USE OF SEALANTS AND BUTTRESSING MATERIAL IN PULMONARY SURGERY

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I have no conflict of interest to declare
INTRODUCTION

• Intra-operative alveolar air leaks are common complications associated with pulmonary resection and other intra-thoracic procedures requiring extensive pleural dissection [Klijian, 2012].

• The intra-operative air leak (IOAL) rate has been reported to be between 48% and 75%, with persistence beyond 7 days in 15%-18% in patients experiencing complications resulting in prolonged air leaks [Klijian, 2012 /, Carvalho et al, 2017].

• Ninety per cent (90%) of patients undergoing lung volume reduction surgery developed air leaks [DeCamp et al, 2006 / Pedersen et al, 2012].
Managing these air leaks requires insertion of a chest tube and longer hospitalization, which potentially could increase morbidity and post-operative costs [Klijian, 2012 / Servais et al, 2018].

Patients who developed air leaks were associated with an increased risk of pneumonia and readmission to the intensive care unit [DeCamp et al, 2006 / Pedersen et al, 2012].

Prolonged air leak represents the most common complication after lung surgery and could lead to extended chest tube drainage time and development of infections, and broncho-pleural fistulae [Milenkovic et al, 2018].

Therefore, controlling IOAL may add benefits to the patient, reduce chest tube duration, length of hospital-stay and associated morbidities, and potentially reduce healthcare cost [Klijian, 2012].
INTRA-OPERATIVE MEANS OF AEROSTASIS

- Sutures
- Staples
- Electrocauterization
- **Air Sealants**
- **Buttressing material**
- Pleural tent
- Pleurodesis
- Transient Diaphragmatic Paralysis
- Pneumoperitoneum
- Thoracoplasty
WHAT IS A SEALANT:

• Air leak is a clinical phenomenon that is associated with the leakage or escape of air from cavity which contains air into spaces that usually under normal circumstances do not have air [Adeyinka & Pierre, 2018].

• Sealant is a material applied to a joint in paste or liquid or patch form that hardens or cures in place, forming a barrier against gas or liquid entry [Turner Benedict].

• Pubmed: lung sealant = 168 papers.
SEALANTS

• NATURAL/BIOLOGICAL

• SYNTHETIC

• SEMISYNTHETIC

• Milenkovic et al, 2018
NATURAL/BIOLOGICAL SEALANTS

• Fibrin/Plasma sealants.
• Fleece-bound sealants (with collagen patch).
WHAT IS FIBRIN?

- **Fibrin** (also called **Factor Ia**) is a fibrous, non-globular protein involved in the clotting of blood.
- **It is formed by the action of the protease thrombin on fibrinogen** which causes it to polymerize. The polymerized fibrin together with platelets forms a hemostatic plug or clot over a wound site.

- **Fibrin glue** (also called **fibrin sealant**) is a surgical formulation used to create a fibrin clot for hemostasis, aerostasis or wound healing.
WHAT IS FIBRIN GLUE?

• **Fibrin glue** is made up of (1) **fibrinogen** (lyophilised pooled human concentrate) and (2) **thrombin** (bovine, which is reconstituted with calcium chloride) that are applied to a site of tissue damage to glue them together.
Thrombin is an enzyme and converts fibrinogen into fibrin monomers between 10 and 60 seconds giving rise to a three-dimensional gel.

• Formulations from different manufacturers may contain **aprotinin** (or another anti-fibrinolytic product), **fibronectin**, and **plasminogen**.

• Fibrin glue is the most common adhesive agent used in surgical practice [Carvalho et al, 2017].
Schematic representation of the technique used to seal a visceral pleural defect by the **intraparenchymal injection of a fibrinogen solution** beneath the defect, combined with the **prior instillation of a thrombin solution on its surface**, to form an infiltrating fibrin layer (rats) => **a superior resistance to airway pressure**[Yamamoto et al, 2016].
## Advantages of Biological/Natural Sealants

<table>
<thead>
<tr>
<th>Advantages</th>
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<td>• Improve surgical outcomes due to <strong>shortened operating time</strong>,</td>
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<td>• lower infection rates and other complications, as well as</td>
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<td>• a <strong>reduction in both air and blood loss</strong>.</td>
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<td>• A good choice in <strong>vascular surgery</strong>, providing an effective means of</td>
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<td>sealing anastomoses prior to blood vessel pressurization and</td>
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<td>vascular clamp removal.</td>
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<td>• <strong>Low inflammation and rapid degradation compared</strong> with those of other</td>
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<td>sealants [Carvalho et al, 2017].</td>
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<td>• They are fully <strong>biodegradable</strong>.</td>
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<td>• In rabbits, after FB sealant, the lung reaction was similar to that</td>
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<td>• The FB are most common sealants used in surgical practice (=&gt; a lot of</td>
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<td>surgical experience).</td>
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Adverse effects/Disadvantages of Biological (Natural) Sealants

• Tranfer of infection (spongiform encephalitis).
• Thromboembolic events.
• Anaphylaxis, sometimes fatal (=> autologous sealant? [Moser et al, 2008]).
• Lack of well designed randomized clinical trials and cost-effectiveness data [Cardillo et al, 2012 / Manell & Gibran, 2014].
• Unclear efficiency [Carvalho et al, 2017].
SYNTHETIC SEALANTS

- Synthetic sealants are usually composed of polyethylene glycol (PEG) or cyanoacrylate and polymers and at least one additional component.

- They are biodegradable agents that are used to act as a fluid barrier, as hemostatic agents and as aerostatic agents.

- They quickly form an adhesive bond and degrade in 1 - 6 weeks.
Cyanoacrylates

- They were **invented in 1942** by the chemist Harry Coove.
- They are liquid monomers that rapidly form polymers in the presence of water and **thereby quickly glue adjacent surfaces together**.
- Octyl-2-Cyanoacrylate achieves its maximum bonding strength within **2.5 minutes of applications**.
- Cyanoacrylates **require moisture** (a small amount) to affect adhesion.
- Cyanoacrylates have **hemostatic and aerostatic effects**.
During the Vietnam War **Cyanoacrylates** were sprayed over open bleeding wounds in an effort to retard bleeding.
Advantages of Synthetic Sealants

• Lower rate of infections.
• Lower rate of anaphylaxis.
• They very quickly achieve their strength.
• “Clear” efficiency [Carvalho et al, 2017].
• Shortened operating time.
Disadvantages of Synthetic Sealants

- They may be more expensive than other products.
- Less common use than FB (=> less surgical experience).
- Cyanoacrylate (CA) may be degraded very slowly in rabbits [Carvalho et al, 2017].
- Intense local reaction: In rabbits, after CA, the lung reaction was different to that observed in the normal phases of scar formation, i.e. a dense lymph-mononuclear inflammatory infiltration with lymphoid aggregates, permeated by cavitation areas [Carvalho et al, 2017].
- CA: Doubtful Biocompatibility [Carvalho et al, 2017].
- CA: Concerns regarding local toxicity = conflicting studies [Carvalho et al, 2017].
SEMISYNTHETIC SEALANTS

• In an effort to have the advantages of both biological and synthetic sealants...

• **Examples:** A single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum **albumin** (HSA) and (2) a synthetic cross-linking component of **polyethylene glycol (PEG)** that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed.

• Serum **albumin** and **glutaraldehyde**. “*Release of glutaraldehyde...causes significant in vitro and in vivo toxicity*” [Fürst, & Banerjee, 2005].
BUTTRESSING MATERIALS

- Bovine pericardium
- Parietal pleura
- Teflon felt
- ePTFE
- Small Intestinal Submucosa (SIS)
- Biosyn
- BASG
- PGA-TMC

This reinforcement occurs by placing a thin piece of material between the tissue and the stapler. After the stapler is fired, the material can reduce the tension in the staple line, seal the staple holes, and reduce the distance between the staples, which decreases leakage, bleeding, and tearing.
DISCUSSION

SURVEY: How often do you use sealants in your practice?

• The survey (n=240) clarified that only a minority of surgeons use sealants routinely in their practice (8%). Conversely, 54% use these products only when indicated, while 21% prefer to have sealants available in the hospital for an exceptional use.

• Worthy of note is that 17% of the participants felt that the use of sealants is limited by their cost [Rocco et al, 2009].
Specific Characteristics

Lung sealants must demonstrate specific characteristics due to the morphologic, functional and immunologic organ complexity:

- Respiratory movements pose additional stress to the reparation site; therefore, strong adhesiveness to the tissue is desirable.
- However, to preserve elastic recoil of the lung, sealant/adhesive should be highly elastic and flexible, as well.
- Nonsterile and potentially septic environment in lungs can predispose wound infection.

- Milenkovic et al, 2018
SPECIFIC CHARACTERISTICS

• **Lungs** are very immunogenic, so sealant should be **biocompatible and biodegradable** to avoid inflammation.

• Potential air or liquid leakages during lung surgery necessitate sealants that tolerate high pressure and wet environment.

• Concerning the complex vascularity of the lungs, sealant/adhesive should also have the function of **hemostasis**.

• **Limited space** sometimes complicates suturing, so sealant/adhesive can be delivered through applicators; in addition, **endoscopic procedures** can be a possible method to deliver sealant.

• *Milenkovic et al, 2018*
An ideal lung sealant:

• should **bind rapidly to lung tissue** in the presence of air, blood, or moisture,
• be able **to withstand inflation procedures of greater than -40 cmH$_2$O**,
• have sufficient flexibility and compliance to permit lung inflation and deflation,
• **absorb** without a trace,
• **be nontoxic**, and
• **eliminate air leaks** [Toker Alper].
DO THE SEALANTS HELP?

• In the survey \((n=240)\) although 49\% of the surgeons seemed **convinced** that sealants do work, they recognize that no definitive evidence is available and 34\% were **uncertain** as to their possible clinical usefulness.

• Not surprisingly, 17\% of the surgeons declared their **skepticism** and their **willingness to be guided in the selection of these products by experts from industry**.

• Major criticisms elicited by currently available studies include the lack of a precise methodology, the usually limited numerosity, the deficient information of the relationship between companies and surgeons testing a sealant, and the presence of significant confounding factors (i.e. postoperative air leak assessment).

• In addition, the definition of costs and reimbursement policies are often a neglected, albeit crucial, point of discussion.

*Rocco et al, 2009*
DO THE SEALANTS HELP?

• “The pleural sealant appears to be safe for patients and is easy for surgeons to apply....No differences in drainage or hospitalization were observed... In this multicenter European study (n=121, sealant group=62 / control group= 59) the use of the pleural sealant significantly reduced intraoperative air leaks after lobectomy. In patients with clinically significant air leaks (grade 2 and 3), significantly fewer patients had postoperative air leaks when treated with the pleural sealant. However, this did not result in a significantly shorter duration of chest drain use and length of hospital stay” [De Leyn et al, 2011].

• “(n=121) The results of this single-center, single surgeon, retrospective review demonstrate a significant reduction in IOAL, chest tube duration, and length of hospital stay in the in patients treated with the sealant...” BUT: “Lung sealants have been shown to help control IOAL’s with a few studies demonstrating a reduction in chest tube duration and/or length of hospital stay” (e.i. Anneg et al, 2007) [Klijian, 2012].
DO THE SEALANTS HELP?

• “Whereas synthetic sealants more reliably decrease the occurrence, magnitude, and duration of air leak than do fibrin sealants, this does not translate consistently into a substantial reduction in the duration of chest tube drainage or hospital stay” [Burt & Shrager, 2014 / Belda-Sanchis et al, REVIEW, 2010].

• “Our results (n=154) indicate no benefit from the use of the two aforementioned sealants in management of intraoperative air leak with respect to hospital stay” [Al-Sahaf et al, 2015].
DO THE SEALANTS HELP?

• “Surgical sealants can be effective in reducing the percentage of patients who have a visible AAL (Alveolar Air Leak) at the conclusion of an operation. However their overall benefit has not been established. Studies do not consistently show that sealants reduce the time to removal of chest drains, decrease the hospital length of stay, or reduce the duration of postoperative air leaks” [Ferguson, Merritt, (textbook), 2014].
DO THE SEALANTS HELP?

• “This article reviews the contemporary literature...An evidence-based analysis of the current literature does not support routine use, prophylactically or for air leaks present at operation, of sealants or buttressing material in pulmonary surgery” [Rice & Blackstone, 2010].

• “Lung sealants are still evolving and this is the proof that the quest for the perfect sealant continues" [Toker Alper].
DO THE BUTTRESSING MATERIALS HELP pts **without** severe emphysema?

- Venuta F. et al (*n=30*), 1998, bovine pericardium, => decreased AALS and decreased hospital stay.

- Miller J.I. Jr et al (*n=80*), 2001, bovine pericardium, reduced duration of AALS and no significant difference hospital stay.
  - [Ferguson, Merritt, 2014].
DO THE BUTTRESSING MATERIALS HELP pts with severe emphysema?

- Stammberger U. et al, randomized three-center study (n=65, bilateral VATS LVRS, 2000), bovine pericardium => significant decrease in AAL (incidence and duration), shorter median drainage time, reduced (but with no statistically significance) hospital stay.
  - [Ferguson, Merritt, 2014].
- Moser et al. (2008) pointed that buttressing adjuncts might result in the extensive inflammatory reaction (potential infective and antigenic risk) with formation of dense adhesions, which enhances difficulty of lung transplantation after LVRS.
  - Huang et al, 2011
CONCLUSIONS

• Evidence: Staple lines in severe emphysematous patients should be **buttressed** to reduce the incidence of air leak when performing non-anatomic pulmonary resections such as LVRS (Evidence quality moderate; weak recommendation), [but: difficulty of lung transplantation?]

• **Lung sealants** have been shown to help control IOAL’s.

• But only a few studies demonstrating a reduction in chest tube duration and/or length of hospital stay. We need well designed randomized clinical trials.

• The quest for the perfect sealant continues.

• Recommendations: There is no current evidence to support the routine use of lung sealants for reducing the incidence of prolonged postoperative air leaks (evidence quality moderate; weak recommendation) => Use of a sealant according to the needs of the particular patient, the presence of a visible IOAL, the surgeon’s personal experience/preference and the budget of the department (cost/availability).
What is the future?

- ACS Appl Mater Interfaces.
- Published online 2017 Jul 6.

**Anti-Cancer** Therapeutic Alginate-Based Tissue Sealants for Lung Repair (Doxorubicin)

- Spencer L. Fenn, Patrick N. Charron, and Rachael A. Oldinski


• Ferguson M.K., Merritt M.E. Difficult Decisions in Thoracic Surgery: An Evidence-Based approach, [Use of topical Sealants], p. 604, 2014


KEFALONIA ISLAND (GREECE)

I THANK YOU VERY MUCH FOR YOUR ATTENTION!
Sir Charles James Napier
Governor of Kefalonia Island
(beg. 19th cent.)
An Exception: A Conqueror but a Benefactor too.

I THANK YOU VERY MUCH FOR YOUR ATTENTION!