates tracheal intubation through its built-in channel. This device can also provide ventilation in a similar way to other laryngeal masks and, therefore, can be used to deliver oxygen prior to intubation and after extubation.²³ It has been used successfully in thoracic surgery.²⁴

The use of luminous and optical stylets to aid intubation in awake or anaesthetised patients with DA has been widely described.^{25,26} However, they are of little use in DLT insertion due to their length and diameter. The latest optical stylets, such as the Shikani Optical Stylet (Clarus Medical, Minneapolis, MN, USA) and the Bonfils Intubation Fiberscope (Karl Storz, Tuttlingen, Germany), are promising options, since both are sufficiently long. The Bonfils can also be used to insert a DLTs measuring 37 Fr or larger.²⁷

Bronchial blockers

The use of an independent BB inserted through an ETT to achieve lung isolation is still the technique of choice in predicted DA in thoracic surgery, when there is no absolute indication for lung separation. For this reason, it is indicated in patients with upper and lower airway abnormalities, limited mouth opening, nasal intubation, and also in previously intubated patient who will not be extubated at the end of surgery. The BB is also the only device available for selective lobar blockade.²⁸

The Univent tube is the first ETT that includes a silicone BB,²⁹ and has also been used in patients with DA.³⁰ However, due to its large external diameter and rigidity, we believe independent BBs are now a far better option.

Introducers or stylets

These are fundamental adjuncts in the treatment of predicted or unforeseen DA in any type of surgery, and are mainly indicated when intubation is hampered by poor laryngoscopic vision. According to the protocol, malleable stylets and introducer catheters can also be used to guide and facilitate intubation. However, malleable stylets do not seem as effective in unforeseen DA, and are only recommended in rapid sequence induction in patients with a full stomach.³¹

Most algorithms include the use of these adjuncts, since there is evidence of their efficacy in cases of difficult intubation.^{32,33} The most widely used and effective is currently the Frova®, which allows continuous oxygenation, spontaneous ventilation monitored with capnography,³⁴ or mechanical ventilation. However, it should not be used as an airway exchanger, since it can cause tracheal injury due to its design.³⁵

Airway exchangers catheters

As the name suggests, AECs are used to replace ETTs with a DLT and vice versa, before or after surgery. Specific AECs have been designed to cater for the rigidity, curvature and length of DLTs: they must be at least 70 cm in length, and have depth markers, an internal channel for oxygen delivery, and adapters for ventilation. Flexible-tip AECs are recommended, as they are less likely to cause injury. The size of the AEC will be determined by the diameter of the DLT (Table 4). The 14 Fr AEC is recommended for a 41 Fr DLT, and the 11 Fr AEC for a 35-37-39 Fr DLT.⁶

To replace an ETT with a DLT, the AEC is passed through the ETT until the depth markers on the EET and the AEC coincide (the AEC should never protrude beyond the tip of the ETT). Then the ETT is withdrawn, leaving the AEC in the trachea. The DLT is introduced through the bronchial lumen of the AEC, taking care not to advance the AEC distally, and guiding the DLT through the vocal cords with conventional laryngoscopy or VL. After the DLT has passed through the vocal cords, the AEC is partially withdrawn and the TDL is advanced with the usual degree of rotation; the final position must be verified by FB. Alternatively, the DLT can be advanced to its final position under FB guidance. The incidence of intubation failure with AECs is higher in DLTs than in ETTs (39.9% vs 9.3%), so extreme caution is required during the exchange procedure.³⁶

When replacing a DLT with an ETT (usually at the end of surgery), the procedure should be controlled under direct laryngoscopy, the jaw should be thrust forward, the neck extended and the ETT rotated to facilitate its passage through the glottis. Some authors recommend inserting 2 AECs (one through the bronchial lumen and another through the tracheal lumen) to ensure successful exchange and facilitate the passage through the glottis.³⁷

Supraglottic airways

Supraglottic airways (SGA) in thoracic surgery are indicated when adequate ventilation and oxygenation cannot be achieved due to a DA, or to facilitate FI. In SGAs that do not permit the passage of an ETT, an Aintree catheter can be introduced into the trachea using FB; subsequently, only the fiberoptic bronchoscope is removed and the Aintree serves as an exchanger catheter to guide the insertion of the ETT.^{38,39} SGAs can also be used as a rescue airway when tube exchange fails.⁴⁰

Among the SGAs currently available, some authors have used the ProSeal or Fastrach laryngeal mask with a BB

Table 4 Relationship between the DLT diameter and airway exchange catheter diameter.

Airway exchanger catheter	DLT						
	41 Fr (ID 5–6 mm, L 42 cm)	39 Fr (ID 4.8–5.5 mm, L 42 cm)	37 Fr (ID 4.5–5.1 mm, L 42 cm)	35 Fr (ID 4.2–4.8 mm, L 42 cm)	32 Fr (ID 53.4 mm, L 42 cm)	28 Fr (ID 3.1–3.8 mm, L 42 cm)	26 Fr (ID 53.4 mm, L 42 cm)
11 Fr (ID 53.7 mm, L 81–100 cm)	Yes	Yes	Yes	Yes	No	No	No
14 Fr (ID 53.7 mm, L 81–100 cm)	Yes	Dif	Dif	No	No	No	No
19 Fr (ID 53.7 mm, L 83 cm)	No	No	No	No	No	No	No

AEC: airway exchange catheter; DLT: double lumen tube; ED: external diameter (mm); Fr: French calibre; ID: internal diameter (mm); L: length (cm). Compatibility between DLT and AEC diameter: Dif (difficult); No (impossible); Yes (easy).

and without an ETT for single lung ventilation in thoracic surgery (videothoroscopic surgery^{41,42} and lobectomy⁴³). The I-gel, meanwhile, has been described in isolated cases for the following indications: thoracic surgery with a BB placed under direct FB vision⁴⁴; FB-guided percutaneous tracheotomy⁴⁵; surgery for subglottic tracheal stenosis; and as a bridging device for safe extubation after removal of the ETT in cases of tracheal stenosis. In addition, this device has few complications and does not require an inflatable cuff, which minimises the risk of ignition when using a CO₂ laser.¹¹

Another SGA, the AuraGain, has an FB channel and sufficient sealing pressure to allow positive pressure ventilation. As such, it can be effective in patients with DA and in surgical tracheobronchial diagnostic and therapeutic techniques that compromise the airway.⁴⁶

Various airway management strategies are used in tracheal surgery, ranging from a simple face mask to the use of extracorporeal life support.⁴⁷ In this context, SGAs have gained importance and are now a reliable alternative to tracheal intubation,^{48,49} relegating tracheostomy to patients with acute respiratory failure.⁵⁰

The Totaltrack, described above, has the advantage of combining an SGA with VL.²³

Extubation

Extubation can be a critical time, especially when intubation has been difficult, and it is important to follow the DAS DA guidelines. Extubation can be complicated by the presence of oedema, bleeding due to injury to the airway mucosa, and secretions. Therefore, airway status at the start and end of surgery often differs, and reintubation can be extremely difficult or impossible.⁴

Need for mechanical ventilation after surgery

When postoperative mechanical ventilation is required and one-lung ventilation or lung isolation is no longer needed, the following manoeuvres should be performed, depending on the device used during surgery.⁶

When a DLT has been used and tube exchange is expected to be fairly straightforward, it should be replaced with an ETT using an AEC. Initially, the TDL is withdrawn to the supracarinal level under FB guidance; then, the AEC is introduced through the bronchial lumen, the DLT is withdrawn and the ETT is inserted over the AEC under laryngoscopic vision. When the exchange is expected to be hazardous, the DLT should be withdrawn under FB guidance until the distal end of the bronchial lumen is above the carina. It is left in this position and both lungs are ventilated through both lumens until the patient can be safely extubated. When lung isolation has been achieved using a BB, this is fully retracted and ventilation continues through the ETT. In the case of a Univent tube, the enclosed BB should be retracted so that the patient can continue to be ventilated through the single lumen tube.

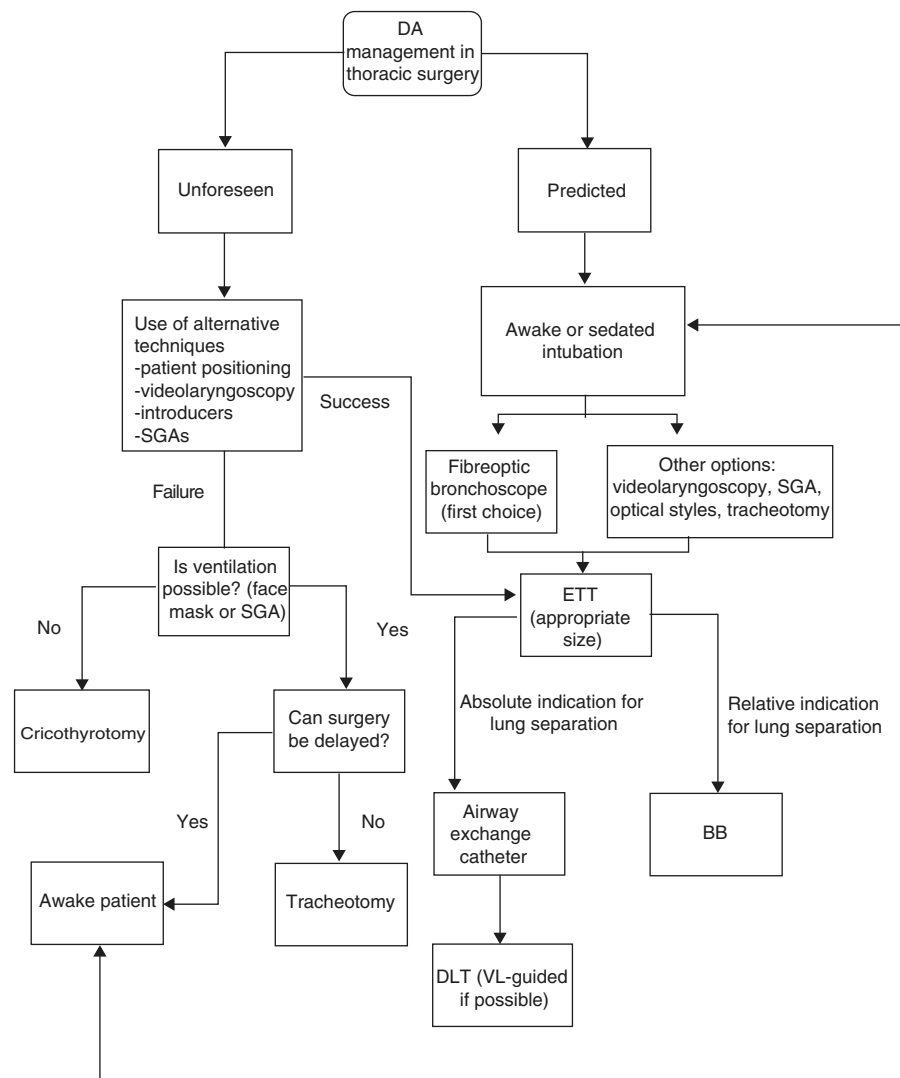


Figure 1 Algorithm for DA in thoracic surgery (Group of Experts in Thoracic Anaesthesia of the SEDAR).

Risk of reintubation

When postoperative mechanical ventilation is not required, but the probability of reintubation is high due to failure to extubate, extubation should carefully planned: ensure the patient is haemodynamically stable, has emerged from anaesthesia, and spontaneous ventilation is adequate with no major air leaks or residual neuromuscular blockade. The need for reintubation is associated with morbid obesity, sleep apnoea syndrome, head and neck surgery and upper abdominal and thorax surgery, among others.^{51,52}

In these cases, an AEC or staged extubation wire (COOK®) should be inserted. Although AECs are less well tolerated, they can circumvent the need for prophylactic tracheotomy.⁵³ Staged extubation catheters leave a very thin guidewire in the trachea, and are therefore always better tolerated and allow patients to swallow and communicate verbally. If reintubation is required, a reintubation catheter is passed over the wire, and an ETT (minimum lumen 7 mm) is passed over the catheter to the required

depth.⁵⁴ Some complications have been reported with this technique, namely, perforation of the tracheobronchial tree, reintubation failure over the AEC⁵⁵ and barotrauma when jet ventilation is required.⁵⁶ Although reintubation failure using an AEC is relatively uncommon, it cannot be ruled out.³⁶ The decision to perform a prophylactic tracheotomy before extubation will be determined by the degree of airway compromise at the end of surgery, the likelihood of postoperative deterioration, the ability to rescue the airway, and the expected duration of significant airway compromise.⁴

Conclusions

The algorithm for DA in thoracic surgery has changed over time as a result of renewed expert consensus and clinical evidence on the usefulness of different devices. The use of VL has now been included in Plan A of the DAS's unexpected DA management algorithm.⁴ This same guideline

recommends preoxygenation and maintenance of oxygenation during intubation manoeuvres, optimising head and neck position, use of VL (noting the need for training in this technique), limiting the number of intubation attempts with direct laryngoscopy and VL (3 + 1), limiting the number of attempts to insert supraglottic devices to 3 (recommending the use of second generation devices), and removing cricoid pressure in the case of difficult intubation.⁴ A suitable degree of neuromuscular blockade is also advised (preferably with rocuronium due to the possibility of immediate reversal with sugammadex^{4,57}). Finally, FI under spontaneous ventilation in the awake or sedated patient is still the safest approach in the predicted DA.^{5,6} For this purpose, various endotracheal topical anaesthesia drugs and sedation techniques can be used, such as remifentanyl, desmetomidine,⁵⁸ or inhalational drugs,⁵⁹ among others.

On the basis of the above, we considered it important to finalise this systematic review of DA management in thoracic surgery with the development of an algorithm (Fig. 1) that can serve as a useful guide for specialists who use these techniques in their routine practice, enabling them to update their understanding of DA management and simplify decision-making in this context.

Ethical disclosures

Protection of human and animal rights. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have adhered to the protocols of their centre of work on patient data publication.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interests

The authors of this article have no conflict of interest with respect to the content of the review article.

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