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Haemodynamics

How to assess haemodynamic alterations?

Several devices use pulse pressure to determine stroke volume, with or without calibration. However, pulse pressure can also be influenced by other factors including vascular tone and arterial stiffness. Lamia et al. [1] evaluated the role of arterial stiffness using radial applanation tonometry. This technique extrapolates central aortic pressure from peripheral recordings. Arterial stiffness was determined using a complex analysis of estimated central aortic pressure curve and stroke volume (independently measured by echocardiography). These authors observed that pulse pressure is dependent on stroke volume, and body surface area and, to a lesser extent, to arterial stiffness. In older patients the contribution of arterial stiffness was more prominent. For a given arterial stiffness stroke volume accounts for 49% of stroke volume variability.

Kozieras et al. [2] investigated the effect of acute increase in systemic vascular resistance on transpulmonary thermodilution indices. Although one may expect cardiac volumes to increase during an acute increase in afterload, the impact on extravascular lung water is less straightforward. To evaluate the impact of errors in measurements and mathematical coupling the authors studied 24 patients with circulatory failure cardiac output and measured global end-diastolic volume and extravascular lung water with transpulmonary thermodilution before and after an acute increase in mean arterial pressure (from 65 to 90 mmHg) by increasing norepinephrine doses. Cardiac index slightly increased (by 3%) while global end diastolic volume increased by 6% and extravascular lung water by 7%. In 8 patients left ventricular dilation was also determined by trans-oesophageal echocardiography; in these patients the changes in end diastolic volume were well correlated with changes in left ventricular end diastolic area. These data suggested that measurements of end diastolic volumes and extravascular lung water are not markedly affected by mathematical coupling of data.

Other methodological aspects were also covered by Heringlake et al. [3] who compared cardiac output measurements obtained by pulmonary arterial thermodilution and thoracic bio-impedance. Despite marked improvements electrical bio-impedance does not yet seem ready for use in critically ill patients. Twenty-nine patients were investigated during cardiac surgery; electrical bio-impedance failed to reliably measure cardiac output, with unacceptably high limits of agreement of 3.2 l/min. Spontaneous changes in cardiac output were underestimated by electrical bio-impedance (14% vs. 38% by thermodilution).

Haemodynamic monitoring by echocardiography is used increasingly in ICUs [4]. Patent foramen ovale should be always detected when a patient is hypoxaemic. The end-inspiratory occlusion manoeuvre enhances the sensi-

tivity of trans-oesophageal echocardiography performed in ventilated ICU patients [5]. The right ventricle is increasingly investigated, especially by echocardiography. The tricuspid annular plane systolic excursion has been recommended to investigate right ventricular function in cardiology. Its use in the ICU helps in assessing both right and left ventricular function [6]. Experienced users can reliably determine most indices. However, training in echocardiography remains a challenge. Vignon et al. [7] evaluated the impact of an accelerated focused training. The students underwent a 3h training course followed by 5 h off hands-on training over a 2-month period. The courses focused on simple indices of left ventricular systolic function, left and right ventricular dilation, and pericardial effusion. Thereafter the performances of the pupils were evaluated; in each patient who required an echocardiography this evaluation was obtained twice within a 1 h, once by a pupil and once by an experienced observer, in a random order. Agreement with the clinical decision was excellent between experienced observers and pupils, as κ values ranged from 0.66 to 0.76 on the different items. In the same issue Charron et al. [8] developed a scoring system to evaluate pupils performances. They based the evaluation on the ability to address simple clinical questions (assessment of cardiac contractility, evaluation of fluid responsiveness, right ventricular dysfunction and pericardial effusion), using semi-quantitative assessment as validated by the same authors [9]. The scoring system focused on quality of the echocardiographic investigation, evaluation of the semi-quantitative data, measurements of reproducible variables and evaluation of the adequacy of the pupil to integrate the findings into a diagnostic and therapeutic algorithm. Although performances were quite moderate at 1 month (median score 21, maximal value 42), these rapidly improved at 3 months (median score 32) and 6 months (median score 37). A satisfactory score of 35 was obtained after having performed at least 20 trans-oesophageal echocardiographic examinations. The accompanying editorial by Poelaert and Mayo [10] acknowledged the specific characteristics of echocardiography in the ICU, as opposed to those in the cardiology or anaesthesiology department, and emphasized the critical role that intensivists should play in defining the optimal training in echocardiography in ICU. These issues were discussed briefly in the journal [11].

Measurement of venous oxygen saturation (SvO_2) is another important aspect of haemodynamic monitoring. SvO_2 has long been used to determine the adequacy of cardiac output as it reflects the balance between oxygen delivery and consumption of all organism. However, SvO_2 requires the presence of a pulmonary artery catheter. SvO_2 thus cannot be measured when less invasive haemodynamic techniques are used. An important question is therefore whether central venous oxygen saturation ($ScvO_2$) can be used as a surrogate for SvO_2 . Sander et al. [12] simultaneously measured $ScvO_2$ and SvO_2 in

60 patients undergoing cardiac surgery at different times before and after institution of cardiopulmonary bypass. Globally the correlation and agreement between the two measurements was satisfactory; however, ScvO₂ differed from SvO₂ in several instances, especially when O₂ extraction is high. When ScvO₂ is normal, above 70%, it is very likely that SvO₂ is also normal. However, when abnormal (below 70%), the correlation between the two variables became poor.

Measuring continuously ScvO₂ may appear attractive. Fiberoptic technology can be applied to both SvO₂ and ScvO₂ measurement. The precise determination of ScvO₂ requires blood sampling and analysis by a blood gas analyser. Molnar et al. [13] showed that fiberoptic measurements can be used reliably to track changes in ScvO₂. Evaluating a newly developed fiberoptic catheter for ScvO₂ monitoring (Cevox, by Pulsion) to intermittent blood gas analysis, more than 500 matched pairs were generated in a heterogeneous group of 53 critically ill patients. There was good correlation between the two measurements, with no significant bias between the two methods, but the limits of agreement were poor (-13.2% to +12.5%). Nevertheless, changes between two successive blood gas measurements were well tracked by changes in fiberoptic measurements.

Optimization of haemodynamic invasive monitoring is possible and important. Subtracting the expiratory change in intra-abdominal (bladder) pressure from end-expiratory central venous pressure (CVP) in spontaneously breathing patients yields a more reliable estimate of transmural CVP than does the uncorrected CVP value [14]. In patients who have a pulmonary artery catheter changes in Paop during Mueller manoeuvres gives a lower estimate of changes in pleural pressure [15]. Prediction of fluid responsiveness was tested in spontaneously breathing patients, showing that Δ pulse pressure and Δ systolic pressure are less reliable to predict fluid challenge in mechanically ventilated patients [16]. Fluid responsiveness may be tested by passive leg raising in both spontaneous and mechanically breathing patients [17].

Transpulmonary thermodilution can assess pulmonary permeability. This is based on two indexes: extravascular lung water/pulmonary blood volume and extravascular lung water index/global end-diastolic volume index. This approach helps in determining the mechanism of pulmonary oedema in critically ill patients.

Another option is the continuous non-invasive cardiac output monitoring (NICOM) based on chest bio-reactance. Cardiac output measured by NICOM had most often acceptable accuracy, precision and responsiveness [18].

Invasive cardiovascular monitoring implies central venous cannulations that may carry a high morbidity rate. A recent study shows that after two unsuccessful cannulation attempts associated complications are very likely. Accordingly, any physician should be replaced after unsuccessful cannulation [19].

Evaluating cardiovascular function

Estimating contractility remains a difficult challenge as most of the measurements available at bedside may be affected by preload and afterload. In experimental conditions and in the cardiac catheterization laboratory the evaluation of cardiac function relies on the analysis of pressure/volume loops. These require the use of specific intravascular catheters and manipulations of preload and afterload with vasopressors and vasodilatory agents (or inferior vena cava occlusion in experimental conditions). Preliminary reports suggest that end-systolic elastance, a load independent index of contractility, may be determined by analysis of arterial trace obtained on a peripheral arterial catheter and volumes determined by echocardiography. Unfortunately, manipulation of preload remains problematic. Kim et al. [20] hypothesized that preload manipulation with apnoeic continuous positive airway pressure (CPAP) is equivalent to inferior vena cava occlusion. End-systolic elastance determinations at three levels of CPAP (5, 10, and 15 cmH₂O) were compared to inferior vena cava occlusion in dogs monitored by intravascular catheters. They observed that end-systolic elastance was reliably measured at 5 cmH₂O but not at the higher levels of CPAP. Whether the low level of CPAP can be sufficient to manipulate preload in critically ill patients requires further evaluation.

Another important aspect of bedside haemodynamic evaluation is the determination of fluid responsiveness. Respiratory variation in stroke volume has been shown to reliably predict fluid responsiveness in patients under mechanical ventilation. However, stroke volume measurements are not always available. Pulse pressure can be used as a surrogate of cardiac output, but it requires invasive pressure measurements. Feissel et al. [21] evaluated whether variations in plethysmographic pulse wave. The plethysmographic pulse wave is proportional to pulse pressure, and the authors therefore hypothesized that respiratory variations in plethysmographic pulse wave would predict fluid responsiveness. In 23 mechanically ventilated patients respiratory variation greater than 14% was associated with an increase in cardiac output. Another important question concerns the prediction of fluid responsiveness in patients breathing spontaneously. One may hypothesize that spontaneous ventilation induces changes in intrathoracic pressures opposed to mechanical ventilation. Two studies [16, 22] showed that respiratory variation in stroke volume as determined by echocardiography failed to predict fluid responsiveness in patients breathing spontaneously. In an attempt to standardize the changes in pressures, Soubrier et al. [16] proposed applying a forced ventilatory manoeuvre, but this manoeuvre failed to improve the accuracy of the test. Lamia et al. [22] and Maizel et al. [17] evaluated the predictive value of a passive leg raising test on fluid responsiveness in patients breathing spontaneously. Both studies measured stroke

volume by echocardiography. The two studies yielded very similar results: an increase in stroke volume by more than 12% [17, 22] was associated with a positive response to fluid challenge. The advantages and limitations of the various tests available to predict fluid responsiveness in patients breathing spontaneously were reviewed in an accompanying editorial [23].

Spöhr et al. [24] achieved additional information on cardiac filling parameters during septic shock. The authors found that the averaged bias in continuous measurement of cardiac output by both a modified pulmonary artery catheter and pulse-contour analysis by the PiCCO system (Pulsion Medical Systems, Munich, Germany) was small, but with wide variability. No correlation was found between global end-diastolic volume and right ventricular end-diastolic volume. The conclusion was that the clinical importance of various cardiac filling parameters needs further investigation.

Biomarkers may be helpful in the detection of patients with altered cardiac function. Nicolas-Robin et al. [25] evaluated the value of N-terminal pro-brain natriuretic peptide (NT-proBNP) and circulating cardiac troponins T and I to diagnosis cardiac dysfunction in 63 brain-dead patients. Left ventricular contractility was determined by trans-oesophageal echocardiography (measuring fractional area change). Even the use of a single biomarker detected most patients with severely altered cardiac dysfunction, but the combination of NT-proBNP and cTNT identified all these patients. The receiver operating characteristic (ROC) curve area analysis showed that this combination of biomarkers gave a better result (0.87) than any other single biomarker (0.72–0.82). These tests can be used as screening for cardiac function, especially in conditions where echocardiography is not easily available.

In particular conditions, such as in patients with acute ischaemic stroke or subarachnoid or intracranial haemorrhage, serum NT-proBNP may be not very useful in detecting acute heart failure or LV dysfunction [26]. Right ventricular failure is often difficult to diagnose in ICU [27]. In haemodynamically stable pulmonary embolism B type natriuretic peptide (BNP) and troponin I measurements are helpful on admission to diagnose or to rule out right ventricular failure [28]. Cardiac consequences of unsuccessful respiratory weaning can also be monitored by plasma measurements of BNP and atrial natriuretic peptide (ANP). ANP appears to be more specific than BNP in detecting successful weaning [29]. This may be related to ANP stored in the atria and directly released during a stimulus while BNP needs to be produced before being released.

Perioperative period of cardiac surgery

Optimal fluid management guided by a global end-diastolic volume index higher than 640 ml/m² associated

with a cardiac index greater than 2.5 l min⁻¹ m⁻² induced a reduction in the dose and duration of catecholamine administration and the duration of mechanical ventilation [30]. A Belgian single-centre survey presented 4 years of follow-up of 156 patients operated on for congenital heart disease [31], showing that Euroscore (the predictive score of mortality after cardiac surgery) overestimates the risk of surgery in adults with congenital heart disease. Although requiring prolonged ICU stay, patients with complex congenital defect had a good outcome. A low perioperative mortality was confirmed in a further study showing a total mortality of 4.4% in 342 adult with congenital heart diseases [32]. Predictive factors were: abnormal thyroid function, creatinine and bilirubin.

Evaluating tissue perfusion

Lactate is a hallmark of tissue hypoxia [33], but multiple factors may explain elevated lactate levels in patients with sepsis [34]. Elevated lactate levels are often considered as indices of hypoperfusion when these are observed on admission during the very early course of sepsis. Measurement of lactate levels has been recommended by recent guidelines [35]. Two articles evaluated the role of lactate measurements during infection, even in patients not yet presenting signs of sepsis. Howell et al. [36] studied patients with infection diagnosed on admission to the emergency department and found that decreased blood pressure and elevated lactate levels were both independently associated with a poor outcome, and that the combination of the two factors was associated with the worst outcome. A total of 1,287 patients were included, 73 of whom died in hospital within 28 days.

Trzeciak et al. [37] used a Bayesian analysis to evaluate the additive value of lactate measurements on clinical evaluation. They investigated 1,177 patients, whose mortality rate was 19%. Admission lactate levels above 4 mmol/l were associated with a six-fold increase in mortality. Elevated lactate levels helped identifying patients at risk of poor outcome, while normal blood lactate cannot be considered reassuring, as it failed to identify patients with a better outcome. The critical role for lactate measurements was further highlighted in an accompanying editorial [38].

Other techniques can be used to evaluate perfusion alterations in septic patients. Creteur et al. [39] measured muscle tissue saturation (StO₂) with near infrared spectroscopy in patients with severe sepsis, ICU controls and healthy volunteers. StO₂ did not distinguish between the different groups. After an ischaemic challenge (transiently occluding forearm blood flow with a cuff, and evaluating the recovery of StO₂ after occlusion) the recovery slope was lower in septic patients than in ICU controls and healthy volunteers, suggesting an impaired microvascular perfusion or impaired O₂ utilization in septic patients.

These alterations were more severe and failed to improve in non-survivors, while they improved over time in survivors. This simple occlusion test appears attractive for identifying patients with severe alterations in tissue perfusion and oxygenation.

How to treat haemodynamic alterations?

Fluid administration is one of the most common therapeutic interventions in critically ill patients, especially in early phases of resuscitation. The effects of fluids may be limited by an increased microvascular permeability. Capillary leak may induce pulmonary and tissue oedema, limiting O₂ exchanges, and the increase in plasma volume. Dubniks et al. [40] evaluated the capacity to expand plasma volume of albumin, gelatin, starches and saline in a model of anaphylactic shock in rats. To compensate for the different volume of distribution a four times larger volume of saline was administered (80 ml/kg) than colloids (20 ml/kg for each of the solutions). All solutions had a lower plasma expanding capacity than in models with normal permeability, but albumin increased more plasma volume (17 ± 3 ml/kg) than gelatin (8 ± 4), starches (7 ± 4) and saline (12 ± 3). These short-term results suggest that albumin had better expanding properties than artificial colloids or saline in this model of increased microvascular permeability.

A place for antioxidants?

Antioxidant substances may be considered, especially in some surgical conditions associated with reactive oxidant species (ROS) generation such as aortic cross-clamping and cardiopulmonary bypass. ROS generation in these conditions is frequently associated with organ dysfunction, such as acute respiratory distress syndrome (ARDS) and renal failure. Several antioxidant substances have been tried including superoxide dismutase (SOD) and desferoxamine, but usually these substances modulate only one of the multiple pathways involved in the effects of ROS. Kick et al. [41] tested the effects of new nutritional formula (Glisodine, a combination of a melon extract and gliadin, containing high amounts of SOD, catalase and glutathione peroxidase) with multiple antioxidant properties in a model of aortic cross-clamping in swine. The diet was administered as a 14-day pretreatment. The diet had no effect on systemic and regional haemodynamics. The levels of plasma SOD, catalase and glutathione peroxidase activity were not affected by aortic clamping; however, erythrocyte glutathione peroxidase was markedly decreased during clamping, and this decrease was blunted by the diet. Although the impact on antioxidant activity may appear very limited, the diet limited apoptotic damage in circulating lymphocytes and spinal cord but not in the kidneys. Nevertheless, this diet did not affect organ

function. These results raise the question of whether we should modulate single or multiple antioxidant pathways.

Cardiac arrest

A 2-year study from Taiwan detected predictive factors of ICU survival in 58 adults successfully resuscitated from cardiac arrest [42]. The study found that 27 patients survived to hospital discharge. Left ventricular ejection fraction less than 40% and isovolumic relaxation time longer than 100 ms, both measured 6 h post-resuscitation, predicted poor outcomes. The same group showed that post-resuscitation accelerated idioventricular rhythm also predicts a poor survival rate [43]. Refractory cardiac arrest recently benefit from extracorporeal life support (ECLS). Over 2 years a French medical ICU centre implanted ECLS under continuous cardiac massage in 17 patients, including 12 poisonings [44]. Three cardiotoxic-poisoned patients were alive at 1-year follow-up without sequelae. This study shows that implantation of ECLS is feasible in any ICU.

Pneumonia, infections and sepsis

Epidemiology

The mortality attributable to ventilator-associated pneumonia (VAP) ranges from 33% to 50%. Nevertheless many studies have found no excess mortality attributable to VAP, suggesting that outcome is related mainly to the severity of the underlying critical illness. This apparent contradiction may be due to differences in severity, early or late onset of VAP, the micro-organisms involved, the appropriateness of the empirical antibiotic treatment or the presence or absence of other infections during ICU stay. To determine the impact of VAP on ICU mortality and whether it is related to time of onset of pneumonia Valles et al. [45] prospectively followed 101 patients undergoing mechanical ventilation for more than 72 h, 40 of whom developed VAP. ICU mortality in the non-VAP group was 27.9%, closely matching Simplified Acute Physiology Score II predicted mortality 27.4%. In contrast, mortality in the VAP group was higher than predicted (45% vs. 26.5%, $p < 0.01$), yielding an attributable mortality of 18.5% (95% CI 3.1–34.8), or a relative risk of 1.7 (95% CI 1.1–23.2). This excess mortality was restricted mainly to patients with late-onset VAP and was only marginally reduced with appropriate empirical antibiotic treatment.

Prompt initiation of appropriate therapy is a cornerstone in VAP management. One way to improve the selection of initial empirical therapy in patients with VAP is to improve knowledge of bacterial species responsible for infection, based on local epidemiology and clinical factors. Using a large database of 196 VAP episodes

documented by quantitative respiratory cultures Agbaht et al. [46] demonstrated that methicillin-sensitive *Staphylococcus aureus* (MSSA) was more frequent in trauma (34.5% vs. 11.5%, $p < 0.01$) but methicillin-resistant *S. aureus* (MRSA) more frequent in non-trauma (2% vs. 11.5%, $p < 0.01$). In trauma patients MSSA episodes were equally distributed between early- and late-onset VAP (51% vs. 49%), but no MRSA episode occurred in the early-onset group. This suggests that the underlying disease should be considered in the initial decision on antibiotic choice. Because no MRSA was isolated during the first 10 days of mechanical ventilation on trauma patients, MRSA coverage in these patients seems necessary only 10 days after admission.

Hospital-acquired infections due to multidrug-resistant Gram-negative bacteria represent a growing problem in many ICUs, making it indispensable that the relevant risk factors be more clearly identified. Confronted with an outbreak of five cases of VAP caused by pandrug-resistant *Pseudomonas aeruginosa* isolates that belonged to the same genotype and were positive for *bla*_{VIM-1}-like genes, Mentzelopoulos et al. [47] conducted a case-control study in which cases were very well matched to contemporary controls. Time from ICU admission and mechanical ventilation duration to first VAP episode were similar. Prolonged exposure to carbapenems and colistin independently predicted pandrug-resistant *P. aeruginosa* pneumonia. The major factor of cross-transmission was the number of open suctioning procedures from outbreak onset to infection control reinforcement. The outbreak was resolved by improving hand hygiene and isolating all cases.

Leptospirosis is a zoonosis caused by the genus *Leptospira interrogans*, which has a high prevalence in tropical regions during rainy seasons and following hurricanes and flooding. Pulmonary forms of leptospirosis have been reported in the literature, but the exact incidence and impact on prognosis remain controversial. In a large retrospective series of 147 laboratory-confirmed leptospirosis Paganin et al. [48] examined the factors associated with severity. Pulmonary forms were more frequent (85%) than in previous reports, with 85 cases (65.3%) having abnormal chest radiography. Independent factors related to ICU admission were: age over 46 years (OR 3.0), creatinine higher than 200 $\mu\text{mol/l}$ (OR 6.7), shock (OR 13.9) and acute respiratory failure (OR 20.7). Mortality was 12.9%. The only factor independently related to mortality was need for mechanical ventilation (OR 20.9). The *Icterohaemorrhagiae* serogroup was found in 62 cases (43%) but was not related to death. These findings confirm that leptospirosis remains a real medical challenge for patients with multiple organ failure.

P. aeruginosa is one the major pathogens causing respiratory tract infections in ICU patients. Treatment is frequently hampered because of the intrinsic and acquired resistance traits of these bacteria. In an Italian ICU over

a 6-month study period 30% of all patients acquired sustained respiratory tract colonization with *P. aeruginosa*, even a higher incidence of infection was monitored (36.7%) [49]. In this unit a dominant clone, identified by pulsed-field gel electrophoresis profiles, accounted for 61% of isolates in 46% of colonized patients, strongly suggesting cross-transmission as an important route of acquisition. In a case-control study [50] antifungal treatment was associated with a reduced risk of developing VAP or tracheobronchial colonization by *P. aeruginosa*. This interesting finding does not seem to be explained by the antimicrobial properties of antifungal agents.

Diagnosis

In the absence of a clinically available gold standard VAP is usually diagnosed according to a combination of criteria: systemic signs of infection, abnormalities on chest radiography, and microbiological identification of pathogens; however, each of these criteria combines high sensitivity with low specificity. In an attempt to improve diagnostic accuracy Schurink et al. [51] examined the performance of a fully automated Bayesian decision-support system previously developed for diagnosing and/or ruling out VAP. The study was based on a retrospective analysis of a large data base of 872 patients admitted to two ICUs, designed to explore the diagnostic and prognostic implications of various VAP signs and symptoms. When used on a daily basis, this decision-support system had an extremely high (> 99%) negative predictive value, permitting the diagnosis of VAP to be excluded in a situation in which the pre-test probability was low. When restricted to the days of antibiotics prescription for presumed respiratory tract infections, the predictions made from the decision-support system had a positive predictive value of 86% and a negative predictive value of 66%.

Luyt et al. [52] reported an interesting conclusion on the diagnosis of nosocomial pneumonia: by applying an invasive bronchoscopic approach there was no delay of the first appropriate antibiotic administration when clinical suspicion of VAP occurred during off-hours. Of the 152 VAP episodes occurring in 101 patients of this single-centre study 66 were diagnosed during off-hours, and the number of inappropriate initial antimicrobial treatments and the antibiotic prescription-to-administration times were the same during day shifts and off-hour shifts.

Sinusitis is a risk factor for VAP; its presence is underestimated and the diagnosis is often difficult. A new ultrasound approach for the bedside diagnosis of sinusitis has been proposed [53]. The authors of the study evaluated a postural change test comparing sinus ultrasound with computed tomography (CT) in cases of partial sinusogram. This investigation examined 150 patients by sinus ultrasound in half-sitting position. Defining partial sinusogram as the visualization of the hyperechogenic posterior

wall of the sinus, a postural change was performed with ultrasound achieved in supine position. When the patient was supine, if the partial sinusogram disappeared, the test was positive, while the lack of disappearance of the partial sinusogram was considered as a mucosal thickening and the test was negative. Radiological maxillary sinusitis, on CT performed on the same day, was defined as the presence of an air-fluid level and its absence as normal sinus or mucosal thickening. Of the 300 sinuses examined 90 had a partial sinusogram. CT confirmed the presence of radiological maxillary sinusitis in 55 cases. Sensitivity, specificity, and positive and negative predictive values of postural change test vs. CT were, respectively, 94.6%, 85.6%, 91.2% and 90.9%. The positive predictive value increased from 61% to 91.2% after the postural change test.

Krüger and colleagues [54] on behalf of the German competence network CAPNETZ Study Group showed that pro-atrial natriuretic peptide (MR-proANP) and pro-vasopressin (CT-proAVP) are useful new biomarkers for severity assessment, risk stratification for and outcome prediction in community-acquired pneumonia (CAP). MR-proANP, CT-proAVP, C-reactive protein (CRP), procalcitonin (PCT) and CRB-65 score were determined on admission in 589 patients with confirmed CAP. MR-proANP, CT-proAVP and PCT levels but not CRP increased with increasing severity of CAP classified according to the CRB-65 score. In ROC analysis for survival, the area under the curve (AUC) values for CT-proAVP (0.86, 95% CI 0.83–0.89) and MR-proANP (0.76, 95% CI 0.72–0.80) were similar to those of CRB-65 (0.73, 95% CI 0.70–0.77). Multivariable Cox proportional-hazards regression analyses including MR-proANP/CT-proAVP, co-existing illnesses and CRB-65 found that increased MR-proANP and CT-proAVP concentrations were the strongest predictors of mortality.

Advances in treatment

In many countries ICU physicians are now confronting very difficult-to-treat micro-organisms, such as multi-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, for which the only potentially effective antimicrobial agent is colistin. New data suggest that colistin can be an effective and safe option in the treatment of VAP caused by these germs. Kallel et al. [55] retrospectively matched 60 patients with VAP caused by multi-drug-resistant *A. baumannii* or *P. aeruginosa* to 60 controls with VAP caused by *A. baumannii* or *P. aeruginosa* susceptible to imipenem. Case patients were treated by colistin intravenously, and control patients were treated by imipenem intravenously. A favourable clinical response to antibiotic therapy occurred in 75% of patients in the colistin group and in 72% of those in the imipenem group ($p = 0.68$). The time to resolution of infectious parameters and the course of the PaO₂/FIO₂ ratio after the initiation

of antibiotic therapy were similar. During the antibiotic course none of the patients in either group developed renal failure.

It is common practice to administer broad-spectrum empirical antibiotics to critically ill patients who are suspected on clinical grounds of developing nosocomial infection. To characterize empirical antibiotic use in patients with suspected nosocomial ICU-acquired infections and to determine the impact of prolonged therapy in the absence of infection Aarts et al. [56] reviewed the data of 195 critically ill ICU patients with suspected infection who had been recruited to a prospective study of the diagnostic utility of a rapid assay of bacterial endotoxin. Empirical antibiotics were prescribed for 143 of 195 (73.3%) patients with suspected nosocomial infection; nevertheless only 39 of them (20.0%) were retrospectively considered as being truly infected. The factors associated with a decision to start empirical therapy included leukocytosis and an increased APACHE II score. However, the most important determinant of the decision to start empirical treatment was the treating hospital, suggesting that there is considerable variability in the clinical threshold for initiating therapy. The authors also found that empirical antibiotic therapy was often continued despite cultures being negative. Patients without nosocomial infection receiving empirical antibiotics for longer than 4 days had higher 28-day mortality (32.1%) than those whose antibiotics were discontinued (7.7%; OR 5.7, 95% CI 1.5–20.9, $p = 0.005$). This study adds to a growing list of studies suggesting that ICU-acquired infection is much more frequent than is confirmed, and that empirical antibiotics are prescribed frequently and are commonly continued even when microbiological confirmation is lacking. Prolonged use of empirical antibiotics was not found to improve outcome in ICU patients, but rather it was suggested that this practice may be harmful.

Effective antibiotic treatment depends on adequate delivery of antibacterial agents to the infection site. Several studies have reported the use of small-volume non-bronchoscopic bronchoalveolar lavage (“mini-BAL”) for measuring epithelial lining fluid (ELF) antibiotic concentrations in critically ill patients with VAP, but the reliability of this method was under question. Boselli et al. [57] thus conducted a study to determine (a) the ELF concentrations of tobramycin obtained after BAL and mini-BAL sampling in critically ill patients with VAP and (b) to compare the reliability of the mini-BAL method with that of the conventional BAL method. Twelve patients were studied after 2 days of therapy by the administration of 7–10 mg/kg tobramycin once daily. Tobramycin exhibited a 12% pulmonary diffusion at 30 min, with ELF peak concentrations less than the susceptibility breakpoint, suggesting that a dose of 7–10 mg/kg daily is insufficient for difficult-to-treat pathogens. Good agreement in Bland-Altman analysis (mean \pm SD bias 0.04 ± 0.38 mg/l) was observed between the two methods of sampling,

underlining that mini-BAL is a reliable method for the measurement of antibiotics in ELF.

Antibiotic therapy of patients with VAP is regarded as a two-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia. The second stage involves de-escalating an initially appropriate antibiotic regimen to avoid overuse of antibiotics. To evaluate the effect of de-escalation therapy on outcomes in patients with VAP Giantsou et al. [58] conducted a prospective study in a well-defined group of 143 patients with VAP confirmed by quantitative tracheal aspirate or BAL. The type of respiratory sample that guided de-escalation therapy was determined by the availability of services. A respiratory sample collection kit (tracheal aspirate or BAL) was delivered to ICU every 12 h and was assigned to the first patient in need. Using the kit assigned to the case, the attending physicians collected the respiratory sample within 12 h after clinical suspicion of VAP. The empirical antibiotic regimen was started after the collection of both tracheal aspirate and BAL. Patients in whom antibiotic therapy was de-escalated had reduced 15-day and 28-day mortality. Of the 62 patients who were assigned to BAL 41 (66.1%) achieved de-escalation of antibiotic therapy. Of the 81 patients who were assigned to quantitative tracheal aspirate 17 (21%) achieved de-escalation. The authors conclude that in patients with VAP appropriately treated and with favourable clinical response mortality and duration of ICU and hospital stay can be further reduced by de-escalating therapy. This finding provides arguments for stopping overuse of antibiotics when alternative regimens with narrower-spectrum or fewer antibiotics are available.

Prevention

Nosocomial infections remain a major problem and effective preventive measures are being eagerly sought. Housing patients in single rooms to prevent cross-transmission of potential pathogens is a currently debated issue. Bracco et al. [59] prospectively compared the rate of nosocomial cross-contamination between patients hosted in six single-bed rooms vs. a six-bed and a two-bed bay room served by the same staff in a 14-bed medico-surgical ICU over a 2.5-year period. They observed that the incidence density of MRSA acquisition was 4.1 (95% CI 2.7–6.3) per 1,000 patient-days in bay rooms vs. 1.3 (0.5–3.4) in single rooms ($p < 0.001$). Multivariate analysis demonstrated that the relative risk of MRSA, *P. aeruginosa* and *Candida* spp. acquisition in single rooms or cubicles vs. bay rooms was 0.65, 0.61 and 0.75, respectively. These data suggest that in an institution where MRSA is not hyperendemic, infection control measures are more effective to prevent cross-transmission of micro-organisms in patients housed in single rooms.

While most experts consider oral care in mechanically ventilated patients as a high priority and a key measure for preventing VAP, the types and frequency of oral care practices in European ICUs are not standardized, as demonstrated in a large survey of 59 ICUs in seven countries [60]. Cleaning the oral cavity was considered difficult by 68% of the respondents (most of whom were registered nurses), and unpleasant or difficult by 32%. Oral care consists principally of mouth washes (88%), usually performed with chlorhexidine once (20%) or twice (31%) daily. Manual toothbrushes were used infrequently (41%) although the literature indicates that these are more effective for thorough cleaning of the oral cavity. In 37% of cases respondents felt that despite their efforts oral health worsened over time in intubated patients. It appeared that current protocols for oral care hygiene are suboptimal, and that they should be improved.

An interesting study [61] found nurses' lack of knowledge regarding evidence-based guidelines for the prevention of VAP. A validated multiple-choice questionnaire developed ad hoc was administered. On the 638 collected questionnaires (response rate 74.6%), 19% of respondents recognized the oral route as the recommended way for intubation. It was known by 49% of respondents that ventilator circuits should be changed for each new patient. Only 13% knew that it is recommended to change ventilatory circuits once weekly. Closed suctioning systems were identified as recommended by 17% of respondents, and 20% knew that these must be changed for each new patient only. Sixty percent recognized subglottic drainage to reduce the incidence of VAP. Semi-recumbent positioning was well known to prevent VAP (90%). The average knowledge level was higher among more experienced nurses and those holding a special degree in emergency and intensive care. The authors concluded that continuing education should include support from current evidence-based guidelines.

Rare infections and complications

During a 4-year period *Mycoplasma hominis*, confirmed by 16S rRNA gene sequencing, was isolated from BAL or pleural fluids in six patients [62]. *M. hominis* is an opportunistic pathogen rarely associated with ICU-acquired infections. In this setting *M. hominis* was the only identified pathogen in four patients with clinical symptoms of VAP. However, the quantities of *M. hominis* in BAL samples and biopsy samples of lung tissue were not available. Therefore it remains uncertain whether *M. hominis* truly caused pulmonary infection in these patients. A rare complication of treatment in ICU is vascular erosion due to central venous catheter use. Walshe and coworkers [63] reported on five patients who developed this complication during a 14-year period in which data were collected from 1,499 patients (incidence 0.17%).

Vascular erosion occurred more frequently in left-sided catheters.

Pharmacokinetics

Vancomycin remains one of the most frequently prescribed antibiotics in ICU patients. However, pharmacokinetics can be rather unpredictable. A retrospective analysis [64] found that renal function, APACHE score, age and serum albumin all affect vancomycin clearance. Moreover, standard doses would have led to a 33% risk of not achieving recommended concentrations for treating *S. aureus* infections. Another prospective study on 12 patients investigated the pharmacokinetics of ceftazidime in critically ill patients [65]. Creatinin clearance appeared to be a good marker of ceftazidime clearance that could be used to individualize treatments. Based on concentrations achieved, ceftazidime was expected to be more successful for treating *Escherichia coli* and *Klebsiella pneumoniae* than *P. aeruginosa* and *Acinetobacter* species. In the latter two pathogens the bactericidal target concentrations were not achieved, even with doses of 6 g per day.

Infection prevention

The only randomized controlled study on the effects of selective decontamination of the digestive tract (SDD) published in recent years was a multicentre study of 401 multiple trauma patients carried out between 1991 and 1994 in Europe, Australia and New Zealand [66]. Because of the generally low prevalence of comorbidity among trauma patients this population has been considered to benefit optimally from SDD. The primary endpoint was mortality from infection or from multiple organ failure during treatment on the ICU or up to 2 weeks after discharge from the ICU. Overall mortality rates were 20.9% with SDD and 22.0% in controls, a difference which did not reach statistical significance. This contribution had an interesting editorial [67].

A randomized trial of urinary catheter change with a 3-day course of antibiotics vs. no catheter change and no antibiotics found that catheter replacement combined with antibiotic therapy did not prevent urosepsis in 50 ICU patients with asymptomatic bacteriuria [68]. Catheter-related infections frequently occur in ICU patients. Jugular or subclavian access are associated with lower infection risks than femoral access sites. Catheter-related bacteraemia was analysed retrospectively in patients with various internal jugular venous catheter positions [69]. A higher incidence of bacteraemia was found in patients with central (4.8/1,000 catheter days) than posterior access (1.2/1,000 catheter days; OR 3.9).

Surveillance

Several studies addressed the incidence and risk factors of ICU-acquired infections. Van der Kooij and coworkers [70] reported on a 3-year surveillance of 2,644 patients in 19 ICUs in The Netherlands. VAP developed in 19% of ventilated patients, and catheter-related bloodstream infection in 3% of those with a central line. Longer device use was a risk factor for both infections. SDD was associated with a 40% reduced risk of developing VAP. In contrast to many other reports, development of a device-associated infection was not associated with a higher risk on mortality.

The incidence and outcome of severe sepsis was determined in 4,500 adult patients consecutively admitted to 21 Finnish ICUs during 4 months [71]. Of these, 470 (10.4%) had severe sepsis, with a corresponding incidence of 0.38 per 1,000 of the Finnish population. Respiratory failure was the most common organ failure (86.2%). Septic shock was present in 77%. ICU, hospital and 1-year mortality rates in patients with severe sepsis were 15.5%, 28.3% and 40.9%, respectively.

A similar surveillance study was performed in German ICUs [72]. In an observational cross-sectional 1-day point-prevalence investigation, data were collected from 3,877 patients in 454 ICUs. In this cohort the incidence of severe sepsis was 11.0%. The estimated number of newly diagnosed cases with severe sepsis in Germany is 76–110 per 100,000 adults, which is lower than in Finland. However, ICU and hospital mortality (48.4% and 55.2%) were strikingly higher than in the Finnish cohort. Despite these seemingly obvious outcome differences it was not possible to identify factors of ICU structure and process that explained variability in outcome and resource use in an international database [73].

Treatment of sepsis

Recombinant human activated protein C (APC-Drotrecogin alfa) is the recommended treatment in patients with severe sepsis. Significant concerns remain regarding its efficacy and the occurrence of bleeding complications. An Italian national pharmaco-surveillance study on clinical use of APC treated 668 patients between 2003 and 2006 and was estimated to cover 79.3% of all patients treated in Italy [74]. Bleeding complications were reported in 10.9% of the treated patients. A comparable bleeding rate was found in a Canadian survey on the use of APC [75]. Serious bleeding events occurred in 10% of the patients, one case (0.4%) being fatal. In the Italian cohort crude ICU mortality was lower in patients treated with APC (46.4%) than in patients eligible for treatment but not receiving APC (54.9%). Multivariate analysis, however, found that APC was associated with higher mortality after scheduled surgery. Interestingly, elevated troponin is thought to result from microthrombi and has been

associated with a poor outcome. John and coworkers [76] investigated whether troponin elevation is associated with different responses to APC. In a relatively small study of 105 patients with severe sepsis and troponin levels determined APC treatment improved outcome in patients categorized in the high troponin group. Prospective studies are of course needed to confirm this observation.

Genetics and mediators in sepsis and acute lung injury

Several genetic studies focusing on polymorphisms in patients with sepsis and acute lung injury were published in 2007. Garcia-Segarra et al. [77] reported that a particular gene polymorphism of the plasminogen activator inhibitor 1 was associated with increased organ failure and mortality in white subjects during sepsis (homozygotes for the 4G allele). This study highlights the importance of fibrinolysis and the molecules controlling it in the pathogenesis of sepsis. NOD2/CARD15 is an intracellular leucine-rich protein important for the recognition of bacterial peptidoglycan and for the control of various immune and inflammatory responses. A coding variant of this protein (Leu1007fsinsC polymorphism) was associated with an increased risk for sepsis-related mortality [78], adding the notion that sepsis outcome depends in part on an efficient innate recognition of bacterial molecules by host pattern recognition receptors such as nucleotide-binding oligomerization domain proteins and Toll-like receptors. Adamzik et al. [79] showed that the promoter region of the NFKB1 gene contains a polymorphism (insertion/deletion polymorphism) that is associated with increased severity but not mortality in patients with ARDS. This study confirms the involvement of the nuclear factor κ B signalling pathway in inflammatory responses of critically ill patients. It suggests that the severity of the disease is related to the magnitude of the inflammatory response governed by molecules of this pathway, determined at the genetic level.

High-mobility group 1 (HMGB1) is the prototypical example of a growing body of newly identified host molecules termed “alarmins”. It has been postulated that these mediators released during tissue injury synergize with molecules from bacteria and participate in the pathogenesis of sepsis and related syndromes in critically ill patients. It has been shown that alarmins stimulate similar signalling pathways in immune cells as those induced by bacterial molecules. Using a gene array technology Silva et al. [80] have reported that many genes were induced by both HMGB1 and Gram-negative endotoxin in neutrophils from patients with sepsis-induced acute lung injury. However, they also showed that some genes induced by lipopolysaccharide were not up-regulated by HMGB1. The magnitude of gene induction was also more important with lipopolysaccharide than with HMGB1. This indicated that the gene expression profile is partially distinct between the two pro-inflammatory molecules,

which suggests that although they share the same receptors (Toll-like receptors), they do not entirely activate the same signalling pathways. Gibot et al. [81] reported plasma levels of HMGB1 during human septic shock. Initial HMGB1 plasma concentration did not predict outcome. HMGB1 levels tended to decrease with time in survivors but increased in patients who eventually died. HMGB1 levels were positively correlated with Sequential Organ Failure Assessment score and proclactonin and lactate levels. Plasma HMGB1 may therefore represent a novel marker of tissue injury and a prognostic factor in patients with septic shock. Septic shock is characterized by massive lymphoid organ depletion in lymphocytes and dendritic cells, which is believed to participate in the immune dysfunction observed in this condition. Guisset et al. [82] reported that the initial circulating dendritic cells level is correlated with outcome in septic shock. The concentration of circulating dendritic cells was negatively correlated with scores of severity, and an initially low level predicted for age-adjusted mortality. This finding is in accordance with those analysing spleens from patients who died of septic shock and suggests that circulating dendritic cells levels may represent a prognostic factor in this condition.

Mechanical ventilation

Patient-ventilator interaction is still a matter of major concern in the ICU. Patient-ventilator asynchrony may have deleterious effects related to increased energy expenditure, abnormal diaphragmatic pattern or difficulty in identifying readiness to wean [83]. In 20 patients undergoing pressure-support ventilation, either non-invasively ($n = 10$) or conventionally ventilated ($n = 10$), Mulqueeny et al. [84] demonstrated the feasibility and efficacy of a new algorithm embedded in a ventilator system to detect the occurrence of impaired patient-ventilator interaction (as ineffective triggering, and double triggering) during mechanical ventilation in real time. The detection of ineffective triggering and double triggering from the algorithm was compared by two operators with the “real” occurrence of the phenomena as assessed using the transdiaphragmatic pressure. The algorithm had an overall sensitivity of 91% and specificity of 97%. Specificity in the conventional ventilated group was higher than with non-invasive ventilation (99% vs. 95%, $p < 0.05$). It was concluded that this software may help the clinician identifying an altered patient-ventilator interaction.

Younes et al. [85] evaluated a new automated approach for monitoring and improving patient-ventilator interaction utilizing a signal generated by the equation of motion, using punctual values for resistance and elastance obtained non-invasively. A prototype incorporating the new technology was tested on pre-existing files that contained airway pressure, flow, volume, and oesophageal/gastric tracings

from 21 patients ventilated in pressure support (PS) and proportional assist ventilation (PAV). Onset and end of inspiratory efforts, ineffective efforts, and patient respiratory rate were identified visually from trans-diaphragmatic pressure and compared to those calculated by the prototype. Prototype showed a reasonable accuracy identifying onset and end of inspiratory efforts, with only small delays compared to the start and the end of efforts identified from trans-diaphragmatic pressure (0.107 ± 0.074 and 0.097 ± 0.096 s, respectively). The monitor detected 80% of ineffective efforts. There was excellent agreement between monitor-determined respiratory rate and actual patient rate over a wide range of rates (17–59/min). This new approach may be useful to monitor patient–ventilator interaction and to obtain accurate estimates of true patient respiratory rate, thus being helpful in improving patient–ventilator synchrony. Optimization of patient–ventilator interaction is particularly important for improving patient tolerance during non-invasive ventilation (NIV). In this context optimal synchronization depends on the avoidance of leaks and on the optimal setting of the ventilator [86].

Ventilator settings, notably when they induce lung overdistension, cause lung injury. Application of positive-end-expiratory pressure (PEEP) may lessen lung injury. de Prost et al. [87] hypothesized that PEEP would prevent alveolar oedema dispersion and reduce protein permeability during high-volume ventilation. A total of 46 rats were studied under various conditions: spontaneous breathing, conventional ventilation and high end-inspiratory volume with numerous tidal volume (Vt) PEEP levels (Vt 29 ml/kg and zero PEEP, Vt 24 ml/kg and PEEP 6 cmH₂O, Vt 24 ml/kg and zero PEEP, and Vt 8 ml/kg and PEEP 8 cmH₂O). Radionuclide-labelled albumin was instilled in a distal airway, and scintigraphy was used to determine the dispersion of the radiotracer. The instilled liquid produced a zone of localized alveolar flooding during spontaneous breathing and conventional ventilation (Vt 8 ml/kg and PEEP 2 cmH₂O). High volume ventilation generated a leakage of radiolabelled albumin from the lungs, and this increase in alveolar permeability was reduced by PEEP. Albumin permeability was affected more by the amplitude of Vt swings than by the overall lung distension. The authors concluded that Vt swings increase alveolar permeability to albumin and PEEP prevents intrapulmonary redistribution of oedema liquid and reduces alveolar permeability to albumin due to high volume ventilation.

Monitoring of functional residual capacity (FRC) is potentially important for assessing pulmonary status and the effect of ventilator setting in patients requiring mechanical ventilation. Measurement of FRC remains a challenge, especially during assisted ventilation. In a lung model and in mechanically ventilated patients Di Marco et al. [88] validated a modified helium dilution technique for measuring FRC during PS and pressure-controlled ventilation that does not require patient disconnection and based

on a closed-circuit bag-in-box system. The technique showed an excellent accuracy in vitro (mean difference between FRC measurements and lung model volume of 0.5%, with 2 SD 5.7%), and a good repeatability during both PS and pressure-controlled ventilation (coefficient of variation of 3.4 and 3.2%, respectively), with small changes in the breathing pattern and PEEP levels during the rebreathing period. The authors concluded that this specifically designed closed helium dilution bag-in-box technique allowed accurate FRC measurement with good repeatability even during partial support ventilation, without exposing patients to ventilator disconnection and relevant changes in PEEP.

Current recommendations for mechanical ventilation in ARDS highlight the importance of limiting end-inspiratory airway pressure and of optimizing alveolar recruitment. As high airway pressures can affect right ventricular function, and the occurrence of right ventricular dysfunction (acute cor pulmonale) can influence outcome in ARDS, Jardin and Vieillard-Baron [89] retrospectively analysed whether the systematic echocardiographic evaluation of right ventricular function would help in assessing a safe level of plateau pressure (Pplat) in ARDS. Airway pressure and echocardiographic data were collected in 352 ARDS patients during two different periods: 1980–1992, when airway pressure was not limited, and 1993–2006 with airway pressure limitation. Mortality rate and incidence of cor pulmonale were 30% and 13% when Pplat was lower than 27 cmH₂O, 42% and 32% with Pplat between 27 and 35 cmH₂O, and 80% and 56% with Pplat higher than 35 cmH₂O. The OR of dying for an increase in Pplat from 18–26 to 27–35 cmH₂O in patients without cor pulmonale was 1.05 ($p = 0.635$), whereas it was 3.32 in patients with cor pulmonale ($p < 0.034$), suggesting that the threshold for a safe Pplat depends on the presence of acute cor pulmonale. The authors concluded that monitoring of right ventricular function by echocardiography at bedside may help to control the safety of Pplat used in ARDS.

It has been suggested that the inflection points on the pressure–volume curve can be used as a tool to set PEEP and optimize lung recruitment in ARDS. In an animal model of saline-lavage lung injury DiRocco et al. [90] used in vivo videomicroscopy of subpleural alveoli to assess whether individual alveolar recruitment/derecruitment is correlated with the lower and upper inflections points on the inflation and deflation limb of the whole-lung pressure–volume curve. The lower inflection point on the inflation limb was correlated neither with the alveolar recruitment nor with the pressure below which microscopic derecruitment was observed. Conversely, a good correlation ($R^2 = 0.898$) was found between this pressure and the upper inflection point on the deflation limb. These findings provide supportive evidence that alveolar recruitment and derecruitment take place at different pressures, and that the use of deflation limb of the pressure–volume curve has

greater inference to alveolar derecruitment than inflation limb.

Mechanical ventilation and positioning

Schellongowski et al. [91] investigated the effects of prolonged lateral steep position during continuous rotation therapy on pulmonary gas exchange, respiratory mechanics and haemodynamics in 12 patients with acute respiratory failure. Blood gas analysis, static lung compliance, blood pressure, cardiac index and pulmonary shunt fraction were evaluated in both supine and in left and right lateral steep position at 62° during continuous rotation therapy (phase I) and stopping rotation for 30 min in supine, left and right lateral steep position (phase II). The two phases revealed no significant changes in PaO₂/FIO₂ ratio, mean arterial blood pressure, pulmonary shunt fraction or cardiac index. Static compliance in lateral steep positions was lower and PaCO₂ higher in comparison to supine position ($p < 0.01$). The final conclusion was that pauses in “extreme” positions should be as short as possible, and that prolonged lateral steep position does not lead to benefits of oxygenation or haemodynamics, with individually unpredictable responses.

Physiotherapy and mechanical ventilation

In a provocative randomized, controlled trial Templeton et al. [92] showed that the impact of providing chest physiotherapy on the duration of mechanical ventilation, outcome and intensive care length of stay was poor. In this study 180 patients ventilated for more than 48 h were randomly allocated to receive physiotherapy after routine daily assessments or limited to receiving decubitus care and tracheal suctioning (controls). Kaplan–Meier analysis censored for death revealed a significant prolongation of median time to become ventilator-free among patients receiving physiotherapy ($p = 0.047$). There were no differences between groups in ICU or hospital mortality rates or length of ICU stay. The number of patients needing re-ventilation for respiratory reasons was similar in the two groups. This contribution, which has the limitation of being a single-centre, single-blind study, received various comment letters [93–98].

Mechanical ventilation and sleep disturbances

Sleep disorders are common in the critically ill. Ventilator settings and ventilatory modalities have a marked effect on sleep quality, and respiratory variables under ventilation during wakefulness are markedly modified by sleep. Alexopoulou et al. [99] examined whether PAV with automatic adjustment of flow and volume assist (PAV⁺)

affects sleep quality in patients already ventilated with PSV and exhibiting good patient–ventilator synchrony. PAV⁺ systematically performs very short end-inspiratory occlusions. Polysomnography was used to characterize the sleep period. Study patients were sedated ($n = 11$) and non-sedated ($n = 9$), and both groups were ventilated at baseline and high levels of support. In sedated patients sleep efficiency was significantly higher with PAV⁺ than with high PSV but did not differ in non-sedated individuals. Periodic breathing happened during high assist in PAV⁺ and PSV and was more frequent in sedated than in non-sedated patients (44% vs. 27%). The authors concluded that PAV⁺ working mechanisms (i. e. frequent and short end-inspiratory occlusions) do not adversely affect sleep quality.

Toublanc et al. [100] analysed the impact of assist-control ventilation (ACV) and low levels (6 cmH₂O) of PSV on sleep quality in patients with acute on chronic respiratory failure. Twenty intubated patients were studied, and polysomnography was used to characterize sleep architecture. Patients were studied in a single night, and PSV and CMV were randomly used for 4 h each (from 10 p.m. to 2 a. m. and from 2 a. m. to 6 a. m.). Ten patients followed a sequence ACV-PSV, and in the other ten the sequence was PSV-ACV. During the first 4-h period (10 p.m.–2 a. m.) wakefulness was significantly lower with ACV than with PSV (30.8% vs. 69%), and this was associated with a significant increase in both stage 1 and stage 2 of non-rapid eye movement sleep with ACV as compared to PSV (34.8% vs. 17.1% and 33% vs. 11.4%, respectively). In the second 4-h period (2 a. m.–6 p.m.) stages 3 and 4 of non-rapid eye movement were observed mainly with ACV (6.3% ACV vs. 0.3% PSV and 5.4% ACV vs. 0% PSV, respectively). A significant negative correlation was found between the perceived sleep quality and the amount of wakefulness. The amount of stage 2 non-rapid eye movement was positively correlated with perceived sleep quality. The authors concluded that ACV is associated with significantly better sleep and better patient perception of sleep quality.

Alterations in circadian rhythm and low melatonin secretion are common in ICU patients. Severity of illness and/or light/darkness conditions may cause such alterations. The regulation of melatonin secretion by darkness and light is abolished in severely ill patients and this may be a part of the general neuro-endocrine response to stress associated [101]. The authors examined the nocturnal release of melatonin in response to 60 min of darkness followed by 60 min of bright light in 20 ICU patients. At baseline (ambient illumination), plasma melatonin was low (less than 10 pg/ml) in 15 subjects and high (more than 50 pg/ml) in 5. No differences in medications or ICU length of stay were observed between these groups. In patients with low plasma melatonin levels this hormone did not change to darkness or light. In patients with high melatonin plasma levels light stimulus did not inhibit

melatonin secretion and melatonin did not change in dark conditions.

Non-invasive ventilation

NIV is more and more “popular” in the ICU, and several contributions were dedicated to its applications and technical improvement. The possibility of applying innovative interfaces or innovative ventilation algorithms/modes may improve NIV performance. In a prospective, controlled, randomized study with cross-over design on hypercapnic patients with chronic obstructive pulmonary disease (COPD), Navalesi et al. [102] made a physiological comparison between two interfaces: the helmet and the facial mask. Ten patients they evaluated gas exchange, inspiratory effort, patient–ventilator synchrony and patient tolerance after 30 min of NIV. Arterial blood gases, inspiratory effort, duration of diaphragm contraction and ventilator assistance, effort-to-support delays, number of ineffective efforts, and patient comfort were assessed. NIV improved gas exchange ($p < 0.05$) and inspiratory effort ($p < 0.01$) with both interfaces. The helmet was less efficient than the mask in reducing inspiratory effort ($p < 0.05$) and worsened the patient–ventilator synchrony. However, patient comfort and duration of the ventilatory assistance did not differ with the two interfaces.

Vignauxl et al. [103] evaluated the performance of NIV modes on ICU ventilators during PS in a bench model study that confirmed that leaks interfere with several key functions of ICU ventilators with wide variations between machines. Eight ICU ventilators were connected to a lung model featuring a plastic head to mimic NIV conditions driven by an ICU ventilator imitating patient effort. Tests were conducted in the absence and presence of leaks. Trigger delay, trigger-associated inspiratory workload and pressurization were tested in conditions of normal respiratory mechanics, and cycling was also assessed in obstructive and restrictive conditions. On most ventilators leaks led to an increase in trigger delay and workload, a decrease in pressurization, and delayed cycling. On most ventilators the NIV mode partly or totally corrected these problems but with wide variation.

Adjustment of the ventilator may be a challenge, however. Automation of certain ventilator settings such as the level of PS may be useful. In 19 patients with hypercapnic acute respiratory failure Battisti et al. [104] tested the feasibility of applying NIV through a bilevel ventilator implementing an algorithm which allowed PS to be adjusted to maintain a preset alveolar ventilation. The safety of this approach and its effects on gas exchange compared to those observed during ventilation with manually set PS. The closed-loop approach was applied safely in all patients and overall provided a level of PS similar to that set manually. As a consequence the magnitude of decrease in PaCO₂ and increase in pH with the two methods was

comparable. These results demonstrated the feasibility of using an algorithm to automatically adjust pressure support during NIV with a home ventilator in patients with acute respiratory failure.

Hypercapnic encephalopathy has classically been regarded as a contraindication to the use of NIV. Scala et al. [105] compared the efficacy and outcome of NIV administered in a respiratory step-down unit with conventional invasive mechanical ventilation (CMV) provided in the ICU in a group of COPD patients with moderate to severe hypercapnic encephalopathy. This bi-centre prospective case-control study carried out by teams with long-term experience analysed 20 well matched patients (NIV cases, and CMV controls). Arterial blood gases were significantly improved in both groups after 2 h treatment. The failure rate of NIV was 35% (7 patients needed endotracheal intubation). The percentage of complications (notably infectious) was significantly lower in the NIV group than in the CMV group (30% vs. 65%). In addition, the duration of ventilatory assistance was significantly lower in the NIV group (5.5 vs. 21.5 days). No mortality differences (hospital and 1-year) were observed between the two groups. The authors concluded that NIV can be advocated in COPD patients with hypercapnic encephalopathy as long as no other contraindications exist, the technique is provided by skilled caregivers in a closely monitored setting, and endotracheal intubation procedures are readily available.

Sedation may represent a crucial issue for poorly tolerant patients. Constantin et al. [106] found that remifentanyl-based sedation is safe and effective in the treatment of NIV failure due to low tolerance. Thirteen patients with NIV failure criteria were sedated (Ramsay scale 2–3) by a continuous infusion of remifentanyl, receiving a total of 125 NIV sessions (1,200 h). Three patients required also propofol. The PaO₂/FIO₂ ratio increased from 134 ± 69 to 187 ± 43 mmHg after 1 h. In the three patients with acute hypercapnic respiratory failure PaCO₂ decreased from 69 ± 7 to 42 ± 5 mmHg. Four patients required endotracheal intubation. Twelve of the 13 patients left the ICU.

Clinical trials on NIV often exclude patients with “do-not-intubate” (DNI) orders, but in daily clinical practice these patients are frequently treated. Fernandez et al. [107] found that NIV offers low expectations for medium-term survival in DNI patients. This retrospective cohort study on 233 patients treated with NIV during 2002–2004 analysed the impact of DNI orders on survival. Survival was better in the 199 patients without DNI orders than in the 36 with DNI orders, both during hospitalization (74% vs. 26%, OR 7.9) and after 6 months (64% vs. 15%, OR 10.2). In both groups the presence of COPD was associated with better prognosis during hospitalization but not in the medium-term.

In the January issue Patroniti et al. [108] continued their investigation on helmet CPAP. In five volunteers they

assessed the behaviour of three different helmets (4Vent, Rüschi; PN500, Harol; CaStar, StarMed) after disconnection from the source of fresh gas flow by monitoring respiratory rate and tidal volume, inspiratory and expiratory CO₂ concentration and FIO₂. Independently of the site of disconnection a rapid increase in CO₂ rebreathing and minute ventilation was observed, with a decrease in inspired O₂ concentration. The presence of the safety valve limited the rebreathing of CO₂ and the increase in minute ventilation but did not protect from a decrease in FIO₂ and loss of PEEP. The authors concluded that a monitoring and alarming system is needed to employ helmet CPAP safely.

Acute Lung Injury and alternative therapies

Tsangaris et al. [109] showed the beneficial effect of surfactant replacement in multiple-trauma patients with lung contusion and acute lung injury, with a good tolerance and oxygenation and compliance improvements. This small trial randomly assigned 16 ventilated patients with post-traumatic lung contusion and PaO₂/FIO₂ less than 150 mmHg to either surfactant administration (instilled bronchoscopically in the involved lung areas; *n* = 8) or standard treatment (*n* = 8). The surfactant group demonstrated an acute improvement in oxygenation compared to both control group and baseline values: PaO₂/FIO₂ increased from 100 ± 20 mmHg at baseline to 140 ± 20 after 6 h, 163 ± 26 at 12 h, and 187 ± 30 mmHg after 24 h. Compliance was significantly increased 6 h after

administration, and this increase remained significant at 24, 48, and 72 h. Finally, at 6 h the response to recruitment manoeuvres was better than in the control group.

The use of perfluorocarbons during partial liquid ventilation has been associated with improved gas exchange, respiratory mechanics and lung structure. Filling the lungs with liquid perfluorocarbons may lead to transient hypoxia, impairment of haemodynamics and barotrauma. Alternative forms of administration of these substances have recently been developed, including nebulization and vaporization. In 18 pigs with acute lung injury induced by means of infusion of oleic acid Spieth et al. [110] compared the histological effects of vaporized perfluorohexane (PFH), partial liquid ventilation (PLV) and standard gas ventilation (GV) and their patterns of distribution. Histopathological analysis revealed less damage with PFH than with GV or PLV in the non-dependent and central regions. PFH and PLV showed less injury in the dependent regions than GV. GV and PFH were associated with less histological damage in the non-dependent than the dependent regions, whereas PLV presented the opposite pattern. Morphometric analysis showed increased aeration in non-dependent than dependent regions with PFH and GV. PLV led to more aeration in the periphery than in central areas. The authors concluded that PFH is associated with more homogeneous attenuation of alveolar damage across the lungs, although this therapy had more pronounced effects in non-dependent zones. Overall these findings suggest that vaporized perfluorocarbon can be advantageous as adjunctive therapy in the treatment of acute lung injury, although further research is needed to confirm these data in patients.

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