Acute Respiratory Distress Syndrome (ARDS)

Time to reconsider the definition

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Contents

History 5

The original ARDS definition by the AECC 6

The ARDS Berlin Definition Criteria 7

ARDS definition criteria updates 8

Diagnostic attempts 10

Chest X-ray 12

CT scan 13

Blood gas analysis 14

Pulmonary artery catheter 15

Thermodilution technologies (extravascular lung water) 16

Lung ultrasound 17

Limitations and weaknesses of the Berlin Definition Criteria 18

The measurement of Extravascular Lung Water Index (ELWI) and Pulmonary Vascular Permeability Index (PVPI) 20

Measurement method 20

Validation 22

Clinical significance 23

The potential role of Extravascular Lung Water Index (ELWI) and Pulmonary Vascular Permeability Index (PVPI) to improve the ARDS definition 24

Summary 27

Figures 28

References 29

Acute respiratory distress syndrome (ARDS) is a syndrome that affects the respiratory system, especially lung function. It is characterized by fast progression and is associated with high mortality rates when not treated immediately. ARDS was first described in 1967. In the following decades, several attempts were made to define and diagnose the condition, based on the diagnostic tools available at that time. [1,2]

Nearly 50 years later, additional clinically established tools are available for monitoring and diagnosis. These have potential to significantly improve the definition criteria, enabling early diagnosis and differentiation of levels of ARDS severity.

Figure 1. Helicopter rescues casualties, Vietnam 1968
https://fine.17qq.com/articles/ckococgdv.html

History

In association with modern warfare, during the Korean and Vietnam Wars, wounded soldiers were rescued from the battlefields by helicopter transport.[2,3] This enabled transfer of the patients to an intensive care surrounding in less than one hour after the traumatic injury. Surprisingly for the treating physicians, these patients often rapidly developed respiratory failure and did not respond to initial oxygen therapy, although most of the patients lacked obvious chest wounds.

The first large scale occurrence of this syndrome was during the Vietnam War. Related to a battle close to the city of Da Nang it was called 'Da Nang lung' or 'Nam lung'.[2] In other early reports it was also called acute progressive lung failure, shock lung, traumatic lung edema or post transfusion lung. Acute respiratory distress syndrome was formally named by Ashbaugh, et al.[1] in 1967 for the first time. It was described as an acute onset of tachypnea, hypoxemia and loss of compliance following a variety of stimuli. Massive bilateral alveolar infiltrates on the chest X-ray were also found as a result of capillary leak into the lung tissue and subsequent development of pulmonary edema.

During the 1970s several attempts were made to characterize ARDS by chest X-ray images, CT scanning and blood gas analysis to measure the level of oxygen and carbon dioxide in the blood. Sources of the syndrome and the associated capillary leakage are manifold, and several underlying diseases have been found, including an inflammatory reaction e.g., after massive blood transfusion, severe burn injury, pancreatitis, trauma, sepsis, and damage due to elective surgery.[2]

The reported annual incidence of ARDS is quite high with 150,000 reported cases in 1989 in the USA,[4] and 130 cases per 200,000 population in 1988 in the United Kingdom.[5] The syndrome is associated with high mortality rates and high treatment costs.

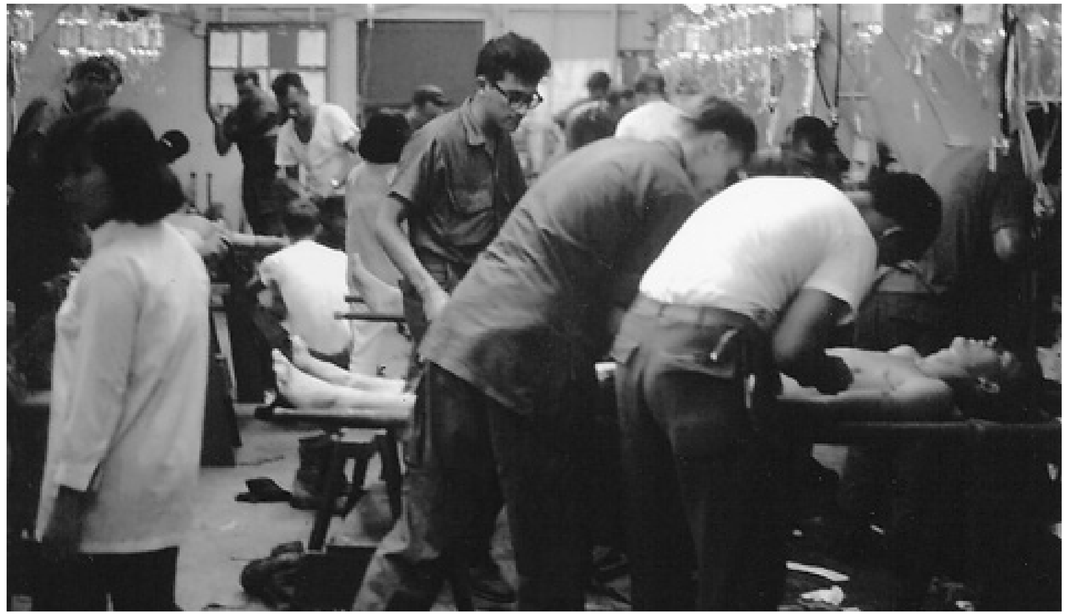


Figure 2. Casualties arrive at the Naval Support Activity Station Hospital in Da Nang, Vietnam in 1968

The original ARDS definition by the AECC

In 1992, almost 30 years after the first article on ARDS, an American-European Consensus Conference (AECC) on ARDS took place with a consensus report published in 1994.[6] In this publication, ARDS was defined as a syndrome of inflammation and increased permeability associated with clinical, radiological, and physiological abnormalities that cannot be completely explained by left atrial or pulmonary capillary hypertension. In addition, a differentiation between acute lung injury (ALI) and ARDS was introduced, dependent on the measured oxygenation values. Finally, the following definition criteria were recommended:

- Acute onset
- PaO_2 (arterial oxygen partial pressure) / FiO_2 (oxygen fraction in the ventilation gas) ratio ≤ 200 mmHg (a value of 200 to 300 was classified as ALI)
- Bilateral infiltrates on frontal chest radiograph (X-ray)
- Pulmonary artery occlusion pressure (PAOP) < 18 mmHg or no clinical evidence of left atrial hypertension

These definition criteria were frequently discussed concerning reliability and validity. Major limitations of the AECC criteria were related to:

- No definition of acute onset[7]
- Inconsistency of the oxygenation parameter not considering ventilator settings[8-10]
- Poor inter-observer reliability of chest X-ray interpretation[11, 12]
- Difficulties in interpreting PAOP and clinical assessment of left atrial hypertension[13-15]

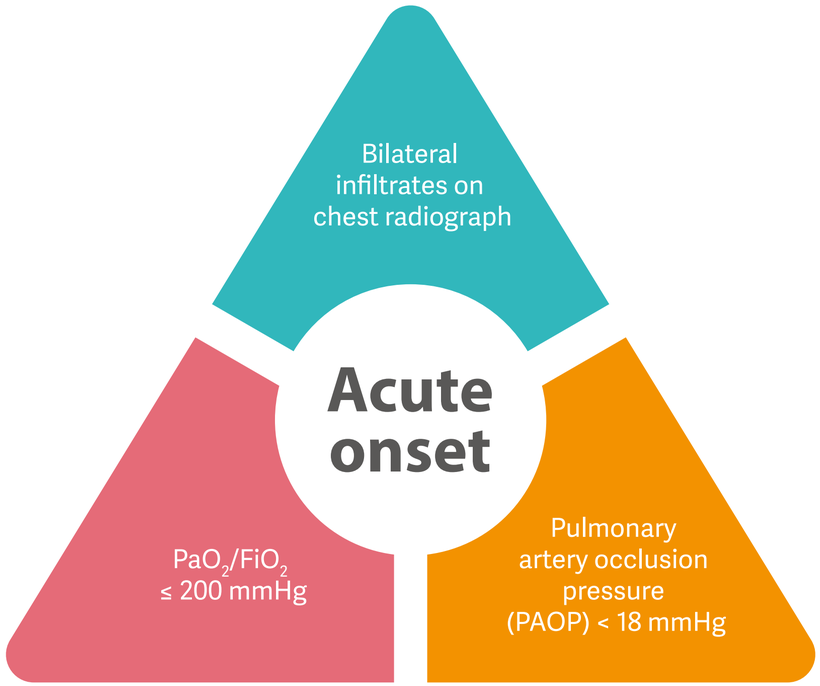


Figure 3. AECC ARDS definition criteria overview

The ARDS Berlin Definition Criteria

It took another nearly 20 years until an update of the ARDS definition criteria was published in 2012.[16] As an initiative of the European Society of Intensive Care Medicine and in cooperation with the American Thoracic Society and the Society of Critical Care Medicine, an expert panel developed the so-called Berlin Definition Criteria. The main changes were related to the introduction of three ARDS subgroups (mild, moderate, severe), based on oxygenation. Young et al.[17] compared in 2018 the AECC definition criteria from 1994 and the Berlin Definition Criteria from 2012, demonstrating only minor differences.

	AECC Definition from 1994	Berlin Definition Criteria from 2012
Timing	Acute onset	Within 1 week of a known clinical insult or new /worsening respiratory symptoms
Chest imaging	Bilateral infiltrates seen on frontal chest radiograph	Chest X-ray or CT scan: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Pulmonary artery wedge pressure ≤18 mmHg when measured, or no clinical evidence of left atrial hypertension	Respiratory failure not fully explained by cardiac failure or fluid overload; objective assessment (e.g.,, echocardiography) required to exclude hydrostatic edema if no risk factor presents
Oxygenation	Acute lung injury criteria: PaO_2/FiO_2 ≤ 300 mmHg (regardless of PEEP level)	Mild ARDS: 200 < PaO_2 / FiO_2 ≤ 300 with PEEP or CPAP ≥ 5cm H_2O
	ARDS criteria: PaO_2/FiO_2 ≤ 200 mmHg (regardless of PEEP level)	Moderate ARDS: 100 < PaO_2 / FiO_2 ≤ 200 with PEEP ≥ 5cm H_2O
		Severe ARDS: PaO_2 / FiO_2 ≤ 100 with PEEP ≥ 5cm H_2O

PEEP: positive end-expiratory pressure, CPAP: continuous positive airway pressure.

Figure 4. Comparison table of the AECC and Berlin definition criteria of ARDS (Yang et al. 2018)

ARDS definition criteria updates

As the ARDS Berlin definition criteria did not add value or improvements, the discussions kept going on.

Due to resource constraints of medical diagnostic equipment in low-income countries the applicability of the Berlin Definition criteria have been evaluated in this specific setting, resulting in the so-called Kigali Modification of the Berlin Definition[18]. In this investigation, using traditional Berlin criteria, no patients would have met criteria for ARDS. In contrast by using the Kigali Modification criteria forty-two (4.0%) of 1,046 hospital admissions met criteria for ARDS.

	Berlin Criteria	Challenges in Resource Poor Settings	Kigali Modification of the Berlin Criteria
Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms	None	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	PaO_2, /FiO_2, ≤300	Scarcity of arterial blood gas diagnostics	SpO_2, /FiO_2, ≤315
PEEP requirement	Minimum 5 cm H_20 PEEP required by invasive mechanical ventilation (non-invasive acceptable for mild ARDS)	Scarcity of mechanical ventilators	No PEEP requirement, consistent with AECC definition
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT	Scarcity of chest radiography resources	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic edema if no risk factor present)	None	Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment, such as echocardiography, to exclude hydrostatic edema if no risk factor present)

Definition of abbreviations: AECC = American-European Consensus Conference; ARDS = acute respiratory distress syndrome; CT = computed tomography; PEEP = positive end-expiratory pressure; SpO_2, = oxygen saturation as measured by pulse oximetry.

Figure 5. Berlin Criteria for ARDS, Challenges in Resource-Poor Settings, and Kigali Modification of the Berlin Criteria to Address These Challenges (Riviello et al. 2016)

In succession of the Corona pandemic with high numbers of COVID-19 patients with severe pulmonary disorders, another attempt was made to improve the ARDS definition criteria[19]. In this perspective discussion it is demanded to target for a formal definition of ARDS, structured around measures of reliability, feasibility, and validity instead of a consensus of experts. The major challenge for a formal definition however is the lack of gold standard diagnostic tests.

The 2023 guidelines on acute respiratory distress syndrome by the European Society of Intensive Care Medicine (ESICM) contains are pro con discussion of the ARDS definition criteria, but did not provide any new insights or recommendations[20].

The most recent publication on the ARDs definition criteria was again based on a Consensus Conference of 32 critical care ARDS experts and subsequently obtained input from members of several critical care societies[21], resulting in the following recommendations:

1. Include HFNO (high flow nasal oxygen) with a minimum flow rate of ≥ 30 liters/min
2. Use arterial oxygen tension (PaO_2)/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 < 315 (if SpO_2 ≤ 97%) to identify hypoxemia
3. Retain bilateral opacities for imaging criteria but add ultrasound as an imaging modality, especially in resource-limited areas
4. In resource-limited settings, do not require PEEP, oxygen flow rate, or specific respiratory support devices

All these attempts finally were not able to provide any clearly defined recommendations based on reliable, feasible and valid measures and resulted in even more complex ARDS definition criteria.

Berlin Definition	Rationale for Updating Criteria	How Addressed in Global Definition
Acute onset within one week of known insult or new or worsening respiratory symptoms	Onset may be more indolent for some insults, such as COVID-19	The inclusion of patients with HFNO will capture patients with a more indolent course, and therefore the timing criteria has not been changed
Bilateral opacities on chest radiograph or computed tomography—not fully explained by effusions, lobar/lung collapse, or nodules	Chest radiography and computed tomography not available in some clinical settings	Ultrasound can be used to identify bilateral loss of lung aeration (multiple B-lines and/or sonsolidations) as long as operator is well-trained in the use of ultrasound
Three severity categories defined by PaO_2/FiO_2 Requirement for invasive or noninvasive mechanical ventilation such that PEEP ≥ 5 cm H_2O required for all categories of oxygenation severity except mild which can also be met with CPAP ≥ 5 cm H_2O	Pulse oximetric measurement of SpO_2/FiO_2, is widely used and validated as a surrogate for PaO_2/FiO_2 HFNO increasingly being used in patients with severe hypoxemia who otherwise meet ARDS criteria Invasive and non-invasive mechanical ventilation not available in resource-variable settings	SpO_2/FiO_2 can be used for diagnosis and assessment of severity if SpO_2 is ≤97%. New category of non-intubated ARDS created for patients on HFNO at ≥30 L/min who otherwise meet ARDS criteria Modified definition of ARDS for resource-variable settings does not require PaO_2/FiO_2, PEEP, or HFNO

Abbreviations: ARDS: Acute respiratory distress syndrome; CPAP: Continuous positive airway pressure; FiO_2: Fraction of inhaled oxygen HFNO: High flow nasal oxygen; NIV: Non-invasive ventilation; PaO_2: Arterial oxygen tension; PEEP: Positive end-expiratory pressure; SpO_2: Pulse oximetric oxygen saturation

Figure 6. Summary of key differences between the new global definition of ARDS and the Berlin definition along with the rationale for updating specific diagnostic criteria

Diagnostic attempts

Several diagnostic tools have become available over recent decades which can potentially support and improve the ARDS definition and classification concerning severity level.

- Chest X-ray
- CT scan
- Blood gas analysis
- Pulmonary artery catheter
- Thermodilution technologies (extravascular lung water)
- Lung ultrasound

Figure 7. Interpretation of a chest X-ray image

Chest X-ray

Interpretation of the chest X-ray concerning pulmonary edema is complex. It has been reported that marked inter-observer errors are frequent.[2,11,12] Even an educational intervention to improve the radiographic identification of ARDS did not improve the ability of correct interpretation of chest X-ray images[22]. The reasons for this limitation are obvious. First of all, the chest X-ray is performed in a special situation. Patients with suspected or already present ARDS are usually treated in an intensive care unit, lying in a bed and often receiving mechanical ventilation. The X-ray equipment needs to come to the patient, and the images have to be taken under observation of the ventilation cycle, with patients positioned accordingly. This can already influence the quality of the image significantly.

Radiography itself is a density measurement. A radiation source emits X-rays that are transmitted through the body. Opposite from the radiation source, a radiographic film collects the transmitted X-rays. Higher densities allow less X-rays to pass through them, resulting in white or bright areas, whereas low density allows more X-ray to pass through, resulting in black or dark areas with several shades of grey in between. Finally, the obtained black & white image requires correct interpretation by experienced radiographers.

The obtained image is influenced by all compartments in the chest including bones, muscles, lung tissue (which is affected by conditions such as atelectasis, fibrosis etc.), skin layers (fat, tissue edema), the heart, blood and blood vessels, gas volume and its distribution, pleural effusion, and also the water in the lung tissue. Thus, extravascular water or pulmonary edema is only one part amongst several others that influences the received image[23].

Furthermore, the medical staff are exposed to a certain amount of radiation during every single chest X-ray procedure.

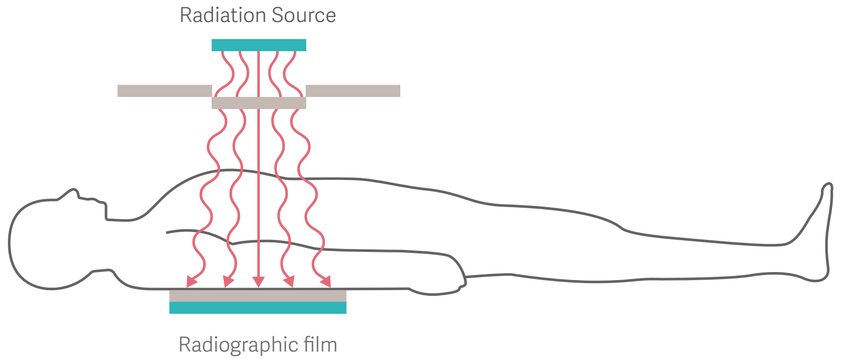
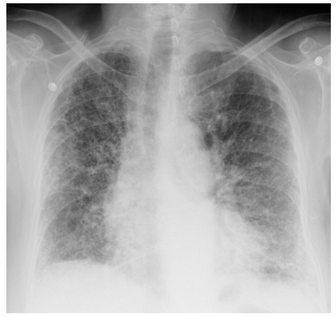


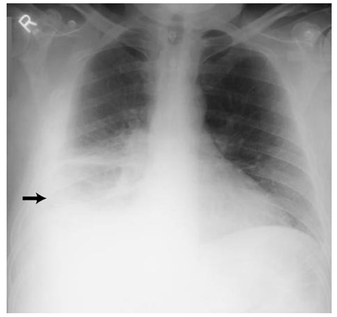
Figure 8. Radiography – Working principle

Figure 9. Examples of chest X-ray images



Pulmonary fibrosis

radiopaedia.org/cases/pulmonary-fibrosis-9



Pleural effusion

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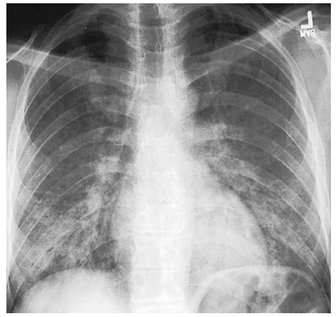

Pneumocystis pneumonia

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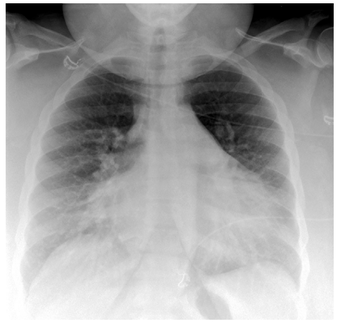

Pulmonary edema

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Figure 10. A critically ill patient during computed tomography (CT) scan

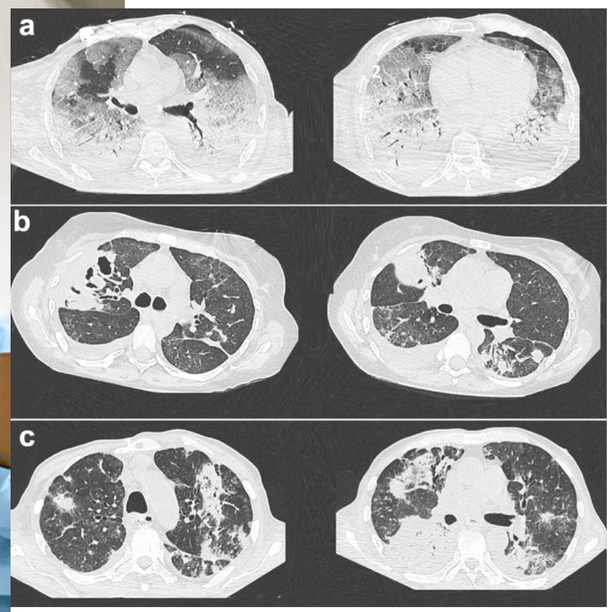

Figure 11. CT scan images in a patient with ARDS

researchgate.net/figure/Chest-CT-scan-images-in-patients-with-ARDS-and-one-or-more-respiratory-tract-culture_fig1_303948473

CT scan

A computerized tomography (CT) scan is also a radiographic investigation, enabling a more sophisticated and detailed image of the lungs. Due to cumbersome equipment, it requires patient transport to the radiology department. Transport of a critically ill and ventilated patient is risky and extremely labor intensive, requiring several accompanying persons, at least one nurse and one physician. Thus, the logistic effort is quite high, meaning that CT scans are only done periodically, and thus usually only a snap shot of information is acquired and repeated measurements in short-term periods are not possible. Furthermore, during a CT scan the patient is exposed to high levels of radiation.[2]

Of note, patients with infectious diseases of the lungs (e.g., COVID-19), where development of pulmonary edema can be expected, should stay in quarantine. Transport throughout the hospital to the Radiology Department for a CT scan should be strictly avoided.

Blood gas analysis

Analysis of blood gases from arterial and venous blood samples is normally easy to perform. Almost all intensive care units have a blood gas analyzer available to measure several parameters such as oxygen saturation, and oxygen and carbon dioxide partial pressures, and measurements can be repeated frequently. The amount of withdrawn blood for the blood samples is limited and acceptable when not performed too frequently.

In ARDS patients the oxygenation is evaluated by the ratio of the oxygen partial pressure (PaO_2) over the fraction of inspiratory oxygen (FiO_2), the so-called Horowitz index, which is used to categorize ARDS severity. The PaO_2/FiO_2 ratio has also limitations, as it is influenced by many ventilator support parameters including FiO_2, positive end expiratory pressure (PEEP), tidal volume, inspiratory pressure, respiratory rate, recruitment maneuvers, patient positioning and extracorporeal lung support.[24,25]

The latest guidelines on acute respiratory distress syndrome by the European Society of Intensive Care Medicine (ESICM) are discussing the use of the ratio of pulse oximetry (SpO_2) over the fraction of inspiratory oxygen (FiO_2). The reason for this consideration is the limited availability of blood gas analyzers in resource poor settings and the broader availability of SpO2. However, in the guidelines it is also mentioned, that there are inaccuracies in the SpO_2 measurements, particularly among patients with darker skin and those in shock and/or with poor distal perfusion.[20]

Figure 12. Image close up of a nurse drawing blood

Pulmonary artery catheter

Another cause of pulmonary edema could be left heart failure, resulting in accumulation of blood in the pulmonary vessels, causing an increase in the hydrostatic pressure in the lungs and finally leading to extravasation of water into the interstitial, intercellular and intra-alveolar spaces.

To exclude pulmonary edema due to left heart insufficiency or failure, or due to general fluid overload, the pulmonary artery occlusion pressure (PAOP) is measured. The measurement requires the placement of a pulmonary artery catheter that is inserted into the central vein and forwarded through the right atrium and right ventricle until the distal tip of the catheter is located in the pulmonary artery. For this procedure a balloon on the tip of the catheter is inflated by 1.5 ml of air causing the distal migration of the catheter. The inflation of the balloon is repeated for each intermittent measurement of the PAOP. The procedure of pulmonary artery catheterization is associated with several severe risks like cardiac valve damage, pulmonary artery rupture, catheter knotting, thrombosis or pulmonary embolism, and infections.[26]

Furthermore, in the interpretation of the PAOP several factors need to be considered that affect its reliability. These are technical factors such as zeroing, correct positioning of the pressure transducer to the heart level, dynamic response and filtering, as well as pulmonary factors including positioning in the correct lung zone, respiratory variations (positive pressure ventilation) and also intra-abdominal hypertension.[27]

Alternative technologies may also be used to exclude cardiac failure or fluid overload, e.g., echocardiography.[16]

Figure 13. Scheme of the insertion and positioning of a pulmonary artery catheter

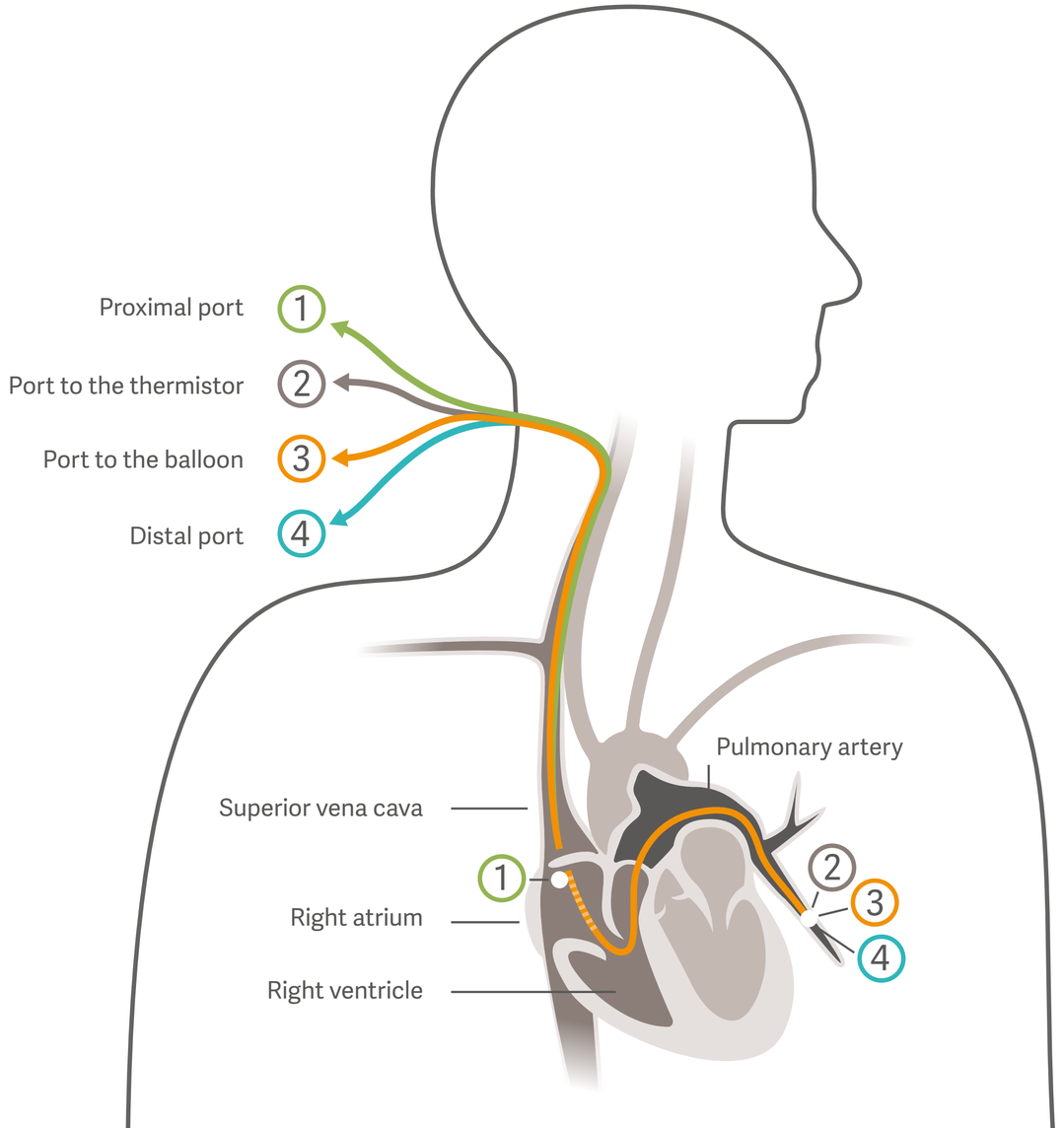

Figure 14. Performance of a PiCCO transpulmonary thermodiltion measurement

Thermodilution technologies (extravascular lung water)

The usefulness of indicator dilution technologies to determine intra- and extravascular fluid amounts, especially the extravascular lung water, to quantify pulmonary edema, was investigated in several experimental and clinical studies in the 1980s.[28,29] These investigations resulted in the establishment of the transpulmonary thermodilution technology with the PiCCO device in 1997.[30] The accuracy of this approach was proven in several experimental and clinical studies,[31-33] clearly showing that transpulmonary thermodilution enables highly accurate determination of the extravascular lung water amount as a direct quantification of pulmonary edema[34].

The measurement can be easily performed directly at the bedside, repeated even in short time intervals, is user independent and is not associated with any additional hazards or risks to the patient. The transpulmonary thermodilution measurement is an invasive approach, requiring the insertion of a central venous catheter for the injection of an indicator bolus (cold saline 0.9%) and a special arterial catheter, usually placed into the femoral artery, for the dilution curve detection due to the temperature change in the arterial blood after bolus injection.[35-38]

Lung ultrasound

A quite new approach to evaluate the situation in the lungs concerning development and presence of pulmonary edema is the use of ultrasound. It was observed that in patients with respiratory problems the ultrasound images of the lungs showed certain disturbances, the so-called B-lines.

The correct application and interpretation of the lung ultrasound to evaluate pulmonary edema requires an experienced user. It is challenging to differentiate between lung water and fibrosis of the lung tissue.[39] Moreover, tracking of changes of lung water by ultrasound seems to be impossible.[40]

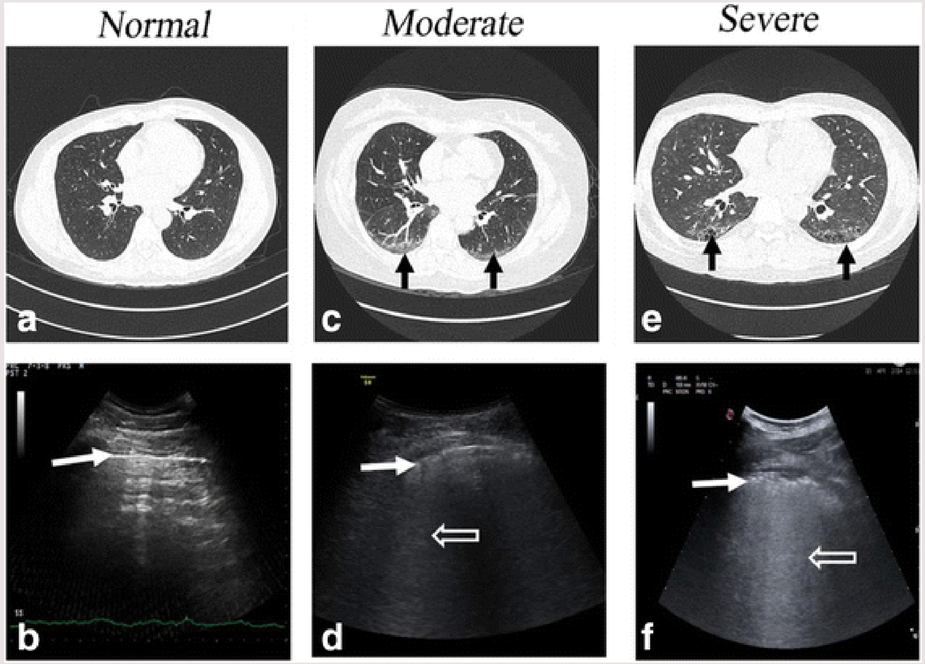

Figure 15. Comparison of ultrasound B-lines and high resolution computed tomography[39]

Limitations and weaknesses of the Berlin Definition Criteria

An expert committee of the European Society of Intensive Care Medicine revised the ARDS Berlin Definition Criteria shortly after its publication in 2012 and clearly stated the need for further improvement based on new information and experience in clinical practice and research.[41] Surprisingly, since then no updates have been published.

The ARDS Berlin Definition Criteria did not include measures of lung injury specific to ARDS including extravascular lung water index (ELWI) and the pulmonary vascular permeability index (PVPI).[42] In particular ELWI predicts progression to acute lung injury more than two days before the patients meet the ARDS definition criteria[43] and is thus more sensitive. Exactly these tools to predict development of ARDS and pulmonary vascular permeability have been demanded.[44] This lack of information leads to a missing or delayed diagnosis of ARDS in a majority of patients and to delayed treatment with potential implications on outcome.[45]

In studies where ELWI and PVPI were measured, a good correlation was found with the degree of ARDS severity according to the ARDS Berlin Definition Criteria classification. Nevertheless, it is recommended to include a subgroup of severity of patients with right ventricular dysfunction.[24]

Critical analysis of the ARDS Berlin Definition Criteria makes the following limitations in each of the single criteria categories evident:

Timing:

It is well known that overwhelming ARDS can develop very quickly, especially in COVID-19 patients: the progression from relatively normal pulmonary conditions to severe respiratory failure can occur within several hours.

"Onset within one week is very unspecific"

Chest imaging:

As already outlined, chest X-rays are complex to interpret regarding the level of pulmonary edema. The image is influenced by several compartments, and pulmonary edema is only one amongst others. Even experienced radiologists have been found to incorrectly interpret a chest X-ray for the level of pulmonary edema.[11,12] It becomes even more difficult when progression of pulmonary edema should be evaluated from a radiographic image of the chest.[46-48] Another weakness of the chest X-ray is its repeatability at the bedside. For logistic reasons it may be possible to only take images every few days, depending on circumstances.

Although the CT scan provides high-quality images, interpretation of the level of pulmonary edema remains difficult to quantify. It is normally not possible to accurately interpret the CT scan in the early phase of edema development.[49,50]

Chest X-rays or CT scan of the lungs neither quantify the severity of pulmonary edema precisely nor detect changes with acceptable sensitivity

Origin of edema:

Pulmonary edema can have two different causes:

- Cardiogenic pulmonary edema due to left heart failure and/or fluid overloading causing an increase in hydrostatic pressure in the pulmonary vascular system leading finally to the extravasation of water into the interstitial space and into the alveoli
- Permeability pulmonary edema due to an inflammatory process that damages the pulmonary vascular vessel walls and increases the vascular permeability, finally leading to the extravasation of water into the lung tissue

As the therapeutic approach is quite different for both causes, it is important to be able to exclude one cause or have the ability for differential diagnosis. Diagnostic attempts to exclude left heart failure can be, e.g., a pulmonary artery catheter with limited diagnostic significance in cases of positive pressure ventilation or intra-abdominal hypertension, or echocardiography requiring expertise in the use and interpretation of echocardiography images.[6]

Another challenge is the fact that both causes of pulmonary edema can be present at the same time which makes the differential diagnosis even more complex.

Differential diagnosis of pulmonary edema is complex, and confirmation of left heart failure does not completely exclude a pulmonary vascular permeability damage

Oxygenation:

The calculation of the ratio between the amount of oxygen bound to blood (oxygen partial pressure of the arterial blood, PaO_2) and the oxygen concentration applied to the lungs (inspiratory oxygen fraction, FiO_2) is used to evaluate oxygenation. However, the PaO_2/FiO_2 ratio depends strongly on the ventilatory settings and modes, patient positioning and extracorporeal lung support.[24] Thus threshold values for oxygenation have to include all of the aforementioned factors, and a strict definition of fixed values may not clearly represent the actual situation.

The recently discussed alternative use of the ratio of pulse oximetry (SpO_2) over the fraction of inspiratory oxygen (FiO_2) also bears limitations due to inaccuracies of SpO_2 in patients with darker skin and those in shock and/or with poor distal perfusion.

Evaluation of the oxygenation by the PaO_2/FiO_2 ratio requires consideration of various ventilation parameters and potential extracorporeal lung support

Summary

In summary, classification and severity grading of ARDS based on the ARDS Berlin Definition Criteria has strong limitations due to several reasons:

- Sensitivity and specificity are very low
- Early detection of the development of ARDS is not possible
- Changes in the situation cannot be obtained in a short time period at the bedside
- In most cases respiratory failure due to massive pulmonary edema can be confirmed and documented, but not detected early

This situation necessitates the integration of further parameters for the ARDS classification to enable direct quantification of pulmonary edema, evaluation of the severity of lung injury and a categorization of pulmonary vascular permeability.

The measurement of extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI)

Measurement method

The measurement of extravascular lung water by transpulmonary thermodilution has a history dating back to the 1980s,[51,52] and was clinically validated in the year 2000.[30] The technology has been in clinical use for more than 20 years and has been extensively described in several review articles.[35,36,53-55]

The measurement principle is based on the central venous injection of a defined amount of an indicator (15 to 20 ml of cold saline 0.9%). After passage through the cardiopulmonary system, the cold concentration (thermodilution) curve is registered via a thermistor-equipped catheter placed into a major artery, usually the femoral artery. The thermodilution curve is analyzed concerning the area under the curve to derive cardiac output and is additionally analyzed concerning transit times (mean transit time, downslope time) to calculate specific volumetric compartments in the chest. Finally, the extravascular lung water is calculated as a measure of the amount of pulmonary edema and indexed to the predicted body weight to derive the extravascular lung water index (ELWI).

The pulmonary vascular permeability index (PVPI) is simply calculated from the ratio between extravascular lung water and pulmonary blood volume, as the relation between the extravascular to the intravascular fluid content in the lungs. The higher the PVPI value (more than 3), the more likely pulmonary edema is caused by permeability damage in the pulmonary vessels. Low PVPI values are usually related to cardiogenic pulmonary edema due to left heart failure and/or fluid overloading.

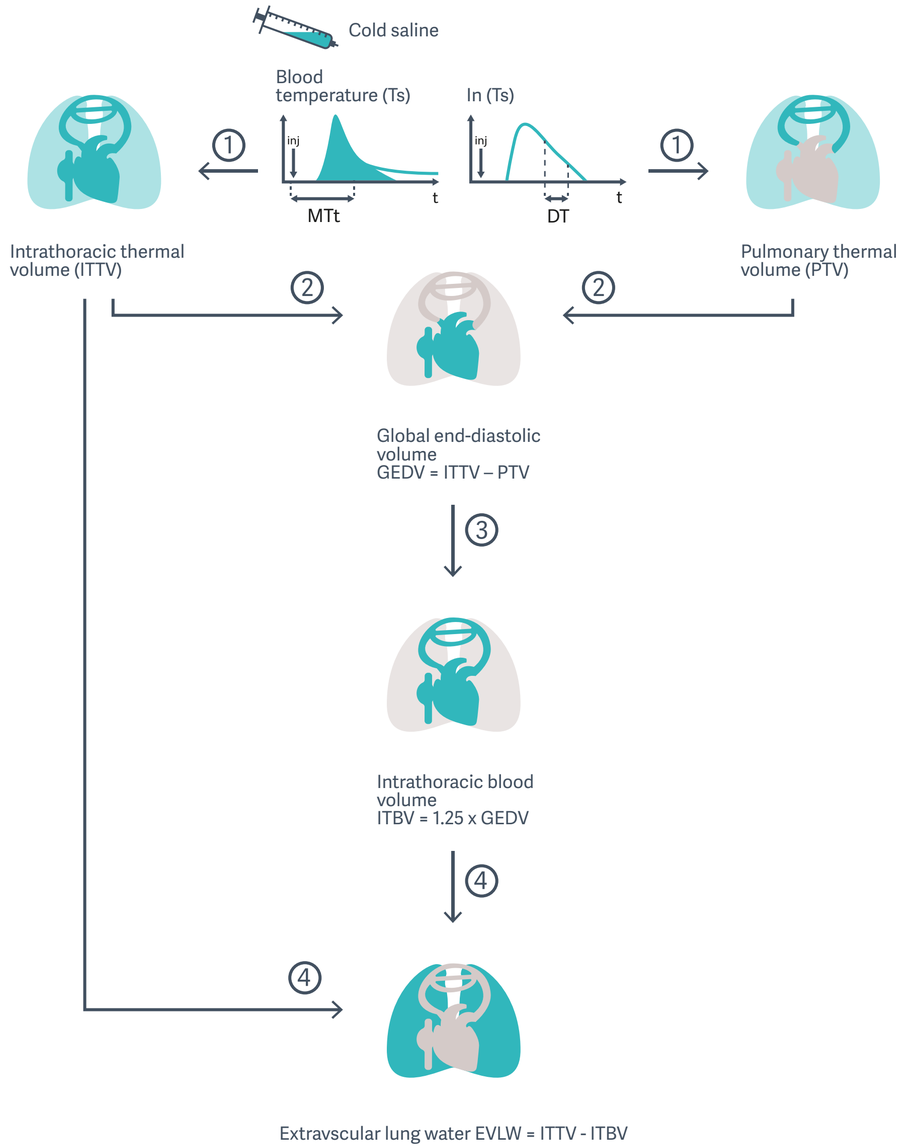

Figure 16. Basic principle of the calculation of extravascular lung water by transpulmonary thermodilution[36]

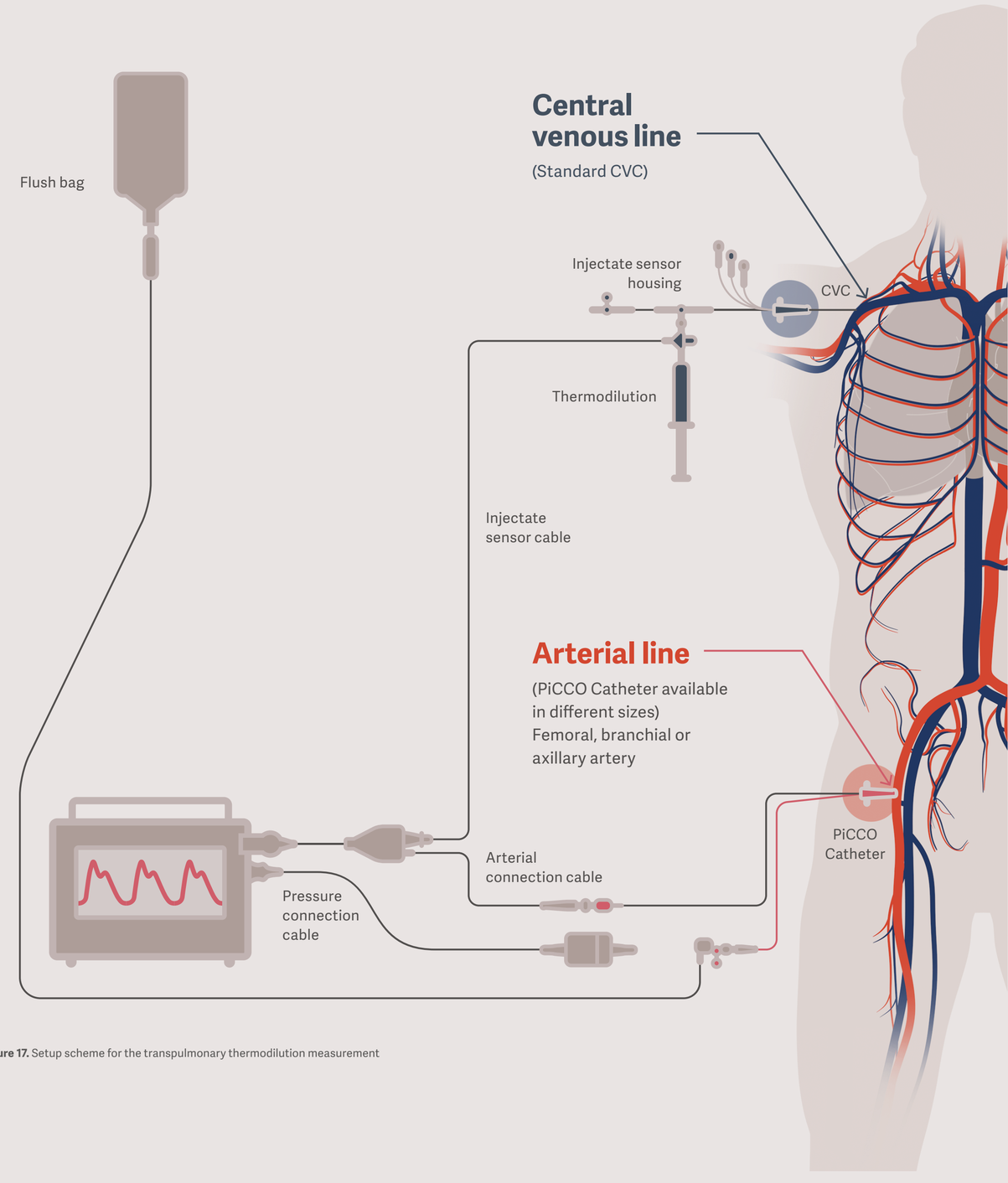

Figure 17. Setup scheme for the transpulmonary thermodilution measurement

Validation

Determination of extravascular lung water index (ELWI) by transpulmonary thermodilution has been validated in several studies, both experiemental[31,32] and human clinical,[33] clearly showing high accuracy compared to the gravimetric lung water measurement and wet weight of the lungs, respectively. It has been also confirmed that pleural effusion does not interfere with the measurement.[56]

This confirms that the measurement of extravascular lung water is reliable and enables a very precise evaluation of the severity of pulmonary edema. Furthermore, its ability to track changes sensitively was confirmed in an experimental study.[57]

Pulmonary vascular permeability index (PVPI) for differential diagnosis of pulmonary edema, especially in ARDS and septic patients, was clinically investigated and its usefulness was confirmed.[55,58-60]

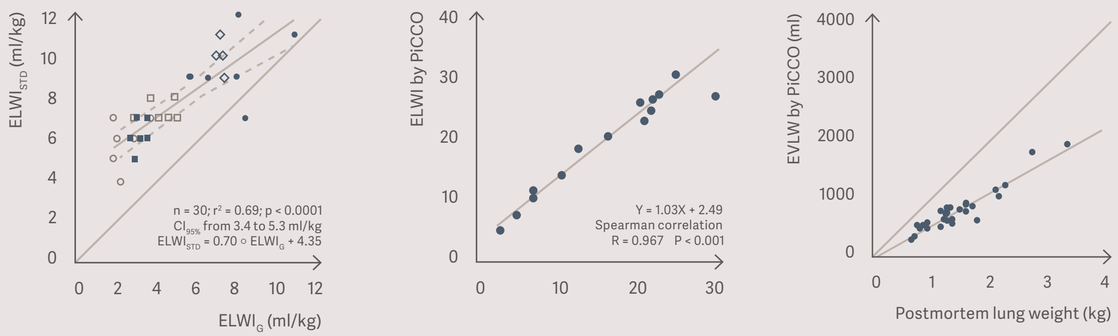

Figure 18. Results from experimental and clinical validation studies on the accuracy of transpulmonary thermodilution to measure extravascular lung water[31-33]

Clinical significance

The clinical significance of ELWI has been investigated concerning its diagnostic accuracy for the presence of lung injury, mortality, prognosis, and the ability to improve fluid management.

In particular, the gap in markers of lung injury in the ARDS Berlin Definition Criteria could be closed by considering ELWI. In an observational cohort study of 51 ICU patients in shock, association of ELWI with the degree of lung injury and mortality was found. Therefore it was concluded that ELWI is of added diagnostic value.[61]

Jozwiak et al. investigated 200 ARDS patients in a medical intensive care unit. It was found that ELWI and PVPI were independent risk factors of day 28 mortality.[62] These findings have been confirmed in numerous studies, e.g., Sakka et al., in 373 critically ill patients;[63] Tagami et al., in a multicenter prospective cohort study including 192 ARDS patients;[64] Wei et al., in 30 severe ARDS patients assisted by extracorporeal lung support (ECLS);[65] and Wang et al., in 121 severely burned adults with ARDS.[66] The related studies were summarized in a review article by Zhang et al.,[67] concluding that ELWI appears to be a good predictor of mortality in critically ill patients.

The usefulness of ELWI for fluid management in ARDS patients has been investigated by Hu et al..[68] In this study, 29 ARDS patients were randomly divided into two groups with fluid management based on ELWI and on pulmonary artery occlusion pressure (PAOP). It was concluded that ELWI restricted fluid management, improved oxygenation and reduced the duration of mechanical ventilation and ICU length-of-stay; thus ELWI has clinical value in terms of fluid management in patients with ARDS.

Similar results have been presented by Yuanbo et al who performed a randomized trial in 302 patients with severe thoracic trauma and ARDS. Patients from the PiCCO/ELWI group had significantly better oxygenation, fewer days of mechanical ventilation and shorter lengths of stay in the ICU.[69]

The potential role of extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI) to improve the ARDS definition

As early as 2012, when the ARDS Berlin Definition Critera were published, an expert group recommended in a consensus paper the use ELWI for the diagnosis of pulmonary edema and, in combination with cardiac filling volumes, to differentiate between hydrostatic/cardiogenic pulmonary edema and permeability edema.[70] One year later the implementation of ELWI and PVPI into the ARDS definition criteria was again strongly recommended in a review article.[71]

Clinical studies confirmed the usefulness of ELWI and PVPI to diagnose and characterize pulmonary edema in ARDS patients. Kushimoto et al. conducted a study in 266 ARDS patients in 23 clinical centers and confirmed that ELWI and PVPI were increased in patients with ARDS. A cut-off value for PVPI to diagnose ARDS was between 2.6 and 2.85 and a PVPI < 1.7 ruling out an ARDS diagnosis.[72]

An expert panel of the European Society of Intensive Care Medicine (ESICM) reviewed monitoring technologies in critically ill patients, and recommended that in ARDS transpulmonary thermodilution or pulmonary artery catheter should be used. It was stated that one major advantage of the transpulmonary thermodilution is the measurement of ELWI, which can be used as a safety parameter during fluid therapy, especially in capillary leak states, where it has been shown to have a prognostic value.[73]

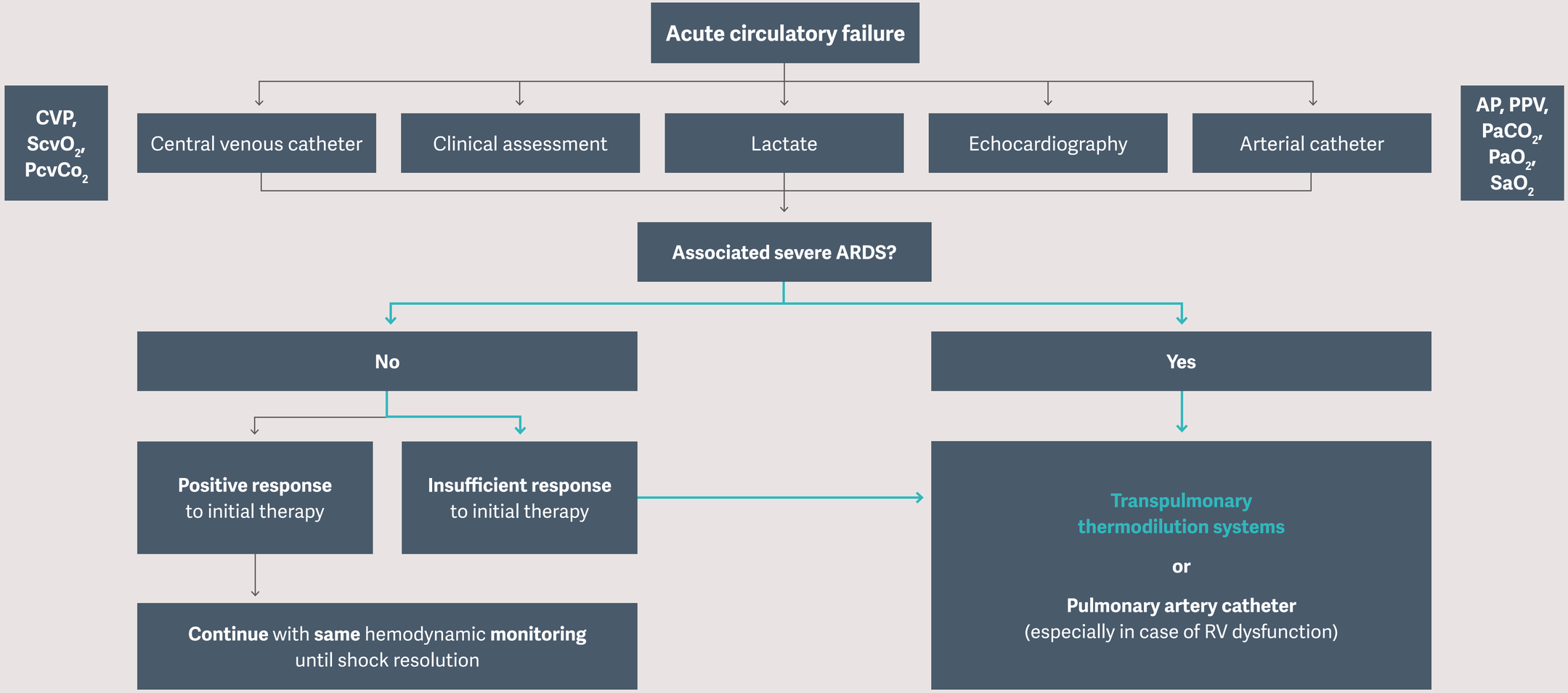

Figure 19. Scheme on hemodynamic monitoring tools and escalation recommended by the European Society of Intensive Care Medicine (ESICM) expert panel[73]

The clinical approach on how to interpret ELWI and PVPI for differential diagnosis of ARDS has been clearly outlined graphically in a review on the ELWI measurement by Tagami & Ong.[37] They also concluded that ELWI and PVPI have a great potential to be included in any future ARDS definition.

Especially during the Coronavirus pandemic, ELWI and PVPI have become more important, as severely ill COVID-19 patients usually show ARDS symptoms. The classification of severity is of utmost importance to decide on appropriate and goal-directed fluid therapy. The clinical relevance of ELWI in severe COVID-19 cases has been shown in recent publications. Rasch et al. found significantly higher ELWI and PVPI values in COVID-19 ARDS patients compared to non-COVID-19 ARDS patients, and that high ELWI values were associated with a prolonged stay in the intensive care unit and increased mortality.[74] This was confirmed by Shi et al. who also found a higher severity level in COVID-19 ARDS patients.[75] Boerma et al.[76] used ELWI and PVPI to evaluate permeability-related lung edema in severe COVID-19 cases.

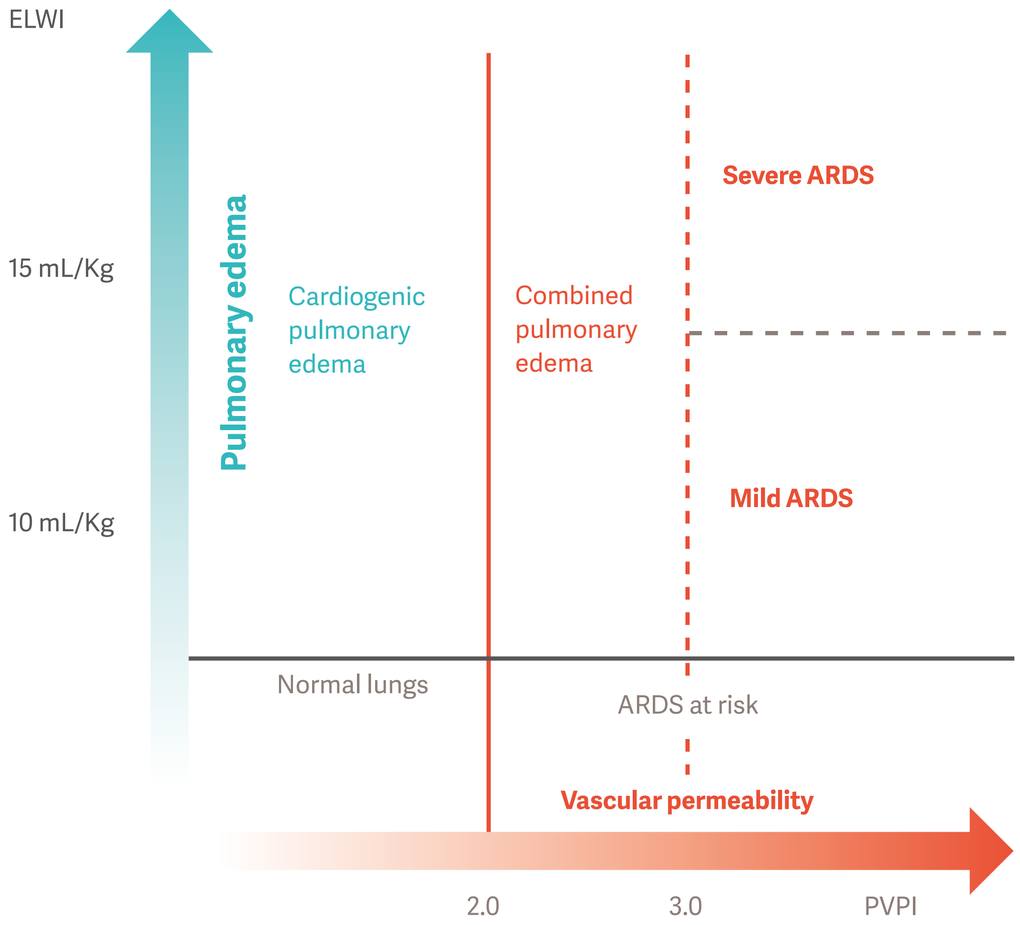

Figure 20. Graphical presentation on the interaction of ELWI and PVPI and how to interpret ARDS severity and categorization[37]

Figure 21: Advanced Patient Monitoring

Summary

After 20 years, the ARDS definition criteria urgently require another update, already demanded by clinical experts. Strong clinical evidence exists that the inclusion of the transpulmonary thermodilution measurement parameters extravascular lung water index (ELWI) and pulmonary vascular permeability index (PVPI) have a huge potential to improve the ARDS definition criteria for:

- evaluation of the lung damage at the bedside, repeatable anytime on demand
- sensitive quantification of the level of pulmonary edema
- differential diagnosis of ARDS
- grading the severity of ARDS

Additionally, ELWI is clinically useful for fluid titration as a safety parameter in patients with pulmonary edema with a huge potential to improve outcomes.

Figures

Figure 1. Helicopter rescues casualties, Vietnam 1968 (https://line.17qq.com/articles/ckococgdv.html)

Figure 2. Casualties arrive at the Naval Support Activity Station Hospital in Da Nang, Vietnam in 1968

Figure 3. AECC ARDS definition criteria overview

Figure 4. Comparison table of the AECC and Berlin definition criteria of ARDS (Yang et al 2018)

Figure 5. Berlin Criteria for ARDS, Challenges in Resource-Poor Settings, and Kigali Modification of the Berlin Criteria to Address These Challenges (Riviello et al. 2016)

Figure 6. Summary of key differences between the new global definition of ARDS and the Berlin definition along with the rationale for updating specific diagnostic criteria

Figure 7. Interpretation of a chest X-ray image

Figure 8. Radiography – working principle

Figure 9. Examples of chest X-ray images

Figure 10. A critically ill patient during computed tomography (CT) scan

Figure 11. CT scan images in a patient with ARDS

Figure 12. Image close up of a nurse drawing blood

Figure 13. Scheme of the insertion and positioning of a pulmonary artery catheter

Figure 14. Performance of a PiCCO transpulmonary thermodiltion measurement

Figure 15. Comparison of ultrasound B-lines and high resolution computed tomography[39]

Figure 16. Basic principle of the calculation of extravascular lung water by transpulmonary thermodilution[36]

Figure 17. Setup scheme for the transpulmonary thermodilution measurement

Figure 18. Results from experimental and clinical validation studies on the accuracy of transpulmonary thermodilution to measure extravascular lung water [31-33]

Figure 19. Scheme on hemodynamic monitoring tools and escalation recommended by the European Society of Intensive Care Medicine (ESICM) expert panel

Figure 20. Graphical presentation on the interaction of ELWI and PVPI and how to interpret ARDS severity and categorization[37]

Figure 21. Advanced Patient Monitoring

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