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Experimental

Also this year ICM published a number of interesting experimental articles, in large part focussed on mechanical ventilation, ARDS and sepsis.

Mechanical ventilation

Ventilator-induced lung injury (VILI) is associated with inadequate inflammatory responses that lead to distal organ dysfunction. A variety of risk factors have been suggested to be involved in the pathogenesis of VILI in acute respiratory distress syndrome (ARDS), and it is noted that the mortality rate decreased in some younger but not other patients with ARDS. To test the hypothesis that aging increases the susceptibility to VILI and organ dysfunction, Dr. Esteban's group [1] conducted a study to mechanically ventilate young and old rats for an hour with a low or high tidal volume. They demonstrated that the high volume ventilatory strategy induced significantly greater systemic hypotension, cytokine production, distal organ dysfunction, and depressed vascular responses to catecholamines in the older than in the younger rats. The authors suggested that elderly subjects appear to be more prone to develop VILI and distal organ dysfunction compared to younger subjects. This interesting article was accompanied by an Editorial [2] to highlight the importance of the observation. Furthermore, the same group of investigators [3] demonstrated in the younger rats that the inflammatory responses and distal organ dysfunction induced by a short period (1 h) of high volume mechanical ventilation were reversible by 24–72 h in the surviving animals. This study suggests an important impact of the length of mechanical ventilation on the recovery of organ function, and multiple time points of a similar study are warranted.

A number of studies have examined a variety of therapeutic approaches by improving ventilatory management or by using pharmacological intervention to reduce VILI in animal models. Allardet-Servent et al. [4] examined the effects of high-frequency percussive ventilation (HFPV), and compared it with high-frequency oscillatory ventilation (HFOV) and low volume ventilation on acute lung injury following gastric juice aspiration in rabbits. The HFPV was administered with a pneumatically powered volumetric diffusive respirator, which combines potential advantages of both high-frequency and convective ventilation. The investigators suggested that HFPV provided similar lung protective effects as did by HFOV and low volume ventilation, thus introduced an interesting therapeutic approach to attenuate VILI. It is noteworthy to mention that the neurally adjusted ventilatory assist (NAVA) has been shown to be protective in some experimental models of lung injury. NAVA utilizes

the electrical activity of the diaphragm (EAdi) to control the timing and pressure of the ventilation delivered independent of pneumatical signal. In a rabbit model of acute lung injury, Beck et al. [5] demonstrated that NAVA can be effective in delivering noninvasive ventilation even when the interface with the subjects was leaky, and can unload the respiratory muscles while maintaining synchrony with the subject's demand.

The assessment of regional lung opening and closing during mechanical ventilation is important to help providing optimal ventilatory management. The electrical impedance tomography (EIT) has been recently examined to indirectly evaluate lung volume. Meier and colleagues [6] investigated whether EIT is capable of monitoring regional lung recruitment and collapse during an incremental and decremental positive end-expiratory pressure (PEEP) trial in pigs. When EIT and computed tomography scans of the same lung slice were simultaneously taken at each PEEP level, the authors observed that EIT is capable of monitoring the regional changes of tidal volume in assessing the beginning of alveolar recruitment and collapse. Drs. Schibler and Calzia [7] made comments in an Editorial and stated that the EIT needs further development, but is a useful tool for monitoring lung function and has the potential to be an integral part of ventilatory management.

Reducing dead space may be a useful approach to eliminate CO₂ during low volume ventilation. Astrom et al. [8] analyzed the volume of expired CO₂ and the volume of CO₂ re-inspired from Y-piece and tubes in a breath-by-breath manner in pigs with acute lung injury after surfactant depletion. The investigators demonstrated that CO₂ elimination can be enhanced by a pattern of ventilation that prolongs the mean distribution time by shorting insufflation time and decreasing flow. This study suggests an alternative approach to reduce possible hypercapnia during low volume ventilation. However, it has been shown in certain conditions that hypercapnia may be protective during mechanical ventilation. Schwartzes et al. [9] examined the effects of hypercapnia on gastric mucosal oxygenation in dogs. The animals were ventilated to achieve an end-tidal CO₂ (etCO₂) ranging 35–70 mmHg. They found that gastric mucosal oxygenation increased in a CO₂-dependent fashion associated with an increase in cardiac output. The enhanced oxygenation in the splanchnic vasculature by permissive hypercapnia may be of interest in certain clinical conditions such as sepsis where gut may play a role as a motor responsible for an uncontrolled inflammatory response. Another interesting and innovative study by Hering et al. [10] merits attention. The investigators monitored hepato-splanchnic perfusion under airway pressure release ventilation (APRV) with or without spontaneous breathing in a pig model of oleic acid induced lung injury. The investigators observed that the liver perfusion was better preserved during APRV with spontaneous breathing,

whereas hepatic blood flow was lower without spontaneous breathing. The beneficial effects of this interesting observation are yet to be explored in critical care settings. It is worthy to read the Editorial by Dr. Calzia [11] accompanying the article.

VILI is associated with disruption of membrane integrity in both vascular capillaries and alveolar epithelium, the alveolocapillary barrier, de Prost and colleagues [12] demonstrated that switching from low to high volume ventilation could result in rapidly leakage of ^{99m}Tc -labeled albumin from the alveolar space into systemic circulation in rats. An intratracheal instillation, but not systemic injection of the β_2 -adrenergic agonist terbutaline prior to high volume ventilation largely attenuated this increased permeability and thus lung wet/dry ratio. An Editorial by Dr. Kuebler [13] made comments that this significant finding opens a new realm of research for pharmacological interventions to protect the alveolar epithelial barrier in the context of VILI.

Hypoxia/ischemia: reoxygenation/reperfusion injury

Reactive oxygen species (ROS) have been implicated in the pathogenesis of hypoxia–reoxygenation injury. In this volume of Intensive Care Medicine, several studies investigated the therapeutic approaches in animal models of hypoxia-induced organ dysfunction. Dr. Cheung's group [14] examined the effects of using different oxygen concentrations during reoxygenation on cardio-renal recovery in hypoxic newborn pigs. The piglets received normocapnic hypoxia (15% oxygen) for 2 h followed by reoxygenation with 18, 21 or 100% oxygen for 1 h then 21% oxygen for 2 h. The investigators reported that the 100% group had increased myocardial oxidative stress and the most cardiac injury following hypoxia–reoxygenation. This study suggested that 100% reoxygenation after moderate hypoxemia should be avoided from the cardiac perspective, and the 18% reoxygenation offers no further benefit regarding the myocardial and renal oxidative state and recovery when compared with 21% oxygen. These results appeared to be in agreement with the observation reported by Douzinas et al. [15] using a hemorrhagic shock and resuscitation model in rabbits. In their study, rabbits were subjected to hemorrhagic shock with a mean arterial pressure of 40 mmHg for 60 min followed by resuscitation by reinfusion of the shed blood under normoxemia (PaO_2 of 95–105 mmHg) or hypoxia (PaO_2 of 35–40 mmHg) condition. The authors demonstrated that hypoxia resuscitation from hemorrhagic shock resulted in a better hemodynamics, a higher renal perfusion, a lower production of ROS and inflammatory cytokines than normoxemic resuscitation. These interesting observations are yet to be further confirmed in other

models of ischemia/hypoxia–reperfusion/reoxygenation in a large sample size.

To explore the efficacy of pharmacological intervention in hypoxia and reoxygenation injury, Dr. Cheung's group [16] further examined the effects of milrinone, a therapeutic agent exerting both inotropic and vasodilatory properties for acute congestive heart failure, in a piglet model of neonatal hypoxia–reoxygenation. After normocapnic alveolar hypoxia (10–15% oxygen) followed by reoxygenation with 100% oxygen then 21% oxygen, milrinone or normal saline was given intravenously. The authors observed that the milrinone-treated animals had higher cardiac output and carotid flow and well-maintained systemic blood pressure than those of saline-treated hypoxic controls. The administration of milrinone prevented pulmonary hypertension seen in control animals after hypoxia–reoxygenation. In a similar model, the investigators also demonstrated that a postresuscitation with the antioxidant agent *N*-acetylcysteine attenuated the increase in cerebral hydrogen peroxide (H_2O_2) and oxidized glutathione levels in the cerebral cortex, probably through a taurine-related mechanism [17].

A secondary brain injury may occur following hypoxia/ischemia–reoxygenation/reperfusion injuries. Geeraerts and colleagues [18] investigated the effects of early versus delayed hypoxic–hypotensive insults to the traumatic brain injury (TBI) induced by the Marmarou model of impact-acceleration head injury in rats. Hypoxia was induced by ventilation with a mixture of O_2 (10%) and N_2 (90%), resulting in a PaO_2 of 40 mmHg, followed by a controlled hemorrhage to reduce the mean arterial pressure to 40 mmHg. The animals were then resuscitated to normoventilation and normotension. The authors reported that a significant decrease in brain oxygenation and cerebral perfusion pressure in the early hypoxia/hypotension group (45 min after TBI), but not in the delayed group (225 min after TBI). This experimental study suggested a high vulnerability of the injured brain to secondary insults of hypoxia and hypotension during the early phase of TBI. An excellent Editorial by Dr. Stahel et al. [19] accompanied the interesting article.

Experimental therapy and monitoring in organ systems

The cerebral vasospasm (CVS) develops in approximately 30% of patients classically at about 4–12 days after aneurysmal subarachnoid hemorrhage (SAH), contributing to high morbidity and mortality. Some clinical and experimental studies have suggested that intrathecal administration of nitric oxide (NO) donors may provide therapeutic benefits for reversing CVS. Marbacher and colleagues [20] demonstrated that the administration of

glyceroltrinitrate and nimodipine indeed prevented the SAH-induced CVS in a rabbit model of SAH. Since the intrathecal administration was carried out at the same location where the experimental SAH was introduced, the effects from the current study should be examined in a model where the SAH bleeding site is independent of the intrathecal drug administration.

Meconium aspiration syndrome includes acute lung injury with lesions of partial alveolar hypoxia characterized by occlusion of small airways and induction of an inflammatory response in pediatric patients. Pulmonary hypertension is a major complication in meconium aspiration-induced acute lung injury due to an increased expression of endothelin-1 (ET-1). Geiger et al. [21] investigated the effects of the endothelin A and B receptor antagonist tezosentan and the inhalational iloprost, a stable prostacyclin analog, in a pig model of acute lung injury induced by meconium aspiration. They demonstrated that intravenous administration of tezosentan improved pulmonary oxygenation associated with a decreased pulmonary hypertension, while inhaled iloprost improved gas exchange only. Although the combination of tezosentan and iloprost led to greatest improvement in oxygenation, it resulted in a decreased systemic arterial pressure. Thus, the ET-1 might be of a target therapeutic molecule in the context of meconium aspiration-induced acute lung injury. In another pig model of pulmonary hypertension induced by hypoxic vasoconstriction, Rex and colleagues [22] reported that epoprostenol (prostacyclin, PGI₂) induced pulmonary vasodilation associated with a paradoxical decrease in right ventricle contractility probably as a result of a close coupling of right ventricle contractility to right ventricle afterload. However, mechanisms other than vasodilation are not excluded for the observed negative inotropic response to epoprostenol in this model of hypoxia-induced pulmonary hypertension.

Under critical conditions such as severe anemia, the fluid management is crucial with respect to prognosis or outcome. Pape and colleagues [23] tested the efficacy of a polyethylene glycol (PEG) modified formulation of liposome-encapsulated hemoglobin (LEH) as blood substitute in dogs. The animals were splenectomized and hemodiluted by exchange of whole blood for iso-oncotic hetastarch, and received either LEH or normal saline at a critical point of oxygen hemoglobin by which oxygen delivery became dependent on oxygen uptake. The authors demonstrated that the LEH-treated animals survived longer associated with an initial more stable cardiovascular condition and better oxygenation than the control animals, but the overall mortality rate was similar. A sustained effect of LEH is warranted to be established in future studies.

An estimate of renal blood flow may provide important information for physicians to manage critically ill patients with acute renal failure. Although renal Doppler ultrasound has been used to measure renal blood flow, its

accuracy has not been formally assessed. Comparing with a classical technique by implanting transit-time flow probes around the left renal artery, Wan and colleagues [24] simultaneously recorded renal blood flow values obtained with Doppler ultrasound in ewes. The blood flow was artificially altered by infusion of dobutamine and nitroprusside in random order and a total of over two hundred paired measurements were performed. The investigators concluded that Doppler-ultrasound-derived estimates of renal blood flow show little correlation with transit-time flow probe measurements, and have low accuracy for clinically significant changes in renal blood flow in large animals.

Experimental studies: sepsis and acute lung injury

Several studies were reported in Intensive Care Medicine during 2008 involving animal models of sepsis and acute lung injury. One of the most used models was the mouse and rat endotoxemia model. In such a model, lipopolysaccharide (LPS, Gram-negative bacterial endotoxin) is injected either intravenously or intraperitoneally. This has to be considered as an exploratory model for many reasons: (1) mice and rats are very resistant to endotoxin compared to humans, and extremely high doses are required to observe morbidity and mortality; (2) the end-organ dysfunction does not resemble to that of human septic shock; (3) the models are usually short in time and animals die or are sacrificed within 6 h after LPS injection; and (4) on many occasions reverse outcomes have been observed when endotoxin was substituted with a live bacteria. The murine cecal ligation and perforation (CLP) model was the second most used model, and better mimics a severe human bacterial infection, i.e., acute peritonitis. Depending on the number of cecal punctures and the diameter of the needle, both the severity and the mortality of the model can be modulated from a chronic peritoneal infection to a lethal septic shock. The third rodent or ovine model that is more and more studied is the injection of live bacteria intravenously, into the peritoneum or the lungs to generate a severe infection leading to a secondary sepsis syndrome. Rodent and ovine infectious models can nowadays be rendered more complex to mimic the human situation by using mechanical ventilation, fluid resuscitation, and antibiotic therapy.

The pathogenic relationship between inflammation and coagulation in the context of sepsis is now well established. Endogenous anti-thrombotic proteins such as activated protein C and antithrombin have shown to carry anti-inflammatory properties. However, the anti-inflammatory pathways used by these proteins to modulate inflammation remain poorly understood. Hagiwara et al. [25] reported that treatment of endotoxemic rats with antithrombin (AT) decreased both lung injury and

lethality. They concomitantly observed lower lung and systemic concentrations of a recently described “alarmin” or “danger signal”, HMGB1 [26]. HMGB1 has been shown to be elevated in human septic shock [27] and to be a predictor of organ dysfunction and outcome in patients with severe sepsis, but not of mortality [28]. This latter protein is a major determinant of rodent endotoxemia lethality. In their study, Hagiwara et al. also report that murine macrophages cultured with antithrombin secrete less HMGB1 and proinflammatory mediators in response to LPS, as a consequence of decreased NF- κ B activation. However, these authors fail to show a direct relationship between HMGB1, the inflammatory response, antithrombin and lethality in this rat endotoxemic model. Using a CLP model in rats, the same group of investigators addressed one more time the possible benefit of administering high doses of intravenous immunoglobulins (IVIG) in the treatment of septic shock [29]. The injection of 1 g/kg of IVIG prevented lung injury, plasma and pulmonary HMGB1 levels, systemic inflammation mediated by NF- κ B, and lethality. It remains controversial whether septic patients may benefit from nonspecific IVIG.

Peroxisome proliferator-activated (PPAR) receptors may play a role in the outcome of animal models of sepsis. In a CLP mouse model, Haraguchi et al. [30] showed that pioglitazone, a PPAR- γ ligand, decreased lethality. Interestingly, this compound was protective even after having performed the CLP. In another elegant study with a CLP model, Tuon et al. [31] tested the cognitive performance of rats up to 2 months after sepsis. To even better mimic the situation of human sepsis, rats submitted to CLP were treated using IV fluids and antibiotics. Rats surviving sepsis were then submitted to a variety of behavioral tests. Tuon et al. observed in these rats a transient impairment of behavior and cognitive functions 10 and 30 days after sepsis, but a nearly full recovery at 2 months. This very interesting work sets up a model to study septic encephalopathy and cognitive impairments observed in patients following sepsis. It follows another report by the same group showing the beneficial effects the antidepressant imipramine in rats surviving from CLP-induced sepsis [32]. The same group of investigators also tested in rats a polypeptide stimulating the nociceptin/orphanin receptor, as well as a selective pharmacological inhibitor of the same receptor after CLP [33]. The inhibitor of the nociceptin/orphanin receptor protected rats from systemic and biological consequences of peritoneal sepsis and decreased lethality. In contrast, the polypeptide ligand activating the nociceptin/orphanin receptor had opposite effects, and increased mortality in this CLP rat model. It is therefore a possibility that this pathway may play a role in sepsis and should be further tested in humans.

The pathogenesis of muscular weakness in critically ill patients remains poorly understood. In a sublethal rat

model injected IV with live *E. coli*, Frick et al. [34] observed a decrease in body mass and systemic inflammation over a period of 14 days. These rats also showed a marked decrease in muscle mass and strength tested by mechanomyography. Levels of acetylcholine receptors were not changed with time. The authors conclude that, in this model, muscular weakness is associated with muscle atrophy due to the inflammatory state rather than up-regulated acetylcholine receptors.

The use of “stress” doses of glucocorticoids in patients with septic shock is currently an intense matter of debate in the critical care community. Whereas older trials with a high baseline mortality rate showed improved survival rate in septic patients treated with small doses of hydrocortisone, a recent large multicentre trial in less severe patients (CORTICUS trial) failed to show survival benefit. Li et al. [35] addressed the question as to whether the risk of death (i.e., the initial severity) may influence the outcome of a “substitutive” glucocorticoid treatment in a mouse *E. coli* pneumonia model. In order to modulate the initial severity, they varied the *E. coli* lung inoculum obtaining a mortality rate in three groups ranging from 12 to 94%. The administration of hydrocortisone in septic animals of various severities tended to increase survival rates and significantly decrease the systemic inflammatory response syndrome; however, independently of the initial severity. These results suggest that factors other than initial severity account for the observed protective effect of glucocorticoids in septic animals, and possibly in humans. Tight glucose control using insulin therapy is another controversial therapy in critically ill patients, particularly in those patients with severe sepsis and septic shock, as recently highlighted by the German VISEP trial. In a model of prolonged critical illness (anesthetized rabbits with a 20% of the body surface third degree burn), Ellger et al. reported it was the normoglycemia (“glucose control”) rather than the possible ancillary effect of insulin that was beneficial in this model. It prevented an excessive and deleterious nitric oxide release possibly through an endothelial protective effect or decreased substrate availability [36].

Using a *Legionella pneumophila* pneumonia model in mice, Ader et al. [37] showed that intratracheal instillation of heparin (co-instilled with bacteria) prevented bacterial dissemination, had a protective effect on the alveolar-capillary barrier, and improved mice survival rate. Interestingly, intratracheal heparin co-instillation increased alveolar concentrations of interferon- γ and interleukin-12, possibly increasing immune defenses against *Legionella*. The authors postulate that heparin interferes with *L. pneumophila* binding to pneumocytes, preventing bacterial binding to cell surface endogenous heparan sulfates.

It has been long known that acute endotoxemia is associated with pulmonary hypertension. Using in vitro (isolated pulmonary vessels) and in vivo models

(endotoxemia in pigs), Rossi et al. [38] showed that the endothelin system was extensively involved in pulmonary venous hypertension, leading an increased pulmonary capillary pressure, an effect that could be inhibited by the endothelin receptor blocker tezosentan. Using another endotoxemic model in rats, Lin and Wan [39] addressed the possible protective role of hyperbaric oxygenation LPS-induced brain activation. They found that hyperbaric oxygenation indeed protected neuronal activation (cFos, NADPH diaphorase and superoxide production) in endotoxin-treated rats.

Despite its undisputable vasopressor effect, vasopressin treatment of patients with septic shock shows variable and intriguing results, in part due to a possible reduction of splanchnic and renal blood perfusion. In a model of anesthetized and ventilated rabbits, Kopel et al. [40] showed that the mesenteric blood flow, as well as the microcirculation in the gut and liver, were preserved in endotoxemic rabbits treated with small “physiological” doses of arginine vasopressin, doses that were able to increase mean arterial pressure. Higher doses were associated with decreased splanchnic organ perfusion. These results tend to support the recently published Canadian “VASST” trial showing benefit in septic patients receiving small doses of vasopressin on top of the nor-epinephrine used to treat the vasodilatory shock.

Nebulization of drugs is already popular in ventilated patients, and is very likely to expand in the near future. This is the case for antibiotics, which can attain higher local and bactericidal concentrations as compared with the IV route. Ferrari et al. [41] compared the efficacy of ultrasonic versus vibrating plate nebulizers for their efficacy to deliver ceftazidime into pig’s lungs. They show that the new vibrating plate nebulizer system is as efficacious as the older ultrasonic nebulizer, with similar ceftazidime concentration deposited into the lung tissue of ventilated animals.

Primary cell cultures are also widely used and of value to test therapeutic concepts *in vitro*. The Ficoll gradient is the classical isolation technique to separate neutrophils from mononuclear cells (monocytes plus lymphocytes) in whole anti-coagulated blood. In healthy subjects’ blood, mononuclear cells float on the top of the Ficoll after centrifugation, whereas neutrophils migrate with red blood cells at the bottom of the tube. Severe bacterial infections and sepsis are conditions associated with a marked recruitment in the circulation of immature neutrophils (band forms). Van den Akker et al. [42] report that the upper Ficoll fraction is highly contaminated with immature neutrophils having buoyancies similar to that of mononuclear cells. Since this Ficoll technique is widely used in sepsis research protocols to separate leukocyte subpopulations, investigators should be aware and take into account the fact that the so-called “mononuclear fraction” can be heavily contaminated with (immature) neutrophils. In another study involving an *in vitro*

endothelial cell culture model (human umbilical vein endothelial cells, HUVECs), Noda et al. [43] showed that endotoxin and hyperglycemia reversed the decreased interleukin-8 expression induced by hypothermia (30°C) in HUVECs.

Acute respiratory failure and ARDS

Pathophysiology

Acute respiratory distress syndrome (ARDS) is the most severe manifestation of acute lung injury (ALI). In patients who survive the acute injury, the process of repair and remodelling may be an independent risk factor determining morbidity and mortality. Dos Santos [44] explored in a review the recent advances in the field of fibroproliferative ARDS/ALI. The determinants of persistent injury and abnormal repair and remodelling may be profoundly affected by both environmental and genetic factors. Cumulative evidence suggests that acute inflammation and fibrosis may be in part independent and interactive processes that are autonomously regulated. The current understanding of these processes is limited by the inability to accurately replicate the complex human physiology in laboratory settings; however, it has recently become apparent that the process of repair and remodelling begins early in the course of ARDS/ALI and may be determined by the type of pulmonary injury. The author concluded that the understanding the mechanisms leading to and regulating fibroproliferative changes may contribute to the development of novel early therapeutic interventions in ARDS/ALI patients.

Negrini and colleagues [45] analyzed the role of the fibrous ECM components, in particular the chondroitin sulfate proteoglycan (CS-PG) and the heparan-sulfate proteoglycan (HS-PG) families on the maintenance of tissue fluid homeostasis. These molecules provide (1) a perivascular and interstitial highly restrictive sieve with respect to plasma proteins, modulating both interstitial protein concentration and transendothelial fluid filtration; (2) a mechanical support to lymphatic vessels sustaining and modulating their draining function, and (3) a rigid three-dimensional low-compliant scaffold opposing fluid accumulation into the interstitial space. The Fragmentation of proteoglycans (PG) induced by increased plasma volume, by degradation through proteolytic or inflammatory agents, by exposure to inspiratory gas mixture with modified oxygen fraction, or by increased tissue strain/stress invariably results in the progressive loosening of PG intermolecular bonds with other ECM components. The loss of the PGs regulatory functions compromises the protective role of the tissue solid matrix progressively leading to interstitial and eventually severe lung edema.

Pulmonary microvascular thrombosis is one of the phenomena implicated in the ARDS pathophysiology. Patients undergoing cardiac surgery sustain significant inflammatory insults to the lungs, a condition known to trigger microvascular thrombosis, and in addition are routinely given anti-fibrinolytic agents, such as aprotinin, to promote thrombosis. In a double-blind, placebo-controlled trial, Dixon et al. [46] investigated if evidence of pulmonary microvascular thrombosis occurs following cardiac surgery and, if so, whether it may be limited by a pre-operative heparin infusion. Twenty patients were administered aprotinin and were randomized to receive a pre-operative heparin infusion or placebo. In the placebo group, cardiac surgery was associated with increased alveolar dead-space fraction levels and with the onset of prothrombin fragment production in the pulmonary circulation, suggesting pulmonary microvascular obstruction. Administration of pre-operative heparin reduced alveolar dead-space fraction and prothrombin fragment production in the pulmonary circulation, and increased baseline levels of systemic tissue plasminogen activator (all $P < 0.05$). These findings provide supporting evidence that pulmonary microvascular thrombosis occurs during cardiac surgery and may be limited by a pre-operative heparin infusion. In the accompanying editorial, Ranucci [47] highlighted the results of recent studies showing that aprotinin use may worsen postoperative outcome in cardiac surgery and explained that the contribution by Dixon et al. offers new insights into the mechanisms by which aprotinin may produce this negative effect.

Urokinase potentiates neutrophil activation and contributes to the severity of pulmonary injury in preclinical models of ALI. In a prospective cohort of healthy European-American adults and 252 patients with infection-associated ALI, Arcaroli and colleagues [48] examined the association between polymorphisms and haplotypes of urokinase with risk for and outcomes from ALI. Six polymorphisms, rs1916341, rs2227562, rs2227564, rs2227566, rs2227571, and rs4065, defining 98% of all urokinase haplotypes, were analyzed. There were no statistically significant associations between any single urokinase polymorphism or haplotype and risk for developing ALI. In contrast, there was a statistically significant relationship between the CGCCCC haplotype and both 60-day mortality and ventilator-free days that remained present in a multivariate analysis controlling for age and sex.

Pulmonary embolism is a common and serious disease. Patients with hemodynamic instability at presentation and those hemodynamically stable with right ventricular dysfunction, have high mortality. The latter, however, are difficult to recognize. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are biomarkers studied in the context of acute pulmonary embolism. The myocardial wall stress

is the most important stimulus for increased synthesis and secretion of BNP. In a review article, Cavallazzi et al. [49] evaluated the available evidence on the accuracy of BNP and NT-proBNP for the diagnosis of right ventricular dysfunction and their value as prognostic factor of in-hospital and short-term mortality in patients with acute pulmonary embolism. A total of 16 studies were evaluated. The pooled diagnostic odds ratio for the diagnosis of right ventricular dysfunction in pulmonary embolism was 39.45 and 24.73 for BNP and NT-proBNP, respectively, and for all cause in-hospital mortality or short-term mortality was 6 and 16.12 for BNP (cutoff 100 pg/ml) and NT-proBNP (cutoff 600 ng/l), respectively. They concluded that both biomarkers are significant predictors of all-cause in-hospital mortality or short-term mortality in patients with pulmonary embolism and right ventricular dysfunction.

Critically ill cancer patients may face multiple organ dysfunction including cardiac failure. The latter, is however, difficult to diagnose as the related clinical signs (dyspnea, rales, tachycardia) are unspecific in those patients. Lefebvre et al. [50] could describe a beneficial role of NT-proBNP to rule out the cardiac origin of an acute respiratory failure in critically ill cancer patients. With specificity and negative predictive value of 100%, a NT-proBNP cutoff value of 500 pg/ml may rule out cardiac dysfunction in those patients.

Two technical articles dealt with pulmonary gas exchange. In one review, the very sophisticated multiple inert gas elimination technique (MIGET) is described by its inventor, Peter D Wagner, and the potential of MIGET to distinguish between different causes of gas exchange impairment are pointed out [51]. The other paper describes the potential value of transcutaneous carbon dioxide monitoring in severe obesity [52].

Supportive therapies

Apart from the protective ventilatory strategies, a number of different supportive approaches have been proposed for acute respiratory failure over the last few years. The use of steroids still represents a matter of major debate.

In the January issue, the journal published a clinical commentary by Meduri and colleagues [53] that compared the design and results of randomized trials investigating prolonged glucocorticoid treatment (≥ 7 days) in patients with acute lung injury-acute respiratory distress syndrome (ALI-ARDS), and review factors affecting response to therapy, including the role of secondary prevention. Retrieving trials from the Cochrane Central Register of Controlled Trials (CENTRAL) and analyzing their quality with Review Manager 4.2.3., the authors selected five trials enrolling 518 patients. All these studies consistently reported significant improvement in gas exchange,

reduction in markers of inflammation, and decreased duration of mechanical ventilation and intensive care unit stay (all $P < 0.05$). Two early small clinical trials showed marked reductions in the relative risk (RR) of death with glucocorticoid therapy (RR = 0.14, 95% CI 0.04–0.53; $P = 0.004$, I² = 0%). Three subsequent larger trials, when combined, although nominally beneficial, did not reproduce the marked reductions in mortality observed in the earlier trials, but achieved a distinct reduction in the RR of death in the larger subgroup of patients ($n = 400$) treated before day 14 of ARDS [82/214 (38%) vs. 98/186 (52.5%), RR = 0.78; 95% CI 0.64–0.96; $P = 0.02$, I² = 0%]. By including in the analysis patients from the NIH trial and in contradiction with that paper, Meduri and colleagues concluded that prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centered outcome variables, and has a distinct survival benefit when initiated before day 14 of ARDS.

Prone positioning is another form of supportive therapy for ARDS. Aiming to demonstrate that prone positioning may have beneficial effects in ARDS patients, when used early and continuously, Fernández et al. [54] present the results of a multicenter randomized clinical trial. This study was initially powered for a total of 250 patients, but only 40 patients were randomized (19 supine position and 21 prone position). The study was aborted early because of small and steadily dropping enrollment. Prone positioned patients had better arterial oxygenation and side effects were minimal. A non-significant difference in mortality between supine and prone treated patients was observed, 62 and 47%, respectively. It was concluded that the study adds data that reinforce the suggestion of a beneficial effect of early continuous prone positioning on survival in ARDS patients.

The effects of prone positioning were deeply analyzed also by Abroug et al. [55] who published a meta-analysis of randomized controlled trials in ARDS or ALI. A total of six trials were analyzed, five trials being included in mortality analysis and oxygenation effects, four trials being included in the ventilator-associated pneumonia, and three trials were used to analyze the ICU length of stay. The main results were: no effects on mortality, no differences in major adverse airway complications, and a significant improvement in oxygenation with proning. They concluded that these studies showed a substantial clinical heterogeneity and an absence of harmful effects attributable to prone position. They indicated that the optimal randomized controlled study aiming to investigate whether prone position should be used in the ARDS, is still to be done.

In the field of acute on chronic respiratory failure heliox, a low density gas mixture composed of helium and oxygen, has been used therapeutically for the acute exacerbation of chronic obstructive respiratory diseases (COPD). Standley et al. [56] determined the extent of

dilution of inhaled heliox by room air with a non-rebreathable reservoir mask compared with a closed delivery circuit providing a tight seal between the mask and face under noninvasive ventilation. This randomized, blinded, crossover study was conducted in six healthy volunteers. When subjects breathed via a standard non-rebreathable reservoir mask, a significant entrainment of air was noted (the within subject median percentage of tracheal nitrogen was 41.7%) and this was affected by changes in breathing pattern. The tracheal nitrogen was almost abolished (2.2%) when heliox was administered through a tightly fitting cushioned face mask. It was concluded that for the full benefits of heliox to be realized in spontaneously breathing individuals, it should be administered via a system with a gas tight seal.

Gosselink et al. [57] published a European Society of Intensive Care Medicine Statement article concerning physiotherapy for adult patients with critical illness. The authors of the Task Force (a joint initiative of the European Society of Intensive Care Medicine and the European Respiratory Society) describe three different areas of particular interest: deconditioning and related complications, a number of relevant respiratory conditions, and emotional problems and communication. In each of these areas, the authors make recommendations for assessment and monitoring and best practice. They concluded that there is a need to standardize pathways for clinical decision-making and education, to define the professional profile of physiotherapists, and increase the awareness of the benefits of prevention and treatment of immobility and deconditioning for critically ill adult patients.

Mechanical ventilation

In a review article Vassilakopoulos and colleagues [58] provide a thorough view on diaphragmatic muscle pathophysiology and the clinical consequences of abolishing spontaneous diaphragmatic contractility (i.e., a decrease in the force generating capacity of this muscle when it is put at rest). This phenomenon is called ventilator-induced diaphragm dysfunction. In the first part of the article, the authors offer an in-depth insight gathered from animal models and encompassing morphological, cellular, and molecular biology aspects. In the second part of the article, the clinical relevance of ventilator-induced diaphragmatic dysfunction is presented. This part gives a comprehensive view on the clinical evidence of the problem, the strategies to prevent it, and suggestions for recovery from a ventilator-induced diaphragm dysfunction. The authors conclude that the diaphragm should remain active because it is plastic and vulnerable and the major clinical implication of the ventilator-induced diaphragm dysfunction is to limit the use of controlled mechanical ventilation to the extent possible.

The effects of mechanical ventilation pertain not only to the diaphragm and the alveolar units, but also to the extracellular matrix. In the issue of April, Pelosi and Rocco [59] focus on the role of the extracellular matrix (ECM) in the biomechanical behavior of the lung parenchyma. The macromolecules (the glycosaminoglycans and the proteoglycans) that are the constituent of the ECM compose a three-dimensional fiber mesh which has important functions in many lung pathophysiological processes: (1) regulating the hydration and water homeostasis, (2) maintaining the structure and function, (3) modulating the inflammatory response, and (4) influencing tissue repair and remodelling. In this review is analyzed how the ventilator-induced lung injury is exerted on the epithelial and endothelial cells, the extracellular matrix, and the peripheral airways through a complex interplay of mechanical forces. The organization of the ECM, mechanotransduction and ECM interactions, and the effects of mechanical ventilation on the ECM were detailed and discussed.

The principles of automation in mechanical ventilation revising the evidence supporting the use of closed-loop systems to facilitate weaning have been discussed in a review article by Burns et al. The first part of this review deals with the general principles of automated systems. It follows with the automated weaning strategies and modes. In this part, mandatory minute ventilation, adaptive support ventilation and SmartCare™ are discussed. On continuation, the differences among automated weaning systems are presented. Finally, the advantages and disadvantages of automated weaning systems. The authors concluded that automation during weaning does not yet supersede the need for close patient observation and monitoring, nor does it supplant the need for clinicians to make important clinical judgements during weaning and regarding critical events such as readiness for extubation. They also underscored the need for additional high quality investigations to evaluate automated weaning systems in different practice settings and diverse patient populations.

However, the simplification of ventilator management and of the weaning process have been recently automated by incorporating advanced closed-loop systems into modern mechanical ventilators [60]. In a cohort of 243 invasively ventilated patients, Arnal et al. [61] evaluated the combinations of VT and RR generated by adaptive support ventilation for various lung conditions. Overall, the respiratory mechanics and expiratory time constants differed significantly with the underlying conditions. In passive patients, combinations of tidal volume (VT) and respiratory rate (RR) differed depending on the patient's respiratory mechanics: COPD had higher VT and lower RR compared to patients with ALI/ARDS. In actively breathing patients, the VT-RR combinations did not differ between COPD, ALI/ARDS, and normal lungs. Thus, while adaptive support ventilation is able to select

different VT-RR combinations based on respiratory mechanics in passive patients, the differences of VT-RR combinations are less clear in actively breathing patients.

SmartCare is a system designed to automate weaning from mechanical ventilation. In a randomized, controlled trial, Rose et al. [62] compared SmartCare to usual management of weaning, in the absence of formal protocols, in 102 patients ready to tolerate pressure support ventilation. Time from the first identified point of suitability for weaning commencement to the state of "separation potential" and time to successful extubation were similar between groups. The estimated probability of reaching "separation potential" was lower with SmartCare compared to controls. Rates of reintubation, noninvasive ventilation post-extubation, tracheostomy, sedation, neuromuscular blockade and use of corticosteroids were comparable between the study groups. Authors concluded that SmartCare did not decrease weaning duration when the system was compared to weaning managed by experienced nurses in a unit with high level of staffing. In the accompanying editorial, Laghi [63] compared these findings with those of previous studies and concluded that computerized weaning, while not outperforming a dedicated team of intensivists and nurses, might be better than physician weaning in units where limited resources inhibit clinicians from contemplating relatively early in a patient's course the ability to breathe unassisted.

Optimization of mechanical ventilation implies the identification and minimization of patient-ventilator asynchrony. Prinianakis et al. [64] tested the hypothesis that, during pressure support ventilation, pressure overshoot often observed before the ventilator cycles off may be caused not only by expiratory muscle recruitment, but also by the relaxation of inspiratory muscles. In 15 ventilated patients, the start of pressure overshoot was observed 32 ± 34 ms after the end of neural inspiration, well before expiratory muscle recruitment. The rate of rise of airway pressure during pressure overshoot was correlated with the rate of decline of transdiaphragmatic pressure and of inspiratory flow. Conclusion was that, during pressure support ventilation, the relaxation of inspiratory muscles accounts for the pressure overshoot above the pre-set level, in addition to the contribution made by the occurrence of expiratory muscle activity. In the accompanying editorial, Younes [65] explained the physiologic basis of the pressure overshoot phenomenon and emphasized that an overshoot need not reflect excessive delayed cycling-off.

Assessment of lung recruitability is important to optimize ventilatory settings in patients with acute respiratory distress syndrome (ARDS). In 26 patients with early ARDS, Demory et al. [66] verified whether the hysteresis of the pressure-volume curve might be used to estimate the recruitability of the lung. Volume increase during a recruitment maneuver was linearly correlated

with the linear compliance of the inflation pressure–volume curve, and with the hysteresis of the pressure–volume curve. Authors concluded that the hysteresis of the pressure–volume curve might be used to assess the recruitability of the lung.

Theoretically, monitoring of lung volume may be important in the ventilatory management of patients with ALI/ARDS. In 36 intubated patients with different pulmonary conditions, Patroniti et al. [67] evaluated the prototype of a new automated method for measuring end-expiratory lung volume (EELV) based on oxygen washin and washout and compared it to the helium dilution method. Oxygen washin and washout showed good agreement with the helium dilution method and good repeatability during both controlled and assisted mechanical ventilation. This simple, automated method could offer the possibility to assess whether the measurement of EELV may help to optimize ventilator parameters, particularly in patients with ALI/ARDS.

Three studies have dealt with the impact of imaging techniques in mechanically ventilated patients. The first study evaluated technical aspects of computed tomographic (CT) densitometry of the lung. Reske et al. [68] studied the impact of CT reconstruction parameters on hyperinflation measurements in 11 mechanically ventilated patients and 5 spontaneously breathing patients. For all patients, hyperinflation varied significantly with every change of reconstruction method. In particular, hyperinflated volume obtained with the sharp filter systematically exceeded that with the standard filter. Independent of the filter used, hyperinflation increased significantly with decreasing slice thickness. These findings may indicate that sharp filters could be inappropriate for quantitative CT assessment of hyperinflation in mechanically ventilated patients.

The second study presented preliminary results on the use of positron emission tomography with 18-F-fluorodeoxyglucose (FDG-PET) in patients at risk of ARDS. Rodrigues et al. [69] tested the hypothesis that molecular imaging by FDG-PET may be useful to identify pathophysiological alterations occurring early in the ARDS course. Four out of eight patients with thoracic trauma and no ARDS on admission subsequently developed ARDS within 1–3 days following the PET scan. Three of the four patients who developed ARDS showed diffuse FDG uptake throughout the entire lungs, while those who did not develop ARDS showed significant FDG uptake only in areas of focal lung opacity on CT. FDG uptake in normally aerated lung regions was higher, although not significantly, for those who subsequently developed ARDS than those who did not. The normally aerated tissue:liver ratio was significantly higher in subjects who developed ARDS than in those who did not. Authors concluded that in their small series, diffuse lung uptake of FDG was detected by PET imaging 1–3 days prior to clinically determined ARDS.

The third study dealt with chest radiography in mechanically ventilated patients. In 165 patients, Clec'h et al. [70] compared the diagnostic, therapeutic and outcome efficacy and safety of a restrictive prescription of chest X-ray (obtained when clinically indicated only) with that of a routine prescription. The rates of new findings and the rates of new findings that prompted therapeutic intervention were significantly higher in the restrictive prescription group than in the routine prescription group (66% vs. 7.2% and 56.4% vs. 5.5%, respectively). The rate of delayed diagnoses in the restrictive prescription group was 0.7%. Clinical outcomes were similar between the two groups. In conclusion, restrictive use of chest radiography was associated with better diagnostic and therapeutic efficacies without impairing outcome.

A large number of studies have been dedicated to the pathophysiology and clinical implementation of both noninvasive and invasive ventilation; El Khatib and colleagues [71] evaluated the effect of pressure support ventilation and positive end-expiratory pressure on the rapid shallow breathing index (RSBI) in ICU patients. The aim of the study was to compare rapid shallow breathing index (RSBI) values under various ventilatory support settings prior to extubation in 36 patients ready for extubation. Patients were enrolled when receiving pressure support ventilation (PSV) of 5 cmH₂O, PEEP of 5 cmH₂O, and FIO₂ of 40% (PS). Subsequently, each patient received a trial of PSV of 0 cmH₂O, PEEP of 5 cmH₂O, and FIO₂ of 40% (CPAP), a trial of PSV of 0 cmH₂O, PEEP of 5 cmH₂O and FIO₂ of 21% (CPAP-R/A), and a 1-min spontaneously breathing room air trial off the ventilator (T-piece). Trials were carried out in random order. Respiratory frequency (*f*) and tidal volume (VT) were measured during PS, CPAP, CPAP-R/A, and T-piece in all patients. RSBI (*f*/VT) was determined for each patient under all experimental conditions, and the average RSBI was compared during PS, CPAP, CPAP-R/A, and T-piece. RSBI was significantly smaller during PS (46 ± 8 bpm/l), CPAP (63 ± 13 bpm/l) and CPAP-R/A (67 ± 14 bpm/l) versus T-piece (100 ± 23 bpm/l). There was no significant difference in RSBI between CPAP and CPAP-R/A. RSBI during CPAP and CPAP-R/A were significantly smaller than RSBI during T-piece. In all patients RSBI values were less than 105 bpm/l during PS, CPAP, and CPAP-R/A. However, during T-piece the RSBI increased to greater than 105 bpm/l in 13 of 36 patients.

Noninvasive ventilation, delivered either by continuous positive airway pressure (CPAP) or pressure support ventilation, is recommended in cardiogenic pulmonary edema (CPE). In 36 patients with severe CPE, Rusterholtz et al. [72] compared noninvasive CPAP and proportional assist ventilation (PAV), with the hypothesis that PAV would be better than CPAP with regard to physiological effects and clinical benefit. Failure rate, defined by the onset of pre-defined intubation criteria, severe arrhythmias

or patient's refusal, was similar between groups (37 vs 41% with CPAP and PAV, respectively). Intubation, myocardial infarction, ICU mortality, and changes in physiological parameters were also similar in the two groups. Although suffering from some limitations, this study suggests that CPAP, a technique widely available, relatively inexpensive, and easy to use, should be preferred in these patients.

In a physiologic study, Ferreira and colleagues [73] evaluated the trigger performance of mid-level ICU mechanical ventilators during assisted ventilation. The aim was to compare the triggering performance of mid-level ICU mechanical ventilators with a standard ICU mechanical ventilator in an experimental bench study. Ten mid-level ICU ventilators were compared to an ICU ventilator at two levels of lung model effort, three combinations of respiratory mechanics (normal, COPD and ARDS) and two modes of ventilation, volume and pressure assist/control. Performance varied widely among ventilators. Mean inspiratory trigger time was <100 ms for only half of the tested ventilators. The mean inspiratory delay time (time from initiation of the breath to return of airway pressure to baseline) was longer than that for the ICU ventilator for all tested ventilators except one. The pressure drop during triggering (P_{trig}) was comparable with that of the ICU ventilator for only two ventilators. Expiratory settling time (time for pressure to return to baseline) had the greatest variability among ventilators. Triggering differences among these mid-level ICU ventilators and with the ICU ventilator were identified. Some of these ventilators had a much poorer triggering response with high inspiratory effort than the ICU ventilator. These ventilators do not perform as well as ICU ventilators in patients with high ventilatory demand.

Another interesting aspect is the possibility of reducing patient-ventilator asynchrony by reducing tidal volume during pressure support ventilation [74]. The aim of this study was to identify ventilatory setting adjustments that improve patient-ventilator synchrony during pressure support ventilation in ventilator-dependent patients by reducing ineffective triggering events without decreasing tolerance. Twelve intubated patients with more than 10% of ineffective breaths while receiving pressure support ventilation were enrolled. Flow, airway pressure, esophageal-pressure, and gastric-pressure signals were used to measure patient inspiratory effort. To decrease ineffective triggering the following ventilator setting adjustments were randomly adjusted: pressure support reduction, insufflation time reduction, and change in end-expiratory pressure.

Reducing pressure support from 20.0 cmH₂O to 13.0 reduced tidal volume (10.2 ml/kg predicted body weight to 5.9) and minimized ineffective triggering events [45% of respiratory efforts (36–52) to 0% (0–7)], completely abolishing ineffective triggering in two-thirds of patients. The ventilator respiratory rate increased due to unmasked

wasted efforts, with no changes in patient respiratory rate [26.5 breaths/min (23.1–31.9) vs. 29.4 (24.6–34.5)], patient effort, or arterial PCO₂. Shortening the insufflation time reduced ineffective triggering events and patient effort, while applying positive.

Rose and colleagues [75] tried to identify the criteria that define and distinguish airway pressure release ventilation and biphasic positive airway pressure. Both modes are pressure-limited and time-cycled. They allow unrestricted spontaneous breathing independent of ventilator cycling, using an active expiratory valve. Authors abstracted data from 50 studies and 18 discussion articles. Compared to BIPAP, APRV was described more frequently as extreme inverse inspiratory:expiratory ratio and used rarely as a noninverse ratio. Authors concluded that ambiguity exists in the criteria that distinguish APRV and BIPAP and, when applied with the same inspiratory:expiratory ratio, no difference exists between the two modes. They also concluded that commercial ventilator branding may further add to confusion and generic naming of ventilator modes combined with consistent definitions of parameters defining and distinguishing APRV and BIPAP would help standardize research designed to investigate the effect of these modes.

Several studies have been dedicated to the choice and performance of innovative interfaces for noninvasive ventilation. Mojoli and colleagues [76] evaluated CO₂ rebreathing during noninvasive ventilation delivered by helmet in a bench study. The Authors applied pressure-control ventilation to a helmet mounted on a physical model. They increased CO₂ production (V/CO_2) from 100 to 550 ml/min and compared mean inhaled CO₂ (iCO₂, mean) with end-inspiratory CO₂ at airway opening (eiCO₂), end-tidal CO₂ at Y-piece (yCO₂) and mean CO₂ inside the helmet (hCO₂). In series 2, they observed, at constant V/CO_2 , effects on CO₂ rebreathing of inspiratory pressure, respiratory mechanics, the inflation of cushions inside the helmet and the addition of a flow-by. The best estimate of CO₂ rebreathing was provided by hCO₂: differences between iCO₂, mean and hCO₂, yCO₂ and eiCO₂ were 0.0 ± 0.1 , 0.4 ± 0.2 and $-1.3 \pm 0.5\%$. In series 2, hCO₂ inversely related to the total ventilation (MV_{total}) delivered to the helmet-patient unit. The increase in inspiratory pressure significantly increased MV_{total} and lowered hCO₂. The low lung compliance halved the patient:helmet ventilation ratio but led to minor changes in MV_{total} and hCO₂. Cushion inflation, although it decreased the helmet's internal volume by 33%, did not affect rebreathing. A 8-l/min flow-by effectively decreased hCO₂.

Helmet ventilation and carbon dioxide rebreathing was also assessed by Racca and colleagues [77]. The Authors examined whether additional helmet flow obtained by a single-circuit and a modified plateau valve applied at the helmet expiratory port (open-circuit ventilators) improves CO₂ washout by increasing helmet

airflow in a group of healthy volunteers. Helmet continuous positive airway pressure and pressure support ventilation delivered by an ICU ventilator (closed-circuit ventilator) and two open-circuit ventilators equipped with a plateau valve placed either at the inspiratory or at the helmet expiratory port. The Authors examined helmet air leaks, breathing pattern, helmet minute ventilation (E_h), minute ventilation washing the helmet (E_{wh}), CO_2 wash-out, and ventilator inspiratory assistance. Air leaks were small and similar in all conditions. Breathing pattern was similar among the different ventilators. Inspiratory and end-tidal CO_2 were lower, while (E_h) and (E_{wh}) were higher only using open-circuit ventilators with the plateau valve placed at the helmet expiratory port. This occurred notwithstanding these ventilators delivered a lower inspiratory assistance. This study suggests that additional helmet flow provided by open-circuit ventilators can lower helmet CO_2 rebreathing. However, inspiratory pressure assistance significantly decreases using open-circuit ventilators, still casting doubts on the choice of the optimal helmet ventilation setup.

Subject-ventilator synchrony during neural versus pneumatically triggered noninvasive helmet ventilation was assessed by Moerer and colleagues [78]. As patient-ventilator synchrony during noninvasive pressure support ventilation with the helmet is often compromised when conventional pneumatic triggering and cycling-off are used, a possible solution to this shortcoming is to replace the pneumatic triggering with neural triggering and cycling-off using the diaphragm electrical activity (EAdi). This signal is insensitive to leaks and to the compliance of the ventilator circuit. Seven healthy human volunteers were enrolled. Pneumatic triggering and cycling-off were compared to neural triggering and cycling-off during NIV delivered with the helmet. Triggering and cycling-off delays, wasted efforts, and breathing comfort were determined during restricted breathing efforts (<20% of voluntary maximum EAdi) with various combinations of pressure support (PSV) (5, 10, 20 cmH_2O) and respiratory rates (10, 20, 30 breath/min). During pneumatic triggering and cycling-off, the subject-ventilator synchrony was progressively more impaired with increasing respiratory rate and levels of PSV ($P < 0.001$). During neural triggering and cycling-off, effect of increasing respiratory rate and levels of PSV on subject-ventilator synchrony was minimal. Breathing comfort was higher during neural triggering than during pneumatic triggering ($P < 0.001$).

Another innovative mode has been evaluated by Xirouchaki [79]. The aim of this study was to examine the effectiveness of sustained use of PAV + in critically ill patients and compare it with pressure support ventilation (PS). A total of 208 critically ill patients mechanically ventilated on controlled modes for at least 36 h and meeting certain criteria were randomized to receive either PS ($n = 100$) or PAV + ($n = 108$). Specific written

algorithms were used to adjust the ventilator settings in each mode. PAV + or PS was continued for 48 h unless the patients met pre-defined criteria either for switching to controlled modes (failure criteria) or for breathing without ventilator assistance. Failure rate was significantly lower in PAV + than that in PS (11.1 vs. 22.0%, $P = 0.040$, OR 0.443, 95% CI 0.206–0.952). The proportion of patients exhibiting major patient-ventilator dys-synchronies at least during one occasion and after adjusting the initial ventilator settings, was significantly lower in PAV + than in PS (5.6 vs. 29.0%, $P < 0.001$, OR 0.1, 95% CI 0.06–0.4). The proportion of patients meeting criteria for unassisted breathing did not differ between modes. The Authors concluded that PAV + may be used as a useful mode of support in critically ill patients. Compared to PS, PAV + increases the probability of remaining on spontaneous breathing, while it considerably reduces the incidence of patient-ventilator asynchronies.

One of the new modalities that is acquiring popularity is the neurally adjusted ventilatory assist (NAVA). In a crossover, prospective, randomized controlled trial conducted on 14 intubated and mechanically ventilated patients, Colombo and colleagues [80] assessed the physiologic response to varying levels of NAVA and pressure support ventilation (PSV). PSV was set to obtain a tidal volume of 6–8 ml/kg with an active inspiration. NAVA was matched with a dedicated software. The assistance was decreased and increased by 50% with both modes. Arterial blood gases (ABGs), tidal volume (VT:/kg), peak EAdi, airway pressure (P_{aw}), neural and flow-based timing. Asynchrony was calculated using the asynchrony index (AI). There was no difference in ABGs regardless of mode and assist level. The differences in breathing pattern, ventilator assistance, and respiratory drive and timing between PSV and NAVA were overall small, but at the highest assist level, the authors found a greater tidal volume and lower breathing frequency in PSV respect to NAVA. During NAVA there was no mismatch between neural and flow-based timing. The researchers concluded that NAVA averted the risk of over-assistance, avoided patient-ventilator asynchrony, and improved patient-ventilator interaction.

The ability of using dynamic airway pressure curve profile and elastance for positive end-expiratory pressure titration has been evaluated by Carvalho and colleagues [81] to assess the ability of three indices derived from the airway pressure curve for titrating positive end-expiratory pressure (PEEP) to minimize mechanical stress, while improving lung aeration assessed by computed tomography (CT). Twelve pigs were anesthetized and mechanically ventilated with tidal volume of 7 ml/kg. In non-injured lungs ($n = 6$), PEEP was set at 16 cmH_2O and stepwise decreased until zero. Acute lung injury was then induced either with oleic acid ($n = 6$) or surfactant depletion ($n = 6$). A recruitment maneuver was performed, the PEEP set at 26 cmH_2O and decreased stepwise until zero. CT

scans were obtained at end-expiratory and end-inspiratory pauses. The elastance of the respiratory system (E_{rs}), the stress index and the percentage of volume-dependent elastance (%E (2)) were estimated. In non-injured and injured lungs, the PEEP at which E_{rs} was lowest (8–4 and 16–12 cmH₂O, respectively) corresponded to the best compromise between recruitment/hyperinflation. In non-injured lungs, stress index and %E (2) correlated with tidal recruitment and hyperinflation. In injured lungs, stress index and %E (2) suggested overdistension at all PEEP levels, whereas the CT scans evidenced tidal recruitment and hyperinflation simultaneously.

Intrapulmonary percussive ventilation (IPV) is a form of high-frequency ventilation superimposed on conventional ventilation. Dellamonica et al. [82] designed a bench study to assess the efficacy of various humidification devices and to measure intrapulmonary pressures and volumes resulting from IPV under various conditions of respiratory system resistance and compliance, and to test the behavior of several ventilators in response to the addition of IPV. Adequate humidification could only be obtained with a heated humidifier placed on the inspiratory line downstream of the IPV device. The IPV device behaved as an additional ventilator that added pressures and volumes to tidal ventilation: end-inspiratory intrapulmonary pressures were increased up to 10 cmH₂O, delivered volumes increased up to 237 ml and a variable level of intrinsic PEEP was generated depending on the driving ventilator used and extrinsic PEEP level. Tested ventilators often showed abnormal function: flow monitoring was unreliable and autotriggering and missing cycles were common. These factors must be taken into account before clinical use of IPV.

The problem of air leaks was analyzed by Andrieu and colleagues [83] who tested in experiments in healthy volunteers, two different approaches to compensate for airway leaks and to provide the desired tidal volume. Both measurement of expired volume to correct for the desired inspired volume and the use of inductive plethysmography enabled full compensation and the plethysmographic technique also allowed correction for expiratory leaks.

Manual ventilation as temporary substitution of the mechanical ventilation is still a common practice.

In intubated patients manually ventilated, Lovat and colleagues [84] using the Smart Bag [a bag device equipped with an inspiratory gas flow-limiting valve (Smart Bag, 0-Two Medical Technologies Inc., Mississauga, ON, Canada)] limited the risks of excessive airway pressure and the fall of the ETCO₂, with hemodynamic effects similar to those of the Standard bag. The eight intubated patients enrolled in this study underwent two sessions of manual ventilation, first with the Standard bag and then with the Smart Bag. Compared with Standard bag, the Smart Bag provided a decrease of inspiratory flow, with a decrease of peak pressure and tidal volume, with similar expiratory time, but increased inspiratory time.

Sleep disturbances are common in critically ill patients and may adversely affect clinical outcomes. In 12 mechanically ventilated patients, Beecroft et al. [85] evaluated the accuracy of two methods used for measuring sleep, actigraphy (monitoring of gross motor activity) and behavioral assessment by the bedside nurse, by comparing them to overnight polysomnography, considered as the reference technique. Polysomnography revealed severe sleep disruption and abnormal sleep architecture. Actigraphy overestimated total sleep time and sleep efficiency. The overall agreement between actigraphy and polysomnography was <65%. Nurse assessment underestimated the number of awakenings. Estimated total sleep time, sleep efficiency and number of awakenings by nurse assessment did not correlate with polysomnographic findings. Authors concluded that actigraphy and behavioral assessment by the bedside nurse are inaccurate and unreliable methods to monitor sleep in critically ill patients.

Endotracheal intubation and tracheostomy

Endotracheal intubation in critically ill patients is typically performed in unstable and with poor physiologic reserve individuals. In addition, many of the medications used in this setting have adverse hemodynamic consequences. The consequence is a high risk of complications. Griesdale et al. [86] characterized the risk of complications related to endotracheal intubation in a Canadian academic ICU where the intubating physicians have varying airway management skills and experience, and second, to determine the risk of complications, ICU and hospital mortality comparing expert to non-expert intubating physicians. This cohort study was performed during 5 months and included 136 patients. There were no deaths during intubation. Experts were successful within two attempts in 94% and non-experts in 82% ($P = 0.03$). Overall risk of complications was 39%, including severe hypoxemia, severe hypotension, esophageal intubation and frank aspiration. The propensity score-adjusted odds ratio for any complication, and for ICU and hospital mortality did not differ between expert and non-expert intubating physician. They concluded that endotracheal intubation in the critically ill is associated with a high risk of complications and that every attempt should be made to reduce complications in this high-risk population.

Air leaks during endotracheal intubation may occur. The Kolobow group [87] describe a standard high volume low pressure cuff draped with a second highly elastic cuff made of low protein guayule natural latex rubber with a layer of gel between the cuffs. This cuff caused less leakage at different intracuff pressures in model experiments as compared to other commercially available tracheal tubes.

Tracheostomy is a common procedure in ventilated ICU patients and may hasten ICU discharge. In a retrospective study, Fernandez et al. [88] evaluated the effect of tracheostomy on ward mortality and its relation to patient vulnerability. This latter variable was assessed by the Sabadell score, a subjective scoring system which classifies patients at ICU discharge according to the expected outcomes at hospital discharge. Over a 3-year period, 936/1,502 (62%) patients survived the ICU and were transferred to the ward; of these, 130 (13.9%) were tracheostomized. Ward mortality was significantly higher in patients with tracheostomy than in those without (26 vs. 7%). Higher ward mortality among tracheostomized patients was observed only in those with intermediate Sabadell score, but not in the “good prognosis” and “expected to die in hospital” groups. Multivariate analysis found three factors associated with ward mortality: age, tracheostomy tube in place, and Sabadell score. The higher mortality rate in patients discharged from the ICU

before decannulation might reflect, however, the greater severity of these patients rather than an increased risk inherent in tracheostomy.

In a prospective, randomized study, Blot et al. [89] compared early tracheotomy (ET) with prolonged intubation (PI) in severely ill patients requiring prolonged MV. Patients were randomized to either ET within 4 days or PI. The primary end-point was 28-day mortality. A sample size of 470 patients was considered necessary to obtain a reduction from 45 to 32% in 28-day mortality. After 30 months, 123 patients had been included (ET = 61, PI = 62) in 25 centers and the study was prematurely closed. All group characteristics were similar upon admission to ICU. No difference was found between the two groups for any of the primary or secondary end-points. Greater comfort was the sole benefit afforded by tracheotomy after subjective self-assessment by patients. An accompanying editorial comments on the lack of power to draw any firm conclusions [90].

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