PROPOSED RESEARCH: Role of dyspnea in the progression of pediatric acute respiratory distress syndrome.

In this section, you are required to develop your proposal by addressing the following aspects: a) Theoretical-conceptual foundations and state of the art supporting the proposal, b) Research hypothesis or questions and objectives, c) Methodology, d) Work plan or Gantt chart, e) Background information demonstrating the capacity of the research team to carry out the proposed work and f) Scientific or technological novelty of the proposal.

A) Theoretical-conceptual and state-of-the-art developments

1. Pediatric acute respiratory distress syndrome: a relevant and global problem.

Pediatric acute respiratory distress syndrome (ARDS) is a life-threatening clinical syndrome characterized by rapid-onset hypoxemia of non-cardiac origin, bilateral pulmonary infiltrates, and decreased lung compliance (1). It is a common condition, triggered mainly by viral pneumonia, affecting up to one in four critically ill children, with a mortality rate ranging from 30% to 40%, even in the best pediatric hospitals worldwide (2,3). The outbreak of ARDS patients overcrowds the adult and pediatric emergency rooms and intensive care units (ICUs) every year during the seasonal respiratory viral epidemics, becoming a global public health problem. Additionally, many potentially pandemic viruses cause ARDS, further straining the healthcare system; recent examples include Influenza A (H1N1), SARS-CoV-1, and SARS-CoV-2 pneumonia. Recently, ARDS associated with SARS-CoV-2 pneumonia was the leading cause of death in adults in Chile during the COVID-19 pandemic (4), and the leading preventable cause of death worldwide (5). Meanwhile, in children under 5 years old, pneumonia is the second leading cause of death in the Americas, and the third leading cause of death worldwide (5). Mechanical ventilation (MV) is the standard of care for patients with moderate to severe ARDS. Nevertheless, it is also associated with complications, such as ventilator-associated pneumonia, disuse muscle atrophy, and airway injury, among others (6). Hence, over the last 20 years, there has been considerable interest in reducing risks directly related to MV. There is a particular emphasis on noninvasive respiratory support therapies, defined as the administration of support averting endotracheal intubation, preventing MV. However, experimental studies and indirect clinical information have given a counterpoint to this approach, suggesting that strenuous respiratory effort for extended periods can also be a *"second hit"* for the lungs, a phenomenon recently known as **"patient self-inflicted lung injury"** (7,8). Patient self-inflicted lung injury emerges as one of the main preventable mechanisms of ARDS progression (9,10). The disconnection between both extremes (to breathe or not to breathe) may lie in the **difficulties in assessing respiratory effort in critically ill patients at the bedside**. This is particularly relevant in three transitional phases of pediatric ARDS, characterized by sudden changes in respiratory effort: in the acute phase, when clinicians judiciously try to prevent intubation, in an intermediate phase (transition from controlled to assisted MV), and in a late phase (weaning from MV) (see below).

2. Dyspnea: relevance & components

Dyspnea is the key symptom in all phases of pediatric ARDS. Since the origins of medicine, clinicians have been extremely concerned regarding dyspnea, but unfortunately, we lack widely used and available tools to directly assess it in real time and bedside, because of its subjective and qualitative nature. Usually, dyspnea has been considered a warning of severity: the more severe the dyspnea, the more severe the ARDS (11). Many semiquantitative dyspnea scores have been attempted, but their lack of validation against a gold standard has discouraged their wide use (12). Meanwhile, the emergence of the concept of patient self-inflicted lung injury renewed the protagonism of dyspnea, being also implicated as a mechanism of ARDS progression (9). ARDS patients usually have a high respiratory drive due to acidosis, hypoxemia, inflammation, and locally generated stimuli in the lungs (13). A vicious circle of high respiratory drive, strong respiratory effort, increased work of breathing, and progression of ARDS leads to a higher drive (14). Currently, the personalization of respiratory support and the improvement of pharmacological and non-pharmacological interventions aimed at relieving dyspnea are a transversal hot topic in critical care medicine (15).

3. Quantification of dyspnea at the bedside

Dyspnea is a multidimensional experience (11). Its evaluation is based on three closely interrelated yet distinct components: **respiratory drive, respiratory effort, and work of breathing** (16). These components are not necessarily proportional to one another. For example, a patient with severe muscle weakness may exhibit a high respiratory drive but a weak respiratory effort. Even in critically ill children without muscle weakness, the independence between respiratory drive and effort was also recently reported

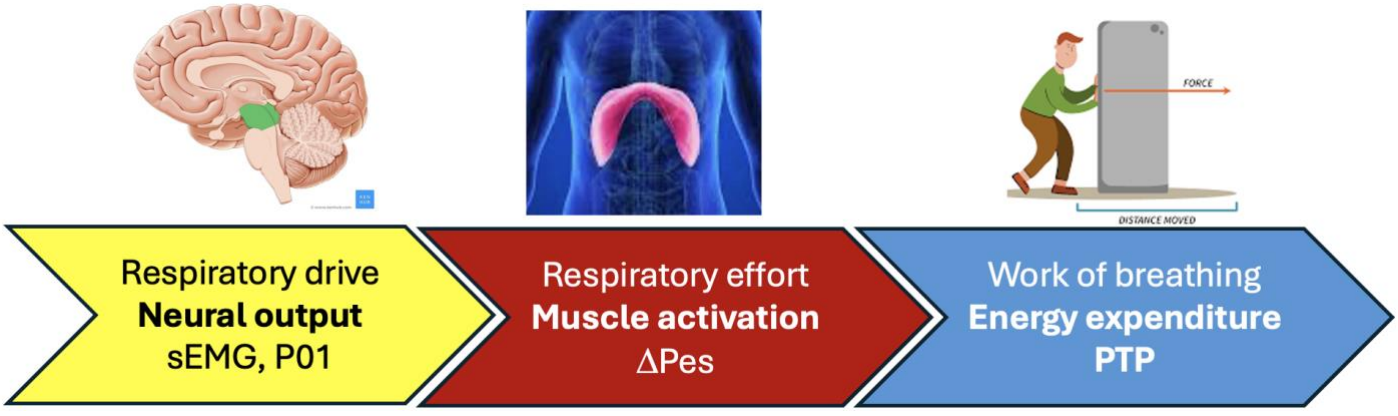
(17). It is important that clinicians can assess each of these components to individualize decisions regarding the adequacy of respiratory support. These three concepts are often used interchangeably in the literature, yet there are important distinctions that we will outline below (Figure 1):

Respiratory drive is the response of the respiratory center to the interaction of various afferent pathways. It is the intensity of the **neural output** of the respiratory center to breathe. The intensity and speed of the response depend on feedback from four main afferent sources: biochemical, mechanical, emotional, and inflammatory (17,18). An increased drive leads to a rapid, shallow breathing pattern, with recruitment of respiratory accessory muscles. The bedside gold standard to assess respiratory drive in mechanically ventilated patients is the **airway occlusion pressure** (P01), which represents the drop in airway pressure during the first 100 milliseconds after an occlusion at the end of expiration. It is a tool used to predict the outcome of weaning from MV and to customize the ventilatory support. A P01 greater than 3.5 cmH2O has a sensitivity of 92% and a specificity of 89% for detecting excessive respiratory drive in adults, but there is no cut-off point in children (19-22). P01 appears to be independent of lung mechanics and diaphragm function, even if the patient has air trapping (23,24). Assessing respiratory drive in patients without MV is extremely challenging today and can only be accurately evaluated through **electromyography of the respiratory muscles** (18), but unfortunately, this does not provide an online quantification.

Respiratory effort is the intensity of the patient's **breathing activity by the respiratory muscles**, influenced by both the efference emanating from the respiratory center and the viscoelastic properties of the respiratory system. The term "effort" integrates time and type of muscle contraction, since not every contraction generates a volume change (i.e., ineffective efforts), but it does generate energy consumption (25). Respiratory muscle activity associated with spontaneous breathing produces a swing of negative pleural pressure. Since esophageal pressure is a surrogate for mean pleural pressure, the **swing of esophageal pressure** is the gold standard to quantify in real-time the respiratory effort at the bedside (26,27).

Work of breathing is the work during an entire respiratory cycle needed to overcome the resistance and elastance imposed by the respiratory system. It is carried out by the respiratory muscles during spontaneous ventilation, or by the mechanical ventilator during controlled and assisted MV, or by both during weaning from MV. So, in the absence of respiratory effort, work of breathing is still present in ICU patients. In spontaneous breathing, the work of breathing indicates **energy expenditure of respiratory muscles** in a parameter known as the **pressure-time product** (PTP). It is calculated as the time integral of the product of pressure and flow: work of breathing = ∫ pressure × flow x dt, involving the entire **thoraco-pulmonary system**, being the gold standard for assessment in both children and adults (28-30). Novel pneumotachographs now incorporate its real-time quantification.

Figure 1. The evaluation of dyspnea is based on three closely interrelated yet distinct and quantifiable components: respiratory drive, respiratory effort, and work of breathing.



4. Strong respiratory effort: a second hit in the acute phase of ARDS

Experimental studies suggest that ARDS may progress due to the patient's strenuous respiratory effort. According to our recent publications, strong respiratory effort leads to increased lung stress and strain, magnifying primary lung injury (31-34). Strong respiratory effort produces intense negative oscillations in pleural pressure, with the consequence of increased transpulmonary pressure and lung perfusion (31). This "*second hit*" occurs mainly on the vascular side of the blood-gas barrier, being morphologically characterized as edema, hyperemia, and alveolar hemorrhage, decreasing regional and global lung aeration (33). But this injury is not exclusive for the lungs; also, load-induced diaphragm injury (or *under-assistance myotrauma*) may occur. Specifically, we reported edema, inflammation, fragmentation of muscle fibers, and even necrosis after only 3 hours of unassisted respiratory effort (34). In a clinical setting, indirect studies have suggested the role of strenuous respiratory effort in the progression of ARDS, highlighting the worse outcome related

to delayed intubation (35). This strongly motivates clinicians to quantify components of dyspnea and lung mechanobiological consequences, aiming for the early detection of lung function decline, before the lung injury progresses to a more evident and less reversible stage.

5. The fragile transition from controlled to assisted MV: dyspnea returns

The acute phase of ARDS is not the only period involving transition between spontaneous ventilation and controlled MV. This transition also occurs sequentially in reverse during two key phases: **the shift from controlled to assisted MV and later, during weaning**. The volume that renews the alveolar gas is displaced by a pressure gradient generated by the contraction of the respiratory muscles and, under respiratory support, by the mechanical ventilator, partially or totally. **In controlled MV, the ventilator delivers the preset volume or pressure regardless of the patient's respiratory effort.** After intubation, controlled MV is commonly used to promote lung protection and allow respiratory muscles rest, thereby reducing energy expenditure (36). Accordingly, a reduction of mortality associated to abolition of respiratory effort due to neuromuscular blockade has been reported in severe ARDS (37). **In assisted MV, the ventilator delivers a preset number of breaths, and the patient may also trigger additional breaths by making a sufficient respiratory effort**. **All respirations (preset and patient-initiated) are performed by the ventilator,** which continues to assume the work of breathing. After achieving clinical stability, assisted MV offers several advantages over controlled MV, avoiding overuse of sedation and paralysis, improving intrapulmonary gas distribution, and preventing ICU-acquired weakness (38). So, controlled MV is primarily used in moderate to severe ARDS, but after stabilization is achieved, a transition to assisted MV begins, during which respiratory muscles progressively return to their normal function. **This transition is complex because it is difficult for the clinicians to configure an adequate level of assistance** and avoid the risks related to under- or over-assistance (patient self-inflicted lung injury and load-induced diaphragm injury, and ICU-acquired weakness, respectively) (39). The key strategies during this phase include preventing excessive respiratory effort, improving the patient-ventilator synchrony, and avoiding lung overstretch and collapse. Therefore, **esophageal manometry and electrical impedance tomography**, respectively, are the gold standard bedside techniques to quantify respiratory effort and early detection of regional lung phenomena in vulnerable lungs. During transitional phases of MV, it has become an emerging therapeutic goal to maintain the patient's effort at physiological levels, integrated in the recent conception of **lungs- and diaphragm-protective ventilation** (40). Despite its importance, the transition from controlled to assisted MV remains poorly studied in critically ill children.

6. Strong respiratory effort: a second hit during weaning from MV

Weaning from MV is the transition from assisted MV to spontaneous ventilation, being another fragile phase where the **patient fully resumes the work of breathing**. **Weaning failure is associated with 30% mortality in children** (41). Although the causes of weaning failure are varied, it has recently been identified that a subgroup of patients develop ***"weaning-induced pulmonary oedema"***. When the positive pressure is decreased and the work of breathing is assumed by the respiratory muscles, the intrathoracic pressure becomes negative again, which leads to a sudden increase in venous return, preload of the right ventricle, and afterload of the left ventricle, inducing acute lung edema and a catastrophic weaning failure. This, together with the adrenergic response associated with increased work of breathing, increases oxygen uptake, causing the heart to fail due to the inability (preexisting or not) to adapt to these demands of delicate heart-lung interdependence (42). Weaning-induced pulmonary oedema leads to increased morbidity, hospital stay, health costs, and mortality (43,44). This entity shares pathophysiological bases with the concept of patient self-inflicted lung injury (45). **Thus, quantifying components of dyspnea is a cornerstone for the early detection of excessive respiratory drive, effort, and work of breathing during weaning from MV**. These factors can negatively impact the outcome in critically ill children. Accordingly, a clinical trial was recently reported in which the use of a computerized decision support tool based on esophageal manometry, called REDvent, shortened the weaning phase in critically ill children. This study reaffirms the importance of quantifying respiratory effort to personalize decision-making (46).

7. Quantification of components of dyspnea in critically ill children

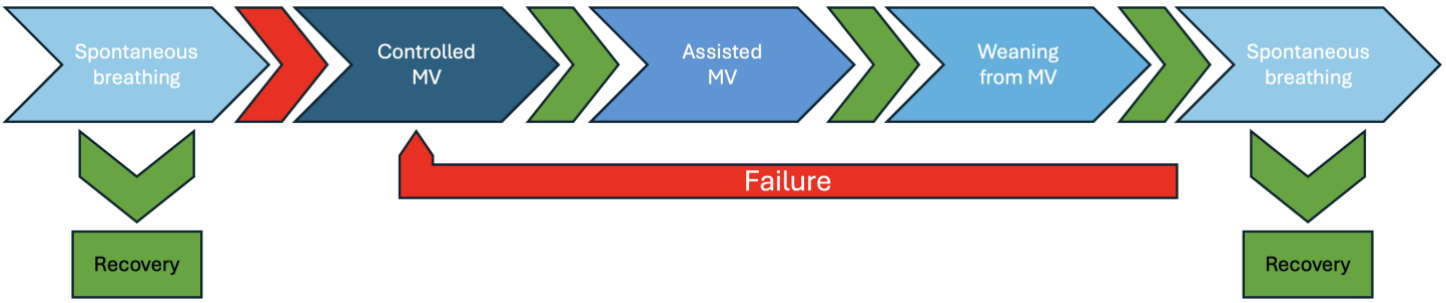
Infants, the population most affected by pediatric ARDS, cannot express the sensation of dyspnea. Respiratory rate is a sensitive but nonspecific marker of respiratory effort, due to the diversity of respiratory patterns in dyspneic patients, ranging from rapid and shallow to slow and deep. Clinical assessment of respiratory compensatory symptoms (nasal flaring and accessory inspiratory and expiratory muscles activation) is sensitive but subjective, affected by the clinician's training and the amount of the patient's adipose tissue. Thus, **clinical assessments of components of dyspnea are not sufficiently accurate** (12). Sensitive and specific tools to quantify components of dyspnea are required.

Regarding **respiratory drive**, most modern mechanical ventilators incorporate **P01** (16). In spontaneously breathing children, respiratory drive can be quantified noninvasively through **surface electromyography of the respiratory muscles** (sEMG) (18). The advantages of sEMG are the direct measurement of respiratory drive at the bedside, noninvasive nature, and the compatibility with any respiratory support therapy (18). But on the other hand, it requires offline analysis by personnel trained in EMG interpretation, impossible to perform in real-time, unlike P01 (17).
Measurements based on esophageal manometry, **swings of esophageal pressure, and pressure-time product**, are considered the gold standard to quantify **respiratory effort and work of breathing**, respectively (25-30). Esophageal pressure is measured using an **esophageal catheter**. There are various models available, including some specifically adapted for enteral feeding in children. As an advantage, they are **no more invasive than a standard enteral feeding tube**, widely used in children with ARDS (47).

8. Recognition of ARDS Progression During Ventilation Transitions: Current Definition

The obvious consequence and primary outcome during each transitional phase of MV is the success or failure of the respiratory support therapy used, defined by escalation of ventilatory support provided due to oxygenation decline. Thus, failure of spontaneous ventilation indicates the need to connect to MV. Concordantly, the need to return to controlled MV during stepped weaning phases is also considered a failure (Figure 2). Unfortunately, in all cases, **failure indicates that the ARDS has already worsened; therefore, progression is associated to higher mortality** (35,48,49). **Currently, the early detection of ARDS progression at the bedside is another hot topic in critical care medicine.** There is recent experimental evidence, some reported by our team, that supports the ability of **regional imaging techniques** to detect this progression promptly (31,32,50-57).

Figure 2. Transitional phases of pediatric ARDS. Green arrows represent the success of the respiratory support therapy used. In opposite, red arrows represent its failure.



9. Biomechanical framework for amplification of lung injury: global and regional deformation

The lung can be described as a pre-stressed network of viscoelastic tissue elements deformed by surface tension and the action of respiratory muscles. This characteristic allows deformation in a time-dependent manner upon applied pressure and return to its initial configuration once the pressure is relieved (58). **Breathing produces a phenomenon of continuous cyclic strain deformation throughout life**, where the applied pressure is the inspiratory pressure. In biomechanical terms, deformation in the lung is measured as strain, which is defined as the ratio between the tidal volume and a reference volume, typically the air volume at the end of passive expiration, the functional residual capacity. **High values of global lung strain deformation are associated with increased mortality in ARDS patients under MV** (59). Indeed, improved clinical outcomes were observed in ARDS patients ventilated with a low tidal volume strategy resulting from the reduction of global lung deformation (34). Understanding the global deformation in the lung has allowed the identification of safer tidal volume thresholds to prevent ventilator-induced lung injury, currently present in all guidelines and consensuses (60,61).

10. Changes of regional lung aeration as an early sign of ARDS progression during controlled MV

The existence of a single 'global' deformation injury threshold is doubtful, considering the heterogeneity of ARDS lungs and the uncertainty regarding the topographical distribution of strain. In injured lungs, there is a broad spectrum of tissue aeration, leading to inhomogeneity of ventilation (62). **Lung inhomogeneity** has been recently proposed as an **injury promoter in ARDS**, given that lung injury can occur despite using a recommended tidal volume and pressures that are considered safe in the ventilation of healthy lungs (62). **"Stress raisers"** are regional strain deformation phenomena capable of amplifying the stress applied in certain localized regions of the lung, appearing in areas of high ventilation inhomogeneity (50,51,63). The harmful effects of high lung regional deformation were confirmed recently in two models of injurious MV, where this is spatially correlated with tissue inflammation (52-54). These studies highlight the relevance of

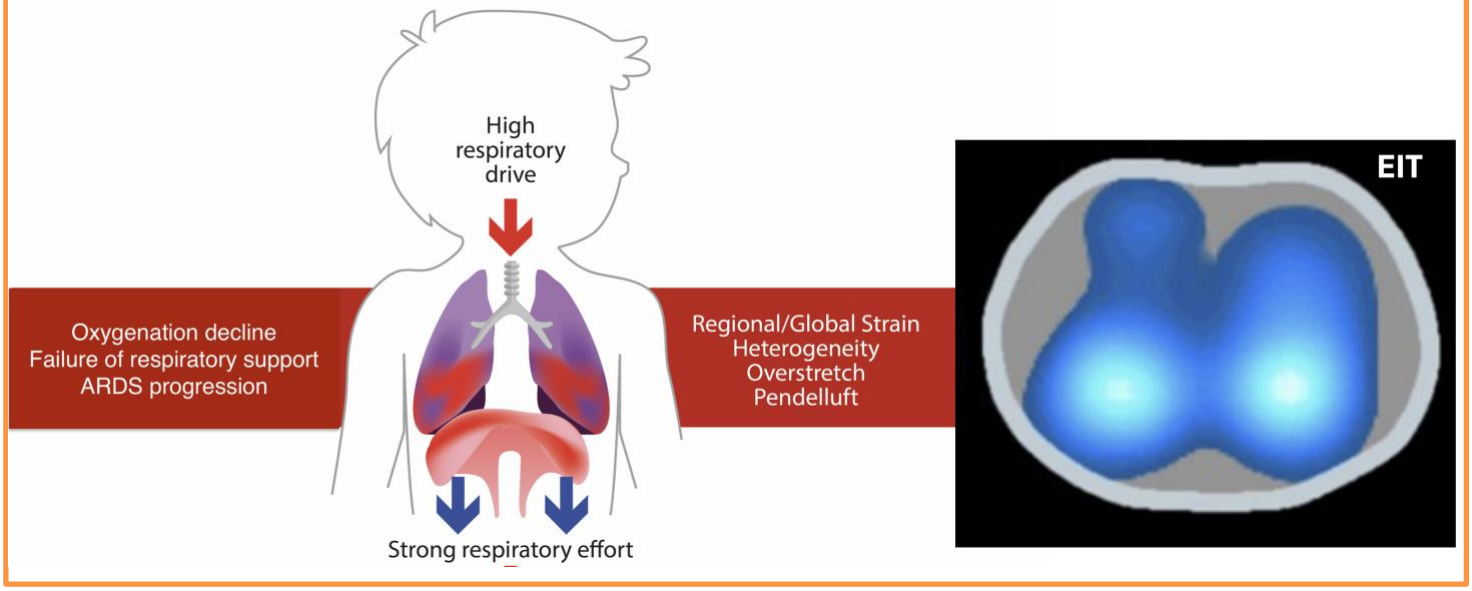
a better understanding of the **spatio-temporal progression of regional strain**, supporting that it is a relevant and prominent "stress raiser" and determinant of **ARDS progression**. Accordingly, clusters of lung tissue based on regional changes in lung aeration **confirmed the role of regional phenomena in the progression of ARDS, and their dynamic nature**, as we recently identified (55).

11. Changes of regional lung aeration as an early sign of ARDS progression during spontaneous ventilation

There is a **paradox regarding respiratory effort and progression of ARDS** during spontaneous ventilation. When the **effort is mild** and the ARDS is non-severe, it improves ventilation in dorsal regions, lung perfusion, and the ventilation–perfusion mismatch. On the contrary, if the **effort is strong** and the ARDS is severe, it promotes regional overstretching, lung edema, and an imbalance between ventilation and perfusion, being a *"second hit"* to the injured lungs (64,65). The internal gas movement (Pendelluft effect) can result in stress raisers such as tidal recruitment, local overstretch, and inhomogeneity, and thereby aggravate injury of the dependent lung regions (64). This paradox can be explained by the **magnitude of the effort and the biomechanical behavior of the lungs**, supported by the theory of fluid-like and solid-like behavior (65). As we have identified in all our studies, **early effects of respiratory effort on lung function occur regionally** (9,31,32,56,65). However, if the injury persists, hypoxemia and lung collapse will eventually progress (31,33,34,56,65). The role of changes in regional aeration during spontaneous ventilation is less known and based on experimental studies. Our findings are detailed below:

Spontaneous ventilation was associated with large swings of esophageal pressure and regional lung inhomogeneity, resulting in progressive hypoxemia and lung injury in a severe ARDS model (31). In another study, comparing ARDS subjects on spontaneous ventilation vs. controlled MV, we found greater regional deformation and heterogeneity in the former, which was concentrated in juxta-diaphragmatic regions (33). Interestingly, there was also a spatial correlation between regional strain and regional expression of genes closely related to inflammatory response and pathological mechanotransduction under strenuous respiratory effort (9). Furthermore, noninvasive respiratory support therapy was not only capable of attenuating lung and diaphragm injury (34) but also reduced regional changes in lung aeration (56). Thus, MV is not mandatory to prevent regional phenomena and ARDS progression. Moreover, in a severe experimental ARDS, low-intensity respiratory effort modulated by extracorporeal membrane oxygenation support did not result in the progression of lung injury compared to ultra-protective MV (the standard of care under extracorporeal support), despite the more dorsal distribution of aeration under modulated spontaneous ventilation (57). In almost half of the studies mentioned, changes in regional aeration were measured at the bedside and in real-time by **Electrical Impedance Tomography** (EIT) (31,57). **These results highlight the relevance of respiratory effort and its modulation on ARDS progression and emphasize that EIT is sensitive in the early detection of these changes** (Figure 3).

Figure 3. Relationship between components of dyspnea and ARDS progression. On the right panel, regional overstretch assessment is shown by EIT, anticipating this progression.



12. Electrical Impedance Tomography: usefulness in detecting changes in regional lung aeration

Although thoracic computed axial tomography is considered the gold standard to acquire a detailed quantification of global and regional lung aeration, collapse, and overstretch, it cannot be performed

sequentially due to its unavailability at the bedside, requiring risky patient transfer out of the pediatric ICU and exposing them to radiation risks. Therefore, EIT emerges as a **noninvasive, radiation-free, dynamic, and real-time alternative imaging technique**, allowing sequential assessment of regional lung aeration at the bedside (66), becoming an effective alternative for the customized titration of ventilatory support, in all transitional phases of pediatric ARDS. Multiple studies, mostly performed in adult patients, have demonstrated the usefulness of EIT to assess regional lung aeration in different experimental and clinical conditions, as well as its utility in adjusting ventilatory support, assessing and preventing lung overdistension and collapse, if the support is customized correctly (67,68). Given technical limitations (electrode belt designed for adult thoracic size), its **use in critically ill children is scarce**. Recently, pediatric belts have been developed, which allow this technology to be used from newborns to adolescents. Hence, small observational studies in children suggest that EIT-guided MV titration reduces regional lung collapse without increasing overdistension, detects changes in the distribution of ventilation in real time, and identifies response to prone positioning, specifically improving the homogeneity of ventilation and recruitment of the dorsal lung regions (69-71). **There are no studies that have evaluated changes in regional lung aeration associated with respiratory effort in critically ill children.**

13. Our proposal

Dyspnea is the main symptom of ARDS, and it may not only be a warning but also be directly connected to its progression. Dyspnea can be quantified through its interrelated components: respiratory drive (neural stimuli), respiratory effort (muscle activation), and work of breathing (energy expenditure). **This project aims to identify mechanical thresholds of dyspnea components to predict early ARDS progression and outcome.** The role of respiratory effort is particularly relevant in three phases of ARDS where a **transition** occurs between **spontaneous and controlled ventilation**: 1) acute, under non-invasive support; 2) intermediate, shift from controlled to assisted MV; and 3) late, weaning from MV. In critically ill children, there are no established thresholds for these components that can predict ARDS progression, and it remains unknown whether regional changes in lung aeration can anticipate the oxygenation decline.

We will use advanced respiratory monitoring tools to quantify the dyspnea components, including **surface electromyography, occlusion maneuvers, and esophageal manometry**. Additionally, **electrical impedance tomography** will be employed to detect **changes in regional aeration**. All tools used are gold standards for each parameter and allow real-time, bedside measurements without adding invasiveness. Moreover, longitudinal integration of these monitoring tools has not been reported during transitional phases of pediatric ARDS. To test our hypothesis, we will quantify dyspnea components and regional lung aeration throughout all transitional phases of pediatric ARDS. In the acute phase, drive will be measured by surface electromyography, and in the other ones, by P01. Esophageal manometry will be used to quantify the effort and work of breathing. Regional lung overstretching, collapse, and heterogeneity will be assessed using electrical impedance tomography.

We will define mechanical thresholds and cut-off points for each dyspnea component that predict early ARDS progression and outcomes at each transitional phase. Based on the study results, we visualize the future development of algorithms to help guide safer transitions, to improve outcomes, and prevent lung sequelae. Our interdisciplinary team of clinicians and biomedical engineers will work to customize respiratory care in critically ill children, optimizing ventilatory assistance across disease stages.

B) Hypothesis and goals

Hypothesis

In spontaneously breathing children with ARDS, we hypothesize that the magnitude of respiratory drive, effort, and work of breathing critically determines the outcome of the respiratory support strategy employed. We further propose that regional imaging-based changes in lung aeration will detect lung function deterioration before oxygenation decline. Across key transitional phases, including the acute phase managed with noninvasive support, the shift from controlled to assisted mechanical ventilation, and the weaning period, dyspnea-related physiological variables may predict early ARDS progression and clinical outcomes.

General and specific goals

The general goal of our proposal is to study the effects of each component of dyspnea, respiratory drive, respiratory effort, and work of breathing, on the early progression of pediatric ARDS and the outcome of the ventilatory support used during all its transitional phases. Thus, we seek to identify the best cut-off point for each of the components of dyspnea that predict early ARDS progression.

To achieve such an overall goal, we propose the following **specific goals**:

Goal #1 To determine the effect of respiratory drive, respiratory effort, and work of breathing on early progression and outcome of noninvasive support during the **acute phase** of pediatric ARDS, and to identify

mechanical thresholds of all components of dyspnea to predict early progression and outcome, based on its quantification.
Goal ♯2 To determine the effect of respiratory drive, respiratory effort, and work of breathing on early progression and outcome during the **shift from controlled to assisted MV** in pediatric ARDS, and to identify mechanical thresholds of all components of dyspnea to predict early progression and outcome, based on its quantification.
Goal ♯3 To determine the effect of respiratory drive, respiratory effort, and work of breathing on early progression and outcome of **weaning from MV** in pediatric ARDS, and to identify mechanical thresholds of all components of dyspnea to predict early progression and outcome, based on its quantification.

c) Methodology and Study design

Prospective observational study in consecutive cohorts of patients with pediatric ARDS. The experimental protocol will be divided into two stages:
Stage 1 (Specific Goal ♯1): Aims to determine the role of components of dyspnea on early progression of pediatric ARDS and outcome of noninvasive respiratory support.
Rationale: Specific mechanical thresholds of respiratory drive, respiratory effort, and work of breathing have not been previously studied to predict the outcome of noninvasive respiratory support. In an experimental setting, we reported that ARDS progression was anticipated by increased respiratory effort, changes in regional lung aeration, and late oxygenation decline, and each of these signs was attenuated by timely noninvasive respiratory support (34). In a patient self-inflicted lung injury model, we also found a significant increase in lung edema and collapse after only 3 hours of unassisted spontaneous breathing. This evolution was concurrent with ARDS progression assessed by histology (33).
Expected results: We expect that noninvasive respiratory support failure will be associated with higher respiratory drive, effort, and work of breathing compared to successfully supported patients. We also expect that regional aeration changes will precede this failure.
Methodology: The investigation will comply with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975. The inclusion criteria for study will be: 1) children younger than 18 years-old; 2) diagnosis of pediatric ARDS, as defined by the 2023 Pediatric Acute Lung Injury Consensus Conference (PALICC2) (61); and 3) consent and assent (when necessary) to participate given by legal guardians and patient, respectively. We will approach all consecutive patients who meet the above criteria at our center between April 1st, 2026, and November 30th, 2029. We will exclude patients with tracheostomy, neuromuscular disease, uncorrected congenital heart diseases, and contraindication of esophageal catheter (choanal atresia, esophageal issues, recent esophageal surgery, etc.) or EIT (pacemakers, defibrillators, and unstable fractures). We will consider any emergency intubation as a criterion of early termination. The sample size was estimated at 36 sex-paired patients and was calculated based on similar previous studies of noninvasive support in children using G*Power Software and the "pwr" R library (77,78). All analyses were performed with an alpha of 0.05 and a power of 0.9.
Failure of non-invasive support will be defined by oxygenation decline (20% drop from baseline) or clinical signs of ventilatory overload (72). Mortality will not be the primary outcome due to its low rate in our pediatric ICU (73-75). The clinical team will be blinded to the analysis related to quantification of components of dyspnea and regional lung aeration.
A) Standard monitoring: We will record arterial blood gases, vital signs, and noninvasive ventilatory settings before the experimental measurements and calculate the PaO2/FiO2 ratio if an arterial catheter is available. If not, we will use noninvasive metrics of gas exchange.
B) Respiratory drive: sEMG of respiratory muscles signals will be acquired by placing electrodes 2cm apart in two respiratory muscles: diaphragm (main) and parasternal intercostal (accessory). Diaphragm monitoring will require electrodes to be placed at the chest wall-abdominal angle of the midclavicular line, while the monitoring of the parasternal intercostal muscles will be performed in the parasternal line of the second intercostal space. sEMG will be acquired using an eight-channel bioamplifier, converted to digital signals, and recorded at 2000Hz by a data acquisition software (Trigno® Avanti System; Delsys, Greater Manchester, UK) (76). The script will be filtered by the EMG signal using notch (Chebyshev type II filter) and band-pass (20–500 Hz) filters. For spectral analysis, the first 5 minutes of recording will be selected, and their power spectral density will be calculated using the Welch method, presenting the results as mean frequency.
C) Respiratory effort (swing of esophageal pressure) and **work of breathing** (pressure time product) will be continuously assessed through **esophageal manometry** using a model of esophageal catheter adapted for enteral feeding of children (i.e., SmartCathG, Carefusion®). These will be introduced nasally in supine position, using the fill volume predetermined by the manufacturer. After ensuring the correct position, the catheter will be connected to a pneumotachograph that will measure both parameters.

D) Early progression of ARDS will be measured by regional strain deformation parameters **derived by EIT**, as follows: 1) End Expiratory Lung Impedance: corresponds to aeration at the end of expiration. It correlates with functional residual capacity, reflected at rest lung aeration (i.e., collapse and overstretch); 2) Tidal Variation of Impedance, representing impedance change generated by tidal aeration; 3) Global Inhomogeneity index, which quantifies the homogeneity of the tidal volume distribution; 4) Impedance Ratio, the dependent and non-dependent regions' air distribution; and finally, 5) Regional Ventilation Delay, representing the temporal delay of lung aeration, associated to heterogeneity and tidal recruitment (31). Image acquisition will last 5 minutes, and simultaneously, ventilatory settings will also be recorded. All these measurements will be carried out before and after the ventilatory transition to evaluate the trajectory.
We will compare subgroups of success or failure of non-invasive support, using statistical tests according to the data distribution. We will correlate changes in regional lung aeration with the outcome of the support. Finally, receiver operator curve analysis to evaluate the specificity and sensitivity for clinically relevant cut-off points of any component of dyspnea for an early prediction of ARDS progression and noninvasive respiratory support failure will be performed. We aimed to identify patient clusters based on dyspnea component and regional lung behavior over time using machine-learning techniques (55). Clustering analysis will be performed using principal component analysis and K-Means algorithms.
Scientific novelty: Until now, there is no literature related to the simultaneous quantification of respiratory drive, effort, and work of breathing throughout sEMG and esophageal manometry-derived assessment to predict the outcome of noninvasive respiratory support in pediatric ARDS. However, there are two closely related studies but focused on customization of noninvasive respiratory support during the acute phase (77,78). The role of regional aeration changes in the early detection of noninvasive respiratory support failure has not been studied in children. The concept of patient self-inflicted lung injury presents a new opportunity to improve clinical outcomes of these patients. All the monitoring tools that we will use are deemed gold standards, which increases their scientific validity. Esophageal manometry and EIT will provide real-time and bedside information, especially useful for future decision-making studies based on these tools.
Pitfalls: Our team has successfully measured respiratory effort through esophageal manometry and regional changes in lung aeration in several experimental studies (31,32,56,57,79-81). However, it is occasionally difficult to ensure optimal esophageal catheter positioning in spontaneously breathing children. If necessary, we will evaluate the diaphragmatic excursion using a surrogate method based on ultrasound (56). We could also alternatively use the lung ultrasound score to assess regional changes in lung aeration when we face technical limitations for using EIT (82-83).

Stage 2 (Specific Goals ♯2 to ♯3): Aims to determine the role of components of dyspnea on early pediatric ARDS progression and outcome of respiratory support during the stepped weaning phases. Lessons from the first stage will allow us to optimize the second stage.
Rationale: Mechanical thresholds of respiratory drive, respiratory effort, and work of breathing have not been previously studied to predict the outcome of stepped weaning phases in pediatric ARDS. Specifically, there are no studies that have examined the role of dyspnea components in the transition from controlled to assisted ventilation in critically ill children. Some studies have identified an association between dyspnea components and the outcome of weaning from MV, but without defined cut-off points. No studies in the aforementioned phases have evaluated changes in regional aeration as a tool for early detection of failure.
Expected results: We expect that ARDS children with failure in any of the consecutive weaning phases will show stronger respiratory drive, respiratory effort, and higher work of breathing than successfully weaned patients. Furthermore, we expect that early changes in lung aeration will anticipate weaning failure.
Methodology: The investigation will comply with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975. The inclusion criteria for the study will be: 1) children younger than 18 years-old; 2) diagnosis of pediatric ARDS, as defined by the 2023 Pediatric Acute Lung Injury Consensus Conference (PALICC2) group (61); 3) use of MV without neuromuscular blockade; and 4) consent to participate given by legal guardians (assent can't be possible in sedated patients). The severity of PARDS will be classified using the 2023 PALICC criteria (61). We will approach all consecutive patients who meet the above criteria at our center between April 1st, 2026, and November 30th, 2029. We will exclude patients with endotracheal tube air leak greater than 20% of tidal volume, tracheostomy, uncorrected congenital heart disease, and contraindication of esophageal catheter or EIT. We will consider any emergency as a criterion for early termination. The sample size was estimated at 32 sex-paired patients and was calculated based on previous pediatric weaning studies (30,84) (alpha of 0.05 and a power of 0.9). We will obtain demographic and clinical information, as well as outcome (weaning success or failure, ventilation-free days at 28 days, and long-term complications). Mortality will not be the primary outcome due to its low rate in our pediatric ICU.

Transition from controlled to assisted MV: Complying with the standard of care, when neuromuscular blockade is indicated, it will be interrupted, with the patient recovering the respiratory effort. All patients will be supported using Assisted MV mode during this phase. **Failure of this transition** will be defined by oxygenation decline (20% drop from baseline) or clinical signs of ventilatory overload (85).
Weaning from MV: The decision to start the weaning process will depend on the fulfillment of standard of care clinical criteria, as follows: control of the disease that caused the connection to MV, effective gas exchange, absence of neuromuscular weakness, conserved mechanism of cough, and hemodynamic stability. Standard spontaneous breathing test on Pressure-support ventilation mode (PS 5 cmH2O, PEEP 5 cmH2O, and FIO2 50% by 1h) will be performed while the patient remains intubated and will evaluate the cardiopulmonary tolerance to maintain spontaneous breathing with minimum respiratory support. The medical team will be blinded to the measurements of variables derived from esophageal pressure monitoring. **Weaning failure** will be defined by oxygenation decline (20% drop from baseline) or clinical signs of ventilatory overload during a spontaneous breathing test (86). In the absence of any of these signals, the spontaneous breathing test will be considered successful, and extubation will be performed.
Extubation failure will be defined as the need for reintubation or rescue noninvasive respiratory support within the first 48 hours.
A) Standard monitoring: We will record arterial blood gases, vital signs, and ventilatory settings before the experimental measurements and calculate the PaO2/FiO2 ratio, oxygenation index, and dead space if an arterial catheter and volumetric capnography are available. If not, we will use noninvasive metrics.
B) Respiratory drive will be assessed by **P01**, recording the average of 3 measurements.
C) Respiratory effort (swing of esophageal pressure) and **work of breathing** (pressure-time product) will be continuously assessed through **esophageal manometry**, after confirming correct position through an occlusion test.
D) Early progression of ARDS will be assessed by **EIT metrics**, as we described previously.
All these measurements will be carried out before and after the ventilatory transition to evaluate the trajectory. Finally, the same statistical methods as those proposed in stage 1 will be performed.
Scientific novelty: there is scarce literature related to the assessment of respiratory drive, effort, and work of breathing through gold standard tools in stepped weaning phases of pediatric ARDS. Most of these studies were focused on customization of respiratory support (18,46,84,87-90) and on predicting work of breathing after extubation (28-30,91). One of them used the tension-time index, an offline measure of respiratory effort based on transdiaphragmatic pressure through a double esophageal and gastric pressure catheter, and it identified a very high sensitivity and specificity in predicting weaning failure (92). However, given its technical complexity, this method was not used in subsequent pediatric studies. Regarding P01, values lower than 1.5 cmH2O suggest insufficient drive, and values higher than 3.5 cmH2O suggest excessive drive in adults with chronic obstructive pulmonary disease (93). In pediatrics, there are no clear cut-off points, but both high and low values seem to be related to weaning failure (94,95). Recently, the REDvent clinical trial used personalized decision-making based on esophageal manometry in comparison to standard care. However, the intervention had a poor impact on the total length of ventilation (nearly half a day), probably triggered to a late definition of ARDS progression, based only on global but not regional parameters (46). Changes in regional lung aeration related to respiratory effort have not been studied in critically ill children. The concept of lung- and diaphragm-protective ventilation presents a new opportunity to improve clinical outcomes for pediatric ARDS patients, delivering precision medicine (15).
Pitfalls: If necessary, we will evaluate the use of surrogate methods based on occlusion maneuvers and validated against esophageal manometry (i.e., Occluded inspiratory airway pressure [ΔPocc] and Pressure muscle index [PMI]) (22,84,96-99). The same other alternatives mentioned in **Stage 1** (Specific Goal ♯1) will be useful. Based on recent experience, we should have no difficulty recruiting pediatric ARDS patients within our estimated sample size (73-75). Should the epidemiological situation change, we could include patients from a second pediatric ICU.

D) Work Plan, schedule, and Gantt chart.

ACTIVITIES	Year1	Year 2	Year 3	Year 4
Stage 1				
Specific aim 1: spontaneous ventilation				
Presentation in Scientific Conference				
Publication of an article				
Stage 2				
Specific aim 2: controlled to assisted MV				
Specific aim 3: weaning from MV				

Presentation in Scientific Conference				
Publication of an article				
Final analysis and closure				
Integrated analysis of measured variables				
Presentation in Scientific Conference				
Publication of an article				

Gray shading: period when the task will be performed.

E) Background information to assess the capacity of the team to implement the proposal

The **principal investigator** (PI) is a Pediatric Intensive Care Physician and has more than 20 years' experience in pediatric ICU. His major area of research interest includes but is not limited to basic and advanced respiratory monitoring tools, customization of invasive and noninvasive respiratory support therapies, rescue therapies, weaning from MV, and prevention of mortality and residual morbidity in a limited resources setting. The PI is specifically interested in pathophysiology and mechanobiology of ARDS, and the role of regional lung phenomena as stress raisers, both translationally (31-34,55,56,100,101) and at the bedside (77-79,86,102-117) (Annex 1, book of Mechanical Ventilation in Pediatrics). Moreover, he uses his background in developing global guidelines to support pediatric ARDS patients, such as PALICC2 (61). In the last year, the results of his latest studies received international recognition (Annex 2).

Dr. Daniel Hurtado's (Engineer, CoI) research focuses on the creation and development of new mathematical models and computational methods based on medical images and signal transduction for understanding the respiratory system, to create computational tools to improve disease diagnosis and treatment in the context of precision medicine, specifically Computational Methods in Biomedical Engineering (32,34,51,52,55,56). He will train thesis students and technical personnel in advanced data analysis. **Dr. María Consuelo Bachmann** (Physical Therapist, CoI) is an expert on bedside advanced respiratory monitoring and support therapies in critically ill adults (74-76,118-120), whose participation will strengthen the full proposal. She will contribute to the training of technical personnel in data acquisition derived from esophageal manometry and assistance with the unbiased analysis derived from EIT, respectively. We will consider a collaboration with **Dr. Joaquín Araos** (Department of Clinical Sciences, Cornell University) for complementary analysis of both signals and medical images (Annexes).

The team's researchers have supervised theses and trained students in topics closely related to the current project. Previous collaborations among the team have allowed us to address and solve past technical challenges, including respiratory effort monitoring and advanced image analysis in spontaneous ventilation, showing the viability of this proposal:

Dr. Hurtado and PI: 1) "Prevention of patient self-inflicted lung injury by noninvasive respiratory support therapies. Focus on respiratory effort, lung strain, mechanotransduction and function of small lung structures" (Fondecyt 1220322) (34,56); 2) "Multiscale modeling of whole-lung respiratory mechanics" (Fondecyt 1220465) (121); 3) "Ventilator induced lung injury: spatial correlation between regional strain, altered mechanotransduction and inflammation" (Fondecyt 1160631) (32,33); and 4) "Pre-clinical validation of a medical imaging-based method for early prediction of mechanical ventilation-induced damage" (Fondef ID17/10301) (55).

Dr. Bachmann and PI: 1) "Role of spontaneous breathing in evolution of lung injury and recovery of respiratory function in severe acute respiratory distress syndrome assisted with extracorporeal membrane oxygenation (ECMO)" (Fondecyt 1161556) (57); and 2) "Spontaneous breathing and progression of lung injury in acute respiratory distress syndrome before connection to mechanical ventilation" (Fondecyt 1171810) (31,122).

F) Scientific or technological novelty of the proposal.

This proposal addresses a critical area of intensive care medicine—the progression of ARDS—from a perspective that has not yet been explored in the pediatric population. To date, no studies have simultaneously quantified respiratory drive, effort, work of breathing, and regional lung aeration using gold standard tools (sEMG, P01, esophageal manometry, and EIT) to predict failure of ventilatory support in children. This proposal is pioneering because: 1) It applies these tools in an integrated, real-time manner throughout all transitional phases of pediatric ARDS; 2) It incorporates regional lung aeration measurements via EIT as a quantifiable and early pathophysiological marker of lung deformation induced by respiratory effort—an aspect rarely studied even in adults; and 3) It aims to define clinical thresholds of dyspnea components that could become decision-making tools for personalized respiratory support.

Furthermore, the expected results will advance the implementation of lung- and diaphragm-protective ventilation based on objective evidence, without increasing invasiveness to usual care, contributing to the development of precision medicine in pediatric critical care.

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- Include in this section the complete list of bibliographic references cited in the Proposal.
- Maximum length for this section: **5 pages**. Use letter size format and Arial font size 10 (or similar).
- **Please note that the instructions highlighted in blue may be disregarded.**

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Servicio de Salud Metropolitano Central
Región Metropolitana
Ministerio de Salud

COMITÉ ETICO CIENTIFICO
Teléfono: 25746943
RMR/MCVS
(Acta N°15/04 N°87/2026)

CERTIFICADO# 87

DR. RAFAEL MENDIZABAL RODRIGUEZ, presidente del Comité Etico Científico (CEC) del Servicio de Salud Metropolitano Central, constituido por resolución exenta N°1303 de fecha 26 de septiembre del 2002 de la Dirección de dicho Servicio y Acreditado por la SEREMI-RM mediante resolución N.° 251343719 del 10 de febrero del 2025, certifica que, en reunión expedita del 07 de mayo de 2026, el CEC SSMC, acusa recibo de la carta fechada el 04 de mayo de 2026 y recibida el 05 de mayo de 2026, firmada por el **Dr. Pablo Cruces Romero**, del Hospital El Carmen de Maipú (HEC), ubicado en Camino a Rinconada N.° 1201, Maipú, quien es el investigador principal del protocolo de investigación titulado "**Rol de la disnea en la progresión del síndrome de distrés respiratorio agudo pediátrico"**, quien solicita incorporar el número de proyecto FONDECYT N.° 1260263, financiado por la Agencia Nacional de Investigación y Desarrollo (ANID), en el protocolo de investigación y en todos sus documentos asociados, específicamente en el **Consentimiento Informado, el Asentimiento Informado y la Pauta de Ingreso para la Evaluación de Proyectos Científicos del CEC MED UNAB.**

Adjunta:

- ✓ Carta conductora.
- ✓ Consentimiento Informado.
- ✓ Asentimiento Informado.
- ✓ Pauta de ingreso para evaluación de proyectos científicos CEC MED UNAB.

Analizados los antecedentes, el Comité de Ética Científico del Servicio de Salud Metropolitano Central aprueba la incorporación del número de Fondecyt N.° 1260263 en los títulos del protocolo, del Consentimiento Informado (CI), Asentimiento Informado (AI) y de la Pauta de ingreso para evaluación de proyectos científicos del CEC MED UNAB, considerando que esta modificación contribuye a la adecuada identificación del proyecto y no altera los aspectos éticos ni metodológicos previamente aprobados.

Se adjunta copia de carta enviada por el investigador, firmada, fechada y timbrada, N.º 128 de recepción.

La reunión expedita, contó con la presencia de la EU. Marlene Valenzuela y del Dr. Rafael Mendizábal.

SERVICIO DE SALUD METROPOLITANO CENTRAL
COMITÉ ÉTICO CIENTÍFICO

EU. MARLENE VALENZUELA SAAVEDRA
SECRETARIA EJECUTIVA CEC SSMC

DR. RAFAEL MENDIZABAL RODRIGUEZ
PRESIDENTE DEL CEC SSMC

FORMULARIO DE CONSENTIMIENTO INFORMADO

PARA INVESTIGACIÓN. VERSIÓN 3 (5 DE MAYO DEL 2026)

RESUMEN

La investigación que se pretende realizar, lleva como título "Rol de la disnea en la progresión del síndrome de distrés respiratorio agudo pediátrico", a cargo del Dr. Pablo Cruces Romero, quien será el Investigador responsable.

Este formulario de consentimiento informado tiene la finalidad de ayudarle a tomar la decisión de participar en este estudio de investigación.

Léalo minuciosamente, y discuta cualquier inquietud que tenga con el investigador responsable a cargo del estudio, o alguno de sus colaboradores.

Este trabajo tiene como objetivo principal identificar si la intensidad de la dificultad para respirar (disnea), permite anticipar un empeoramiento de la función de sus pulmones. Su hijo o representado ha sido invitado a participar ya que posee el perfil para la investigación.

1. **TITULO:**

"Rol de la disnea en la progresión del síndrome de distrés respiratorio agudo pediátrico"

2. **Investigador principal:**

Dr. Pablo Cruces Romero

Médico, Unidad de Paciente Crítico Pediátrica Hospital el Carmen Dr Luis Valentín Ferrada.

Profesor Titular, Facultad de Ciencias de la Vida, Universidad Andrés Bello.

Mail: pablo.cruces@unab.cl

Teléfonos de contacto: (2) 2612 0641 y (2) 2612 0638

3. **Co-investigadores:**

Dra. María Consuelo Bachmann

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Doctora en Ciencias Médicas, Escuela de Kinesiología, Universidad de los Andes.

Dr. Daniel Hurtado

Doctor en Ciencias de la Ingeniería. Instituto de Ingeniería Biológica y Médica de la Pontificia Universidad Católica de Chile .

Teléfonos de contacto: (2) 2612 0641 y (2) 2612 0638

4. **Institución patrocinadora**:

Proyecto Fondecyt Regular 1260263, Agencia Nacional de Investigación y Desarrollo de Chile.

5. **Propósito del estudio:**

El propósito de este estudio es explorar si la magnitud de dificultad para respirar puede anticipar la progresión del síndrome de distrés respiratorio agudo pediátrico, definida como una disminución significativa del oxígeno en la sangre. Además queremos evaluar si cambios en la distribución del aire en los pulmones preceden esta disminución del oxígeno.

6. **Descripción del procedimiento:**

A los participantes se les medirá secuencialmente el esfuerzo para respirar durante un período de 5 minutos. Se utilizarán técnicas no invasivas (electromiografía de superficie o maniobras habituales durante la ventilación mecánica) o que no adicionan disconfort al cuidado habitual (manometría esofágica, técnica que utiliza un catéter específico que permite medir la fuerza de los músculos respiratorios además de la alimentación, en reemplazo de una sonda de alimentación habitual). Además se evaluará la distribución del aire en sus pulmones de manera no invasiva y libre de radiación, usando un cinturón sobre su pecho, llamado tomografía de impedancia eléctrica. Estas mediciones se realizarán de manera inicial y posterior a estabilización o necesidad de cambio de soporte respiratorio.

7. **Riesgos y beneficios:**

La investigación no adicionará riesgos ni costos a los cuidados habituales de una Unidad de Cuidados Intensivos. El catéter de presión esofágica no generará más incomodidad que una sonda la alimentación habitual, de uso habitual en niños gravemente enfermos. Los otros dispositivos no son invasivos, pudiendo generar a lo más una incomodidad mínima durante su instalación, la cual se realizará por breves períodos.

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No se prevé que haya beneficios directos para los participantes, pero su contribución ayudará a mejorar la comprensión de su enfermedad y ayudarnos a entregarles a futuros pacientes un cuidado aún más personalizado.

8. Confidencialidad:

Toda la información que proporcionen tus evaluaciones será tratada de forma confidencial. La identidad de su hijo/hija/representado no será revelada. Los datos serán almacenados de forma segura y solo el equipo investigador tendrá acceso a ellos, los datos de los participantes serán codificados ej: Patricio Muñoz, 2 meses = PM2(1) y así sucesivamente. Los resultados de este estudio serán publicados en revista científica, garantizando la confidencialidad de los participantes.

9. Voluntariedad de la participación:

Su participación en este estudio es completamente voluntaria. Si en algún momento desea retirarse, puede hacerlo sin ninguna penalización o explicación, manteniendo la misma calidad del cuidado.

10. Compensación:

No se ofrecerá compensación económica por su participación en este estudio.

11. Derechos del participante:

Usted tiene derecho a hacer preguntas sobre el estudio en cualquier momento y a recibir una copia de este consentimiento informado. Si en algún momento tiene preguntas sobre el estudio o de la participación de su hijo/hija/representado, puede ponerse en contacto con el investigador principal. Se le informará y/o derivará a un especialista si se encuentra algún problema de salud distinto al diagnóstico inicial.

12. Preguntas y contacto:

Si tiene preguntas acerca del proyecto, puede contactar al Dr. Pablo Cruces presencialmente, al correo: pablo.cruces@unab.cl o a los Teléfonos de contacto: (2) 2612 0641 y (2) 2612 0638

Si tiene preguntas acerca de sus derechos como participante, Ud. podrá dirigirse al presidente del Comité Ético Científico del Servicio de Salud Metropolitano Central (CEC-SSMC), Dr. Rafael Mendizábal, con oficina ubicada en Villavicencio 361, 1° piso, Santiago Centro, Fono: 225746958 -225743520.

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12. Consentimiento del participante:

He leído y comprendido la información sobre este estudio. He tenido la oportunidad de hacer preguntas y todas han sido respondidas de manera satisfactoria. Entiendo que la participación de mi hijo/hija/representado es voluntaria y que puedo retirarme del estudio en cualquier momento sin consecuencias. Al firmar este documento, acepto participar en este estudio.

Nombre del participante: _____

Nombre del padre, madre o representante legal: _____

Firma del padre, madre o representante legal: _____

Fecha: _____

Nombre de la persona que toma el consentimiento: _____

Firma de la persona que toma el consentimiento: _____

Fecha: _____

Nombre del investigador principal: Dr. Pablo Cruces

Firma del investigador: _____

Fecha: _____

Nombre del Director/a o su representante: _____

Firma del Director/a o su representante: _____

Fecha: _____

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