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REVIEW

Fluid administration and monitoring in ARDS: which management?

Philippe Vignon[1,2,3,16*], Bruno Evrard[1,2,3], Pierre Asfar[4], Mattia Busana[5], Carolyn S. Calfee[6], Silvia Coppola[7,8,9], Julien Demiselle[4], Guillaume Geri[10,11,12], Mathieu Jozwiak[13,14], Greg S. Martin[15], Luciano Gattinoni[5] and Davide Chiumello[7,8,9]

Abstract

Modalities of fluid management in patients sustaining the acute respiratory distress syndrome (ARDS) are challenging and controversial. Optimal fluid management should provide adequate oxygen delivery to the body, while avoiding inadvertent increase in lung edema which further impairs gas exchange. In ARDS patients, positive fluid balance has been associated with prolonged mechanical ventilation, longer ICU and hospital stay, and higher mortality. Accordingly, a restrictive strategy has been compared to a more liberal approach in randomized controlled trials conducted in various clinical settings. Restrictive strategies included fluid restriction guided by the monitoring of extravascular lung water, pulmonary capillary wedge or central venous pressure, and furosemide targeted to diuresis and/or albumin replacement in hypoproteinemic patients. Overall, restrictive strategies improved oxygenation significantly and reduced duration of mechanical ventilation, but had no significant effect on mortality. Fluid management may require different approaches depending on the time course of ARDS (i.e., early vs. late period). The effects of fluid strategy management according to ARDS phenotypes remain to be evaluated. Since ARDS is frequently associated with sepsis-induced acute circulatory failure, the prediction of fluid responsiveness is crucial in these patients to avoid hemodynamically inefficient—hence respiratory detrimental—fluid administration. Specific hemodynamic indices of fluid responsiveness or mini-fluid challenges should be preferably used. Since the positive airway pressure contributes to positive fluid balance in ventilated ARDS patients, it should be kept as low as possible. As soon as the hemodynamic status is stabilized, correction of cumulated fluid retention may rely on diuretics administration or renal replacement therapy.

Keywords: Acute respiratory distress syndrome, Pulmonary edema, Fluid therapies, Water–electrolyte balance, Prognosis

*Correspondence: philippe.vignon@unilim.fr
[16] Réanimation Polyvalente, CHU Dupuytren, 2 Avenue Martin Luther King, 87042 Limoges, France
Full author information is available at the end of the article

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Introduction

Patients with the acute respiratory distress syndrome (ARDS) are characterized, to different degrees, by an alteration in pulmonary endothelial and epithelial permeability with associated lung edema. Acute circulatory failure is highly prevalent and potentially prognostic in ARDS patients [1]. Optimal fluid management in these patients remains challenging and controversial because it should provide an adequate oxygen delivery while avoiding inadvertent increase in lung edema, thus balancing a liberal versus a restrictive fluid strategy approach. Positive fluid balance and low serum albumin concentration have been found to be independent risk factors for ARDS development [2]. Moreover, an increased body weight related to cumulative fluid balance has been associated with a worse outcome [3].

The present manuscript will describe the management of fluid balance according to both the cause and the timing of ARDS while summarizing the randomized controlled trials (RCT) assessing a restrictive versus liberal strategy of fluid administration in this clinical setting.

Pathophysiology of ARDS and fluid therapy

The fundamental pathophysiologic hallmark of ARDS is increased permeability of the alveolar-capillary barrier, leading to non-cardiogenic pulmonary edema. When the normally well-regulated endothelial barrier is disrupted (e.g., direct damage from pathogens, indirect effects of pro-inflammatory signaling molecules, endothelial cell activation), plasma and inflammatory cells leak into the interstitial space and result in interstitial edema [4]. Hydrostatic and osmotic forces predict fluid movement from the vascular space to the interstitium, particularly with contemporary understanding of the extracellular matrix and the endothelial glycocalyx layer [4]. Once the normally tight alveolar epithelial barrier is breached, alveolar edema ensues and is then further worsened by a decrease in alveolar fluid clearance, leading to alveolar flooding and worsening of gas exchange.

As the airspaces are becoming flooded with fluid, the systemic inflammation and ensuing endothelial permeability present in many ARDS patients lead to third spacing and relative intravascular volume depletion, manifesting as hypotension in a large proportion of ARDS patients [5, 6]. The requirement for positive-pressure ventilation in many patients makes adequate cardiac preload vitally important, and patients frequently sustain concomitant vasodilatory shock and/or decreased cardiac output related to sepsis. Accordingly, fluid resuscitation is key in the early management of ARDS patients. However, even modest increases in pulmonary hydrostatic pressures in the setting of an inordinately permeable alveolar-capillary barrier can lead to significant increases in pulmonary edema formation [7]. Further complicating the problem, increases in pulmonary hydrostatic pressure can directly exacerbate local inflammation and increased permeability, likely via mechanical stretch of pulmonary vascular endothelial cells [8]. Thus, one of the fundamental challenges in the care of the ARDS patient is how to walk the tightrope between reducing fluid accumulation in the alveolar space and providing adequate intravascular volume to support cardiac output and vital tissue perfusion (Fig. 1).

Take-home message

Optimal fluid management in patients with the acute respiratory distress syndrome remains challenging and controversial because it should provide adequate oxygen delivery to the body while avoiding inadvertent increase in lung edema. We discuss the restrictive versus liberal strategy of fluid administration and describe the management of fluid balance in these patients with frequently associated acute circulatory failure.

Fluid balance and outcome

Clinical data from patients with ARDS confirm that fluid overload is deleterious for patient outcomes. Early in the course of critical illness, positive fluid balance prior to the development of ARDS portends its development and a higher risk of dying [9]. Net positive fluid balance occurs in the majority of patients at the onset of ARDS even when closely monitored, and predicts prolonged mechanical ventilation, longer intensive care unit (ICU) and hospital stay, and higher mortality [10, 11]. Similarly, increased hydrostatic pressure is common in ARDS patients, at least intermittently during the course of the disease, and associated with a higher risk of death [6, 12]. Intravenous fluid administration is necessary in many critically ill patients, and the ebb and flow phenomenon across time in these patients is evident in observing the lowest mortality for sepsis and ARDS patients receiving adequate early fluid administration followed by later conservative fluid management, compared to patients who received either inadequate early fluids or more liberal later fluid administration [13].

Restrictive vs. liberal fluid strategies

Compared to healthy subjects, ARDS patients present a higher amount of extravascular lung water (EVLW) for a given arterial pulmonary pressure and a linear increase in the fluid shift from capillaries to alveoli consequent to any increase in the pulmonary pressure [14]. Thus, a strategy aimed at reducing the level of pulmonary pressure should reduce the pulmonary pressure gradient,

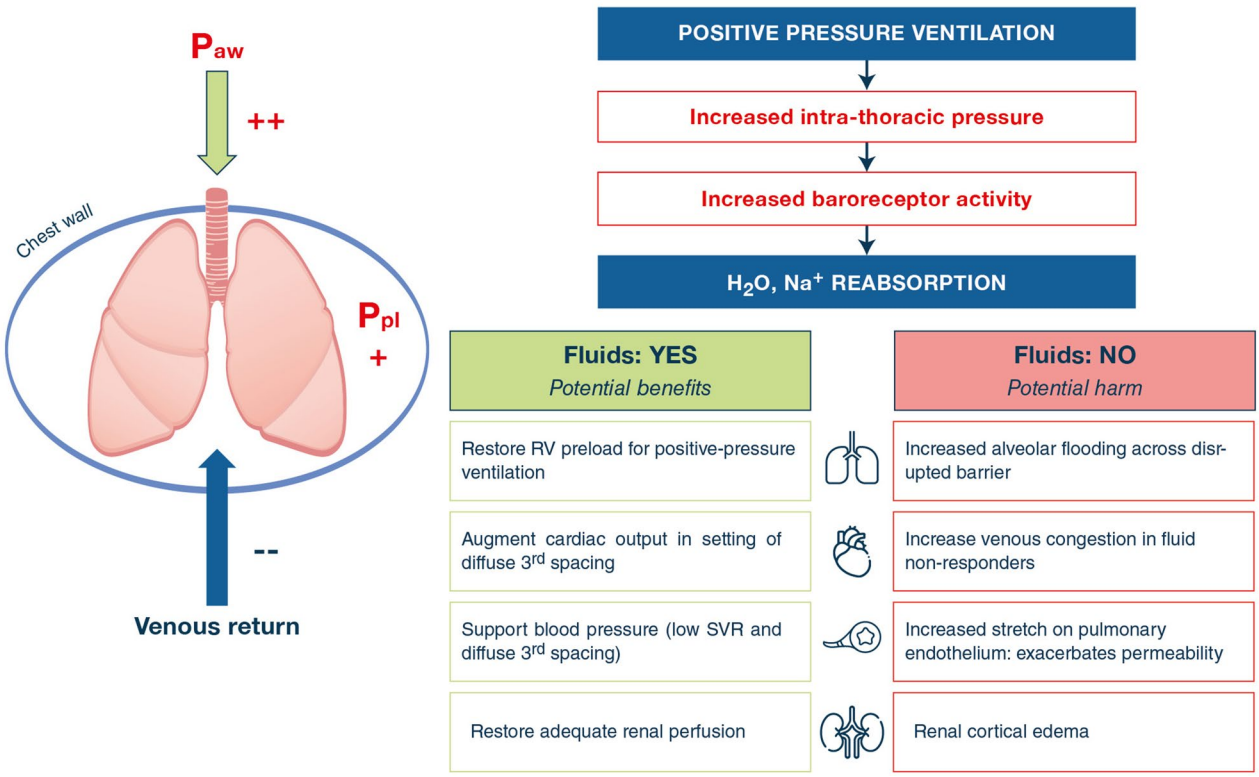

Fig. 1 Schematic representation of summarized effects of positive-pressure ventilation on fluid balance and of the potential benefit–risk ratio of fluid administration in patients with the acute respiratory distress syndrome. *H_2O* water, *Na^+* sodium, *Paw* airway pressure, *Ppl* pleural pressure

hence limit fluid accumulation into the lung and potentially improve outcome. Humprey et al. [15] showed that ARDS patients, in whom pulmonary capillary wedge pressure (PCWP) was reduced of at least 25% within 48 h after ICU admission, had a better outcome compared to patients without such reduction. A retrospective study showed that EVLW was significantly higher in non-survivors than in survivors, and in ARDS patients compared to all other critically ill patients [16]. However, these data cannot determine if a larger fluid administration is only an indirect marker of ARDS severity or if it contributes to lung hypoxemia, and to heart and renal failure [1, 17].

To assess if a restrictive fluid management with or without diuretic therapy could improve patient outcome, several RCTs have been performed (Table 1). In a pioneer study, Mitchell et al. [18] randomized 101 ARDS patients to receive a fluid management strategy based on the monitoring of either PCWP ($n=49$) or EVLW ($n=52$). Patients managed with EVLW compared to PCWP monitoring had a significantly lower cumulative fluid balance and duration of mechanical ventilation, but similar vasopressor requirements and mortality rate [18]. Subsequently, a large RCT evaluated a conservative compared to a liberal fluid strategy in ARDS patients according to therapeutic algorithms based on the value of PCWP or central venous pressure (CVP) [6]. More than one thousand patients were enrolled with a mean time from ARDS onset to ICU admission of 42 h. The conservative group received significantly less fluids compared to the liberal group from Day 1 to 4, resulting in a lower cumulative fluid balance on Day 7 (-136 ± 491 mL vs 6992 ± 502 mL: $p<0.001$). When compared to the liberal strategy, the conservative group had a better oxygenation, lung compliance and higher number of ventilator-free days (14.6 ± 0.5 vs 12.1 ± 0.5 days: $p<0.001$), but without statistically significant difference in the requirement of renal replacement therapy and mortality rate at 60 days (25.5% vs 28.4%: $p=0.30$) [6]. Surgical ARDS patients who are often younger and with lower comorbidities compared to medical ARDS patients, develop ARDS in the context of multiple organ failure and thus might seem to require a different fluid management approach. In a subgroup analysis of the FACTT trial performed in surgical ARDS patients, the conservative group had a significantly lower fluid balance during the first week following ICU admission and higher ventilator-free days compared

Table 1 Studies assessing the effects of fluid management (restrictive vs. liberal) on blood oxygenation, duration of mechanical ventilation, length of ICU stay, and mortality in adult patients with the acute respiratory distress syndrome

Authors, year	Study aim	Number of patients	Study design	Oxygenation	Duration of mechanical ventilation	Ventilator free days	Length of ICU stay	Mortality
Mitchell et al. (1992) [18]	To evaluate a fluid restriction strategy according to EVLW or PCWP	101	RCT	Similar	Significantly lower in the PCWP group	–	Similar	No statistical difference on ICU and hospital mortality
Widerman et al. (2006)	To evaluate a fluid restriction strategy according to CVP or PCWP	1001	RCT	Significantly higher in conservative group	–	Significantly higher in conservative group	Higher number of ICU-free days in conservative group	No statistical difference on 60-day mortality
Stewart et al. (2009) [19][a]	To evaluate a fluid restriction strategy according to CVP or PCWP in surgical patients	244	Post-hoc analysis	–	–	Significantly higher in conservative strategy	Higher number of ICU-free days in conservative group	No statistical difference on 60-day mortality
Martin et al. (2002) [21]	To evaluate the effects of albumin replacement and furosemide targeted to diuresis, weight loss and serum total protein in hypoproteinemic patients	37	RCT	Significantly higher in the albumin group	–	–	–	No statistical difference on ICU and 30-day mortality
Martin et al. (2005) [22]	To evaluate the effects of albumin replacement and furosemide or albumin replacement alone titrated to fluid loss and serum total protein in hypoproteinemic patients	40	RCT	Significantly higher in the albumin group	Significantly lower in the albumin group	Significantly higher in the albumin group	Similar	No statistical difference on ICU and 30-day mortality

RCT randomized controlled trial, *EVLW* extravascular lung water, *PCWP* pulmonary capillary wedge pressure, *CVP* central venous pressure

[a] Subgroup analysis of the study by Wiederman et al.

to the liberal group [19]. These data suggest that conservative fluid management has potential beneficial effects, irrespective of ARDS etiology. A recent study applying a latent class sub-analysis on the patients enrolled in the FACTT trial, described two ARDS phenotypes with distinct responses to fluid management strategy [20]. When randomized to conservative fluid strategy, the hyperinflammatory phenotype characterized by higher levels of inflammatory cytokines had a higher mortality rate whereas the hypoinflammatory phenotype exhibited a lower mortality rate [20]. Accordingly, ARDS subtypes may require different approaches regarding fluid management, though these results have not been prospectively validated.

ARDS patients are clinically characterized by low serum protein levels and hypoalbuminemia (i.e., decreased oncotic pressure) which can contribute to the development of pulmonary edema. Accordingly, the increase of intravascular oncotic pressure may reduce lung interstitial edema according to the degree of endothelial dysfunction [14]. A small-size RCT conducted in ARDS patients mainly due to trauma evaluated a strategy of continuous infusion of furosemide together with 25 g of 25% human albumin to achieve a daily weight loss > 1 kg compared to standard of care [21]. The intervention group had a significantly higher diuresis, reduction in body weight and better oxygenation without deleterious effects on hemodynamics and renal function [21]. To evaluate the respective role of furosemide and albumin, the same authors randomized ARDS patients to receive either furosemide and albumin ($n = 20$), or solely furosemide ($n = 20$) for 3 days [22]. Patients treated with furosemide plus albumin had a significantly higher increase in oxygenation, serum albumin levels and lower cumulative fluid balance [22].

Incorporating the major RCTs on fluid management in ARDS in a systematic review, a recent meta-analysis found that a conservative fluid strategy resulted in a decreased length of ICU stay and increased ventilator-free days, but without significant benefit on mortality [23].

Assessment of fluid responsiveness

The ROSE (Resuscitation, Optimization, Stabilization, Evacuation) concept identifies four successive phases for fluid therapy, each of them having specific clinical and biological goals [24, 25]. In the initial resuscitation phase, according to the 1-h bundle, early and rapid administration of crystalloids is recommended in all patients with arterial hypotension or increased blood lactate level (> 4 mmol/L) to achieve adequate perfusion pressure [24–26]. Thereafter, during the optimization phase, fluids should be administered according to individual needs [24, 25]. Thus, the assessment of fluid responsiveness (FR) is particularly relevant in ARDS patients with persistent circulatory failure during the optimization phase, to avoid detrimental fluid overload without any associated beneficial hemodynamic effects. This potential threat increases over time since FR rapidly declines during the first hours of septic shock resuscitation [27]. As a general rule, the identification of FR in a given patient does not mean that he actually requires fluid loading since the primary goal of resuscitation is to optimize oxygen delivery and tissue perfusion to meet the metabolic demands of the organism, rather than normalizing any dynamic index of FR [28].

The pulmonary artery catheter (PAC), still suggested by some to be used in patients with severe shock and associated ARDS [29–31], is not accurate to predict FR. Transpulmonary thermodilution (TPTD) and critical care echocardiography (CCE) are currently the most frequently used techniques to hemodynamically assess critically-ill patients at the bedside, especially when ventilated for ARDS. All parameters used to predict FR during these hemodynamic assessments have limitations, including in ARDS patients (Fig. 2).

Hemodynamic benefit of fluid administration can be evaluated using the different FR indices provided by TPTD-derived real-time pulse wave analysis: increase in cardiac output (> 10%) induced by a 90° passive leg raising (PLR) or by an end-expiratory occlusion test (increase > 5%), and respiratory variations of continuous pulse-pressure (PPV) and stroke volume (SVV) [32]. Importantly, low tidal volume used for protective ventilation in ARDS patients does not preclude the use of PPV and SVV as indicators of FR [32]. Indeed, it has been shown that an increase in the absolute value of PPV > 3.5% and SVV > 2.5% during a tidal volume challenge (i.e., an increase in tidal volume from 6 to 8 mL/kg of predicted body weight for 1 min) could reliably predict FR [33]. The deleterious effects of excessive fluid administration can also be evaluated using two quantitative parameters provided by TPTD: the EVLW which correlates with the severity of pulmonary edema and the pulmonary vascular permeability index, a marker of lung capillary leak. Both are independent predictors of mortality and may indicate the risk of fluid accumulation in the lungs of ARDS patients [34]. Thus, when the risks of fluid administration are deemed to overcome potential benefits (i.e., high values of EVLW and pulmonary vascular permeability index in severely hypoxemic ARDS patients), vasopressor support may be considered even in the presence of preload reserve.

CCE provides unparalleled information in ARDS patients since it identifies potential limitations of TPTD for accurate hemodynamic evaluation, including

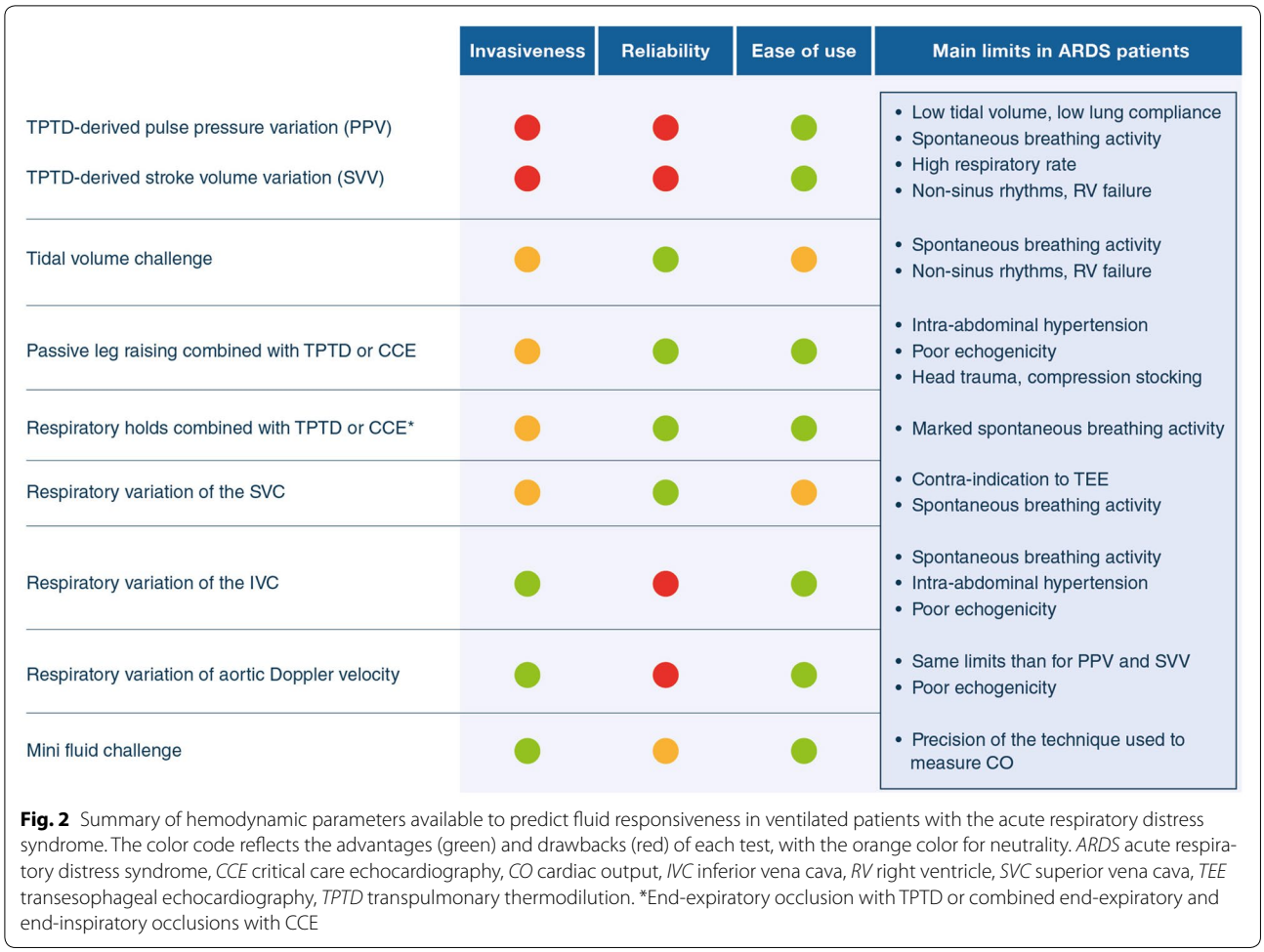

Fig. 2 Summary of hemodynamic parameters available to predict fluid responsiveness in ventilated patients with the acute respiratory distress syndrome. The color code reflects the advantages (green) and drawbacks (red) of each test, with the orange color for neutrality. *ARDS* acute respiratory distress syndrome, *CCE* critical care echocardiography, *CO* cardiac output, *IVC* inferior vena cava, *RV* right ventricle, *SVC* superior vena cava, *TEE* transesophageal echocardiography, *TPTD* transpulmonary thermodilution. *End-expiratory occlusion with TPTD or combined end-expiratory and end-inspiratory occlusions with CCE

potential source of errors for FR assessment such as right ventricular (RV) failure [35]. Since RV failure may alter the response to fluids despite significant PPV [36] and elevated intra-abdominal pressure may result in false-negative PLR [37], both conditions should be ruled out before inferring therapeutic changes (Fig. 3). The decreased performance of PPV in predicting FR has been well described by Mahjoub et al. [38] who have reported that a PPV > 12% was associated with a 34% false-positive rate to predict FR in a population of critically ill patients. Interestingly, these patients could be adequately reclassified as non-responders based on the presence of decreased Doppler peak velocity of tricuspid annular motion, a surrogate marker of RV dysfunction [38]. These findings may suggest that "significant" PPV was related to RV afterload variations in non-responders while it reflected RV preload variations in fluid-responders. Indeed, the failing RV becomes more sensitive to an increase of its afterload and is less affected by preload variation [39]. In this case, PPV is predominantly mediated by inspiratory changes in transpulmonary pressure, and fluid loading is unable to increase left ventricular stroke volume and to reduce PPV. This situation is commonly encountered in ARDS patients with low pulmonary compliance, elevated transpulmonary pressure, and frequently associated RV dysfunction [40]. Accordingly, PPV should not be interpreted per se as a marker of FR in ventilated ARDS patients, but rather as a warning sign that should trigger a comprehensive hemodynamic assessment using CCE to seek for underlying RV failure [41]. Respiratory variation of the superior vena cava is the most specific dynamic parameters of FR but requires to perform a transesophageal echocardiography [42]. Accordingly, it accurately indicates the absence of FR in patients with RV failure [41]. In contrast, respiratory variation of aortic Doppler velocity shares the same limitations than PPV [41, 42]. Respiratory variation of the inferior vena cava is mainly assessed using surface echocardiography and appears as the least accurate CCE indicator of FR since it may be altered by the level of

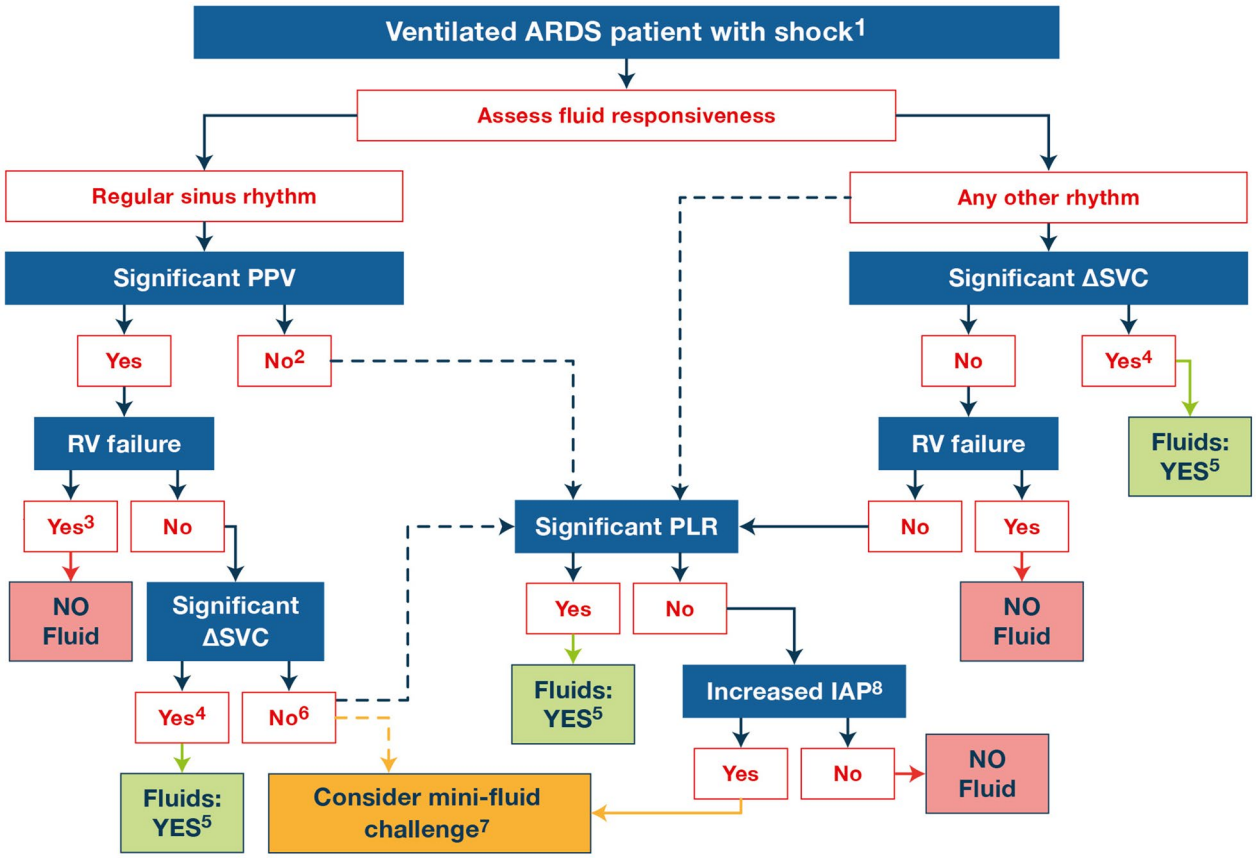

Fig. 3 Proposed diagnostic algorithm in ventilated ARDS patients presenting with shock based on a hemodynamic assessment using critical care echocardiography during the resuscitation and optimization periods [24]. Fluid responsiveness should be assessed to avoid hemodynamically inefficient and potentially respiratory detrimental fluids administration. In patients with sinus rhythm, pulse pressure variation can be used as a warning sign for identifying the mechanism of left ventricular load dependency revealed by heart–lung interactions (i.e., right ventricular failure vs hypovolemia responsible for Δ-down; rarely severe left ventricular failure responsible for Δ-up). In patients with other cardiac rhythms, respiratory variations of the superior vena cava diameter are the most specific parameter to predict fluid responsiveness which requires transesophageal echocardiography. Alternatively, a passive leg raising may be used to assess fluid responsiveness. When values of hemodynamic indices are within the "grey zone" or in the presence of increased intra-abdominal pressure (risk of false-negative result), mini-fluid challenges may be considered. [1]The diagnostic workup must include the precise clinical setting, ongoing therapy, clinical hemodynamic assessment and biological markers of tissue hypoperfusion. In ARDS patients, specific parameters of fluid responsiveness should be preferred.[2]When pulse pressure variation is in the "grey zone", a passive leg raising may be performed to seek for fluid responsiveness. [3]Right ventricular failure typically associates an acute dilatation of the right ventricular cavity and increased central venous pressure secondary to systemic venous congestion [36]. [4]In ARDS patients, a ΔSVC cut-off of 31% predicts fluid responsiveness with a 90% specificity, at the expense of a low sensitivity of 43% [42]. Associated echocardiography findings consistent with decreased cardiac preload are frequently associated (e.g., hyperkinetic right ventricle with small cavity size, decreased diameter of the inferior vena cava with marked respiratory variation, significant respiratory variation of maximal left ventricular outflow tract Doppler velocity [41]. [5]Repeated small aliquots (e.g., 250 mL) are preferable; both efficacy (percentage of increase of left ventricular stroke volume when compared to baseline) and tolerance (absence of significant increase in left ventricular filling pressure) of fluid challenge should be assessed using serial hemodynamic assessment. [6]To increase the sensitivity of superior vena cava respiratory variation, lower threshold value can be used (e.g. a 4% cut-off has a sensitivity of 89%) [42], or a mini-fluid challenge can be considered. [7]: mini-fluid challenges consist in administrating intravenously a small volume of fluids over a very short period of time (e.g., 50–100 mL within 1 min) [46–48]. [8]Intra-abdominal pressure should best be measured in patients at high risk of intra- abdominal hypertension [44] since elevated values may result in falsely negative passive leg raising [37]. *ARDS* acute respiratory distress syndrome, *ΔSVC* respiratory variation of the superior vena cava diameter, *IAP* intra-abdominal pressure, *PPV* pulse pressure variation, *RV* right ventricle

intra-abdominal pressure [43]. Although not specifically validated in ARDS patients, the response of left ventricular stroke volume reflected by aortic Doppler velocity–time integral changes to PLR is valuable to assess FR in ventilated patients [41]. Nevertheless, intra-abdominal pressure should be measured in ARDS patients at risk of intra-abdominal hypertension to interpret with caution hemodynamic effects of PLR [44]. Finally, the added effects of consecutive end-expiratory and end-inspiratory occlusions on aortic Doppler velocity–time integral can also reliably assess FR in ARDS patients [45].

Fluid challenge is still widely used in critically ill patients, but with marked heterogeneous practices. Importantly, fluid challenge allows the assessment of FR but not its prediction. Unnecessary fluid challenge must be avoided, especially in hypoxemic ARDS patients, since it contributes to positive hydric balance without expected beneficial hemodynamic effects. To optimize the specificity of CCE indices indicating FR, higher threshold values can be used (Fig. 3), at the expense of sensitivity [42]. Alternatively, mini-fluid challenges (a 50–100 mL fluid infusion within 1 min) can be performed. Changes in PPV or SVV [46], in cardiac output derived from pulse wave analysis [47], or in aortic velocity–time integral measured by CCE [48] induced by the rapid administration of 100 mL of fluids reliably predict FR. Nevertheless, the precision of the technique used to assess the response of cardiac output during the mini-fluid challenge must be taken into account since induced variations are small [49]. Finally, the tolerance of the fluid challenge must also be repeatedly assessed, either using TPTD-derived EVLW or left ventricular filling pressure assessed with CCE [41].

Origin of positive fluid balance and modality of correction

Cumulated fluid balance in ARDS patients is multifactorial, especially in the presence of associated circulatory failure with low systemic vascular resistance requiring fluid resuscitation. In mechanically ventilated ARDS patients, positive airway pressure substantially contributes to positive fluid balance (Fig. 1). The increase in airway pressure raises intrathoracic pressure which in turn leads to a decrease in central arterial blood volume [50]. The resulting activation of baroreceptors increases the vasomotor tone, and the reabsorption of both sodium and water aimed at increasing blood volume [51].

However, in ARDS patients, the determinant of hemodynamic changes is the pleural pressure rather than the airway pressure. Indeed, the change in pleural pressure equals the product of airway pressure and the ratio between chest wall and respiratory system elastance [52]. This ratio in ARDS patients averages 0.3, ranging from 0.2 to 0.9 [53]. Accordingly, for the same change in airway pressure, a tremendous difference of pleural pressure change may be observed. Importantly, greater is the increase in pleural pressure, greater is its effect on fluid retention. What primarily accounts for fluid retention is the mean pleural pressure, of which the positive end-expiratory pressure (PEEP) is a major determinant. Indeed, for the same fluid input, the water retention in a 46-h experiment was twice as much important in animals treated with PEEP than without PEEP [54]. Similarly, for the same mechanical power, we found that the positive fluid balance was dramatically higher in animals treated with high levels of PEEP [55]. Nevertheless, fluid retention ceases when a new equilibrium is reached after 2–3 days [54].

Theoretically, used type of fluid could result in differences of water retention, as to reach the same intravascular volume (the goal of fluid administration). Lower amount of fluids is required if colloids as albumin are associated with the crystalloid administration, when compared to crystalloids alone [56]. However, particularly in full-blown ARDS, the increased vessel permeability may reduce the expected oncotic effect of the colloids used for blood volume expansion. What is rarely considered is how the infused fluids are distributed through the body compartments. In a 70-kg man, 1 l of intravenously infused crystalloids would increase the intravascular volume (the real aim of fluid therapy) by only 250 ml at equilibrium (which is likely reached in minutes), while the remaining 750 ml would be distributed in the interstitial space [57]. Accordingly, large fluid retentions may be associated with concomitantly reduced intravascular volume.

Fluid retention is the unavoidable "price" to pay to allow the use of positive-pressure mechanical ventilation. Importantly, the consequences of positive fluid balance are not limited to the lung (partly protected by the high intra-alveolar pressure) but also involve other organs which interstitial edema may deeply affect the function [55]. Consequently, excessive fluid retention must be ideally prevented, or corrected. Prevention is based on keeping the positive airway pressure, especially PEEP, at a minimal level compatible with adequate oxygen transport and organs function. Correction of fluid retention may rely on diuretics administration or renal replacement therapy. The combined treatment with furosemide and albumin may accelerate by 1–2 days the correction of body fluid excess [21, 58] (if ARDS is not in full-blown phase). Otherwise, particularly if the kidney function is impaired or the airway pressure used are such that the hormonal response is fully shifted towards sodium and water reabsorption, renal replacement therapy should be considered. Indications and limits of this approach have been recently reviewed [59].

Practical management of fluid balance according to the cause and timing of ARDS

To ensure that the management of fluid balance in ARDS patients is optimal, the clinician must carefully weigh the benefit–risk ratio of therapeutic interventions. With the exception of severe viral pneumonitis without cardiac involvement, ARDS is most frequently not isolated in ICU patients, but rather associated with circulatory failure [1]. In these patients, hypovolemia may further jeopardize organ perfusion whereas fluid overload may worsen lung function. Greater volume of fluid administered is associated with higher mortality after adjustment on severity [60].

According to the four-hit model of shock with ebb and flow phases [24], fluid resuscitation should be given initially to restore or maintain systemic hemodynamics when required, with constant concerns regarding its potential deleterious effects on gas exchange. To do so, prediction of FR together with close hemodynamic and tissue perfusion monitoring is key (Fig. 4). Once stabilization of hemodynamics is obtained, fluid balance should then be normalized in evacuating excess fluids administered during the resuscitation and optimization phases [24]. In practice, fluid management at the early phase of isolated ARDS aims at counteracting potential deleterious hemodynamic effects of positive-pressure ventilation (Fig. 1). During the resuscitation and optimization phases of shocked ARDS patients [24], hemodynamic assessment combining CCE and CVP used as a safety marker to detect potential fluid overload or RV failure [36], associated with indices of tissue dysoxia (e.g., lactate, $ScvO_2$, $P[a\text{-}v]CO_2$) should be favored [28, 61]. Nevertheless, the

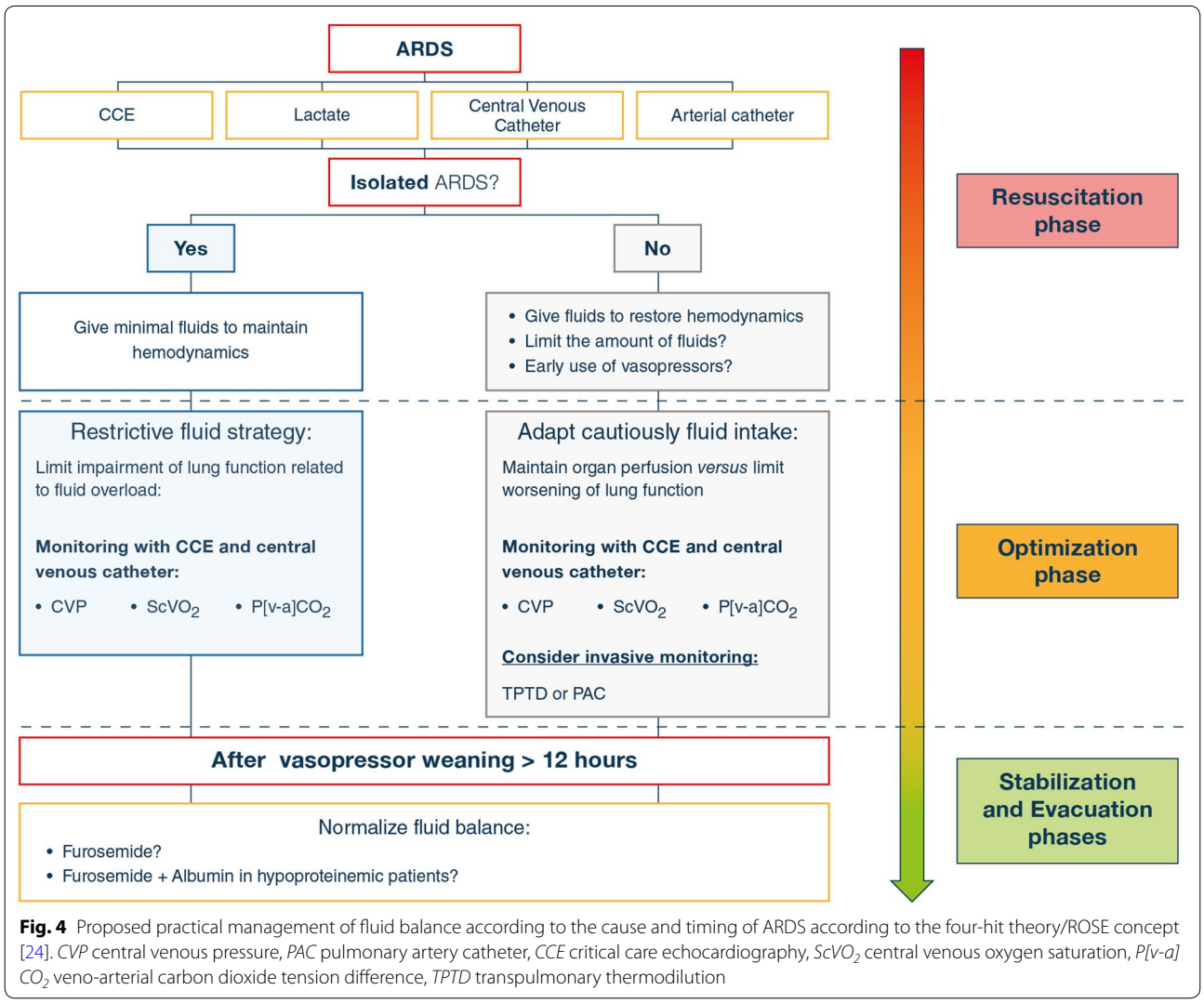

Fig. 4 Proposed practical management of fluid balance according to the cause and timing of ARDS according to the four-hit theory/ROSE concept [24]. *CVP* central venous pressure, *PAC* pulmonary artery catheter, *CCE* critical care echocardiography, *$ScVO_2$* central venous oxygen saturation, *$P[v\text{-}a]CO_2$* veno-arterial carbon dioxide tension difference, *TPTD* transpulmonary thermodilution

type of hemodynamic monitoring to guide fluid management in this specific population remains controversial. Although CCE is widely used as a first-line hemodynamic assessment tool at the bedside due to its unparalleled advantage of accurately identifying FR and potential RV failure [35], some experts still suggest the use of invasive monitoring using either TPTD or PAC during the early phase of resuscitation in this specific clinical setting [30, 32]. During the stabilization and evacuation phases, the main goal of fluid management is to restore an equilibrated (i.e., nil) fluid balance to facilitate ventilator weaning (Fig. 4). The precise timing for considering conservative fluid management and de-resuscitative measures remains to determine [23]. In the FACTT trial, the conservative strategy was initiated when shock had been resolved for > 12 h (i.e., off vasopressor support) [6]. In addition, the best therapeutic strategy to achieve this goal in RCTs has not yet been established (e.g., furosemide, furosemide combined with albumin) [22, 23]. Of note, the administration of albumin in the presence of altered lung permeability could result in a higher albumin and fluid loss in the extravascular space with a possible worsening of the ARDS [62]. Finally, alternative therapeutic strategies based on other hemodynamic or pathophysiological targets remain to be evaluated (e.g., EVLW).

To limit fluid administration, several approaches have been proposed in patients with septic shock. The first approach is to restrict the volume of fluids administered during ICU stay, after the resuscitation phase (i.e., after the initial management of septic shock). This restrictive strategy was tested in RCTs [63, 64]. It succeeded in significantly reducing administered resuscitation fluid volume, without increasing the rate of new organ failures. Importantly, these trials were not adequately powered to assess patient-centered outcomes [63, 64]. The second approach is the early administration of norepinephrine as a strategy to reduce fluid administration in increasing venous return secondary to splanchnic vasoconstriction. Hamzaoui et al. [65] showed that early norepinephrine administration in septic shock patients to reach and maintain a mean arterial pressure around 65–70 mm Hg, increases venous return and cardiac output. Recently, Pemprikul et al. [66] have tested the strategy of an early administration of fixed low doses of norepinephrine (0.05 µg/kg/min) compared to standard of care in a RCT enrolling patients with septic shock. In the intervention arm, the control of shock at 6 h was more frequent, with a lower incidence of cardiogenic pulmonary edema and new-onset arrhythmias. Nevertheless, the median fluid volume administered exceeded 5 L on Day 1 and was similar in both groups [66]. These two therapeutic approaches were combined in the REFRESH pilot trial [67]. Ninety-nine patients with suspected sepsis and hypotension were randomized in the Emergency Department to receive either a restricted fluid regimen (norepinephrine if the mean arterial pressure remained < 65 mmHg after 1 L of fluid loading), or standard of care. Not surprisingly, the median fluid volume administered during the first 6 h was significantly lower in the intervention arm than in controls, with a 30% relative reduction in total fluids administered up to 24 h and no safety signal. Nevertheless, both the low illness severity and mortality rate limit the external validity of this pilot trial [67]. Finally, one should keep in mind that fluids administered for hemodynamic resuscitation only account for approximately 10–30% of daily fluid intakes during the ICU stay [68, 69].

Fluid therapy in COVID-19 patients with ARDS should also be based on the timing of the disease. In the early phase, patients are characterized by a low amount of lung edema, near-normal elastance and low amount of atelectasis (phenotype L), whereas in the later phase, patients present with a higher amount of lung edema, atelectasis and elastance (phenotype H) [70]. Accordingly, the phenotype L should require a lower amount of fluid compared to phenotype H due to lower alteration in lung permeability and mean airway pressure (i.e., lower PEEP and transpulmonary pressure).

Future directions

As critical care medicine moves towards a personalized medicine approach, it will be important to consider how fluid therapy can be similarly individualized. Prior studies have focused on the use of physiologic data, particularly dynamic indices of FR, as tools to help bedside providers individualize fluid management. There is considerable complexity to personalizing fluid therapy as recent studies have suggested that clinical–biological phenotypes of ARDS may respond differently to fluid management [20] and that race/ethnicity may be associated with differences in FR [71, 72]. Integrating the full breadth of clinical and physiological data to accurately identify the diverse phenotypes is an important first step prior to testing them prospectively for intended widespread clinical implementation.

Conclusion

ARDS is characterized by an increased endothelial and epithelial permeability which promotes the passage of fluid into lung interstitial and alveolar space. Since ARDS is frequently associated with shock, fluid management is key to restore adequate organ perfusion while avoiding diffuse tissue edema and positive fluid balance. Initial resuscitation should be guided by close hemodynamic monitoring aimed at predicting FR and avoiding undue venous congestion. Positive airway pressure should be

kept as low as possible since it contributes to positive fluid balance. Once the patient is hemodynamically stable, subsequent management should be based on the evacuation of excess fluids to normalize cumulated fluid balance and facilitate ventilator weaning. Although various restrictive strategies aimed at reducing fluid administration have not yet been shown to improve mortality, tailored therapeutic management based on ARDS subphenotypes remains to be tested to improve patient-centered outcome.

Author details
[1] Medical-Surgical ICU, Dupuytren Teaching Hospital, 87000 Limoges, France. [2] Inserm CIC-1435, Dupuytren Teaching Hospital, 87000 Limoges, France. [3] Faculty of Medicine, University of Limoges, 87000 Limoges, France. [4] Service de Médecine Intensive Réanimation, Médecine Hyperbare, CHU Angers, 4 rue Larrey 49933, Angers Cedex 9, France. [5] Department of Anesthesiology and Intensive Care Medicine, University of Göttingen Medical Center, Göttingen, Germany. [6] Departments of Medicine and Anesthesia, Allergy and Sleep Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, USA. [7] SC Anestesia e Rianimazione, Ospedale San Paolo, Polo Universitario, ASST Santi Paolo e Carlo, Milan, Italy. [8] Dipartimento di Scienze Della Salute, Università Degli Studi Di Milano, Milan, Italy. [9] Centro Ricerca Coordinata di Insufficienza Respiratoria, Milan, Italy. [10] Medical-Surgical Intensive Care Unit, Ambroise Paré University Hospital, APHP, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France. [11] Paris-Saclay University, Saint-Aubin, France. [12] Inserm UMR-1018, CESP, Villejuif, France. [13] Medical Intensive Care Unit, University Hospital, APHP, Centre, Cochin Hospital, 27 rue du faubourg Saint Jacques, 75014 Paris, France. [14] Paris University, Paris, France. [15] Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory University School of Medicine and Grady Memorial Hospital, Atlanta, GA, USA. [16] Réanimation Polyvalente, CHU Dupuytren, 2 Avenue Martin Luther King, 87042 Limoges, France.

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PV and DC elaborated the structure of the manuscript, coordinated co-authors' contributions, and drafted the manuscript. BE, PA, MB, CSC, SC, JD, GG, MJ, GSM, and LG drafted and reviewed the manuscript.

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