Thesis Proposal

Title: Modeling the Avalanche Phenomenon to Optimize Ventilator Settings in Cases of Mechanical Ventilation (Acute Respiratory Distress Syndrome)

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Abstract
Acute Respiratory Distress Syndrome (ARDS) is common in intensive care and is associated with high mortality, particularly during the COVID-19 pandemic. Mechanical ventilation is essential but can cause lung injury, notably through the cyclic opening and closing of alveoli and airways with each respiratory cycle.

Significant data suggests complete airway closure in a large proportion of ARDS patients. However, animal and mathematical models suggest that some pulmonary regions continue to open beyond the airway opening pressure. The size distribution of these reopened lung regions and the time intervals between them during pulmonary inflation follow a power-law distribution, akin to avalanches.

Our objectives are to describe the prevalence of this "avalanche" phenomenon in ARDS and to study the behavior of lung elastic pressure during pulmonary deflation.

We plan to include 50 adult patients with moderate-to-severe ARDS and perform low-flow pressure-volume curves between 5 and 40 cm H2O. Pressure and flow signals will be recorded for research purposes.

If the "avalanche" phenomenon is confirmed in humans, it could guide ventilator settings to minimize cyclic opening and closing of lung regions, thereby reducing ventilation-induced lung injury.

State of the Art with General and Scientific Interest
ARDS is characterized by hypoxemia caused by acute inflammatory lung edema (ARDS Definition Task Force et al., 2012). It results from various injuries, including infections (e.g., COVID-19-related pneumonia) and non-infectious injuries (e.g., pancreatitis or non-cardiogenic shock) (Ferguson et al., 2012). ARDS typically accounts for 10% of all ICU admissions and 23% of mechanically ventilated patients (Bellani et al., 2016). During the COVID-19 pandemic, these rates increased significantly, with over 2,500 ARDS patients admitted to French ICUs in two months (COVID-ICU Group et al., 2021). Despite advancements in management, ARDS remains associated with high mortality rates, reaching 40–50% in severe cases (Bellani et al., 2016; COVID-ICU Group, 2021).

While lifesaving, mechanical ventilation can exacerbate lung injuries. Experimental studies (Dreyfuss et al., 1988; Webb & Tierney, 1974), later confirmed by a major clinical trial (ARDS Network et al., 2000), showed that ventilation with low tidal volumes and inspiratory pressures was associated with reduced "overdistension"-related lung injuries. However, low tidal volume ventilation can lead to cyclic lung collapse during expiration and reopening during inspiration, causing atelectrauma and subsequent lung injury, as suggested by experiments (Broche et al., 2019; Muscedere et al., 1994) and autopsy findings (Rouby et al., 1993).

Complete airway closure can be detected at the bedside using a low-flow inflation pressure-volume curve (Chen et al., 2018). In some patients, the initial slope of the curve is very flat, then sharply increases above a threshold known as the airway opening pressure.

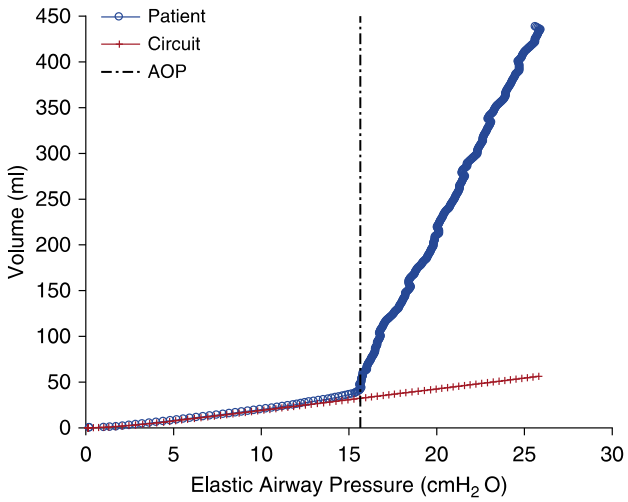

Figure 1. Low-flow inflation pressure-volume curve in an ARDS patient with airway closure. The blue line represents airway pressure, the red line shows pressure evolution in an occluded circuit, and the dashed black vertical line indicates the airway opening pressure.

This elasticity modification (ΔPressure/ΔVolume) has been reported in approximately 40% of ARDS patients. In ex-vivo experiments, this phenomenon occurs only in air-filled lungs and is absent in liquid-filled lungs (Hughes et al., 1970).

However, lung pressure does not increase linearly beyond the airway opening pressure. In low-flow inflation of isolated animal lungs, intermittent pressure drops during volume increases (negative elasticity, Figure 2) have been observed above the airway opening pressure (Alencar et al., 2002; Suki et al., 1994). This suggests reopening of new lung segments and pressure propagation through the airway tree: during inflation, if pressure exceeds the opening pressure of downstream airways, these open, leading to the reopening of further lung segments and pressure propagation deeper into the airway tree. The probability distribution of these negative elasticity events and their timing during inflation shows a power-law distribution, similar to avalanches (Alencar et al., 2002; Suki et al., 1994).

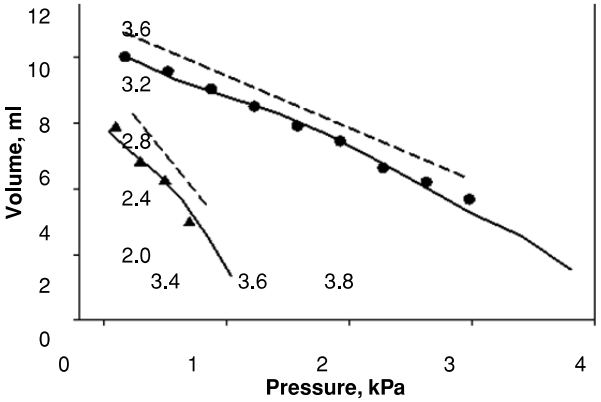

Figure 2. Low-flow inflation pressure-volume curve in an isolated rat lung. The initial portion of the curve is flat, suggesting complete airway closure. As the volume increases, the pressure drops (negative elasticity), indicating the opening of new lung segments (Béla Suki & Stamenović, 2011).

To date, such an avalanche phenomenon has not been described in humans. We hypothesize that previous reports missed it due to insufficient sampling rates during low-flow inflation pressure-volume curve measurements.

Research Hypotheses
We hypothesize that the avalanche phenomenon occurs in ARDS patients with airway closure.

Study Objectives
Our primary objective is to describe the prevalence of the avalanche phenomenon in ARDS patients to optimize ventilator settings.
Our secondary objective is to describe the low-flow deflation curve in ARDS patients with airway closure.

Scientific and Medical Context (National and International)
Airway closure in ARDS patients has been studied by a few teams. The first description was made by Chen in 8 of 30 ARDS patients (Chen, 2018). Subsequent studies reported its incidence in small ARDS cohorts (Yonis, 2018; Guérin, 2020). In collaboration with the team that first described airway closure, we investigated its mechanisms (Coudroy, 2019) and showed that surfactant depletion was associated with airway opening pressure and the mechanical determinants and consequences of airway closure (Coudroy, 2020).

The avalanche phenomenon has been described by only one research team (Boston, MA, USA) in experimental animal models (Suki, 1994, 2000; Alencar, 2002; Hantos, 2004) and mathematical models (Suki, 1998). It has never been described in humans.

Research Plan

1. Finalizing a laboratory prototype:
    - Pressure-controlled actuator.
    - Pressure/flow measurements at the entry of a flexible structure (artificial lung).
    - Testing campaigns for various artificial lung configurations.

2. Data processing from the artificial lung and clinical data. Characterization of clinical data (non-stationary nature) related to the avalanche phenomenon.
3. Modeling:
    - Step 1: Macroscopic lung approach.
    - Step 2: Lung model with initial bronchial tree levels.
    - Step 3: Lung model with full bronchial tree.
4. Combining models: power-law model (clinical) and physical model (fluid mechanics).
5. Experimental data exploitation to build a database and use machine learning to refine the model.
6. Ventilator control to ensure effective breathing without causing lung damage.