Royaume du Maroc المملكة المغربية

Université Sidi Mohamed Ben Abdellah

كلية الطب والصيدلة

FACULTÉ DE MÉDECINE ET DE PHARMACIE

YEAR 2021

Thesis N°297/21

PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

(About 23 cases)

THESIS

SUPPORTED AND PRESENTED PUBLICLY ON 15/11/2021

By

Ms. ZENDAH BAYAN

Born on October 03th, 1992 in Palestine

TO OBTAIN MEDICAL DOCTORATE DEGREE

KEYWORDS:

PARDS – PALICC definition – Lung protective strategy – Evolution and mortality

JURY

M. **HARANDOU MUSTAPHA**..... Professor of **Anesthesiology & Reanimation**	PRESIDENT & PROTRACTOR
M. BOUKATTA BRAHIM..... Professor of **Anesthesiology & Reanimation**	JUDGES
M. **BERDAI MOHAMED ADNANE**..... Professor Aggregate of **Anesthesiology & Reanimation**	JUDGES
Mrs.KOJMANE WIDADE..... Aggregate Professor of Pediatrics	JUDGES
M. BENLAMKADDEM SAID..... Assistant Professor of **Anesthesiology & Reanimation**	ASSOCIATE MEMBER

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AECC : American-European Consensus Conference
ALI : Acute lung injury
ARDS : Acute respiratory distress syndrome
AWL : Alveolar wall liquid
CMV : Conventional mechanical ventilation
CPAP : Continuous positive airway pressure
CPD : Continuous distending pressure
CT Scan : Computed tomography scan
DAMPS : Danger associated molecular patterns
ECCO2R : Extracorporeal Carbon Dioxide Removal
ECMO : Extra corporeal membrane oxygenation
EELV : End expiratory lung volume
FIO2 : Fraction of inspired oxygen
FRC : Functional residual capacity
HFOV : High-frequency oscillatory ventilation
IBW : Ideal body weight
ICU : Intensive care unit
IT : Inspiratory time
IL : Interleukin
iNO : inhaled nitric oxide
MAP : Mean airway pressure
MMPS : Matrix metalloproteinases
NAVA : Neurally adjusted Ventilatory Assist
NETs : Neutrophil extracellular traps

NMB : Neuromuscular blockades

OI : Oxygenation index

OSI : Oxygenation saturation index

PALICC : Pediatric Acute Lung Injury Consensus Conference

PAO2 : Partial pressure of arterial oxygen

PARDS : Pediatric acute respiratory distress syndrome

PEEP : Positive end expiratory pressure

PICU : Pediatric intensive care unit

PIP : Peak inspiratory pressure

PP : Prone position

RM : Recruitment maneuvers

SAO2 : Oxygen saturation

SIRS : Systemic inflammatory response syndrome

Spo2 : Peripheral capillary oxygen saturation

TRALI : Transfusion related acute lung injury

VA ECMO : Veno-arterial extra corporeal membrane oxygenation

VILI : Ventilator induced lung injury

Vt : Tidal volume

I. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening pulmonary condition and one of the major challenges in modern ICU. In ARDS, there is a disruption of alveolar epithelial-endothelial barrier leading to accumulation of non-cardiogenic pulmonary edema due to inflammation and apoptosis which results in type I respiratory failure characterized by severe hypoxemia. ARDS can be triggered by heterogenous pulmonary (direct lung injury) or extra-pulmonary (indirect lung injury) etiologies. The primary etiologies are pneumonia, sepsis, aspiration, near drowning, and other clinical conditions respectively.

ARDS was first described by Ashbaugh et al. in 1967 in 12 patients series who suffered from severe hypoxemia refractory to oxygen supplement [1]. Multiple definitions were proposed since the first description of ARDS including the 1994 American-European Consensus Conference (AECC) definition [2] and the berlin definition in 2012 [3]. Although these definitions were set primarily for use in adult population, until recently, they were also employed in the pediatric setting. Due to limitations of previous definitions when applied on paediatric population, the pediatric Acute Lung Injury Consensus Conference (PALICC) published in 2015 a pediatric-specific definition for ARDS [4]. However, mortality remains high in PARDS and in 2020, an investigation conducted by Christina Rufener revealed a failure in PARDS diagnosing which may have impact on PARDS outcome [5].

Unfortunately, there is no specific therapy for PARDS and the management remains supportive. Primarily therapies include mechanical ventilation that may also aggravate lung injury, sedation, and fluid management. Ancillary therapies include High frequency ventilation, Nitric oxide, Recruitment manoeuvres, surfactant, steroids, prone position, neuromuscular blockades, and extracorporeal membrane oxygenation (ECMO). Clinical researches are still on the way to define the best treatment strategy for PARDS.

The impact of PARDS is not limited to PICU stay. Survivors can experience multiple sequalae including fibrosis, decreased lung reserve, post-traumatic stress disorder due to the exposure to multiple events when taken in charge, and cognitive deficits which may impact child development.

II. OBJECTIVES

- Define PARDS
- Pathophysiology of PARDS
- Epidemiology of PARDS.
- Diagnosis of PARDS.
- Management of PARDS.
- Evolution of PARDS.

III. MATERIALS AND METHODS

- **Study design**: Hospital based retrospective study.
- **Setting**: *Service de Reanimation mere-enfant CHU-HASSAN II – FES.*
- **Sample size**: 23 patients
- **Inclusion criteria:**

1. Hypoxemia within 7 days of a clinical insult.
2. Respiratory failure not fully explained by cardiac failure or fluid overload.
3. Chest imaging with new infiltrate(s) consistent with pulmonary parenchymal disease.
4. PF ratio $\leq$ 300 or SpO_2/FiO_2 (SF) ratio $\leq$ 264 if on NIV (Oro-nasal mask CPAP $\geq$ 5 cmH_2O or BiPAP).
5. Age 1 month to 15 years old.

- **Exclusion criteria:**

1. Cyanotic heart disease.
2. Active perinatal lung disease.
3. Within 7 days of cardiopulmonary bypass.

Methodology.

This is a retrospective study using hospital database during 32 months January 2019-September 2021 in patients aged from 1 month to 15 years old. The study was conducted in mother and child ICU at University Hospital HASSAN II-FES. Patients fulfilling Berlin criteria were selected. History, physical examination, chest radiographs and arterial blood gas analysis were collected from hospital data base HOSIX. Baseline characteristics including comorbidities, routine investigations were documented in Microsoft excel sheet.

➢ Study proforma.

❖ Identity.

- Age.
- Sex.
- Weight.

❖ Patient medical history.

- Comorbidities.
- Medications.
- Surgery.
- Family history.

❖ Clinical examination at Admission.

- General.
- Hemodynamic.
- Respiratory.
- **Lab test.**
  - Blood count.
  - Blood chemistry.
  - Liver function enzymes.
  - Blood coagulation.
  - Inflammatory analysis.
  - **Blood gas analysis.**

1. PH.
2. PaO2.
3. PaCO2.
4. $HCO3^-$.
5. PaO2/FiO2.

- **PARDS Diagnosis.**
  - Chest x ray.
  - CT scan.
  - Echography ultrasound.
  - Onset.
  - P/F ration.
- **Cause of PARDS /cause of admission.**
  - **Direct.**
    - Pneumonia
    - Aspiration
    - Inhalation injury
    - Drowning
    - Pulmonary contusion
  - **INDIRECT.**
    - Sepsis/Systemic inflammatory response syndrome
    - Major trauma
    - Cardiopulmonary bypass
    - Severe Burns
    - Pancreatitis
    - Shock
    - Massive Transfusion or TRALI
    - Drug overdose

❖ **Management.**

- **Invasive mechanical ventilation:**
    - Respiratory criteria, neurologic criteria.
    - Mode.
    - Respiratory rate.
    - Fio2.
    - Vt.
    - PEEP.
    - PIP.
- **Non-invasive:**
    - Cpap.
    - Bipap.
- **Fluide management.**
- **Sedation.**
- **Prone positioning.**
- **Recruitment manoeuvres.**
- **Neuromuscular blockades.**
- **Nitric oxide.**
- **Surfactant.**
- **Steroids.**
- **ECMO.**

❖ **Evolution/out come.**

- Duration of hospital stay..
- Duration of intubation.
- Improved / death.

IV. RESULTS

A total of 23 patients were admitted in our PICU and classified based on the Berlin criteria. Patients history, clinical examination, Po2/Fio2, and labs were all analyzed in prior to extract the following data:

A) Epidemiological characteristics in our series.

1) Patients characteristics.

➢ Incidence.

Number of patients admitted to PICU in University hospital HASSAN II during our study (January 2019 – September 2021) were 850 patients with 23 patient were diagnosed with PARDS making an incidence of 2.7%.

➢ Age distribution.

PARDS is more frequent in children less than 5 YO in our series with percentage of 73% of PARDS cases (17 of 23 patients), 9% of patients from 5 YO to 10 YO (2 of 23 patients) and 18% of patients aged from 11 YO to 14 YO (4 of 23 patients). **FIGURE 1** The mean age in our study was 4.6 years old.

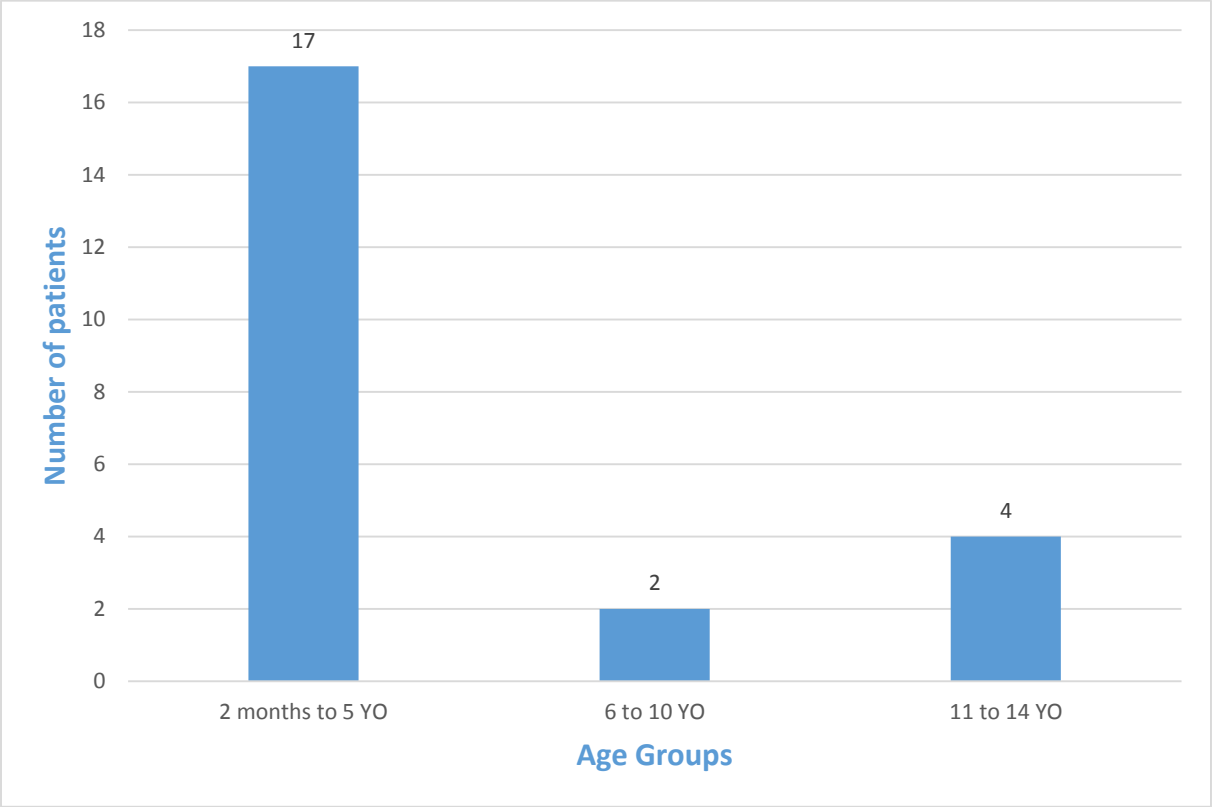


FIGURE 1. AGE DISTRIBUTION ACCORDING TO AGE GROUPS.

➢ Sex distribution.

Boys were more likely to develop ARDS in our study with 74% of cases were males (17 patient) while 26% presented females (6 patients). The Sex ration M/F was 2.8. **FIGURE 2.**

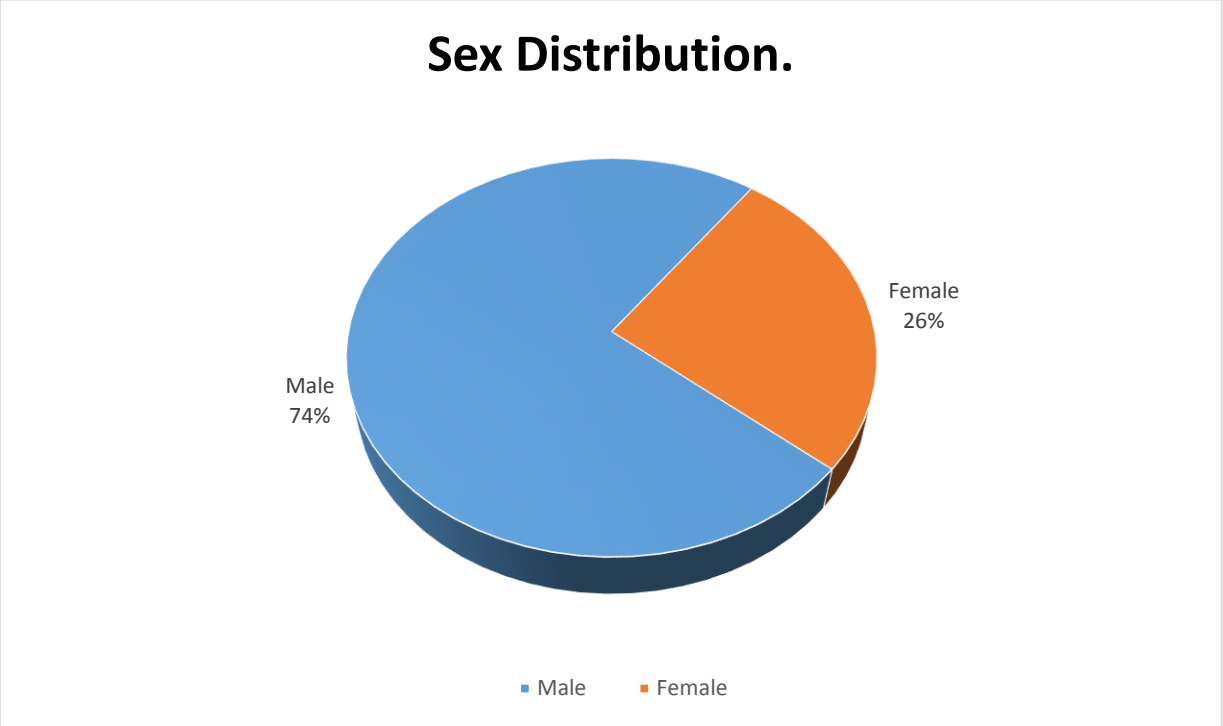


FIGURE 2. SEX DISTRIBUTION IN OUR SERIES.

➢ Cause of admission.

The causes of admission are listed in **TABLE 1.**

TABLE 1. THE DIFFERENT CAUSES OF ADMISSION IN OUR SERIES.

Cause of admission	Number of cases	Percentage
Respiratory destress	12	52%
Major trauma	5	22%
Sepsis	3	13%
Severe burn	1	4.3
Diabetic ketoacidosis	1	4.3
Status epilepticus	1	4.3
TOTAL	**23**	**100%**

➢ Comorbidities.

Three patients had pre-existing comorbidity including 1 case with cerebral tumor, 1 case with type 1 diabetes, and 1 case with valvular heart disease. **TABLE 2.**

TABLE 2. DISTRIBUTION OF COMORBIDITIES IN OUR SERIES.

Comorbidity.	Number of cases.
Cerebral tumor	1
Type 1 diabetes	1
Valvular Heart disease	1
None	20
TOTAL	**23**

➢ Clinical data at admission.

- Respiratory failure in 60% (14 of 23 patient). The mean Spo2 is 78% with a minimum of 52% and a maximum of 92%.
- Circulatory failure in 17% (04 of 23 patient).
- Renal failure in 13% (03 of 23 patients).
- Neurological impairment in 30% (07 of 23 patients).

FIGURE 3. shows clinical data distribution according to organ failure.

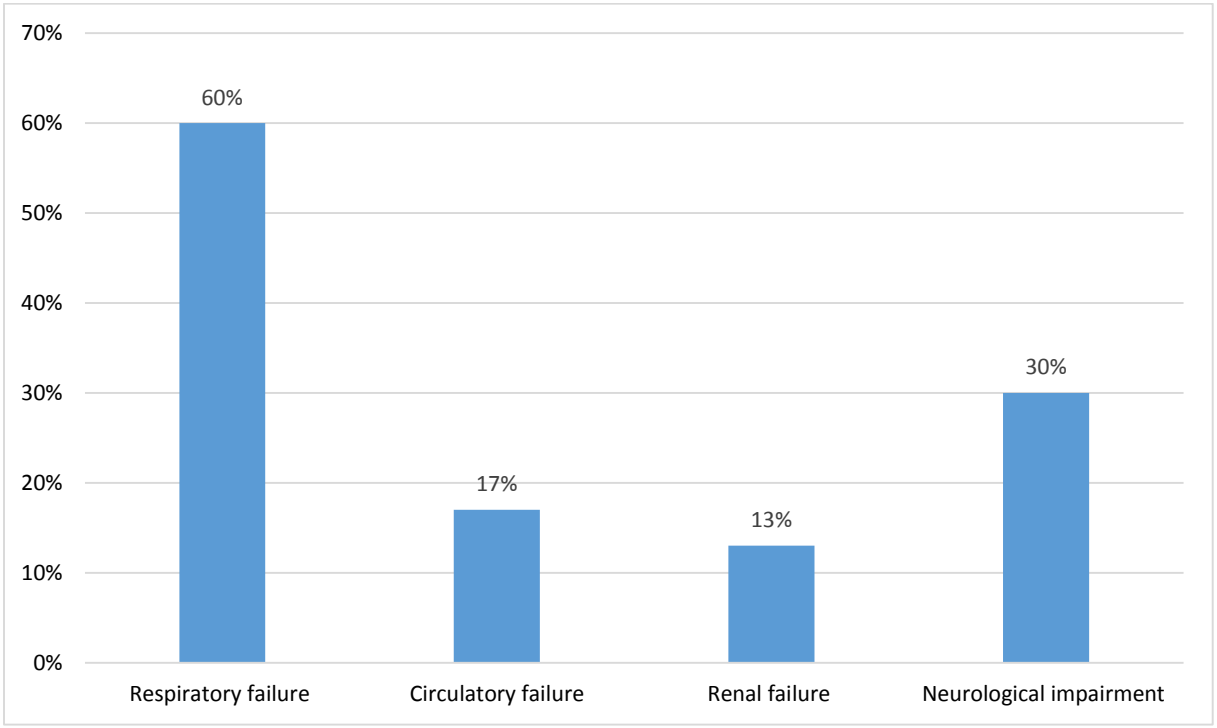


FIGURE 3. DISTRIBUTION OF DIFFERENT FAILURE AFFECTIONS AT ADMISSION.

2) Characteristics of PARDS in our series.

➢ Onset day.

Number of patients diagnosed with ARDS at admission were 10 (43% of cases).

Number of patients diagnosed with ARDS during hospital stay were 13 (57% of cases).

The mean onset day prior to admission day was two days. **TABLE 4.**

TABLE 3. ONSET DAY PRIOR TO ADMISSION AND HOSPITAL STAY.

	Number of patients	Percentage
ARDS diagnosis at admission	10	43%
ARDS onset at PICU stay	13	57%

➢ Distribution of presumed etiologies.

1) Pulmonary causes:

- Pneumonia 48% (11 patients).
- Aspiration 22% (5 patients).
- Contusion 4% (1 patient).
- Foreign object 4% (1 patient).

2) Extra Pulmonary causes:

- Sepsis/SIRS 13% (3 patients).
- Major Trauma 4% (1 patient).
- Severe Burn 4% (1 patient).

The principal causes in our series are shown in **TABLE 5**. And **Figure 3.**

TABLE 4. DISTRIBUTION OF PRINCIPAL PRESUMED CAUSES OF PARDS.

	Etiology	N. of cases	Percentage
Pulmonary	Bacterial pneumonia	7	48%
	Viral pneumonia	4	
	Aspiration	5	22%
	Contusion	1	4%
	Foreign Object	1	4%
Extra Pulmonary	Sepsis/SIRS	3	13%
	Severe Burn	1	4%
	Major trauma	1	4%
	Total	**23**	**100%**

The germs detected in bacterial pneumonia were Streptococcus pneumoniae, Staphylococcus aureus with positive Panton-Valentine leukocidin (PVL). Rhinovirus and adenovirus were detected by PCR in Viral pneumonia.

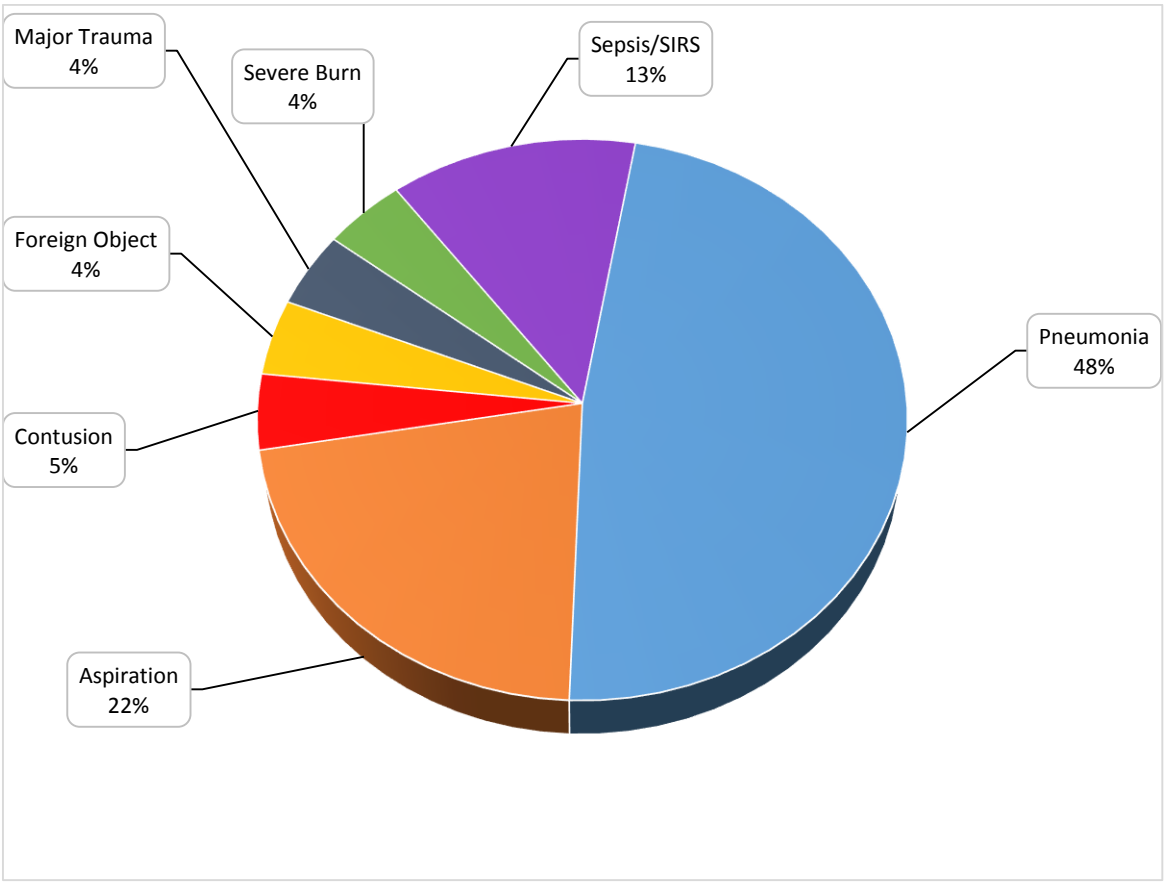


FIGURE 4. DISTRIBUTION OF PRESUMED CAUSES FOR PARDS IN OUR STUDY.

➢ Risk stratification.

The severity of illness was based on the berlin criteria using P/F ratio stratifying ARDS as Mild, Moderate, and sever as follows:

P/F 200-300 for mild.

P/F 100-200 for moderate.

P/F<100 for severe.

P/F ratio were used in all patients except one patient where OSI were used due to shortage of blood gas analyzer. The OSI at diagnosis was 7.3 stratified as moderate. The mean P/f ration is 172 with minimal of 60 and maximal of 294.

The distribution of cases in prior to group severity are shown in **FIGURE 5. TABLE 6, 7, and 8.**

TABLE 5. DISTRIBUTION OF CASES ACCORDING TO SEVERITY GROUPS.

Risk stratification.	Number of cases.	Percentage.
Mild	3	13%
Moderate	12	52%
Severe	8	35%

TABLE 6. DISTRIBUTION OF CASES ACCORDING TO DIRECT OR INDIRECT CAUSE AND SEVERITY OF ILLNESS.

	Mild		Moderate		severe	
	N.	%	N.	%	N.	%
Pulmonary	3	13%	9	39%	6	26%
Extra Pulmonary	0	0	3	13%	2	9%

TABLE 7. DISTRIBUTION OF CASES ACCORDING TO GENDER AND SEVERITY OF ILLNESS.

	Mild		Moderate		Severe	
	N.	%	N.	%	N.	%
Male	3	13%	9	39%	5	22%
Female	0	0%	3	13%	3	13%

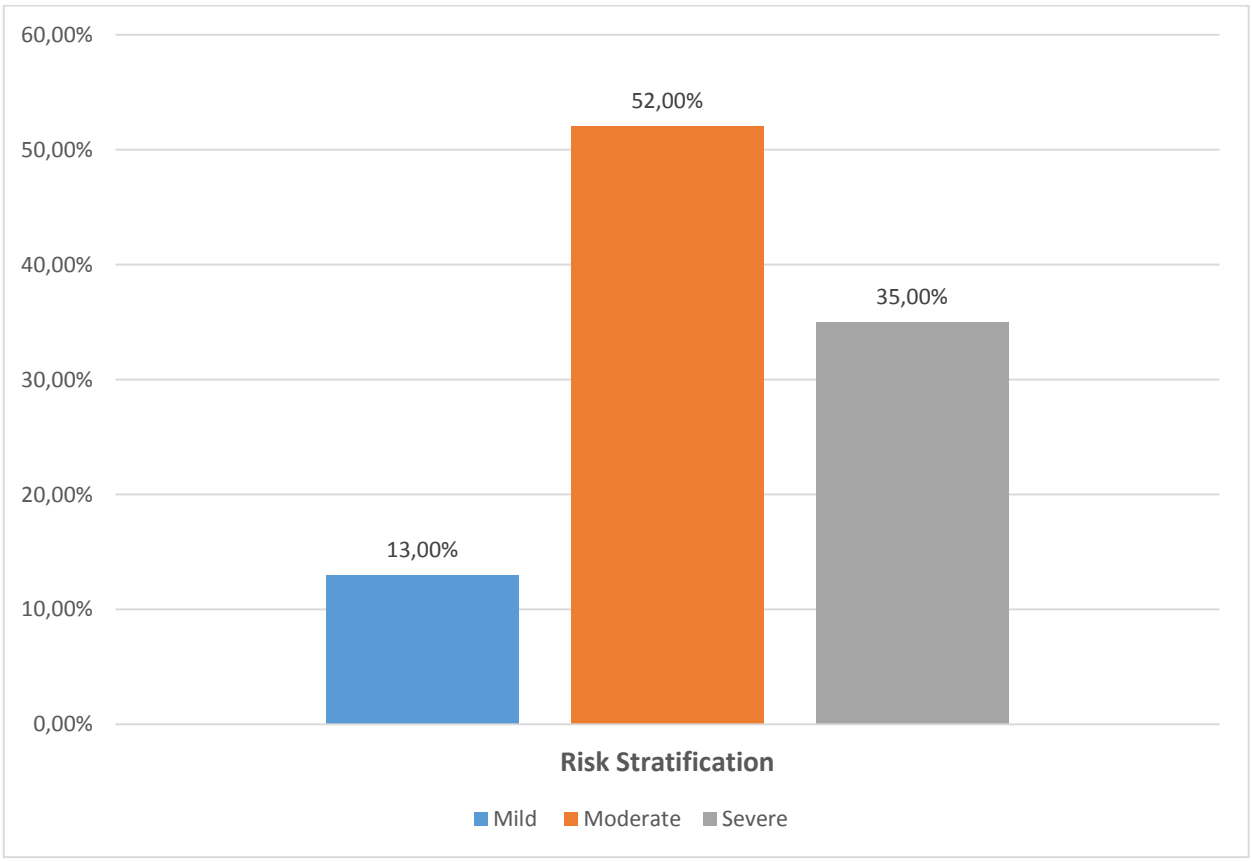


FIGURE 5. REPARTITION OF PATIENTS BASED ON GROUP SEVERITY.

B) Management of PARDS.

1. Mechanical ventilation.

➢ Invasive ventilation.

22 cases (95% of patients) were invasively ventilated. 10 of 22 cases (45% of invasively ventilated patients) were intubated at admission. 7 of 22 cases (32% of invasively ventilated patients) were already under mechanical ventilation. 5 cases (23% of invasively ventilated patients) were intubated during hospitalization.

The mean duration of invasive ventilation were 13.5 days with extremes ranging between 4 and 30 days.

The complications presented in intubated patients were as follows:

- Pneumothorax in 7 patients (30% of cases).
- Atelectasis in 4 patients (17% of cases).
- Ventilator associated pneumonia in 13 patients (56% of cases) the principal germs detected :
  - Acinetobacter Baumannii in 8 patients.
  - Klebsiella pneumoniae in 4 patients.
  - Pseudomonas aeruginosa in 3 patients.
  - Serratia marcescens in 1 patient.
  - Polybacterial in 5 patients.

➢ **Non-invasive ventilation.**

One patient was exclusively treated with NIV with duration of 8 days. 22 patients were systematically under NIV in post extubation.

Protective lung strategy were applied to all patients with the objectives of:

- PH>7.25.
- Pco2<55 mmhg.
- Pao2 50-80 mmhg

Protective lung strategy settings were as follows:

- Tidal volume of 6 ml/kg of ideal body weight [IBW= 2 x (age in years + 4)].
- Plateau pressure < 30 cmH2O.
- PEEP/Fio2 table were used to choose PEEP with a range of 5 and 15 cmH2O.
- Permissive hypoxemia with saturation between 88-92%

➢ All patients under mechanical ventilation were sedated under the association of fentanyl and midazolam with objective of minimal effective sedation.

2. Prone Position.

Prone position were applied on 6 patients (26% of cases). 1 patient with moderate PARDS, 5 patients with severe PARDS. The indication of PP was in patients with P/F < 150 and was applied for duration of 16 hours per day.

3. NO.

The indication of using NO for ARDS was P/F < 100. iNO was applied in 8 patients with severe PARDS (35% of cases).

The dose of NO were not registered during our study period, NO was delivered using a manometer with a flow rate range between 0.2 and 1.5L/minute. Image 1.

IMAGE 1. Showing the manometer used for delivering iNO dose from 0.2 to 1.5 liter per minute. *University hospital center HASSAN II PICU.*

4. Recruitment maneuvers.

RM were applied on 13 patients(56% of cases). 6 of 13 had moderate PARDS, 7 of 13 patients had severe PARDS.

5. ECMO.

VV ECMO was applied on one patient aged 12 YO weighted 32Kg. His medical history includes Rheumatic fever, Mitral and aortic insufficiency. He was admitted for respiratory destress with fever. Physical examination revealed 39 C fever, heartbeat of 124 bpm, and Spo2 94% under three litters of oxygen. Chest X ray found unilateral infiltrates at right. Labs found a bacterial pneumonia with staphylococcus aureus without decompensation of rheumatic fever. The evolution was marked by the installation of ARDS with Spo2 of 82% under 10 liters of oxygen with P/F ratio of 110. The patient was intubated and sedated by midazolam and fentanyl. He was under protective lung strategy with Vt 6 ml/kg, Fio2 75%, plateau pressure 28 mmhg, PeeP 12. During his PICU stay his cardiopathy decompensated with the apparition of vegetations of mitral valve. His labs found renal and hepatic failure. The patient needed an immediate surgical intervention that was successful except his Spo2 was 63% under 100% Fio2 with P/F ratio of 46. The decision on per operational stage was to put the patient under ECMO to avoid any cardiac decompensation.

VV ECMO were used, the first cannula sized 21F was introduced in femoral vein gaining the inferior vena cava. The other cannula sized 17F for reinjection of oxygenated blood into right internal jugular vein. The ECMO was stopped after six days of application.

The evolution was marked by the improvements of P/F 450. Spo2 100% under 40% of Fio2. Chest images found no infiltrations. An evaluating were done after 6 months with satisfying results including restore of functional capacity with no sequalae. **IMAGE 2.**

IMAGE 2. A 12YO patient with severe PARDS under VV ECMO at University Hospital HASSAN II-PICU department-FES.

6. Other.

NMB: Rocuronium was administered in 17 patient (74% of cases).

Steroids: prednisolone was administered in 10 patients (43% of cases. It should be noted that the indication of steroids was not for ARDS. It was primary used for viral pneumonia and sepsis.

C) Evolution.

P/F ratio were used in all patients except one patient where OSI was used due to shortage of blood gas analyzer. The OSI was 7.3 stratified as moderate in the first day, 3.16 in third day, 3.5 in 7th day.

The evolution of the mean P/F ratio of all patients in PICU stay is shown in **FIGURE 6.**

The evolution of the mean P/F ratio in day 1, day 3, and day 7 according to severity is shown in **FIGURE 7.**

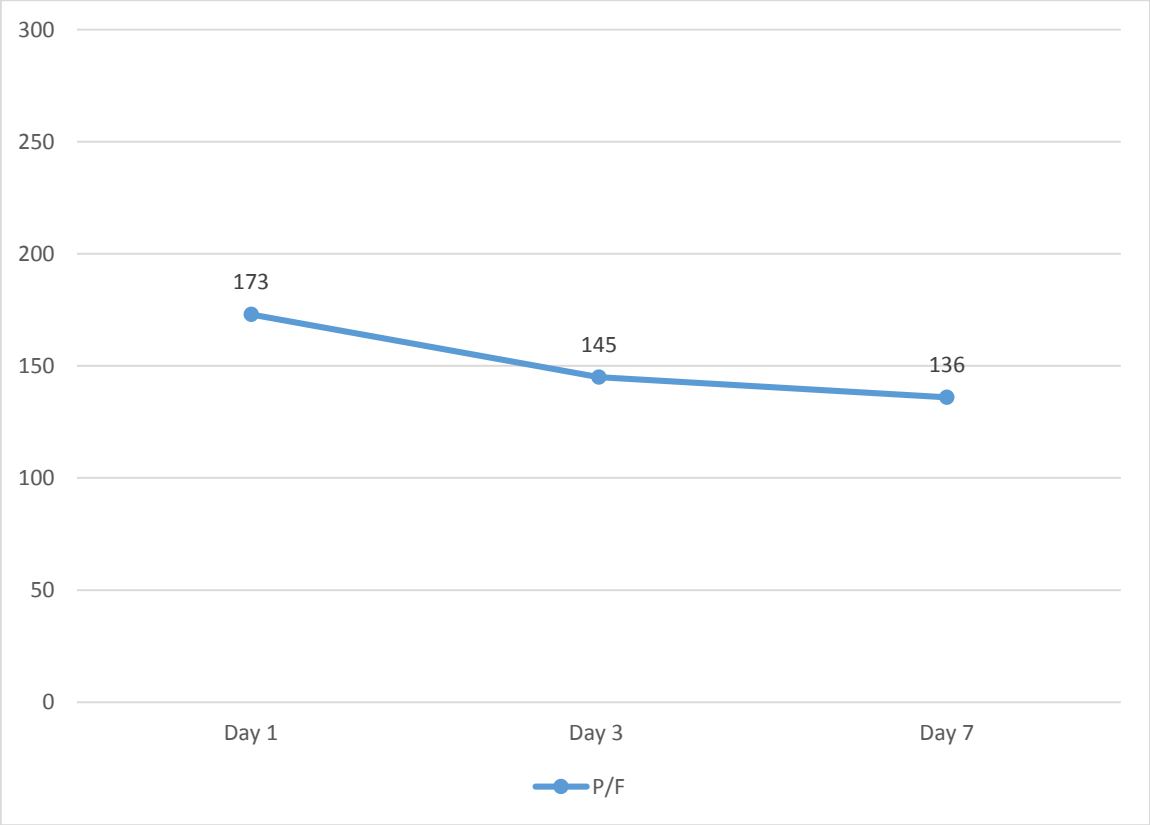


FIGURE 6. EVOLUTION OF MEAN P/F RATIO OF ALL PATIENTS DURING PICU STAY.

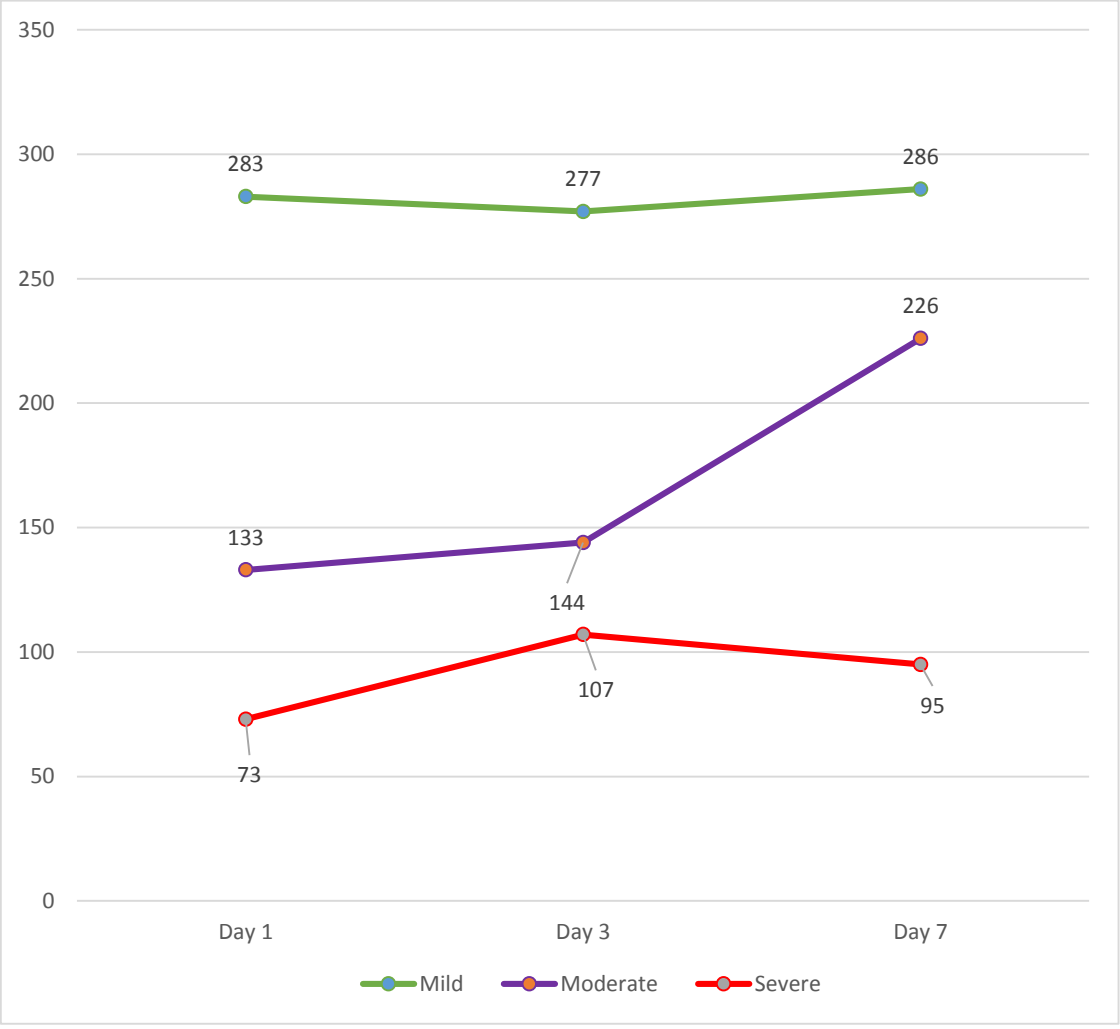


FIGURE 7. P/F RATIO EVOLUTION ACCORDING TO RISK STRATIFICATION IN DAY 1, DAY 3, DAY 7.

1. Length of PICU stay.

The mean PICU stay was 20 days ranging between 4 and 51 days. Severe cases had the most mean PICU stay with 28 days. The mean PICU stay according to severity are shown in **TABLE 10**.

TABLE 8. HOSPITAL STAY IN ALL PATIENTS AND ACCORDING TO SEVERITY.

Category	Mean PICU in days
All patients	20
Mild	13.3
Moderate	17.3
Severe	28

2. Mortality

➢ Mortality rate.

Number of PARDS cases admitted to PICU HassanII hospital during our study (January 2019 – January 2021) were 23 with 8 cases of non survivors. Mortality rate was 34%. **FIGURE 8.**

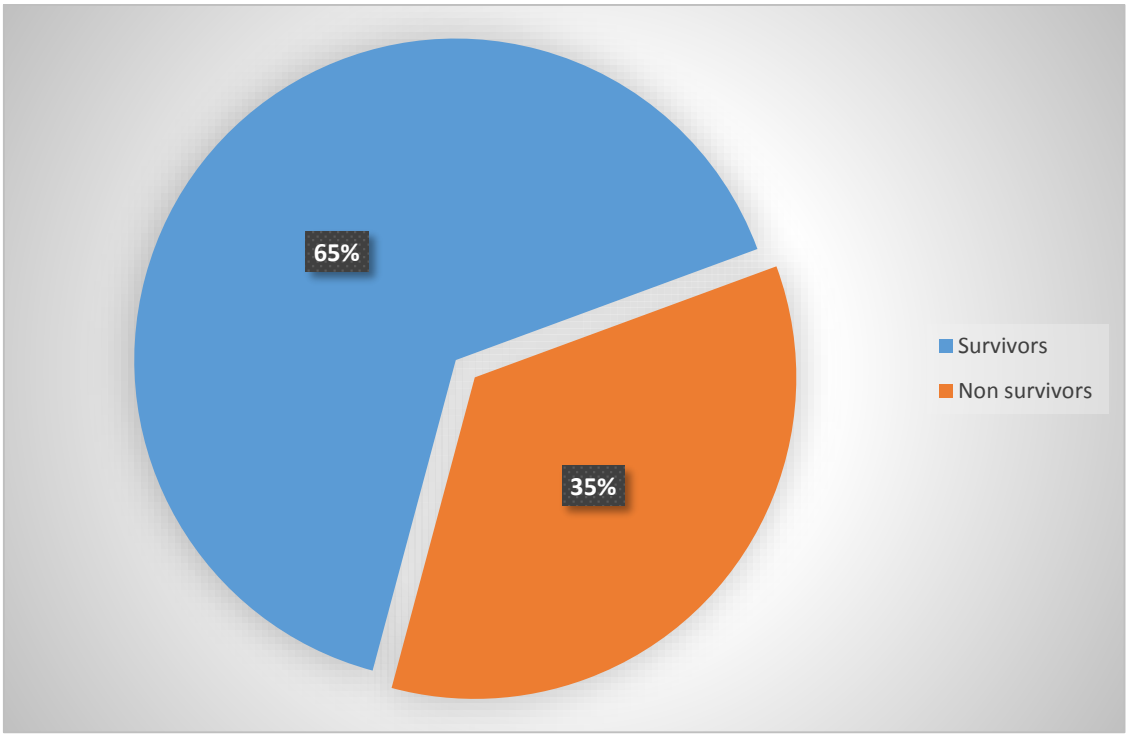


FIGURE 8. DISTRIBUTION OF MORTALITY RATE IN OUR SERIES.

➢ **Mortality and gender.**

07 of 17 males did not survive making a percentage of 30% of all patients while one of six females did not survive making a percentage of 4.3% of all patients. **FIGURE 9.**

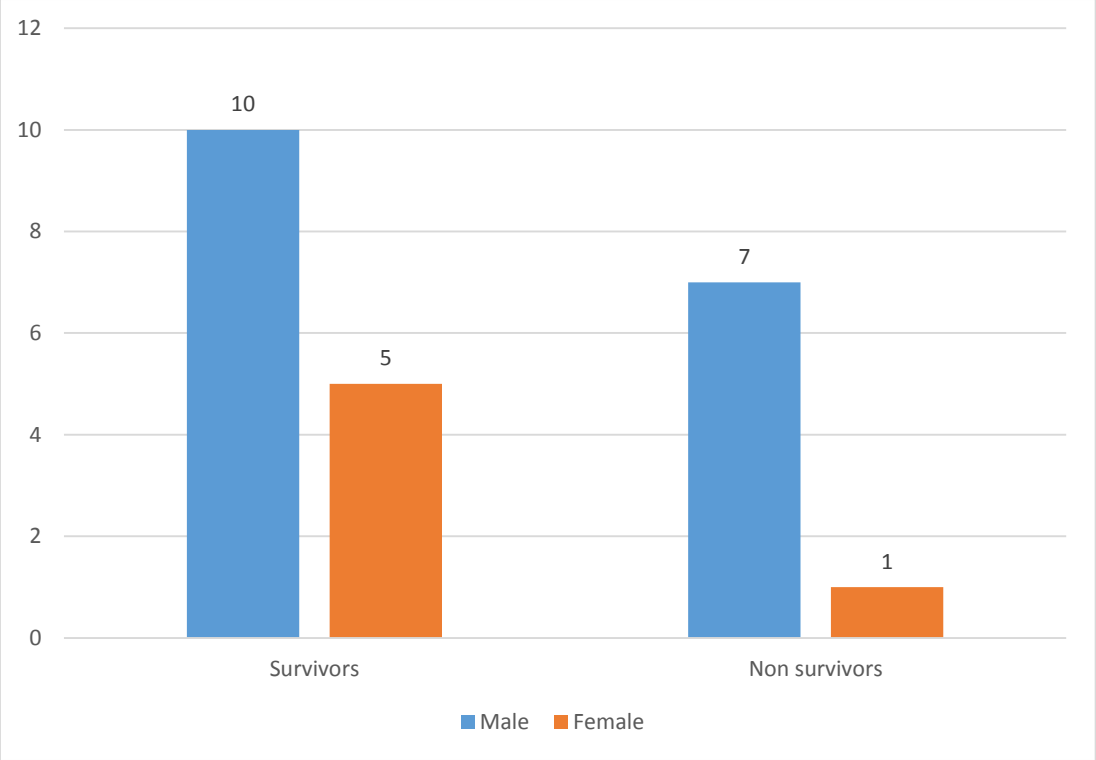


FIGURE 9. DISTRIBUTION OF MORTALITY AND GENDER.

➢ **Mortality and comorbidities.**

Three patients had pre-existing comorbidity. 1 case with cerebral tumor, 1 case with type1 diabetes, and 1 case with valvular heart disease. The distribution of survivors and non survivors in patient with comorbidities is as follows:

- **Survivors**: patient with type 1 diabetes, patient with valvular heart disease.
- **Non survivor**: patient with cerebral tumor.

➢ **Mortality according to etiologies.**

Mortality rate was lower in PARDS triggered by direct lung injury with 38% of non survivors with 25% mortality rate in pneumonia, 12.5% for aspiration. It was higher in PARDS triggered by indirect lung injury with 62% of non survivors with Sepsis/SIRS presented in 38% of death while severe burn and major trauma presented in 12.5% for each. **TABLE 12.** how the mortality according to the principal etiologies in our series.

TABLE 9. SHOWING CAUSES OF PARDS AND MORTALITY IN OUR SERIES.

	Cause	Survivors	Non survivors	Total
Direct	Pneumonia	9	2	11
	Aspiration	4	1	5
	Contusion	1	-	1
	Foreign Object	1	-	1
Indirect	Sepsis/SIRS	-	3	3
	Severe Burn	-	1	1
	Major trauma	-	1	1

- **Mortality according to severity.**

The mortality rate according to group severity is in **TABLE 10** as follows:

- Mild group: none of mild cases did not survive.
- Moderate group: 4 of 23 patients did not survive(17% of all patients).
- Severe group: 4 of 23 patients did not survive(17 of all patients).

TABLE 10. MORTALITY ACCORDING TO SEVERITY GROUPS IN OUR SERIES.

	Survivors		Non survivors		Total	
	N.	%	N.	%	N.	%
Mild	3	15%	0	0	3	15%
Moderate	8	34%	4	17%	12	51%
Severe	4	17%	4	17%	8	34%
All patients	15	66%	8	34%	23	100%

V. DISCUSSION

1. Definitions of ARDS.

The acute respiratory distress syndrome (ARDS) is an acute onset of noncardiogenic pulmonary oedema resulting in severe hypoxemia that requires mechanical ventilation. ARDS was first described in 1967 by Ashbaugh and his colleagues with case series report of 12 patients with presentation of cyanosis refractory to oxygen supplementation and poor lung compliance with diffuse lung infiltrates seen on the chest radiograph. They called it adult respiratory distress syndrome [1] .

The first definition of ARDS was proposed in 1994 by the AECC (American and European Consensus Conference) classified mild ARDS as acute lung injury (ALI) [2]. ALI/ARDS was defined as acute onset of severe hypoxia with bilateral opacities on chest radiograph in the absence of clinical evidence of left ventricular failure. P/F ratio <300 for ALI and <200 for ARDS.

In 2012, experts developed the Berlin definition with several changes were made on the AECC definition [3]. **TABLE 11.**

a) A.L.I was eliminated and replaced with P/F ratio 200–300 for mild, P/F 100–200 for moderate, and P/F < 100 for severe ARDS.
b) Minimal ventilator settings of a positive-end expiratory pressure (PEEP) of 5 cm H2O was required.
c) Reference to the pulmonary capillary wedge pressure was removed.

The Berlin Definition of Acute Respiratory Distress Syndrome	
	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

TABLE 11. THE BERLIN DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME.

The acute lung injury (ALI) or ARDS in children was first based on adult data determined by the 1994 American-European Consensus Conference (AECC) and the subsequent 2012 Berlin definition. Recognizing that ARDS in children may be different than adults, an international panel of experts in 2015 convened the Pediatric Acute Lung Injury Consensus Conference (PALICC) to establish new definition specific for children. **TABLE 12** [6].

- Age: exclude patients with perinatal-related lung disease
- Timing: respiratory failure within 1 week of known insult
- Origin: respiratory failure not fully explained by cardiac function or fluid overload
- Imaging: new unilateral or bilateral infiltrate or infiltrates consistent with acute pulmonary parenchymal disease
- Oxygenation: invasive mechanical ventilation severity stratification is as follows:
  - OI ≥4 to <8 or OSI ≥5 to <7.5 is mild PARDS
  - OI ≥8 to <16 or OSI ≥7.5 to <12.3 is moderate PARDS
  - OI ≥16 or OSI ≥12.3 is severe PARDS
- Oxygenation: noninvasive mechanical ventilation severity (not stratified) is as follows:
  - Full face-mask bi-level ventilation or CPAP ≥5 cmH_2O and
  - PaO_2/FiO_2 ≤300 or SaO_2/FiO_2 ≤264

TABLE 12. THE PALICC CRITERIA FOR PARDS.

CPAP, CONTINUOUS POSITIVE AIRWAY PRESSURE; FIO2, FRACTION OF INSPIRED OXYGEN; MAP, MEAN AIRWAY PRESSURE; OI, OXYGENATION INDEX (WHICH IS (MAP×FIO2×100)/PAO2); OSI, OXYGEN SATURATION INDEX (WHICH IS (MAP×FIO2×100)/SPO2, WITH SPO2 ≤97% REQUIRED FOR ASSESSMENT; PAO2, PARTIAL PRESSURE OF ARTERIAL OXYGEN; SAO2, OXYGEN SATURATION; SPO2, PERIPHERAL CAPILLARY OXYGEN SATURATION.

The 2015 PALICC definition broadens the radiographic requirement to include any new parenchymal infiltrate(s) justified by the variability in radiographic interpretations among clinicians and the infiltrations has no impact on patients outcome. Additional key differences in the PARDS definition include allowing use of pulse oximetry to avoid underestimating ARDS prevalence in children if arterial blood oxygenation measurements are not available. And the utilization of the OI or OSI rather than the PaO2/FiO2 ratio to assess hypoxemia.

2. Definitions and essentials in mechanical ventilation.

2.1 Respiratory mechanics.

Understanding respiratory mechanics is indispensable when managing patients under mechanical ventilation. it's essential in terms of adapting respiratory parameters to patient needs and decision making when problem is diagnosed.

The mechanics of a respiratory cycle (inspiration, expiration) are determined by three variables: flow, volume, and pressure. The interplay among the three variables depends on the characteristics of lung parenchyma and chest wall. These characteristics can be altered in certain diseases such as ARDS.

Pulmonary ventilation is driven by gradient of pressure within the thorax described by Boyle's law. Trans-airway pressure is the pressure gradient between airway opening and alveolus, required to overcome the resistance of the airways and drive the gas flow through the airways. Transpulmonary pressure is the difference between the pressure in the alveolar space and pressure in the pleural space, It increases either with increase in alveolar pressure (such as in positive-pressure ventilation) or with a decrease in pleural pressure, such as in negative-pressure ventilation. Transthoracic pressure is the difference in pressure between alveolar space and body surface, required to distend the lung along with the thoracic cage. Trans-respiratory pressure is the difference between the airway opening pressure and the pressure at the body surface and thus has two components: trans-airway pressure, which overcomes the resistance of airways, and transthoracic pressure, which overcomes the elastance of the lungs and chest wall. **FIGURE 10**.

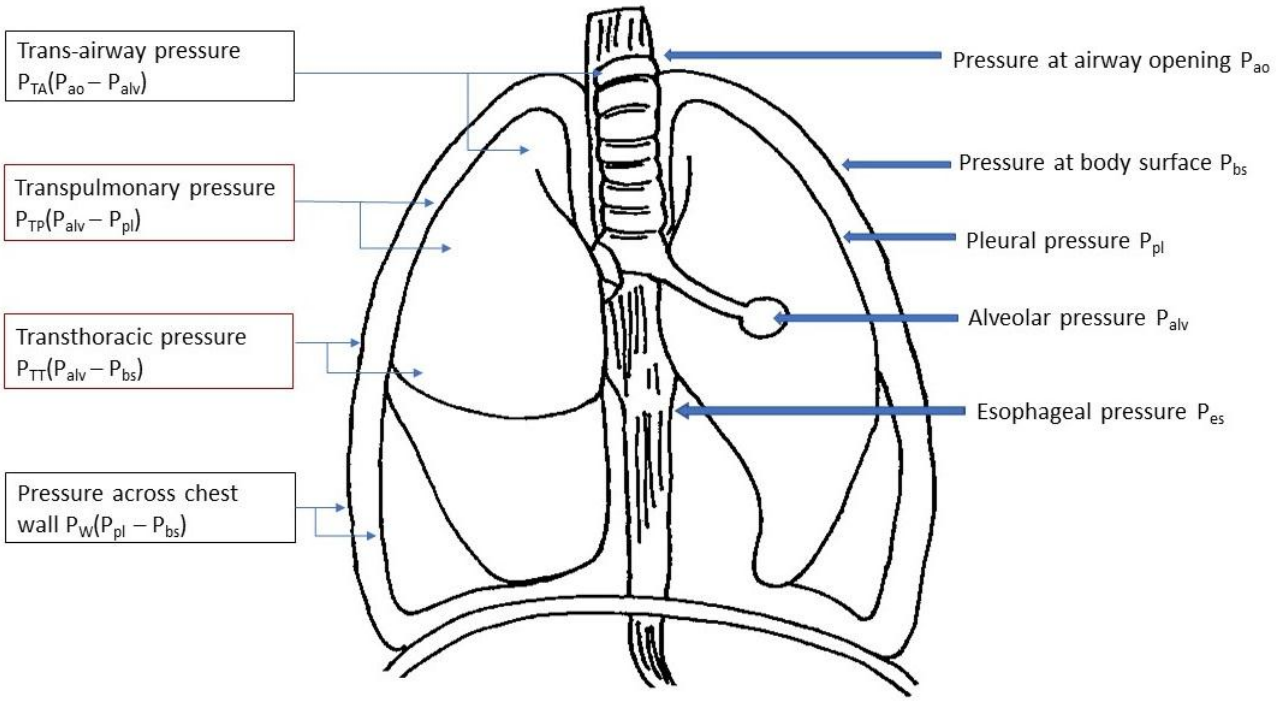


FIGURE 10. THE DIFFERENT PRESSURES AMONG THE RESPIRATORY SYSTEM.

(FIGURE BY SIMRAN KAUR MATTA, MD WWW.ACPHOSPITALIST.ORG)

2.1.1. Elastic Recoil

During autopsy, the lungs deflate when they're taken out of the thoracic cavity and in the other hand, the chest wall increases slightly in volume once the lungs are removed. This occurs because the isolated lungs and chest wall each have their own resting or equilibrium volumes. The lungs tend to occupy the smallest volume and chest wall which tends to occupy the maximum volume due to their elastic recoil. **FIGURE 11.**

Sources of the elastic recoil are elastin and collagen in the lungs, cartilage and muscle in the chest wall.

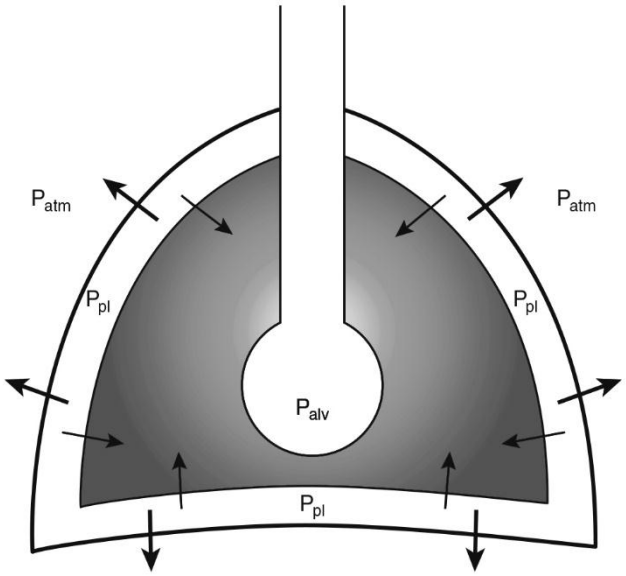


FIGURE 11. SIMPLIFIED DIAGRAM SHOWING PRESSURES ON BOTH SIDES OF CHEST WALL (HEAVY LINE) AND LUNG (SHADED AREA).

THIN ARROWS SHOW DIRECTION OF ELASTIC RECOIL OF LUNG (AT RESTING END-EXPIRATORY POSITION). THICK ARROWS SHOW DIRECTION OF ELASTIC RECOIL OF CHEST WALL. P_{ALV} = ALVEOLAR PRESSURE; P_{ATM} = ATMOSPHERIC PRESSURE; P_{PL} = PLEURAL PRESSURE.

*(from Pittsburgh Critical Care Medicine, Mechanical Ventilation book by **John W. Kreit**)*

2.1.2. Viscous Forces

When applied pressure is achieved to overcome elastic recoil and gas drives into and out of the lungs through the tracheobronchial tree, additional pressure is required to overcome both the friction generated by gas molecules as they move over the surface of the airways, and the cohesive forces between these molecules. Together, these are referred to as viscous forces.

Viscous forces are quantified by resistance (R), which is the ratio of the intramural pressure gradient ($\triangle P_{IM}$) and the resulting Flow (V).

$$R = \Delta P_{IM} / V$$

2.1.3. Compliance and Resistance

Elastic recoil and viscous forces play a very important role in the mechanics of ventilation and both reflect the characteristics of each individual chest wall and lungs in course of disease. Elastic recoil is most often expressed in terms of compliance (C), which is the ratio of the volume change ($\triangle V$) produced by a change in transpulmonary pressure P_{TP} ($\triangle P_{TP} = P_{ALV} - P_{PL}$).

$$C = \Delta V / \Delta P_{TP}$$

Compliance and elastic recoil are inversely related (Elastance = 1/C). When elastic recoil is high, a given pressure change produces a relatively small change in volume, and compliance is low. When elastic recoil is low, the same pressure change produces a much greater change in volume, and compliance is high.

2.1.4. Applied Forces

At any time during inspiration and expiration, sufficient pressure must be applied (P_{APP}) to overcome the viscous forces (P_V) and elastic recoil (P_{ER}) of the lungs and chest wall.

$$P_{APP} = P_{ER} + P_V$$

P_{ER} is the trans-pulmonary pressure of the respiratory system in the absence of gas flow, and is equal to the change in volume (ΔV) divided by respiratory system compliance (CRS), while P_V is the Trans-airway pressure gradient that drives the flow, and P_V equals the product of resistance (R) and flow (V). Rearranging the equation above.

$$P_{APP} = (\Delta V/C_{RS}) + (R \times V)$$

This is called the equation of motion of the respiratory system and it describes the pressure changes related to resistance, flow, volume and compliance.

At any time during the respiratory cycle, the applied pressure must vary directly with resistance, flow rate, and volume and inversely with respiratory system compliance. The pressure required during inspiration is normally supplied by the diaphragm and the other inspiratory muscles. In case of certain pathologies, it can be provided by mechanical ventilator for patients.

2.2.1 In spontaneous Ventilation

- **Inspiration**

The inspiratory muscles don't inflate the lungs directly. Rather, they expand the chest wall, and lung volume increases because the visceral and parietal pleura are attached by a thin layer of pleural fluid. Pleural pressure is normally negative (sub-atmospheric) at endexpiration. That's because the opposing elastic recoil of the lungs and chest wall pulls the visceral and parietal pleura in opposite directions, which slightly increases the volume of the pleural space and decreases its pressure.

As the inspiratory muscles expand the chest wall, lung volume and lung elastic recoil increase. This causes a further drop in P_{PL} , which reaches its lowest (most negative) value at the end of inspiration. The volume of the lungs increases faster than they can fill with air, and P_{ALV} falls. Since P_{AW} remains zero (atmospheric pressure), this produces a pressure gradient that drives air into the lungs. As the lungs fill with air, P_{ALV} rises until both it and air flow return to zero at the end of inspiration. **FIGURE 12.** shows how P_{PL} , P_{ALV}, flow, and volume change throughout inspiration.

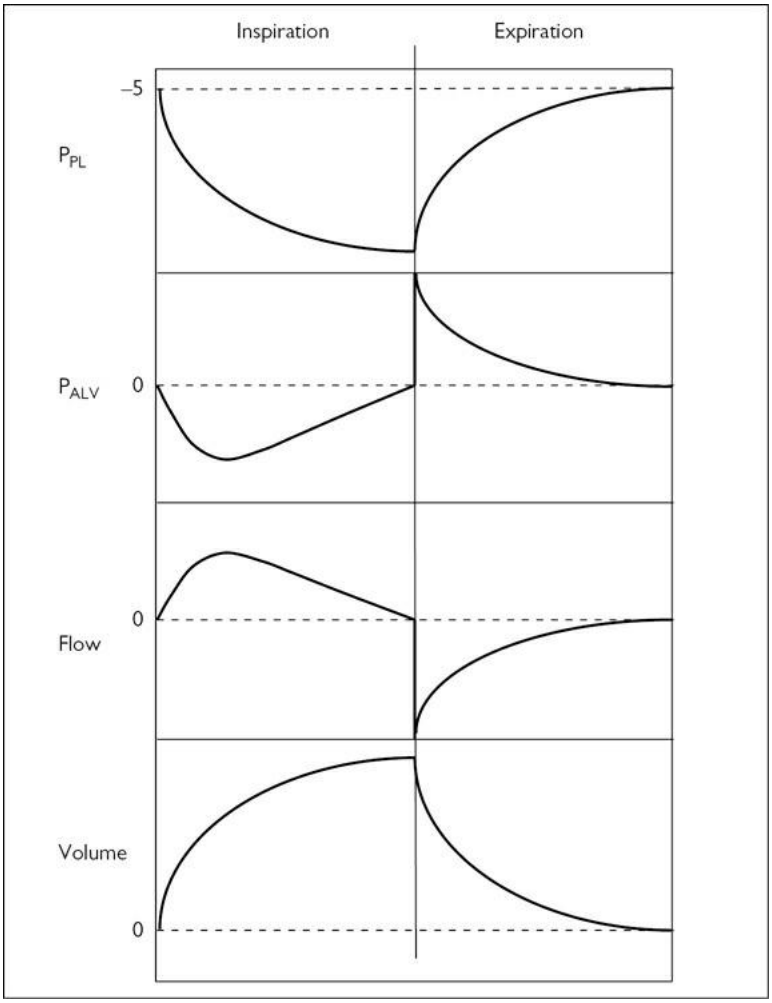


FIGURE 12. THE CHANGE IN PLEURAL (P_{PL}) AND ALVEOLAR (P_{ALV}) PRESSURE, FLOW, AND VOLUME DURING A SPONTANEOUS BREATH. PRESSURE AT THE MOUTH (PAW) REMAINS ZERO (ATMOSPHERIC PRESSURE) DURING SPONTANEOUS VENTILATION.

(FROM PITTSBURGH CRITICAL CARE MEDICINE, MECHANICAL VENTILATION BOOK BY JOHN W. KREIT)

Since the respiratory muscles generate all the pressure (P_{MUS}) required during inspiration, the equation of motion during spontaneous ventilation can be written as following.

$$P_{mus} = (R \times V) + (\Delta V / C_{rs})$$

- **Expiration**

As gas leaves the lungs and the respiratory system returns toward its equilibrium volume, pressure is required only to overcome the viscous forces produced by air flow. In the absence of expiratory muscle activity, the pressure is provided solely by the stored elastic recoil of the respiratory system. Lung volume falls faster than air can leave, P_{ALV} rises above P_{AW} **Figure 12.1**. During such a passive exhalation, P_{ALV} and flow fall exponentially and reach zero only when the respiratory system has returned to its equilibrium position. As lung volume and elastic recoil fall throughout expiration, P_{PL} also becomes less negative and gradually returns to its baseline value.

2.2.2 In Mechanical Ventilation

- **Inspiration**

Mechanical ventilators apply positive (supra-atmospheric) pressure to the airway. In the absence of patient effort, the pressure supplied by the ventilator (P_{AW}) during inspiration, at all times, equal the sum of the pressures needed to balance elastic recoil and overcome viscous forces. During such a passive inflation, P_{ER} is equal to P_{ALV} and the equation of motion becomes.

$$P_{AW} = (R \times V) + (\Delta P/C_{RS})$$

FIGURE 13. shows plots of P_{AW}, P_{ALV}, P_{PL} , flow, and volume during a passive mechanical breath with constant inspiratory flow. An end-inspiratory pause is also shown, during which the delivered volume is held in the lungs for a short time before expiration begins. Since flow is constant, lung volume increases at a constant rate. Assuming that compliance doesn't change during inspiration, there is linear rise in P_{ALV} ($\Delta V/C_{RS}$). Also assuming that resistance doesn't change, P_V ($R\times V$) will be constant. Since P_{AW} is the sum of P_V and P_{ALV}, P_{AW} must also rise at a constant rate.

Pleural pressure increases throughout inspiration as the lungs are inflated and the visceral and parietal pleura are forced closer together. Pleural pressure becomes positive once the chest wall exceeds its equilibrium volume. As lung volume increases, there is a progressive rise in lung transpulmonary pressure (the gradient between P_{ALV} and P_{PL}).

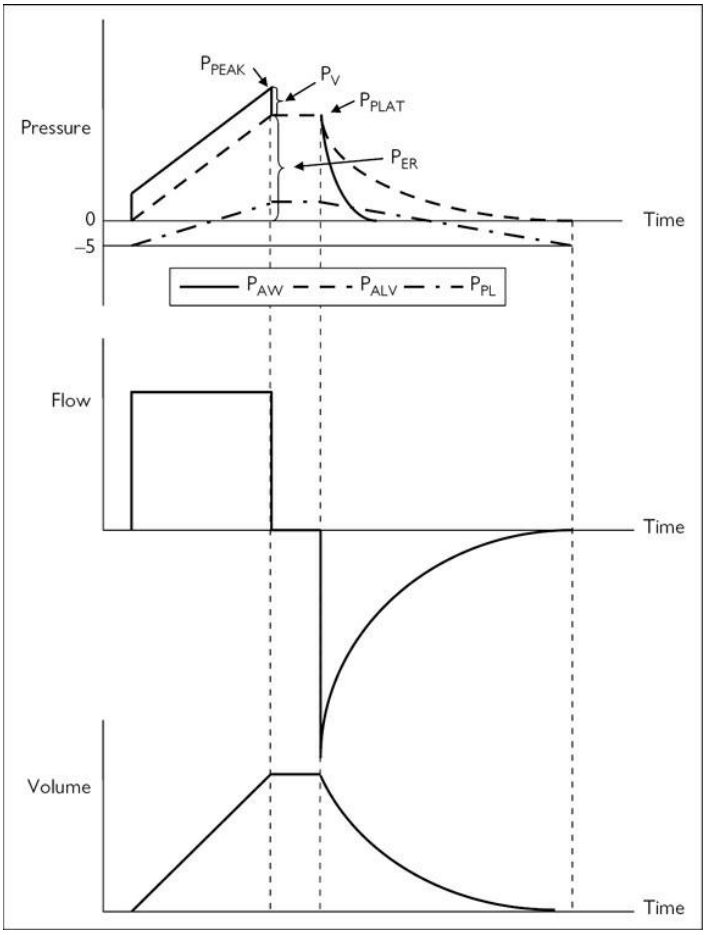


FIGURE 13. SCHEMATIC DIAGRAM OF AIRWAY (P_{AW}), ALVEOLAR (P_{ALV}), AND PLEURAL (P_{PL}) PRESSURE, FLOW, AND VOLUME VERSUS TIME DURING A PASSIVE MECHANICAL BREATH WITH CONSTANT INSPIRATORY FLOW. PEAK (P_{PEAK}) AND PLATEAU (P_{PLAT}) PRESSURE AND THE PRESSURE NEEDED TO BALANCE ELASTIC RECOIL (P_{ER}) AND OVERCOME VISCOUS FORCES (P_V) ARE SHOWN.

(FROM PITTSBURGH CRITICAL CARE MEDICINE MECHANICAL VENTILATION BOOK BY JOHN W. KREIT)

- **Expiration**

Like spontaneous breathing, expiration is normally passive during mechanical ventilation, and gas flow is driven by the stored elastic recoil of the respiratory system. Flow reaches zero, and P_{ALV} and P_{PL} return to their baseline levels only when the entire tidal volume has been exhaled and the respiratory system has returned to its equilibrium position. **FIGURE 13.**

2.3 Respiratory mechanics applied in MV.

The peak airway pressure (P_{PEAK}) is the maximum airway pressure (P_{AW}) reached during a mechanical breath and can be read from the P_{AW}–time curve or the digital display on the ventilator user interface.

During a passive, volume control (VC) breath with constant inspiratory flow, P_{AW} increases linearly with the delivered volume, and P_{PEAK} is reached at end-inspiration (Figure). During pressure control (PC), adaptive pressure control (aPC), pressure support (PS), and adaptive pressure support (aPS) breaths, P_{PEAK} equals the constant P_{AW} maintained throughout inspiration.

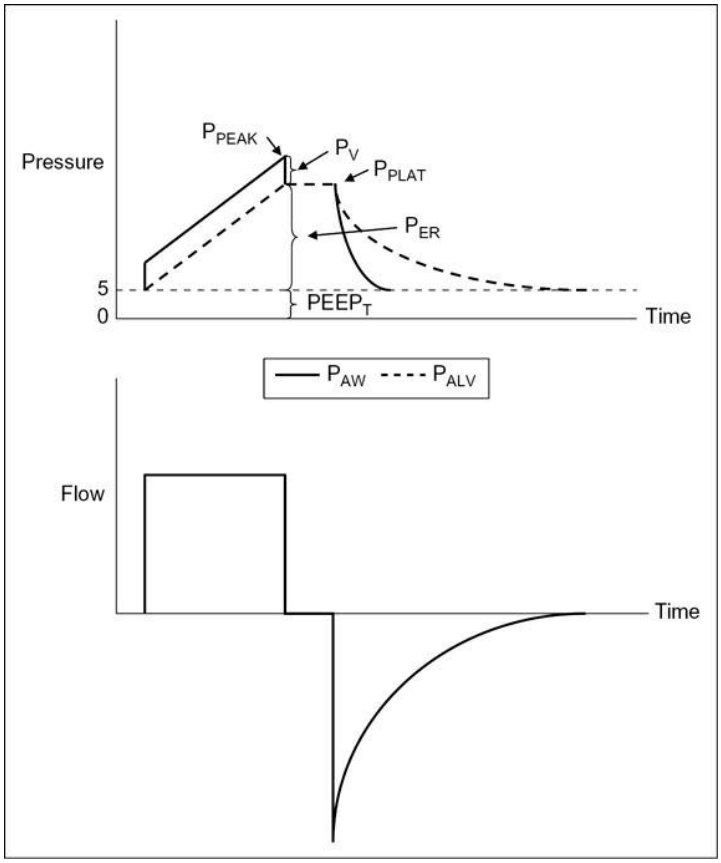


FIGURE 14. SIMULTANEOUS PLOTS OF AIRWAY PRESSURE (P_{AW}) , ALVEOLAR PRESSURE (P_{ALV}) , AND FLOW VS. TIME DURING A PASSIVE, VOLUME CONTROL BREATH WITH CONSTANT INSPIRATORY FLOW AND A BRIEF END-INSPIRATORY PAUSE. TOTAL PEEP (PEEPT) OF 5 CMH2O IS PRESENT.

DURING THE END-INSPIRATORY PAUSE, PEAK AIRWAY PRESSURE (P_{PEAK}) RAPIDLY FALLS TO PLATEAU PRESSURE (P_{PLAT}), WHICH EQUALS ALVEOLAR PRESSURE AT END-INSPIRATION AND THE TOTAL ELASTIC RECOIL PRESSURE OF THE RESPIRATORY SYSTEM. THE DIFFERENCE BETWEEN P_{PLAT} AND PEEPT IS THE PRESSURE NEEDED TO BALANCE THE ELASTIC RECOIL GENERATED BY THE TIDAL VOLUME (P_{ER}). THE DIFFERENCE BETWEEN P_{PEAK} AND P_{PLAT} IS THE PRESSURE NEEDED TO OVERCOME VISCOUS FORCES (PV) JUST BEFORE THE END-INSPIRATORY PAUSE.

(MECHANICAL VENTILATION. PITTSBURGH CRITICAL CARE MEDICINE BOOK BY JOHN W. KREIT)

The plateau pressure (P_{PLAT}) is measured during an end-inspiratory pause, which holds the tidal volume in the lungs for a short time before expiration is allowed to proceed. **FIGURE 14.** shows the effect of an end-inspiratory pause during a passive VC breath. Since there are no viscous forces in the absence of flow, P_{PLAT} is the end-inspiratory alveolar pressure (P_{ALV}). P_{PLAT} can be read from either the graphical or the digital display on the user interface.

During expiration, the respiratory system reaches its equilibrium volume when the elastic recoil of the lungs and the chest wall are equal and opposite. At that point, the respiratory system has no remaining elastic recoil, and P_{ALV} is zero (atmospheric pressure). Mechanical ventilators can, however, be set to increase the equilibrium volume by maintaining positive (supra atmospheric) pressure throughout expiration. This is referred to as positive end-expiratory pressure (PEEP). Total PEEP (PEEPT) is the sum of set or extrinsic PEEP (PEEPE) and intrinsic PEEP (PEEPI) due to dynamic hyperinflation. Total PEEP equals end-expiratory P_{ALV}, which is the total elastic recoil pressure of the respiratory system just before the next mechanical breath. As shown in **FIGURE 14.** P_{ALV} and flow decrease exponentially during expiration, and flow stops only when P_{ALV} has returned to zero (atmospheric pressure) or to the level of PEEPE .

Both the compliance and resistance of the respiratory system can be calculated from measurements obtained during a passive, VC breath **FIGURE 14**. Respiratory system compliance (C_{RS}) over the tidal volume range is equal to the set tidal volume (V_T) divided by the pressure needed to overcome elastic recoil (P_{ER}), which is the difference between P_{ALV} at the end of inspiration (P_{PLAT}) and the end of expiration (PEEPT).

$$C_{RS} = V_T / (P_{PLAT} - PEEPT)$$

Respiratory system resistance (R_{RS}) is equal to the pressure needed to overcome viscous forces (P_V) divided by the end-inspiratory flow rate (V_{EI}) . Since viscous forces disappear during an end-inspiratory pause, P_V is the difference between P_{PEAK} and P_{PLAT}.

$$R_{RS} = (P_{PEAK} - P_{PLAT}) / V_{EI}$$

In patients with ARDS, respiratory system compliance is reduced because extra pressure is needed to open the collapsed alveoli and because minimum volume breathed overinflates healthy aerated alveoli. Moreover, hypoxemia resistant to high fraction of inspired oxygen is one of the major defining elements in ARDS. The refractory hypoxemia is due to the perfusion of fluid-filled and atelectatic alveoli, which produces a right-to-left intra-pulmonary shunt. As the proportion of the cardiac output passing through unventilated alveoli rises, increases in FiO2 have less and less effect on PaO2 , and the P/F ratio falls [7].

3. Conventional mechanical ventilation.

Numerous decisions need to be made once it is determined that a patient requires mechanical ventilation, including ventilator settings, the mode of mechanical ventilation, and the control variables. Importantly, some parameters need to be set for every patient (eg, fraction of inspired oxygen [FiO_2]) whereas others, such as tidal volume (V_t) or inspiratory time (I_T), are dependent on the mode of ventilation selected. The selection of the mode is based on clinician familiarity or institutional preferences.

3.1 Ventilator settings.

- **Tidal volume (V_t).**

  V_t is the quantity of gas delivered with each breath. In general, target tidal volumes in pediatrics range between 5 and 8 mL/kg of ideal body weight (IBW).

- **Positive end-expiratory pressure (PEEP).**

  PEEP is important in preventing airway closure or alveolar collapse and can improve oxygenation.

- **Peak inspiratory pressure (PIP).**

  Ventilators may allow PIP to be set directly or may have a setting for the delta pressure. PIP may also be a dependent variable in modes in which tidal volume is set.

- **Pressure support.**

Pressure support is the amount of support provided by the ventilator to augment each spontaneous breath. Pressure support can be used by itself or in conjunction with other modes of ventilation. Common settings are 5 to 10 cm H_2O, based upon effectiveness of respiratory effort and the diameter of the endotracheal tube.

- **Respiratory rate (RR).**

RR is the number of breaths per minute. The RR may include programmed breaths from the ventilator, spontaneous breaths from the patient, or a combination of the two.

- **Inspiratory time (I_T).**

I_T is the period of time over which the ventilator delivers a breath. Initial settings are largely dependent on age but may be adjusted based on underlying pathophysiology. I_T can also be defined in relation to expiration and the respiratory cycle. The normal I:E ratio is 1:2 or 1:3.

- **Fraction of inspired oxygen (FiO_2).**

Initial FiO_2 is set based on the patient's supplemental oxygen requirement prior to intubation and the clinicians overall assessment of the patient's needs. For patients with initial requirements >0.6, the clinician should ensure planned weaning to a FiO_2 of 0.6 or lower when possible. Common target parameters include maintaining oxygen saturation (SpO_2) of 92 to 97 percent for patients with healthy lungs, but permitting a SpO_2 of 88 to 92 percent or an arterial oxygen tension (PaO_2) >55 mmHg for patients with severe lung disease or acute respiratory distress syndrome (ARDS).

- **Trigger.**

The trigger is the mechanism by which the ventilator initiates an assisted breath. In pediatrics, changes in airflow are used most commonly to trigger breaths, although negative deflection of pressure can also be used. Trigger thresholds are adjusted for age, typically from 0.4 to 1.0 L/minute for infants and up to 0.8 to 2 L/minute for adolescents. Pressure trigger threshold is commonly set at -1 cm H_2O in pediatrics. In those patients without adequate spontaneous respiratory effort, time can be a trigger.

- **Flow rate.**

Flow rates and patterns vary based upon the ventilator mode chosen and clinician settings. The peak inspiratory flow rate can be set directly on the ventilator (constant inspiratory flow modes) or can be calculated by the ventilator for a set V_t (or PIP) and I_T (variable inspiratory flow modes). The inspiratory flow pattern can be adjusted based on the mode of ventilation chosen (eg, variable decelerating flow in pressure-controlled or pressure regulated volume-controlled ventilation).

- **Cycling**.

Cycling identifies the method by which the ventilator is programmed to transition (ie, cycle) from an active inspiratory breath to passive exhalation. Ventilators can be set to use flow or time to define this transition. Flow cycling is commonly set at 25 percent of peak inspiratory flow rate.

3.2 Conventional mechanical ventilation modes.

The mode refers to the method of inspiratory support. Its selection is generally based on clinician familiarity and institutional preferences since there is a paucity of evidence indicating that the mode affects clinical outcome.

Common modes of mechanical ventilation are described in **TABLE 13.**

Modes of mechanical ventilation

Mode	Breath strategy (target)	Trigger		Cycle (breath termination)	Types of breaths		
		Ventilator	Patient		Mandatory	Assisted	Spontaneous
CMV	Volume-limited	Yes	No	Volume	Yes	No	No
	Pressure-limited	Yes	No	Time	Yes	No	No
AC	Volume-limited	Yes	Yes	Volume	Yes	Yes	No
	Pressure-limited	Yes	Yes	Time	Yes	Yes	No
IMV	Volume-limited	Yes	Yes	Volume	Yes	Yes*	Yes*
	Pressure-limited	Yes	Yes	Time	Yes	Yes*	Yes*
APRV		Yes	Yes	Time	Yes	Yes*	Yes*
PSV	Pressure-limited	No	Yes	Flow	No	Yes	No
CPAP		No	No	Flow	No	No	Yes
Tube compensation		No	Yes	Flow	No	No	Yes

Types of breaths:

Mandatory: Breaths are initiated by the ventilator and the ventilator performs the work of inspiration during those breaths

Assisted: Breaths are initiated by the patient, but the ventilator performs at least some of the work of inspiration for those patient initiated breaths

Spontaneous: Breaths are initiated by the patient and the patient performs the entire work of inspiration for those patient initiated breaths

CMV: controlled mechanical ventilation; AC: assist control; IMV: intermittent mandatory ventilation; PSV: pressure support ventilation; CPAP: continuous positive airway pressure; APRV: airway pressure release ventilation; BPAP: bilevel positive airway pressure.

* Note that there is overlap between the types of breaths that can be generated during various modes of ventilation. This overlap is dependent on the ventilator settings. As examples, APRV and IMV are capable of assisted breaths (pressure support added) or spontaneous breaths (no pressure support added). Both assisted and spontaneous breaths depend on the patient's ability to trigger the ventilator.

TABLE 13. THE DIFFERENT MODES OF MECHANICAL VENTILATION AND THE ACCORDING STRATEGY, TRIGGER, CYCLE, AND TYPE OF BREATH FOR EACH MODE.

(FROM UPTODATE.COM BY ROBERT C HYZY, MD, SHIJING JIA, MD GRAPHIC 77391 VERSION 5.0)

Three modes are used in the current pediatric clinical practice the AC, PSV, and the SIMV mode.

1. Assist control (AC).

All programmed breaths are delivered within a fixed inspiratory time (IT). A minimum preset number of breaths are delivered, though a patient may breathe above the programmed respiratory rate. Each breath may be initiated by either the patient or the ventilator, but once initiated, the ventilator will deliver the entire breath during the selected IT or I:E ratio. This mode of ventilation might be used in a patient who has little or no spontaneous respiratory effort either due to pharmacologic sedation with or without neuromuscular blockade, or secondary to underlying illness or injury.

2. Spontaneous (supported) ventilation.

All breaths are spontaneous (ie, patient initiated), and the ventilator augments the patient effort with pressure or volume as set by the clinician. The most common support mode is pressure support ventilation (PSV). PSV applies positive pressure for the duration of each spontaneous breath, thereby increasing tidal volume and offloading the work of breathing.

3. Synchronous intermittent mandatory ventilation (SIMV).

SIMV provides a range of support. The patient's ventilation includes a combination of mandatory and spontaneous breaths. Either the patient or the ventilator can initiate each supported breath, for which the ventilator will deliver the entire breath up to the set respiratory rate. All spontaneous patient breaths beyond the programmed minimum will be unsupported by the ventilator (unless additional PS is specifically programmed, called SIMV + PS). With SIMV, the ventilator breaths are synchronized with patient inspiratory effort. When a mandatory breath is due, the ventilator will wait very briefly for the patient to initiate. If no spontaneous breath is identified, time will trigger the ventilator. With SIMV, the ventilator settings can be adjusted to titrate the amount of support provided.

4. Neurally adjusted ventilatory assist ventilation (NAVA).

Novel modes of ventilation have been developed with alternative triggers. The most common of these approaches is NAVA. It's an investigational ventilatory mode in which the electrical discharge from the diaphragm (ie, diaphragmatic excitation; EAdi) is used to trigger a mechanical breath. When a deflection in the EA_{di} signal greater than the set threshold (typically 0.5 microvolts) is detected by a catheter embedded in a gastric tube, a mechanical breath is delivered. The degree of assist varies with the amplitude of the detected EAdi and an assist level set by the clinician such that there is breath-to-breath variation in the tidal volume. The set assist level is determined by a short empirical adjustment period where the assist level is increased to detect a comfortable and consistent tidal volume for the patient and an EAdi signal that remains flat. **FIGURE 15.**

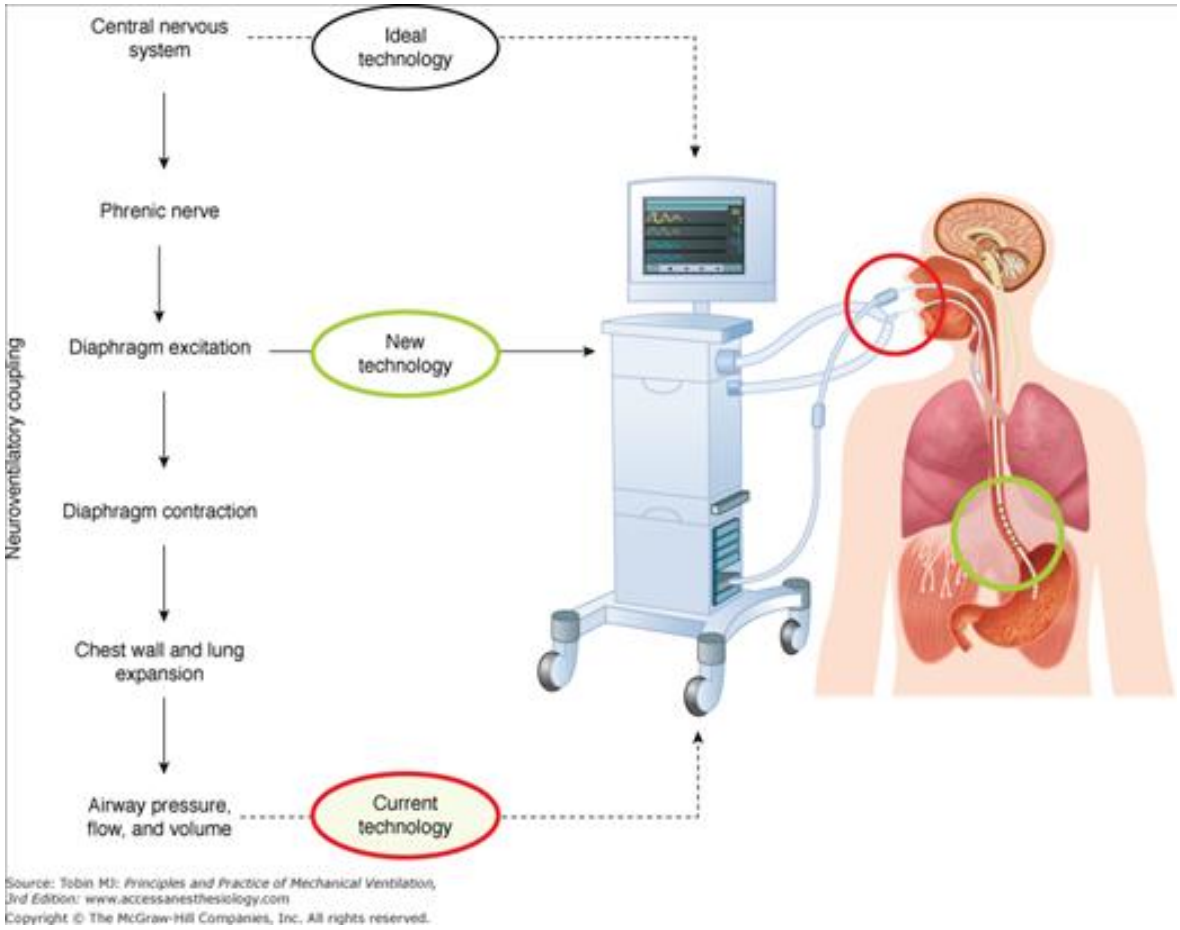


FIGURE 15. GRAPHIC SHOWING NAVA.

LEFT: CHAIN OF EVENTS INVOLVED IN SPONTANEOUS BREATHING, BEGINNING WITH THE RESPIRATORY CENTERS IN THE CENTRAL NERVOUS SYSTEM, THEN PHRENIC-NERVE TRANSMISSION, DIAPHRAGMATIC ELECTRICAL ACTIVITY, DIAPHRAGMATIC CONTRACTION, AND ENDING WITH AIRWAY PRESSURE, FLOW, AND VOLUME (THE NEUROVENTILATORY COUPLING).. DURING NAVA, ELECTRICAL ACTIVITY OF THE DIAPHRAGM IS USED TO CONTROL THE VENTILATOR. RIGHT SIDE: SCHEMATIC OF SETUP FOR NAVA. A FEEDING CATHETER EQUIPPED WITH AN ARRAY OF MINIATURIZED ELECTRODES IS PASSED DOWN THE ESOPHAGUS, WHERE THE ELECTRICAL ACTIVITY OF THE DIAPHRAGM IS RECORDED (GREEN CIRCLE). DIAPHRAGMATIC ELECTRICAL ACTIVITY IS PROCESSED INTO A WAVEFORM, AND IS USED FOR MONITORING NEURAL RESPIRATORY DRIVE (IN ALL MODES) AND FOR CONTROLLING THE TIMING AND MAGNITUDE OF VENTILATOR-DELIVERED PRESSURE DURING NAVA.

Neural-ventilator coupling (ie, time between a spontaneous breath and the delivery of a mechanical breath) is faster with NAVA than with conventional modes of mechanical ventilation. Thus, NAVA has the potential to improve patient-ventilator synchrony (eg, in patients with chronic obstructive pulmonary disease). The success of NAVA depends upon an intact ventilatory drive (ie, patient has to be spontaneously breathing) and is not a plausible mode of ventilation in patients who have blunted or no respiratory drive (eg, hypoventilation due to heavy sedation or cervical spinal cord injury).

3.3 Ventilator control variables.

Each of the previous mode types of mechanical ventilation can be either pressure-controlled, volume-controlled or a combination of both.

* **Pressure-controlled ventilation.**

The clinician sets the PIP and PEEP on the ventilator. Each breath is delivered over a pre-set inspiratory time (IT). As a result, tidal volume and inspiratory flow will be variable, based largely upon the patient's respiratory mechanics (eg, lung compliance and airway resistance). This mode is the most mode utilized in ARDS.

* **Volume-controlled ventilation.**

The tidal volume and inspiratory flow rate (square wave, constant flow) are set on the ventilator. As a result, the tidal volume will be consistently delivered with each breath with variable peak inspiratory pressures. The flow rate can be adjusted to change the IT.

* **Dual-controlled ventilation** (eg, pressure-regulated volume control [PRVC]).

PRVC is a type of ventilation in which breaths are pressure controlled, but the ventilator adjusts the inspiratory flow to target a desired tidal volume. If the delivered tidal volume is low, the ventilator increases the inspiratory pressure on the subsequent breath. This permits effective breath-by-breath tidal volume delivery while minimizing peak pressures by adapting to the changing respiratory mechanics (resistance and compliance) in the patient.

VOLUME-LIMITED or PRESSURE-LIMITED ?

Pressure-limited ventilation is associated with lower peak airway pressures, a more homogeneous gas distribution (less regional alveolar overdistension), improved patient-ventilator synchrony. while volume-limited ventilation only guarantee a constant tidal volume, ensuring a minimum minute ventilation.

3.4. Mechanical ventilation consequences.

3.4.1. Pulmonary effects.

- **Barotrauma.**
- **Ventilator-associated lung injury.**
- **Auto-PEEP.**

Incomplete expiration prior to the initiation of the next breath causes progressive air trapping (ie, dynamic hyperinflation). This accumulation of air increases alveolar pressure at the end of expiration, which is referred to as auto-PEEP. In other words, inspiration is initiated before expiratory airflow from the preceding breath has ceased.

- **Heterogeneous ventilation.**

The distribution of positive pressure ventilation is never uniform because the amount of ventilation is a function of three factors that vary from region to region within the lungs: alveolar compliance, airway resistance, and dependency (upper versus lower lung zones). Compliant, non-dependent regions with minimal airway resistance will be best ventilated. In contrast, stiff, dependent regions with increased airway resistance will be least ventilated.

- **Ventilation/perfusion mismatch.**

Mechanical ventilation can alter two opposing forms of ventilation/perfusion mismatch (V/Q mismatch), dead space (areas that are overventilated relative to perfusion; V>Q) and shunt (areas that are underventilated relative to perfusion; V<Q). By increasing ventilation (V), the institution of positive pressure ventilation will worsen dead space but improve shunt.

- **Increased dead space.**

Dead space reflects the surface area within the lung that is not involved in gas exchange. It is the sum of the anatomic plus alveolar dead space. Alveolar dead space (also known as physiologic dead space) consists of alveoli that are not involved in gas exchange due to insufficient perfusion (ie, overventilated relative to perfusion). Positive pressure ventilation tends to increase alveolar dead space by increasing ventilation in alveoli that do not have a corresponding increase in perfusion, thereby worsening V/Q mismatch and hypercapnia.

- **Reduced shunt.**

An intraparenchymal shunt exists where there is blood flow through pulmonary parenchyma that is not involved in gas exchange because of insufficient alveolar ventilation. Patients with respiratory failure frequently have increased intraparenchymal shunting due to areas of focal atelectasis that continue to be perfused (ie, regions that are underventilated relative to perfusion). Treating atelectasis with positive pressure ventilation can reduce intraparenchymal shunting by improving alveolar ventilation, thereby improving V/Q matching and oxygenation. This is particularly true if PEEP is added.

- **Diaphragm.**

Mechanical ventilation itself causes diaphragmatic muscle atrophy, a phenomenon called ventilator induced diaphragmatic dysfunction (VIDD). Controlled mechanical ventilation may lead to a very rapid type of disuse atrophy involving the diaphragmatic muscle fibers, which can develop within the first day of mechanical ventilation. The optimal approach to potentially obviate this phenomenon clinically is unknown. Diaphragmatic atrophy during mechanical ventilation may be associated with prolonged mechanical ventilation, difficulty weaning, prolonged ICU stay, and a higher risk of complications.

3.4.2. SYSTEMIC EFFECTS.

- **Hemodynamics.**

Positive pressure ventilation frequently decreases cardiac output, which may cause hypotension. There are several mechanisms that contribute to the fall in cardiac output:

- **Decreased venous return.**

The amount of venous return is determined by the pressure gradient from the extrathoracic systemic veins to the right atrium. Intrathoracic and right atrial pressure increase during positive pressure ventilation, thereby reducing the gradient for venous return. This effect is accentuated by auto-PEEP, applied PEEP, or intravascular hypovolemia.

- **Reduced right ventricular output.**

Alveolar inflation during positive pressure ventilation compresses the pulmonary vascular bed. This increases pulmonary vascular resistance, thereby reducing right ventricular output. In a study of 21 patients with ARDS, titrating the PEEP from 5 cm H_2O to achieve a plateau pressure of 30 cm H_2O was associated with a fall in cardiac output and an increase in right ventricular afterload[14]. This effect was mitigated by increasing the central venous blood volume via a passive leg raise maneuver.

- **Reduced left ventricular output.**

Increased pulmonary vascular resistance can shift the interventricular septum to the left, impair diastolic filling of the left ventricle, and reduce left ventricular output.

In contrast to these adverse effects, positive pressure ventilation may be beneficial in patients with left ventricular failure. Specifically, increased intrathoracic pressure can improve left ventricular performance by decreasing both venous return and left ventricular afterload [15].

These hemodynamic effects are the result of positive airway pressure being transmitted to the surrounding structures of the thorax. The extent to which this occurs varies according to chest wall and lung compliance. Transmission of airway pressure is greatest when there is low chest wall compliance (eg, fibrothorax) or high lung compliance (eg, emphysema); it is least when there is high chest wall compliance (eg, sternotomy) or low lung compliance (eg, ARDS, heart failure).

4. Non-invasive Ventilation.

NIV is a mechanical ventilation support that delivers continuous positive airway pressure (CPAP) or bilevel positive airway support (BPAP) through interface (e.g, nasal prongs or mask, face mask, or helmet) without endotracheal intubation.

1.CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP).

Continuous positive airway pressure refers to the delivery of a continuous level of positive airway pressure. It is functionally similar to PEEP. The ventilator does not cycle during CPAP, no additional pressure above the level of CPAP is provided, and patients must initiate all breaths.

2.BILEVEL POSITIVE AIRWAY PRESSURE (BPAP).

Bilevel positive airway pressure is a mode used during non-invasive positive pressure ventilation (NPPV). It delivers a pre-set inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The tidal volume correlates with the difference between the IPAP and the EPAP.

The term "BiPAP" is often used incorrectly to refer to the BPAP mode. BiPAP is the name of a portable ventilator manufactured by Respironics Corporation; it is just one of many ventilators that can deliver BPAP.

5. PATHOPHYSIOLOGY OF PARDS.

The lung parenchyma undergoes substantial structural remodelling and growth during childhood with maturation to be complete sometime in adolescence. At birth, there are less than 50 million alveoli and most of alveolarization occurs by 2 years of age. A typical pair of fully developed human lungs contains about 500 million alveoli , producing ~50 m2 of surface area to serve the purpose of gas exchange.

Alveoli consists of a single layer of alveolar epithelial cells, capillary endothelial cells. Intervening the epithelial and endothelial layers is the basement membranes. both cell layers form the alveolar epithelial/endothelial barrier. **FIGURE 16.**

The alveolar epithelium consists of:

1- Type I cells which are large thin cells that make up 90% of the alveolar surface area and they are the primary site of gas exchange.

2- Cuboidal alveolar type II cells that make 10% of the alveolar surface area, and they are responsible for surfactant production, regulating the removal of excess alveolar fluid through sodium-dependant channels, and proliferation, differentiation into type I cells after injury.

The thin barrier is absolutely essential for normal lung function due to its role in allowing gas exchange, while maintaining separation between the aqueous and gaseous compartments.

The oncotic pressure, low hydrostatic pressure, ions transport channels, and the interstitial lymphatic drainage form the hemodynamic properties of the pulmonary circulation that allow the formation of a thin layer of fluid called alveolar wall liquid (AWL). The AWL coats the inside surface of the alveolar epithelium and it facilitates gas exchange and provide a liquid milieu for dispersal of surfactant molecules, which are important both in reducing surface tension and in preventing alveolar collapse.

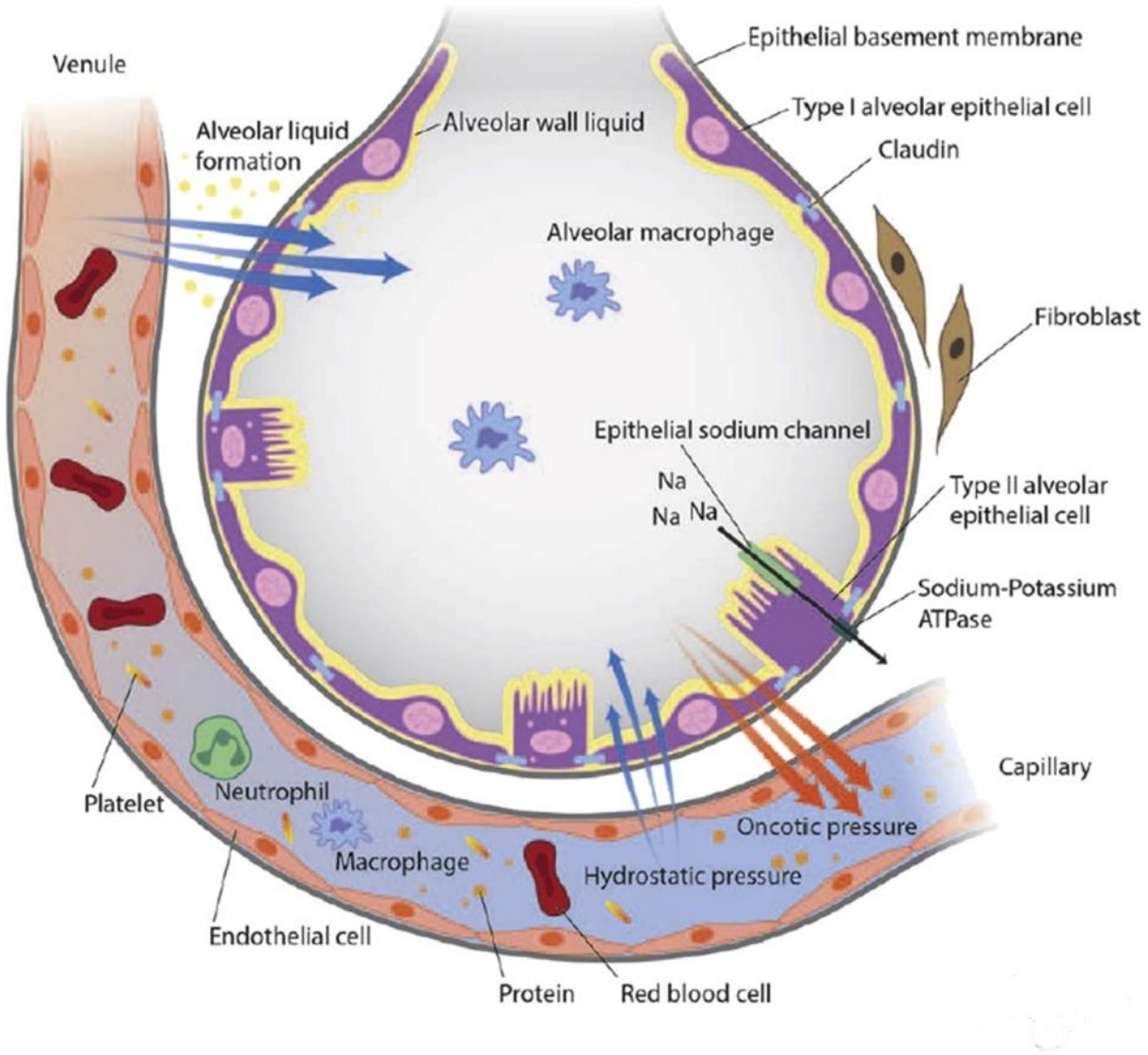


FIGURE 16. SCHEMATIC OF HEALTHY ALVEOLI.

THE ALVEOLAR EPITHELIUM AND CAPILLARY ENDOTHELIUM ARE INTACT. THE CHARACTERISTICS OF THE PULMONARY CIRCULATION AND INTACT EPITHELIAL ENDOTHELIAL BARRIER ALLOW FOR FORMATION OF THE ALVEOLAR WALL LIQUID (AWL) WHILE MAINTAINING THE AIRFILLED, FLUID−FREE, STATUS OF THE ALVEOLI. THE AWL FACILITATES GAS EXCHANGE AND IS A MEDIUM FOR DISPERSAL OF SURFACTANT, WHICH IS ESSENTIAL FOR MAINTAINING ALVEOLAR STABILITY AND HOST DEFENSES. THE INTACT SODIUM−DEPENDENT VECTORIAL TRANSPORT ACROSS TYPE II ALVEOLAR EPITHELIAL CELLS REGULATES THE REMOVAL OF EXCESS ALVEOLAR FLUID.

In ARDS, there is a destruction of the alveolocapillary barrier with initiation of cascades of inflammation **FIGURE 17**. The natural history of ARDS occurs in 3 time course phases.

a) Acute Phase 1-7 days.

The acute phase lasts for and occurs after activation of the immune system in response to a clinical insult. It is characterized by:

- The disruption of the alveolocapillary interface leading to interstitial and alveolar protein rich edema.
- Accumulation of neutrophils, macrophages and red blood cells in alveoli with extensive release of cytokines.

b) Reparative phase 7-21 days.

In this phase, alveolar edema is reabsorbed and there is early repair with proliferation of alveolar epithelial type II cells. Type II cells differentiate into new type I cells to reform the alveolar wall. There is also fibroblasts proliferation and re-organization of lung tissue with some collagen deposition.

c) Fibrotic phase >21 days.

This phase is accompanied by further accumulation of mononuclear cells and alveolar macrophages in alveoli and progression of fibrosis along with alveolar epithelial repair. In most patients resolution progresses without fibrosis with gradual reabsorption of formed edema and regression of inflammation. Fibrosis Develops in certain patients secondary to excessive collagen deposition.

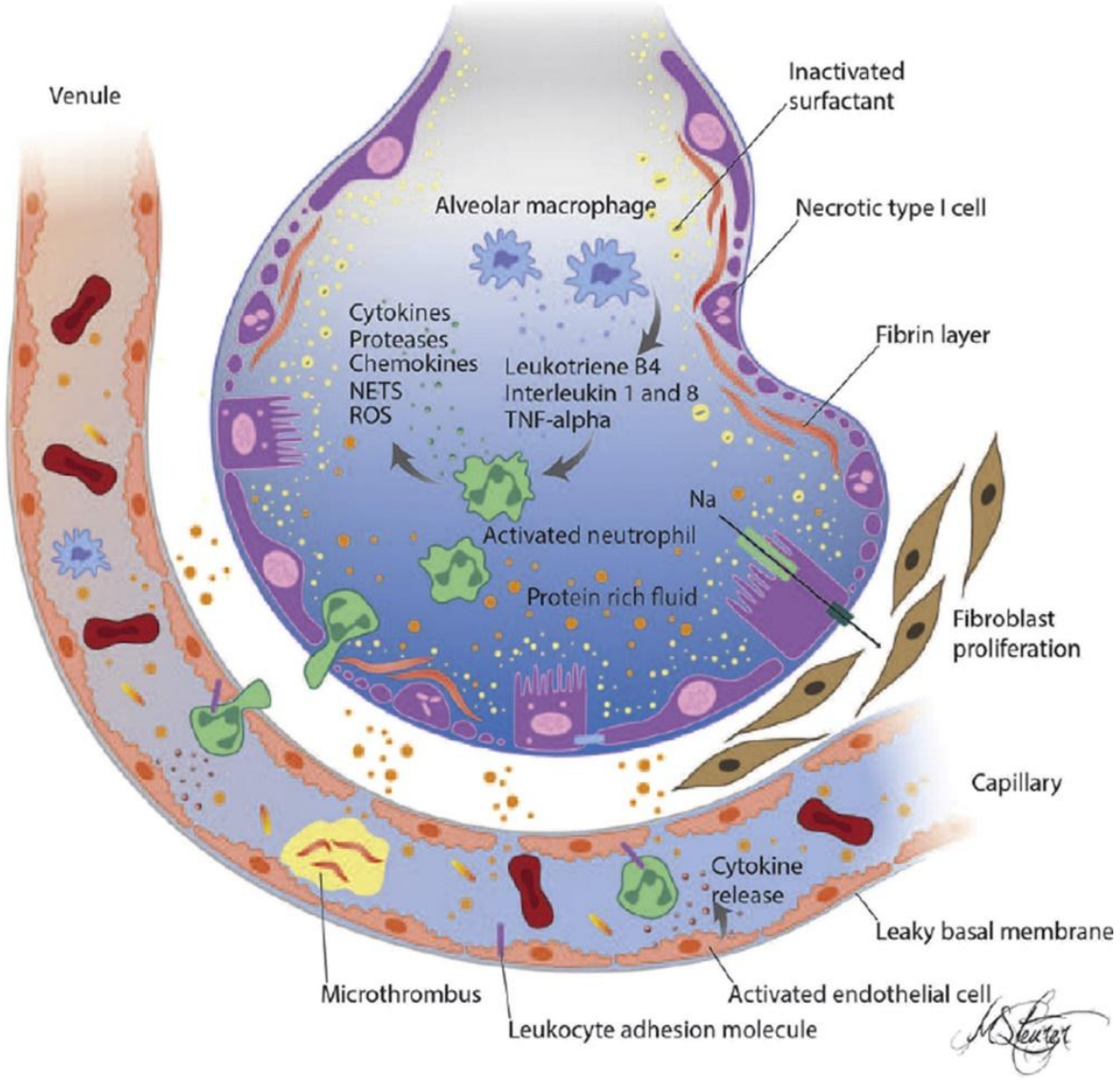


FIGURE 17. SCHEMATIC OF PATHOPHYSIOLOGY IN ARDS.

THERE IS A LOSS OF EPITHELIAL AND ENDOTHELIAL BARRIER INTEGRITY AND LOSS OF FUNCTION LEADING TO INCREASED PERMEABILITY PULMONARY EDEMA. SOLUTES AND LARGE MOLECULES SUCH AS ALBUMIN ENTER THE ALVEOLAR SPACE. IN THE PRESENCE OF PROINFLAMMATORY MEDIATORS AND ACTIVATED ENDOTHELIUM, LEUKOCYTES TRAFFIC INTO THE PULMONARY INTERSTITIUM AND ALVEOLI. THERE IS ACTIVATION OF COAGULATION AND DEPOSITION OF FIBRIN IN CAPILLARIES AND ALVEOLI WITH INCREASED CONCENTRATIONS OF FIBRINOGEN AND FIBRINDEGRADATION PRODUCTS IN THE EDEMA FLUID. SURFACTANT DEPLETION AND DEGRADATION RESULT IN LARGE INCREASES IN SURFACE TENSION AND LOSS OF ALVEOLAR SHAPE AND INTEGRITY. RECOVERY IS PRECEDED BY FIBROBLAST PROLIFERATION NETS: NEUTROPHIL EXTRACELLULAR TRAPS, ROS: REACTIVE OXYGEN SPECIES.

(FROM SAPRU A, FLORI H. PATHOBIOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME).

5.1. INFLAMMATORY DYSFUNCTION.

Inflammation is essential to fight against pathogens and limit its dissemination. Many alterations in epithelial and endothelial structure occurs when inflammatory response is mediated by the immune system. However, the release of anti-inflammatory agents make the balance needed and make the immune response not exaggerated. In ARDS, there is imbalance in these agents leading to exaggerated immune response that would further cause damage to epithelial endothelial barrier.

If the initial insult is in the lung (pneumonia, aspiration, pulmonary contusion, and so forth), Inflammation mediated by the innate immune system, in response to infectious agents or tissue damage, is triggered by the presence of pathogen-associated molecular patterns, such as lipopolysaccharide (LPS) found in molecules derived from pathogens and/or danger associated molecular patterns (DAMPs). Pathogen-associated molecular patterns and DAMPs interact with Toll-like receptors expressed on macrophages and dendritic cells. This promotes the release of cytokines and chemokines (IL-1B, TNF-a, IL-6, and IL-8) and result in activated leukocytes most important neutrophils.

The role of neutrophils is to protect the host by phagocytizing organisms and releasing antimicrobial agents such as Reactive Oxygen Species, proteases (serine and matrix metalloproteinases [MMPs]), and antimicrobial polypeptides associated with the release of NETs (neutrophil extracellular traps), which are fibrillary networks composed of chromatin (DNA and histones). These antimicrobial proteins and NETs released by neutrophils may paradoxically cause damage to the barrier.

In cases where the triggering inflammatory insult is indirect (non-pulmonary sepsis, trauma, transfusion, and so forth), systemic inflammation results in release of cytokines and activated neutrophils along with stimulated macrophages in blood circulation. The activated leukocytes and the exaggerated immune response gain the pulmonary circulation, interacts with pulmonary endothelium causing cellular hyperpermeability and disruption of the barrier.

5.2. THROMBOSIS AND FIBRINOLYSIS DYSFUNCTION.

Inflammation and coagulation are critical host defense in response to infection or injury. The lung endothelium provides the surface that integrates inflammatory pathways of the innate immune system with the coagulation cascade. Endothelial Cells orchestrate the immune and hemostatic response by shifting from their normal antithrombotic and anti-inflammatory phenotype to an “activated” state of endothelial “dysfunction”, characterized by prothrombotic and proadhesive properties. launched by a variety of stimuli, including hypoxia, cytokines, chemokines, inflammatory mediators, and activated platelets and neutrophils.

Key events in this transformation are the expression of adhesion molecules to leukocytes and platelets on the Endothelium Cell surface in addition to the expression of activators of the humoral clotting system, including tissue factors (TF) and Von Willebrand factor (vWF) .

Intravascular thrombi may form on denuded vessel walls following Endothelial Cells desquamation via activation of the intrinsic coagulation pathway(I, II, IX, X, XI, and XII). They may also form by activation of the extrinsic pathway (I, II, VII, and X) initiated by TF expression on endothelial cell and other cells, including macrophages. Cytokines such as IL-6, induce TF expression along with vWF mediating platelet adhesion, whereas TNF-α blocks the fibrinolytic and coagulation-inhibiting pathways.

Initiation of the extrinsic coagulation pathway by TF leads to proteolytic cleavage of prothrombin and thrombin release, which has important downstream effects, including cleavage of fibrinogen to fibrin to form fibrin layer and platelet activation by binding to proteinase-activated receptors. Thrombin also acts on endothelium cells via proteinase-activated receptors and evokes several effects, including calcium release, endothelial contraction, and increased permeability.

5.3. ALVEOLAR EPITHELIAL DYSFUNCTION AND INJURY.

During ARDS, there is substantial damage to the lung epithelium. AT-I cell necrosis, partially mediated by neutrophils, results in loss of tight junction proteins. Tight junctions in the lung epithelium control paracellular permeability to solutes, proteins, and ions. This leads to impaired removal of excess alveolar fluid by AT-II cell through the sodium-dependant vectorial transport. The most important of these junction proteins belongs to the claudin family, such as Claudin-4 that is expressed at high levels in both AT-I and AT-II cells.

5.4. PULMONARY ENDOTHELIAL DYSFUNCTION AND INJURY.

While proinflammatory process is ongoing, endothelial activation is followed by functional and, at a second stage, structural endothelial injury. Activated pulmonary endothelium expresses leukocyte adhesion molecules and produces cytokines, making it procoagulant and upregulates leukocyte antigen molecules.

Thrombomodulin is a transmembrane protein found on the surface of endothelial cells that facilitates the thrombin-mediated conversion of natural anticoagulant protein C to activated protein C, has roles in coagulation, fibrinolysis, and inflammation causing alteration in endothelium structure. Endothelial-specific proteins, such as vascular endothelial growth factor (VEGF), and angiotensin-converting enzyme (ACE) are incriminated in endothelial damage.

5.5. SURFACTANT DYSFUNCTION.

Surfactant is produced by AT-II cells, its composed of 90% lipid and 10% protein. The lipid content contains primarily phospholipid (dipalmitoylphosphatidylcholine) which is responsible for the biophysical function of surfactant. The large hydrophilic proteins, surfactant protein (SP)-A and SP-D, play an important role in host defense and immune modulation, whereas hydrophobic proteins, SP-B and SP-C takes part in modulating biophysical properties by reducing

surface tension at the air-water interface in the alveoli, thereby preventing collapse of alveoli at end-expiration.

Oxidation of phospholipid and SP-B results in changes of phospholipid composition and loss of SP-B. The loss in surfactant activity increases surface tension causing fall in pulmonary compliance and alveolar instability translated by areas of atelectasis [8].

5.6. VENTILATOR INDUCED LUNG INJURY (VILI).

BAROTRAUMA, VOLUTRAUMA, ATELECTRAUMA and BIOTRAUMA.

Mechanical ventilation is indispensable advanced life support in patients undergoes general anesthesia for surgery or critical ill patients in ICU for adequate gas exchange. however, MV may induce injury to healthy lungs or cause further damage in already damaged lungs such as in ARDS. Lung damage or injury is termed ventilator induced lung injury (VILI). In 1970s, preclinical studies has suggested the contribution of hight tidal volume and elevated plateau pressure to worsen lung injury [9]. For many years The standard therapy with mechanical ventilation support included high tidal volumes (12-15ml per kg PBW). The first clinical importance of VILI was provided by the landmark of ARDS network in 2000 suggesting low tidal volume ventilation is associated with decreased mortality by 9% [10]. The landmark of low tidal volume has led to the concept of lung protective strategy, which is based on low tidal volume(3-6ml per kg PBW) and limited plateau pressure (30 cm H_2O) to minimize lung injury. Nevertheless, the debate is still ongoing about the optimal ventilator strategy .

Ventilation at high pressures can lead to barotrauma, manifested in pneumothorax or subcutaneous emphysema. High tidal volumes in mechanical ventilation cause alveolar overdistension and lung strain (the associated deformation of a structure to an external load in relation to its resting state). The applied forces

cause mechanical destruction of anatomical lung structure. The key inciting features of biophysical lung injury are alveolar overdistention (volutrauma, barotruama), and the repetitive opening of collapsed alveoli (atelectrauma) **(FIGURE 18-B)**. Overstretching and the cyclic opening-closing of alveoli results in injury and releasement of inflammatory mediators that may cause further injury to lung and distal organs (biotrauma) **(FIGURE 18-C)** [11]. The exact mechanism of volutrauma still unknown. However, it has been proposed that stretch-activated ion channels, such as 2-poredomain potassium channels, may play an important role in the development and propagation of ventilator induced lung injury by regulating inflammatory mediator secretion, epithelial cell detachment, and cytoskeletal remodelling [12].

Volutrauma, barotrauma can be minimized by the use of low tidal volume and limited plateau pressure. Atelectrauma is minimized by the application of continuous positive pressure at end expiratory (PEEP) to maintain the alveoli open during MV.

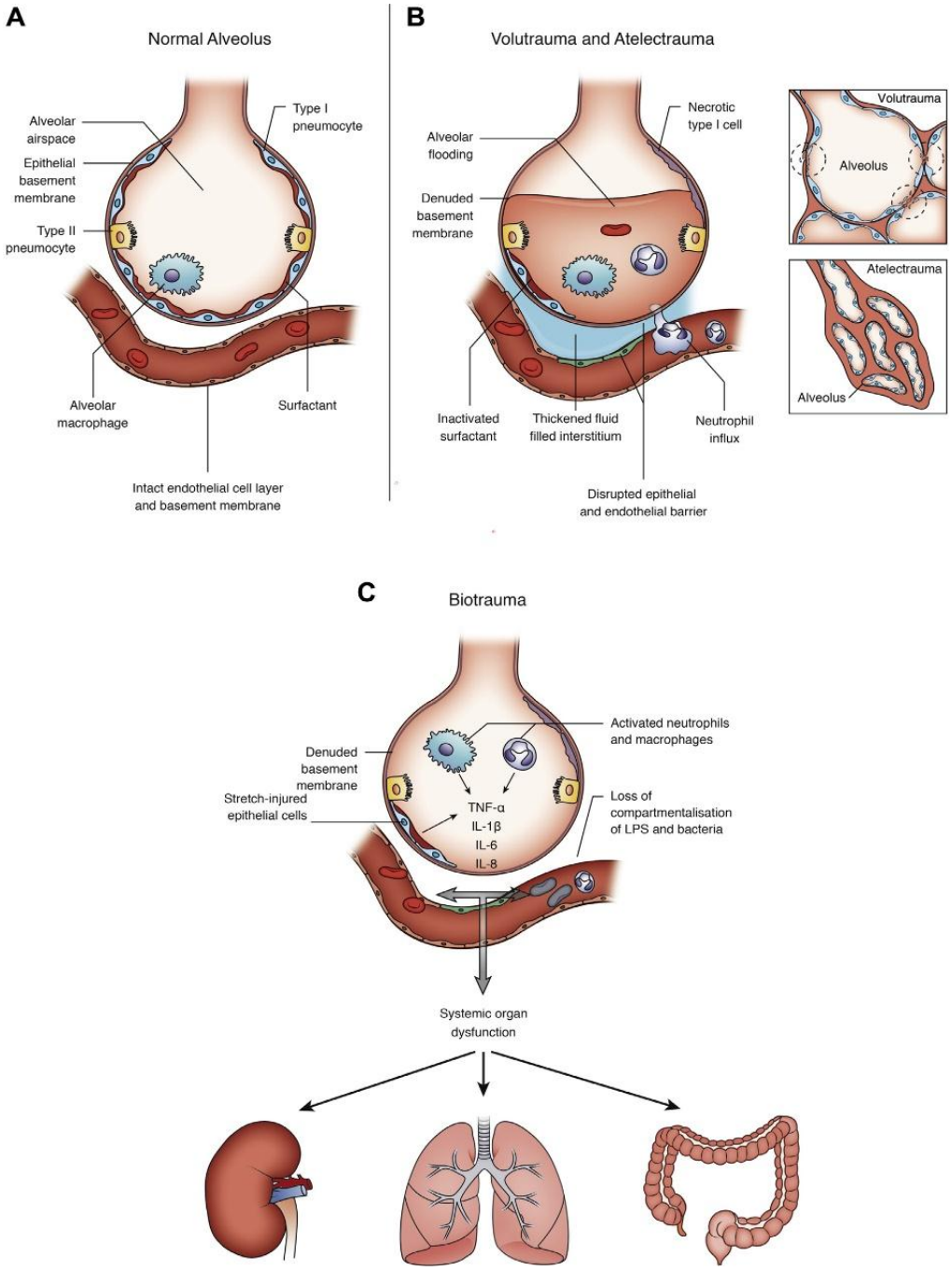


FIGURE 18. A, THE NORMAL ALVEOLUS. B, INJURED ALVEOLI. VOLUTRAUMA AND ATELECTRAUMA DURING MECHANICAL VENTILATION RESULT IN FURTHER DISRUPTION OF THE ALVEOLAR–CAPILLARY BARRIER AND INCREASED PERMEABILITY, A HALLMARK OF EXPERIMENTAL VILI. C, MECHANICAL FORCES ALSO INDUCE AN INCREASE IN THE CONCENTRATIONS OF PROINFLAMMATORY MEDIATORS IN THE DISTAL AIRSPACES OF THE LUNG. THE LOSS OF COMPARTMENTALIZATION IN THE LUNG RESULTS IN THE RELEASE OF THESE MEDIATORS INTO THE SYSTEMIC CIRCULATION WHERE THEY MAY PLAY A ROLE IN END–ORGAN DYSFUNCTION (BIOTRAUMA).

(from Biotrauma and Ventilator-Induced Lung Injury Clinical Implications by Gerard F. Curley et al. journal.publications.chestnet.org)

5.7. Resolution and repair.

Return of normal structure and function involves resolution of inflammation, repair of the lung epithelial/endothelial, and removal of fluid without the generation of fibrotic tissue **FIGURE 19**.

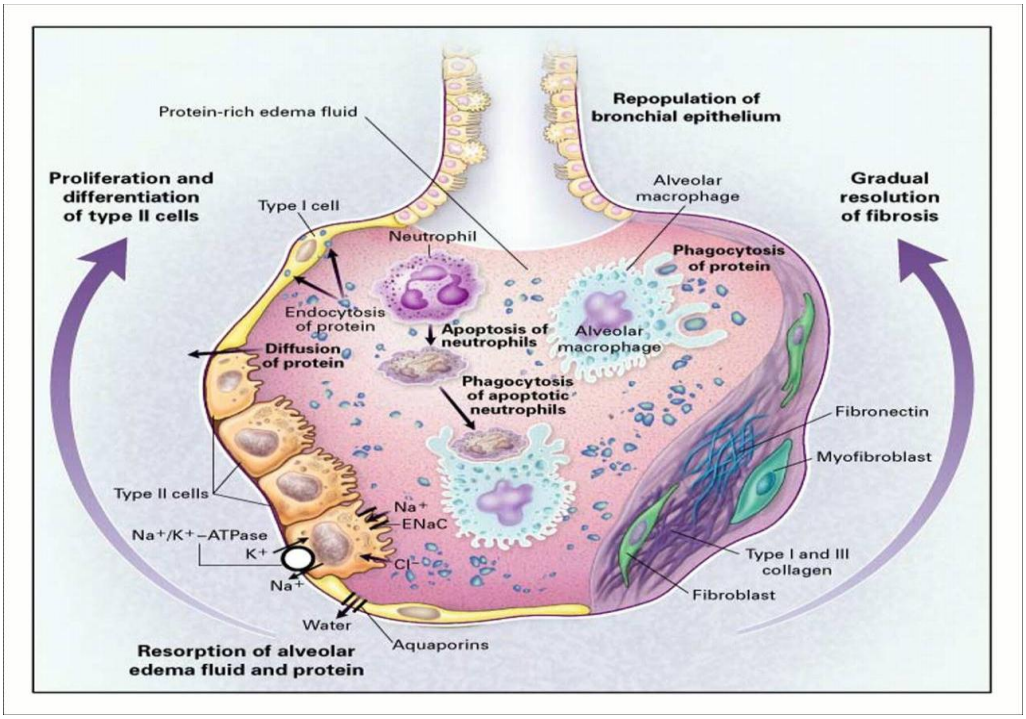


FIGURE 19. MECHANISMS OF RESOLUTION AND REPAIR OF INJURED ALVEOLI.

(from Bakowitz. The Scandinavian Journal of Trauma, 2012

http://www.sjtrem.com/content/20/1/54)

Ending an acute inflammatory event is an active, carefully orchestrated process that begins early in the inflammatory response . Although anti-inflammatory mediators are involved in limiting inflammation, there are also proresolution mediators that act to end inflammation and restore tissue homeostasis without causing immune suppression. Proresolution mediators include several classes of signalling molecules generated from polyunsaturated fatty acids: lipoxins, resolvins, and protectins. These agents signal the recruitment of macrophages, the phagocytosis of apoptotic

neutrophils, the secretion of anti-inflammatory molecules such as IL-10 and transforming growth factor (TGF)-β.

Very little is known about the repair of the lung endothelium; however, platelets have been implicated in extrapulmonary vascular repair and remodelling, suggesting they may have a role in endothelium repair. In contrast, repair of the epithelium has been subject to much research.

Epithelium repair is a complex process involves epithelial cell migration, proliferation and differentiation. During the early stages of epithelial repair, Scar tissue is formed to preserve alveolar integrity and prevent further alveolar edema. This fibrotic tissue is removed by matrix metalloproteinases (MMPs), a family of enzymes that digest extracellular fibers during the repair process and appear to be involved in facilitating migration of progenitor cells, and in remodeling Extra Cellular Matrix (ECM). Migration and proliferation of the epithelial progenitor cells are regulated by a variety of soluble factors released in response to injury in the lung. These factors include members of the epidermal growth factor family (epidermal growth factor and TGF-α) and fibroblast growth factor family (hepatocyte growth factor, KGF, fibroblast growth factor-10).

Progenitor epithelial cells responsible for repair of the alveolar epithelium are AT-II cells that migrate, proliferate, and differentiate into type I cells. However, recent studies in rodent models suggest that there may be other lung progenitor cells involved in repair of the lung epithelium, including Clara cells, integrin α6β4 alveolar epithelial cells, and Scgb1a1-expressing cells. Interestingly, there is also evidence of lung stem cells population in human lungs that may be involved in repair of lung alveoli. Once the alveolar permeability barrier is re-established, removal of lung edema occurs via the active transport of sodium and chloride through epithelial cell ion channels (eNAC and CFTR).

Fibroproliferative response is driven by fibrocytes, fibroblasts and myofibroblast, leading to deposition of fibronectin, collagens I and III, and other components of the extracellular matrix. Pulmonary fibrosis is due to excessive deposition of fibronectin and collagens. That is a result of imbalance between profibrotic (e.g. transforming growth factor (TGF)-β, interleukin-1β, platelet-derived growth factor and lysophosphatidic acid) and antifibrotic (e.g. prostaglandin E2, keratinocyte growth factor and hepatocyte growth factor) [13].

6. DIAGNOSIS OF PARDS.

Most of the time ARDS occurs in hospitalized or critically ill patients. Most patients present in the acute onset of ARDS with shortness of breath. If the cause is pneumonia, the patient may present with cough produces purulent sputum. Physical examination may reveal signs of moderate or severe respiratory distress, increased work of breathing, tachycardia, drop in oxygen saturation on room air or resistant to oxygen supplement, hypoxemia may manifest with cyanosis in fingernail beds. Clinical deterioration may be hyper acute such in transfusion related acute lung injury (TRALI) or may develop slowly over a period of hours to days.

The PALICC group set criteria to establish the diagnosis of PARDS [6] (**Table 4)**.

Age	Exclude patients with perinatal related lung disease			
Timing	Within 7 d of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Noninvasive ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥ 5 cm H_2O[2] PF ration ≤ 300 SF ration ≤ 264[1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.[3]			
Chronic Lung Disease	Standard criteria above for age, timing and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular Dysfunction	Standard criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

TABLE 14. PALICC CRITERIA FOR PARDS.

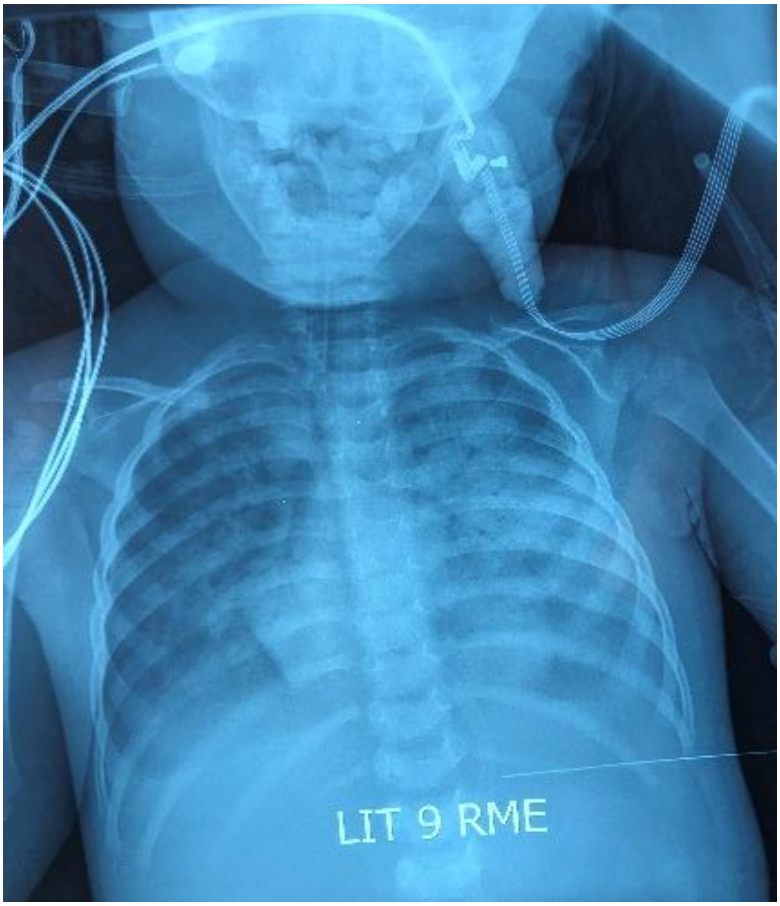
CPAP, CONTINUOUS POSITIVE AIRWAY PRESSURE; PF RATION, PAO2/FIO2; SF RATION, SPO2/FIO2; PAO2, ARTERIAL OXYGEN PARTIAL PRESSURE; FIO2, FRACTION OF INSPIRED OXYGEN; OI, OXYGENATION INDEX = [(FIO2 X MEAN AIRWAY PRESSURE X 100)/PAO2]; OSI, OXYGEN SATURATION INDEX = [(FIO2 X MEAN AIRWAY PRESSURE X 100)/ SPO2].

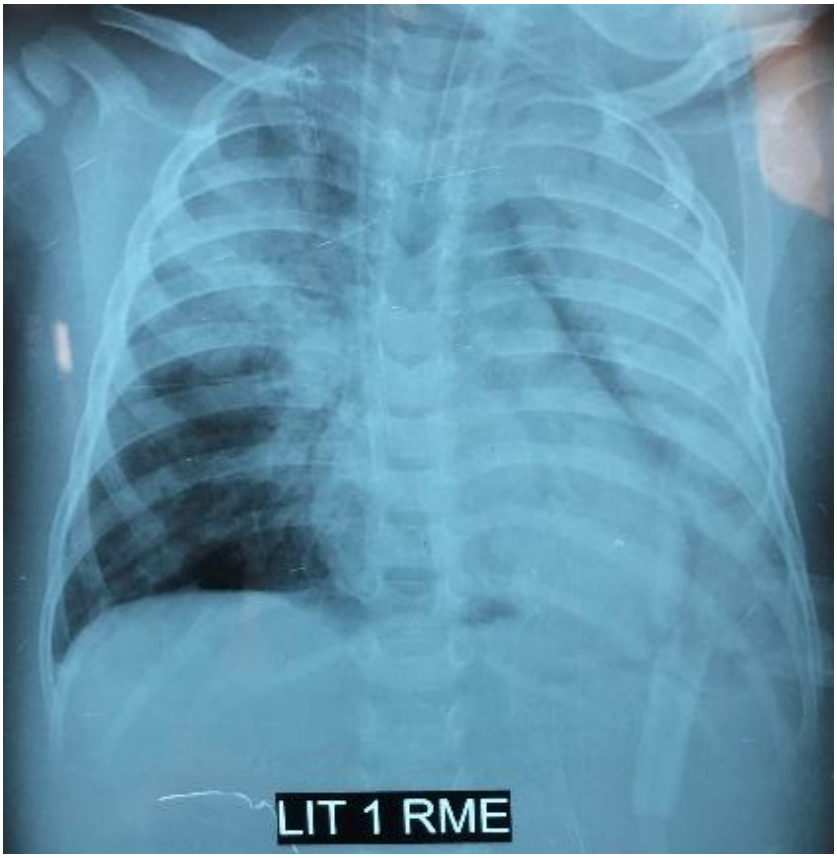
(1) Use PaO2-based metric when available. If PaO2 not available, wean FIO2 to maintain SpO2 97% to calculate OSI or oxygen saturation/FIO2 ratio.

(2) For non-intubated patients treated with supplemental oxygen or nasal modes of non-invasive ventilation.

(3)Acute respiratory distress syndrome severity groups stratified by OI or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease.

- **Chest images of PARDS.**





Chest x ray showing bilateral infiltrates in severe ARDS patients at CHU-Fes.

- **Chest CT.**

  Chest CT were performed for all patients.

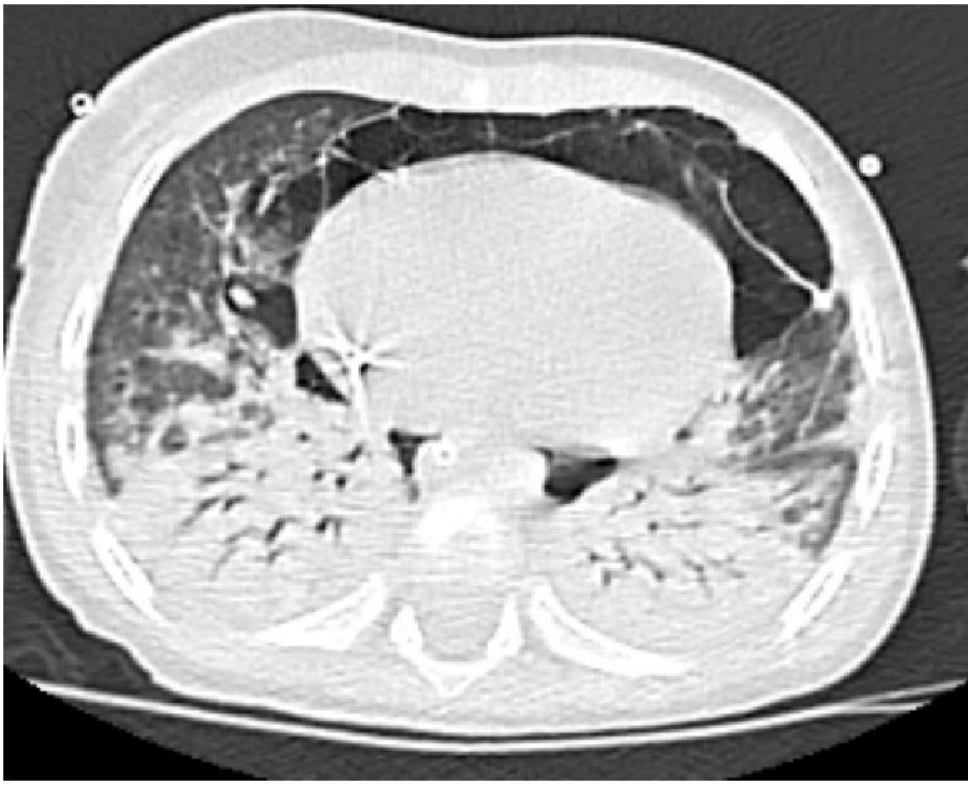


Image A . Thoracic CT scan of 1 YO patient presented with severe ARDS showing bilateral infiltrates with pneumopericardium. *Service de Reanimation mere-enfant CHU-HASSAN II*

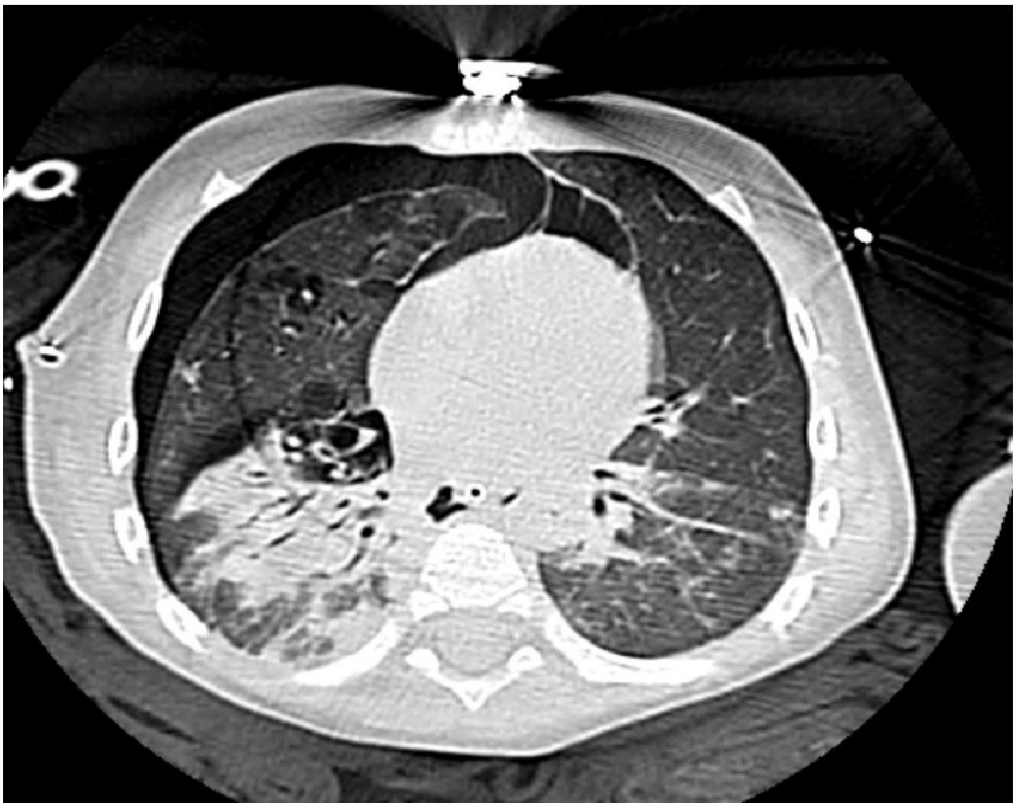


Image B. Thoracic CT scan of 1 YO patient admitted for major trauma. She was diagnosed with severe ARDS during PICU stay with CT scan showing bilateral infiltrates with right pneumothorax. *Service de Reanimation mere-enfant CHU-HASSAN II*

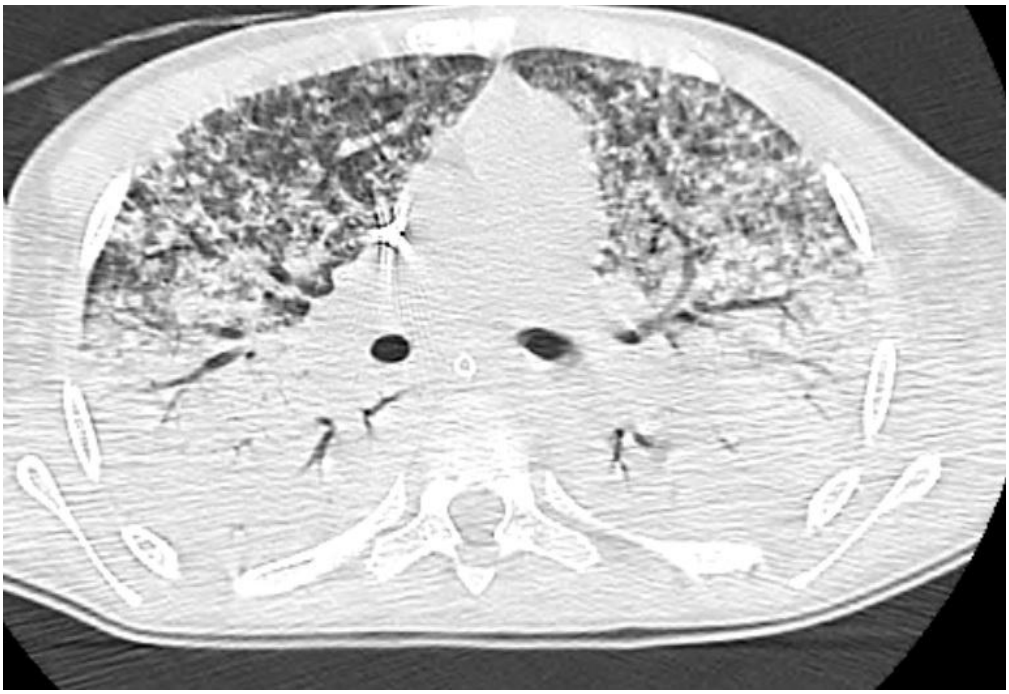


Image C. Thoracic CT scan of patient with severe ARDS showing bilateral infiltrates. *Service de Reanimation mere-enfant CHU-HASSAN II*

Risk stratification.

The severity of illness was based on the berlin criteria using P/F ratio stratifying ARDS as Mild, Moderate, and severe as follows:

- P/F 200-300 for mild.
- P/F 100-200 for moderate.
- P/F<100 for severe.

TABLE 15. Shows the proportion of group severity in literature compared to our study.

TABLE 15. PERCENTAGE OF GROUP SEVERITY OF ILLNESS IN LITERATURE.

SEVERITY	KHEMANI 2018	Our study
Mild	24%	13%
Moderate	44%	52%
Severe	28%	35%
Number of patients	1134	23

7. EPIDEMIOLOGY

7.1 Incidence.

In one study conducted by Erickson in 2007 the incidence was 2.2% of total PICU admission [14]. In a systematic review of 29 paediatric studies in 2016 the incidence was 3.5 [15].

According to the PARDIE cross-sectional study of 145 international Paediatric ICUs, the estimated international population-based incidence of PARDS (ages 2 weeks to 17 years) is between 2.2–5.7 per 100,000 person-years. The estimated international PICU admissions-based incidence of PARDS is between 2.3– 3.2%. The incidence was found higher in high income countries than in lower income countries [16].

The estimated PICU admissions-based incidence of PARDS in our series was 2.7%. **TABLE 16.**

TABLE 16. INCIDENCE IN DIFFERENT STUDIES COMPARED TO OUR STUDY.

STUDY	YEAR	INCIDNCE
Erickson. [14]	2007	2.2%
Systematic review of 29 studies. [15].	2016	3.5%
PARDIE. [16]	2018	2.3-3.2%
Our series.	2021	2.7%

7.2 Age.

ARDS is more frequent in children aged < 5 years old while the occurrence of ARDS decreases in older children. In Flori study in 2005, 58% of ARDS in patients under 5 YO, followed by 26% occurrence in children aged between 6 and 12 YO and 16% occurrence in infants aged more than 12 YO [17].

In another study conducted by Deluca in 2013, 72% of ARDS in patient under 5 years old followed by 22% in children aged between 6 years old and 12 years old and finally 5.9% in children aged more than 12 years old [18].

In our series the results were similar to the previous studies with 73% of children between 2 months and 5 YO followed by 17% of PARDS occurrence in infants aged between 6 and 12 YO and finally 8.6% of occurrence in children aged above 12 YO. **TABLE 17.**

The elevated frequency of PARDS in children under 5 YO may be explained by the immaturity of the immunity system along with lung development and maturation that occurs in that range of age.

TABLE 17. DISTRIBUTION OF AGE GROUPS IN DIFFERENT STUDIES.

AGE GROUPS	FLORI 2005 [17]	DELUCA 2013 [18].	OUR SERIES
2 months-5 YO	58%	72%	73%
6-12 YO	26%	22%	17%
>12 YO	16%	5.9%	8.6%

7.3 Sex ration.

According to PARDIE study ARDS sex ratio M/F was 1.5 [19]. In one study conducted by Deluca in 2013 sex ration is 1.1 [18]. Another study by Flori in 2005 sex ratio was 1.3 [17]. **TABLE 18.**

In all conducted studies, ARDS is more frequent in boys than girls including our series with sex ratio M/F of 2.8. The high predominance of males maybe explained by the small number of cases studied in our series.

TABLE 18. SEX RATIO IN DIFFERENT STUDIES COMPARED TO OUR STUDY.

Study	Year	Sex ratio M/F
FLORI [17]	2005	1.3
DELUCA [17]	2013	1.1
PARDIE [16]	2018	1.5
OUR SERIES	2021	2.8

7.4 Comorbidities.

Three patients presented with comorbidities including 1 case with cerebral tumor, 1 case with type 1 diabetes, and 1 case with valvular heart disease.

7.5 Body Weight.

The mean weight in Deluca was 7.5kg while in PARDIE study was 14.5kg [18] [19].

in our series the mean weight was 17.7kg with extremes of 5kg and 51kg.

8. CAUSES OF PARDS.

Causes or risk factors for developing PARDS can result from direct insult (i.e., lung injury originating on the alveolar side of the alveolar-capillary membrane) or can result from indirect insult by systemic immunity reaction in response to extrapulmonary aggression [15]. The different causes of PARDS are listed in **Table 19**.

TABLE 19. THE DIRECT AND INDIRECT CAUSES OF PARDS.

Causes of Pediatric Acute Respiratory Distress Syndrome	
Direct Lung Injury (Alveolar-Epithelial)	**Indirect Lung Injury (Alveolar-Capillary)**
Pneumonia Aspiration Inhalation injury Drowning Pulmonary contusion	Sepsis/Systemic inflammatory response syndrome Major trauma Cardiopulmonary bypass Severe Burns Pancreatitis Shock Massive Transfusion or TRALI Drug overdose

In the PARDIE study, pneumonia presented with 67% and sepsis with 19% of cases were the most common PARDS risk factors. Followed by aspiration 8% and trauma 4% [19].

In our series we noticed predominance of pneumonia in 48% followed by 22% with aspiration, 13% for sepsis and 4% for each of other causes.

9. MANAGEMENT.

Due to the complex pathogenesis of PARDS, no pharmacologic treatments aimed the underlying pathogenesis have been shown to be effective, and management remains essentially supportive with lung-protective mechanical ventilation.

Primary therapies:

- Mechanical ventilation.
- Sedation.
- Fluid Management.

Adjunctive therapies:

- High frequency ventilation. -Nitric oxide.
- Recruitment manoeuvres. -Surfactant.
- Prone position. -Steroids.
- Neuromuscular blockade. -Extracorporeal membrane oxygenation (ECMO).

9.1. CONVENTIONAL MECHANICAL VENTILATION.

CMV is indispensable for assuring adequate gas exchange for patients with acute respiratory failure. However, it may exacerbate, or even initiate, lung injury and inflammation, that is Ventilator-Induced lung Injury (VILI) [20]. The development of VILI has led to the concept of lung-protective ventilation which is based on two primary principles, the first is to avoid overdistension (volutrauma and barotrauma), the second is to minimize the cyclic opening and closing of the alveoli (atelectrauma) [4]. This approach is aimed to minimize injurious effects on the lung and distal organs (biotrauma).

In 2017, the European society for pediatric and neonatal intensive care developed and voted on list of 152 recommendations for mechanical ventilation of critically ill children. Unfortunately, none of the various modes of mechanical ventilation has been demonstrated to improve the outcome in the pediatric population, including the patients with PARDS [21].

LUNG PROTECTIVE STRATEGY.

9.1.1. Tidal Volume.

The tidal volume is the amount of air delivered with each breath. The physiologic tidal volumes in a normal person are in the range of 6–8mL/kg PBW. With the landmark of ARDS Network trial in 2000, Low tidal volume ventilation has been a standard of care in mechanically ventilated patients with ARDS. The ARDS Network trial found that mechanical ventilation with lower tidal volume (6 mL/kg compared to 12 mL/kg of IBW and limited plateau pressure (<30 cm H2O compared to<50 cm H2O) resulted in significant decrease in mortality and more ventilator-free days. Pediatric intensivists have relied on the landmark ARDS Network trial evaluating adults with ALI and ARDS. Thus, the PALICC group recommended tidal volumes of 3–6 mL/kg for patients with poor compliance, and 5–8 mL/kg for patients with more preserved respiratory compliance [6].

The recommendations regarding Vt targets were voted by weak agreement (88% agreement) among PALICC group. The weak agreement may be explained by the variability of study results. Some observational studies demonstrated decreased mortality [22], other observational studies in children with hypoxemic respiratory failure showed more ventilator-free days with higher tidal volume [23]

Two studies, the first in China in 2012 and the second in Netherlands in 2014, both couldn't identify a clear relationship between Vt and mortality [24] [25]. More recently, a conducted study in 2019 by Khemani did not find a consistent association between tidal volume(calculated based on actual body weight and two different formulations of ideal body weight) and outcome, although an association may exist in subgroups such as overweight patients and severe PARDS [26].

The recent Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) in 2017 stated that no sufficient data to recommend the optimal Vt. Nonetheless, the

PEMVECC recommended targeting physiologic Vt and to avoid Vt >10 mL/kg ideal bodyweight voted with strong agreement [21].

9.1.2. Positive End Expiratory Pressure (PEEP).

PEEP creates an open lung strategy by preventing lung collapse and atelectotrauma caused by reopening collapsed alveoli with each breath cycle. By increasing end-expiratory lung volume, PEEP recruits collapsed alveoli, thereby reducing shunt fraction and increasing PaO2 and SaO2 . However, PEEP may reduce venous return, Left Ventricle preload, and cardiac output. This means that PEEP may improve PaO2, SaO2, and O2 content while decreasing oxygen delivery to the tissues. Furthermore, PEEP may worsen lung injury by contributing to alveolar over-distention during a mechanical breath.

The selection of PEEP is based on the characteristics, extent, and duration of each patient's lung disease. Hence, PEEP have to be selected for each individual patient to achieve a successful open lung strategy and to minimize PEEP effects. Attempts to individualize PEEP have focused primarily on techniques that assess respiratory mechanics, gas exchange, or both.

- **Methods Assessing Gas Exchange.**
  - **PEEP is set at the lowest level needed to maintain adequate SpO_2.**

This method is referred as the "least PEEP", because the lowest possible PEEP is used to achieve a predetermined SpO_2 . In this method, PEEP is increased until a minimum SpO_2 (90-93%) is reached. As the patient improves, PEEP is reduced before, after, or with FIO2 in order to keep SpO2 within this same range. There are several advantages to this approach. It's easy to do, PEEP is repeatedly assessed and adjusted throughout the course of the disease, and there is a reasonable correlation between SpO_2 and alveolar recruitment. On the other hand, PEEP is not directly linked with alveolar recruitment because the selected level is dependent on the FiO_2.

- **PEEP is selected to maximize SpO_2 or systemic O_2 delivery.**

This approach is to perform incremental or decremental PEEP titration to identify the least PEEP level that maximizes SpO2 or systemic oxygen delivery. Calculating oxygen delivery at multiple PEEP levels is time consuming and requires repeated mesurements of cardiac output. Titrating based on SpO2 takes relatively little time compared to oxygen delivery, but like the least PEEP approach, best PEEP depends on FIO2 , and there is no way to assess for PEEP-induced VILI.

- **PEEP is chosen to maximize CO_2 excretion or minimize alveolar dead space.**

Ventilation can be assessed instead of oxygenation. Alternatively, Highest CO_2 Excretion and Lowest Dead Space. Volume capnography continuously displays exhaled volume versus the expired CO_2 fractional concentration FCO_2 or partial pressure PCO_2. These data can be used to determine the volume of CO_2 exhaled per breath and per minute, the volume of the physiologic and alveolar dead space, and several dead space to volume ratios. Alveolar recruitment augments CO_2 excretion by increasing the surface area of the gas–blood interface and reduces alveolar and physiologic dead space by diverting gas from previously over-ventilated alveoli. Alveolar over-distension, on the other hand, leads to excessive alveolar volume and reduced capillary blood flow, which generates high regions, increases alveolar and physiologic dead space, and reduces CO2 excretion. Accordingly, best PEEP is the level associated with the highest CO2 excretion and the lowest alveolar and physiologic dead space.

➢ **Methods Assessing Respiratory Mechanics.**

- **PEEP is chosen to maximize respiratory system compliance.**

Highest Compliance method of determining best PEEP is to calculate respiratory system compliance from measurements of plateau and end-expiratory pressure during stepwise PEEP titration. The level that produces the highest compliance is best PEEP. However, A large randomized trial recently reported higher patient mortality

when PEEP was adjusted to maximize compliance. Although several explanations have been proposed, this method of choosing PEEP cannot currently be recommended.

- **PEEP is set to maintain the ''stress index'' between 0.9 and 1.1**

The pressure needed to balance the elastic recoil of the respiratory system increases with lung volume, and the slope of pressure versus volume equals the elastance of the respiratory system. If inspiratory flow is constant, time can be substituted for volume, and the pressure required to overcome viscous forces can be assumed to be constant. This means that the slope of airway pressure P_{AW} versus time during each mechanical breath approximates respiratory system elastance.

If elastance is constant throughout inspiration, the slope of this relationship will also be constant **(FIGURE 20-A)**. If elastance increases (compliance falls), progressively more pressure is needed to balance elastic recoil, and the plot of P_{AW} vs. time will be convex **(FIGURE 20-B)**. If elastance falls (compliance increases), the curve will be concave **(FIGURE 20-C)**. Studies in both ARDS patients and animal models suggest that increasing elastance reflects alveolar over-distention (too much PEEP), whereas falling elastance reflects ongoing alveolar recruitment during inspiration and presumed de-recruitment during expiration (insufficient PEEP).

Although a significant change in elastance can sometimes be determined visually, the degree of convexity or concavity has also been quantified by fitting the P_{AW}-time curve to a power equation containing three variables (a, b, and c) and the inspiratory time (TI):

$$P_{TP} = a \times t^b + c$$

In this equation, the coefficient (b) is referred to as the "stress index" and reflects the slope of the P_{AW}-time curve. If $b = 1$, the curve is straight, indicating no change in elastance during the mechanical breath. If $b > 1$, elastance increases, and if $b < 1$, elastance falls during inspiration. The coefficient (a) represents the slope of

the pressure-time relationship in the time 0 to time 1 interval, and the coefficient (c) is the value of pressure at time 0.

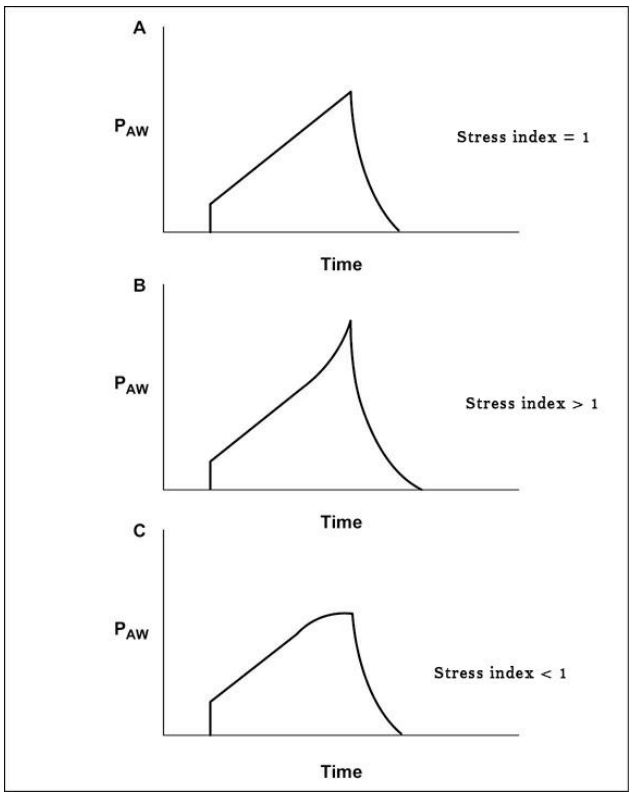


FIGURE 20. DURING A MECHANICAL BREATH WITH CONSTANT INSPIRATORY FLOW,

THE SLOPE OF THE AIRWAY PRESSURE (P_{AW})–TIME RELATIONSHIP EQUALS THE ELASTANCE OF THE RESPIRATORY SYSTEM. IF ELASTANCE REMAINS CONSTANT (A), THE SLOPE IS ALSO CONSTANT AND STRESS INDEX=1. IF THE SLOPE INCREASES (B), ELASTANCE INCREASES (COMPLIANCE FALLS) AND STRESS INDEX>1. IF THE SLOPE DECREASES (C), ELASTANCE FALLS (COMPLIANCE INCREASES) AND STRESS INDEX<1.

- **Lower Inflection Point.**

In many ARDS patients, the plot of volume versus pressure, when measured in the absence of gas flow, has a characteristic shaped appearance. Since the slope of this curve equals compliance, some investigators have equated the abrupt increase in slope at the “lower inflection point” (LIP) with the pressure needed to recruit all available alveoli (i.e., best PEEP). Using the same reasoning, flattening of the curve at the “upper inflection point” (UIP) indicates alveolar overdistention and suggests an excessively high tidal volume. **FIGURE 21.**

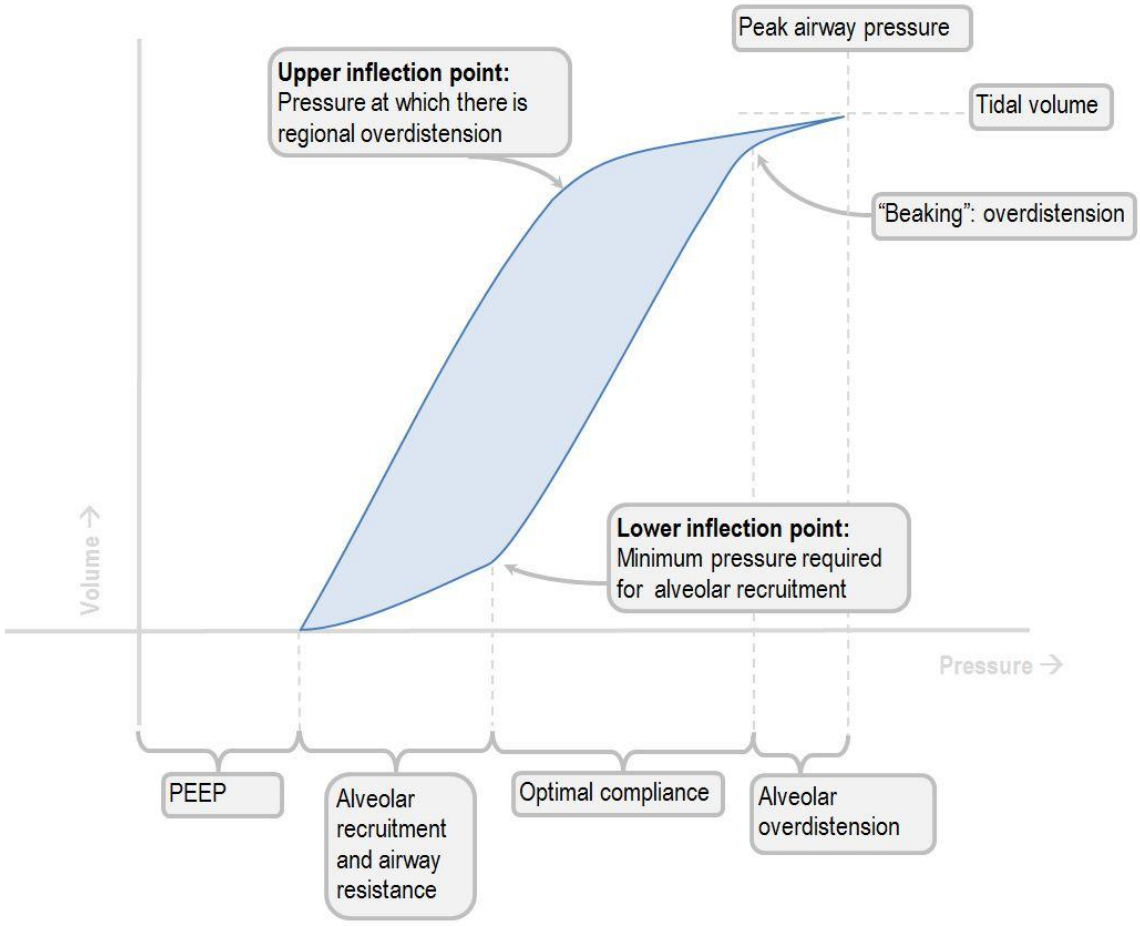


FIGURE 21. PRESSURE–VOLUME LOOP IN A VOLUME–CONTROL MODE OF VENTILATION.

This method of determining best PEEP has a number of major drawbacks that have limited its use. First, accurate determination of the LIP requires that measurements be performed on zero PEEP. This is potentially hazardous in patients with ARDS, especially if repeated measurements are performed. Second, even when performed correctly, there is no discernible LIP in a significant portion of patients.

Some tables pairing levels of FIO2 and PEEP have been published with a number of randomized ARDS trials. These tables were developed by the investigators to standardize care in using higher PEEP and low systemic oxygen saturation. Most tables are identical to the one used in the ARDSnet low tidal volume trial [7].

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

Unfortunately, none of the previous methods were accepted to be optimal in identifying the level of PEEP that optimizes gas exchange while minimizing cyclical recruitment-decruitment and over-distention of alveoli [7] [4].

The initial PEEP settings of 5 to 8 cm H_2O are commonly used in pediatrics. The required PEEP depends largely on the disease process(es). In patients with low lung compliance from acute lung injury or increased abdominal pressure, higher PEEP may be necessary to oxygenate the patient [27]. Two meta-analyses in adults with ARDS indicate that higher PEEP is associated with lower hospital mortality [28] [29]. A recent pediatric multicenter retrospective study by Khemani et al. also demonstrated that PEEP levels lower than the ARDS Network model were associated with higher mortality [30]. PALICC strongly recommends the use of PEEP up to 15 cm H2O or greater for severe PARDS.

9.1.3. Peak inspiratory pressure (PIP) and Plateau pressure.

PIP is the maximum pressure attended at end inspiration. Since the plateau pressure must always be the same or lower than the PIP, depending on the degree of inspiratory airways resistance. The pediatric clinician often substitutes PIP for plateau pressure due to the use of variable flows, and air leakage with uncuffed endotracheal tubes that is often used. This approach, theoretically, provide more accurate reflection of lung protection.

Consistent with the ARDS Network study, the publications by Erickson et al. and Khemani et al. reveal a linear association between mortality and peak inspiratory pressure (PIP) [22] [23] but it is unclear whether this is causal or simply reflects more severe lung injury [31].

PALICC recommends that plateau pressure should be limited to 28 cm H2O, allowing for slightly higher plateau pressures (29 –32 cm H2O) for patients with reduced chest wall compliance.

9.1.4. Gas exchange.

Specific oxygenation and ventilation goals may vary between patients and often within the same patient over time such in ARDS. The oxygenation and ventilation goals should be titrated based on the balance between perceived risk(s) of ventilatory support and the potential benefit to the patient.

- **Oxygenation.**

High fractions of oxygen may be toxic and cause potential injurious effects to lung parenchyma. The toxicity of hyperoxia includes immuno-modulating effects, free radical- induced lung injury, and higher systemic oxygen saturation requiring increased ventilator settings. Several adult and pediatric studies noted that increased systemic oxygen saturation has not been correlated with improved outcomes. In the landmark of ARDS network, low Vt group had lower systemic oxygen saturation with low mortality [10]. PALICC recommended higher PEEP and lower systemic oxygenation goals with worsening ARDS. In the PALICC guidelines, the PEEP recommendation for mild ARDS is $<$10 cm H2O, with goal systemic oxygen saturation of 92-97%. The experts further recommended that lower goal systemic oxygen saturation levels of 88-92% be considered for severe ARDS with PEEP$\geq$10. This approach that aims to reduce lung injury is termed permissive hypoxemia [32]. When the concept of permissive hypoxemia is used, PALICC recommended to follow markers of oxygen deliver and monitoring central venous saturation [8].

- **Ventilation.**

Low tidal volume ventilation physiologically leads to hypercapnia but most undesirable effects are reversible and acidosis itself may attenuate VILI [33]. Similarly to permissive hypoxemia, PALICC recommends a permissive hypercapnia with a pH range of 7.15–7.30 as a management strategy to minimize ventilator-induced lung injury for patients with moderate-to-severe PARDS. However, is not applicable to all patient groups. Generally, this strategy should be avoided in patients with intracranial hypertension, severe pulmonary hypertension, select congenital heart disease lesions, hemodynamic instability, and significant ventricular dysfunction [6].

9.1.5. Driving Pressure

Respiratory system compliance in ARDS is a strong determinant of volume received by the remaining functional lung. Driving pressure (∆P) is a newer concept defined as VT/respiratory system compliance (or plateau pressure minus PEEP), where Vt is essentially normalized to functional lung size (instead of predicated lung size in healthy persons). Recent data in the adult ARDS population have shown that the driving pressure is more closely related to mortality than PIP or PEEP alone. A 1-SD increment (approximately 7 cm H2O) in driving pressure was associated with increased mortality [34]. No corresponding data exist for PARDS, and PALICC did not address this relatively new concept.

9.2. SEDATION

Adequate sedation diminish anxiety and pain, facilitates synchronization in patients with mechanical ventilation and permits invasive procedures to be performed. It has been described as the level of sedation at which patients are asleep but easily arousable. In PICU practice, this means that a child is conscious, breathes in synergy with the ventilator, and is tolerant of or compliant with other therapeutic procedures.

Both under- and oversedation are undesirable, as these conditions may adversely affect patient outcomes, mechanical ventilation duration, and PICU stay. Oversedation delays recovery, as greater sedatives consumption is associated with longer duration of ventilation as well as extubation failure. Oversedation also induces tolerance and withdrawal syndrome manifesting in central nervous system activation, gastrointestinal disturbances and sympathetic hyperactivity. Undersedation, on the other hand, may cause distress and adverse events such as unintentional extubation or displacement of catheters, may lead to adverse memories (posttraumatic-stress syndrome) and increased need for nursing requirements.

The most often used sedation agents in PICU patients are opiates alone or in combination with benzodiazepine [35].

❖ **Opiates.**

Opioids are used commonly to provide analgesia for children with PARDS. Fentanyl and morphine are frequently used agents [36].

- ***Morphine*** is metabolized by gluconuridation in the liver. Morphine may cause histamine release and vasodilation. Thus, its use maybe inappropriate for patients with hemodynamic instability. Dosing recommendations in the ICU include a bolus dose of 0.05–0.1 mg/kg and a starting infusion of 10–30 μg/kg/h. Opioid tolerance is mainly limited to the depressant actions such as analgesia, respiratory depression, anxiolysis, and drowsiness, but not

constipation. The tolerance appears more rapidly with infusions and is not common with opioid dosing for less than 3 days. With prolonged administration, tolerance levels as high as 20× normal dosing can occur [37].

- ***Fentanyl*** is a synthetic opiate. Due to its lipid solubility, its onset is very rapid, and clinical effects of a single bolus are short due to rapid redistribution. With long-term infusion, fentanyl accumulates in fat, and its elimination half-life is about 4 hours. It is metabolized in the liver to nor-fentanyl and hydroxy fentanyl derivatives, both of which are inactive. Fentanyl bolus doses of ≥5 μg/kg may be associated with chest wall rigidity, which can be treated with neuromuscular blockade or naloxone. Fentanyl has minimal hemodynamic effects. Dosing in the ICU is by bolus (1 μg/kg) and/or infusion (1–3 μg/kg/h) with higher doses as tolerance develops [37].
- ***Remifentanil*** is a newer synthetic opiate metabolized by plasma esterases. Because it has a short half-life, the depth of sedation is rapidly reflected by changes in the infusion rate without the need for bolus administration. It is more potent than fentanyl. For sedation, 0.1–0.4 mcg/kg/minutes are similar in effect to 1–4 mcg/kg/hour fentanyl. It has a stable cardiovascular profile similar to fentanyl, and may be appropriate for PICU patients with severe renal/ hepatic disease or who may require a rapid awakening for neurologic assessment [37].

❖ **Benzodiazepine.**

Benzodiazepines are commonly used to provide sedation in the ICU. They bind to benzodiazepines receptors in the brain, which are part of the GABAA receptor. The opening of the chloride channel hyperpolarizes the neuron, resulting in anxiolysis, sedation, amnesia, euphoria, muscle relaxation, and anticonvulsant effects, but no analgesia. They have negative inotropic and chronotropic effects, especially when the sympathetic response has been abolished [36].

- *Midazolam* is an imidazobenzodiazepine with a short elimination half-life of about 2 hours. Infusion starting dose is usually about 0.03- 0.05 mg/kg/hour. It is metabolized in the liver. Due to its extensive protein binding, hepatic or renal failure can have a significant effect on the free midazolam levels as well as the excretion of the active metabolite hydroxymidazolam. This can result in a significant prolongation of the half-life in critically ill patients [37].
- *Lorazepam* has a slow onset and a long halflife (14 hours). Metabolism is via gluconuridation pathways without active metabolites and is less impacted by hepatic dysfunction than midazolam. It is typically used as an intermittent medication at doses of 0.05–0.10 mg/kg, as infusions may cause propylene glycol toxicity [37].
- *Diazepam* has a long half-life (24 hours) and is metabolized to several long-acting active metabolites (12–90 hours). These properties have resulted in its rare use in the ICU. It is fast acting when given orally for indications such as anxiolysis and is effective when given rectally for seizure management [37].

❖ **Other sedative agents.**

- *Propofol* is a rapid-onset, short-acting, highly lipid-soluble IV anesthetic agent. Propofol has a rapid redistribution phase (half-life ~3 minutes) and is rapidly cleared by the liver; however, its half-life after prolonged infusion is context sensitive and may be greater than 6 hours. Propofol can cause severe hypotension, especially when given by bolus and if the child is critically ill and dependent on sympathetic tone for blood pressure stability. Its use as a prolonged infusion, especially at higher doses (>4 mg/kg/ hour), is associated with the often-fatal propofol infusion syndrome. PRIS consists of refractory metabolic acidosis with fatal myocardial failure, bradycardia, lipemia, and rhabdomyolysis, potentially related to mitochondrial dysfunction.

- *Dexmedetomidine* is a selective α2 adrenergic agonist that causes sedation, analgesia, and an inhibition of sympathetic activity. Its elimination half-life in children is about 2 hours but is prolonged with hepatic failure. Advantages of dexmedetomidine include minimal respiratory depressant effect and less hypotension. Bradycardia is a common side effect, especially if a loading dose is given. The sedation from dexmedetomidine can result in a sleeping patient who is easily aroused when stimulated. This may be desirable in some settings such as use of non-invasive ventilation, periextubation, and following cardiac surgery. In children, dexmedetomidine may reduce opiate requirements, improve time within targeted sedation ranges, and reduce delirium [37].

In the past, clinicians favoured early deep sedation in mechanically ventilated patients, as it was thought to improve their oxygenation status, decrease pain, and minimize negative perception of experiences [38]. In 2013, adult guidelines suggested light sedation might be associated with improvement in outcomes without increasing negative sequelae of increased physiologic stress and studies have shown a survival benefit associated with light sedation in ARDS [39]. Of note, clinician may use deep sedation to minimize the risk of ventilator asynchrony when permissive hypercapnia is used in PARDS. Recent emerging literature suggest dexmedetomidine is superior than midazolam by reducing delirium that can be highly problematic in children, leading to prolonged mechanical ventilation, increase in PICU and hospital length of stay, higher number of sequelae post-discharge, and increased morbidity and mortality [40].

The PALICC recommended targeted sedation with minimal yet effective dose and to ensure that patients can tolerate mechanical ventilation to optimize oxygen delivery, oxygen consumption, and work of breathing. Further recommendations

include the use of pain and sedation scales to monitor and titrate sedation to decrease the use of sedatives, analgesics, and decrease the prevalence of delirium [6].

FIGURE 21. showing a validated tools that are used to monitor pain, sedation, and delirium prospectively in order to optimize sedation in PARDS.

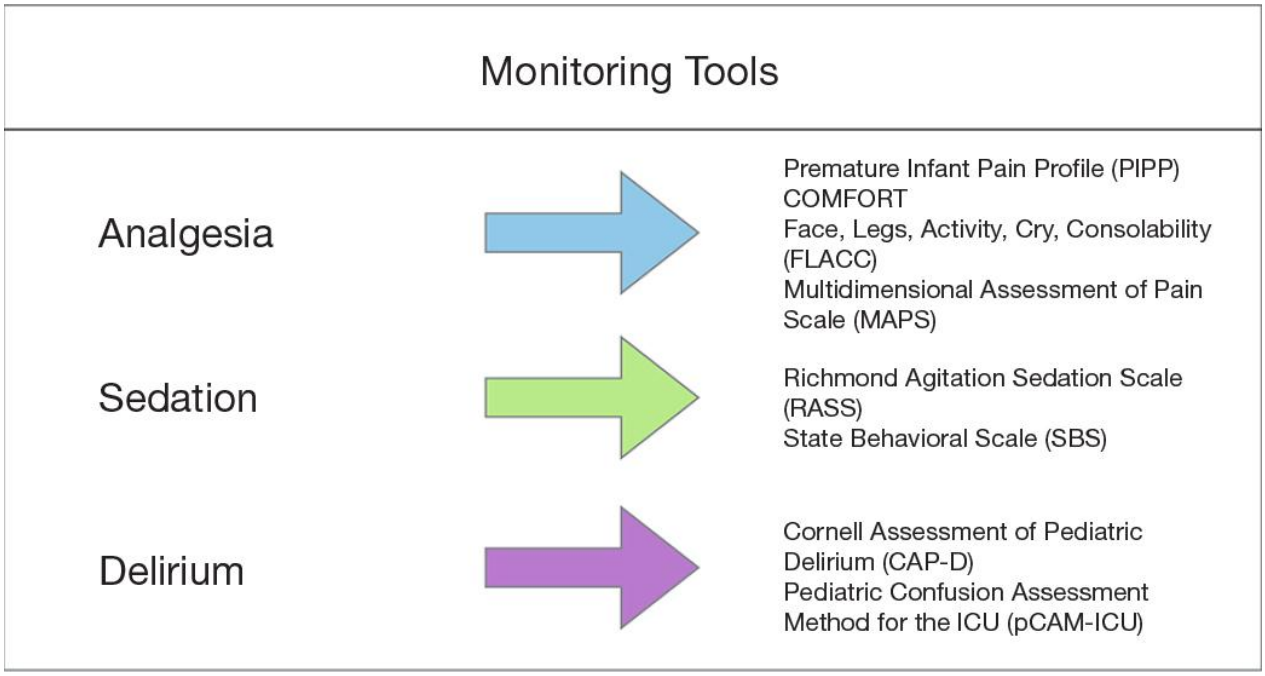


FIGURE 22. VALIDATED MONITORING TOOLS USED TO OPTIMIZE SEDATION IN ICU.

(from Sedation strategies in children with pediatric acute respiratory distress syndrome (PARDS) DOI: 10.21037/atm.2019.09.16)

9.3. FLUID MANAGEMENT

Fluid treatment is a major component of ARDS management and two opposing strategies exist:

- Fluid resuscitation to maintain adequate cardiac output and extrapulmonary organ function in the setting of widespread inflammation.
- Fluid restriction to minimize pulmonary edema as fluid overload increases inflammation and inflammation itself may increase fluid overload.

The current literature on fluid balance in PARDS is sparse but demonstrates that fluid overload is associated with worsening clinical outcome. In 2011, a post hoc analysis of an observational study for PARDS suggested that positive fluid balance was associated with increased mortality and prolonged mechanical ventilation [41].

From adult data, the multicentered, randomized Fluid and Catheter Treatment Trial (FACTT) comparing conservative versus liberal fluid management strategies for adults with ARDS favored the conservative approach, as it improved lung function, shortened duration of mechanical ventilation, and reduced ICU stay without increasing extrapulmonary organ failure [42].

More recently, Valentine et al. applied a Bayesian statistical approach based on the FACTT findings to a multicenter observational pediatric study. The authors demonstrated an inverse relationship between positive cumulative fluid balance and ventilator-free days [43].

The two opposite strategies reveal the need of balance between end-organ function and the development of pulmonary edema. PALICC recommends that after initial resuscitation, a goal-directed fluid management protocol should be set to maintain intravascular volume while minimizing fluid overload.

9.4. HIGH-FREQUENCY OSCILLATORY VENTILATION

HFOV is a tool for lungprotective ventilation. The device generates a continuous distending pressure (CDP), often referred to as mean airway pressure (mPaw), through introduction of bias flow into the circuit. This CDP generates and maintains end-expiratory lung volume (EELV), attenuating atelectrauma. Pressure oscillations are superimposed on the CDP at a frequency (F) of 3–15 Hz by an electromagnetically driven piston membrane apparatus. The oscillatory pressure amplitude (ΔP) is highly attenuated over the endotracheal tube and the airways and results in the delivery of a very small Vt, usually lower than the anatomical dead space (1–2 mL/kg) [44].

Despite low VT delivered, HFOV can't be considered ideal for lungprotective strategy. Experimental studies suggest that high respiratory rates can cause cellular injury by influencing the elastic properties of pulmonary epithelium, leading to increased local stress and edema formation. The use of high mPaw (and therefore high PEEP) during HFOV is thought to prevent atelectasis. However, it is possible that such elevated pressures may necessarily result in volutrauma. Finally, through elevated mPaw, HFOV can have a profound impact on the right ventricle by increasing afterload and reducing preload, though HFOV must be carefully applied to avoid hemodynamic impairment [45].

The 3100 A/B HFO ventilator (SensorMedics, Yorba Linda, California) is the most commonly used HFOV device in pediatrics which was approved for use in neonates in 1991 and for older infants and children in 1995. **IMAGE 3.**

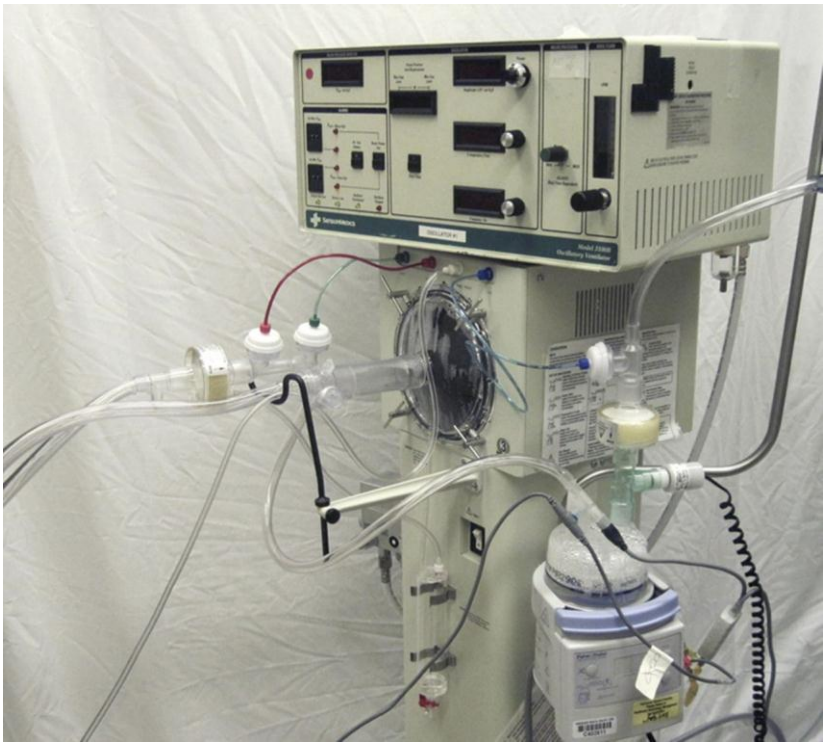


IMAGE 3. HFO ventilator 3100 A/B model.

(from http://rc.rcjournal.com/content/57/4/531).

The early studies of HFOV in adults were promising until recently, the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) and High Frequency Oscillation in ARDS (OSCAR) clinical trials both found no benefit and potential harm associated with HFOV [46].

Same as adults, a 1994 RCT showed potential benefit from early HFOV use in pediatric respiratory failure but subsequent pediatric studies have demonstrated no clear benefit with HFOV [47]. A recent retrospective, observational administrative database study of >9,000 children with acute respiratory failure found longer duration of mechanical ventilation and higher mortality associated with HFOV compared with CMV [48]. More recently in 2017, a Turkish RCT of 200 children with PARDS found that HFOV improved oxygenation but showed no difference in mortality, duration of mechanical ventilation, or length of stay compared to CMV [49].

Despite the lacking of definitive data in these investigations evaluating HFOV in pediatric ARDS, when CMV fails, HFOV is often used as a ‘‘rescue’’ strategy for refractory hypoxemia.

9.5. RECRUITMENT MANOEUVRES

Lung volume recruitment procedures have a role to play as an adjunct to pressure-limited ventilatory strategies. Recruitment maneuvers have been suggested to be of use in certain situations.

1- Lung recruitment maneuvers may be used to open nonaerated lung zones, particularly early in the course of disease in patients who are ventilated with low tidal volumes. In this situation the expected benefit is in improving oxygenation and preventing further lung injury. Multiple recruitment maneuvers may be needed to achieve a satisfactory response. Adequate levels of PEEP are required to maintain the recruitment effect.

2- Lung recruitment maneuvers may aid in the choice of appropriate PEEP setting. The response to recruitment, assessed by measuring oxygenation and lung compliance, can identify patients with extensive recruitable lung and those with a low recruitment potential. Patients in the latter group may require only relatively low levels of PEEP, in the range of 5–10 cmH2O. In patients with a clear response to a recruitment maneuver the PEEP level required to prevent derecruitment can be assessed by a decremental PEEP trial. Following the recruitment maneuver, PEEP is gradually reduced (e.g. 2 cmH2O every minute) while monitoring oxygen saturation continuously. The PEEP at which oxygen desaturation occurs is noted, and PEEP is set 2 cmH2O above this level following another recruitment maneuver.

3- Lung recruitment maneuvers may be used to recruit the lung after interventions associated with derecruitment, including ventilator disconnects and endotracheal suctioning.

In ARDS, the heterogenic environment of aerated lung and the nonaerated lung which consists of collapsed or consolidated alveoli is challenging when patients are mechanically ventilated. In the presence of inadequate PEEP to maintain alveolar

patency through the respiratory cycle, the applied PEEP to the lung increases lung volume but because no additional alveoli are recruited the tidal ventilation is applied to the single alveolar unit and this unit experiences all of the strain as Positive pressure ventilation generates tensions at the interfaces between aerated and nonaerated lung [50].

With the advent of small tidal volume ventilation, lung recruitment has gained new interest in ARDS patients as low tidal volume ventilation strategy is associated with progressive lung collapse and the elevated requirements for inspired oxygen concentrations cause what called absorption atelectasis [51]. The absorption atelectasis can occur by two mechanisms:

In the first mechanism, the atmosphere is composed of 78% nitrogen and 21% oxygen. Since oxygen is exchanged at the alveoli-capillary membrane, nitrogen is a major component for the alveoli's state of inflation. If a large volume of nitrogen in the alveoli is replaced with oxygen, the oxygen may subsequently be absorbed in to the blood reducing the volume of the alveoli, resulting in a form of alveolar collapse.

In the second mechanism, if the inspired VA/Q ratio of a lung unit is reduced, a point is reached where the rate at which inspired gas entering the alveolus is exactly balanced by gas uptake from the alveolus into the blood. If the inspired VA/Q ratio is less than this, the lung unit will collapse. This is likely when FIO2 is high and the gas uptake is large [52].

There is diverse methods for lung recruitment and can be applied by increasing volume or pressure over time:

- A sustained high-pressure inflation technique uses pressures from 35 to 50 cm H2O for a duration of 20–40 secs.
- The intermittent sigh technique uses three consecutive sighs set at 45-cm H2O pressures.
- Other methods of recruitment are intermittent increase in (PEEP) or peak inspiratory pressure for brief periods.

Recruitability of a diseased lung depends on various factors. Among others, it is dependent on the type of lung disease (e.g., diffuse alveolar disease vs pneumonia-like alveolar consolidations), time course (e.g., early vs late PARDS), and mechanics of the respiratory system (e.g., pulmonary compliance). In general, patients with predominant decreased lung compliance show less positive response to recruitment maneuvers than patients with decreased chest wall compliance. However, lung pathology characterized predominantly by alveolar collapse or by inflammatory edema demonstrates a high potential for lung recruitment, despite being characterized mechanically by a low lung compliance. Similarly, application of a recruitment maneuver can improve oxygenation in patients with early ARDS (predominant inflammatory edema) who do not have impairment of chest wall mechanics [53].

Because it is often impossible to predict how an individual patient will respond to a lung recruitment attempt, careful individual PEEP titration is the reasonable approach and has been shown to be efficient in terms of improvement of oxygenation and safe in patients with PARDS. There is no consensus on the optimal performance of RMs and No data exist on the effect of recruitment maneuvers on mortality, morbidity, length of stay, or duration of mechanical ventilation [54].

9.6. PRONE POSITION.

PP was introduced in 1970s as a method to improve lung mechanics and oxygenation in mechanically ventilated patients. The improvement of oxygenation during prone ventilation is multifactorial, it improves gas exchange by ameliorating the ventral-dorsal transpulmonary pressure difference, reducing dorsal lung compression, and improving lung perfusion. This may lead to a reduction in mechanical factors associated with VILI, such as an inhomogeneous distribution of pleural pressure (Ppl), and reduction in atelectatic lung regions. Changes in the distribution of extravascular lung water and secretions may also play a role [55].

Increased functional residual capacity (FRC) has also been proposed, but these changes were not dominant in most studies performed and any increment in FRC that occurs after prone position neither fully explains the proning-related improvements in oxygenation nor the reduced propensity to VILI. The regional distribution of transpulmonary forces across the lung appear to be of greater importance [56].

- **Supine position.**

When supine, the distending pressure across the lung is estimated by the transpulmonary pressure (Ptp), which is defined as the difference between the alveolar pressure (P_{al}) and pleural pressure (P_{pl}); $P_{tp} = P_{al} - P_{pl}$. When an individual is supine, the dorsal P_{PL} is greater than ventral P_{PL}. The pleural pressure P_{PL}, which drives the chest wall, lifts up the ventral chest wall, moves caudally to the diaphragm, and has little effect on the dorsal chest wall, which lies in contact with the firm supporting surface **(FIGURE 22-a,b)**. As a result, the ventral P_{TP} exceeds the dorsal P_{TP} and there is greater expansion of the ventral alveoli than the dorsal alveoli.

Other factors play role, the heart weight which compresses the medial posterior lung parenchyma and the diaphragm compresses the posterior-caudal lung parenchyma. The latter is caused by the abdominal contents displacing the diaphragm cranially, which can be exacerbated by a loss of diaphragmatic tone due to sedation and/or paralysis or increased abdominal pressure like obesity. This contributes to differences in density distribution throughout the lung parenchyma.

The effect of inhomogeneous transpulmonary pressure is exaggerated in supine patients with ARDS. When the difference between the dorsal and ventral pleural pressures is increased. The result is a tendency towards overinflation of the ventral alveoli and atelectasis of the dorsal alveoli. The contributions of heart weight and abdominal pressure to lung collapse are overshadowed by the increase in superimposed pressure of the excess lung weight which remains the main cause. Resulting in exaggeration of the dependent lung collapse in the supine position unlike the nondependent lung which tends to be overinflated leading to VILI, Increased VA/Q mismatch and shunt since blood flow and alveolar collapse are dominant in dorsal regions.

- **Prone position.**

In prone position **(FIGURE 22-c,d)** the dorsal chest wall lifts up and the ventral chest wall is impeded from expanding by the bed surface. Because the dorsal chest wall is less compliant than the ventral chest wall, the overall effect of prone positioning is to decrease overall chest wall compliance. As a result, there is reduction in the difference between the dorsal and ventral P_{TP}. This leads to a decrease in the ventral alveolar overinflation and the dorsal alveolar collapse. Therefore makes ventilation more homogeneous. Moreover, the heart becomes dependent, lying on the sternum, potentially decreasing medial posterior lung compression and the diaphragm is displaced caudally especially in obese patients decreasing compression of the posterior-caudal lung parenchyma.

Reaeration in dorsal lung regions has been demonstrated in animals and humans with ARDS. Prone ventilation recruits dorsal alveoli that had collapsed during the supine ventilation. The lung recruitment in dorsal regions, which continue to receive most of the blood flow while in prone position, results in reduction of shunt and better VA/Q matching. In addition, increases in cardiac output have been observed and thought to be due to the effect of increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction resulting in increases in right ventricular preload and decreased right ventricular afterload and a decrease in pulmonary vascular resistance. It was previously hypothesized that prone ventilation permits the redistribution of blood flow based on gravitational gradient. However, most studies indicate that the blood flow pattern changes only modestly upon turning prone [57].

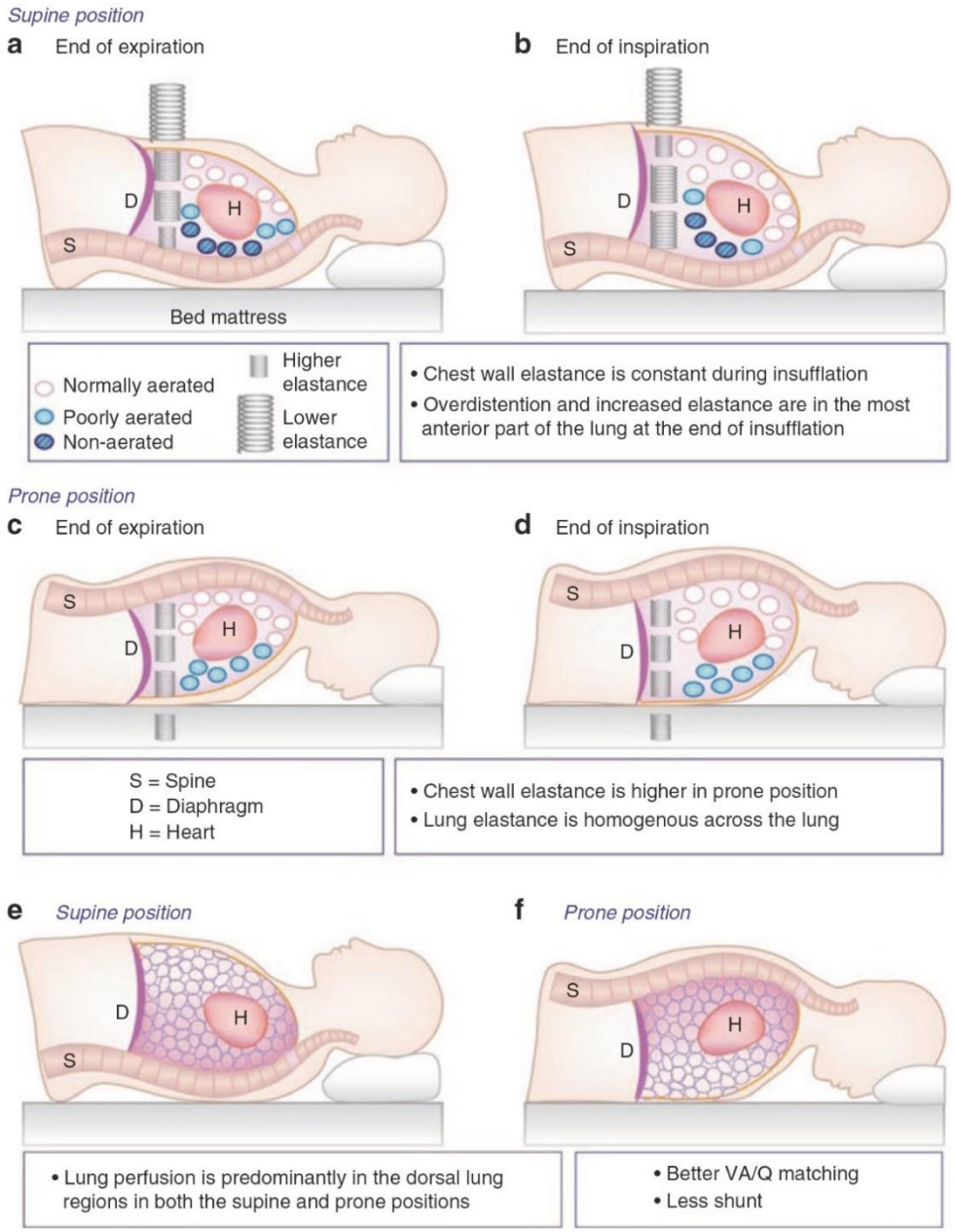


FIGURE 23. DISTRIBUTION OF AERATED, POORLY AERATED, AND NON-AERATED LUNG REGIONS AT END EXPIRATION (A AND C) AND END INSPIRATION (B AND D) IN SUPINE AND IN PRONE POSITION. THE SPRINGS ARE THE ELASTANCE SHOWN FOR THE LUNG AND THE CHEST WALL. PANELS (E AND F) DISPLAY THE DISTRIBUTION OF LUNG PERFUSION IN SUPINE AND IN PRONE POSITION.

(FROM GUÉRIN C. 2017 PRONE POSITION. IN: CHIUMELLO D. (EDS) ACUTE RESPIRATORY DISTRESS SYNDROME. SPRINGER, CHAM.)

In total, prone positioning improves oxygenation by optimizing lung recruitment and ventilation–perfusion matching which many patients sustain even after they return to the supine position while receiving appropriate PEEP and recruitment manoeuvres. Beyond its value in improving gas exchange, prone positioning helps protect against VILI by distributing stress and strain more homogeneously through the lung parenchyma.

The use of prone ventilation has not been studied in non-ARDS populations and the rationale for it is limited. Its indicated for patients with severe ARDS who fail to improve despite optimizing ventilator settings or as a bridge to extracorporeal membrane oxygenation (ECMO). Its recommended in patients with severe forms of ARDS and it's not recommended in mild to moderate ARDS as it may expose the patient to unnecessary risk of complications in the absence of proven benefits.

Prone position should be performed 24 to 72 hours in the early stages of the disease, as in the acute phase there is less consolidation in the lungs. The optimal duration of prone positioning is unknown. Most studies in adults have used either repeated sessions of prone ventilation lasting six to eight hours per day or prolonged prone ventilation lasting 17 to 20 hours per day. A recent metanalysis in 2014 of 11 RCTs included the PROSEVA study showed a mortality benefit for prone positioning when coupled with Lung protective ventilation in severe ARDS, the mean duration in prone position in PROSEVA was 17 hours per day with an average of four sessions in total per patient. which reported a 50% mortality reduction with prone positioning in adults with severe ARDS [55].

Unlike many other management strategies in PARDS, a multicenter RCT evaluating prone positioning in pediatrics is available and demonstrated proning to be safe, but found no difference in duration of mechanical ventilation, mortality, or other health outcomes [58]. The ongoing PROSpect study which estimated to accomplish in 2024 hopes to better determine its efficacy in severe PARDS [59].

Contraindications
Shock (eg, persistent mean aterial pressure <65 mmHg)
Acute bleeding (eg, hemorrhagic shock, massive hemoptysis)
Multiple fractures or trauma (eg, unstable fractures of femur, pelvis, face)
Spinal instability
Raised intracranial pressure >30 mmHg or cerebral perfusion pressure <60 mmHg
Tracheal surgery or sternotomy within two weeks

Relative contraindications
Recent DVT treated for <2 days
Anterior chest tube(s) with air leaks
Major abdominal surgery
Recent pacemaker
Clinical conditions limiting life expectancy (eg, oxygen or ventilator-dependent respiratory failure)
Severe burns
Lung transplant recipient

Complications
Nerve compression (eg, brachial plexus injury)
Crush injury or traumatic rhabdomyolysis
Venous stasis (eg, facial edema)
Dislodging endotracheal tube, vascular catheters or drainage tubes
Diaphragm limitation
Pressure sores (eg, facial)
Retinal damage
Transient reduction in arterial oxygen saturation. Transient arrhythmias
Vomiting

- **PRONE PROCEDURE.**

Prone procedure do not require special equipment but requires a coordinated effort among intensivists and nurses for each turn and undertaken with great care to minimize the risk of any complications.

Preparation

1. Check for contraindications.
2. Consider possible adverse effects of prone positioning on chest tube drainage.
3. Whenever possible, explain the manoeuvre to the patient and/or their family.
5. Inspect and confirm that the endotracheal tube and all central and large bore peripheral catheters are firmly secured.
6. Consider exactly how the patient's head, neck, and shoulder girdle will be supported after they are turned prone. Assemble all needed pillows, foam pads, or other types of supports that might be needed.
7. Stop tube feeding, check for residual, fully evacuate the stomach, and cap or clamp the feeding and gastric tubes.
8. Prepare endotracheal suctioning equipment, and review what the process will be if copious airway secretions abruptly interfere with ventilation.
9. Decide whether the turn will be rightward or leftward.
10. Prepare all intravenous tubing and other catheters and tubing for connection when the patient is prone.

The Turning Procedure.

1. Place one (or more) people on both sides of the bed (to be responsible for the turning processes) and another at the head of the bed (to assure the central lines and the endotracheal tube do not become dislodged or kinked).
2. Increase the FI O2 to 1.0 and note the mode of ventilation, the tidal volume, the minute ventilation, and the peak and plateau airway pressures.
3. Pull the patient to the edge of the bed furthest from whichever lateral decubitus position will be used while turning.
4. Place a new draw sheet on the side of the bed that the patient will face when in this lateral decubitus position. Leave most of the sheet hanging.
5. Turn the patient to the lateral decubitus position with the dependent arm tucked slightly under the thorax. As the turning progresses the nondependent arm can be raised in a cocked position over the patient's head. Alternatively, the turn can progress using a log-rolling procedure.
6. Remove ECG leads and patches. Suction the airway, mouth, and nasal passages if necessary.
7. Continue turning to the prone position.
8. Reposition in the center of the bed using the new draw sheet.
9. If the patient is on a standard hospital bed, turn his/her face toward the ventilator. Assure that the airway is not kinked and has not migrated during the turning process. Suction the airway if necessary.
10. Support the face and shoulders appropriately avoiding any contact of the supporting padding with the orbits or the eyes.
11. Position the arms for patient comfort. If the patient cannot communicate avoid any type of arm extension that might result in a brachial plexus injury.

12. Auscultate the chest to check for right mainstem intubation. Reassess the tidal volume and minute ventilation.
13. Adjust all tubing and reassess connections and functions.
14. Reattach ECG patches and leads to the back.
15. Tilt the patient into reverse Trendelenberg. Slight, intermittent lateral repositioning (20–30°) should also be used, changing sides at least every 2 hours. Consideration should be given to the need for additional analgesic sedation and neuromuscular blockades to insure the child comfort and safety throughout the turn.
16. Document a thorough skin assessment every shift, specifically inspecting weight bearing, ventral surfaces [60].

This link is a free available video illustrating the procedure from the ongoing PROSpect study about the efficacy of prone position in children with severe ARDS.

https://www.youtube.com/watch?v=YRscvBb0Ajk.

Additional link is also free available video for adult proning which has the same aspects as children proning.

https://www.youtube.com/watch?v=lcBPaHQUvXY.

9.7. NITRIC OXIDE.

Nitric oxide is composed of two atoms that form a gaseous molecule. It is found naturally in the atmosphere and produced in various parts of the body specifically in the vascular endothelium and causes relaxation of smooth muscle. The production of nitric oxide in the body is done by the action of nitric oxide synthase (NOS) enzyme that converts to nitric oxide. Three isoforms of nitric oxide synthase (NOS) exist :

1. Neuronal NOS (nNOS) that is involved in neurotransmission.
2. Inducible NOS (iNOS), involved in the immune response.
3. Endothelial nitric oxide synthase (eNOS) which produces NO that acts specifically on endothelial smooth muscle cells.

The eNOS enzyme converts l-arginine to produce NO that penetrates the cell membrane which binds to the soluble guanylyl cyclase (sGC) and activates it forming cGMP cGMP binds to the cGMP-dependent protein kinase **Figure 20**. The activated protein kinase then affixes to ionic channels of the cell membrane and the sarcoplasmic reticulum, which has the effect of decreasing the influx of calcium to the cell, increasing the ejection of calcium from the cell, sequestering the calcium within the sarcoplasmic reticulum, and decreasing calcium mobilization. The net effect of these reactions makes less calcium available for depolarization and contraction, which leads to smooth muscle relaxation [61].

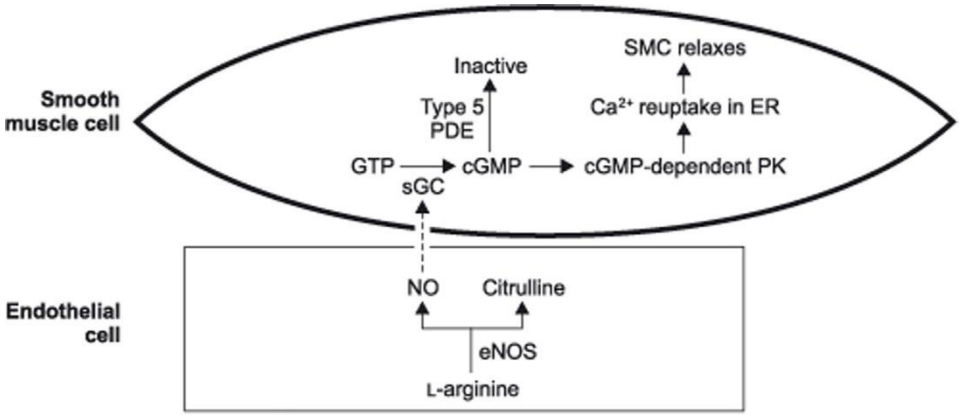


FIGURE 24. THE MECHANISM OF INHALED NO.

(FROM HUNT JL, BRONICKI RA AND ANAS N (2016) ROLE OF INHALED NITRIC OXIDE IN THE MANAGEMENT OF SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME. FRONT. PEDIATR. 4:74. DOI: 10.3389/FPED.2016.00074)

- **NO Benefits in PARDS.**

The inhaled NO is delivered directly to the pulmonary vascular endothelial cells causing the endothelial smooth muscle relaxation. The pulmonary vasodilation reduces intrapulmonary shunting when lung disease is present, which allows for increased ventilation/perfusion (V/Q) matching and improved oxygenation.

In addition to its effect on endothelial smooth muscle, NO also affects platelet activity. It has been observed in vitro that NO activates the guanylate cyclase inside platelets, which increases intraplatelet cGMP. The resulting activation of cGMP-dependent protein kinase causes a reduction in fibrinogen biding to glycoprotein GP IIb/IIIa, which induces partial inhibition of platelet aggregation.

Nitric oxide has also been noted to have a number of potentially important effects on the immune system. NO decreases Th1 proliferation and IL-2 synthesis but increases IL-4 synthesis from Th2 cells. By decreasing Th1 and increasing Th2 responses, NO may inhibit the inflammatory response to viral and bacterial infections. Additionally, NO has an effect on leukocyte adhesion and recruitment to sites of infection and has direct effect on a variety of organisms by directly inhibiting the growth of some viruses, bacteria, parasites, and fungi [62].

- **NO Dosage.**

The absorption of NO is systemic after inhalation. When exposed to the blood stream it combines with hemoglobin that is 60% to 100% oxygenated. The result is inactivation of NO and the vasodilatation effect is limited to the lung vasculature. However, Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation, and elevated nitrogen dioxide may cause acute lung injury.

Generally used dose in clinical practice ranges between 0.13 and 80 ppm (parts per million) and the exposure limit set by the Occupational Safety and Health Administration for nitric oxide in the USA is 25 ppm [63]. Different doses are used depending on the indication. As an example, initial dose for ARDS is 5-10 ppm then titration for the lowest effective dose should performed, comparing to 20-40 used for pulmonary hypertension and 5-20 in right ventricular dysfunction. In neonates >34 weeks gestational age with hypoxic respiratory failure associated with pulmonary hypertension the dose used is 20 ppm. Randomized clinical trial was performed in children with ARDS to check dose-response effects of 0.13 to 16 ppm of iNO. They found no difference in effect between high and low dose 1ppm vs 16ppm [64].

- **Clinical implications.**

Doses > 20 ppm are used with caution as its associated with the risk of toxicity by formation of NO_2 and methemoglobin and doses > 40 ppm provides minimal additional clinical benefit and its used rarely in some situations. Methemoglobin concentrations and inspired NO_2 should be monitored when the dose > 20ppm are used. Methemoglobinemia investigation should be performed within 4 to 8 hours after initiation and periodically throughout treatment.

Abrupt discontinuation should be avoided as it causes rebound pulmonary hypertension syndrome leading to worsening oxygenation, and increasing pulmonary artery pressure. Signs and symptoms of rebound pulmonary hypertension syndrome include hypoxemia, systemic hypotension, bradycardia, and reduced cardiac output. When rebound is detected, NO should be implicated immediately. To avoid rebound, NO is weaned by titrating down in many steps (pause several hours at each step) and monitor for hypoxemia.

If toxicity occurs, NO_2 levels >3 ppm or methemoglobin levels $>7\%$, its treated by reducing the dose of or discontinuing nitric oxide. In case methemoglobinemia do not resolve with dosage reduction or discontinuation of iNO. Therapy may require intravenous vitamin C, intravenous methylene blue, or blood transfusion, depending on the clinical situation [65].

INO can be considered in patients with documented pulmonary hypertension or severe right ventricular dysfunction or as a rescue from or bridge to ECMO [66]. A multicenter randomized controlled trial in 2015 found the use of iNO was associated with a significantly reduced duration of mechanical ventilation and significantly greater rate of extracorporeal membrane oxygenation–free survival [67]. The PALICC group did not recommend routine use of iNO [6].

It should be noted that a manometer is used in practice to deliver the desired INO dose with settings of 0.2L to 1.5L/minute. In order to determine the desired dose in liter per minute the clinician use a formula to convert ppm into liter per minute. **IMAGE 4, 5.**

$$NO\ concentration\ (ppm) = NOflow * \frac{1}{Minute\ ventilation} * Tank\ concentration(450ppm).$$

IMAGE 4. Nitiric oxide tank used in our department. Image from *University hospital center HASSAN II PICU.*

IMAGE 5. Showing the manometer used for delivering iNO dose from 0.2 to 1.5 liter per minute. *University hospital center HASSAN II PICU.*

9.8. EXOGENOUS SURFACTANT.

Surfactant is naturally produced by AT-II cells and has an important role in reducing surface tension on air-water interface to keep the alveoli open and prevent its collapse, other roles include host defense and immune modulation. Exogenous surfactant can be delivered via an endotracheal tube and in conjunction with mechanical ventilation [8].

In pathogenesis of PARDS, there is dysfunction of surfactant which may explain fluid filled alveolar collapse. Neonatal ARDS is characterized by surfactant deficiency due to immature AT-II cells. Exogenous surfactant use in the neonatal respiratory distress syndrome has dramatically improved outcome in this population and made exogenous surfactant a standard of care in premature newborns [68]. Because of this observation, it's tempting to extrapolate surfactant strategy in older children with hypoxemic respiratory failure.

Many case reports and patient series showed Exogenous surfactant use in children ARDS has promising benefits. As a result, surfactant use was studied extensively in clinical trials. An uncontrolled trial in 1996 of calf lung surfactant extract (calfactant) showed dramatic improvement in oxygenation in 29 children with acute hypoxic respiratory failure [69]. Two subsequent studies of porcine surfactant (curosurf) in children with bronchiolitis required invasive ventilation demonstrated improved oxygenation, decreased duration of mechanical ventilation, and decreased ICU length of stay [70]. Willson et al. then conducted a prospective RCT that demonstrated the use of calfactant in children with acute hypoxic respiratory failure also showed improved oxygenation and decreased length of ventilation and ICU stay, with no difference in mortality [71].

The promising findings in these small clinical trials led to the largest multicentred randomized placebo controlled trial on surfactant use to date in PARDS. More than 150 infants and children with respiratory failure were randomized to receive calfactant versus placebo air. The trial demonstrated improved oxygenation, but no difference in duration of ventilation or length of stay [72]. Subsequent trials of calfactant in direct-injury for adults and children also failed to show improvement in outcome such as mortality, ventilation time, or Length of stay [73].

Early successes have been frustrated by the recent failure in showing improvement of outcome in the use of exogenous surfactant [74]. The PALICC did not recommend the routine use of surfactant in PARDS and Further study is warranted to evaluate specific populations, dosing forms, and delivery regimen.

9.9. STEROIDS.

Glucocorticoids are drugs which initiates various actions through binding with the glucocorticoid receptor, having a similar effect to the naturally occurring hormone cortisol. Commonly used glucocorticoids include hydrocortisone, prednisone, methylprednisolone, and dexamethasone. They are used in many aspects in medical care as anti-inflammatory drugs which can be beneficial in PARDS in controlling dysregulated inflammation. Nevertheless, because of their broad mechanism of action effecting multiple systems, patients may develop multiple adverse effects [75]. These effects may be of clinical significance in critical ill patients with PARDS and includes:

- Gastrointestinal bleeding
- Immunosuppression leading to worsening of an existing infection.
- Metabolic effects such as hyperglycemia, retention of sodium chloride and water and loss of potassium.
- Hypertension.
- Psychiatric effects such as insomnia, psychosis and delirium
- Decrease in growth with prolonged use.

The use of steroids has been studied in adults more than children. These studies showed mixed results with some studies showing clear benefit while others do not. The most positive result came with studies by Meduri et al. in 2018. In this meta-analysis evaluating 9 RCTs, subjects were randomized to the treatment arm received 2 mg/kg methylprednisolone for 14 days which was then weaned slowly through day 32. The study reported moderate-to-high evidence that steroid therapy is safe and reduces duration of mechanical ventilation, ICU length of stay, and mortality [76].

Recently, task force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) published recommendations for the management of critical illness-related corticosteroid insufficiency (54).

They reviewed 9 trials of prolonged administration of corticosteroids in adults with ARDS. In their review they consistently found the steroid group had decreased markers of inflammation, decreased duration of mechanical ventilation and decreased hospital mortality by 7% in mild ARDS and 11% in severe ARDS. The only risk found in the glucocorticoid group was for hyperglycemia in the first 36 hours after starting steroids without any increased risk of morbidity. There was no increased risk of neuromuscular weakness, gastrointestinal bleeding or nosocomial infection in the steroid group compared with placebo [77].

Recent trials in children failed to show a survival benefit for corticosteroids in ARDS. Drago et al. completed the first RCT of corticosteroids in children with PARDS (51). Thirty-five PARDS patients were randomized to receive placebo versus methylprednisolone 2 mg/kg bolus followed by a continuous infusion of 1 mg/kg/day for 7 days then a slow taper over the subsequent 7 days. Patients in the steroid group had improved PaO2/FiO2 at day 8 and less need for oxygen at ICU transfer. However, there was no significant difference in length of ICU stay, length of hospital stay, ventilator free days or hospital mortality [78].

the 2015 PALICC guidelines do not recommend corticosteroids as routine therapy in PARDS. Their recommendation against steroid use in PARDS and met the “strong agreement” standard. The authors highlighted the need for future research to identify populations most likely to benefit from steroids as well as optimal dosing regimens [6].

In 2017, the European Paediatric Mechanical Ventilation Consensus Conference (PEMVECC), stated there were no specific recommendations on corticosteroids use in PARDS other than use in post-extubation stridor prevention [21].

The most promising results have been in trials in adults population utilizing low to moderate doses (equivalent to methylprednisolone 1–2 mg/kg/day), begun

relatively early (< 3 days in the course of early ARDS or < 14 days in the course of late ARDS). Current pediatric data and guidelines are against the use of steroids in PARDS and authors have established the clear need of future large study groups to identify the population in benefit.

9.10. NEUROMUSCULAR BLOCKADES.

NMBAs are used in diverse clinical scenarios in prevention of unwanted total skeletal muscle movement. It may be administered as a single dose to facilitate procedures such as endotracheal intubation or by a continuous infusion when more prolonged immobilization is needed. These agents provide no amnestic, analgesic, or sedative properties, and should not be used without the coadministration of an amnestic agent (i.e., benzodiazepine, propofol, ketamine, inhalational anesthetic agent). The depth of neuromuscular blockade can be monitored by the using of train of four (TOF) [79].

Two general classes of NMBAs (depolarizing and nondepolarizing agents) exist for clinical use. Depolarizing agents, such as succinylcholine, mimic acetylcholine. They bind to the acetylcholine receptor at the neuromuscular junction and activate it. Succinylcholine is used only for rapid neuromuscular blockade during endotracheal intubation.

The nondepolarizing NMBAs act as competitive antagonist competing with and blocking the effects of acetylcholine at the receptor without activating the acetylcholine receptor. The nondepolarizing agents are divided into two groups based on their basic chemical structure: aminosteroid (i.e. Pancuronium, Rocuronium, Vecuronium, and Pipecuronium) and benzylisoquinolinium (i.e. Mivacurium, Atracurium, Cisatracurium, and Doxacurium).

- *Vecuronium* is an aminosteroid NMBA that was released for clinical use in the 1980s. In doses of 0.1–0.15 mg/kg, complete neuromuscular blockade with conditions adequate for endotracheal intubation is provided in 90 seconds with a clinical duration of action of 30–40 minutes (intermediate-acting agent). The onset of complete neuromuscular blockade can be achieved more rapidly by increasing the dose to 0.3 mg/kg. With the larger dose, the onset time is

approximately 60–75 seconds, but the duration of neuromuscular blockade is prolonged to 60–90 minutes. Even with higher doses, vecuronium has no cardiovascular effects. Metabolism is both hepatic (70–80%) and renal (20–30%).

- *Rocuronium* is a desacetoxy analog of vecuronium. It remains one of the newer aminosteroid NMBAs, having been released for clinical use in the early 1990s. With a dose of 0.6 mg/kg, the duration of action is 20–40 minutes. Larger doses (1–1.2 mg/kg) are frequently used during rapid sequence intubation. As with other agents, the duration of action increases when larger doses are administered so that 60–90 minutes of neuromuscular blockade occurs following a dose of 1.0 mg/kg. A mild vagolytic effect may increase heart rate in the range of 10–20 beats per minute and mean arterial pressure following bolus dosing. Rocuronium undergoes primarily hepatic metabolism, so clinical effects last longer in children with hepatic insufficiency. There is also a mild prolongation of the clinical effect when rocuronium is administered to patients with renal failure [80].
- *Cisatracurium* is a nondepolarizing NMBA of the benzylisoquinolinium class. Acceptable conditions for endotracheal intubation are provided in approximately 2 minutes with cisatracurium. Hemodynamic effects are minimal. Metabolism of cisatracurium occurs via Hofmann degradation, a pH- and temperature-dependent chemical process, to form laudanosine and the monoquaternary acrylate metabolite. The metabolic pathway is not affected by renal or hepatic function, thereby providing stable pharmacokinetics even in the setting of multisystem organ failure.

➢ **Indications for neuromuscular blockade in the pediatric ICU.**

1. Facilitation of procedures or diagnostic studies.

– Endotracheal intubation.

- Central line placement.
- Radiological imaging (MRI, CT scanning).

2. Intensive care indications.

- To facilitate mechanical ventilation (especially high-frequency techniques).
- Control increased intracranial pressure.
- Eliminate shivering (therapeutic hypothermia).
- Decrease peripheral oxygen utilization.
- Control severe agitation unresponsive to adequate sedation.
- Maintain immobilization after surgical procedures.
- Decrease the risk of pulmonary vasospasm in patients with pulmonary hypertension.
- Management of tetanus.

3. Immobilization during interhospital or intrahospital transport [81].

Adult clinical trials and guidelines support NMB use in adults with early severe ARDS. A prospective physiologic study by Wilsterman et al. showed improved OI in pediatric patients with acute hypoxemic respiratory failure who received continuous NMB during mechanical ventilation [82]. PALICC recommends considering NMB in children with PARDS if sedation alone is inadequate to achieve effective mechanical ventilation, targeting the minimal effective dose [6].

9.11. EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO).

Mechanical ventilation is supportive but not physiologic. Despite the consideration of low tidal volumes, unfortunately some patients cannot adequately be managed with non-injurious pressures or volumes and, at some point, ventilatory lung injury potentially exceeds lung recovery. That is when ECMO is generally considered in order to avoid toxic ventilator setting. The main issue is that there is no objective or proven means to weigh the risks of continuing mechanical ventilation versus initiating ECMO.

ECMO consists of a small number of essential components: a pump, an oxygenator, a heat exchanger, cannula(s), tubing (circuit), and various monitoring components that includes pump inlet pressure monitor, pre- and post-oxygenator pressures, flow monitors, air bubble detector, and oxygen saturation/blood gas. FIGURE 24.

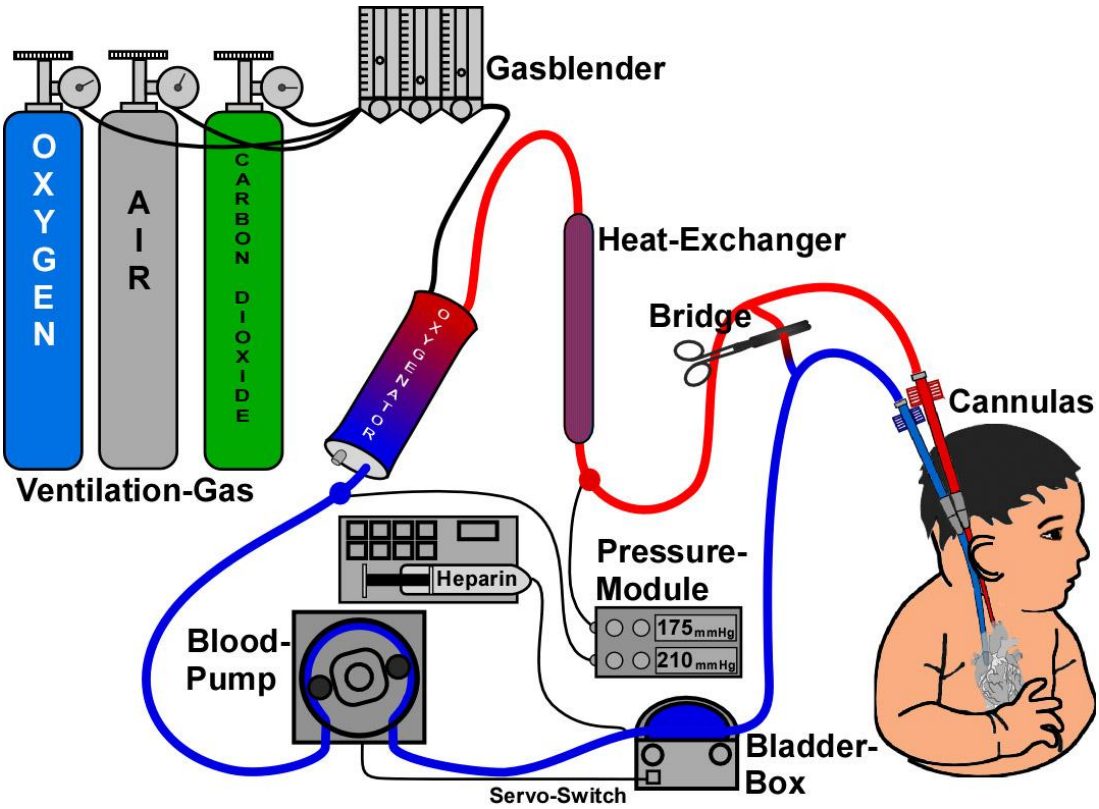


FIGURE 25.STANDARD ECMO CIRCUIT.

(From https://commons.wikimedia.org/wiki/File:Ecmo_schema-1-.jpg)

There are essentially three different types of ECMO systems that may be used in children with PARDS: veno-arterial extracorporeal membrane oxygenation (VA ECMO); veno-venous extracorporeal membrane oxygenation (VV ECMO); and extracorporeal carbon dioxide removal (ECCO2R) [83].

❖ **Veno-arterial Extracorporeal Membrane Oxygenation (VA ECMO).**

VA ECMO extracts blood from the venous side of the circulation, oxygenates it, and returns it to the arterial side. In children, venous access is most often achieved via the internal jugular vein, but femoral venous access and direct access via sternotomy (usually in postoperative cardiac patients) are also possible. The arterial return is generally the carotid artery in small children.

Disadvantages:

1. Blood return to the systemic circulation risks emboli (clot, debris, air) from the circuit going directly to the central nervous system.
2. The sacrifice of the carotid artery or potential limb ischemia when the femoral artery is used for blood return.
3. During femoral artery cannulation, a small reperfusion cannula may be placed distal to the site of femoral cannulation in order to perfuse the distal limb [84].

❖ **Veno-venous Extracorporeal Membrane Oxygenation (VV ECMO).**

VV ECMO extracts blood from the venous side of the circulation, oxygenates it, and returns it to the venous side. Because blood is taken from and then returned to the venous side, a variable amount of recirculation occurs and this may limit the resultant arterial oxygen saturation. The absence of cardiac support also precludes the use of VV ECMO for children with severe cardiac failure. Formerly, two sites of venous access were required for VV ECMO (usually the internal jugular and a femoral vein), but the newer double-lumen cannulas allow use of a single vessel – generally the internal jugular vein. These cannulas have a larger diameter, may be difficult to

position, and have been associated with a significant incidence of perforation (5–30%) [85]. Properly positioned, however, they minimize recirculation by directing oxygenated blood across the tricuspid valve and allow use of a single access site. VV ECMO has a lower risk of neurologic injury and avoids sacrificing an arterial vessel or rendering a limb possibly ischemic but does not support a failing heart [86].

❖ **Extracorporeal Carbon Dioxide Removal (ECCO2R).**

ECCO2R can either be veno-venous, veno-arterial, and with or without an interposed pump. ECCO2R is primarily used to achieve CO2 removal, accomplishing ventilation with potentially less injurious ventilator pressures or volumes. Effective CO2 removal can be achieved with a fraction of the flows necessary to achieve oxygenation, due to the superior solubility and diffusion of CO2 relative to oxygen.

- **ECMO for PARDS.**

The use of ECMO on any patient is challenging due to the none straightforward indications. Overarching considerations may include:

1. Is the trajectory of the lung injury such that the risks of ECMO are outweighed by the risks of continuing mechanical ventilatory support at potentially injurious settings?
2. Is the lung injury recoverable or, if not, is lung transplantation feasible?
3. Is there evidence of other organ failures and, if so, are the additional organ failures potentially recoverable?
4. What are the family's beliefs and considerations regarding the goals of care?

Specific indications and relative contraindications are listed in Table.

Indications and relative contraindications in ECMO for PARDS are shown in **TABLE 20.**

TABLE 20. THE INDICATIONS AND RELATIVE CONTRAINDICATIONS OF ECMO.

Indications	Relative contraindications
Severe refractory hypoxemia (e.g., P:F ratio 40)	Duration of mechanical ventilation >14–21 days before ECMO
Toxic ventilator settings (e.g., Pplat >32, MAP >25–30)	Recent intracranial surgery or hemorrhage
Refractory hypercarbia	Chronic illness with poor long-term prognosis
Refractory air leaks	

- **ECMO complications.**

The most common complication is bleeding and thrombosis that is associated with significant morbidity and mortality. Coagulation problems are largely related to the exposure of blood on nonbiologic surface. ECMO patients are also at high risk of infection due to the exposure to foreign objects and the need for the interruption of the circuit to take labs or medicament administration.

The ECMO complications include:

1. Bleeding and thrombosis.
2. Infection.
3. Organ dysfunction due to hemolysis.
4. Central nervous system infarct and bleeding.
5. Cannula problems such as perforation and site bleeding.

Despite the lack of data about ECMO use in children, it increased substantially from 2009 to 2015, with a 50% increase in the number of centers reporting pediatric ECMO cases to the ELSO registry and a 24% annual increase in pediatric ECMO cases over that time period. Survival to hospital discharge for children with respiratory failure supported with ECMO is 60%, with variable outcome based on etiology [87].

10. EVOLUTION.

10.1 PICU stay.

The mean length of PICU stay in Flori study is 14.8 days [17]. In Deluca study the mean length of PICU stay is 10 days [18]. In our series the mean length of PICU stay is elevated with 20 days compared with the previous two studies. **TABLE 21.**

TABLE 21. MEAN LENGTH OF PICU STAY IN OUR SERIES COMPARED TO LITERATURE.

Study	YEAR	Mean length of PICU stay in days
FlORI. [17]	2005	14.8
DELUCA. [18]	2013	10
OUR SERIES.	2021	20

10.2 Mortality.

Mortality rates of PARDS is decreasing over time from 48% to 17% [88]. This may be explained by the adoption of low tidal volume strategy and high peep extracted from adult data in addition to protocolized sepsis care and timely antibiotics. The evolving of definitions for PARDS also contributed into lower mortality rates with the final definition of PALICC group which liberated the definition by including unilateral infiltrates in chest Xray.

Different studies reported different percentages of mortality and the estimated mortality in these studies vary between 17-35% [89]. In Erickson study in 2007 the mortality was 35%. It was high in PARDS triggered by direct lung injury with 40% in patients with pneumonia, 4.9% in patients with aspiration, while burn and near drowning presented in 2.4% for each. Non survivors with indirect lung injury presented with 31% for sepsis and 4.9% in non-pulmonary trauma [22]. In FLORI in 2005 and in

Deluca study in 2013 the mortality rates were as low as 22% and 17% respectively [17] [18].

In PARDIE multicentred cross sectional study the overall mortality was 17%. It is lowest in PARDS triggered by direct lung injury with 12% mortality rate in patients with pneumonia and 22% in patients with aspiration. It was highest in those with indirect lung injury from sepsis and/or shock with 30% [19].

In our series the mortality rate was 35%. It was lower in PARDS triggered by direct lung injury with 16% (3 cases of 18) of non survivors. 18% (2 cases of 11) of mortality rate in pneumonia, 20% (1 case of 5) in aspiration. It was significantly higher in PARDS triggered by indirect lung injury with no survivors. **TABLE 22.**

It should be noted that viral infections such as respiratory syncytial virus and influenza virus are more frequently life-threatening cause of PARDS [90]. A history of prematurity, cancer, left ventricular dysfunction or immune compromise are risk factors for mortality [91].

TABLE 22. MORTALITY RATES IN LITERATURE COMPARING TO OUR STUDY.

Study	Year	Mortality rates
FLORI. [17]	2005	22%
ERICKSON. [21]	2007	35%
DELUCA. [18]	2013	17%
PARDIE. [19]	2018	17%
OUR STUDY.	2021	35%

VI. CONCLUSION

PARDS is a life-threatening pulmonary condition and one of major challenges in modern PICU. Despite medicine has developed since the first description of ARDS in adults, mortality in PARDS remains very high. Early detecting and management of ARDS is crucial for patients survivor where the interest of a goal directed protocol and the need of predictive tools is indispensable to determine patients at risk. The main cause of PARDS is dominated by pneumonia and sepsis, the management of PARDS is supportive and based on lung protective strategy.

VII. STUDY LIMITATIONS

- Small number of cases.
- PALICC criteria were not applied on most of cases.
- Pediatric risk of mortality (PRISM III) score was not calculated.
- Post discharge evaluation was not registered.
- Outcome was based only on mortality without ventilator free days nor duration of mechanical ventilation as automatic registration were not used.

ABSTRACT

Introduction.

Acute respiratory distress syndrome (ARDS) is an acute onset of severe hypoxemia due to the disruption of alveolar epithelial-endothelial barrier resulting in accumulation of non-cardiogenic pulmonary edema, occurs by direct or indirect insult.

Material and methods.

This is a retrospective study using hospital database during 32 months (January 2019-September 202). During our study, 23 patients had PARDS at admission or during hospital stay at mother and child ICU-University Hospital HASSAN II-FES.

Objectives of the study.

- Define PARDS
- Pathophysiology of PARDS
- Epidemiology of PARDS.
- Diagnosis of PARDS.
- Management of PARDS
- Evolution of PARDS.

Results.

In our study, 23 patients presented with ARDS at admission or during PICU stay. The incidence of PARDS in our department during our two years study was 2.7%. The mean age in our study was 4.6 YO with 73% infants and children under 5 YO. Boys were more likely to develop PARDS with sex ration M/F of 2.8. comorbidities were found in 3 patients.

Most of our patients presented with bilateral infiltrates while one presented with unilateral infiltrates at diagnosis. Chest X ray and Thoracic CT scan was performed in all of our patients. PARDS diagnosis at admission occurred in 10 patients (43% of cases) while ARDS onset at PICU stay occurred in 13 patients (57% of cases).

The main cause of PARDS was pneumonia in 48% of PARDS, aspiration in 22%, sepsis in 13%. While major trauma, foreign object, contusion and burns presented in 4% of cases for each. 13% of cases presented with Mild PARDS, 52% of cases with Moderate PARDS, and 35% of cases with severe PARDS. The mean P/F ratio was 172 for all patients and the mean P/F ratio in mild cases at first 24 hours was 283, in moderate cases was 133, and in severe cases was 73. OSI was used in one patient stratified as moderate PARDS with an OSI of 7.3.

Protective lung strategy was applied on 22 patients while noninvasive ventilation was applied on one patient. Prone position was indicated in 6 patients (26% of cases) with P/F<150. Inhaled Nitric Oxide (iNO) was used in 8 patients (35% of cases) with severe PARDS while VV ECMO was used on one patient with a satisfying post discharge evaluation.

The mean length of PICU stay was 20 days for all patients. The mean PICU stay for mild cases was 13.3 days while for moderate cases was 17.3 days and in severe cases was 28 days. In our series the mortality rate was 35%. It was lower in PARDS triggered by direct lung injury with 16% (3 cases of 18) of non survivors. 18% (2 cases of 11) of mortality rate in pneumonia, 20% (1 case of 5) in aspiration. It was significantly higher in PARDS triggered by indirect lung injury with no survivors (4 cases).

Conclusion.

PARDS is a life-threatening pulmonary condition and one of major challenges in modern PICU. Despite medicine has developed since the first description of ARDS in adults, mortality in PARDS remains high. Early detecting and management of ARDS is crucial for patients survivor where the interest of a goal directed protocol and the need of predictive tools is indispensable to determine patients at risk. The main cause of PARDS is dominated by pneumonia and sepsis, the management of PARDS is supportive and based on lung protective strategy.

Résumé

Définition.

Le syndrome de détresse respiratoire aigüe (SDRA) est un œdème pulmonaire d'origine non cardiogénique qui se manifeste par l'hypoxémie sévère survenant à la suite d'une agression directe ou indirecte de la membrane alvéolocapillaire.

Matériels et méthodes.

C'est une étude rétrospective couvrant une période de 36 mois (Janvier 2019 à Septembre 2021). Durant notre étude, 23 patients présentant un SDRA à l'admission ou lors de séjour au service de réanimation de mère et enfant au CHU HASSAN II FES.

Objectifs de l'étude.

- Définir un SDRA Pédiatrique (SDRAP).
- Physiopathologie du SDRAP.
- Épidémiologie du SDRAP.
- Diagnostic du SDRAP.
- Prise en charge du SDRAP.
- Évolution du SDRAP.

Résultats.

Durant notre étude, 23 patients présentant un SDRA à l'admission ou lors de l'hospitalisation au service de réanimation mère enfant. L'incidence du SDRAP dans notre service était de 1.9 %. L'âge moyen était de 4,6 ans avec 73 % d'enfants ayant moins de 5 ans. Les enfants de sexe masculin sont plus susceptibles à développer un SDRAP avec un sexe ratio H/F=2,8. Des comorbidités ont été retrouvés chez 3 de nos patients.

La majorité de nos patients ont présenté un infiltrat inflammatoire bilatéral, alors qu'un seul patient a présenté un infiltrat unilatéral au moment du diagnostic.

Tous nos patients ont bénéficié d'une radiographie standard pulmonaire et d'un scanner thoracique. Le diagnostic du SDRAP a été établi chez 10 patients à l'admission (43% des cas), alors qu'il est survenu chez 13 patients lors de séjour hospitalier dans notre service (57% des cas).

La cause principale du SDRAP était la pneumonie dans 48% des cas, l'inhalation dans 22 % des cas, le sepsis dans 13 % des cas, et 4% pour chacun des cas de traumatismes majeurs, contusion ,brûlures et corps étranger. 13% des cas ont présenté un SDRAP dans sa forme légère, 52% des cas un SDRAP modéré, et 35% des cas un SDRAP sévère. Le ratio P/F moyen était de 172 chez tous nos patients. Dans les premières 24 heures, le P/F moyen dans les formes légères était de 283, 133 dans les formes modérées, et 73 dans les formes sévères. L'OSI (oxygen saturation index) a été utilisé chez un de nos patients stratifié comme SDRAP modéré (OSI=7,3).

La ventilation protectrice a été appliquée chez 22 de nos patients, alors que la ventilation non invasive a été utilisée chez un seul patient. Le décubitus ventral a été indiqué chez 6 patients (26% des cas) avec un P/F<150. L'oxyde d'azote inhalé (NOi) a été utilisé chez 8 patients présentant un SDRAP sévère (35 % des cas), alors que l'ECMO a été utilisé chez un seul de nos malades dont l'évolution ultérieure était très satisfaisante.

La durée moyenne d'hospitalisation était de 20 jours chez tous nos patients. Pour les formes légères, la durée moyenne était de 13.3 jours, 17.3 jours pour les formes modérées, et 28 jours pour les formes sévères. Le taux de mortalité dans notre étude était de 34%. Le taux de mortalité était bas dans le SDRAP direct avec 16% (3 cas sur 18). Le taux de mortalité chez les patients atteint d'une pneumonie était de 18% (2 cas sur 11), et dans l'inhalation de 20% (1 cas sur 5). Le taux de mortalité était significativement élevé dans les SDRAP indirect avec aucun survivant (5 cas).

Conclusion.

Le SDRAP est une affection pulmonaire mortelle et l'un des principaux défis dans la réanimation pédiatrique moderne. Bien que la médecine se soit développée depuis la première description du SDRA chez les adultes en 1967, la mortalité dans le SDRAP reste élevée. Le diagnostic et la prise en charge précoces sont cruciaux pour la survie des patients, d'où l'intérêt d'un protocole bien codifié et la nécessité d'outils prédictifs qui peuvent être indispensables pour déterminer les patients à risque. Les principales etiologies du SDRAP chez les enfants sont la pneumonie et le sepsis. La prise en charge est essentiellement basée sur la ventilation protectrice.

ملخص :

مقدمة:

متلازمة الضائقة التنفسية الحادة هي وذمة رئوية نافذة غير قلبية، ناتجة عن الضرر المباشر أو الغير مباشر للاغشية السنخية الشعرية و ترتبط بإلتهاب رئوي و نقص شديد في نسبة الاكسيجين في الدم.

المواد و الطرق:

هذا العمل يمثل دراسة مرجعية لدى المرضى المصابين بمتلازمة الضائقة التنفسية الحادة بمستشفى الحسن الثاني بفاس في مصلحة التخدير و الانعاش للأم والطفل خلال فترة زمنية مدتها 36 شهر (يناير 2019 – سبتمبر 2021).

الأهداف الرئيسية للدراسة:

1. تعريف المتلازمة.
2. الفيزيولوجيا المرضية.
3. الخصائص الوبائية للمتلازمة.
4. تشخيص المتلازمة.
5. طرق العلاج.
6. تطور المرض.

النتائج:

خلال فترة الدراسة تم تشخيص 23 مريضاً بمتلازمة الضائقة التنفسية الحادة. المعدل العام لحصول المتلازمة يقدر ب 1.9%.

نسبة حدوث المتلازمة عند الذكور أكثر من الإناث بنسبة بين الجنسين تقدر ب 2.8%. متوسط العمر في الدراسة هو 4.6 سنين و عدد المرضى المتواجد عندهم سوابق مرضية هو 3 مرضى.

جميع المرضى استفادو من صورة أشعة سينية بلاضافة لصورة مقطعية للصدر. الأمراض المعدية و حالات التعفن كانت من أهم أسباب حدوث المتلازمة.

كان توزيع شدة المرض وفقاً للأتي:

1. 15% من الحالات كانت طفيفة.
2. 52% من الحالات كانت متوسطة.
3. 35% من الحالات كانت شديدة.

بلغ متوسط الاقامة في مصلحة الانعاش 20 يوم بينما بلغ معدل الإماتة 35% من الحالات.

الإستنتاج:

متلازمة الضائقة التنفسية الحادة هي عبء كبير و تشكل واحدة من أهم المعوقات التي تواجها أقسام الانعاش الجد متطورة مما يستلزم السرعة في البدء في العلاج او توفير أدوات لمعرفة المرضى المعرضين للاصابة بهذه المتلازمة. أهم أسباب حدوث المتلازمة هم التهابات الرئة و التعفنات. العلاج يستند أساسياً على التنفس الاصطناعي.

References

[1] Ashbaugh DG, Bigelow DB, Petty TL, et al., "Acute respiratory distress in adults," *lancet,* 1967.

[2] Bernard GR, Artigas A, Brigham KL, et al., "Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination.," *Intensive Care Med,* 1994.

[3] The ARDS Definition Task Force, Ranieri V, Rubenfeld G, Thompson BT, et al., "Acute respiratory distress syndrome.," *JAMA,* 2012.

[4] Rimensberger PC, Cheifetz IM., "Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference," *Pediatr Crit Care Med,* 2015.

[5] Rufener, C., Kopstick, A., & Orwoll, B., "PEDIATRIC ARDS: CLINICIAN RECOGNITION SINCE THE RELEASE OF THE PEDIATRIC ACUTE LUNG INJURY CONSENSUS CONFERENCE DEFINITION.," *Chest,* 2020.

[6] Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. , vol. 16:428–439, 2015.

[7] John W. Kreit (Author), John A. Kellum (Series Editor), Mechanical Ventilation: Physiology and Practice (Pittsburgh Critical Care Medicine), New York: Oxford University Press, (2018).

[8] Sapru A, Flori H, Quasney MW, Dahmer MK,, "Pediatric Acute Lung Injury Consensus Conference Group Pathobiology of acute respiratory distress syndrome.," 2015.

[9] Webb, H. H. & Tierney, D. F et al., "Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure," *Am. Rev. Respir.,* 1974.

[10] Brower, R. G. et al., "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.," *N. Engl. J. Med,* 2000.

[11] Gerard F Curley, John G Laffey, Haibo Zhang, Arthur S Slutsky., "Biotrauma and Ventilator-Induced Lung Injury.," *American College of Chest Physicians.,* Nov 2016 .

[12] A. Schwingshackl., "The role of stretch-activated ion channels in acute respiratory distress syndrome: finally a new target?," *Am J Physiol Lung Cell Mol Physiol.,* 2016 .

[13] Michael A. Matthay, Rachel L. Zemans, Guy A. Zimmerman, Yaseen M. Arabi, , "Acute respiratory distress syndrome," *Nat Rev Dis Primers,* 2019.

[14] S. A. N. A. N. G. Y. M. P. E. W. B. Erickson S, "Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study.," *Pediatr Crit Care Med.,* 2007.

[15] Schouten LR, et al, " Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis.," *Crit. Care Med,* 2016.

[16] Schouten LR, et al. , "Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis.," *Crit. Care Med,* 2016.

[17] Flori HR, Glidden DV, Rutherford GW, Matthay MA., "Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality.," *Am J Respir Crit Care Med.,* 2005.

[18] De Luca D, Piastra M, Chidini G, Tissieres P, Calderini E, Essouri S, Medina Villanueva A, Vivanco Allende A, Pons-Odena M, Perez-Baena L, Hermon M, Tridente A, Conti G, Antonelli M, Kneyber M., "The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus," *Intensive Care Med,* 2013.

[19] Khemani RG, et al., " Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study.," *Lancet Respir. Med. ,* 2018.

[20] Ranieri VM, Suter PM, Tortorella C, et al. , "Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial.," *JAMA,* 1999.

[21] Kneyber MCJ, Luca D, Calderini E, et al , "Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC)," *Intensive Care Med,* 2017.

[22] Erickson S, Schibler A, Numa A, et al. , "Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study.," *Pediatr Crit Care Med,* 2007.

[23] Khemani RG, Conti D, Alonzo TA, et al., "Effect of tidal volume in children with acute hypoxemic respiratory failure.," *Intensive Care Med,* 2009.

[24] Zhu YF, Xu F, Lu XL, et al., "Chinese Collaborative Study Group for Pediatric Hypoxemic Respiratory Failure: Mortality and morbidity of acute hypoxemic respiratory failure and acute respiratory distress syndrome in infants and young children.," *Chin Med J,* 2012.

[25] De Jager, P., Burgerhof, J. G. M., van Heerde, M., Albers, M. J. I. J., Markhorst, D. G., & Kneyber, M. C. J. doi:, "Tidal Volume and Mortality in Mechanically Ventilated Children," *Critical Care Medicine,* (2014).

[26] Imber, D. A., Thomas, N. J., & Yehya, N. , " Association Between Tidal Volumes Adjusted for Ideal Body Weight and Outcomes in Pediatric Acute Respiratory Distress Syndrome.," *Pediatric Critical Care Medicine,* 2019.

[27] McKown, A. C., & Ware, L. B., "Pediatric Acute Respiratory Distress Syndrome: Increase the Positive End-Expiratory Pressure?," *American Journal of Respiratory and Critical Care Medicine,* 2018.

[28] Phoenix SI, Paravastu S, Columb M, et al. , "Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis.," *Anesthesiology,* 2009.

[29] Briel M, Meade M, Mercat A, et al. , "Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis," *JAMA,* 2010.

[30] . Khemani RG, Parvathaneni K, Yehya N, et al. , "Positive endexpiratory pressure lower than the ARDS network protocol is associated with higher pediatric acute respiratory distress syndrome mortality.," *Am J Respir Crit Care Med,* 2018.

[31] Thomas, N., & Yehya, N., "Sepsis and Pediatric Acute Respiratory Distress Syndrome," *Journal of Pediatric Intensive Care,* 2018.

[32] Abdelsalam M, Cheifetz IM., "Goal-directed therapy for severely hypoxic patients with acute respiratory distress syndrome: permissive hypoxemia.," *Respir Care,* Vols. 55(11):1483-1490, 2010.

[33] Contreras M, Ansari B, Curley G, et al., "Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-kappaB-dependent mechanism," *Crit Care Med,* 2012.

[34] Amato MB, Meade MO, Slutsky AS, et al. , "Driving pressure and survival in the acute respiratory distress syndrome.," *N Engl J Med,* 2015.

[35] Ann, Tobias JD., "Acute pain management in infants and childrenPart 2: Intravenous opioids, intravenous nonsteroidal antiinflammatory drugs, and managing adverse effects.," *Pediatr Ann,* 2014.

[36] Zuppa AF, Curley MAQ., "Sedation Analgesia and Neuromuscular Blockade in Pediatric Critical Care: Overview and Current Landscape," *Pediatr Clin North Am,* 2017.

[37] Minardi, C., Sahillioglu, E., Astuto, M., Colombo, M., & Mauricio Ingelmo., "Sedation and Analgesia in Pediatric Intensive Care.," *Current Drug Targets,* 2012.

[38] Lynne Rosenberg, Chani Traube, "Sedation strategies in children with pediatric acute respiratory," *Ann Transl Med,* 2019.

[39] Shehabi Y, Bellomo R, Kadiman S, et al., "Sedation Intensity in the First 48 Hours of Mechanical Ventilation and 180- Day Mortality: A Multinational Prospective Longitudinal Cohort Study," *Crit Care Med,* 2018.

[40] Stephan M. Jakob, MD; Esko Ruokonen; R. Michael Grounds et al, " Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation.," *JAMA,* 2012.

[41] Flori HR, Church G, Liu KD, et al., “Positive fluid balance is associated with higher mortality and prolonged mechanical ventilation in pediatric patients with acute lung injury,” *Crit Care Res Pract,* 2011.

[42] W. HP, “A perspective on the fluids and catheters treatment trial (FACTT). Fluid restriction is superior in acute lung injury and ARDS,” *Cleve Clin J Med,* 2008.

[43] Valentine SL, Sapru A, Higgerson RA, Spinella PC, Flori HR, Graham DA, Brett M, Convery M, Christie LM, Karamessinis L, Randolph AG;, “Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network; Acute Respiratory Distress Syndrome Clinical Research Network (ARDSNet). Fluid balance in critically ill children with acute lung injury.,” *Crit Care Med.,* 2012.

[44] Gerstmann DR, Fouke JM, Winter DC, Taylor AF, deLemos RA., “Proximal, tracheal, and alveolar pressures during high-frequency oscillatory ventilation in a normal rabbit model.,” *Pediatr Res.,* 1990.

[45] Sklar MC, Patel BK, Beitler JR, Piraino T, Goligher EC. , “Optimal Ventilator Strategies in Acute Respiratory Distress Syndrome.,” *Crit Care Med.,* 2019.

[46] Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO;, “OSCILLATE Trial Investigators; Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome.,” *N Engl J Med,* 2013.

[47] Arnold JH, Hanson JH, Toro-Figuero LO, Gutiérrez J, Berens RJ, Anglin DL., "Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure.," *Crit Care Med.,* 1994.

[48] Gupta P, Green JW, Tang X, Gall CM, Gossett JM, Rice TB, Kacmarek RM, Wetzel RC., “Comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure.,” *JAMA Pediatr. ,* 2014.

[49] El-Nawawy A, Moustafa A, Heshmat H, Abouahmed A., “High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: A randomized controlled study.,” *Turk J Pediatr,* 2017.

[50] H. DR., "Recruitment Maneuvers and PEEP Titration.," *Respir Care.,* 2015.

[51] Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L., "Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver.," *Am J Respir Crit Care Med.,* 2001.

[52] Derosa S, Borges JB, Segelsjö M, Tannoia A, Pellegrini M, Larsson A, Perchiazzi G, Hedenstierna G., "Reabsorption atelectasis in a porcine model of ARDS: regional and temporal effects of airway closure, oxygen, and distending pressure.," *J Appl Physiol,* 1985.

[53] M. S. Lapinsky SE, "Bench-to-bedside review: Recruitment and recruiting maneuvers.," *Crit Care.,* 2005.

[54] Boriosi JP, Sapru A, Hanson JH, et al. , "Efficacy and safety of lung recruitment in pediatric patients with acute lung injury.," *Pediatr Crit Care Med.,* 2011.

[55] Guérin, C., Reignier, J., Richard, J.-C., Beuret, P., Gacouin, A., Boulain, T., … Ayzac, L., " Prone Positioning in Severe Acute Respiratory Distress Syndrome.," *New England Journal of Medicine,* 2013.

[56] Numa AH, Hammer J, Newth CJ., "Effect of Prone and Supine Positions on Functional Residual Capacity, Oxygenation, and Respiratory Mechanics in Ventilated Infants and Children.," *American Journal of Respiratory and Critical Care Medicine,* 1997.

[57] Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D., " Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure.," *Anesthesiology,* 1991.

[58] Curley, M. A., Hibberd, P. L., Fineman, L. D., Wypij, D., Shih, M. C., Thompson, J. E., Grant, M. J., Barr, F. E., Cvijanovich, N. Z., Sorce, L., Luckett, P. M., Matthay, M. A., & Arnold, J. H., "Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial.," *JAMA,* Vols. 294,2 (2005): 229-37, 2005.

[59] "The PRone and OScillation Pediatric Clinical Trial (PROSpect). .," 2018.

[60] Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. , "The pragmatics of prone positioning.," *Am J Respir Crit Care Med.,* 2002.

[61] Vallance P, Hingorani A. , "Endothelial nitric oxide in humans in health and disease.," *Int J Exp Pathol.,* 1999.

[62] Hunt JL, Bronicki RA and Anas N, "Role of Inhaled Nitric Oxide in the Management of Severe Acute Respiratory Distress Syndrome.," *Front. Pediatr,* 2016.

[63] O. S. a. H. Administration. [Online]. Available: https://www.osha.gov/chemicaldata/20.

[64] Tang SF, Sherwood MC, Miller OI., "Randomised trial of three doses of inhaled nitric oxide in acute respiratory distress syndromeRandomised trial of three doses of inhaled nitric oxide in acute respiratory distress syndrome," *Arch Dis Child.,* 1998 .

[65] Uptodate, NO clinical guidance., James R Klinger, MD, 2021.

[66] Dowell, J. C., Thomas, N. J., & Yehya, N. , "Association of Response to Inhaled Nitric Oxide and Duration of Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome," *Pediatric Critical Care Medicine,* 2017.

[67] Bronicki, R. A., Fortenberry, J., Schreiber, M., Checchia, P. A., & Anas, N. G., "Multicenter Randomized Controlled Trial of Inhaled Nitric Oxide for Pediatric Acute Respiratory Distress Syndrome.," *The Journal of Pediatrics,* 2015.

[68] Corbet A, Bucciarelli R, Goldman S, Mammel M, Wold D, Long W., "Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multicenter controlled trial.," *J Pediatr,* Vols. 118(2):277-84, 1991.

[69] Willson DF, Jiao JH, Bauman LA, Zaritsky A, Craft H, Dockery K, Conrad D, Dalton H., "Calf's lung surfactant extract in acute hypoxemic respiratory failure in children," *Crit Care Med,* 1996.

[70] C. G. V. R. G. E. M. G. Luchetti M, "Porcine-derived surfactant treatment of severe bronchiolitis.," *Acta Anaesthesiol Scand.,* 1998.

[71] Willson DF, Zaritsky A, Bauman LA, Dockery K, James RL, Conrad D, Craft H, Novotny WE, Egan EA, Dalton H., "Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure.," *Crit Care Med.,* 1999.

[72] Luchetti M, Ferrero F, Gallini C, Natale A, Pigna A, Tortorolo L, Marraro G., "Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure.," *Pediatr Crit Care Med.,* 2002.

[73] Möller JC, Schaible T, Roll C, Schiffmann JH, Bindl L, Schrod L, Reiss I, Kohl M, Demirakca S, Hentschel R, Paul T, Vierzig A, Groneck P, von Seefeld H, Schumacher H, Gortner L, "Surfactant ARDS Study Group. Treatment with bovine surfactant in severe acute respiratory distress syndrome in children: a randomized multicenter study," *Intensive Care Med.,* 2003.

[74] Thomas NJ, Spear D, Wasserman E, Pon S, Markovitz B, Singh AR, Li S, Gertz SJ, Rowan CM, Kunselman A, Tamburro RF, "CALIPSO: A Randomized Controlled Trial of Calfactant for Acute Lung Injury in Pediatric Stem Cell and Oncology Patients. Biol Blood Marrow Transplant.," *Biol Blood Marrow Transplant,* 2018.

[75] P. M. G. T. e. a. Ferrara G, "Clinical Use and Molecular Action of Corticosteroids in the Pediatric Age," *Int J Mol Sci,* vol. 20(2):444., 2019.

[76] Meduri, G. U., Siemieniuk, R. A. C., Ness, R. A., & Seyler, S. J., " Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS.," *Journal of Intensive Care,* 2018.

[77] Annane, D., Pastores, S. M., Rochwerg, B., Arlt, W., Balk, R. A., Beishuizen, A., Van den Berghe, G., "Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I)," *Critical Care Medicine,* Vols. 45(12), 2078–2088, 2017.

[78] Drago BB, Kimura D, Rovnaghi CR, Schwingshackl A, Rayburn M, Meduri GU, Anand KJ., "Double-blind, placebo-controlled pilot randomized trial of methylprednisolone infusion in pediatric acute respiratory distress syndrome.," *Pediatr Crit Care Med.,* Vols. Mar;16(3):e74-81., 2015.

[79] Lundstrøm LH, Duez CHV, Nørskov AK, Rosenstock CV, Thomsen JL, Møller AM, Strande S, Wetterslev J., "Effects of avoidance or use of neuromuscular blocking agents on outcomes in tracheal intubation: a Cochrane systematic review.," *Br J Anaesth,* 2018.

[80] D. J. B. L. Robertson EN, "Pharmacokinetics and pharmacodynamics of rocuronium in patients with and without renal failure," *Eur J Anaesthesiol.,* 2005.

[81] Renew, J.R., Ratzlaff, R., Hernandez-Torres, V. et al., "Neuromuscular blockade management in the critically Ill patient.," *j intensive care,* 2020.

[82] Wilsterman MEF, de Jager P, Blokpoel R, et al., "Short-term effects of neuromuscular blockade on global and regional lung mechanics, oxygenation and ventilation in pediatric acute hypoxemic respiratory failure.," *Ann Intensive Care,* 2016.

[83] Ratnani I, Tuazon D, Zainab A, Uddin F., "The Role and Impact of Extracorporeal Membrane Oxygenation in Critical Care," *Methodist Debakey Cardiovasc J.,* 2018.

[84] Rollins MD, Hubbard A, Zabrocki L, Barnhart DC, Bratton SL., "Extracorporeal membrane oxygenation cannulation trends for pediatric respiratory failure and central nervous system injury.," *J Pediatr Surg.,* 2012.

[85] B. D., "Bicaval dual-lumen cannula for venovenous extracorporeal membrane oxygenation: Avalon© cannula in childhood disease.," *Perfusion.,* 2015.

[86] Barrett CS, Bratton SL, Salvin JW, Laussen PC, Rycus PT, Thiagarajan RR., "Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation.," *Pediatr Crit Care Med,* Vols. Jul;10(4):445-51, 2009.

[87] Barbaro RP, Paden ML, Guner YS, Raman L, Ryerson LM, Alexander P, Nasr VG, Bembea MM, Rycus PT, Thiagarajan RR; ELSO member centers., "Pediatric Extracorporeal Life Support Organization Registry International Report 2016," *ASAIO J.,* Vols. Jul/Aug;63(4):456-463, 2017.

[88] Judith Ju-Ming Wong, Tsee Foong Loh, Daniela Testoni, Joo Guan Yeo, Yee Hui Mok, and Jan Hau Lee, "Epidemiology of Pediatric Acute Respiratory Distress Syndrome in Singapore: Risk Factors and Predictive Respiratory Indices for Mortality," *Front Pediatr.,* 2014.

[89] Schouten LR, et al., "Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis.," *Crit. Care Med,* 2016.

[90] Nye S, Whitley RJ, Kong M. , "Viral infection in the development and progression of pediatric acute respiratory distress syndrome," *Front. Pediatr.,* 2016.

[91] Yehya N, Keim G, Thomas NJ. , "Subtypes of pediatric acute respiratory distress syndrome have different predictors of mortality.," *Intensive Care Med,* 2018.

[92] Kneyber, M. C. J., Zhang, H., & Slutsky, A. S. , "Ventilator-induced Lung Injury: Similarity and Differences Between Children and Adults," *American Journal of Respiratory and Critical Care Medicine,* 2014.

Royaume du Maroc المملكة المغربية

Université Sidi Mohamed Ben Abdellah

كلية الطب والصيدلة
FACULTÉ DE MÉDECINE ET DE PHARMACIE

سنـــة 2021

أطروحة رقم 21/297

متلازمة الضائقة التنفسية الحادة عند الأطفال

(بصدد 23 حالة)

الأطروحة

قدمت و نوقشت علانية يوم 2021/11/15

من طرف

السيد بيان زندح

المزدادة في 1992/10/03 فلسطين

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية

متلازمة الضائقة التنفسية الحادة عند الأطفال - تعريف PALICC - التنفس الاصطناعي - الفتك

اللجنة

السيد مصطفى هرندو ..... أستاذ في التخدير و الإنعاش	الرئيس والمشرف
السيد بوكطة ابراهيم ..... أستاذ في التخدير و الإنعاش	الأعضاء
السيد محمد عدنان بردعي ..... أستاذ مبرز في التخدير و الإنعاش	
السيدة وداد قجمان ..... أستاذة مبرزة في جراحة الأطفال	
السيد سعيد بن المقدم ..... أستاذ مساعد في التخدير و الإنعاش	عضو مشارك