The complex care of severe emphysema: role of awake lung volume reduction surgery

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Abstract: The resectional lung volume reduction surgery (LVRS) procedure entailing nonanatomic resection of destroyed lung regions through general anesthesia with single-lung ventilation has shown to offer significant and long-lasting improvements in respiratory function, exercise capacity, quality of life and survival, particularly in patients with upper-lobe predominant emphysema and low exercise capacity. However mortality and morbidity rates as high as 5% and 59%, respectively, have led to a progressive underuse and have stimulated investigation towards less invasive surgical and bronchoscopic nonresectional methods that could assure equivalent clinical results with less morbidity. We have developed an original nonresectional LVRS method, which entails plication of the most severely emphysematous target areas performed in awake patients through thoracic epidural anesthesia (TEA). Clinical results of this ultra-minimally invasive procedure have been highly encouraging and in a uni-center randomized study, intermediate-term outcomes paralleled those of resectional LVRS with shorter hospital stay and fewer side-effects. In this review article we analyze indications, technical details and results of awake LVRS taking into consideration the available data from the literature.

Keywords: Emphysema; chronic obstructive pulmonary disease (COPD); lung volume reduction surgery (LVRS); awake thoracic surgery; awake VATS; nonintubated thoracic surgery; nonintubated VATS

Authors' introduction:

Figure 1 is a picture including the authors of the article with other representatives of the ATSRG, a multidisciplinary team aimed at accomplishment and promotion of pioneering and comprehensive clinical investigations focused on awake and nonintubated thoracic surgery.

Introduction

Emphysema, one of the chronic obstructive pulmonary disease (COPD) phenotypes, is an irreversible, progressively debilitating condition, which is estimated to account for about one third of all diagnoses of COPD (1). Due to continuing use of tobacco and biomass fuels as well as to aging populations, emphysema is associated with a global social and economic burden and it is projected to become within 2030 the third leading cause of death (2-4).

In advanced stages, emphysema reduces both lung elastic recoil and mechanical support of peripheral bronchioles eventually leading to early expiratory airway collapse, severe gas trapping and lung hyperinflation.

Standard management of emphysema entails smoking cessation, pharmacological treatment with bronchodilators and anti-inflammatory drugs, supplemental oxygen and rehabilitation.

However, in patients with severe emphysema, medical therapy is poorly effective and interventional treatment including lung volume reduction surgery (LVRS) can be considered.

The standard LVRS procedure, which entails

Figure 1 Core representatives of the ATSRG. From the left: Drs Benedetto Cristino, Augusto Orlandi, Eugenio Pompeo, Umberto Tarantino, Tiziana Frittelli (General Director of the Policlinico Tor Vergata), Leonardo Palombi, Paola Rogliani, Roberto Massa, Mario Dauri.

nonanatomic resection of destroyed lung regions through general anesthesia with single-lung ventilation (resectional LVRS) (5), has shown to offer significant and long-lasting improvements in respiratory function, exercise capacity, quality of life and survival, particularly in patients with upper-lobe predominant emphysema and low exercise capacity (6). Unfortunately, several complications can occur with resectional LVRS leading to mortality and morbidity rates as high as 5% and 59%, respectively (7).

These figures, have led to a reportedly underuse of resectional LVRS and have stimulated investigation towards less invasive surgical and bronchoscopic (8-10) nonresectional methods that could assure equivalent clinical results with fewer morbidity.

In order to overcome the main drawbacks of resectional LVRS, we have developed an original nonresectional LVRS method, which can be performed in fully awake patients (11). Clinical results of this ultra-minimally invasive procedure have been highly encouraging (12) and in a uni-center randomized study, intermediate-term outcomes paralleled those of resectional LVRS with shorter hospital stay and fewer side-effects (13).

In this article we analyze indications, technical details and results of awake LVRS taking into consideration the available data from the literature.

Background

Resectional LVRS

Resectional LVRS was initially proposed by Brantigan and Mueller in 1957 (14). The procedure entailed non-anatomic resection of emphysematous lung tissue performed through staged thoracotomy and was aimed at reducing the overall lung volume to re-configure the chest wall and diaphragm, and restore radial traction on the bronchi, thereby relieving expiratory flow obstruction. At that time, despite significant subjective benefit occurred in most of patients, the lack of objective benefit documentation and a high mortality rate of 18% (15), led to rapid abandonment of LVRS. Following a dormant phase of 4 decades, LVRS was eventually re-vitalized by Cooper and coworkers (5) who proposed technical refinements including the use of median sternotomy for simultaneous bilateral, staple resection of the lungs. In a first series this method resulted in no mortality and significant improvements in subjective dyspnea, pulmonary function, exercise tolerance and quality of life measures. Thereafter, similar satisfactory results have been reproduced by means of video-assisted thoracic surgery (VATS) LVRS performed either unilaterally (16-18) or bilaterally (19-21).

The large National Emphysema Treatment Trial (NETT) (6) confirmed greater and long-lasting benefit as well as a survival advantage of resectional LVRS when

Table 1 Proposed criteria for awake nonresectional LVRS

Inclusion criteria

   Age 40-80 years

   Severe, heterogeneous emphysema, at the HRCT

   Dyspnea at rest or with minimal physical activity (mMRC score ≥2)

   Moderate to severe obstructive defect with FEV_1 ≤50% but >20% predicted

   Functional aspects of hyperinflation with RV >170% predicted and total lung capacity >110% predicted on body plethysmography

   Resting room PaO_2 >45 mmHg

   Impaired exercise capacity but 6MWT distance >150 m

   ASA score ≤3

   Quit smoking since at least 4 months

Exclusion criteria

   BMI <18 and >29

   Homogeneous emphysema with no target areas for LVRS, at the HRCT

   Need of ventilatory assistance

   DLCO <20% predicted on single breath technique

   Significant bronchitis with increased inspiratory airway resistance and/or abundant daily sputum production

   Resting $PaCO_2$ >55 mmHg

   Pulmonary hypertension with mean PA pressure >35 mmHg or peak systolic PA pressure >50 mmHg on Doppler echocardiography

   Any comorbid condition that would significantly increase operative risk including unstable, untreated coronary artery disease or ventricular arrhythmia

   Neoplastic disease with life expectancy <12 months

LVRS, lung volume reduction surgery; HRCT, high resolution computed tomography; mMRC, modified Medical Research Council dyspnea score; FEV_1, forced expiratory volume in one second; RV, residual volume; PaO_2, arterial oxygen pressure; 6MWT, six-minute walking test; ASA, American Society of Anesthesiology score; BMI, body mass index; DLCO, diffusion capacity for carbon monoxide; $PaCO_2$, arterial carbon dioxide pressure; PA, pulmonary artery.

compared to maximized medical therapy, particularly in patients with upper-lobe predominant emphysema and low exercise capacity. However, in the NETT operative mortality was 5% and overall morbidity was 59% (7). Time spent for postoperative recovery was often prolonged with about 30% of patients being still hospitalized or in rehabilitation facilities 1 month after surgery. As a result, the cost-effectiveness of LVRS has been questioned (22) progressively leading to a generalized underuse of this procedure in recent years (23).

Nonresectional LVRS by awake anesthesia (awake LVRS)

Historical background of nonresectional LVRS with lung plication can be dated back to the Brantigan's work in which both resection and plication of emphysematous lung tissue was already described to achieve an adequate reduction in the lung volume (24).

In 1992, Crosa-Dorado *et al.* (25) proposed multiple fold plications of emphysematous bullae carried out by thoracotomy with the aid of a custom-made folding forceps. In 1998, Swanson and co-workers (26) slightly modified the method proposed by Crosa-Dorado to make it suitable for VATS application. A further original fold plication method has been proposed in 1999 by Iwasaki *et al.* (27).

All the previously mentioned nonresectional LVRS procedures entailed use of general anesthesia with single-lung ventilation.

In 2006, we (11) reported feasibility and early results of an original nonresectional LVRS technique entailing introflexive plication of the most emphysematous lung regions, which was developed by one of the authors (EP) to be ideally performed in spontaneously ventilating awake patients through thoracic epidural anesthesia (TEA). This method respected the basic concepts of resectional LVRS including a reduction of about 30% of the lung volume, suturing performed along a single ideal line and use of stapling devices. Yet, it added potential advantages including avoidance of any loss in lung tissue, peripheral, interrupted suturing which was hypothesized to be more flexible, avoidance of any pleural discontinuation and creation of inlay buttress by the plicated bullous tissue. These technical refinements were aimed at facilitating immediate postoperative re-expansion of the lung and at reducing risks of prolonged air leaks, which accounts as the most frequent side-effect of resectional LVRS.
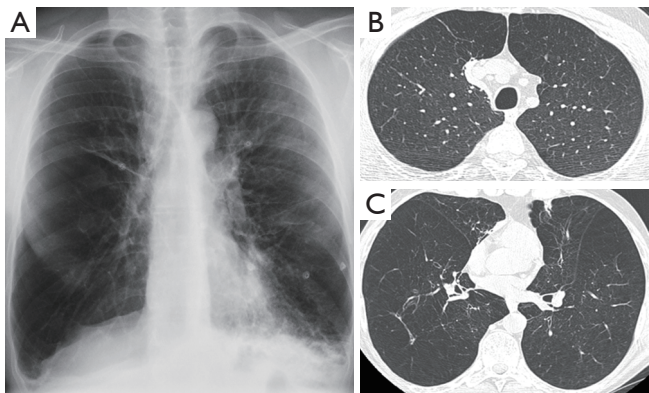
Selection criteria

Inclusion and exclusion criteria for awake LVRS do not differ significantly from those of resectional LVRS (28) (*Table 1*).

Patients complaining of disabling dyspnea with moderate-to-severe obstructive defect and limited exercise capacity that are not reversed by maximized medical therapy, with radiologic evidence of lung hyperinflation hyperinflation and flat diaphragms on chest X-ray, are potential candidates and must undergo high-resolution computed tomography (HRCT), assessment of static lung volumes by body plethysmography, and of diffusing capacity
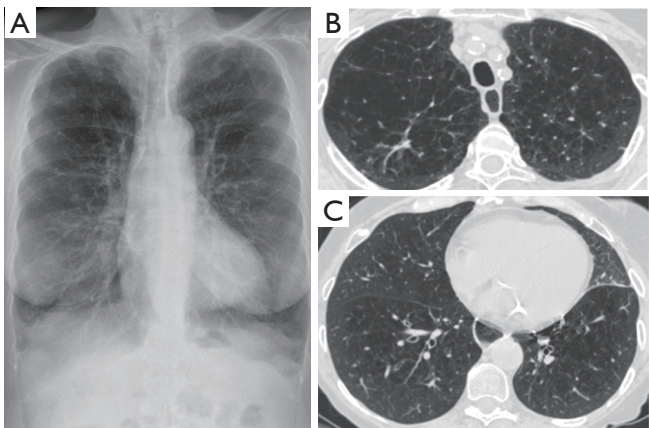
Figure 2 Radiologic features of a good candidate for awake LVRS. (A) Chest X-ray shows signs of lung hyperinflation resulting in flattened diaphragms and chest wall distention. (B,C) HRCT shows on axial scans, heterogeneous severe emphysema with more severe involvement of the upper lobes (B) and relatively better preserved lower/middle lobes (C). HRCT, high-resolution computed tomography.

Table 2 Technical differences between intubated and awake anesthesia

Anesthesia characteristics	Non-awake	Awake
Pre-medication	Yes	No
Type	General	Regional*
Ventilation	Mechanical	Spontaneous
Tracheal intubation	Yes	No
Diaphragm paralysis	Yes	No
Consciousness	No	Yes
Amnesia	Yes	No
Coughing reflex	No	Yes
Need of weaning	Yes	No
Need of additional sedation	No	Optional
Need of additional oxygen	Yes	Yes

*Thoracic epidural anesthesia; intercostal or paravertebral blocks.

Figure 3 Radiologic features of a moderately good candidate for awake LVRS showing lung and chest wall iperdistension with flattened diaphragm (A) and heterogeneous severe emphysema with more severe involvement of the lower lobes (B,C).

for carbon monoxide (DLCO).

Optimal candidates for awake LVRS disclose increased residual volume (RV) on body plethysmography and heterogeneous, severe emphysema on HRCT. In particular, we have found that as already shown with non-awake LVRS, patients with upper lobe-predominant emphysema are ideal candidates for awake LVRS and those who can achieve the greater magnitude of improvements (*Figure 2*). However, patients with lower-lobe predominant heterogeneous disease also can meaningfully benefit from the awake

procedure (*Figure 3*).

On the other hand, the finding that forced expiratory volume in one second (FEV_1) ≤20% predicted and either homogeneous emphysema or DLCO ≤20% predicted, resulted in a mortality rate of 16% following resectional LVRS, has led to consider patients with these characteristics as non-eligible for the operation (29) even though results achieved by the awake LVRS in this patients' subgroup has not yet been reported.

Moderate hypoxemia is commonly found in candidates for awake LVRS and does not represent an exclusion criterion.

Stable abstinence from cigarette smoking is mandatory to minimize operative risks and can help confirm the patient's motivation to undergo the operation.

Specific contraindications for awake LVRS include morbid obesity, unwillingness to undergo an awake surgical procedure, excessive anxious symptoms or HRCT findings showing signs of an obliterated pleural cavity on side chosen for LVRS.

Anesthesia

The main differences between awake and nonawake anesthesia are summarized in *Table 2*.

Our preferred type of anesthesia for awake LVRS is TEA carried out in fully awake, spontaneously ventilating patients. The objective of TEA is to achieve somatosensory and motor block between the T1-T8 level while preserving

diaphragmatic motion.

The epidural catheter is inserted at T4-T5 level. During the procedure, the anesthetic regimen entails continuous infusion of ropivacaine 0.5% and sufentanil 1.66 µg/mL into the epidural space whereas supplemental oxygen is delivered through a Venturi mask to maintain oxygen saturation above 90%.

At end-procedure, the anesthetic regimen is changed to ropivacaine 0.16% plus sufentanil 1 µg/mL at 2-5 mL/h and the epidural catheter is removed on the second postoperative day.

In patients with spinal deformity or coagulation disorders contraindicating the use of TEA, awake LVRS is accomplished through paravertebral (30) or intercostal blocks.

Conversion to general anesthesia is considered in patients showing poor tolerability of an awake procedure or whenever unexpected operative findings or technical difficulty are deemed better manageable by general anesthesia. This is induced by intravenous propofol (1.5-2 mg/kg), fentanyl (0.1 mg) and vecuronium (0.1 mg/kg) and is maintained by fentanyl and vecuronium with a continuous infusion of propofol. A left-sided double-lumen tube is used for single-lung ventilation. Intraoperative conversion from awake to general anesthesia is routinely carried out without changing the patient position and with the aid of a videolaryngoscope and a fiberoptic bronchoscope to facilitate tracheal intubation and obtain a correct position of the double lumen tube, respectively.

After surgery, patients undergoing awake LVRS stay in the recovery room for about 30 min and are then directly transferred to the ward where they can immediately start drinking, eating and walking under physiotherapist assistance.

Surgical technique

The patient position is lateral decubitus as for thoracotomy. The operating table is usually not flexed below the chest to facilitate ventilation of the dependent lung. The video monitor is placed at the head of the table. Surgical access entails placement of four flexible trocars. The camera port is placed in the sixth intercostal space along the midaxilllary line while operating ports for instrumentation are placed in the third and/or fifth intercostal space along the anterior axillary line, and in the fourth intercostal space along the posterior axillary line. A 30°, 10 mm camera is used to optimize vision during spontaneous ventilation. Pleural adhesions, if present, are divided by sharp and blunt dissection.

The goal of nonresectional LVRS is to plicate as much emphysematous tissue as possible. The most destroyed lung regions targeted for plication on the basis of the HRCT imaging are recognized intraoperatively with the aid of instrumental palpation of the lung.

Whenever, the hyperinflation of the lung counteracts the lung collapse induced by creation of the surgical pneumothorax, we employ an endopaddle to push down the lung and improve exposure and surgical manoeuvring.

Subsequently, the apical side of the emphysematous target area is grasped by two ring forceps while pushing downward the tissue in between with a cotton swab. The next step entails simultaneous grasping of both redundant lung edges and peripheral suturing of the plicated area by a 45 mm, non-cutting endoscopic stapler. In a similar manner, two other cartridges are fired in the ventral and dorsal side of the targeted area to perform a linear, interrupted suture line. As a result, the upper lobe volume is reduced by about 50% without any loss in lung tissue and the lung is remodelled to achieve a trapezoidal shape. In patients with lower lobe predominant emphysema, multiple smaller plications are carried out to reduce in a uniform manner the overall lung volume (*Figure 4*).

The main differences between resectional and nonresectional LVRS are detailed in *Table 3*.

Surgical strategy

Simultaneous bilateral LVRS has shown to produce superior benefit than unilateral treatment and is the preferred strategy of treatment in several Institutions (31,32). However, we have reported that in patients with asymmetric emphysema undergoingt unilateral LVRS on the most emphysematous lung, the improvement in FEV_1 compared that achieved by one-stage bilateral treatment (33,34). This is possibly due to mobility of the mediastinum, which can induce interdependence effects leading a single procedure to improve ventilation in both lungs.

Moreover, it has been shown that yearly deterioration in FEV_1 was greater following bilateral than after unilateral LVRS (35). These features summed up to the easier patients' tolerability of unilateral rather than bilateral simultaneous treatment, have led us to prefer a staged bilateral strategy of treatment. In fact, although there are no prospective studies comparing staged *vs*. 1-stage bilateral LVRS, in a previous retrospective analysis by our group, staged bilateral LVRS resulted in more stable improvements in FEV_1, forced vital capacity (FVC), 6-minute walking test (6MWT) and RV
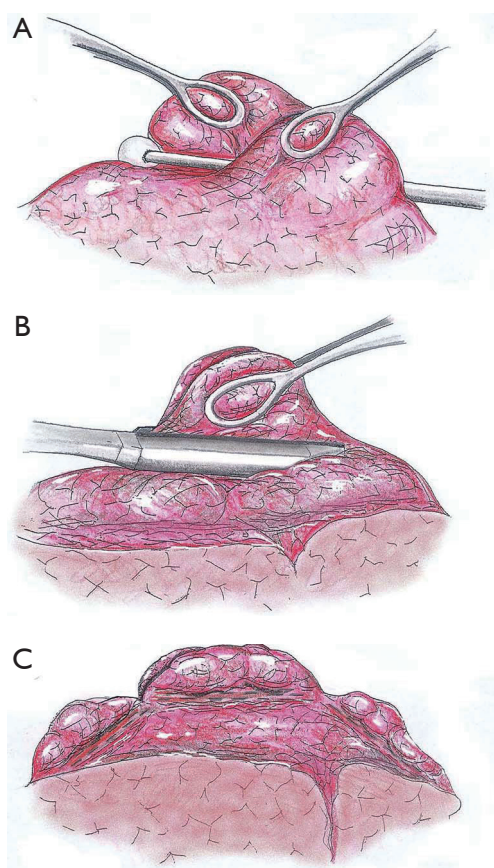
Figure 4 Art drawing illustrating the simple technical steps of the awake nonresectional LVRS method. (A) The most emphysematous lung tissue is grasped and plicated between the ring forceps; (B) plicated tissue is sutured peripherally by non-cutting endostapler; (C) the maneuver is repeated 3 times to achieve lung volume reduction and remodeling with trapezoidal shape to fit easily the apex of the pleaural cavity. Reprinted from *the Annals of Thoracic Surgery* (12), with permission.

Table 3 Technical differences between resectional and nonresectional LVRS

Characteristic	Resectional	Nonresectional
Tissue resection	Yes, nonanatomical	No
Suture type	Mechanical continuous	Mechanical interrupted
Suture length (mm)	≥225	125
Suture position	Deep	Peripheral
Pleural discontinuation	Yes	No
Buttress	Optional, heterologous	Yes, folded visceral pleura
Remodeling shape	Trapezoidal	Trapezoidal
Volume reduction (one lung) (%)	≥30	≥30

Results

As far as perioperative outcome of awake LVRS is concerned, in a comparative analysis, 66 patients undergoing awake nonresectional LVRS were compared with 66 patients undergoing non-awake resectional LVRS. Prolonged air-leak (>7 days) occurred in 18% of the patients in the awake group *vs.* 40% in the control group (P=0.007) with an overall duration of 5.2 days in the awake group and of 7.9 days in the control group (P<0.0002). As a consequence hospital stay was 6.3 *vs.* 9.2 days, respectively (P<0.0001) (37).

Clinical benefits of awake LVRS are expected to be equivalent to those achievable by resectional LVRS and include improvements in respiratory function, exercise capacity, subjective dyspnea, quality of life measures and survival (38). Other less frequently reported benefits include improvements in oxygenation (39), body weight and nutritional status (40), cardiac function (41,42), cognitive function (43), alveolar ventilation (44), and breathing pattern (45).

So far there exist only a limited number of publications reporting on the intermediate-term results of awake LVRS.

In a 42 patients retrospective series, we reported no 90-day mortality with significant 2-year improvements in 6MWT, FEV$_1$, FVC, RV as well as in the multidimensional body mass index, airflow obstruction, dyspnea, and exercise capacity index (BODE), which has shown to represent a useful predictor of survival in COPD patients (12).

In a more recent study, 63 patients were randomized to receive unilateral VATS LVRS performed by either the awake nonresectional method in 32 patients or by the non-awake resectional method in 31 patients. Comparative

than 1-stage bilateral LVRS (36).

As a result, our current strategy of treatment entails unilateral awake LVRS performed initially on the most severely emphysematous lung and postponement of the contralateral procedure until when the benefits achieved by the first operation are lost.

In our hands, more than 95% of awake LVRS procedures are performed by VATS whereas we deserve thoracotomy to patients with history of previous major thoracic surgery on side chosen for LVRS, in those with radiologic signs of diffuse, fibrous adhesions as well as whenever unexpected intraoperative findings or complications lead us to consider convertion to thoracotomy the safest choice.

assessment of results between awake and non-awake groups have shown that 1 h after surgery, oxygenation as expressed by the ratio of arterial oxygen tension to fraction of inspired oxygen as well as arterial carbon dioxide tension, were significantly better in the awake group. Mortality and morbidity rates were 0 *vs.* 3.2% and 22% *vs.* 52% (P<0.01); median hospital stay was 6 *vs.* 7.5 days (P<0.04) with 21 *vs.* 10 patients discharged within 6 days (P=0.01). Moreover, at 6 months, FEV_1, which was the clinical primary outcome measure, improved significantly in both study groups (0.28 *vs.* 0.29 L) with no intergroup difference. In addition in both groups, improvements in FEV_1, 6MWT, FVC, RV and physical functioning quality of life measure, lasted more than 24 months. At 36 months, both freedom from contralateral treatment (55% *vs.* 50%; P=0.5) and survival (81% *vs.* 87%; P=0.5) where similar between study groups (13).

Redo LVRS

A particular poor risk sub-cohort that can meaningfully benefit by avoidance of intubated anesthesia is that entailing emphysematous patients who have lost the benefits achieved by a successful LVRS and who develop new target areas in the lung that are amenable of reoperation. In these patients the postoperative functional deterioration usually progresses along several years. As a result, redo-LVRS remains in most of instances the only therapeutic choice since many of these patients are older than 65 years of age and cannot be included in a lung transplantation waiting list.

In a 17 patients series on redo LVRS entailing completion lobectomy in seven patients and intubated resectional or awake nonresectional redo LVRS in five patients each, the mean age was 66 years whereas interval time between the first LVRS procedure and the reoperation was of 55 months. The 90-day operative mortality was 12% and included two patients who underwent one completion lobectomy and one nonanatomic lung resection under non-awake anesthesia.

The mean hospital stay was 9 days and significant improvements lasting for up to 12 months occurred in FEV_1 (P<0.001), FVC (P<0.002), RV (P<0.001), 6MWT (P<0.001), and dyspnea index (P<0.001). Six months after surgery, 11 patients had an FEV_1 improvement of 200 mL or more (46).

Conclusions

LVRS, has been shown to represent a highly effective treatment modality for properly selected patients with severe emphysema although in recent years it remains unexpectedly underused. Decker and co-workers (23) have reported that amongst the Society of Thoracic Surgeons database only 528 patients underwent non-awake LVRS during an 8.5-year period. This figure has led them to highlight the need to invest in future analyses to identify determinants of adjusted surgery-specific quality assessments.

What is arguable is that the Achilles heel of resectional LVRS is not related to doubts on its efficacy but rather to fears of the significant perioperative morbidity that has been associated with this treatment modality and that can meaningfully increase health care costs.

Within the framework of available investigational methods, the awake nonresectional LVRS method, which does not entail use of any expensive device, avoids removal of lung tissue and can be quickly performed in spontaneously ventilating awake subjects, has shown promise in uni-center studies and awaits now to be tested through well designed, multi-institutional controlled trials.

Having matured an experience with several types of thoracic surgery procedures performed through awake anesthesia we can affirm that candidate to LVRS due to emphysema are amongst the patients who can benefit most from an awake anesthesia management. In fact, we have found that perioperative breathing pattern, oxygenation promptness of resumption of daily-life activities, and hospital stay are dramatically better in patients undergoing awake LVRS if compared with those of patients operated on by general anesthesia with single-lung ventilation.

In conclusion, the fear of performing awake LVRS in delicate subjects with severe emphysema and poor pulmonary function is fully understandable as nicely underlined during the discussion about a paper on awake LVRS presented at an international meeting, when one of the moderators affirmed: "It is a little intimidating for some of us to think about having one of these critically ill patients be wide awake while we make holes in their chest and operate on them" (12).

Nonetheless, experience with nonintubated and awake thoracic surgery is increasing worldwide and it is possible that in the near future, a number of thoracic surgeons who will have gained confidence with both non-awake and awake LVRS will rather consider somewhat more intimidating performing LVRS in intubated, non-awake patients.

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ATSRG picture.

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