

Non-intubated thoracic surgery: an Asian perspective

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Abstract: Thoracic surgery without the use of modern general anesthesia and endotracheal intubation has a surprisingly long history in Asia. Over a half century ago, thoracic operations via thoracotomy were performed in China using acupuncture for pain suppression in awake patients. Today, East Asia continues to pioneer major thoracic operations using non-intubated techniques. A number of centers in Asia have now emerged as leaders in the development of the technique, production of clinical data, and training for the use of non-intubated thoracic surgery. Wider adoption of the non-intubated strategy across Asia is still relatively limited by the quality and evidence of the evidence thus far. However, encouraging developments in shaping and improving clinical research for non-intubated thoracic surgery in Asia suggest that this part of the world will continue to hold a central role in the future of the technique.

Keywords: Anesthesia; enhanced recovery after surgery (ERAS); non-intubated; tubeless; video-assisted thoracic surgery (VATS)

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A brief history of non-intubated thoracic surgery in Asia

The history of non-intubated thoracic surgery in Asia goes back further than many surgeons today realize. According to the *Huangdi Neijin* (The Yellow Emperor's Classic), acupuncture has been used in China as a therapeutic measure for at least 4,000 years (1-3). Acupuncture has been proven through centuries of clinical practice to be an effective means of relieving or even eliminating pain. It was therefore a natural progression in the modern era for Chinese surgeons and anesthetists to transfer the power of acupuncture to surgical operations. Reports of acupuncture for acupuncture-assisted anesthesia in China date back to the 1950s (3,4). Since then, the range of operations performed under acupuncture-assisted anesthesia have included a vast spectrum from simple tonsillectomy and appendectomy to ultra-major operations such as craniotomy and cardiac surgery (2-4). Observers from the West witnessed open heart operations performed in fully awake patients who were even able to drink and converse whist their hearts were being operated on (4). Not surprisingly, major pulmonary surgery via thoracotomy could also be performed with acupuncture instead of general anesthesia (GA).

This use of acupuncture-assisted anesthesia gradually declined since the 1970s. The reasons for this included: lengthy preoperative breathing training of patients required before surgery; greater pressure on surgeons to be extremely gentle, meticulous, and speedy; and anecdotal reports of psychological after-effects in some patients (4). The increasing availability of safe, affordable GA also played a key role (3-5). Today, acupuncture-assisted anesthesia is

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still being used and clinically researched in China, albeit in much smaller numbers (5,6).

Modern non-intubated thoracic surgery—in the form we recognize today—is often attributed to Dr. Eugenio Pompeo's team in Italy who described their series of thoracoscopic surgeries performed in conscious, nonintubated, spontaneous breathing patients in the noughties. These included wedge resections, lung volume reduction, and mediastinal tumor resection (7,8). However, it is often overlooked that at around the same time in Asia, Dr. Al-Abdullatief in Saudi Arabia was already demonstrating cases of major anatomical lung resections via thoracotomy with the patient awake or minimally sedated (9).

Non-intubated thoracic surgery really came into the spotlight in Asia and the world following the publications of Dr. Jin-shing Chen's group in Taipei in the early 21st Century (10). While Dr. Al-Abdullatief used stellate ganglion block to attenuate cough reflex (9), Chen's group used an ipsilateral intrathoracic vagal block to achieve control of the cough reflex (10,11). In addition, intravenous opioid and propofol were titrated with monitoring of anesthesia depth to further control respiratory rate and alleviate anxiety of patients. Dr. Chen reported the completion of video-assisted thoracic surgery (VATS) lobectomy under non-intubated spontaneous breathing anesthesia in a landmark paper in 2011 (10). Around the same time, Dr. Jianxing He's team in Guangzhou also began systematically carrying out non-intubated anesthesia thoracic surgery, expanding their repertoire to include wedge resection, lung volume reduction, myasthenia gravis thymectomy and radical resection of lung cancer (12,13). Dr. He's group were later able to complete even complex procedures such as bronchoplasty and tracheal/ carinal resections in non-intubated spontaneous breathing patients (13,14). Dr. He has gone on to propose the concept of "tubeless" VATS, whereby the endotracheal tube, the intercostal chest tube (drain), and the urinary tube (catheter) are all not routinely used (15).

The work of Dr. Chen and Dr. He in particular has popularized the practice of non-intubated thoracic surgery worldwide in recent years. Dr. He has demonstrated live surgeries with this approach that have been broadcast worldwide, and he has held multiple symposia to share this knowledge (16). Today, this technique has been widely used in thoracic surgery in many centers throughout China, and is also gaining proponents across East Asia (17). Any review of the current literature will reveal that a disproportionately large number of the clinical research on non-intubated thoracic surgery now comes from East Asia (18,19). In 2016, the European Society of Thoracic Surgeons Greek Pioneer Prize was won by Dr. Kun Qiao's group from Shenzhen for a study on non-intubated thoracic surgery (20).

The remarkable rise of non-intubated thoracic surgery in Asia over the last 10 years should not be a surprise. As has been previously discussed, Asia represents a surgical community that is currently both more ambitious to catch and surpass international standards, and less tethered by conventions and conservatism when exploring such newer techniques (21). The sheer volumes of thoracic surgical operations in Asia are well known to be large, and this inevitably helps the adoption, refining and teaching of these advanced approaches (22,23). It may also be speculated that the lower incidence and/or degree of obesity amongst East Asian patients in general may also be a more favorable factor when performing non-intubated thoracic surgery.

Asian evidence for non-intubated thoracic surgery

Asian experience with non-intubated thoracic surgery has provided valuable evidence for its practice both in terms of technical aspects on how to perform it, and also in terms of clinical data showing its potential clinical role.

Application of non-intubated thoracic surgery

A key element of non-intubated thoracic surgery is effective analgesic control to ensure the patient experiences no pain during the procedure. It is recognized that epidural neural blockade can cause complications (such as epidural bleeding, general spinal anesthesia, nerve injury, hypotension, respiratory depression, headache, and so on), and thoracic paraspinal nerve blockade is technically challenging even requirements for experienced anesthesiologists. Experience in Asia suggests that 2% lidocaine + 0.375% ropivacaine + betamethasone local injection for intercostal nerve blockade at the 2 to 9 intercostal spaces achieved a stable analgesic effect during and after operation (12). Most importantly, this method also reduces the possibility of complications of the other regional blockade methods mentioned above.

Besides pain suppression, it is also recognized that cough suppression is vital. Both Dr. Chen's and Dr. He's groups have noted that coughing may occur during nonintubated thoracic surgery, and this can rarely result in major adverse events, such as bleeding (10-16). To suppress

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coughing, intrathoracic vagus nerve block during nonintubated thoracic surgery is often used by injecting a local anesthetic to the vicinity of the vagus nerve around the upper mediastinal level (12). For some procedures, spray application of a local anesthetic to the visceral pleural surfaces may also achieve cough suppression.

Monitoring the depth of anesthesia is particularly crucial during non-intubated thoracic surgery to ensure the safety of patients. Studies in Asia have shown that maintaining the Bispectral index (BIS) value between 40 and 60 can enable patients to achieve sufficient sedation depth, avoid intraoperative awareness, but also avoid the occurrence of excessive sedation (24). During the operation, analgesic and sedative drugs should be titrated to maintain the respiratory rate at 12–20 breaths per minute to best facilitate the operation. Dr. Chen's group has shown that even short spells of mild to moderate hypercapnia are usually tolerable, and quickly returns to normal with hyperventilation (10).

The experience from Dr. He's unit has also helped define triggers for conversion to endotracheal intubation during the operation (25):

- (I) SpO₂ <85%, which does not improve after adequate hyperventilation;
- (II) PaCO₂ ≥80 mmHg or pH <7.15 on two successive arterial blood gases tests taken at 15-minute intervals or more) after adequate hyperventilation;
- (III) Heart rate >100 bpm, or systolic blood pressure changes >30% of the baseline value;
- (IV) Atrial or ventricular extrasystole ≥6 beats per minute (not caused by surgical stimulation);
- (V) Excessive lung ventilation/movement lasting >5 minutes after adequate sedation;
- (VI) Significant bleeding obscuring the operation field;
- (VII) Excessive airways secretions/blood resulting in dyspnea and increased airway resistance;
- (VIII) Persistent coughing >2 times/min.

With growing experience, it was recognized by Dr. He's group that the potential benefits of non-intubated thoracic surgery are maximized by incorporation of it into a strategy of "tubeless" VATS, where even chest tube and urinary catheter placements are not used (15). It can be argued that any advantages from avoiding endotracheal intubation and muscle relaxation ought not be negated by the morbidity from a chest tube and urinary catheter. The Guangzhou group has since demonstrated the feasibility of this "tubeless" strategy for sleeve lobectomy, tracheal reconstruction, carina reconstruction and uniportal VATS tracheal reconstruction from 2014 to 2016 (14,26-28).

Clinical Outcomes of non-intubated thoracic surgery

In recent years, case series from Asia have demonstrated that non-intubated thoracic surgery may have certain potential advantages over traditional GA. By avoiding endotracheal intubation, mechanical injury to the trachea and vocal cords is said to be minimized (12). By avoiding positive pressure ventilation, alveolar barotrauma is also said to be minimized (29). The avoidance of muscle relaxants is also said to contribute to expedite post-operative patient recovery immediately after surgery (11,30). The latter may be especially relevant during thymectomy for patients with myasthenia gravis (31).

It is striking that the evolution of published evidence for non-intubated thoracic surgery has developed at an extraordinary pace in Asia. Many major case series from this emerging strategy in Asia clustered around the early part of the 2010s (9-11). A handful of comparative studies were then published, including both propensity-score matched comparisons and some small randomized trials (12,13). One example of a propensity-score matched comparison came from Guangzhou in 2016, and this assessed patients with non-small cell lung cancer undergoing VATS anatomical resection (282 lobectomies and 57 segmentectomies) (13). Patients receiving non-intubated thoracic surgery had shorter post-operative fasting time, reduced postoperative chest drainage volume, and shorter hospital stay. Another small propensity-score matched comparison came from Shenzhen in 2016, comparing outcomes during the learning curve experience for non-intubated VATS (20). Even in the early learning curve, patients receiving non-intubated uniportal VATS lobectomy/segmentectomy had comparable mean operation time, blood loss, postoperative chest tube drainage, postoperative length of stay, and complication rates as those receiving conventional GA. However, patients who underwent non-intubated surgery had a lower incidence of sore throat, earlier resumption of eating, and earlier independent mobilization after surgery.

Since then, a series of meta-analyses have been produced by Asian (especially Chinese) authors comparing nonintubated thoracic surgery with traditional thoracic surgery under GA (18,19,30,32-34). This rapid progression from case series to meta-analyses is in stark contrast to the more gradual evolution seen with most other surgical advances. The progression from case reports to meta-analyses with conventional VATS, for example, occurred over a period of more than 20 years (35,36). Nonetheless, some of these Asian meta-analyses have provided the basis for proponents

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of the non-intubated thoracic surgery to validate their practices. Early meta-analyses in 2016–2018 suggested shorter operating times, shorter post-operative lengths of stay, lower complication rates, and shorter postoperative fasting times (30,32).

A 2019 meta-analysis was conducted by the Guangzhou group, with 27 studies including 2,537 patients entered in the analysis. A total of 1,283 patients underwent nonintubated VATS; intubated VATS was performed on the other 1,254 patients. Overall, the non-intubated VATS group had fewer postoperative overall complications [odds ratio (OR) 0.505; P<0.001]; shorter postoperative fasting times [standardized mean difference (SMD) -2.653; P<0.001]; shorter hospital stays (SMD -0.581; P<0.001); shorter operative times (SMD -0.174; P=0.041); shorter anaesthesia times (SMD -0.710; P<0.001) and a lower mortality rate (OR 0.123; P=0.020) (34). The average visual analogue scale (VAS) for pain was also lower with non-intubated thoracic surgery. In addition, there was no significant difference in the incidence of cardiovascular complications, blood loss and conversion to thoracotomy between the two groups. Around the same time, a few other meta-analyses have also emerged from China (18,19,33). They show similar findings overall.

Does the future of non-intubated thoracic surgery lie in Asia?

The case against

The proliferation of meta-analyses on the subject of nonintubated thoracic surgery appears to suggest a maturation of the clinical evidence around this strategy. However, this masks an inconvenient truth: the rate of publication of meta-analyses is now out-stripping the publication of original studies provided useful clinical data on this subject (18,19,33). Have there been so many original studies on non-intubated thoracic surgery to warrant at least one or more new meta-analysis on it every year for the past 5 years looking at essentially the same outcome measures? The answer is sadly no.

To a large extent, this phenomenon is a reflection of an unhealthy trend amongst some Asian authors to increasingly turn to writing meta-analyses instead of conducting original research on their own patients (37-41). There are multiple reasons for this, ranging from the fact that using statistical software to churn out meta-analyses often requires much less work than following up many patients in a clinical study, to the realization that medical journals tend to favor accepting meta-analyses as potential "citation gainers" to boost their Impact Factor, sometimes overlooking the flaws in the process (38-41). The reality is that many meta-analyses (regrettably many from Asia) are badly flawed. Despite "bias analysis" and Funnel plots, many meta-analyses are riddled with bias simply because of inherent publication bias associated with any new technique such as non-intubated thoracic surgery (37). The selection of papers for inclusion into the meta-analyses is also often inadequately stringent (39-41). In the meta-analyses for non-intubated thoracic surgery, it is seen that the included papers often report on a very heterogeneous mix of different operations and yet are lumped together for statistical analysis. It is also worrying that the meta-analyses tend to include multiple papers from the same hospitals, raising the real possibility of over-lapping patients and over-counting of patients.

A closer look at the different meta-analyses published over the past several years confirms that they do indeed tend to include the same handful of original studies (18,19,30,32-34). Most of those repeatedly used studies are from 2016 or before. There are few original studies from more recent years. It should also be noted that despite the supposed advantages in Asia of large surgical volumes, there are not so many original studies producing original clinical data from Asia in the last several years. What studies have been produced tend to be retrospective case series only, and comparative or prospective studies are painfully rare (18,19,30,32-34). The potential of Asia surgical centers to lead the way in providing important clinical evidence on non-intubated thoracic surgery has not been fully realized thus far. Instead, it seems that the trend for meta-analysis has eclipsed original research.

Another noted feature is that even among the few original studies being repeatedly referenced in reviews and metaanalyses, most are still originating from a small handful of centers. From Europe, the bulk of the papers quoted are from Drs. Pompeo, Mineo, Tacconi, *et al.* who have worked together (7,8). From Asia, most of the papers are from the units of Dr. Chen, Dr. He and a few others in China (10-16). Other than these core non-intubated thoracic surgery centers, only sporadic small series have been published (9,17,20). This points to the fact that despite the purported benefits of non-intubated thoracic surgery, it has not been widely embraced across Asia. Its use is still—at the time of this writing—mostly confined to a small group of enthusiast centers in Asia. Unless the adoption of non-intubated thoracic surgery picks up across Asia, the clinical evidence for it will remain based on a very narrow base from expert centers only, and cannot reveal its role beyond that base.

Part of the reason that non-intubated thoracic surgery has not been used in most centers across Asia is perhaps that there is little incentive at present to adopt it. Asia is known for its particularly high rate of using minimally invasive surgical approaches for thoracic surgery, and for the exemplary clinical outcomes achieved (22,36). In this context, many Asian surgeons have opined that on top of the poor quality of evidence produced thus far, the strategy of non-intubated thoracic surgery also seems to be a solution to no problem that actually exists (42). If VATS and uniportal VATS is already giving great results, the "additional" benefits promised by non-intubated surgery seem insignificant. Moreover, modern anesthesia is so safe nowadays that the need to avoid so-called risk of airway "trauma" seems over-stated. Thus far, no compelling argument has yet been framed to persuade non-users to adopt non-intubated thoracic surgery. This is partly demonstrated by the fact that the published studies from Asia and elsewhere in the world have not vet identified a reliable outcome measure to document its benefit. Parameters such as operating times, post-operative lengths of stay, and complication rates are subject to too many confounding variables and cannot be attributed solely to the use of a non-intubated technique given the designs of currently published studies. The time of resumption of eating after surgery also seems trivial: the benefit of eating a couple of hours earlier hardly seems important (unless future evidence proves otherwise). Most curiously, some authors have chosen to use chest drain durations as an outcome measure, even though there seems no logical reason why the use of an endotracheal tube should affect post-operative air leaks or fluid outputs in any substantial way. The lack of specific outcome measures to gauge the role of non-intubated thoracic surgery suggests that even its best proponents may be at a loss when seeking to convince skeptics.

The case in favor

Despite the pessimism expressed above, if non-intubated thoracic surgery is to have any future in this specialty it is likely to find that future in Asia. As noted above, the large operation volumes found in many surgical centers in Asia provides fertile ground for the growth of any new surgical technique. For example, uniportal VATS lobectomy may have originated in Europe (43,44), but it flourished into a global surgical phenomenon in Asia. The high and ultra-high volume surgical centers in East Asia allowed the technique to be perfected, developed and ultimately taught (21-23). Certain centers in China have emerged as leading training centers in uniportal VATS for surgeons from around the world (23). Crucially, those centers have produced the large volume of clinical data that have gradually cemented the technique as an established one in global practice. In the same way, the leading Asian centers in non-intubated thoracic surgery need also to provide the academic support for their clinical development. These centers need to take the lead in producing high-quality scientific data from their high volume of clinical work, and show by example that the way forwards is through novel clinical studies rather than short-cut meta-analyses. They must also set themselves up as training centers for the technique. To this end, it is noted that Dr. Jianxing He's center at the Guangzhou Medical University has already begun holding international courses on tubeless VATS since 2015 (16).

In terms of clinical research, it is also encouraging to see that in recent years, Asian surgeons have begun exploring other areas of potential advantage for non-intubated technique beyond the usual "complication rate, length of stay" framework. As mentioned above, the specific suitability of non-intubated VATS for thymectomy in patients with myasthenia gravis has been explored (31). One study from Guangzhou has demonstrated that the non-intubated approach may reduce the incidence of postoperative myasthenic crisis and of postoperative prolonged tracheal intubation (31). Future studies may focus on other patient sub-groups who may particularly benefit, such as those with anticipated difficult intubations or those who may be at particular risk from barotrauma, and so on (29).

Increasingly in Asia, it has been noted that with the reduction of other morbidities with VATS, post-operative coughing is emerging to the fore as a clinically significant complaint in some patients (45-49). Some Asian studies have postulated that this coughing may be related to the mode of anesthesia (46,49). In this context, it is interesting that one study from Shenzhen has associated non-intubated VATS with a lower incidence of sore throat (20). Another study from Guangzhou has further found the first evidence to suggest that non-intubated VATS may give lower incidence and severity of post-operative coughing compared to conventional GA (46). This may be an important first step in identifying the appropriate outcome measures to define

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the role of non-intubated thoracic surgery. Hopefully, other similarly pertinent outcome measures will continue to emerge.

Conclusions

Non-intubated thoracic surgery has found a welcoming and nurturing home in Asia which has allowed it to thrive. Fine details of the technique have been perfected in East Asia, and Asian surgeons are amongst those providing important early clinical data on its use. The clinical evidence surrounding non-intubated thoracic surgery remains flawed and limited in volume. However, it is also Asia which potentially offers the best prospects for the next higher level of clinical research in this strategy to emerge, and the best centers for training surgeons wishing to learn it.

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