Abstract

Purpose of refresher course

This refresher course reviews the rationale for using intravenous anaesthesia for thoracic operations and the drugs and equipment required.

Recent findings

Recent studies examining whether intravenous anaesthesia offers a physiological advantage over inhalational anaesthesia for thoracic surgery remain inconclusive. Nevertheless, intravenous anaesthesia is inarguably preferable for certain thoracic procedures incompatible with effective delivery of inhalational anaesthetics. Additionally, TIVA offers advantages in procedures conducted in non-ideal environments, such as offsite or austere scenarios.

Summary

TIVA is indicated for procedures in which inhalational anaesthetics may not be safely or effectively delivered, including endobronchial procedures using flexible or rigid bronchoscopy and proximal airway-disrupting surgeries. TIVA may also be beneficial in lung volume reduction surgery, lung transplantation, and thymectomy. In addition, TIVA is safer and more practical for thoracic procedures performed outside of the operating room, such as offsite locations, in the military field, or impoverished areas of the world. Propofol, dexmedetomidine, ketamine, and remifentanil may be used in combination with anaesthetic depth monitoring to execute an effective TIVA regimen. Target controlled infusion may improve the delivery of TIVA and is a focus for future research.

Rationale for total intravenous anaesthesia

Traditional inhalational anaesthetics have been associated (at least in animal studies) with a direct inhibition of hypoxic pulmonary vasoconstriction (HPV), the reflex arteriolar constriction that diverts blood from hypoxic segments of lung to normal areas of lung, thereby decreasing shunt fraction. In thoracic procedures, this inhibition of HPV may be detrimental to patient oxygenation levels during one-lung ventilation. In contrast, intravenous anaesthetics do not appear to directly inhibit HPV, in vitro or in patients. Consequently, interest has focused on whether total intravenous anaesthesia (TIVA) might provide better oxygenation and less shunt fraction than inhaled anaesthetics in thoracic procedures. As little work has been done to answer this question more recently, research published in the last decade is summarised here.

Several studies have shown an advantage to using TIVA. Abe et al studied patients receiving either isoflurane or sevoflurane followed by TIVA (propofol). PaO2 increased significantly and shunt fraction decreased significantly after the initiation of TIVA.1 In another study, PaO2, was also significantly higher in patients who received TIVA for pulmonary resection than in those who received volatile anaesthetics.2 Recently, Özcan et al compared oxygenation and shunt fraction in 100 patients undergoing one of four anaesthesia techniques during one-lung ventilation: TIVA with or without thoracic epidural anaesthesia (TEA), and isoflurane with or without TEA. Patient oxygenation was significantly higher and shunt was significantly lower in the two groups receiving TIVA; the addition of TEA in either study group had no significant effect.3

Alternatively, a few studies fail to support any advantage of TIVA. Beck et al studied 40 patients who received either propofol or sevoflurane
during one-lung ventilation for thoracic surgery. They found no significant difference in shunt fraction between the two groups. Haemodynamic variables known to influence HPV (cardiac index, mixed venous oxygen tension, and arterial carbon dioxide partial pressure) were also similar between the two groups. Pruszkowski et al compared oxygenation levels in patients undergoing lung lobectomy. The patients received a thoracic epidural and either sevoflurane or propofol at levels required to maintain a bispectral index (BIS) between 40 and 60. The authors found no difference in PaO₂, levels between the sevoflurane and propofol groups. They suggest that the titration of anaesthetics to appropriate BIS levels (which distinguished their study) could avoid potential negative effects of inhalational anaesthetics on haemodynamics that affect shunt. Lastly, Von Dossow et al divided 50 patients undergoing pulmonary surgery into two groups, isoflurane with TEA or TIVA (propofol), and measured shunt fraction, PaO₂, and cardiac output. They found that the decrease in PaO₂ level following the conversion from two-lung to one-lung ventilation was less in the isoflurane group. Shunt fraction remained the same in both groups. Cardiac output was greater in the TIVA group, which may have contributed to the effect on PaO₂.

Most likely, even though inhalational anaesthetics suppress HPV, other factors such as surgical manipulation, cardiac output, mixed venous oxygen tension, and positive end-expiratory pressure may have a greater influence on shunt fraction than the influence of inhalational agents on HPV. Therefore, further studies are required to define the clinical significance of inhaled anaesthetics on HPV in thoracic surgery.

Although neither TIVA nor inhaled anaesthetic agents provides a clear physiologic advantage over the other for thoracic surgery, there is solid rationale for the use of TIVA in certain circumstances (see Table I):

- When the delivery of inhaled anaesthetics is impossible or disadvantageous, due to the nature of the operation;
- In scenarios where traditional anaesthetic delivery systems may be unavailing or impractical.

**TIVA in special thoracic surgical conditions**

Procedures or trauma that disrupt the trachea and carina complicate the delivery of inhaled anaesthesia. When the proximal airways are breached, volatile agents may escape and the quantity of anaesthesia reaching the patient is uncertain. Also, the operating room is at risk of pollution from the escaped anaesthetics, posing a hazard to personnel. This situation is most likely during cross-field ventilation, a technique in which the distal airways (main bronchi) are directly intubated in the surgical field to facilitate ventilation and oxygenation. Intubation and exubation is often repeated, and airway seals are frequently compromised. Also, certain cases may require high frequency jet ventilation or other specialised modes of ventilation incompatible with the delivery of inhalational anaesthetics.

Patients undergoing lung volume reduction surgery (LRS) also benefit from a TIVA approach. Because these patients suffer from chronic obstructive pulmonary disease (COPD) and have increased dead space, end-tidal volatile anaesthetic concentration is inaccurate and anaesthetic levels questionable. Also, air trapping is common and the elimination of volatile anaesthetic may be hindered, delaying awakening and extubation.

In the case of lung transplantation, volatile anaesthetics have several drawbacks. During lung transplantation, the right ventricle is subject to increased afterload and potential failure, and the cardiodepressant effects of volatile anaesthetics could be detrimental. In addition, significant intrapulmonary shunt and dead space in the transplanted lung interfere with the accuracy of end-tidal anaesthetic measurements. Consequently, narcotic-based anaesthetic regimens are usually administered for lung transplantation surgery. However, this is not always an ideal solution, because narcotic levels may decline unpredictably during the procedure. This decline has several possible causes: (1) narcotics may be sequestered in the CPB circuit in cases using cardiopulmonary bypass (CPB); (2) narcotics tend to accumulate in lung tissue during first pass, and a considerable amount of drug might be removed when the diseased, native lung is resected; and (3) when the donor lung is transplanted, first pass uptake is repeated and systemic narcotic levels may again drop. When narcotic levels drop, more volatile anaesthetics and/or narcotics must be given; but with older anaesthetics, over-accumulation and delayed awakening may occur. Neuer, rapidly metabolised intravenous anaesthetics, on the other hand, are able to rapidly counter changes in anaesthetic depth without significant risk of over-accumulation. Furthermore, in pulmonary transplant surgery requiring CPB (i.e. double-lung or heart-lung transplant), TIVA allows an uninterrupted transition to the CPB phase and back to native circulation.

Endobronchial procedures that use flexible or rigid bronchoscopy (e.g. stent placement, dilatation, biopsy, and laser procedures) also benefit from a TIVA approach. These procedures are frequently complicated by periods of apnoea, the need for special ventilatory techniques such as high frequency jet ventilation, and compromised airway seals. Thus, the delivery of volatile anaesthetics may be problematical. Furthermore, these procedures frequently involve repeated alternating periods of high and low stimulation, and intravenous anaesthetics can be more rapidly titrated to meet fluctuating demands. Lastly, accurate measurements of volatile anaesthetics by standard mass spectrometry are hindered in procedures where helium/oxygen will be used.

Lastly, patients with myasthenia gravis undergoing thymectomy may benefit from a TIVA approach. Myasthenia gravis (MG) is associated with autoimmune damage to the acetylcholine (ACH) receptors; therefore, patients exhibit baseline muscle weakness. The thymus gland is implicated in the autoimmune response against the ACH receptors; in a select population of those with MG, symptoms improve post-thymectomy. MG patients are exquisitely sensitive to neuromuscular blocking agents and volatile anaesthetics, which may cause prolonged paralysis or residual muscle weakness. The ideal anaesthetic for such patients would avoid neuromuscular blocking agents and volatile anaesthetics. Successful thymectomies have been performed without neuromuscular blocking agents using TIVA ± high thoracic epidurals. Conditions for intubation and surgery were excellent.

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**Table I: Rationale for the use of TIVA in certain circumstances**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rationale</th>
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<tr>
<td>One-lung ventilation</td>
<td>When the delivery of inhaled anaesthetics is impossible or disadvantageous, due to the nature of the operation.</td>
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<tr>
<td>Trauma to the trachea and carina</td>
<td>In scenarios where traditional anaesthetic delivery systems may be unavailing or impractical.</td>
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<tr>
<td>Lung transplantation</td>
<td>An uninterrupted transition to the CPB phase and back to native circulation.</td>
</tr>
<tr>
<td>Endobronchial procedures</td>
<td>Allows an uninterrupted transition to the CPB phase and back to native circulation.</td>
</tr>
<tr>
<td>Myasthenia gravis undergoing thymectomy</td>
<td>Avoid neuromuscular blocking agents and volatile anaesthetics.</td>
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TIVA is the anaesthetic administration system of choice in scenarios where the logistics of having fully functional anaesthesia machines may be impractical or impossible. For example, offsite anaesthesia has recently become more commonplace. Many minimally invasive thoracic procedures are being carried out in non-operating room “procedure suites.” In these circumstances, TIVA is more versatile because its administration does not require a full anaesthesia machine setup, and it can provide different levels of anaesthesia (from MAC/sedation to general).\(^1,2\)

TIVA also offers several advantages in austere environments such as battlefields, disaster zones, and developing nations. For example, volatile anaesthetics are considered hazardous materials—they are difficult to store, transport, and they generate waste gases that must be properly scavenged. In contrast, TIVA agents are more easily stored, transported, and disposed. A second advantage is the reduced logistical footprint—basic TIVA equipment (infusion pump and ventilator) eliminates the traditional anaesthesia machine. Additionally, TIVA equipment is more robust than traditional anaesthesia machines and is more likely to perform reliably in less-than-ideal conditions. Although specialised anaesthesia machines developed for military applications are available, they are more costly and complex than a simple ventilator and infusion pump setup. In fact, in its most basic form, TIVA can be administered with only a syringe and ambu-bag, which is even simpler than a basic draw-over (volatile) system. Hospitals in developed countries are routinely set up for inhalational anaesthetics; thus, TIVA is usually more costly, due to the price of the agents. In developing nations, however, the cost of hardware and its maintenance usually outweighs the cost of drug, making TIVA a more economical option.

**Intravenous anaesthetic agents**

Several intravenous anaesthetic agents may be used in combination to execute an effective TIVA regimen. Propofol, the model drug for TIVA, and useful adjuncts for TIVA—dexmedetomidine, ketamine, and remifentanil—are reviewed below.

**Propofol**

Propofol remains the mainstay drug for TIVA. In addition to its favourable pharmacodynamic and pharmacokinetic profile, propofol offers distinct benefits over inhaled anaesthetics. In studies comparing propofol with inhaled anaesthetics in thoracic procedures, propofol reduced the postoperative decline of lung function after lung resection and inhibited the catecholamine surge and adrenocorticotropic hormone (ACTH) response during lung lobectomy.\(^14,15\) Studies of propofol in non-thoracic operations have also shown advantages that may apply to thoracic procedures; propofol reduced coughing during emergence from anaesthesia and the depression in bronchial mucus transport velocity associated with general anaesthesia.\(^16,17\) In addition, the stress hormone response and the expression of pro-inflammatory cytokines in alveolar macrophages were lower in patients receiving propofol than in those receiving inhaled anaesthetics.\(^16,19\)

**Dexmedetomidine**

Dexmedetomidine is an alpha-2 agonist sedative-analgesic that inhibits endogenous norepinephrine release. Dexmedetomidine is eight times more selective for the alpha-2 receptor than clonidine, with an alpha-2:alpha-1 receptor ratio of 1 600:1.\(^20\) Evidence suggests that its main effector sites are the locus coeruleus for sedative action and the spinal cord for analgesic action. In addition to its direct sedative-analgesic properties, dexmedetomidine also reduces opioid requirements and minimum alveolar concentration levels for inhalational anaesthetics.\(^21,22\)

In thoracic surgery, dexmedetomidine may offer several physiologic benefits. It reduces peri-operative oxygen consumption and the sympathetic response to surgical stimulus, which may confer cardioprotective benefits.\(^21,22,24\) In studies of thoracic surgery patients, the use of dexmedetomidine as an adjunct to epidural analgesia reduced the need for epidural fentanyl and resulted in post-operative diuresis and favourable indices of glomerular filtration, suggesting enhanced renal function.\(^25,26\) In patients with pulmonary hypertension undergoing mitral valve replacement, dexmedetomidine lessened the rise in systemic and pulmonary vascular resistance post-sternotomy and decreased mean arterial, mean pulmonary artery, and pulmonary capillary wedge pressures.\(^26\) Lastly, patients recovering from thoracic surgery may benefit from the reduced occurrence of respiratory depression and postoperative shivering associated with dexmedetomidine.\(^27,29\)

**Remifentanil**

Remifentanil is an ultra short-acting fentanyl derivative that is particularly suited to thoracic procedures. The rapid onset time (one minute) and short duration of action (3 - 10 minutes)\[^{42}\] make remifentanil ideal for managing the fluctuating periods of high and low surgical stimulation that characterise most thoracic procedures.\(^4,6\) Because thoracic epidural anaesthesia is the main modality for pain relief in most thoracic surgeries, there is little need for long-acting IV narcotics that may prolong extubation and cause post-operative respiratory depression. Some situations, however, (e.g. multiple surgical sites) require supplemental longer-acting narcotics for adequate post-operative analgesia. In these cases, remifentanil may be co-administered with longer-acting narcotics to provide intra-operative analgesia for periods of high surgical stimuli without risk of over-accumulation of the accompanying narcotics.

**Ketamine**

Ketamine is an N-methyl-D-aspartate receptor antagonist that induces a “dissociative state” in which sensory input (sight, hearing, touch) normally perceived by the patient is blocked from reaching consciousness. Because of its profound analgesic, sedative, and amnestic properties, it is occasionally used as an adjunct to propofol in TIVA regimens. Ketamine is particularly valuable for thoracic surgery because it (1) has bronchodilating properties; (2) does not depress respiration; (3) may reduce pain for up to three months post-operatively when used in conjunction with TEA for thoracotomy;
(4) reduces narcotic requirement; and (5) exerts sympathomimetic effects, which may be beneficial in thoracic trauma and in situations where perfusion pressure must be maintained in the presence of volume restriction.40

Infusion Systems

Traditionally, TIVA is administered through volume infusion pumps that deliver a preset dose per unit of time. Dosages are based on recommended minimum infusion rates and titrated to clinical effect through measurement of haemodynamics and subjective patient assessment. However, intravenous agents have a narrow therapeutic window that may be difficult to target and maintain.44 Target-controlled infusion (TCI) systems have been developed to administer intravenous anaesthesia based on real-time pharmacokinetic models to achieve serum concentrations specific for the intravenous agent in use. These systems reduce the subjective estimation of TIVA delivery, may deliver more consistent levels of anaesthesia, and can automatically tailor the dose of anaesthetic to specific phases of the surgery. Research and development are currently focused on accounting for inter-patient variability, handling a greater variety of intravenous agents and multiple co-administered intravenous agents, and achieving effect site control via closed loop systems. TCI systems are currently available in Europe, but have yet to be introduced commercially in the US.

Anaesthetic Depth Monitors

Anaesthetic depth monitors analyse and process a patient’s spontaneous electroencephalogram (EEG) and/or mid-latency auditory-evoked potentials (MLAEP) to gauge hypnotic depth.45 To date, however, studies have failed to show that anaesthetic depth monitors are consistently capable of either detecting intra-operative awareness or distinguishing between consciousness states, although anecdotal reports are encouraging.46 This may be of concern to anaesthesia providers who consider TIVA more difficult to administer and worry that the risk of intra-operative awareness may be increased. Many of these providers are less familiar with TIVA administration than volatile anaesthetic administration; for instance, they may be less familiar with the concept of Cₚ₅₀ — the concentration of intravenous agent that prevents reaction to a given stimulus in 50% of patients — than with the analogous minimum alveolar concentration for volatile anaesthetics. And even with advanced delivery systems such as TCI, direct control of effect site concentrations is currently not available.

However, an increased risk of intra-operative recall in TIVA has never been documented using the Brice interview (the primary diagnostic structured interview for the assessment of intra-operative recall).47 Furthermore, the anaesthetic depth monitor is more properly used as part of a larger overall clinical assessment scheme. Certainly, in combination with other clinical signs of inadequate hypnosis, themselves nonspecific, anaesthetic depth monitors may help in the titration of intravenous anaesthesia. This may be particularly important for unstable patients susceptible to the cardiovascular depressant effects associated with moderate to high doses of anaesthetic agents.48 In fact, in a study of non-cardiac surgery patients, mortality was correlated with cumulative deep hypnotic time as measured by bispectral index (BIS) < 45.49

Table I. Situations in which TIVA may be indicated

<table>
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<tr>
<th>Special surgical conditions</th>
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<tr>
<td>Tracheal/carinal surgery</td>
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<td>Lung volume reduction surgery</td>
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<td>Lung transplantation</td>
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<td>Endobronchial procedures</td>
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<td>Thymectomy</td>
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<th>Non-ideal environments</th>
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<td>Offsite locations requiring anaesthesia</td>
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<td>Austere environments (military, developing countries)</td>
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Conclusion

As thoracic surgical procedures grow more and more complex, thoracic anaesthesiologists must continue to tailor their techniques. The recent evolution of intravenous agents and delivery systems has made TIVA a viable alternative to inhalational anaesthesia. Current research focuses on the development of new intravenous agents with improved pharmacokinetic and pharmacodynamic profiles. Additional research is aimed at developing delivery systems capable of determining effect site concentration and compensating for inter-patient variability. Further development of TIVA will expand the choices of the anaesthesiologist in difficult surgical situations or environments.

References


