Hemodynamic effects of positive end-expiratory pressure

Adrien Joseph[a,*], *Matthieu Petit*[a,b,*] *and Antoine Vieillard-Baron*[a,b]

Purpose of review
Positive end-expiratory pressure (PEEP) is required in the Berlin definition of acute respiratory distress syndrome and is a cornerstone of its treatment. Application of PEEP increases airway pressure and modifies pleural and transpulmonary pressures according to respiratory mechanics, resulting in blood volume alteration into the pulmonary circulation. This can in turn affect right ventricular preload, afterload and function. At the opposite, PEEP may improve left ventricular function, providing no deleterious effect occurs on the right ventricle.

Recent findings
This review examines the impact of PEEP on cardiac function with regards to heart-lung interactions, and describes its consequences on organs perfusion and function, including the kidney, gut, liver and the brain. PEEP in itself is not beneficious nor detrimental on end-organ hemodynamics, but its hemodynamic effects vary according to both respiratory mechanics and association with other hemodynamic variables such as central venous or mean arterial pressure. There are parallels in the means of preventing deleterious impact of PEEP on the lungs, heart, kidney, liver and central nervous system.

Summary
The quest for optimal PEEP settings has been a prominent goal in ARDS research for the last decades. Intensive care physician must maintain a high degree of vigilance towards hemodynamic effects of PEEP on cardiac function and end-organs circulation.

Keywords
acute kidney injury, acute respiratory distress syndrome, hemodynamics, positive end-expiratory pressure, right ventricle

INTRODUCTION

The acute respiratory distress syndrome (ARDS) has been first described in 1967 in a case series of 12 patients with new onset hypoxemia refractory to supplemental oxygen, bilateral infiltrates on chest radiograph, and reduced respiratory system compliance [1]. Since then, several definitions have been proposed: in 1994 with the American-European consensus conference on ARDS [2] and in 2012 leading to the so-called Berlin definition [3]. This includes respiratory failure within 1 week of a known insult or new and/or worsening respiratory symptoms, not fully explained by cardiac dysfunction or volume overload, bilateral opacities on chest X-ray or computed tomography and hypoxemia defined as paO_2/FiO_2 less than 300 mmHg on at least a PEEP of 5 cmH_2O. This definition has been updated after the COVID-19 pandemic to include patients treated with high-flow-nasal oxygen and a SpO_2/FiO_2 less than 315 [4].

In the past 50 years, tremendous progress were made in understanding the epidemiology and pathophysiology of ARDS [5]. Undoubtedly, no other intensive care syndrome has been as extensively studied, especially concerning the ventilatory strategy.

[a]Medical Intensive Care Unit, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris, Boulogne-Billancourt and [b]Inserm, CESP, Paris-Saclay University, Université de Versailles Saint-Quentin-en-Yvelines, Villejuif, France

Correspondence to Antoine Vieillard-Baron, Pr, Medical Intensive Care Unit, Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris, 9 Av. Charles de Gaulle, Boulogne-Billancourt 92100, France.
Tel: +33149095605; fax: +33 1 49 09 58 92;
e-mail: antoine.vieillard-baron@aphp.fr

[*]Adrien Joseph and Matthieu Petit contributed equally to this study.

Curr Opin Crit Care 2024, 30:10–19

DOI:10.1097/MCC.0000000000001124

KEY POINTS

- Application of PEEP modifies pleural and transpulmonary pressures, hence affecting pulmonary circulation and cardiac function.
- Excessive PEEP may alter organs perfusion and function, including the kidney, gut, liver and brain.
- The balance between alveolar recruitment and overinflation induced by PEEP mainly mediates the deleterious impact of PEEP on organ perfusion and function. It is predictable with difficulty and must be then reassessed frequently.

Positive end-expiratory pressure (PEEP) is required in the Berlin definition of ARDS [3], while its presence to define ARDS was recently extensively debated [6▪▪]. The quest for optimal PEEP settings has been a prominent goal in ARDS research for the last decades [7]. Indeed, application of PEEP leads to beneficial but also detrimental effects, mostly hemodynamic, and the benefit/risk balance is difficult to address as related to its level, the generated driving pressure and the severity of lung injury. In the recent ESICM guidelines, experts were unable to make a recommendation for or against the routine application of 'high' versus 'low' PEEP [6▪▪].

While the beneficial effects of PEEP have been described since the original description of ARDS [8], adverse effects are indeed numerous, among them circulatory failure is key as associated with a poor prognosis [9]. In a randomized controlled trial, the ART investigators reported that a (very) high PEEP strategy, along with recruitment maneuvers, increased mortality compared to a lower PEEP strategy [10]. Interestingly, 1 h after randomization, 34.8% of patients in the high PEEP group required commencement or increase of vasopressors or hypotension compared to 28% in the low PEEP group [10], and this increase did not seem to be temporally associated with recruitment maneuvers. This potential effect of PEEP on hemodynamics is especially of importance as many patients treated for ARDS have already a circulatory impairment. In a systematic review and meta-analysis on the impact of PEEP on outcome, more than 65% of patients with ARDS required vasopressors during their ICU stay [11].

PEEP is often proposed to maintain or restore oxygenation, and to prevent cyclic alveolar collapse and ventilator induced lung injury. If so, it could protect the heart and the hemodynamics. Katira *et al.* [12] nicely re-emphasized that a moderate tidal volume with zero PEEP (high driving pressure) induced acute lung injury in animals compared to the same tidal volume but application of PEEP (low driving pressure). What was remarkable in their study is that right ventricular failure was progressively observed in the former condition while not in the later [12].

This review will first examine the impact of PEEP on cardiac function with regards to heart-lung interactions, and second will describe its consequences on organ perfusion and function, including the kidney, gut, liver and the brain.

IMPACT OF POSITIVE END-EXPIRATORY PRESSURE ON CARDIAC FUNCTION

Anatomical and physiological considerations

Intrathoracic cardiopulmonary vascular system contains about 17% of the vascular volume, 9% being in the pulmonary circulation responsible to generate the left ventricular preload and stroke volume (SV) [13]. Then, every phenomenon that affects the amount of blood into the pulmonary circulation directly alters SV and hemodynamics.

Cardiac cavities (in the absence of pericardial effusion) and some great vessels such as superior vena cava or pulmonary arteries are directly submitted to pleural pressure (Ppl) while pulmonary capillaries are submitted to transpulmonary pressure (TPP), which is the distending pressure of the lungs. The pericardium is an acutely inextensible envelope around the heart, which means that every change in one ventricular volume will affect the other through the interventricular septum, a phenomenon called ventricular interdependence [14].

Tidal ventilation and application of PEEP increase airway pressures (Paw) and then modify Ppl and TPP, according to respiratory mechanics, resulting in blood volume alteration into the pulmonary circulation [15]. This is mainly mediated by changes in right ventricular preload, afterload and function. At the opposite, through its action on the left ventricle, PEEP may improve left ventricular function and SV in certain type of patients, providing no deleterious effect occurs on the right side.

Effect of positive end-expiratory pressure on the right ventricle

According to Guyton physiology, the systemic venous return (Qvr) can be written as follows: $Qrv = (Pms-Pra)/Rvr$ where Pms is the mean systemic filling pressure, Pra is the right atrial pressure and Rvr the resistance to venous return. In most cases, application of PEEP decreases the systemic venous return but does not always decrease right ventricular preload, especially in patients ventilated for ARDS. Briefly, it depends on respiratory mechanisms and

volemia. Augmentation of PEEP inducing a drop in right ventricular preload means that the right ventricle acts on the steep part of the Frank-Starling curve (preload dependent part). In this situation, Ppl is usually more affected than TPP by PEEP and hypovolemia is frequently present [16]. Qvr decreases either because Pra is simply increased by transmission of Ppl or because Rvr is increased due to an 'adaptive' phenomenon through baroreceptors on the chest [17] or due to collapse of the superior vena cava [18]. Lai *et al.* [19▪] recently reported in 66 patients ventilated with a high PEEP (66% of them for an ARDS) that PEEP reduction (12 to 7 cmH_2O) only induced an increase in cardiac output when patients were fluid-responsive (then the right ventricle working on the steep part of the Frank-Starling curve).

However, augmentation of PEEP may also decrease Qvr as a consequence of an increase in right ventricular preload. In this case, Pra is increased because PEEP induces an increase in right ventricular afterload with an obstruction of the right ventricular ejection [20] leading to dilatation of the right heart. When lung compliance is severely impaired [21] and pulmonary hyperinflation occurs [22], airway pressure is less transmitted to pleural pressure and TPP is more affected by augmentation of PEEP, a situation much more frequently observed in patients ventilated for an ARDS. Such patients are especially sensitive to this effect as ARDS is also a disease of the pulmonary circulation [23] and is associated with pulmonary hypertension [24]. When PEEP is increased, expected beneficial changes are the recruitment of nonventilated areas with a distribution of gas in the dependent region of the lung (mostly the posterior parts in supine position). However, when gas is more distributed in the nondependent areas (mostly the anterior parts in supine position), hyperinflation occurs in this area with compression of pulmonary capillaries by TPP and finally an increase in right ventricular afterload with hemodynamic compromise. Valta *et al.* [25] reported that at PEEP 12 cmH_2O, the percentage of lung recruitment only regarded 25% of the delta in functional residual capacity (FRC) induced by PEEP. We found similar results [26]. Using the pulmonary artery catheter, Jardin *et al.* [27] reported in ARDS the adverse effect of PEEP on right ventricular afterload and function at end-expiration during a PEEP trial from 0 to 15 cmH_2O. They found a progressive increase in right ventricular afterload with a progressive decrease in right ventricular SV [27]. More recently, we reported similar results using critical care echocardiography [28]. To summarize, this is the balance between recruitment and hyperinflation, the Yin and the Yang discussed by Rouby and Brochard [29], that determines the effect of PEEP on right ventricular function. PEEP can result in alveolar recruitment and when the Yin (recruitment) is predominant, increase in PEEP may even decrease right ventricular afterload and improve right ventricular function and hemodynamics. In this situation, PEEP also frequently decreases hypoxic pulmonary vasoconstriction. Figure 1 summarizes different situations where PEEP may unload or overload the right ventricle. It depends on the level of PEEP, the severity of the baby-lung and its potential restoration (how decreased and normalized is FRC), and the transpulmonary pressure generated by PEEP.

Effect of positive end-expiratory pressure on the left ventricle

On one side, it is expected that PEEP improves left ventricular function and SV by decreasing left ventricular afterload. By increasing ITP, PEEP increases the pressure around all the structure in the thorax, more than the one in the abdominal cavity, relative to atmospheric pressure creating a pressure gradient between the left ventricle (LV) and the aorta and the rest of systemic circulation, working at the atmosphere pressure. Thus, increased ITP decrease the transmural left ventricular pressure and the force necessary to eject blood into the circulation [30,31]. In the other side, left ventricular diastolic function can be altered by augmentation of PEEP [32]. This occurs when right ventricle (RV) is overloaded by PEEP as discussed above. In this case, augmentation in right ventricular size and pressure shifts the interventricular septum towards the left ventricle, impairing its filling [33].

CONSEQUENCES ON ORGAN PERFUSION AND FUNCTION

During the last decades, seminal studies have highlighted the complexity of the interorgan cross talk between the lungs, kidney and heart [34,35]. In this sense, PEEP participate in this cross talk through its hemodynamic, inflammatory and neurohormonal effects.

In the following sections, we will describe the effects of PEEP on the kidney, gut, liver and cerebral circulation, emphasizing the clinical impact of PEEP settings in the context of multiorgan failure (Fig. 2). As discussed above, the impact of PEEP depends on its respective effects on the lungs and then as a consequence on cardiac function and organ congestion being part of the definition of right ventricular failure [36]. However, impact of PEEP is at least unpredictable and should be regularly monitored.

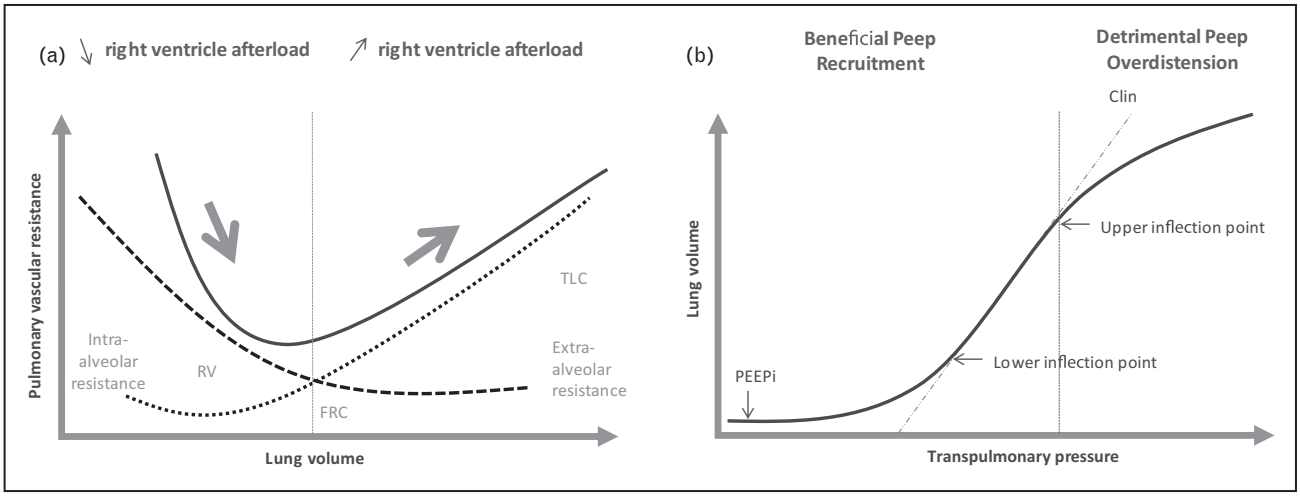

FIGURE 1. Differential hemodynamic effects of beneficial and detrimental positive end-expiratory pressure (PEEP). (a) Relationship between lung volume and pulmonary vascular resistance. As lung volume increases toward total lung capacity (TLC) or decreases toward residual volume (RV), pulmonary vascular resistance increases and impacts right ventricular afterload. Pulmonary vascular resistance increases with hyperinflation because of increased intraalveolar pulmonary arteries resistance, whereas it increases with lung collapse because of increased extraalveolar pulmonary arteries resistance. (b) Pressure volume curve showing the effects of PEEP, which becomes detrimental in the overdistension (right-hand) zone. Clin, compliance of the intermediate, linear segment of the pressure volume slope; FRC, functional residual capacity; Peepi, intrinsic PEEP; TPP, transpulmonary pressure.

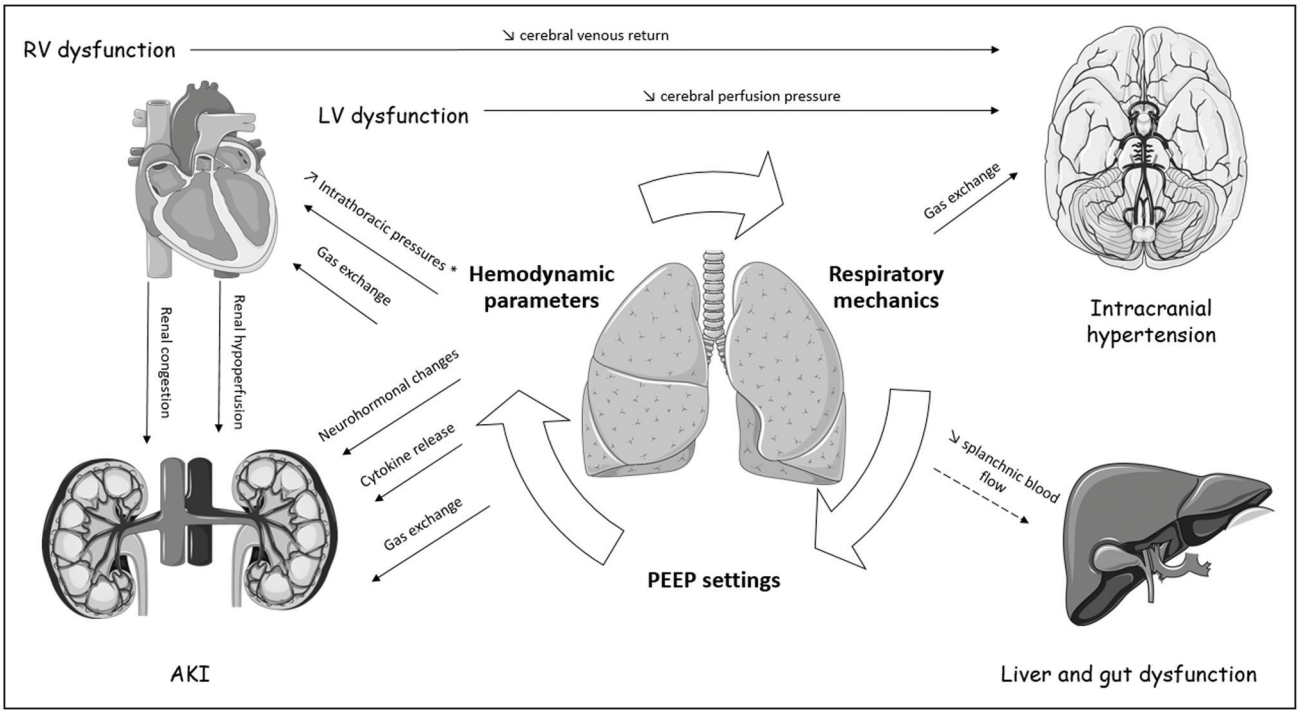

FIGURE 2. Impact of positive end-expiratory pressure on cardiac function and end-organs circulation Dotted lines represent associations with uncertain clinical significance. * Intrathoracic pressures refer to pleural and transpulmonary pressures. AKI, acute kidney injury; LV, left ventricle; RV, right ventricle.

Impact of positive end-expiratory pressure on renal hemodynamics and risk of acute kidney injury

Acute kidney injury (AKI) affects more than half of ICU patients and deeply impact prognosis [37]. On the one hand, AKI patients are twice as likely to require invasive mechanical ventilation [35–38], but on the other hand, patients under mechanical ventilation also face a threefold increase in the risk of kidney injury [39,40].

Acute respiratory failure in itself is associated with an increased risk of developing AKI [41,42], and in addition, application of mechanical ventilation has long been suspected to participate in worsening renal function [30,43], prompting authors to coin the term *ventilator-induced kidney injury* [25]. The mechanisms by which mechanical ventilation contributes to AKI are multifactorial and implicate the release of inflammatory mediators as a result of biotrauma [42,44–48], decrease in renal blood flow secondary to hypercapnia [49–52], hemodynamic and neurohormonal processes [35] related to elevation of intrathoracic pressure and renal toxicity of concomitant medication (e.g. inhaled nitric oxide [53,54]).

From a mechanistic point of view and as described above, application of PEEP may increase Pra. As Pra, also referred to as central venous pressure (CVP), acts as the outflow pressure of renal blood flow, elevated CVP results in increased renal venous pressure, also called *renal congestion*. Renal venous hypertension reverberates on increased efferent pressures, increased intraglomerular hydrostatic pressure, and reduced net filtration pressure, ultimately leading to glomerular capillaries collapse [55]. Venous congestion, rather than impairment of cardiac output, is considered to be the main driver for kidney injury during decompensated heart failure [56], while the key actor in patients with shock is probably the mean perfusion pressure (mean arterial pressure minus CVP) [57]. Similarly, CVP has been consistently associated with an increased risk of AKI in ICU patients [58]. More specifically, in patients undergoing mechanical ventilation, a recent study found a synergistic detrimental effect of CVP and PEEP levels on worsening kidney function [59]. Additionally, PEEP-induced right ventricular dysfunction can result in elevated abdominal pressure, which can also alter kidney function [60,61]. Reduced left ventricular preload and cardiac output as adverse effects of alveolar overdistension can jeopardize renal blood flow [34], even though this mechanism probably contributes less to PEEP-induced renal dysfunction [56].

PEEP-induced neuro-hormonal alterations can also cause fluid retention. The sympathetic nervous system, renin angiotensin aldosterone system and antidiuretic hormone are stimulated after application of PEEP [62]. Interestingly, in kidney transplant recipients, renal denervation does not seem to mitigate the effect of PEEP, suggesting that this effect is perfusion pressure-dependent rather than hormone-induced [63].

Apart from renal congestion, injurious mechanical ventilation with high tidal volume and low PEEP has been shown to induce systemic inflammation in the context of ARDS, with the release of IL-1B, IL-6, IL-8 TNF-alpha, MCP-1 and VEGF, leading to epithelial cell apoptosis [64,65]. On the contrary, lung protective ventilation with PEEP based on the pressure-volume curve is associated with lower concentrations of inflammatory markers in plasma and bronchoalveolar lavage [66,67], even though these findings have not been replicated in the ALVEOLI trial [68]. Interestingly, preclinical data and dosage from patients' serum suggest that the Fas-Fas ligand system, implicated in the regulation of cell death and immune tolerance, is involved in renal tubular epithelial cell apoptosis, highlighting a therapeutic potential for blockade of this pathway in ARDS-induced kidney and multiorgan dysfunction [65].

To sum up, the effects of PEEP on kidney hemodynamics and function are not straightforward. an interplay between effect of PEEP on lung mechanics, cardiac function, CVP and fluid status more likely influence the risk of AKI during mechanical ventilation [59,69]. Whether a given ventilation strategy would potentially protect the kidney without sacrificing the support of the respiratory system deserves further investigations.

Impact of positive end-expiratory pressure on gastrointestinal and liver circulation

Similar to AKI, the deleterious effects of inadequate PEEP levels on pulmonary mechanics can translate into increased venous pressure that reverberates on gastrointestinal and liver hemodynamics. Since the splanchnic perfusion is particularly sensitive and a small reduction in perfusion can compromise its barrier function, decreased mesenteric and portal blood flows have been suspected to precipitate the progression to multiorgan dysfunction in patients with ARDS [70,71].

In another model than ARDS, for example decompensated advanced heart failure, Nikolaou *et al*. [72] suggested that congestion induces bile duct congestion and then increase of alkaline phosphatase, while liver ischemia induces centrolobular cell necrosis and then rather augmentation of transaminases. Early liver dysfunction, as reflected by increased serum bilirubin levels in the initial phase of ARDS, is seen in approximately 15–20% of

patients and is strongly associated with the 90-day mortality rate [73,74]. Although lung-liver interactions have been extensively studied, mostly with respect to the regulation of inflammation and repair mechanisms [75], sound data on the impact of ventilator parameters on the development of gastrointestinal and liver failure are currently lacking. Experimental models from the 1980 to 1990s showed an inverse relation between PEEP levels and splanchnic blood flow, mainly driven by a reduction in cardiac output, while splanchnic oxygen consumption is usually maintained by compensatory increase in oxygen extraction [76,77]. On the other hand, increased rates of epithelial cell apoptosis were also noted in the small intestine villi in animals subject to injurious mechanical ventilation with high tidal volumes (15–17 ml/kg) and low PEEP (0–3 cmH_2O) [65].

In humans, several small studies did not show any alteration in gastric mucosal perfusion [78] or splanchnic blood flow using continuous infusion of indocyanine green dye [79] in response to PEEP increase, but due to the lack of recent data with contemporary ventilatory management of ARDS, it is difficult to draw conclusions about the clinical significance of these findings, and the role of PEEP in gastrointestinal and liver failure in ARDS patients remains to be determined.

The Venous Excess Ultrasound Grading System (VExUS) score, a four-step ultrasound protocol evaluating the inferior vena cava, renal vein, but also the hepatic and portal vein by Doppler, has been proposed as a means to measure venous congestion [80]. It correlates with Pra [81] and can predict acute renal injury after cardiopulmonary bypass [82]; however, its clinical significance in the context of ventilation and PEEP-induced venous congestion and liver injury remains to be evaluated.

Outside the context of ARDS, application of different levels of PEEP during liver transplantation does not seem to affect liver hemodynamics and function, despite increased CVP [83–85].

Impact of positive end-expiratory pressure on cerebral circulation

Mechanical ventilation is a mainstay in the management of patients with neurological failure. Furthermore, acute lung injury is the most common extracranial complication in patients with acute brain injury, affecting as much as 35% of patients [86]. Although the impact of $paCO_2$ on intracranial pressure (ICP) is well documented and accounted for, the impact of ventilator settings and PEEP on cerebral hemodynamics is less appreciated [87].

PEEP can affect ICP through distinct mechanisms. First, modifications in $paCO_2$ related to lung recruitment/overdistention can modulate arterial inflow. Then, increased intrathoracic and jugular pressures impedes cerebral venous return. Greater inflow or less blood outflow will ultimately lead to raised ICP once the capacity to displace cerebrospinal fluid is exceeded. Lastly, in cases where PEEP levels impair cardiac output, lower cerebral perfusion pressure beyond cerebral autoregulatory mechanisms will thereby decrease ICP. In case of impaired cerebral autoregulation, a linear relationship exists between mean arterial pressure and cerebral perfusion pressure and any impact of PEEP on cardiac output will translate into changes in cerebral perfusion pressure, potentially compromising brain perfusion.

Unsurprisingly, application of moderate levels of PEEP in patients undergoing extracranial surgery (uninjured brains) does not seem to affect ICP [88,89]. On the contrary, raising PEEP levels will translate into increased ICP in neurosurgical intensive care patients, not always clinically relevant and not systematically followed by decreased cerebral perfusion pressure [90–94]. In a recent monocentric study, PEEP increments increased ICP in 58% and brain tissue oxygenation ($PbtO_2$) in 21% of patients, but these changes were largely unpredictable and no correlation was found between ΔPEEP and $\Delta PbtO_2$ or ΔICP [95▪].

Rather than initial compliance of the respiratory system, alveolar recruitment and changes in respiratory compliance after application of PEEP is associated with changes in ICP, highlighting the importance of optimal PEEP titration and integration of respiratory mechanics in the prediction of the hemodynamic effects of PEEP on distant organs [91,95▪,96,97]. Some authors proposed P_{IC}Gap, representing the gap between baseline intracranial and CVP, as a potential predictor of ICP responsiveness to PEEP adjustments [98]. This comes back to the idea that PEEP by itself is not beneficious nor detrimental on end-organ hemodynamics, but its effects depends on respiratory mechanics and association with other hemodynamic variables such as CVP [59].

Based on these considerations, applying a lung protective ventilation strategy in brain-injured patients with ARDS should not be discouraged, and optimal PEEP level should be determined using conventional respiratory and hemodynamic parameters as well as monitoring of ICP [93,99,100▪]. Therefore, a ventilation strategy taking account of the cerebral consequences of PEEP (and other respiratory parameters) has a most prominent place in neurosurgical patients with prior or at risk of intracranial hypertension. Otherwise, the cerebral consequences of PEEP in the context of ARDS without neurological failure is less likely to be clinically significant.

HEMODYNAMIC IMPACT OF POSITIVE END-EXPIRATORY PRESSURE IN RANDOMIZED CONTROLLED TRIALS

The most reliable evidence of the impact of PEEP on cardiac output and end-organs function is expected to come from randomized controlled trials which, throughout the history of ARDS, strived to determine the best PEEP settings [7]. This is summarized in Table 1.

Interpretation of these results are made difficult by concurrent interventions on tidal volumes, ventilator strategies and recruitment maneuvers, as well as exclusion of patients with acute brain injury/elevated ICP or chronic liver disease. Moreover, impact on brain, gut and liver function are seldom reported. However, higher PEEP levels combined with lung recruitment maneuvers seem to be associated with a harmful cardiovascular impact [2,3], whereas PEEP titration based on respiratory mechanics seems to be associated with increases in cardiac output and hemodynamic stability [101–103].

CONCLUSION

Ideal PEEP settings should aim to a balance between its capability to re-open the collapsed lung and the

Table 1. Impact of positive end-expiratory pressure on cardiac, kidney, gut, liver and central nervous system circulations in the main randomized controlled trials with different PEEP settings

	PEEP settings	Effect on blood pressure/cardiac output	Effect on kidney function	Effect on gut and liver functions	Effect on central nervous system
Amato, NEJM. 1998 [112]	9.3 ± 0.5 versus 13.2 ± 0.4 cmH_2O (with protective ventilation strategy)	NA	RRT: 5 (21%) versus 7 (24%) patients, $P > 0.10$	One death from diffuse gastrointestinal bleeding in the protective ventilation group	NA
ARDS Net, NEJM. 2000 [67]	8.6 ± 3.6 versus 9.4 ± 3.6 cmH_2O (with lower tidal volumes)	Days without circulatory failure: 19 ± 10 versus 17 ± 11 days, $P = 0.004$	Days without renal failure 20 ± 11 versus 18 ± 11 days, $P = 0.005$	NA	NA
Ranieri, JAMA. 2000 [113]	6.5 ± 1.7 versus 14.8 ± 2.7 cmH_2O	Cardiovascular failure: 8 (36%) versus 3 (14%)	AKI: 19 (86%) versus 4 (18%), $P = 0.04$	5 (23%) versus 1 (5%) liver dysfunction	Neurological failure: 4 (18%) versus 0 (0%)
Brower, NEJM. 2004 (ALVEOLI) [68]	8.3 ± 3.2 versus 13.2 ± 3.5 cmH_2O	No significant differences in the number of days without circulatory, hepatic, or renal failure	NA		
Villar, CCM. 2006 [102]	9.0 ± 2.7 versus 14.1 ± 2.8 cmH_2O (PEEP above the lower inflection point of the pressure volume curve of the respiratory system)	Cardiovascular failure: 28 (62%) versus 9 (18%), $P < 0.001$ Cardiac index 4.7 ± 1.4 versus 5.8 ± 1.5 l/min/m^2, $P < 0.05$	18 (40%) versus 21 (42%)	Liver failure 8 (17.8%) versus 4 (8%) Gastrointestinal failure 8 (17.8%) versus 8 (16%)	8 (18%) versus 5 (10%)
Manzano, CCM. 2008 [114]	0.12 ± 0.7 versus 5.78 ± 1.0 cmH_2O	NA	RRT: 3 (5%) versus 1 (2%)	NA	NA
Mercat, JAMA. 2008 (EXPRESS) [103]	7.1 ± 1.8 versus 14.6 ± 3.2 cmH_2O	Cardiovascular failure–free days: 21 (4–26) versus 23 (10–26) days, $P = 0.09$	Renal-failure free days: 27.5 (8.0–28.0) versus 28.0 (11.0–28.0) days, $P = 0.23$	NA	NA
Talmor, NEJM. 2008 [109]	10 ± 4 versus 17 ± 6 cmH_2O (guided by esophageal pressure)	Shock-free days: 17 (0–21) versus 14 (0–21) days, $P = 0.47$	NA	NA	NA
Meade, JAMA. 2008 (LOVS) [106]	10.1 ± 3.0 versus 15.6 ± 3.9 cmH_2O	Days of vasopressor: 5 (2–9) versus 4 (2–8) days	RRT: 85 (19%) versus 71 (17%)	NA	NA
Pintado, ERJ. 2013 [104]	10 ± 3 versus 12 ± 2 cmH_2O (compliance-guided)	Hemodynamic failure-free days at day 28: 16 (0–23.75) versus 22 (0–25) days, $P = 0.04$	Renal-failure-free days at 28 days: 28 (0–28) versus 28 (0–28), $P = 0.39$	Hepatic-failure-free days at 28 days 28 (0–28) versus 28 (0–28) $P = 0.08$	NA
Kacmarek, CCM. 2016 [105]	11.6 ± 2.5 versus 15.8 ± 3.8 cmH_2O	Cardiac failure as the primary cause of death 1 (3%) versus 1 (4%) Multiple organ failure as the primary cause of death 10 (33%) versus 4 (16%)	NA	NA	NA
Cavalcanti, JAMA. 2017 (ART) [10]	12.0 ± 0.6 versus 16.2 ± 0.7 cmH_2O (+ lung recruitment maneuver)	Hypotension 144 (28%) versus 174 (35%), $P = 0.03$	NA	NA	NA
Hodgson, AJRCCM. 2019 (PHARLAP) [101]	11.7 ± 3.0 versus 16.1 ± 3.6 cmH_2O (with staircase recruitment maneuver)	Severe hypotension 12 (21%) versus 20 (35%), $P = 0.12$	NA	NA	NA
Beitler, JAMA. 2019 [111]	16 ± 4 versus 17 ± 6 cmH_2O (guided by esophageal pressure)	NA	RRT: 21 (21%) versus 32 (33%), $P = 0.056$	NA	NA

Effects related to PEEP (reported as low versus high PEEP) are difficult to analyze, as modification in PEEP is usually integrated in a more global ventilator strategy.

risk of overdistension in already open alveoli. In this narrative review, we describe the pathophysiological effects of PEEP on cardiac function and on end-organs circulation, emphasizing the duality of the hemodynamic impact of PEEP depending on both respiratory mechanics and association with other hemodynamic variables such as CVP or mean arterial pressure. There are parallels in the means of preventing deleterious impact of PEEP on the lungs, heart, kidney, liver and brain. Whether PEEP titration should be based on respiratory system compliance [102,104], oxygenation [68,105], pressure-volume curve [106,107] or transpulmonary pressure [108–110] remains intensely debated [6▪▪]. In our opinion, a PEEP setting protocol should also take into account the hemodynamic effects of PEEP. Monitoring of cardiac output, right ventricular function and intrathoracic pressures are a cornerstone in the treatment of ARDS and a first step in the prevention of the pitfalls of PEEP on end-organ hemodynamics [6▪▪]. Intensive care physicians should maintain a high degree of vigilance towards hemodynamic effects of PEEP.

Acknowledgements

None.

Financial support and sponsorship

No financial support was obtained for this work.

Conflicts of interest

A.V.B. reports having received personal fees from Air liquid from clinical research, outside of the submitted work. The remaining authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967; 2:319–323.
2. Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824.
3. ARDS Definition Task Force. Ranieri VM, Rubenfeld GD, Thompson BT, *et al.* Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307:2526–2533.
4. Matthay MA, Arabi Y, Arroliga AC, *et al.* A new global definition of acute respiratory distress syndrome. Am J Respir Crit Care Med 2023; doi: 10.1164/rccm.202303-0558WS. [Online ahead of print]
5. Pham T, Rubenfeld GD. Fifty years of research in ARDS. The epidemiology of acute respiratory distress syndrome. A 50th birthday review. Am J Respir Crit Care Med 2017; 195:860–870.
6. ▪▪ Grasselli G, Calfee CS, Camporota L, *et al.* ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 2023; 49:727–759.

ESICM guidelines summarize current knowledge about the pathophysiology of ARDS, propose a new definition and treatment recommendations. In these guidelines, experts were unable to make a recommendation for or against the routine application of 'high' versus 'low' PEEP.

7. Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ARDS. Setting positive end-expiratory pressure in acute respiratory distress syndrome. Am J Respir Crit Care Med 2017; 195:1429–1438.
8. Ashbaugh DG, Petty TL, Bigelow DB, Harris TM. Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. J Thorac Cardiovasc Surg 1969; 57:31–41.
9. Vieillard-Baron A, Matthay M, Teboul JL, *et al.* Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. Intensive Care Med 2016; 42:739–749.
10. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, *et al.* Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017; 318:1335–1345.
11. 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; 303:865–873.
12. Katira BH, Giesinger RE, Engelberts D, *et al.* Adverse heart-lung interactions in ventilator-induced lung injury. Am J Respir Crit Care Med 2017; 196:1411–1421.
13. Milnor WR, Jose AD, Mcgaff CJ. Pulmonary vascular volume, resistance, and compliance in man. Circulation 1960; 22:130–137.
14. Petit M, Vieillard-Baron A. Ventricular interdependence in critically ill patients: from physiology to bedside. Front Physiol 2023; 14:1232340.
15. Vieillard-Baron A, Jardin F. Right level of positive end-expiratory pressure in acute respiratory distress syndrome. Am J Respir Crit Care Med 2003; 167:1576–1577.
16. Puybasset L, Gusman P, Muller JC, *et al.* Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome. Intensive Care Med 2000; 26:1215–1227.
17. Nanas S, Magder S. Adaptations of the peripheral circulation to PEEP. Am Rev Respir Dis 1992; 146:688–693.
18. Jardin F, Vieillard-Baron A. Ultrasonographic examination of the venae cavae. Intensive Care Med 2006; 32:203–206.
19. ▪ Lai C, Shi R, Beurton A, *et al.* The increase in cardiac output induced by a decrease in positive end-expiratory pressure reliably detects volume responsiveness: the PEEP-test study. Crit Care 2023; 27:136.

In this study, a PEEP decrease is used to predict fluid responsiveness. The use of PEEP variations to evaluate fluid responsiveness is an interesting application of the hemodynamic effects of PEEP described in the review.

20. Scharf SM, Caldini P, Ingram RH. Cardiovascular effects of increasing airway pressure in the dog. Am J Physiol 1977; 232:H35–H43.
21. Jardin F, Genevray B, Brun-Ney D, Bourdarias JP. Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. Chest 1985; 88:653–658.
22. Gattinoni L, Caironi P, Cressoni M, *et al.* Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354:1775–1786.
23. Price LC, McAuley DF, Marino PS, *et al.* Pathophysiology of pulmonary hypertension in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2012; 302:L803–L815.
24. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977; 296:476–480.
25. Valta P, Takala J, Eissa NT, Milic-Emili J. Does alveolar recruitment occur with positive end-expiratory pressure in adult respiratory distress syndrome patients? J Crit Care 1993; 8:34–42.
26. Vieillard-Baron A, Prin S, Chergui K, *et al.* Early patterns of static pressure-volume loops in ARDS and their relations with PEEP-induced recruitment. Intensive Care Med 2003; 29:1929–1935.
27. Jardin F, Brun-Ney D, Cazaux P, *et al.* Relation between transpulmonary pressure and right ventricular isovolumetric pressure change during respiratory support. Cathet Cardiovasc Diagn 1989; 16:215–220.
28. Mekontso Dessap A, Charron C, Devaquet J, *et al.* Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive Care Med 2009; 35:1850–1858.
29. Rouby JJ, Brochard L. Tidal recruitment and overinflation in acute respiratory distress syndrome: yin and yang. Am J Respir Crit Care Med 2007; 175:104–106.
30. Fessler HE, Brower RG, Wise RA, Permutt S. Effects of systolic and diastolic positive pleural pressure pulses with altered cardiac contractility. J Appl Physiol 1992; 73:498–505.
31. Pinsky MR, Summer WR, Wise RA, *et al.* Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol Respir Environ Exerc Physiol 1983; 54:950–955.
32. Scharf SM, Brown R, Saunders N, *et al.* Changes in canine left ventricular size and configuration with positive end-expiratory pressure. Circ Res 1979; 44:672–678.
33. Jardin F, Farcot JC, Boisante L, *et al.* Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981; 304:387–392.

34. Husain-Syed F, McCullough PA, Birk HW, *et al.* Cardio-pulmonary-renal interactions: a multidisciplinary approach. J Am Coll Cardiol 2015; 65:2433–2448.
35. Joannidis M, Forni LG, Klein SJ, *et al.* Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. Intensive Care Med 2020; 46:654–672.
36. Vieillard-Baron A, Naeije R, Haddad F, *et al.* Diagnostic workup, etiologies and management of acute right ventricle failure: a state-of-the-art paper. Intensive Care Med 2018; 44:774–790.
37. Hoste EAJ, Bagshaw SM, Bellomo R, *et al.* Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41:1411–1423.
38. Ostermann M, Chang RWS. Impact of different types of organ failure on outcome in intensive care unit patients with acute kidney injury. J Crit Care 2011; 26:635.e1–635.e10.
39. Darmon M, Clec'h C, Adrie C, *et al.* Acute respiratory distress syndrome and risk of AKI among critically ill patients. Clin J Am Soc Nephrol 2014; 9:1347–1353.
40. van den Akker JPC, Egal M, Groeneveld ABJ. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. Crit Care 2013; 17:R98.
41. Barakat MF, McDonald HI, Collier TJ, *et al.* Acute kidney injury in stable COPD and at exacerbation. Int J Chron Obstruct Pulmon Dis 2015; 10:2067–2077.
42. Murugan R, Karajala-Subramanyam V, Lee M, *et al.* Acute kidney injury in nonsevere pneumonia is associated with an increased immune response and lower survival. Kidney Int 2010; 77:527–535.
43. Hirsch JS, Ng JH, Ross DW, *et al.* Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020; 98:209-218
44. Koyner JL, Murray PT. Mechanical ventilation and lung-kidney interactions. Clin J Am Soc Nephrol 2008; 3:562–570.
45. Fontanarosa PB, Ranieri VM, Giunta F, *et al.* Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–44.
46. Kuiper JW, Vaschetto R, Della Corte F, *et al.* Bench-to-bedside review: ventilation-induced renal injury through systemic mediator release–just theory or a causal relationship? Crit Care 2011; 15:228.
47. Liu KD, Glidden DV, Eisner MD, *et al.* Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. Crit Care Med 2007; 35:2755–2761.
48. Pickkers P, Darmon M, Hoste E, *et al.* Acute kidney injury in the critically ill: an updated review on pathophysiology and management. Intensive Care Med 2021; 47:835–850.
49. Sharkey RA, Mulloy EM, O'Neill SJ. The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. Chest 1999; 115:1588–1592.
50. Anand IS, Chandrashekhar Y, Ferrari R, *et al.* Pathogenesis of congestive state in chronic obstructive pulmonary disease. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. Circulation 1992; 86:12–21.
51. Hemlin M, Ljungman S, Carlson J, *et al.* The effects of hypoxia and hypercapnia on renal and heart function, haemodynamics and plasma hormone levels in stable COPD patients. Clin Respir J 2007; 1:80–90.
52. Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. Chest 2018; 154:185–195.
53. Sy R, Hy W, Hh L, *et al.* Inhaled nitric oxide and the risk of renal dysfunction in patients with acute respiratory distress syndrome: a propensity-matched cohort study. Crit Care 2016; 20:389.
54. Ruan SY, Huang TM, Wu HY, *et al.* Inhaled nitric oxide therapy and risk of renal dysfunction: a systematic review and meta-analysis of randomized trials. Crit Care 2015; 19:137.
55. Valenza F, Sibilla S, Porro GA, *et al.* An improved in vivo rat model for the study of mechanical ventilatory support effects on organs distal to the lung. Crit Care Med 2000; 28:3697–3704.
56. Mullens W, Abrahams Z, Francis GS, *et al.* Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009; 53:589–596.
57. Panwar R, Tarvade S, Lanyon N, *et al.* Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock. A multicenter, prospective cohort study. Am J Respir Crit Care Med 2020; 202:1407–1418.
58. Chen KP, Cavender S, Lee J, *et al.* Peripheral edema, central venous pressure, and risk of AKI in critical illness. Clin J Am Soc Nephrol 2016; 11:602–608.
59. Geri G, Ferrer L, Tran N, *et al.* Cardio-pulmonary-renal interactions in ICU patients. Role of mechanical ventilation, venous congestion and perfusion deficit on worsening of renal function: insights from the MIMIC-III database. J Crit Care 2021; 64:100–107.
60. Mullens W, Abrahams Z, Skouri HN, *et al.* Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 2008; 51:300–306.
61. Rogers WK, Garcia L. Intraabdominal hypertension, abdominal compartment syndrome, and the open abdomen. Chest 2018; 153:238–250.
62. Annat G, Viale JP, Bui Xuan B, *et al.* Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 1983; 58:136–141.
63. Jacob LP, Chazalet JJ, Payen DM, *et al.* Renal hemodynamic and functional effect of PEEP ventilation in human renal transplantations. Am J Respir Crit Care Med 1995; 152:103–107.
64. Gurkan OU, O'Donnell C, Brower R, *et al.* Differential effects of mechanical ventilatory strategy on lung injury and systemic organ inflammation in mice. Am J Physiol Lung Cell Mol Physiol 2003; 285:L710–718.
65. Imai Y, Parodo J, Kajikawa O, *et al.* Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 2003; 289:2104–2112.
66. 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; 282:54–61.
67. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, *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; 342:1301–1308.
68. Brower RG, Lanken PN, MacIntyre N, *et al.* Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351:327–336.
69. Rocha NN, Samary CS, Antunes MA, *et al.* The impact of fluid status and decremental PEEP strategy on cardiac function and lung and kidney damage in mild-moderate experimental acute respiratory distress syndrome. Respir Res 2021; 22:214.
70. Putensen C, Wrigge H, Hering R. The effects of mechanical ventilation on the gut and abdomen. Curr Opin Crit Care 2006; 12:160–165.
71. Dorinsky PM, Gadek JE. Mechanisms of multiple nonpulmonary organ failure in ARDS. Chest 1989; 96:885–892.
72. Nikolaou M, Parissis J, Yilmaz MB, *et al.* Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. Eur Heart J 2013; 34:742–749.
73. Dizier S, Forel JM, Ayzac L, *et al.* Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: a post-hoc analysis of the ACURASYS and PROSEVA studies. PLoS One 2015; 10:e0144278.
74. Schwartz DB, Bone RC, Balk RA, Szidon JP. Hepatic dysfunction in the adult respiratory distress syndrome. Chest 1989; 95:871–875.
75. Herrero R, Sánchez G, Asensio I, *et al.* Liver-lung interactions in acute respiratory distress syndrome. Intensive Care Med Exp 2020; 8(Suppl 1):48.
76. Matuschak GM, Pinsky MR, Rogers RM. Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 1987; 62:1377–1383.
77. Johnson DJ, Johannigman JA, Branson RD, *et al.* The effect of low dose dopamine on gut hemodynamics during PEEP ventilation for acute lung injury. J Surg Res 1991; 50:344–349.
78. Bruhn A, Hernandez G, Bugedo G, Castillo L. Effects of positive end-expiratory pressure on gastric mucosal perfusion in acute respiratory distress syndrome. Crit Care 2004; 8:R306–311.
79. Kiefer P, Nunes S, Kosonen P, Takala J. Effect of positive end-expiratory pressure on splanchnic perfusion in acute lung injury. Intensive Care Med 2000; 26:376–383.
80. Jury D, Shaw AD. Utility of bedside ultrasound derived hepatic and renal parenchymal flow patterns to guide management of acute kidney injury. Curr Opin Crit Care 2021; 27:587–592.
81. Longino A, Martin K, Leyba K, *et al.* Correlation between the VExUS score and right atrial pressure: a pilot prospective observational study. Crit Care 2023; 27:205.
82. Beaubien-Souligny W, Benkreira A, Robillard P, *et al.* Alterations in portal vein flow and intrarenal venous flow are associated with acute kidney injury after cardiac surgery: a prospective observational cohort study. J Am Heart Assoc 2018; 7:e009961.
83. Krenn CG, Krafft P, Schaefer B, *et al.* Effects of positive end-expiratory pressure on hemodynamics and indocyanine green kinetics in patients after orthotopic liver transplantation. Crit Care Med 2000; 28:1760–1765.
84. Saner FH, Pavlakovic G, Gu Y, *et al.* Effects of positive end-expiratory pressure on systemic haemodynamics, with special interest to central venous and common iliac venous pressure in liver transplanted patients. Eur J Anaesthesiol 2006; 23:766–771.
85. Bıcakcıoglu M, Aydogan MS, Sayan H, *et al.* Effects of different positive end-expiratory pressure values on liver function and indocyanine green clearance test in liver transplantation donors: a prospective, randomized, double-blind study. Transplant Proc 2015; 47:1190–1193.
86. Hoesch RE, Lin E, Young M, *et al.* Acute lung injury in critical neurological illness. Crit Care Med 2012; 40:587–593.
87. Chen H, Menon DK, Kavanagh BP. Impact of altered airway pressure on intracranial pressure, perfusion, and oxygenation: a narrative review. Crit Care Med 2019; 47:254–263.
88. Chin JH, Kim WJ, Lee J, *et al.* Effect of positive end-expiratory pressure on the sonographic optic nerve sheath diameter as a surrogate for intracranial pressure during robot-assisted laparoscopic prostatectomy: a randomized controlled trial. PLoS One 2017; 12:e0170369.

89. Robba C, Bragazzi NL, Bertuccio A, *et al.* Effects of prone position and positive end-expiratory pressure on noninvasive estimators of ICP: a pilot study. J Neurosurg Anesthesiol 2017; 29:243–250.

90. McGuire G, Crossley D, Richards J, Wong D. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. Crit Care Med 1997; 25:1059–1062.

91. Robba C, Ball L, Nogas S, *et al.* Effects of positive end-expiratory pressure on lung recruitment, respiratory mechanics, and intracranial pressure in mechanically ventilated brain-injured patients. Front Physiol 2021; 12:711273.

92. Apuzzo JL, Wiess MH, Petersons V, *et al.* Effect of positive end expiratory pressure ventilation on intracranial pressure in man. J Neurosurg 1977; 46:227–232.

93. Boone MD, Jinadasa SP, Mueller A, *et al.* The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. Neurocrit Care 2017; 26:174–181.

94. Zhang XY, Yang ZJ, Wang QX, Fan HR. Impact of positive end-expiratory pressure on cerebral injury patients with hypoxemia. Am J Emerg Med 2011; 29:699–703.

95. ■ Gouvea Bogossian E, Cantos J, Farinella A, *et al.* The effect of increased positive end expiratory pressure on brain tissue oxygenation and intracranial pressure in acute brain injury patients. Sci Rep 2023; 13:16657.

In this monocentric study, the authors did not find any correlation between increments of PEEP and variations in brain tissue oxygenation or intracranial pressure. Half of the patients have increased intracranial pressure after PEEP increment and 21% improved their brain tissue oxygenation. Low baseline brain tissue oxygenation was the only factor associated with a significant increase in brain oxygenation after PEEP increase.

96. Robba C, Ball L, Battaglini D, *et al.* Effects of positive end-expiratory pressure on lung ultrasound patterns and their correlation with intracranial pressure in mechanically ventilated brain injured patients. Crit Care 2022; 26:31.

97. Mascia L, Grasso S, Fiore T, *et al.* Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. Intensive Care Med 2005; 31:373–379.

98. Caricato A, Conti G, Della Corte F, *et al.* Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. J Trauma 2005; 58:571–576.

99. Li HP, Lin YN, Cheng ZH, *et al.* Intracranial-to-central venous pressure gap predicts the responsiveness of intracranial pressure to PEEP in patients with traumatic brain injury: a prospective cohort study. BMC Neurol 2020; 20:234.

100. ■ Beqiri E, Smielewski P, Guérin C, *et al.* Neurological and respiratory effects of lung protective ventilation in acute brain injury patients without lung injury: brain vent, a single centre randomized interventional study. Crit Care 2023; 27:115.

This randomized study shows that most patients with acute brain injury do not experience any cerebral adverse effect of lung protective ventilation with high PEEP, assuming that adequate monitoring is performed.

101. Hodgson CL, Cooper DJ, Arabi Y, *et al.* Maximal recruitment open lung ventilation in acute respiratory distress syndrome (PHARLAP). A phase II, multicenter randomized controlled clinical trial. Am J Respir Crit Care Med 2019; 200:1363–1372.

102. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 2006; 34:1311–1318.

103. Mercat A, Richard JCM, Vielle B, *et al.* Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299:646–655.

104. Pintado MC, de Pablo R, Trascasa M, *et al.* Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. Respir Care 2013; 58:1416–1423.

105. Kacmarek RM, Villar J, Sulemanji D, *et al.* Open lung approach for the acute respiratory distress syndrome: a pilot, randomized controlled trial. Crit Care Med 2016; 44:32–42.

106. Meade MO, Cook DJ, Guyatt GH, *et al.* Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299:637–645.

107. Mergoni M, Volpi A, Bricchi C, Rossi A. Lower inflection point and recruitment with PEEP in ventilated patients with acute respiratory failure. J Appl Physiol 2001; 91:441–450.

108. Albaiceta GM, Luyando LH, Parra D, *et al.* Inspiratory vs. expiratory pressure-volume curves to set end-expiratory pressure in acute lung injury. Intensive Care Med 2005; 31:1370–1378.

109. Grieco DL, Chen L, Brochard L. Transpulmonary pressure: importance and limits. Ann Transl Med 2017; 5:285–1285.

110. Talmor D, Sarge T, Malhotra A, *et al.* Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359:2095–2104.

111. Beitler JR, Sarge T, Banner-Goodspeed VM, *et al.* Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory Distress syndrome: a randomized clinical trial. JAMA 2019; 321:846–857.

112. Amato MB, Barbas CS, Medeiros DM, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347–354.

113. Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–44.

114. Manzano F, Fernández-Mondéjar E, Colmenero M, *et al.* Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med 2008; 36:2225–2231.