Protocol: **Clamping the Double Lumen Tube :**

A novel technique to optimize One-Lung Ventilation.

Third part of "Lung Isolation Strategies" research program

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Introduction:

One-lung ventilation (OLV) is a major consideration in thoracic anesthesia. Lung isolation, through the use of double-lumen tube (DLT) or bronchial blocker (BB), offers to the surgeon the intra-thoracic access he needs for the surgery. With the use of a DLT, the non-ventilated lung is isolated by disconnecting its specific lumen from the ventilator and keeping it opened to ambient air. With a BB, the BB cuff is inflated in the bronchus after a brief apnea period. Thereafter, only the dependent lung is ventilated.

Until recently, studies evaluating the quality of lung collapse with the use of DLT versus BB showed contradicting results and were not conclusive.(1)(2) However, in 2016, *Bussières' reaserch group* obtained a faster lung collapse with the use of a BB with its internal channel occluded and a second period of apnea at pleural opening.(3)

A review of the literature could not explain in details these results. In the 2000s, lung collapse during OLV was described as undergoing two distinct phases; the first phase occuring at the opening of the pleural cavity and corresponding to a quick but partial collapse secondary to the elastic recoil of the lung. The second phase, a slower one, being the reabsorption, by the vascular capillary bed, of the gas contained into the alveoli; the speed of this second phase being directly proportional to the solubility coefficient of the gas.(4)(5)

Since no previous studies had explanation for *Bussières'* unexpected results(3), they conducted a physiologic study to extensively determine the physiology of the non-ventilated lung (NVL) during OLV with the use of DLT and BB. Their results

demonstrated that during lung isolation, while the chest is closed, there is a buildup of negative pressure in the NVL until pleural opening, when the lumen of the DLT or the internal channel of the BB are occluded. This phenomenon was observed for both lung isolation devices (BB and DLT). They also observed an absorption of ambient air through the lumen of the DLT and the internal channel of the BB when the lumen of both device was open to ambient air(6) (Results are shown in Figure 3). These results probably explain why *Bussières* obtained a faster lung collapse with BB in their study(3). By occluding the internal channel of the BB they prevented the aspiration of ambient air in the NVL. This condition may have accelerated the absorption atelectasis of the NVL that occurs during the second phase of lung collapse by obtaining an initial lower lung volume containing a higher alveolar partial pressure of oxygen (P_AO_2) in the BB group.

Since these recent findings demonstrate that both lung isolation devices cause negative pressure and an aspiration of ambient air, it is possible that the occlusion of the specific lumen of the NVL of a DLT could reproduce the physiology of the lung isolation obtained with a BB with its internal channel occluded.

The hypothesis is that by withholding gas exchange between the NVL and ambient air from the beginning of OLV to the pleural opening, the resorption atelectasis will be facilitated. Consequently, lung collapse of the NVL will occur faster when clamping its specific lumen on the DLT instead of letting it communicate with ambient air like anesthesiologists usually do.

It is important to note that this actual study is the third of a research program named « Lung Isolation Strategy » . The two first one, mentionned earlier, have both already won the prestigious *“Canadian Cardiac, Vascular and Thoracic: Raymond Martineau*

Award" in 2013 and 2017.

The first outcome of this study is to measure the time required to obtain complete lung collapse (CLC) in patients requiring OLV for VATS with DLT by comparing two techniques :

1- Control group : Leaving the specific lumen of the NVL opened to ambient air like the usual practice.
2- Experimental group : Clamping the specific lumen of the NVL from 30 seconds following the beginning of the OLV to the pleural opening.

This end-point is obtained by a video posteriori evaluation (CLC-video).

The secondary outcomes include :

1) The guess of which technique is used, by the thoracic surgeon, 20 minutes after pleural opening.
2) A clinical evaluation, by the thoracic surgeon, of the quality of the surgical exposure following lung collapse using a visual scale graduated from 1 to 3, at 0, 10 and 20 minutes following pleural opening (Figure 1).
3) The time required to obtain CLC. This end-point is assessed clinically by the surgeon during the surgery (CLC-clinical).
4) A measure of the expiratory volume (EV) at pleural opening for 60 sec.
    a. A mesure of the P_AO2 of the EV.
5) A measure of the P_AO2 of the expiratory flow at the beginning of OLV for 60 sec.
6) The time required for completion of the surgery (from pleural opening to closure of the last trocar insertion site).
7) The number and type of interventions needed to optimize lung collapse during the observation period.

8) An evaluation of the quality of OLV 25 minutes after pleural opening with :

a. PaO_2

b. SaO_2

Methods:

After obtaining local scientific board and IRB approval and registering the protocol on ClinicalTrials.gov, a prospective randomized study of a cohort of 30 patients undergoing elective VATS requiring OLV will be established.

Inclusion criteria :

1- Elective lung reserction (lobectomies) by VATS requiring OLV.

2- More than 18 years old.

3- Having read, understand and signed the consent form presented at the pre-operative evaluation.

Exclusion criteria :

A- Pre-operative

1- Known or anticipated difficult tracheal intubation.

2- Bronchoscopic or CT-scan findings contraindicating the insertion of a DLT.

3- Severe COPD or asthma (FEV1 <50%).

4- Prior intrathoracic surgery (including cardiac surgeries).

5- Pleural or interstitial pathology.

6- Previous chemotherapy or thoracic radiotherapy.

7- Acute or chronic pulmonary infection.

8- Endobronchial mass.

9- Tracheostomy.

B- Post-randomisation

1- Bronchoscopic findings contraindicating the insertion of DLT.

2- VATS findings that cancel the surgery.

3- Severe desaturation ($SatO_2$ < 90%) during the observation period.

4- Any need to reinflate the collapse lung.

Every excluded patient in the post-randomization period is replaced by the next patient until the obtention of 15 patients per group.

Randomisation

Just before induction of anesthesia and according to the computerized randomization list generated by the statistical department, each patient is allocated to one of the following groups:

1. Control group : OLV with the specific lumen of the NVL opened to ambient air.
2. Experimental group : OLV with a clamp on the specific lumen of the NVL.

Study planning

The study period begins at the induction of anesthesia. The observation period begins at the opening of the pleura by the surgeon and lasts for a minimum of 20 minutes or until CLC.

Stages:

SCREENING

Patients are recruited in the preoperative clinic. Investigators are reviewing files in order to find eligible canditates and then meet them to explain the project in details.

RANDOMISATION

INDUCTION

1. If cardiac rhythm is inferior to 100 bpm, patient receives 0.2 mg of intravenous glycopyrrolate to optimize condition of use of FOB for positioning and verification of lung isolation devices.
2. Anesthesia induction following usual practice.
3. Intubation with Left-DLT (L-DLT). The dimension of the DLT is based on *Brodsky's* recommandations(7) and is positioned with the FOB following *Bussières and Slinger's* recommandations(8).
4. Bilateral lung ventilation is adjusted with a tidal volume (TV) of 6-8 mL/kg x 10 breaths/min, a FiO_2 at 1.0 and a PEEP at 5 cmH_2O to obtain an $EtCO_2$ between 35 and 45 mmHg.
5. Lateral decubitus positioning.
6. Confirmation of the adequate placement of the L-DTL with an FOB.
7. Inflation of the bronchial cuff.
8. Confirmation of adequate seal of the bronchial cuff by continuous spirometry.

ONE-LUNG VENTILATION / CLOSED CHEST

1. OLV begin with a TV of 4-6 mL/kg x 14-18 breaths/min with a FiO_2 gradually tapered to 0.50 if tolerated (Sat O_2 ≥ 92%) and PEEP at 5 cmH_2O.
2. Period of 60 seconds for both groups during which :
    a. The specific lumen of the NVL is disconnected from the ventilator.
    b. An O_2 analyzor is connected to the NVL lumen and the O_2 content is obtained at :
        i. 15 sec
        ii. 35 sec
        iii. 55 sec
3. Depending on the group :
    a. Control group : Leaving the specific lumen of the NVL opened to ambient air.
    b. Experimental group : Clamping the specific lumen of the NVL.

***OLV during closed chest period should have a duration of at least 10 minutes and no more than 15 minutes.

JUST BEFORE PLEURAL OPENING

4. Activation of the surgical camera and video recording for the posteriori evaluation (CLC-video).
5. A one-liter collection bag (Roxon, Etobicoke, ON, Canada) is connected to the specific lumen of the NVL via a three way valve (Hans Rudolph inc, Shawnee, Kansas, United States) (Figure 2).
6. Depending on the group :
    a. Control group : the NVL lumen of the DLT that is opened to ambient air is now placed in-line with the collection bag.
    b. Experimental group : the NVL lumen of the DLT that is clamped is placed il-line with the collection bag then the clamp on the specific lumen of the NVL is removed at pleural opening.

PLEURAL OPENING

7. Period of 60 seconds for both groups at pleural opening during which EV2 is collected in the collection bag:
    a. EV measurement : the collection bag content is precisely measured with a calibrated syringe of one liter (Hans Rudolph inc, Shawnee, Kansas, United States) via the three way valve (Figure 2). This measurement will be later confirmed by a pneumotachometer.
    b. P_AO2 measurement : The O_2 analyzor is still connected to the NVL lumen and the O_2 content is obtained at :
        i. 15 sec
        ii. 35 sec
        iii. 55 sec

OPEN CHEST

8. The specific lumen of the NVL is opened to ambient air in both groups.
9. Evaluation by the surgeon of the quality of lung collapse according to visual scale (figure 1). This evaluation is done at different times :
    a. At pleural opening (0 min).
    b. 10 min following pleural opening.
    c. 20 min following pleural opening.
10. During all the observation period an external observer is regularly asking the surgeon to advise when the lung reaches CLC.
11.
12. Surgeon blind estimation of the technique used (clamped or not), 20 min following pleural opening.
13. After 20 min, the external observer stays in the operating room until the occurrence of CLC-clinical.
14. Arterial blood gas 25 minutes following beginning of OLV.
15. End of the observation period.
16. Posteriori evaluation of video recordings by three blinded evaluators of the timing of CLC-video.

“A POSTERIORI” VIDEO EVALUATION

The primary outcome is answered by a posteriori evaluation, once video recordings of the 30 patients will be available. These recordings are analyzed by three different investigators who are identifying the timing of CLC-video. The panel is blinded and identical for each and every patient in order to avoid evaluator bias. The video clips reviewed are mixed from random group and time sequences, and scored using the same standardized visual scale (Figure 1).

Protocol particularities :

- During the observation period, if the lung collapse is not adequate, some additional maneuvers are tried and recorded:
    1. FOB to confirm the positioning of the DLT.
    2. FOB to aspirate any secretion in the bronchial tree.
    3. FOB for endobronchial aerial aspiration.
- The external observator is one research assistant that can't be blinded because he is directing all the manipulations. In order to reduce bias in evaluating CLC-clinical timing, the external observator is never to be suggesting CLC to the surgeon. He is, however, at regular intervals, reminding the surgeon to advise the research team when he thinks that CLC-clinical has occurred.
- The time required to obtain CLC-video and CLC-clinical is the period between pleural opening and obtention of CLC; described as the maximal exposure for the surgeon and a purple coloration of the NVL. An example is shown in Figure 1 (picture 3).
- A maximum of 4 surgeons are participating to the study in order to get enough patients during a limited time frame. These surgeons are experienced with this kind of project, in fact, they were part of the first study of this research program (5) that used the same visual scale to qualify lung collapse during surgery and on a posteriori video recording evaluation.

Production deadline

With the workflow at IUCPQ-UL, a three months period is enough to complete the recruitment. We plan to realize the study between September 2017 and January 2018. Last year, 107 VATS lobectomies were performed between September to December 2016.

Statistical analysis

Following the results obtained by the study done by *Bussieres et al.*(3), assuming a time for complete collapse of 10 +/- 4 minutes with a clamped DLT (similar to BB occluded) and 25 +/- 24 minutes with a DLT opened to room air with an alpha of 0.05 and a power of >0.95, a sample size at 15 patients per group is estimated to be required; a total of 30 patients (15 subjects per group) will be randomized.

The magnitude of interobserver agreement regarding the video examination data will be determined using a weighted Kappa statistic where 0-0.20 would denote slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement, and >0.81 almost perfect agreement.

The secondary outcomes will be formally tested if the primary comparison is significant at a two-sided level of 5%. A hierarchical testing procedure will be performed, with the variables in the following order :

1. The guess of which technique was used, by the thoracic surgeon, 20 minutes after pleural opening.
2. A clinical evaluation, by the thoracic surgeon, of the quality of the surgical exposure following lung collapse using a visual scale graduated from 1 to 3, at 0, 10 and 20 minutes following pleural opening (Figure 1).
3. The time required to obtain CLC. This end-point will be assessed clinically by the surgeon during the surgery (CLC-clinical).

4. A measure of the expiratory volume (EV) at pleural opening for 60 sec.
    a. A mesure of the P_AO2 of the EV.
5. A measure of the P_AO2 of the expiratory flow at the beginning of OLV for 60 sec.
6. The time required for completion of the surgery (from pleural opening to closure of the last trocar insertion site).
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8. An evaluation of the quality of OLV with :
    a. PaO_2
    b. SaO_2

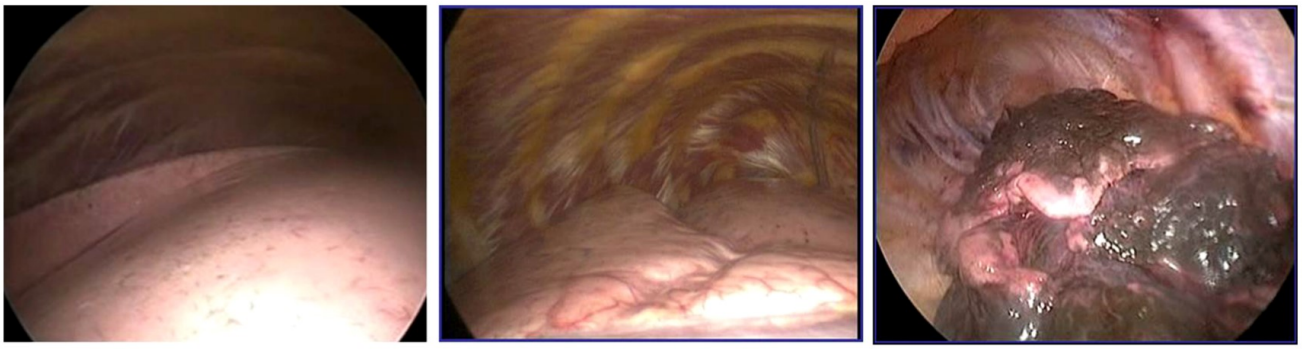
All data will be analyzed using the statistical package program SAS v9.3 (SAS Institute Inc., Cary,NC). Data will be log-transformed prior to undergoing analysis of variance (ANOVA). Statistical results from these parameters will be expressed with transformed values. The Tukey's multiple comparison technique will be applied *post-hoc* to the ANOVA to compare pairs of group means. The univariate normality assumption will be verified using the graphical representations and the Shapiro-Wilk test. The Brown and Forsythe's variation of Levene's test statistic will be used to verify the homogeneity of variances. Results will be declared significant with p-values < 0.05 for two-tailed tests.

Perspectives

In order to obtain proper visualization of structures and a clear surgical field during VATS, an optimal lung collapse is essential. That is exactly why finding a simple way to obtain a better and faster lung deflation would be very useful. If the proposed hypothesis is confirmed, this would provoke a new paradigm in the way we use the DLT. The usual technique leaving the lumen of the NVL opened to ambient air would be replaced by the use of a clamp on this DLT lumen from the beginning of the OLV until pleural opening.

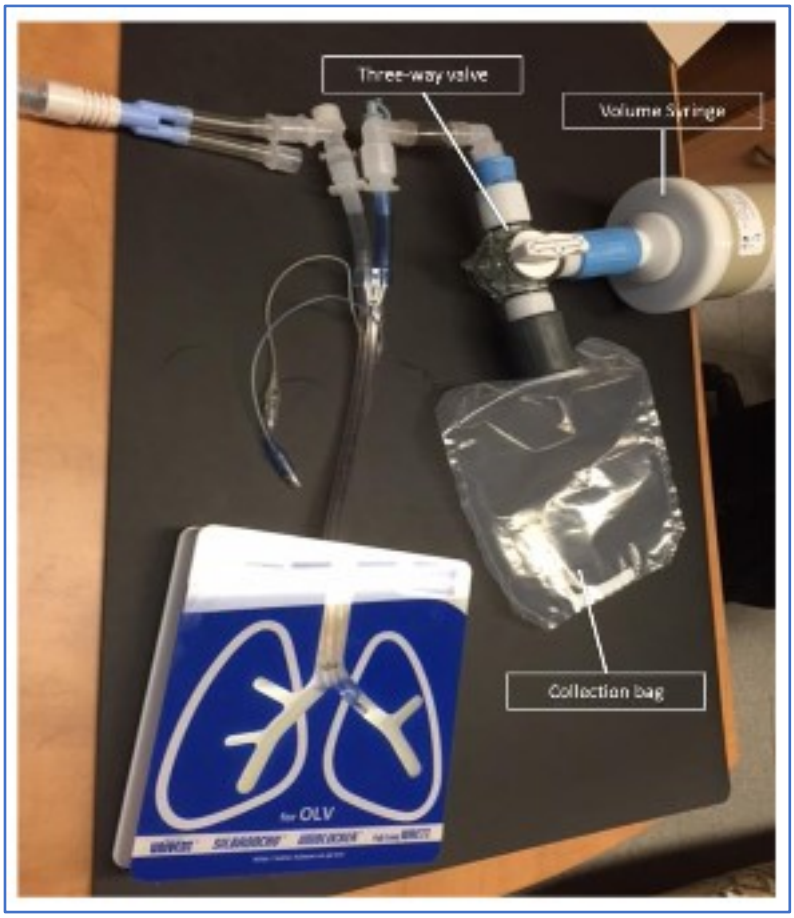
The anticipated results might allow us to describe an inovative technique with the objective of achieving a faster and better lung collapse.

Figure 1 : **Visual scale for lung collapse quality evaluation**



	1. No collapse	2. Partial collapse	3. Complete collapse
Collapse	+/-	+	++
Space in thoracic cavity	+/-	+	++
Atelectasis	-	+	++
Purple color	-	+/-	++
Satisfactory	-	+	++

<u>Figure 2</u> : Expiratory volume determination in DLT.



<u>Figure 3 :</u> Results of *Physiology of Lung Collapse during One-Lung Ventilation : Underlying Mechanisms (6)*

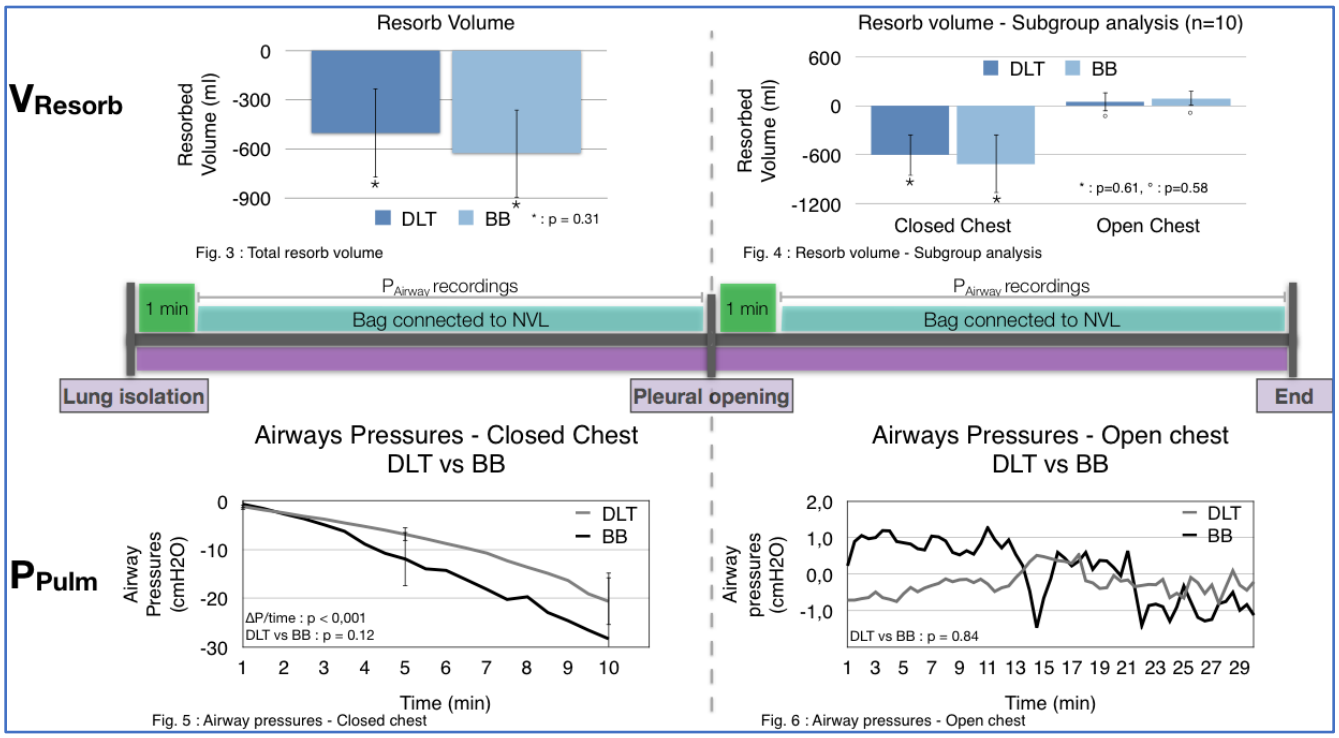


Fig. 3 : Total resorb volume

Fig. 4 : Resorb volume - Subgroup analysis

Fig. 5 : Airway pressures - Closed chest

Fig. 6 : Airway pressures - Open chest

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