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Chairman: Univ.-Prof. Dr. Alfons F. Hammerle, MBA

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Editorial

4th Central European Congress of Intensive Care Medicine – Best Evidence in Practice – 140th Anniversary of Nobel Laureate Karl Landsteiner

It gives us particular pleasure to present the abstract book for the 4th Central European Congress of Intensive Care Medicine (CECIM). In the first instance, this year is particularly notable in that we have the unique opportunity to honour the 140th birthday of the first Austrian Nobel Laureate for physiology and medicine, the immunologist, Dr. Karl Landsteiner. This is especially befitting not only to pay tribute to the outstanding and groundbreaking work Landsteiner carried out with respect to his discovery and identification of blood groups (first published in the Wiener Klinische Wochenschrift in 1901), but also because he was indeed born in 1868, in the historic & cultural city of Baden bei Wien, the chosen location for the congress. Thus we are able to combine history, culture and medicine in one event and so reinforce the basic concept behind the Central European Congress of Intensive Care Medicine.

Furthermore we are very proud to have won support and patronage of the Karl Landsteiner Society for the congress, as well as, the planned foundation of an Austrian Interdisciplinary Society for Intensive Care Medicine. The mission of the Karl Landsteiner Society is to promote research and advancement in medical practice. Its practice-oriented approach and emphasis on the provision of a platform for interdisciplinary research projects and international networking, make the Karl Landsteiner Society an ideal partner for this event. In a special section of this supplement several institutes of the Karl Landsteiner Society present the results of their research.

Under the motto “Best Evidence in Practice” this year’s aim, was to place special importance on communication. Due to the broad range of disciplines, and diversity among patients and conditions, communication remains one of the most powerful and important tools

in intensive care medicine. The wide ranging topics addressed in this supplement highlight the heterogeneity of our discipline and are a testimony to the level of interest and support we have raised for the congress. Topics such as airway management, pain management, infections, sepsis, haemodynamics and economics are just a few of the subjects covered in this edition.

In addition the occasion of the 4th CECIM offered an appropriate framework to appeal to all Austrian physicians working in the field of intensive care medicine to support the foundation of an Austrian Interdisciplinary Society for Intensive Care Medicine (AISICM). Demographic changes and technological developments as well as changes in the health care system emphasise the argument for the need for a society which reflects the interdisciplinarity of intensive care medicine and provides a platform for exchange of knowledge between its members, as well as, members of other important expert societies.

Only through effective communication between disciplines can we identify more pertinent future research questions and learn how to put the knowledge gained into practice.

Finally we wish to thank all the authors for their most informative and interesting papers, and hope the 4th CECIM provides a lively forum for exchange of knowledge and stimulating discussion.

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Meeting endorsed by the European Society of Intensive Care Medicine

4th Central European Congress of Intensive Care Medicine – Best Evidence in Practice – collected abstracts

Ultrasound diagnostics of the respiratory system

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Objective. Availability of an ultrasound device at the critical care setting significantly enhances possible diagnostic ways and makes the management of critically ill patients more effective. Exploration of pleural space, quantification of pleural fluid and eventual exclusion of anterior pneumothorax should be an integral part of transthoracic echocardiography in unstable patients. Time factor is particularly important during admission of severe trauma where patient's survival depends on correctly launched diagnostic algorithm. Ultrasound plays a key role here. Interrogation with linear probe helps to visualize airway and before performing percutaneous dilatational tracheostomy.

Chest ultrasonography. Shows better sensitivity and specificity for diagnosis of pleural effusion than chest X-ray which shows sensitivity of 80–83%. X-ray may not detect up to 300–500 ml of fluid in pleural space. Ultrasound excludes atelectasis, consolidation and elevated diaphragm and eliminates potentially deleterious “thoracocentesis”. It is faster than radiologic examination, may be repeated at the bedside and has significantly lower rates of complications than drainage without ultrasound assistance. Patients with successful thoracocentesis demonstrate a trend towards shorter stay in the ICU and towards lower mortality. The benefit of pleural tap in smaller pleural effusions can be weighted against the risk of complications as pneumothorax and bleeding particularly in patients on mechanical ventilation or thrombopenic. Experienced intensivists should also determine the quality of pleural fluid, i.e. transudate/exsudate, pyothorax, blood with clots or septations.

Pneumothorax is serious complication on mechanical ventilation which requires immediate response. X-ray has unsatisfactory sensitivity and does not detect up to 30% of pneumothoraces in supine patients. Importantly, at least half of these progresses into tension pneumothorax. The diagnosis is based on examination of pleural layers which present as a border between echolucent soft tissues and echocontrasting aerated lung. “Pleural sliding” is caused by periodical shifting of parietal on visceral pleura during the respiratory cycle. A “comet phenomenon” originates from pleural line vertically across the whole sector and has dynamic synchronization with lung sliding in the form of pendulum movement. Presence of pleural sliding has 100% negative predictive value for the diagnosis of pneumothorax. “Lung pulse”, i.e. transmission of heart pulse is more visible in diminished lung sliding as it is for example in atelectasis. “Lung point” (Fig. 1) is the border between normal “sliding” and its absence in the zone of separation of pleural layers with air which is typical for pneumothorax. If lung sliding is not found under anterior chest wall in supine patient the diagnosis of pneumothorax can be confirmed with finding of “lung point” typically when moving the probe laterally and towards axillary line. Lung point has a specificity of 100% for diagnosis of pneumothorax and may also show the extent of pneumothorax.

Atelectasis and consolidations of lung tissue are detectable in contact with pleura. Dynamic bronchogram can be seen as a sign of air entry into hepatized tissue in inspiration – typically (60%) in infectious alveolar consolidation (pneumonia). The absence of dynamic bronchogram is more likely seen in atelectasis.

Interstitial syndrome represents increased amount of fluid in interlobular septa. It can be found in ALI, ARDS, cardi-

ac lung edema, pneumonia, exacerbation of chronic interstitial processes. Diffuse “lung rockets” are found typically under anterolateral chest wall (B lines). Clinical importance is in early stages of dyspnea when X-ray is still negative.

Examination of diaphragm is performed at the level of liver and spleen. Normal amplitude is between 10–20 mm, below 5 mm is pathologic movement. Exam is of particular importance for patients after cardiothoracic surgery (phrenic nerve).

Chest examination in trauma patients. Most of fatalities on severe trauma happen during the first dozens of minutes after hospital admission (up to 48%) and are often related to airway management, chest trauma and haemorrhagic shock. Ability of ultrasound to quickly detect free fluid and to facilitate drainage under ultrasound control makes it an ideal first line investigation tool. Targeted interrogation of pericardium and both pleural cavities for haemothorax and pneumothorax is completed with rapid diagnosis/exclusion of haemoperitoneum and pneumoperitoneum. Immediate drainage, thoracotomy or laparotomy can be indicated without delay caused by transporting a patient even to a close CT scan. CT scan including head CT is better performed after initial ultrasound examination which overall makes Focused Assessment with Sonography for Trauma (FAST).

Upper airway and trachea. The application of ultrasound lays in diagnosis of endotracheal tube position particularly when biluminal tube is used. If the endotracheal tube is correctly inserted the bilateral diaphragmatic movement can be seen as well as bilateral pleural sliding. Pleural sliding is absent with remarkable “lung pulse” in case of lung exclusion from ventilation. This examination somehow replaces auscultation and bronchoscopy which might be hampered in biluminal tubes of smaller size. Interrogation of neck before percutaneous dilatational tracheostomy (PDTs) helps to indicate the procedure by exclusion of significant thyroid isthmus and by defining vascular structures in front of trachea. The correct site for PDTs can be found with the aid of ultrasound and the endotracheal tube can be pulled back under ultrasound control before the procedure. Tracheal size can be measured which

Fig. 1. Pneumothorax. Lung point is taken with transthoracic probe in anterior axillary line. M-mode cursor in the sector above is positioned across the zone of pneumothorax at inspiration. Normal pattern is in the left part of the sector which gets under M-mode beam at expiration

helps to choose the correct cannula together with knowledge of the anticipated depth of preparation.

Conclusion. The cost of multimodal ultrasonic device is substantial however, the device may save lives and save time, complications and money for the department in the hands of skilled intensivist. The outputs of large spectrum of examinations are immediately applied by physician who performs these examinations. Patient is spared often complicated transport to the radiology suite for CT scan, load of radiation and contrast. Current development of the ultrasound techniques promises further applications in so far unexplored areas of intensive care medicine. This abstract shows basics of chest ultrasound applications, most of them require further research and protocols that are not available in current proceedings in radiology.

Bariatric surgery

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In the last decades, the prevalence of obesity in the western world has reached alarming dimensions, with the portion of morbidly obese patients increasing.

While conservative treatment or drug medication fails in achieving lasting weight reduction [1], bariatric surgery offers a long-lasting weight reduction from 25–75% of the excess weight and provides resolution or improvement of the obesity-related co-morbidities like type 2 diabetes mellitus, hyperlipidemia, hypercholesterolemia, hypertension and obstructive sleep apnea. After proved failure of conservative weight loss attempts, patients with a BMI of more than 40 kg/m² are eligible for a bariatric procedure, or in case of co-existing co-morbidities in a BMI of more than 35 kg/m². Preoperative workup consists in a psychological and endocrine exploration [2].

Two different principles lead to sustained weight loss in bariatric surgery: restriction and malabsorption. By limiting the volume of food intake (restriction) and impairing nutrient absorption (malabsorption) gastric bypass combines both principles. Different to that, gastric banding or sleeve gastrectomy are strictly restrictive procedures.

Adjustable gastric banding. In gastric banding, the band is placed around the upper part of the stomach; forming a pouch with a volume of 10–15 ml. Food intake leads to pouch distension and induces satiety. A tube connects the band to a port placed subcutaneously, enabling individual adjustments of the inner diameter of the band. Thus, an individual degree of restriction can be achieved. Comparing the different bariatric procedures, gastric banding provides the least invasive procedure, with the least incidence of complications in the early postoperative course. Furthermore, gastric banding is the only complete reversible surgical intervention. Severe deficiencies of iron, vitamins or calcium are not observed after gastric banding. An excessive weight loss of 41–54% in the first 24 months can be achieved [3], but beside these good results in the early follow up, long term results [4] are limited by a variety of band-related complications like band migration through the gastric wall (1–5%), band slipping (1–10%), pouch dilation (1–10%) or esophageal dilation (5–10%).

Roux-en-Y gastric bypass. While gastric banding is still the most commonly performed bariatric procedure in Europe and Australia, many high-volume bariatric centers in Austria performed more gastric bypasses than gastric bandings in 2007. In Gastric bypass, a small pouch (15–25 ml) is formed and completely divided from the remnant stomach. A loop of small bowel is connected to this pouch in a Roux-en-Y fashion, so that the ingested food bypasses the upper parts of the small intestine. Thus, mild malabsorption is combined to the restric-

tive effect of the small gastric pouch. As the bypassed upper parts of the small intestine are the predominantly regions of vitamin or iron absorption, deficiencies in iron, vitamin B12 or calcium can be found after gastric bypass. Therefore life-long supplementations and surveillance is indicated in these patients. Gastric bypass achieves an excessive weight loss of 55–75%, while quality of life is found to be superior compared to gastric banding [5].

Sleeve gastrectomy. In Sleeve gastrectomy the stomach is reduced to a narrow gastric tube by resecting the major parts of corpus together with the complete fundus. Advantages of this restrictive procedure are the accessibility of the upper GI tract for endoscopic exploration or intervention. In Sleeve gastrectomy, an excessive weight loss of up to 60% can be achieved, but no long-term data on weight loss or weight regain following this type of bariatric surgery are published so far. Beside restriction, a reduction of the hunger inducing hormone Ghrelin was found after Sleeve gastrectomy [6], this effect might contribute to the weight loss. As Sleeve gastrectomy is not established bariatric procedure so far, it should be performed only in prospective studies in specialized bariatric centers.

Bilio-pancreatic diversion. In bilio-pancreatic diversion (BPD or Scopinaro procedure), the stomach is reduced to a volume of 200–500 ml and connected to a loop of small intestine of 250 cm length. Fat absorption is therefore limited to the last 50 cm of the small bowel, leading to frequent and fatty bowel movements. The BPD achieves the best and longest lasting weight reduction with an excessive weight loss of up to 75% [7], but deficiencies of calcium, iron or even protein are more frequent than after other bariatric procedures [7, 8].

Duodenal switch. In this procedure restriction (sleeve gastrectomy) is combined with malabsorption (common limb of 100 cm). Different to the BPD, dumping is avoided by the preservation of the function of the pylorus. The incidence of gastro-intestinal symptoms like nausea, vomiting and frequency of bowel movements or the observation of deficiencies of vitamins, protein, iron, calcium are comparable in both procedures. The duodenal switch achieves a mean excessive weight loss of 72% [9]. In both, BPD and Duodenal Switch a life long stringent follow-up and surveillance is mandatory.

Gastric stimulation. Gastric stimulation is a very new and investigational bariatric procedure. It should be only performed within clinical trials, since the long-term outcome is not clear yet. A new, promising system (Tantalus™) uses 3 pairs of bipolar electrodes, which are implanted in the gastric wall. This system is able to detect food intake and enhances antral contractions, leading to earlier satiety and therefore to a decrease in food intake. In a phase I study gastric stimulation with the Tantalus system resulted in a 26% reduction of Excess weight after 12 months [10].

Improvement of co-morbidities after bariatric surgery. Bariatric surgery offers substantial long-term weight loss in morbidly obese patients. Furthermore remission/resolution or amelioration of co-morbidities (like hypertension, hyperlipidemia, sleep apnea and diabetes) can be found: H. Buchwald et al. described in a recently published meta-analysis a total remission of type 2 diabetes in 76.8% of patients undergoing different kinds of bariatric procedures [3]. Gastric banding resulted in remission of diabetes in 47% of patients, compared 84% after gastric bypass and 98.9% after Biliopancreatic Diversion or Duodenal Switch [3].

Bariatric surgery leads to decreased overall mortality, mostly due to a reduction in cancer associated deaths and cardiac infarction [1, 11, 12].

Conclusions. Bariatric surgery is the most effective treatment for morbid obesity and obesity-related co-morbidities. An Excessive weight loss of 25 to 75% can be achieved, depending on the surgical procedure. Furthermore, type 2 diabetes can be resolved in up to 47–98% of all patients. Malabsorptive procedures achieve a better weight reduction, compared to restrictive procedures like gastric banding or sleeve gastrectomy,

but vitamin, iron or calcium deficiencies are found more commonly after malabsorptive procedures.

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Non-invasive hemodynamic monitoring – Initial experience with the ultrasonic cardiac output monitoring (USCOM) device and correlation to invasive measurements

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Background. Hemodynamic monitoring is of particular importance, especially in critically ill patients on an intensive care unit. This study aimed to compare hemodynamic parameters assessed by non-invasive measurements using a novel Doppler device (USCOM: ultrasonic cardiac output monitoring) with invasive measurements based on the PiCCO system (PiCCO: pulse-induced contour cardiac output).

Patients and methods. 53 patients on mechanical ventilation and catecholamine support (median age 45 years, median SAPS II Score 43), were examined using both the USCOM and PiCCO device (n = 53) and in selected individuals, additionally by a Swan-Ganz catheter (PAC, n = 4).

Results. 103 paired measurements were evaluated. Mean non-invasive and invasive values were 3.74 ± 1.3 L/min/m² vs 3.8 ± 1.4 L/min/m² (USCOM vs PiCCO) and 2.7 ± 0.32 L/min/m² vs 2.89 ± 0.47 L/min/m² (USCOM vs PAC), respectively ($r = 0.64$, $p < 0.05$). Changes in CI determined by USCOM were in good agreement with changes in CI determined with PiCCO (Δ CI PiCCO vs Δ CI USCOM: $r = 0.75$, $p < 0.05$).

In 9 patients paralleled USCOM and PiCCO CO measurements were undertaken to evaluate the hemodynamic influence of PEEP. Within a PEEP level of 8 cm H₂O the median CO was 0.7 L/min lower when compared to mechanical ventilation without PEEP.

Summary. Using the ultrasonic cardiac output monitoring (USCOM) device, it is possible to determine non-invasive beat-to-beat analyses of essential hemodynamic parameters without the possible complications associated with invasive methods such as PAC or the PiCCO device. USCOM CO correlated well with invasive CO measurements and therefore provides an interesting tool in the arsenal of hemodynamic measurement devices in critically ill patients on the ICU.

The pathogenesis of acute kidney injury in sepsis

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Introduction. The kidney is a common “victim organ” of various insults in critically ill patients. Sepsis and septic shock are the dominant causes of acute kidney injury (AKI), accounting for nearly 50% of episodes of acute renal failure. Despite our substantial progress in the understanding of mechanisms involved in septic acute kidney injury there is still a huge pool of questions preclusive of the development of effective therapeutic strategies [1,2]. This review briefly summarizes our current knowledge of pathophysiological mechanisms of septic AKI.

Renal hemodynamics in sepsis: a challenging concept. Clinicians round the world are very familiar with the term acute tubular necrosis (ATN) and ATN is supposed to be the most frequent mechanism of AKI in patients hospitalized in the intensive care units. ATN is a structural change, a histopathological entity. Unfortunately, no clear data showing ATN to be the structural basis of AKI in septic patients are available. There are no published studies of renal biopsies which would provide conclusive evidence for the presence of tubular necrosis in septic patients. This type of morphological changes is typically attributed to renal ischemia (vasoconstriction) and/or toxins. This is certainly true in low flow states, such as cardiogenic or hemorrhagic shock. However, the typical hemodynamic response in resuscitated sepsis or septic shock is profound vasodilatation with high cardiac output (i.e. hyperdynamic state). Indeed, clinically relevant models of hyperdynamic sepsis have recently challenged the conventional presumption of renal vasoconstriction as a prerequisite for the development of AKI and “proof of concept” that septic AKI may represent a unique form of hyperemic AKI has been introduced. In fact, cardiac output appears to be the dominant predictor of both renal blood flow and renal vascular resistance in sepsis [3, 4].

Renal microcirculation: the Achilles heel of septic AKI? The assessment of total renal blood flow is insufficient for predicting renal tissue oxygenation, because it does not necessarily represent changes in cortical and medullary microcirculation.

tion. It seems reasonable to argue that changes in the intraglomerular hemodynamics are likely involved in the deterioration of glomerular filtration. However, the exact response of both afferent and efferent arterioles in the course of sepsis is completely unknown. Interestingly, there is widely held concept of a fall in transcapillary hydraulic pressure due to afferent arteriolar vasoconstriction leading to the reduction in GFR. However, significant renal vasodilatation, increased renal artery blood flow and reduced glomerular filtration with preserved tubular functions observed in recent experimental studies suggest a provocative hypothesis: decreased rather than increased glomerular vascular resistance affecting both the afferent and efferent arterioles might explain the fall in glomerular filtration at least at early stages of sepsis. The lack of effectiveness or even worse outcome in clinical trials investigating various vasodilators in septic AKI and, conversely, increased urine output and creatinine clearance in septic shock patients treated with vasopressin, fit well with the above hypothesis [3].

New imaging techniques allowing direct visualisation of kidney microcirculation have helped us to reveal that microvascular dysfunction plays a crucial role in initiating and extending tubular cells dysfunction. In experimental setting, several authors observed early and profound decline in cortical peritubular capillary perfusion preceding tubular epithelial cell injury and clinically detectable kidney dysfunction [5]. Although the pathogenesis of renal microvascular injury is certainly multifactorial, there is emerging evidence supporting the role of oxidative stress and nitric oxide in mediating these abnormalities [5].

Renal epithelial cell dysfunction. Although the renal macro- and microcirculatory alterations play an important role in the pathogenesis of septic AKI, there is growing evidence that other mechanisms, including the interaction of the inflammatory response and coagulation, renal tubular apoptosis and a variety of cellular events contribute significantly to the pathogenesis of AKI [3,4]. Moreover, tubular cells dysfunction that ranges from sublethal to lethal injury – depending on the severity and duration of the insults – might be potentiated by tubular cells themselves. Indeed, it is proximal tubular epithelium that has significant capacity to generate number of mediators that, in turn, can potentiate the inflammatory response. Finally, the absence of gross histological changes offers another intriguing hypothesis, namely “hibernation”-like adaptation characterized by a consecutive reduction of energy demands that allows to buy time for organ (kidney) recovery. The key organelle is the mitochondrion, the powerplant of the cell, where dysfunction in oxidative phosphorylation mediated, among others, by nitric oxide and reactive oxygen species can result in hypometabolic state resembling hibernation. In this view, reduced glomerular filtration may, in fact, represent “acute renal success”, rather than acute renal failure. Nevertheless, a definitive understanding of all of these intriguing hypotheses remains open.

Conclusion. Sepsis-induced AKI is a result of multiple interacting mechanisms. Due to the lack of our ability to analyze precisely the kidney pathophysiology in humans, the fundamental step is the use of animal models designed to meet the criteria of human sepsis together with implementing new robust techniques like proteomics, thereby allowing us to understand the pathogenesis and development of useful diagnostic and treatment strategies to prevent AKI or to hasten its recovery.

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Economic aspects in ICU

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Intensive care is well known about its high expenditure. It is largely attributed to the need for highly trained staff, expensive equipment and intensive use of diagnostics, pharmaceuticals and interventions. It is estimated that intensive care costs represent up to 20% of all hospital costs. The high intensive care expenditure has come into focus in recent years, since increasing health care cost could not match the Gross Domestic Product increase in many countries (Table 1). It is therefore very important to incorporate cost-effectiveness into everyday practice.

Major part of the intensive care cost is fixed, e.g. it is unrelated to the casemix (Table 2). It accounts for about 60–70% and is largely due to personnel cost. The variable cost includes drugs, nutrition, infusions including bloods and blood products, consumables, imaging and laboratory tests. Wide variability has been shown between diagnostic groups, the highest cost being multiple trauma, unscheduled major abdominal surgery, acute lung injury and the lowest being post coronary bypass surgery and ischaemic stroke. Interestingly, there is evidence that ICU physicians generate different variable costs mainly due to differences in practice. Length of stay is tightly associated with costs, and a large proportion of this variation is explained by differences in basic practice patterns. The high daily cost of intensive care therefore opens a new strategy of reducing length of ICU stay. How can it be done? Standardization of care practice through protocols and care pathways has been shown to be cost effective. Interventions which have shown to be cost-effective by reduction of length of stay include prevention of nosocomial infection and protocol-driven mechanical ventilation and weaning. Catheter-related nosocomial infection can be prevented by using full asepsis, real-time ultrasound and antibiotic impregnated catheters for central venous cannulation. Regarding ventilation, daily sedation hold can reduce ventilation time by 2 days and length of ICU stay by >3 days. These measures form an integral part of quality care. Reduction in ICU length of stay, however, does not

Table 1. Health expenditure per capita (US\$)

	1995	2004	% of GDP
Poland	423	805	9.7 / 9.6
Hungary	685	1 323	7.4 / 8.3
Czech Republic	902	1 361	7.0 / 7.3
Italy	1 534	2 392	7.1 / 8.4
Austria	2 229	3 124	9.7 / 9.6
Switzerland	2 573	4 077	9.7 / 11.6

Table 2. Cost of intensive care in Europe

	France	Germany	UK	Hungary
ICU cost per day	957 €	923 €	1396 €	144 €
Fixed costs	67.2%	62%	67.5%	41.3%

mean direct cost saving; it means per ICU case saving only. Reducing the cost of intensive care is very limited: the frequency of laboratory and radiology tests, the use of generic versus name-brand drugs and the specific indications for transfusion are some opportunities for physicians.

Cost control is becoming not just the task of the health policy expert or the hospital administrator – it is also task of the individual ICU clinician.

Early detection of intrauterine infection

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Introduction. The diagnosis of early onset neonatal infection remains one of the greatest challenges in perinatal medicine. At birth the diagnosis must be based on the history of pregnancy and take into account a number of risk factors, such as preterm premature rupture of membranes with, usually, late recognized subclinical intrauterine infection. Early onset neonatal infection is associated with an ascending infection from the cervix and the intact membranes during pregnancy act as an effective barrier against infection of the amniotic fluid [1]. Intrauterine infection at any time during pregnancy is an important risk factor for neonatal sepsis and is a frequent cause of mortality and morbidity in the newborn infants.

If promptly started, antibiotic therapy can reduce its sequelae and improve the prognosis. However, the number of tests that obstetrician can rely on for the early diagnosis of infection is quite limited. Culture tests are not immune from the risk of contamination and the measurement of interleukins in the amniotic fluid and maternal blood serum is not yet routine. The usefulness of PCT as a diagnostic tool of maternal-fetal infections is currently evaluated and the results of recent studies suggest the usefulness of PCT for early diagnosis of neonatal sepsis with varying results [2].

The aim of this study was to consider the patterns of PCT response in normal pregnancy and in pregnancies complicated with premature rupture of the membranes and to compare the results of PCT with those of CRP and to assess their diagnostic accuracy both to mothers and the neonates.

Material and methods. A total of 120 mothers with singleton pregnancies were enrolled in this study. 60 pregnancies were complicated with the premature rupture of membranes, and 60 were control ones.

The characteristics of the study group and control group are shown in Table 1 and 2.

Clinical chorioamnionitis was diagnosed when maternal temperature was $\geq 38^\circ\text{C}$, leukocytosis $> 15.000 \times 10^9/\text{L}$, maternal (> 100 beats/min) and fetal tachycardia (> 160 beats/min) [3].

Early neonatal onset bacterial infection was recognized during the first 48 hours of life based on maternal findings and the presence of clinical signs in the neonate: respiratory (apnea, tachypnea $> 60/\text{min}$, high ventilator settings or oxygen), cardiovascular (hypotension, poor peripheral perfusion, tachy/bradycardia), neurological (seizures, hypotonia), skin color (pallor, cyanosis, jaundice) and positive blood culture [3].

An immunoluminometric assay for the measurement of serum PCT concentration was performed with Brahms KRYPTOR kit. The lowest detection limit of PCT using this method was 0.1 ng/ml.

All values are expressed as median (min-max). Statistical analyses were conducted using non-parametric Mann-Whitney test, Fischer exact test, χ^2 test and Cruskal-Wall test.

Results were considered statistically significant at $p < 0.001$.

Results. All results are shown in Tables 1–5.

Discussion. Sepsis is a condition that markedly influences mortality and morbidity in neonatal intensive care units. The main risk factors associated with neonatal sepsis are chorioamnionitis and preterm delivery [4]. One of the most important goals of recent research in the field of neonatology is to find a highly sensitive and specific method for early sepsis detection. Available laboratory tests lack the necessary sensitivity and specificity. This concentrates efforts on discovering new infection markers [5].

The pathogenesis of premature rupture of membranes resulting in preterm birth remains unknown, but many hypotheses have been suggested. Intrauterine infection and subsequent inflammation may synergistically weaken the membranes because of the combined effects of microbia, host inflammatory cell and cytokine-regulated protease production [6].

The frequency of perinatal infections and other pregnancy complications is adversely correlated to the gestational age at delivery and sepsis is a condition that markedly influences mortality and morbidity in neonatal intensive care units [7]. In patients with preterm rupture of membranes, the incidence of a severe neonatal morbidity rate was reported as 55% in patients with chorioamnionitis and 18% in those without [3]. In our study group 38% of patients were with chorioamnionitis out of which 30% had neonatal infection and 27% of those neonates were admitted to NICU. Clinical chorioamnionitis and antibiotics administration were significantly higher in study group ($p < 0.001$) (Table 2). We did not find the importance of the mode of delivery to the neonatal outcome. Apgar scores in the first and in the fifth minute as well as birth weight were

Table 1. The demographic characteristics of the groups

	Study group (n = 60)	Control group (n = 60)	P-value
Maternal age (years)	28.5	27.5	.641
Gestational age at delivery (weeks)	36.5	38	.020
Multiparous (median)	1	0	.266
Birth weight (g)	3110	3395	.027
Apgar 1 minute (points)	10	10	.048
Apgar 5 minute (points)	10	10	.027

Table 2. The clinical characteristics of the groups

	Study group (n = 60)	Control group (n = 60)	P-value
Preterm delivery	32 (53.3)	24 (40)	.143
Section cesarea	24 (40)	19 (31.7)	.341
Clinical chorioamnionitis	23 (38.3)	6 (10)	<0.001
Antenatal antibiotic administration	36 (60)	14 (23.3)	<0.001
Cervical cerclage	5 (8.3)	11 (18.3)	.107
Neonatal infection	18 (30)	6 (10)	.006
NICU admission	16 (26.7)	4 (6.7)	.003

Table 3. The comparison of PCT and CRP kinetics in study and control group

	Study group	Control group	P-value
PCT (median)	.054	.036	<0.001
CRP (median)	8.4	4.5	.025

Table 4. The comparison of PCT and CRP levels in chorioamnionitis

	Chorioamnionitis	Control	P-value
PCT (median)	.063	.042	<0.001
CRP (median)	14	4.5	<0.001

Table 5. The comparison of PCT /CRP levels according to NICU admission

	NICU		P-value
PCT (median)	.060	.042	.001
CRP (median)	12.5	5	.007

lower in the study group (Table 1). Although the usefulness of procalcitonin (PCT) in clinical practice is increasing, there is no enough data available to establish the role of procalcitonin in the pathophysiology of pregnancy. In our study we found statistically difference in PCT levels in study group compare to control one ($p < 0.001$) (Table 3). We did not find that for CRP, so serum PCT levels seemed to be a better diagnostic marker superior to serum CRP levels in terms of early diagnosis of chorioamnionitis and neonatal infection.

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Acute renal failure in intensive care unit

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Acute renal failure (ARF) is a clinical syndrome characterized with electrolyte and water disturbances, azothemia, metabolic acidosis and symptoms of basic illness. Very common

reason for ARF in ICU patients is septic event from different etiology.

Acute renal failure in ICU is as a rule only a part of the problem in patients with multiple organ failure. All supportive procedures are in the function of maintenance of impaired organ function, and they mostly aid in overcoming acute disorders in critically ill. The most important condition for a favorable outcome is control of the underlying disease, mainly sepsis [1]. Multiple organ failure (MOF) is a clinical syndrome even more common, than isolated ARF observed in ICU patients and burdened with a high mortality rate. It is well known that a higher number of failing organs results in an increased death rate. As pointed out in the introduction, evaluation of the role of a supportive procedure is hindered by the fact that the principal indicator of the outcome is the underlying disease itself. Since sepsis is the also most frequent cause of multiple organ failure in surgical as well as medical intensive care, only control over sepsis allows evaluation of the procedure of extracorporeal circulation. Which supportive therapy in the patients with ARF should be chosen is the question. In current literature there is no prospective randomized study, which documented better patient survival on continuous in relation to intermittent procedures. The majority of intensivists advocate this technique of renal function replacement due to generally accepted opinion that it has less effect on circulation of already hemodynamically unstable patients. In oral communications it is not infrequent to hear that this procedure is “probably better”. It is indisputable that intermittent haemodialysis can affect hyperkalemia and volume excess faster, and it solves more rapidly the acute threat of electrolyte and water disturbances. Weekly dose of hemodialysis in chronic renal failure is defined, mainly by the quotient $Kt/V > 1.2$. The required dose of extracorporeal elimination in acute renal failure is not defined well enough, however it does not essentially differ from the said quotient. It has been well established that cytokines affect the severity of the septic process. According to some recent publications CRRT might play a significant role in the elimination of pro-inflammatory cytokines, in addition to clearing nitrogen products as well as other medium and large sized molecules. The possible removal of pro-inflammatory mediators may permit a blockade of systemic inflammation, a modulation of the altered immune response in these patients, and it may lead to a partial or total restoration of the lost homeostasis [2, 3]. On the other side according meta analysis in published and unpublished trials in any language CRRT in comparison to IHD does not improve survival or renal recovery in unselected critically ill patients with ARF. On the other hand, continuous procedure of hemofiltration has less effect on the stability of circulation. In our prospective randomized study with 104 patients, we also did not observed any difference in 28 days survival, in total survival, as well as in circulatory instability between two treatment modalities. The number of hypotensive attacks defined by blood pressure fall over 10 mmHg in our group of patients on continuous procedures was not significantly smaller [4]. However, there is a randomized prospective study which showed better survival with high volume hemofiltration 35 ml/kg/h compared to low volume ultrafiltration in which 25 l of volume are replaced in 24 hours [5]. When choosing the method of extracorporeal circulation, despite the fact that prospective randomized studies did not prove better survival using one of them, intensivists are advised to use the method with fewer side effects and of greater benefit in a given case. Our prospective randomized study did not show a statistically significant difference between the two methods of renal replacement therapy. Survival rates were not affected and neither was the occurrence of hemodynamic instability. We therefore believe that the management of the underlying condition outweighs the choice of the procedure of renal replacement. Currently, the use of these methods in the world varies. Almost all intensive care units in England utilize continuous methods. In USA intermittent procedures are used

more commonly than continuous ones, which is similar to the situation presently found in Croatia. We believe that both methods are complementary; IHD for faster elimination of electrolytes and waste products elimination, CRRT for regulation of higher calories requirements and for hemodynamically unstable patients. The expectations that one method is superior to the other in the term of better survival have not been corroborated by the current data available in the literature. The choice of the method should be individualized because both methods have advantages and disadvantages. ARF, which is an integral part of MOF, is a problem frequently encountered in critically ill patient treated in the ICU, but outcome of these patients depends closely on the control of basic event. Evaluation of each of the supportive procedures is therefore hindered by the fact that the underlying disease has the crucial effect on survival and the type of supportive procedure less so. It is our opinion that these patients will more likely be treated by continuous methods by appropriately trained ICU personnel.

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Outcome predictors in haematological malignancies in ICU

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Introduction. Development of complications and/or progression of complications in the patients with haematologic malignancies often lead to unfavourable outcomes in ICU. Reasons for ICU admission of patients with malignant neoplasm of haematopoietic system most frequently are severe sepsis and septic shock and organ failures.

Table 1. Haematological malignancies in patients admitted to medical ICU

Haematological malignancy	N	%
Acute myeloblastic leukaemia	18	40%
Acute lymphoblastic leukaemia	3	6.7%
Non-Hodgkin Lymphoma	16	35.6%
Chronic lymphocytic leukaemia	1	2.2%
Plasmocytoma	3	6.7%
All other	4	8.9%
Total	45	100%

Table 2. Main reasons for admission to ICU

Reason for ICU admission	N	%
Respiratory failure	41	91.1%
Severe sepsis or septic shock	36	90.0%
Renal failure	15	42.9%
Altered consciousness	11	31.5%
Metabolic (non-renal) disorder	10	28.6%
Heart failure	6	17.6%

Fundamental question which emerges from everyday practice is: “When is it most favourable to admit those patients to an ICU and to initiate organ replacement treatments regarding their short and long term outcomes?”

Patients and methods. The study included patients with haematologic malignancies admitted to Medical ICU, University Hospital. Inclusion criteria were: adult age (≥ 18 years), failure of at least one organ system. Severity of illness was classified by Simplified Acute Physiology (SAPS II) Score and Karnofsky performance score (KPS). Outcome measures were: 28-day survival and survival at discharge from the hospital. Potential predictors of mortality: patient's age and sex, underlying haematological malignancy, type of previous treatment, type of organ failure, time from occurrence of respiratory failure to initiation of respiratory support, SAPS II and KPS scores at ICU admission.

MedCalc™ statistical software was used for statistical analyses. Categorical variables are presented as absolute and

Table 3. Predictors of ICU survival

Parameter	Non-survivors	Survivors	P
SAPS II score	70 (40–95)	55 (42–73)	0.037
Respiratory failure at ICU admission	38/39 (97.4%)	3/6 (50%)	0.002
Platelets (platelets $\times 10^9/L$)	18 (1–177)	137 (5–437)	0.013
Age (years)	64 (18–85)	57 (46–64)	0.137
Sex (M/F)	17/22	3/3	0.883
Karnofsky performance score	20 (10–50)	30 (10–40)	0.114
Negative microbiology	9/39 (23.1%)	3/6 (50%)	0.132
Fungal infection	9/39 (23.1%)	2/6 (33.3%)	0.972
Severe sepsis at ICU admission	32/39 (82.1%)	4/6 (66.6%)	0.1840
Renal failure at ICU admission	12/39 (30.7%)	3/6 (50%)	0.834
Leukopenia at ICU admission	23/39 (58.9%)	4/6 (66.6%)	0.616
Recovery of granulocytes	23/39 (58.9%)	5/6 (83.3%)	0.488
Anemia (haemoglobin, g/L)	80 (40–174)	132 (61–168)	0.074
Start of mechanical ventilation (hours)	9 (0–218)	0	0.118
Primary haematological malignancy	–	–	0.927
Different kinds of haematological therapy before ICU admission	–	–	0.721

Table 4. Logistic regression for parameters predictive of mortality

Parameter	O.R. (95% CI)	P
Respiratory failure at ICU admission	1.08 (0.96–1.20)	0.018
SAPS II score	8.95 (3.7–21.6)	0.043
Platelets (platelets $\times$ 109/L)	0.98 (0.94–1.01)	0.013
<i>O.R.</i> odds ratio; <i>CI</i> confidence interval		

relative frequencies, continuous variables as medians with ranges. Logistic regression was used in multivariate analysis of potential independent predictors of outcome.

Results. The result of our study are presented in the Table 1–4.

Discussion. Respiratory failure with or without neutropenia in patients with malignant haematology diseases is commonly a consequence of sepsis. Respiratory failure is occurring either as a consequence of severe bacterial or fungal pneumonias or often fatal viral interstitial pneumonias. Acute respiratory distress syndrome (ARDS) is also often contributing or even major causative factor in respiratory failure. Renal failure is also very common, and can exist as a part of severe sepsis, or a consequence of nephrotoxic drugs.

Differently from some centres that advocate non-invasive mechanical ventilation as the first method of respiratory support with endotracheal intubation as a back-up in case of further respiratory deterioration, our patients were firstly intubated and ventilated [1–3].

High mortality of such patients led to evaluation of potential outcome predictors at the time of ICU admission. It has been shown that respiratory failure and haemodynamic parameters significantly influence prognosis, while age, sex and primary haematological disease had not influence [4]. These data are in concordance with a part of our results where respiratory failure, SAPS II score and platelet count were shown to be predictors. Low leukocyte count, shown to be the best predictor of mortality was not confirmed as such in our study.

Higher mortality rates in our patients could partly be explained by late referral to the ICU, when organ failure has progressed so much that it already needed organ support or organ replacement therapies. Most of our patients were for instance mechanically ventilated within the first hour of ICU admission. High SAPS II score at the moment of ICU admission (higher than SAPS II score reported in other papers) can also confirm relatively late timing of ICU admission. Earlier admission of patients with haematological malignancies and deterioration in organ function, especially respiratory failure may very much improve survival. Non-invasive mechanical ventilation could than be used more frequently and more successfully. ICU admission and treatments with organ supportive therapies can lead them through this high risk period and give them a chance of recovery and long term survival.

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Continuous renal replacement therapy (CRRT) or intermittent haemodialysis (IHD) in ARF and MOF

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Acute renal failure is as a rule only a part of the problem in patients with multiple organ failure. All supportive procedures are in the function of maintenance of impaired organ function, and they mostly aid in overcoming acute disorders in critically ill. The most important condition for a favorable outcome is control of the underlying disease, mainly sepsis [1]. In the light of this knowledge the place of intermittent hemodialysis procedures should be viewed, compared to continuous hemofiltration procedures and their effect on the survival of critically ill. Multiple organ failure is a clinical syndrome burdened with a high mortality rate. It is well known that a higher number of failing organs results in an increased death rate. One organ failure results in the death rate of 25–30%, two organs 50–60%, three organs 80% or more, and four organs 100%. As pointed out in the introduction, evaluation of the role of a supportive procedure is hindered by the fact that the principal indicator of the outcome is the underlying disease itself. In current literature there is no prospective randomized study, which showed better patient survival on continuous in relation to intermittent procedures. In order to answer the question what is the procedure of choice in critically ill patients, one must eliminate certain forms of intermittent hemodialysis which by themselves carry frequent problems during extracorporeal circulation. Since the machines with controlled ultrafiltration and bicarbonate dialysate imply smaller incidence of complications, only these devices can be considered comparable with continuous hemofiltration. Meta-analysis of a number of studies, which compared biocompatible to bioincompatible membranes gave advantage to biocompatible membrane, we used machines with controlled ultrafiltration, bicarbonate dialysate solution, and biocompatible polysulfone membrane in our study. It is indisputable that hemodialysis can affect hyperkalemia and volume excess faster, and it solves more rapidly the acute threat of electrolyte and water derangements. Weekly dose of hemodialysis in chronic renal failure is defined, mainly by the quotient $Kt/V > 1.2$. The required dose of extracorporeal elimination in acute renal failure is not defined well enough, however it does not essentially differ from the said quotient. The length of intermittent procedure is also not well defined. It mostly lasts 3–4 hours, but some used prolonged intermittent dialysis lasting 9 hours and did not obtain different survival compared to continuous procedures. It has been well established that cytokines affect the severity of the septic process. The possible removal of proinflammatory mediators may permit a blockade of systemic inflammation, a modulation of the altered immune response in these patients, and it may lead to a partial or total restoration of the lost homeostasis. A statistically significant reduction in heart rate, increase in systemic vascular resistance and systolic blood pressure were documented in the group of patients who underwent CRRT. On the other side according meta analysis in published and unpublished trials in any language CRRT in comparison to IHD does not improve survival or renal recovery in unselected critically ill patients with ARF. On the other hand, continuous procedure of hemofiltration has less effect on the stability of circulation. Comparison of value of intermittent hemodialysis with continuous procedures of hemofiltration should therefore be considered in the light of the mentioned fact. In our pro-

spective randomised study with 104 patients, we also did not observed any difference in 28 days survival, in total survival, as well as in circulatory instability between two treatment modalities. Even in subgroup of 80 patients with sepsis and septic shock there were no difference in survival. Sepsis was the underlying disorder in 52 and septic shock in 28 patients out of 104 patients analyzed in this study. The statistical evaluation of the obtained data revealed no significant difference in patient outcome between the two observed methods of renal replacement therapy [2]. The number of hypotensive attacks defined by blood pressure fall over 10 mmHg in our group of patients on continuous procedures was not significantly smaller. However, there is a randomized prospective study which showed better survival with high volume hemofiltration 35 ml/kg/h compared to low volume ultrafiltration in which 25 l of volume are replaced in 24 hours. We were not able to validate this difference. When choosing the method of extracorporeal circulation, despite the fact that prospective randomized studies did not prove better survival using one of them, intensivists are advised to use the method with less side effects, and of greater benefit in a given case. Our prospective randomized study did not show a statistically significant difference between the two methods of renal replacement therapy. Survival rates were not affected and neither was the occurrence of hemodynamic instability. We therefore believe that the management of the underlying condition outweighs the choice of the procedure of renal replacement. We believe that both methods are complementary; IHD for faster elimination of electrolytes and waste products elimination, CRRT for regulation of higher calories requirements and for hemodynamically unstable patients. The expectations that one method is superior to the other in the term of better survival have not been corroborated by the current data available in the literature.

Conclusion. The choice of the method should be individualized because both methods have advantages and disadvantages. ARF, which is an integral part of MOF, is a problem frequently encountered in critically ill patient treated in the ICU, but outcome of these patients depends closely on the control of basic event. Evaluation of each of the supportive procedures is therefore hindered by the fact that the underlying disease has the crucial effect on survival and the type of supportive procedure less so.

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Diabetic patients in intensive care unit: increased risk and some specificities

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Introduction. Diabetes mellitus (DM) with its chronic and acute complications puts patients with the disease at higher risk in case of acute illness. Although patients with diabetes usually are recognized as patients with increased risk when admitted to intensive care units, this risk is not addressed in any of the scoring systems commonly used in intensive care medicine. Most commonly used score that accounts for chronic health is APACHE II score [1], but it does not score any points for diabetes. Some complications of diabetes, primarily chronic renal failure, may score some points in most of the scores,

but there are many other complications such as cardiomyopathy, microvascular and macrovascular disease that certainly put the patient with diabetes at additional risk.

On the other hand, patients with diabetes and good glycaemic control have fewer chronic complications and should be at lesser risk. The influence of hyperglycaemia during acute illness has been proven to be harmful, which has led to strict glucose control, which has become one of the recommendations in the Surviving Sepsis Campaign [2]. The influence of medium-term glycaemic control which may alter immunologic and inflammatory responses has not been investigated.

We have analysed patients with sepsis and diabetes in medical ICU to determine the additional risk that could be attributed to the disease. Also, we have compared the course and outcome of sepsis according to different levels of HbA1c as a measure of medium-term glycaemic control.

Methods. To evaluate diabetes as a risk factor, data from a medical ICU in a university hospital during the time of five years were analysed. Patients with sepsis as the primary admission diagnosis were included and split to diabetes and non-diabetes groups. The diagnosis of diabetes mellitus had to be established prior to the admission to the hospital, according to the ADA or WHO criteria [3]. Patients with newly diagnosed diabetes during the ICU stay were not included in any of the groups. Hyperglycaemia in non-diabetics during the ICU stay did not exclude patients from the non-diabetes group if DM was not confirmed before discharge. APACHE II and SOFA [4] score were calculated for all patients. HbA1c was measured for all patients with diabetes.

ICU and hospital mortality and length of stay (LOS) were the outcome measures; incidence of organ failure was a measure of disease course.

MedCalc statistical software was used for data analyses. Non-parametric tests were used regardless of distribution type for all comparisons.

Results. Sepsis was the most common primary admission diagnosis in our ICU during the analysed period: of total 2205 admissions, there were 356 (16.1%) patients with sepsis, 78 of them (21.9%) with diabetes mellitus diagnosed prior to admission. There was no statistically significant difference between the groups either in age, sex distribution, APACHE II score or SOFA score at admission.

Mortality in the ICU was 34.7%; median ICU LOS was 8 (95% CI 7–9.3) days.

Patient with DM, compared to non-diabetics had higher mortality (38.9% vs. 34.1%; $P=0.60$) and longer ICU LOS (median 6 vs. 10 days; $P<0.001$). In the subgroup of patients who developed severe sepsis, those with DM had higher number of failing organs (median 2 vs. 1; $P=0.024$). The most common organ failure in both diabetes and non-diabetes groups was renal failure, followed by respiratory failure. In a logistic regression, DM was found to be related to lethal outcome, together with admission APACHE II and SOFA scores.

In the diabetes group, surviving patients had significantly lower HbA1c levels (6.6% vs. 9.6%; $P=0.001$). In a multiple regression model HbA1c was found to relate to LOS together with SOFA score and age. HbA1c was found to be independently related to ICU outcome together with SOFA score.

Conclusions. Although some chronic effects of diabetes mellitus can be included in multi-parameter scoring systems such as APACHE II score, the disease itself is not scored. We have shown on patients with sepsis, the most common diagnosis in ICU, that diabetes mellitus is an independent predictor of mortality and LOS and that it has significantly higher incidence of organ failure. Patients with DM should be given appropriate attention as high risk patients in the ICU. HbA1c was shown to be predictive of mortality and hospital LOS of patients with sepsis and a history of DM. Chronic hyperglycaemia and consequent increased formation of glycation products in blood and tissues may influence inflammatory and immune response [5–7] and thus be responsible for increased risk.

Proper glycoregulation in diabetic patients could reduce the risks in the event of infection.

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Update in pain management in ICU patients

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Pain in critically ill patients has been addressed widely in the context of sedation and analgesia in ventilated patients. However beyond ventilation, the underlying causes of pain are numerous in these patients. They experience pain due to the disease, trauma or surgery, invasive procedures, therapeutic devices, immobility, and routine procedures such as turning and positioning. Increasing information demonstrates, that adequate pain management in critically ill patients affects short- and longterm outcome. At date little controlled data are available on the adequacy of pain assessment and the efficacy of pain therapy under the particular circumstances of ICU patients [1].

Pain assessment in the ICU. The assessment of pain is regarded the key information for adequate pain therapy. However, the tools range from self-assessment to pain assessment by the personal depending on the patient. Self assessment of pain is regarded the golden standard in acute postoperative pain. The same applies for acute pain in ICU patients independent of its origin (trauma, large surgery or the disease itself). Consciousness, cognitive capacity and collaboration are prerequisite for the successful use of all tools of pain assessment.

Visual analog scales (VAS), numerical rating scales or verbal rating scales provide adequate information on the patients' pain intensity and the respective treatment success.

In contrast, less is known about the quality of pain assessment by the personal in ICU patients with impaired self-assessment.

In sedated patients on the other hand, pain is indirectly assessed. Various symptoms and parameters are combined to determine a score. The Richmond Agitation Sedation Scale (RASS) is a structured assessment of agitation or sedation using a simple scoring system Sessler et al. (2002) [3]. Pain, how-

ever, may only be indirectly assessed in agitated patients. Therefore the Behavioral Pain Scale (BPS) is assessing the facial expression, movement of upper limbs and compliance with the ventilation [1, 3]. Using the BPS, Changes et al. found high pain scores in ICU patients. More than 60 % of the patients experienced at least one painful event within 4 hours of observation. Training of the staff, a systemic evaluation of pain, and defined limits to initiate interventions improved significantly the quality of pain management in the ICU.

Pain management. A choice of analgesics is available with non-opioids, opioids, ketamine and local or regional blocks. Prevalence of organ failure or dysfunction, mainly renal or hepatic impairment is high in ICU patients. They are often more susceptible to the sedative side effects of analgesics. Pharmacokinetic and -dynamic changes may alter efficacy and side effect profile of analgesics. Another aspect is opioid tolerance and opioid-induced hyperalgesia as a consequence of continuous opioid analgesia for sedation. Particularly during withdrawal from sedation, pain and hyperalgesia may develop and provide serious need of effective pain therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs are contraindicated in patients with severe renal dysfunction. Together with hypovolemia or in combination with ACE-inhibitors NSAIDs are relatively contraindicated, because of an increased risk of renal impairment in patients with reduced renal function. Paracetamol and dipyrone (metamizol) represent another group of non-opioids, which do not interfere with the peripheral COX-inhibitory mechanisms and are therefore adequate in the treatment of patients with renal dysfunction. Coxibes are contraindicated in postoperative patients after coronary bypass surgery.

Typically the metabolite of paracetamol accumulates in higher daily doses intrahepatically and dosing is therefore limited to 80–100 mg/kg/day in healthy patients. However, hepatic dysfunction in ICU patients may relevantly reduce this daily dose and should be considered. All NSAIDs bear a risk of hepatic side effects. This applies particularly for patients with co-existing hepatic dysfunction. In conclusion: NSAIDs and coxibes should be carefully used in patients with renal and hepatic dysfunction.

Opioids are non-toxic and are therefore widely used in ICU-patients. Depending on the pharmacokinetic characteristics of the opioids hepatic and renal impairment may influence the elimination time of the drug itself or of its metabolites. This is particularly true for morphine with morphine-6-glucuronid as an active, mainly sedative metabolite with renal elimination. Therefore in renal dysfunction morphine should be replaced by other opioids, like hydromorphone, buprenorphine, piritramid or sufentanil. Recently, as an alternative, remifentanyl has been applied as continuous dose-adapted perfusion.

Opioids are mostly given iv. Patient controlled or nurse controlled analgesia (P/NCA) using defined increments of opioids with or without pain pump constitute the first choice of opioid treatment in awake and communicative patients. Dose adaptation to the individual patients' need is required particularly in patients with preceding opioid analgesia. In most institutions the use of pain pumps is restricted for the patients in transition to the ward, since availability of iv treatment in ICU is routine. It is noteworthy, that continuous opioid infusion via pain pump is not performed on normal wards for safety reasons. Exclusively bolus options are used for p.c.a.

In ICU patients with impaired communication, opioid analgesia may be applied either by incremental doses or as add-on increments together with continuous opioids.

The role of ketamine in ICU pain management is the treatment of opioid tolerance and hyperalgesia. There is increasing information that ketamine acts anti-hyperalgesic and is therefore particularly effective to treat opioid-induced hyperalgesia [2]. Ketamine is applied in small doses to prevent psychomimetic side effects.

The routine application of regional anaesthesia (mainly epidural catheters) in ICU patients is under controversial discussion with benefits on respiratory function and early rehabilitation on one hand and risk of infection or epidural bleeding in critically ill patients on the other hand. However, local blocks reduce the repetitive pain stimulation of ICU patients like central venous catheter placement or thoracic drainage. Even in sedated patients local anaesthetics can therefore be recommended.

Although there is surprisingly little information on particular pain management in ICU patients available, the general concepts derived from postoperative pain management are transferred to the ICU: Application of balanced analgesia using a combination of analgesics wherever possible. Individual dose titration at patient's need is mandatory and attention on pain control not only at rest but particularly at movements, nursing care procedures and interventions.

In conclusion, pain management in the ICU is a challenging issue. No information on the validity of pain assessment tools in awake patients, that are impaired in communication to a certain degree, is available. The use of non-opioids is limited because of interactions with organ dysfunctions. Balanced analgesia, opioids alone or in combination with ketamine are analgesics of choice. Education and early pain treatment of the frequent painful events during intensive care is recommended.

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A physiology based approach to hemodynamic management of septic shock patients

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Introduction. Severe SIRS and Sepsis Shock remain clinical syndromes with high morbidity and mortality. Cardiovascular failure seems to play a key role in the subsequent development of the multiple organ dysfunction syndrome (MODS) and in one of our studies involving 3700 intensive care unit patients cardiovascular failure was besides CNS-failure the second most important independent predictor of ICU-mortality [1]. Rivers et al. recently published their data on the development of inflammatory response and activation of apoptosis in patients included in their "early goal directed therapy study" [2]. The most interesting finding was that the severity of tissue hypoperfusion as assessed by arterial lactate values and central venous oxygen saturation at admission was by far the most important determinant of the magnitude of subsequent inflammation and apoptosis developing during the resuscitation process. Quite similar, Howell et al. recently showed that occult hypoperfusion is a main determinant of mortality in pa-

tients with suspected infection [3]. However, hemodynamic resuscitation in septic shock is not always an easy task to do. Severe hypotension often poorly responds to volume therapy. In addition the administration of catecholamines may be accompanied by undesirable side-effects which may be harmful and even worsen the prognosis of patients. Catecholamine toxicity occurring during cardiovascular resuscitation seems to be a growing problem in elderly patients with preexisting cardiovascular diseases treated in our intensive care units. In this presentation an overview on the pathophysiology of hemodynamic failure in septic shock and a concept of a rational physiology based approach to the hemodynamic management of these patients is given.

The hemodynamic problems associated with septic shock. Figure 1 illustrates the principle hemodynamic problem associated with septic shock. Our cardiovascular system is programmed to keep a predefined perfusion pressure relatively constant during normal life. This is accomplished by modulating vascular conductivity (= reciprocal value of vascular resistance) and cardiac output. Every increase in vascular conductivity, e.g. during dynamic exercise, must be met by an appropriate increase in cardiac output to keep mean arterial blood pressure (MAP) relatively constant. In severe SIRS and Sepsis vascular conductivity progressively increases due to liberation of a large quantity of vasodilatory mediators, in particular nitric oxide. To keep MAP constant, cardiac output has to increase. Unfortunately, in systemic inflammation hypovolemia and myocardial dysfunction often prevents an appropriate increase in systemic blood flow leading to hypotension and shock thereby augmenting tissue hypoperfusion.

Physiologically, the basic mechanisms of increasing cardiac output in the normal heart are a modest increase in stroke volume (approximately 20–25%) and a progressive increase in heart rate until the maximum systemic blood flow is achieved. In septic shock myocardial performance due to systolic and diastolic dysfunction is often compromised. Therefore an adequate stroke volume increase may be prevented. Stress associated with critical illness and exogenous catecholamine delivery may disproportionate increase heart rate compromising left ventricular blood flow. This situation may be catastrophic in particular in patients with pre-existing limited coronary reserve. Additionally clinicians should keep in mind that even with a normally functioning heart maximum cardiac output would be greatly reduced in a sedentary lying patient because of a lack of the muscle pump to augment venous return to the heart [4].

Recently small studies in patients with septic shock demonstrate that both prolonged elevated heart rate and hypotension are associated with a dismal outcome [5–7].

Fig. 1

Fig. 2

Rational resuscitation of a septic shock patient. To demonstrate how hemodynamic resuscitation may be performed on a rational based treatment algorithm we best start with a practical example: Figure 2 presents a patient suffering from community acquired pneumonia who was admitted to our intensive care unit in advanced septic shock. After introduction of a pulmonary artery catheter the hemodynamic values demonstrated severely compromised cardiac performance. The patient exhibited tachycardia due to atrial fibrillation and showed significant ST-segment elevations in ECG-leads V1–V3 suggesting significant myocardial ischemia or impending myocardial infarction. This graph shows the calculated vascular conductivity of this patient together with a hypothetical curve exhibiting the behaviour of MAP over a wide range of vascular conductivity at the present cardiac output of 4 l/min.

There should be no doubt that current hemodynamics of this patient signifies severe hypovolemia and therefore volume resuscitation infusing both crystalloids and colloids has to be rapidly performed. By infusing volume we increase mean circulatory filling pressure of the systemic circulation thereby increasing venous return to the heart and augmenting cardiac output along a defined cardiac function curve [8]. However when we proceed along the steep part of the patients cardiac function curve we finally end up at the upper flat part of the Frank Starling relationship. At that point cardiac output will no more respond to volume loading and at a certain vascular conductivity there will be no more increase in MAP. In contrast, at that stage further volume loading will only augment tissue oedema formation and unnecessarily increase end diastolic left ventricular filling pressure thereby decreasing left coronary perfusion pressure in particular to subendocardial regions of the left ventricle.

Figure 3 demonstrates the cardiovascular situation of the patient after volume resuscitation and also points at the different possibilities to further correct hypotension. At the given vascular conductivity, volume loading alone results in an increase in cardiac output of 1,5 l/min thereby increasing MAP by 12 mmHg. The patient is still hypotensive and in this situation MAP can only be increased to “normal” values by either augmenting systemic blood flow using positive inotropic agents or by decreasing vascular conductivity with vasopressor agents or finally by a combination of both. The still low central venous oxygen saturation in this patient suggests insufficient blood flow to peripheral tissues so that the combination of inotropes and vasopressors for restoration of normal hemodynamics seems to most rational.

One major problem associated with the use of sympathomimetic drugs, e.g. dobutamine, norepinephrine, epineph-

Fig. 3

rine is the associated toxicity which may occur when higher dosages of the drugs are necessary to normalize hemodynamics [9–14]. In clinical praxis, this toxicity very often manifests as new onset tachyarrhythmias, signs of myocardial ischemia and the occurrence of pulmonary hypertension. Experimental data clearly demonstrate that, at least in the heart myocardial toxicity of sympathomimetic drugs is mediated through β_1 -adrenergic receptors. At the cellular level, induction of inflammation and cell death by apoptosis and necrosis has been demonstrated. β_1 -adrenoreceptor blockade significantly blunts catecholamine induced myocardial toxicity [13]. Unfortunately, when giving high doses of sympathomimetic drugs clinicians are frequently faced with the problem of decreasing drug response but without blunted side-effects. In one study in patients with systemic inflammation and advanced MODS we observed a striking rise in mortality when norepinephrine was raised to dosages in excess of 0.6 $\mu\text{g/kg/min}$. In a recent investigation, Kumar et al. reported higher baseline heart rate and weakened cardiac output response to a stepwise increasing infusion of dobutamine in patients dying from severe sepsis and septic shock when compared to survivors [15].

Therefore a rational approach to stabilize the hemodynamics of the presented patient would be a combination of drugs with different pharmacology aimed at minimizing over-

Fig. 4

Fig. 5

all catecholamine toxicity while improving MAP and systemic blood flow to physiologic values [16–19].

Figure 4 presents the final hemodynamic treatment of the patient resulting in a physiologic MAP and CO and normal central venous oxygen saturation. After volume resuscitation this patient received norepinephrine, a continuous infusion of hydrocortisone and arginine vasopressin to reduce vascular conductivity thereby increasing MAP. At the same time a phosphodiesterase III inhibitor was infused to increase systemic blood flow and tachycardic atrial fibrillation was treated with a continuous infusion of amiodarone.

Final conclusions. Figure 5 presents the general principles of hemodynamic therapy which should be applied to critically ill patients suffering from vasodilatory shock who are already volume resuscitated. These principles are mainly based on physiologic and pharmacologic reasoning and are supported by numerous animal experiments and mostly small interventional or observational studies obtained in healthy and critically ill humans.

Our major goals in treatment of septic shock after adequate volume resuscitation should be the manipulation of vascular conductivity and systemic blood flow to ensure adequate oxygen supply to organs within their autoregulatory limits while minimizing catecholamine toxicity by combining drugs which either restore catecholamine responsiveness or exert their effects via receptors and mechanisms that are not related to the sympathoadrenergic system. Our current treatment algorithm in septic shock patients represents a step by step escalating protocol which includes all possibilities of rational pharmacologic interventions for stabilisation of hemodynamics. This treatment protocol has already been applied in more than 400 patients and has resulted in a very low ICU and hospital mortality.

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Evidence-Based Medicine in Intensive Care

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Introduction. Sackett et al. defined Evidence Based Medicine (EBM) as “the conscientious, explicit, and judicious use of current best evidence in making decisions on the care of individual patients.” The practice of evidence based medicine means integrating individual clinical expertise into the best available external clinical evidence derived from systematic research [1]. EBM plays a vital role in the decision making process and randomised controlled trials (RCT) are certainly a powerful instrument when it comes to generating the evidence. However, particularly in the field of intensive care medicine (ICU), RCT’s are not always available or performed. Each clinical therapeutic decision must, therefore, be made on the basis of the available evidence. Ideally RCTs should be included in

this process whenever possible, but not to the exclusion of all other forms of evidence [2].

Intensive care medicine deals more with syndromes rather than clearly defined diseases. Defining such syndromes at a diagnostic and prognostic level is often difficult because the definitions are based on non-specific and non-selective criteria, which are frequently a matter for debate. This predicament is just one of the reasons why it is so difficult to practice EBM in intensive care medicine. Other reasons are outcome indicators: in intensive care medicine the conditions to be treated are typically associated with very high mortality rates. This obviously makes mortality an important outcome, but potentially very hard to improve, so that a large number of patients are required to demonstrate a significant survival advantage [3].

What is evidence in practice? A very important objective of evidence based medicine is to test how far the results of the different studies are applicable in clinical practice (recommendations). Table 1 provides a framework for assessing the quality of a particular study or body of evidence.

Treatment decisions involve a trade off between benefits on the one hand, and risks, burden, and costs on the other. Some studies provide recommendations for the management of typical patients. To integrate these recommendations with their own clinical judgement, and with an individual patient's values and preferences, clinicians need to understand the basis for the recommendation. A systematic approach to grading the strength of management recommendations can minimize bias and aid interpretation [3]. Table 2 suggests an approach for grading the strength of recommendations. It should also be noted that resource limitations in some institutions and countries may prevent physicians from complying with particular recommendations [4].

Method. A search was carried out in order to determine the best evidence in practice with regard to intensive care medicine and establish whether recommendations based on this evidence were made. We performed a Medline search for the years 2007 to 2008 to find studies in intensive care medicine with a high level of evidence. Furthermore we examined whether a recommendation was given as a result of the study.

Search terms included *evidence-based medicine AND intensive care medicine*. Our limitations were *clinical trial, meta-analysis, practice guideline, randomized controlled trial review, published in the previous two years, core clinical journal*.

A "manual" search was also carried out for studies published from May 2007 to April 2008, in the renowned journal

Table 1. Assessment of the Quality of Evidence [4]

- *Underlying methodology*
 - A RCT
 - B Downgraded RCT or upgraded observational studies
 - C Well-executed observational studies
 - D Case series or expert opinion
- *Factors that may decrease the strength of evidence*
 - 1. Poor quality with regards planning and implementation of available RCTs suggesting high likelihood of bias
 - 2. Inconsistency of results (including problems with subgroup analyses)
 - 3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
 - 4. Imprecise results
 - 5. High likelihood of a reporting bias
- *Main factors that may increase the strength of evidence*
 - 1. Large magnitude of effect (direct evidence, relative risk (RR) >2 with no plausible confounders)
 - 2. Very large magnitude of effect with RR >5 and no threats to validity (by two levels)
 - 3. Dose response gradient

RCT randomized controlled trial; RR relative risk

Table 2. Strength-of-Recommendation Grades [4]

Strength of recommendation – Basis for recommendation

- A Consistent, good-quality patient-oriented evidence*
- B Inconsistent or limited-quality patient-oriented evidence*
- C Consensus, disease-oriented evidence*, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening

*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).

"Monitor of Intensive Care Medicine", a current awareness journal for intensivists.

Results. 18 level one clinical trials were found in the "Monitor of Intensive Care Medicine" with a clinical recommendation given in almost every case.

The Medline search using the search term "*intensive care AND evidence based medicine*" yielded eleven reviews, one meta-analysis, one case series, and one questionnaire inquiry.

The search term "*ventilation AND evidence based medicine*" yielded five relevant reviews, the term "*coagulation AND evidence based medicine*" one relevant review and the term "*sepsis AND evidence based medicine*" two results.

Discussion. Though it is apparent that the evidence based approach is increasingly finding its way into Intensive Care Medicine, many challenges remain. As summarised by Grasselli et al: "1) we need better definitions of the common critical care syndromes (e.g. sepsis, ARDS ...); 2) we also need to increase the number of physiologic studies, to increase our understanding of pathophysiology and etiology of diseases; and 3) the creation of a large network of research ICUs (ideally with comparable levels of patient care) to carry out randomized clinical trials is necessary to increase the enrolment of adequate numbers of patients, such as occurs in the oncology and cardiovascular setting" [3]. The importance of the role scientific studies as a basis for decision making was further shown by Laurie et al. In March 2008, the role of basic science research in Australian intensive care practice was studied. A questionnaire was sent to all registered fellows and trainees of the Joint Faculty of Intensive Care Medicine who were resident in Australia. The result was that 74% of respondents believed basic science has an "important" or "very important" influence on clinical decision-making [7].

Future research is needed to develop evidence-based recommendations for every part of ICU.

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Superimposed high frequency jet ventilation leads to deterioration of inflammatory changes of airway mucosa

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Introduction. Superimposed high frequency jet ventilation (SHFJV) applied with a special jet adapter has been used to improve oxygenation and gas exchange in patients with acute lung injury [1]. However, technical problems include gas conditioning and may result in severe airway mucosal damage. Therefore, patients with ALI were examined endoscopically before and during SHFJV to assess airway mucosa.

Material and methods. Ten patients with ALI ($\text{paO}_2/\text{FIO}_2 < 300$) and preexisting inflammatory tracheal mucosa were included into the study age 62 ± 15 yrs). Endoscopic control of airways was performed before and every 24 hours after transition of ventilation from the conventional mode to SHFJV for 3 days. Gas conditioning with a continuous infusion of saline propelled in front of the HF jet stream and a warmed side stream of gas for entrainment was performed. Degree of mucosal injection and signs of dessication were determined semi-quantitatively.

Results. During SHFJV deterioration of mucosal appearance was obvious in all patients studied. Despite an improvement of oxygenation ($n = 9/10$), marked signs of epithelial damage, dessication, and development of clots of secretions and dark laminae of blood leading to partial obstruction ($> 50\%$ ID) of airways in some cases (2/10) after 24 hours of SHFJV, were observed.

Conclusion. Despite improvement of oxygenation SHFJV leads to deterioration of mucosal condition in patients with preexisting mucosal inflammation. Future technical developments have to concentrate on improvements in gas conditioning of inspired gases during long term jet ventilation.

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Procalcitonin in hantavirus infections

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Background. Procalcitonin (PCT) concentration increases in a setting of systemic bacterial infection, while patients with viral infections have normal or only slightly increased PCT serum levels. PCT is a more accurate marker for bacterial infection when differentiating bacterial infections from viral infections than C-reactive protein (CRP). In patients with hantavirus infections levels of CRP are usually elevated to levels found in serious bacterial diseases. On the other hand, there have been no reports in the literature on serum PCT concentration in patients with hemorrhagic fever with renal syndrome (HFRS).

tration in patients with hemorrhagic fever with renal syndrome (HFRS).

Patients 36 adult patients with HFRS, 30 with sepsis, and 19 with tick-borne encephalitis (TBE) were included in this retrospective study.

Results. The median PCT level in patients with HFRS was 0.52 ng/ml (range 0.08–11.71 ng/ml), in the group with sepsis 4.33 ng/ml (range 0.08–161.1 ng/ml) and in patients with viral meningitis 0.08 ng/ml (range 0.05–0.12 ng/ml). The difference between groups was statistically significant ($p < 0.05$). Higher PCT level was found in patients with HFRS caused by Dobrava virus (0.82 ng/ml; range 0.09–3.61 ng/ml) than in those with Puumala virus infections (0.50 ng/ml; range 0.08–11.71 ng/ml). However, the difference was not statistically significant ($p = 0.378$).

Conclusions. This study confirmed previous findings demonstrating the association of elevated PCT with bacterial infection. However, increased PCT serum concentration was also found in patients with HFRS with overlapping results between viral and bacterial infections. According to the PCT level we can discriminate TBE but not HFRS from sepsis.

Perioperative considerations in patients receiving dual antiplatelet therapy

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Because of a change of current practice of interventional cardiology, anaesthesiologists are confronted with an increasing number of patients receiving dual antiplatelet therapy after stent implantation in the coronary vascular system, aorta, carotid artery, or peripheral vessels. This lecture will focus on the perioperative management of dual antiplatelet therapy after coronary stent implantation because of the high risk for thrombosis after discontinuation of antiplatelet drugs in this clinical setting.

Indication for dual antiplatelet therapy: stent implantation. In patients with coronary artery disease, stent implantation reduces mortality and reinfarction rate [1]. Two types of stents exist: bare-metal stents (BMS) and drug-eluting stents (DES) with sirolimus or paclitaxel coating. Excessive neointima formation within the stent lumen leads to stent thrombosis (re-stenosis) with its clinical manifestations angina, acute myocardial infarction, and sudden cardiac death. Mortality of stent thrombosis is high (up to 20%). Especially patients with recent stent implantation are at risk. Re-stenosis may occur early after BMS implantation in 10–30% and after DES implantation in 5–10% [2]. Approved indication for DES include the treatment of discrete, previously untreated lesions, however, currently off-label use in patients with complex conditions is common thus further increasing the risk for re-stenosis. Together, delayed endothelialisation, local hypersensitivity reactions, and late stent thrombosis is the rationale for prolonged dual antiplatelet therapy after DES placement.

Dual antiplatelet drug regimen. Stent implantation is a thrombogenic procedure and initiates complex interactions between the surface of a stent and blood components, including the activation of platelets and coagulation factors. Platelets are suggested to play a pivotal role in this process. This is the rationale for antiplatelet therapy after stenting. Combined inhibition of two intracellular platelet activation pathways is more efficacious than monotherapy [3]. Furthermore, individual drug-resistance (up to 30%) supports the concept of dual antiplatelet therapy. Currently, the combination of two antiplatelet drugs is recommended to antagonize platelet hyperactivity:

- a) Aspirin antagonizes the production of thromboxane A₂ by irreversible inhibition of cyclooxygenase 1 (COX-1).

- b) Thienopyridines clopidogrel (Plavix®) or ticlopidine inhibit irreversibly the binding of adenosine diphosphate (ADP) at the P2Y₁₂-receptor.

Spontaneous bleeding problems (such as mucosal bleeding) are rare in patients under dual antiplatelet therapy but provocation of surgery or tooth pull may be associated with increased blood loss. Importantly, despite increased bleeding event rates, massive life-threatening blood loss was not observed in patients under dual antiplatelet therapy [4].

Dimension of time. The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (AHA/ACC/ACS Science Advisory) guidelines [5, 6] recommend that after implantation of a BMS, clopidogrel must be continued for 3–4 weeks (level of evidence 1A) and aspirin lifelong. After DES, clopidogrel should be administered for 12 months and aspirin lifelong (level of evidence 1C). Premature discontinuation of clopidogrel increases the risk of perioperative stent thrombosis.

The perioperative strategy. Perioperative management of these patients needs to balance the risk of stent thrombosis by preoperative discontinuation of antiplatelet drugs against the risk of surgical bleeding by continuation. Interdisciplinary risk stratification involves the cardiologist, the surgeon and the anaesthesiologist. The new AHA/ACC/SCA Science Advisory particularly addresses the problem of perioperative management of dual antiplatelet therapy based on expert opinion and limited scientific evidence.

1. *Elective noncardiac procedures* should be postponed until the mandated clopidogrel therapy will end (1 month after BMS, 12 months after DES). *Cardiac procedures* (causal therapy of coronary artery disease) can be performed without a time interval.
2. In *emergency cases* all perioperative care givers should be aware of the increased risk of intra- and postoperative bleeding and close interdisciplinary collaboration is recommended. It is important to note that the risk of stent thrombosis was reported to be more pronounced and relevant compared to the bleeding risk. In the only prospective outcome study [7] 44.7% suffered from complications after surgery, but most of them were of cardiac nature and not bleeding complications.
If bleeding becomes the leading clinical problem desmopressin, antifibrinolytics, and platelet transfusion may reverse platelet function. Both aspirin and clopidogrel cannot be antagonized pharmacologically. Symptomatic bleeding management should not induce a procoagulant status.
3. In *semi-elective or urgent cases* the management should be tailored to the thrombosis/bleeding tolerance [8]:
 - In high bleeding + low thrombosis risk scenarios it can be necessary to discontinue clopidogrel and aspirin.
 - In high thrombosis + low bleeding risk scenarios it may be recommended to continue dual antiplatelet drug therapy until the day or the day before noncardiac surgery.
 - In the intermediate cases clopidogrel may be stopped but aspirin should be continued if at all possible.
4. If *preoperative evaluation* suspects coronary artery disease further diagnostic and/or therapeutic interventions may be indicated in order to optimize the patient's condition. In these preoperative patients as well as in patients, who are likely to require surgical procedures within the next 12 months, BMS should be inserted and DES should be avoided. Another controversially discussed alternative is percutaneous transluminal coronary angioplasty (PTCA) without stenting.
5. In the *postoperative period*, dual antiplatelet therapy should be re-started as soon as possible. Acute myocardial infarction after stent thrombosis usually occurs in the

postoperative period and not intraoperatively. Accordingly, all professions and medical disciplines should be aware of and monitor clinical symptoms. Adequate therapeutic and logistic consequences should be defined in advance such as haemodynamic stabilization and transfer of the patient to an interventional cardiology unit with the facility of re-PTCA and re-opening of the occluded stent.

Platelet function monitoring. The Platelet Function Analyzer PFA-100 rapidly identifies aspirin effects and platelet disorders prior to surgery. Major limitation of the PFA-100 is its insensitivity for the biological effect of clopidogrel. Platelet count is not indicative for platelet function and *in vivo* bleeding time lacks specificity and sensitivity. COX-1 inhibition induced by aspirin can be detected by platelet aggregometry using arachidonic acid, epinephrine, or collagen. P2Y₁₂ receptor blockade induced by clopidogrel can be analyzed by using ADP as agonist. Although aggregometry is promising for quantitative analysis of platelet function during dual antiplatelet therapy, there is still no generally accepted consensus and the relationship between platelet function abnormalities and abnormal clinical bleeding or thrombosis still remains unclear. Drug-monitoring and dose titration using platelet function tests may help to improve clinical outcome of critically ill patients on dual antiplatelet therapy in future.

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Airway Management in Emergencies: Tracheal Intubation versus supraglottic airway devices

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Tracheal intubation (TI) still represents the gold standard in emergency airway management. However, TI is often difficult especially in prehospital emergency situations or inten-

sive care patients. First attempt success rates published in pre-hospital emergencies range from 67 to 85%, which implies that a second or third attempt of laryngoscopy is necessary in about 20% of patients, increasing the risks of hypoxia and aspiration of gastric contents [1]. Similarly, airway management in intensive care is characterized by higher complications rates compared with elective airway management for surgical procedures in the OR. Schwartz et al. [2] evaluated nearly 300 intubations in 238 intensive care patients and reported a percentage of difficult intubations in 8% and esophageal intubation in again 8%. Aspiration of gastric contents occurred in 4% of all procedures. The reasons for obviously increased difficulty in airway management of intensive care patients are inappropriate patient positioning, soft tissue swelling induced by highly positive fluid balances and edema formation and laryngeal trauma due to long term translaryngeal intubation.

In those cases where intubation is difficult, every further attempt of laryngoscopy increases the chance of laryngeal injury, swelling and bleeding. Since nobody dies because you try to intubate him, but some die because you do not stop trying to intubate them, the question arises whether other airway options exist, minimizing the risks of tracheal intubation. In 2005 William C. Wilson proposed the difficult airway algorithm in trauma [3], incorporating several modifications of the original ASA difficult airway algorithm for the use in trauma and emergencies [4, 5]. Both difficult airway algorithms separate an emergency pathway from a non-emergency pathway. The later pathway requires adequate face mask ventilation and oxygenation and sufficient time is left for alternative approaches to intubation (e.g. flexible fiberoptic scope). In case of inadequate face mask ventilation the insertion of a laryngeal mask airway™ (LMA) has to be considered immediately. In case that both face mask and LMA fail, the emergency pathway (cannot-intubate-cannot-face-mask-ventilate) recommends non-invasive airway ventilation using other supraglottic devices like esophageal-tracheal Combitube™ (ETC), ventilation via the rigid bronchoscope or transtracheal jet ventilation. Emergency invasive airway management (coniotomy or emergency tracheotomy) represents the last step of the algorithm.

Within the last twenty years several supraglottic airway devices were introduced into clinical practice, like the different LMA models (e.g. LMA classic™, Fastrach™, ProSeal™; LMA Deutschland GmbH, Bonn, Germany), the ETC (Tyco-Kendall, Mansfield, MA), Laryngeal tube™ (LT, VBM Medizintechnik, Sulz, Germany), Easytube™ (Teleflex Medical GmbH, Kernen, Germany), CobraPLA (Engineered Medical Systems Inc., Indianapolis, IN, USA), Intubating laryngeal airway (Cookgas ILA™, St. Louis, MO, USA) and several more. All those devices can be inserted blindly without the use of a laryngoscope. All airway gadgets are to be positioned within the patient's hypopharynx or proximal esophagus, directly opposite to laryngeal inlet. Therefore, sufficient ventilation and oxygenation can be obtained in patients after unsuccessful laryngoscopy.

However, supraglottic airway devices are characterized by certain typical disadvantages compared with the gold standard tracheal intubation. First, protection against aspiration of gastric contents is inferior to tracheal intubation (best protection with ETC, least protection with LMA classic); second, airway pressures are limited because gas leaks do occur using airway pressures between 16 and >30 cmH₂O (poorest sealing with LMA classic and best sealing with ETC, Easytube or LMA ProSeal); third, blind tracheal suctioning is impossible with all devices and fourth, education and ongoing training is necessary with all devices for a safe use in real emergency situations (most intensive training necessary with ETC, least with laryngeal tube). In emergency situations all those disadvantages are of minor importance since just one objective has to be achieved, namely sufficient oxygenation of the vital organs. Furthermore, emergency situations are inappropriate situations for the first time use of a new airway gadget. All devices have to be used in manikin trainings and clinical routine before employment in

emergency situations. In case of an airway catastrophe, intensive care physicians should focus on just one supraglottic device and should use the device they are most familiar with. Wiese et al. [6] performed a manikin-study on mask ventilation vs laryngeal tube during resuscitation by intensive care nurses. Use of the disposable LT significantly reduced the no-flow time and the authors therefore concluded that LT is a safe airway for personnel not experienced in tracheal intubation.

Another very important topic is safe extubation in intensive care patients with difficult airways. In these special collective we recommend the use of airway exchange catheters (AEC), on the one hand to allow continuous tracheal oxygen insufflation and on the other hand to facilitate reintubation if necessary. Mort TC [7] reviewed a prospectively collected data base on patients extubated via an AEC and reported a percentage of successful reintubations of 92% in 51 patients.

In conclusion we recommend the installation of an airway cart in every ICU, equipped with different supraglottic airways at different sizes, tube exchangers, a fiberoptic bronchoscope, a rigid scope (e.g. Bullard™ or Airtraq™) and coniotomy equipment in order to minimize patients risks after failed or inadvertent in- or extubation. Therefore, continuing medical education has to focus on this special topic and alternative airway devices have to be used and trained in manikins as well as under controlled conditions in the operating theater.

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Risks of perioperative anaemia and transfusion

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Anemia is a clinically important and increasingly frequent finding in patients presenting for surgery. Low Hemoglobin has been found to be generally associated with increased morbidity and mortality, both in large epidemiological studies in community-dwelling persons, and in critically ill patients and in the perioperative setting [1–4]. Especially in patients presenting for surgery, a significant association of anemia with increased perioperative morbidity and mortality has long been established in a multitude of settings and in both cardiac and noncardiac surgery [1–6]. Due to demographic developments in the last decades, especially in developed countries, more elderly patients are being admitted to hospitals to undergo surgery. Due to the decrease of the average hemoglobin level with

old age, many of these patients present with substantial preoperative anemia. In addition to the primary diagnosis warranting surgery and often facilitating preoperative anemia, these patients also suffer from many cardiac and noncardiac comorbidities that increase the perioperative risk *per se*.

Thus, in a majority of these patients, the probability to suffer from a postoperative adverse event is inherently high and is particularly aggravated when severe coronary artery disease is present. However, only few studies describe in detail the exact relationship between the individual degree of preoperative anemia and specific adverse postoperative outcomes and do not quantify the impact of preexisting comorbidities on this association. In addition, it is largely unknown whether the effects of anemia on outcome are caused by low hemoglobin levels *per se* or by association with other risk factors frequently prevalent in anemic patients. Therefore, to fully understand the nature of these risks, it is paramount to provide detailed information about the incidence, degree, and major causes leading to anemia, especially in preoperative patients.

Recent data of large multicenter trials on patients undergoing CABG surgery show that preoperative anemia should be interpreted as symptom for an underlying severe disease or other comorbid risk factors rather than as a disease in itself which can inherently be treated by augmenting an arbitrarily defined decreased lab value, such as low Hemoglobin, by transfusion of allogeneic red blood cells [4, 7, 8]. To assess the impact of low Hemoglobin on the postoperative outcome more precisely and in a clinically relevant fashion, a patient's individual comorbidities, as well as other concomitant patient and procedure-related risk factors, have to be taken into account. Therefore, the impact of perioperative anemia on adverse outcome may be substantially different for each individual patient, as well as a patient's individual Hemoglobin threshold that marks the cutoff point for a significant increase in postoperative complications. Several studies on postoperative adverse outcome of anemic patients have shown that the kidneys may be more vulnerable than any other organ system to low Hemoglobin levels, especially after a large intraoperative decrease of red blood cells and when renal dysfunction was preexistent prior to surgery [3, 4, 7–9].

Because most of these data have not been available until recently, the general practice and scientific opinion has always assumed that transfusion of red blood cells would, in all patients and in all settings, invariably reverse the previously described risks associated with anemia. While there is well-documented knowledge about the immediate danger of allogeneic blood involving the risks of infection, early and late-onset transfusion reactions or any other allergic or compatibility issues, or other pitfalls such as clerical errors, only few data are available about the medium and long-range effects of blood transfusions. Recently, the scientific and clinical attention has focussed on novel syndromes or adverse outcomes associated with allogeneic blood, especially for the immediate postoperative period: Transfusion-associated lung injury (TRALI) has recently been defined as morbid entity and has substantially shifted towards the center of scientific research during the last few years. Also, the immediate and long-term effects of allogeneic blood on the immunologic system have recently been described and summarized by the term Transfusion-Induced Immunomodulation (TRIM). Many large investigations try to define the impact of transfusions on the incidence of postoperative infections (i.e. pneumonia, septicemia and wound infections), as well as on the recurrence incidence of (mostly gastrointestinal) cancer, but up to date, no conclusive consensus has been reached as to the clinical impact of these available data [10–13].

On the other hand, only few studies have provided scientifically valid evidence about the possible beneficial effects of RBC transfusions [14]. Only recently, a few authors have tried to describe the impact of allogeneic blood transfusions in large, controlled, prospective studies [12, 15]. Only sparse and

mostly retrospective data exist about the possible therapeutic effects of transfusions in precisely defined patient groups, taking into account the individual comorbidities or other concomitant risk factors, and assessing the risk/benefit ratios for various specific clinical settings and major primary diseases.

Therefore, no conclusive evidence exists to provide precise and clinically useful recommendations for the use of allogeneic blood transfusions, or any other alternative methods for the optimal therapeutic approach in patients with perioperative anemia. In these patients, optimal perioperative management and clinical care should include the avoidance of unwarranted blood loss (and thus the development or aggravation of anemia), the limitation of unnecessary diagnostic blood samples, careful monitoring of perioperative coagulation and the comprehensive use of alternative blood saving techniques.

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The real open lung story-a personal view of 40 years research on mechanical ventilation

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Every year, thousands of patients receive ventilatory support during surgery. Mechanical ventilation has also become an important therapy in the treatment of patients with an impaired pulmonary function and, in particular, in patients suffering from the acute respiratory distress syndrome, which is characterized by acute respiratory failure with changes to the endogenous surfactant system and permeability changes of the alveolo-capillary membrane.

Already early after the introduction of mechanical ventilation in the 1950s it became realized that mechanical ventilation has several potential drawbacks and complications. Modes of mechanical ventilation, which combine high end-inspiratory lung volumes with low end-expiratory lung volumes, have been shown in healthy animals to induce permeability changes comparable to those seen in ARDS. These permeability changes as a result of mechanical ventilation have led to a growing realization that some of the pathophysiological changes seen in ARDS, may be a consequence of our ventilatory interventions, rather than a consequence of the primary disease process.

Despite ventilator support measures, the mortality of ARDS has not really decreased since it was first described in 1967 – and multiple organ failure – possibly resulting from ARDS – is now the leading cause of death in our hospitals. Although the exact mechanisms of the transition of ARDS into multi-organ failure is still unclear, bacteremia/endotoxemia and systemically circulating inflammatory mediators are thought to play an important role in the pathogenesis of the disease process. Given the possible harmful effect of mechanical ventilation, one reason for the high mortality of ARDS may be the fact that there is no routinely available early indicator to monitor and recognise metabolic changes to the lung as a result of our ventilatory interventions. However, a few studies in the recent past clearly showed that by applying so-called protective ventilator strategies, mortality could be significantly reduced – telling us that many of the problems in intensive care are produced by ourselves.

In the medical world there is a paradox related to atelectasis! Every medical student knows that our lung has a tendency to collapse. If our lung has a certain amount of atelectasis we just make 1 or 2 deep breaths and the whole lung is open again. We can monitor this with a stethoscope – and if the lung opens we hear crackles. When we sleep our lung is collapsing – especially on the side on which we are sleeping. If this collapsed area becomes too large we just turn from the right side to the left side, or vice versa; or from prone to supine position. In other words, we do not allow the existence of collapsed lung regions. We open them unconsciously and repeat this maneuver many times during the entire day. All this has been known for hundreds of years.

Now what happens in the hospital with a seriously ill patient? The patient may get a pain killer for pain relief, or he may even get mechanically ventilated due to his respiratory insufficiency. Due to all the drugs which the patient may get, he is unable to undertake a few deep breaths to get rid of his atelectasis. We will recognise this nowadays by measuring oxygen saturation, which will decrease, and we will compensate this by giving supplementary oxygen.

In a case of acute respiratory failure (ARF) or ARDS the tendency to collapse is even much greater due to a shortage of a sufficient amount of active surfactant in the alveoli. The shortage of active surfactant can only be compensated by a sufficient level of counter pressure – which is called positive end-expiratory pressure, or in short PEEP.

The very frustrating story is, however, that nobody knows and may not know in the coming 50–100 years, to what extent the alveolar surfactant is impaired. Thus we do not know which exact counter pressure has to be applied to avoid collapse of the surfactant-deficient alveoli.

Besides this point, there is another problem which we have to consider: the gravity. If a human being lies down on his back the alveoli at the bottom need a higher counter pressure to compensate the weight from the upper lung parts and from the heart, than the upper lung parts. If the patient gets a pneumonia or a lung edema, these gravity factors are becoming even more important.

Thus 3 factors promote atelectasis:

1. physiological tendency of the alveoli to collapse
2. surfactant impairment, and
3. gravity.

These facts are well recognized by the practitioner in the ICU, but almost no interventions were done in the past to overcome the presence of atelectasis.

And since hundreds of years it is known that if a patient gets atelectasis the risk that these areas become infected is very high – and pneumonia was one of the main causes of deaths in the time before antibiotics were available.

Let's jump back 47 years ago to 1961. I had finished my high school and decided I would like to be a doctor. But for the medical school there were too many applicants, but if one would work in a hospital as an orderly the chances were not so bad to get 1–2 years later a place at the medical school. Looking for such a position I finally found one as a lab assistant in the department of Clinical Respiratory Physiology in the Research Institute for Lung Diseases in Berlin-Buch – at that time the leading hospital for lung diseases in eastern Europe with almost all research facilities available. At my first visit to the lab I got quite depressed because I would like to be a doctor and not an engineer! But a few weeks later it became fun to be an assistant to a doctor working almost as an engineer. I had to do a lot of things but I did not understand what I was doing!

E.g. I was involved in investigations of patients under anesthesia and with muscle relaxants. Most of the patients suffered from tuberculosis and the question was – if the surgeon takes out the infected lung, will the remaining lung be able to cover sufficiently the required gas exchange, and will the right heart be able to compensate for the possibly increased right ventricular afterload.

To answer this question, the patient was intubated with a double-lumen tube under anesthesia, and to be able to perform all the required tests it was also necessary to paralyze the patient – at that time with curare. The lung which should be removed was functionally inactivated by an intra-alveolar pressure of 40–50 cm of water, which led to a complete perfusion blockade. The required pressure was generated by a powerful blower – like from a vacuum cleaner. During this blockade, the oxygen uptake was measured from the remaining lung. If it was sufficient, the surgeon got the information that after removing the infected lung the patient will survive, or will not die due to respiratory problems.

My function as lab assistant during this investigation was to keep the paralyzed patient alive – I had to ventilate him, either in a positive pressure ventilation or, if the patient was put into a tank, to measure thorax-wall mechanics in a negative respectively sub-atmospheric pressure mode. The so-called respirator was a self-made closed-circle spiograph with a CO₂ absorber and a built-in blower developed by Johannes Vogel. The moveable spirometer was covered with a container which was also connected to a powerful blower via a 3-way stopcock. The blower itself generated pressures up to 80–90 cm water. In one position of the stopcock the flow went into the container and – depending on the pressure which was regulated by a mechanical resistor – the spirometer went down and thus inflated.

ing the lungs of the patient with pure oxygen. The respiratory rate was preset by a metronome according to the preset beat. I moved the stopcock for inspiration in one position and then 1–2–3–4 beats later, again to the other position for expiration. I had to do this for about 1 hour – sometimes for an extended investigation even for almost 2 hours.

I'm not entirely sure – but maybe this was the first application of a pure pressure-controlled, time-cycled ventilator mode.

During this time, besides the clinical question, my former Chairman Dr. Vogel was even more interested to measure lung mechanics and thorax-wall mechanics in combination with functional residual capacity (FRC) measurements to get specific compliance figures.

To study thorax-lung mechanics, a pressure-volume recording had to be performed. This was done by a so-called *stufen-atmung* which can be translated as step-by-step breathing. From a basic pressure ventilation of 15 cm water and zero PEEP the inspiratory pressure was increased for 4–5 seconds stepwise by 5 cm water, and for expiration reduced by 10 cm water. The corresponding volumes were registered by the spirometer. This was done for the registration of the inspiratory limb and vice versa for the expiratory limb. The pressures went up to an average of 50 cm water. From these recordings pressure-volume loops were constructed.

These were I'm 100% sure my first successful recruitment maneuvers – but done unconsciously.

I also had no idea if the applied pressures for 4–5 seconds will harm the lung or not, the only fact I realized from all these patients was that they awakened, started spontaneous breathing even during intubation, and left the examination room without any additional respiratory problems.

Six years later – after finishing my medical studies at Charité in Berlin – I started my training in clinical physiology in Vogel's department. One of my first experimental duties was to analyze pressure-volume curves from guinea pigs with and without acute respiratory distress syndrome due to the injection of an anti-lung serum. The burning question was: is there a real increase in functional residual capacity after applying an intra-alveolar pressure of 40–50 cm water, or is it just some plastic behaviour of the lung due to the properties of the alveolar surfactant system. A prerequisite to answer this question was the availability of an equipment which could measure the FRC in small living animals. Of course such equipment was commercially not available.

Thus I developed a unit based on the oxygen wash-in/wash-out technique in a closed circuit system by using a polarographic oxygen sensor. A similar principal is now – 30 years later – available in some commercial ventilators. I performed these FRC measurements before and after pressure-volume recordings. Especially in surfactant-impaired lungs the FRC was always increased after pressure-volume recordings. My interpretation of the results 35 years ago was related more to lung recruitment than to the behaviour of the pulmonary surfactant system. At that time we did not correlate the FRC measurements with arterial blood gas measurements.

Now let's move to the year 1976. I was still living in east Berlin but I got a 1-year grant from the World Health Organisation to work in Sweden. I decided to go for surfactant research to Bengt Robertson in Stockholm who had visited me a few times before in my lab in Berlin – and to Bjorn Jonson's lab in Lund. My main interest in Bjorn's lab was to investigate if the Servo-Ventilator can really measure accurate small tidal volumes – which are required when one decides to use this ventilator to ventilate immature babies.

To test the delivered tidal volume from the ventilator we constructed a body plethysmograph as gold standard for volume measurements. We studied healthy and surfactant-depleted rabbits with bodyweights of between 0.8 and 3.5 kilograms, used all available knobs on the ventilator and put them in all possible directions – and to my surprise if the ventilator

was accurately calibrated the tidal volume measurements correlated highly with the measurements of the body plethysmograph. Then I started to discuss with Bjorn if it would also be possible to use the Servo-Ventilator 900B as pressure-regulated time-cycled ventilator – a mode which we used for our patients during broncho spirometry and for all of our animal experiments in Berlin. A lot of discussion took place because he was so proud on his invention of the flow regulator and now someone was asking for some ventilator modes which did not require his newly invented flow regulator!

Finally, by putting the working pressure at the required pressure level and putting the minute volume almost to infinite and adding electronically the pause time to the inspiratory time, we created the perfect pressure-controlled time-cycled ventilator with all monitoring functions!

We then did the same that we did with volume-controlled ventilation, now again in random order, changing respiratory rates, pause time, I/E ratios etc. both in volume-controlled and pressure-controlled ventilation. This time, at each ventilator setting we also took blood samples and found that, in the surfactant-deficient rabbits at pressure-controlled mode with a very long inspiratory time, the arterial oxygen tension was always significantly higher in comparison to constant flow ventilation with a short inspiratory time. We finally ventilated 2 groups of animals for 2 hours only for morphological studies one with a short inspiratory time – and the other with a longer inspiratory time in which intrinsic PEEP was resulting. The analyses were done by Bengt Robertson blindly in Stockholm.

The results were quite impressive. The pressure required to get a PaO₂ of 100 mm mercury at 100% oxygen at 80% inspiratory time was only about 20 cm water – at the shorter inspiratory time 38–40 cm water were required to get the same PaO₂ of 100–120 mm mercury. All the latter lungs showed widespread atelectasis, hyaline membranes, necrosis, and desquamation of airway epithelium – whereas lungs ventilated with lower pressures showed only some minor morphological changes which may have been introduced by surfactant depletion. Our interpretation of these differences in morphology were the following: this is now a quotation from our publication from 1982 in Critical Care Medicine.

"The shear forces can be considerable at non-homogenous expansion of lungs. Such shear forces may be the dominant reason for structural damage to the bronchial and alveolar epithelium as it is also typical for the respiratory distress syndrome. These potentially damaging shear forces all appear at each closure and opening of lung units. And from this we concluded that: the ventilatory support of RDS and ARDS should subtly open up closed units and keep them stable open, but should avoid local or general hyperinflation".

End of quotation.

In the summer of 1977 I went back to Berlin with a modified Servo ventilator 900B in my luggage – the east German authorities were quite happy with this present! We immediately repeated the rabbit experiments in larger animals – in which it was possible to measure all cardio-circulatory parameters – and we could confirm our results from Lund. The pressure-controlled ventilation with a prolonged inspiratory phase was always superior to improve gas exchange in comparison to flow-constant ventilation. We observed also that circulation was not seriously impaired as long as the inspiratory pressure was just balancing the retractive forces of the stiff alveoli. Under these conditions the applied pressure will not be transmitted to the vascular bed.

To get an impression why PO₂ was always higher in pressure-controlled ventilation with a long inspiratory phase – we opened the chest of a few animals to be able to watch the behaviour of the surfactant-deficient lung in dependence of different ventilator settings. We observed the following: in flow constant ventilation with an I/E ratio of 1:2 – the non-dependent parts of the lung were inflated first, followed by some more dependent parts, and finally by the really dependent al-

veoli. Some collapsed alveoli in the non-dependent part opened only at end inspiration. Atelectatic areas in the dependent part stayed atelectatic, even at end inspiration. The average tidal volume which was applied was between 10 and 15 ml/kg bodyweight, resulting in plateau pressures between 30 and 40 cm water.

At PEEP levels between 5 and 10 cm water a large amount of aerated alveoli collapsed again during expiration.

To avoid any collapse, PEEP levels of 15 to 20 cm water were required resulting however in dangerously high peak airway pressures of 50 to 60 cm water.

Switching over to pressure-controlled ventilation we saw that the recruitable alveoli were opened already at the beginning of inspiration, and prolonging the inspiratory phase finally to 80% the expiratory time was getting so short that even the dependent alveoli had no chance to collapse again.

The used inspiratory pressures were between 20 and 30 cm water and the PEEP levels as in volume-controlled mode between 5 and 10 cm water. But also in this mode there were quite substantial areas that stayed atelectatic during the whole respiratory cycle. These areas belonged to the dependent part of the surfactant-deficient lung.

But then I remembered what I did in the early 1960s as a young lab assistant in Vogel's lab during broncho spirometry at pressure-volume recordings. I applied pressures of 50 and sometimes by accident up to 60 cm water for 3 to 4 seconds without harming the patient. Thus we did the same with our surfactant-deficient animal lungs.

After applying pressures of 50–60 cm water – in some animals even up to 70 but only for 2–3 breaths – we were able to recruit macroscopically complete the whole lung, even the most dependent parts. Another fascinating observation was that after a recruitment maneuver the lungs stayed open even at a pressure of only 20–30 cm water and at PEEP levels of only 5–10 cm water.

In an other animal model of respiratory insufficiency – a virus pneumonia – which was ventilated with a peak pressure of 30 cm water and a PEEP of 10 cm water, resulting in almost no ventilation at all – we were also able to demonstrate the beneficial effects of higher recruitment – and PEEP pressures.

After increasing the peak pressure to 40 cm water the non-dependent parts got ventilated. But only after increasing the peak pressure to 50 cm water the dependent parts also got aerated but collapsed again during expiration. Only a further increase of the PEEP level to 18 cm water stabilized the whole lung.

With all these observations we were very happy and now we had seen in vivo what one has to do to overcome atelectatic areas in stiff lungs. As one knows – seeing is believing!

And I was 100% sure that human lungs will behave in the same way.

Enthusiastically we were waiting for our first patient.

In the autumn of 1977 (more than 30 years ago – just one day before my 35th birthday) we got our first patient, and I celebrated this birthday on the next day at his bedside! Barbara Handley – a classmate from medical school – was the physician in charge. This patient was a 35-year-old man who had a traffic accident and very severe trauma of the thorax and lungs, combined with shock.

He was admitted to our intensive care unit in Berlin-Buch.

During volume-controlled ventilation the chest X-ray showed only a few ventilated lung areas. Minute ventilation was 14 l of pure oxygen. PEEP higher than 8 cm water could not be applied because of the large parenchyma defects. Arterial oxygen tension was between 30 and 40 mm mercury and PaCO₂ varied between 75 and 91 mm mercury under these conditions. After a recruitment maneuver with a pressure of about 50 cm water and pressure-controlled ventilation with an I/E ratio of 4:1 and a peak pressure of only 34 cm water, PaO₂ had increased to a value more than twice within 10 minutes. PaCO₂ was down to 46 mm mercury. Arterial oxygenation, CO₂ elimination and

compliance improved despite further lowering of the peak pressure.

After 3 days with this breathing pattern, the arterial end-expiratory CO₂ gradient was nearly zero, indicating that substantial disturbances of ventilation perfusion and of diffusion no longer existed.

The chest x-ray after 4 days had improved dramatically.

Everybody who watched us was impressed by the improving of the patient's condition.

At that time – 30 years ago – nobody considered to do randomised controlled prospective studies. Our new strategy of pressure-controlled time-cycled inverse ratio ventilation with an initial very short application of a high pressure was just applied – and the resulting blood gases convinced the whole department in Berlin-Buch to apply this technique in all patients with severe respiratory failure.

Our experimental and first clinical results were nationally presented for the first time in Berlin in 1978 at the East German Anesthesia meeting and internationally at the Intensive Care Congress in Paris in 1980.

Our main messages at that time in our lectures and our poster were:

- First: one must overcome a critical opening pressure,
- second: this opening pressure must be maintained for a sufficiently long period of time, and
- third: during expiration no critical time that would allow closure of lung units should pass.

The following 5 years were from my point of view with respect to mechanical ventilation of ARDS patients not very spectacular because we believed that we had more or less solved all the problems. That's why we focused our whole research for the development of a surfactant preparation to treat patients with ARDS.

Nevertheless, in this time we did some experiments in which we could show that it is very important to apply this concept very early to avoid a vicious cycle of permeability changes, surfactant inactivation, stiff lung, higher pressures required, etc. From these animal experiments we got the information that if you start to ventilate a sick lung immediately after intubation according to our open lung strategy – lung function and lung morphology does not deteriorate further.

Before I left east Berlin we even started ventilating patients who required mechanical ventilation due to ARF with quite high PEEP levels after a recruitment maneuver with 50–55 cm water. We got the impression at that time that the lung function of patients treated in this way did not deteriorate.

In the summer of 1985 I escaped from east Berlin and got finally the position as research director in Prof. Wilhelm Erdmann's department of anesthesia and also got my own experimental department at the medical faculty of the Erasmus University.

The Dijkzigt Hospital at that time had 7 different ICUs. From our young colleagues who were in training for anesthesia and had to work in one or another ICU, I learned that many patients were ventilated in a volume-controlled mode – but even more frustrating was to hear that a lot of these patients were ventilated with very low or zero PEEP. To overcome this situation we discussed this and came to the conclusion that a Hands-On course under in vivo conditions in which colleagues could immediately see what they were doing would be the best solution. We organized such courses and my colleagues then saw and learned what I actually meant with an Open Lung. In the meantime I have given this Hands-on course more than 120 times during the last 15 years in many parts of the world.

In 1992 I published the editorial; Open up the Lung & Keep the Lung Open – which – according to the journal of Intensive Care Medicine – belongs in less than 15 years to the citation classics of the intensive care literature. In this editorial I describe what one has to do and what one should do to Open up

the Lung, and how to keep the lung open during mechanical ventilation.

Even if the principles which I describe in this editorial are not applied overall today, at least everyone who talks about mechanical ventilation is using a part of that sentence, or the whole sentence, in their scientific presentations.

In the early 1990s during a lecture tour through South America I also visited Marcelo Amato and Carmen Barbas in Sao Paulo. There we tried to apply our Open Lung Concept in a patient with a severe respiratory failure. I remember that the ventilator we had to use was not a very advanced one, but the patient improved and this was followed by much discussion about optimal ventilation settings in ARDS. Marcelo – at that time a young pneumologist – understood almost everything and let's say as a result of all these discussions he performed the first randomized prospective study comparing a so-called gold standard in mechanical ventilation with our Open Lung Concept – which he later called the Open Lung Approach.

This study made him very famous because he could show for the first time that by applying an almost optimal mode of mechanical ventilation this will reduce the mortality of patients with severe respiratory failure in combination with sepsis or other organ failure.

Again, this shows us what I postulated in the beginning of my story – that a lot of problems seen in the ICU are created by ourselves!

Marcelo Amato used for the recruitment procedure a peak pressure of 40 cm water which lasted for 40 seconds – why he applied this particular type of recruitment I do not know.

In the meantime, however, Marcelo and his colleagues from Sao Paulo learned that a lot of patients require higher recruitment pressures than 40 cm water. They have applied this successfully and have also published articles about this.

The medical progress related to mechanical ventilation and fluid therapy on the ICUs worldwide is still rather slow. However, the publication of our Editorial “Open up the Lung, and Keep the Lung Open” – and all our other publications from the department as well as our teaching activities worldwide – have at least helped a little bit to make sure that the fear to apply PEEP levels of 15 cm water or even higher has almost disappeared in many ICUs. This will help to improve the chance for our ventilated patients to survive.

Now after all the stories I have mentioned – one now knows almost everything about how the Open Lung Concept was born, and developed to its present form of application in patients on the ICU and also in operating theatres.

But even now – 10 years after Amato's publication that the open lung strategy reduces mortality – there is still a discussion about the rationale for the open lung management and how and when to do it.

Just as many roads lead to Rome, there may be different ways to apply the Open Lung Concept. But I am 100% sure that – based on the fact that God the Father or Mother Nature created us with an open lung – we should do our best to keep the lungs of our ICU patients also open to prevent all the known complications from atelectasis.

After my 40 years of research in the field of ARDS and mechanical ventilation – I still have the impression that the sentence that William James wrote more than 100 years ago –

*When a thing was new people said: “it is not true”.
Later, when the truth became obvious, people said:
“anyway, it is not important”, and when its importance could not
be denied, people said, “anyway, it is not new”.*

still applies to our situation in the 21st century and prevents a faster introduction of new discoveries in many fields of the medical world into the daily clinical practice.

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See Pub Med: Lachmann B and mechanical ventilation.

In-vivo and in-vitro effects of activated Protein C

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The systemic inflammatory reaction in the course of sepsis causes an activation of the coagulation system which can range from a subtle alteration of certain sensitive laboratory parameters to an overt DIC, consisting of an uncontrolled consumption of coagulation factors with microthrombosis and subsequent bleeding. This sometimes catastrophic event is initiated by the expression of tissue factor (TF) on several cell types triggered by cytokines and mediators of inflammation. Following the activation of factor VII and subsequently factor X, prothrombin is finally transformed into thrombin, the key actor of coagulation. Beside its procoagulatory effects, exerted through the conversion of fibrinogen to fibrin and the activation of platelets, thrombin exhibits also anticoagulatory characteristics by activating the protein C pathway. Protein C is a physiological serineprotease. The inactive form of protein C is activated by endothelium-bound thrombomodulin, which is activated by thrombin itself. In concert with its co-factor protein S and the endothelial protein C receptor (EPCR), activated protein C (aPC) inhibits the physiological coagulation by proteolytically degrading coagulation co-factors Va and VIIIa, thereby inhibiting the de novo formation of thrombin. Under physiological conditions, the protein C dependent balance of the coagulation system seems of particular importance for maintaining the microcirculation in the capillaries.

In sepsis, the protein C pathway is disturbed in several ways. Firstly, the competitive synthesis of acute phase proteins can cause a reduction in the plasma levels of the inactive zymogen protein C. Secondly, degradation of protein C by proteolytic enzymes and thirdly consumption due to the ongoing coagulation process can further aggravate the diminution. Additionally, activation of the inactive form of protein C can be impaired by a downregulation of the expression of thrombomodulin and of the EPCR on the endothelium due to circulating cytokines. Furthermore, a relative protein S deficiency due to complexation of protein S with C4b-binding protein can inhibit the activation as well.

Studies in septic patients revealed that up to 90% actually displayed a decrease of the protein C plasma concentration, when compared with healthy subjects [1]. Similarly, the plasma level of the activated form of protein C has been shown to be reduced in patients with severe sepsis. However, the disturbances of the protein C pathway in sepsis may not only promote the formation of excess thrombin, thereby shifting the balance of the coagulation system towards a procoagulatory state. Recent investigations revealed a number of additional properties of aPC regarding coagulation and inflammation pathways as well, supporting the application of aPC in severe sepsis to reinstall the balance of pro- and anticoagulatory effects, and thereby avoiding the development of deleterious intravascular coagulation and subsequent organ failure.

Besides the controlled inhibition of thrombin formation, fibrinolysis is another physiological opponent of excess coagulation. Activation of fibrinolysis is achieved by the release of tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA) and the subsequent transformation of plasminogen to plasmin. Plasmin hydrolyses fibrin to d-dimers, thereby controlling excess coagulation and avoiding intravascular clotting.

However, analogous to coagulation, fibrinolysis is also controlled by inhibitors of the plasminogen activators. The plasminogen activator inhibitor (PAI-1) is synthesized in the endothelium and inactivates t-PA and u-PA by forming complexes with both of them. After being activated by thrombin, the thrombin activated fibrinolysis inhibitor (TAFI) is another inhibitor of fibrinolysis, specifically modulating the fibrin mol-

ecule to avoid binding of plasmin and subsequent hydrolysis. Activated protein C participates in several ways in this complex interaction of activators and inhibitors of fibrin synthesis and degradation. The activation of TAFI is directly impeded by the inhibition of thrombin formation. Additionally, aPC can inactivate PAI-1 by binding it in complexes, thereby increasing indirectly the fibrinolytic activity of t-PA. Taking these effects into account it becomes clear, that the sepsis induced reduction of activated protein C plasma level causes not only an increase in thrombin formation, but also a decrease of fibrinolysis, further supporting the imbalance of the coagulation system in sepsis. However, the clinical impact of these effects remains difficult to judge. In the PROWESS study, the application of recombinant activated protein C resulted in a decrease of d-dimers [2], possibly as a result of an indirect inhibition of fibrinolysis by the reduction of thrombin formation. Whether the profibrinolytic characteristics of activated protein C are of clinical impact remains to be determined.

Thrombin not only triggers the coagulation but also inflammation e.g. by inducing the expression of adhesion molecules on the endothelium. Similarly, inflammatory cytokines can activate the coagulation system by triggering TF expression on monocytes, inhibiting the expression on thrombomodulin on endothelial cells and activating the complement system. Activated protein C seems to participate in this crosstalk of inflammation and coagulation. Again, this could be an indirect effect by inhibiting thrombin formation. However, in-vitro data suggest direct effects of activated protein C, independent of thrombin formation as well. This could comprise of a suppression of leucocyte adhesion on the endothelium, an inhibition of the liberation of proinflammatory cytokines, triggered by endotoxin, or the synthesis of interleukins by endothelial cells. Some of these effects could be exerted via binding of aPC to the endothelial protein C receptor and co-stimulation of other protease activated receptors (PAR). In vitro experiments showed an inhibition of the transcription factor NF- κ B by aPC in endothelial cells and monocytes. Since NF- κ B has a key role in activating the expression of genes coding for a number of proinflammatory cytokines, aPC could exert some of its direct anti-inflammatory effects via these pathways.

The clinical impact of these effects however, remains largely unknown. Preliminary data from large clinical trials is inconclusive.

The same accounts for possible antiapoptotic effects of activated protein C by suppressing the expression of proapoptotic genes in endothelial cells, and a protein C dependent increase of proliferation in some cell types, possibly improving wound healing processes. Additionally, the relevance of in vitro effects on the development of fibrosis, ischemia-reperfusion syndrome and neuroprotection after stroke for future therapeutic strategies remains to be investigated. Potential future indications for activated protein C could include the improvement of microcirculation and the manipulation of healing processes in a variety of diseases.

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Near infrared spectroscopy for evaluation of global and skeletal muscle oxygenation in critically ill

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Clinicians realize the limitations of the physical examination in detecting compensated shock states, the severity of uncompensated states, and in determining the adequacy of resuscitation in order to prevent subsequent multisystem organ failure and death.

The paper is focused on near-infrared spectroscopy (NIRS) signal from skeletal muscle during severe heart failure/cardiogenic shock or severe sepsis/septic shock. The ultimate goal of such techniques is to prevent misassessment of patients and inadequate resuscitation, which are believed to be major initiators in the development of multisystem organ failure and death.

Introduction. The primary physiological task of the cardiovascular system is to deliver enough oxygen (O_2) to meet the metabolic demands of the body. Shock and tissue hypoxia occur when the cardiorespiratory system is unable to cover metabolic demand adequately. Sustained tissue hypoxia is one of the most important cofactors in the pathophysiology of organ dysfunction [1]. Therefore determining the adequacy of global systemic and tissue oxygenation in critically ill patients is central to ascertain the health of the patient.

Unfortunately, traditional clinical signs of tissue perfusion that have been used over the last century (capillary refill, mental status, heart rate, pulse pressure, systemic blood pressure and even urine output) are now recognized as being limited in their ability to act as sensitive indicators of tissue perfusion [2]. Therefore, detecting compensated shock (which is the most common presentation of shock) continues to remain a tremendous challenge. Even after beginning resuscitation from a state of uncompensated shock, mounting evidence exists that supports ongoing inadequate tissue perfusion despite normalization of these historic indices [3]. Over the last two decades, an intense search for more sensitive monitoring technology and methods to serve as resuscitation end-points has and continues to take place. Perhaps a misnomer, an ideal endpoint to resuscitation of shock states should also serve as an ideal marker of the presence of an altered state of oxygen delivery at its earliest stages, even before clinical signs of such a state are evident. Conversely, the chosen monitoring modality or endpoint should be capable of ensuring that the patient is fully resuscitated and can be maintained once the endpoint is normalized.

Maintenance of adequate oxygen delivery (DO_2) is essential to preserve organ function, as a sustained low DO_2 is a path to organ failure and death [4]. DO_2 does not have influence on oxygen consumption (VO_2) until it reaches critically low values (DO_{2crit}), when VO_2 starts to fall. However, when DO_2 reaches a critical threshold, tissue extraction of oxygen cannot be increased further to meet tissue demands. It is at this point that VO_2 becomes directly dependent on DO_2 (DO_{2crit}) and cells begin to convert mainly to anaerobic metabolism as manifested by significant increases in metabolic byproducts, and other cellular entities reflective of this state such as lactate, NADH, and reduced cytochrome oxidase (CtOx). Each individual organ has its own biphasic relationship with differing points of DO_{2crit} , which can vary significantly based on the severity of the insult, the system's metabolic activity, vascular responsiveness to a myriad of mediators, and type of insult.

Low cardiac output states (cardiogenic, hypovolemic and obstructive types of shock), anemic and hypoxic hypoxemia are characterized by a decreased DO_2 but preserved oxygen extraction ratio ($OER = \text{the ratio of } DO_2 \text{ to } VO_2, VO_2/DO_2$) so that DO_{2crit} remains normal. In distributive shock, the oxygen extraction capability is altered so that the critical oxygen extraction ratio is typically decreased. These situations are typically

associated with an increased DO_{2crit} , and VO_2 can become dependant on DO_2 even when the latter is normal or elevated. Unfortunately global measurements of DO_2 and VO_2 may not be sensitive enough to be clinically relevant.

Laboratory and clinical evaluation. In terms of absolute use, the majority of clinical near-infrared spectroscopy (NIRS) work has been performed in an attempt to monitor the state of cerebral oxygenation in neonatal critical care and in adults during operative interventions such as carotid endarterectomy, subarachnoid hemorrhage surgery, or cardiopulmonary bypass. The aggressive application of NIRS in the assessment of trauma has lagged until recently.

NIRS has been used in the laboratory and clinic to evaluate the state of tissue oxygenation by assessing hemoglobin oxygen saturation within a tissue (StO_2).

The basis for the use of NIRS is an attempt to move beyond the crude physical examination to better avoid tissue dysoxia based on the principles depicted in by examining an assessable tissue bed whose oxygen transport characteristics would be sensitive to changes in DO_2 . Thus, determination of regional StO_2 in a tissue expected to experience reduced DO_2 after acute injury might provide an early warning that global hypoperfusion is occurring prior to reaching whole body DO_{2crit} or significant alterations in vital signs. Additionally, it would allow clinicians to guide resuscitations better, thus reducing chances that occult tissue hypoxia is still occurring despite restoration of circulating blood volume and "normal" vital signs. For these reasons, it may not be obvious of what value monitoring the CtOx redox state would be if StO_2 were being monitored in the same tissue. Changes in StO_2 would provide an earlier warning sign of impending dysoxia and during resuscitation would help the clinician ensure that oxygen delivery to the tissue had been restored to a level well above that required to simply reverse dysoxia. As expected, regional CtOx redox state has been shown to correlate strongly with regional VO_2 ($r^2 = 0.9$) only when VO_2 became dependent on DO_2 (below DO_{2crit}) [5]. It is not surprising that detection of CtOx redox state reduction as a marker of regional tissue dysoxia would occur prior to detection of systemic lactate, since lactate must be produced intracellularly, transported out of the cell, and exceed the limits of metabolism by the liver and renal cortex before being detected in abnormal amounts.

NIRS of skeletal muscle in sepsis and septic shock during stagnant ischemia. Sepsis is the cause of near 15% of admissions to non-coronary intensive care units in France and leading cause of death in noncoronary intensive care units in USA [6]. Its high mortality is mainly caused by multiple organ failure. The pathogenesis of multiple organ failure has not been completely explained yet. Although microvascular flow redistribution undoubtedly occurs, studies in animals and patients with sepsis have shown increased tissue oxygen tension [7]. Since increased severity of sepsis is associated with a progressive fall in tissue oxygen consumption, but with a rise in tissue oxygen tension, the problem is probably one of reduced cellular use of oxygen rather than tissue hypoxia per se. Further studies have confirmed association between nitric oxide overproduction, antioxidant depletion, and mitochondrial dysfunction that relate to organ failure and eventual outcome of septic shock [8].

In our previous research thenar muscle tissue deoxygenation during stagnant ischemia [9]. Upper limb ischemia was induced by rapid automatic pneumatic cuff inflation around upper arm (Fig. 1). During upper arm ischemia reperfusion test several StO_2 parameters can be studied: average StO_2 before arterial cuffing/occlusion; StO_2 downslope during cuffing – the deoxygenation rate ($\Delta down StO_2/sec$); StO_2 upslope ($\Delta up StO_2/sec$); hyperaemia (overshoot of StO_2 above baseline).

The study confirmed that thenar muscle tissue deoxygenation during stagnant ischemia at admission (after haemodynamic stabilization) is significantly slower in septic shock patients compared to severe sepsis, localized infection and

Fig. 1. An original thenar StO_2 recording after arterial upper arm cuffing, and cuffing release (upper arm ischemia reperfusion test). During upper arm ischemia reperfusion test several StO_2 parameters can be studied: average StO_2 before arterial cuffing/occlusion; StO_2 downslope during cuffing – the deoxygenation rate ($\Delta down StO_2/sec$); StO_2 upslope ($\Delta up StO_2/sec$); hyperaemia (overshoot of StO_2 above baseline)

healthy controls. The rate of StO_2 decrease correlated tightly with Sequential organ failure assessment score (SOFA) score and weakly with norepinephrine requirement, plasma lactate and C-reactive protein concentrations. During improvement of sepsis muscle tissue deoxygenation rate increases in both septic shock and severe sepsis group.

Our results are in accordance with those reported in a baboon model of septic shock [10]. In these primates NIRS determined rate of skeletal muscle enzyme CtOx a, a3 reduction during stagnant ischemia was decreased in gram negative septic shock. This data was interpreted as being consistent with the presence of a defect in the ability of the enzyme to accept electrons from oxygen or a limitation in the availability of the reducing equivalents.

In resuscitated septic shock patients muscle tissue perfusion and oxygen consumption were approximately twice that of non-septic patients and healthy controls [11]. The increase in oxygen demand was however matched only by an increase in oxygen supply and not also by an increase in oxygen extraction as in normal muscles during exercise, therefore, a defect in tissue oxygen extraction was hypothesized.

In laboratory models, mitochondrial respiration is often increased in the early phase of acute critical illness, but consistently falls with protracted inflammation (> 12–16 hours) [12].

NIRS of skeletal muscle in heart failure and cardiogenic shock with or without severe sepsis/septic shock. Measurement of mixed venous oxygen saturation (SvO_2) from the pulmonary artery is used for the calculations of oxygen consumption and has been advocated as an indirect index of tissue oxygenation and prognostic predictor in critically ill patients [13]. In recently published paper we studied skeletal muscle oxygenation in severe left heart failure with or without additional severe sepsis/septic shock and compared it with SvO_2 [14]. The hypothesis was that StO_2 could estimate SvO_2 in patients severe left heart failure and preserved oxygen extraction capability (without severe sepsis/septic shock), because blood flowing through upper limb muscles could importantly contribute to flow through superior vena cava. On the other hand in patients with decreased oxygen extraction capability (with severe sepsis/septic shock), we expected disagreement between StO_2 and SvO_2 , because in these patients, higher oxygen extraction probably can take place in other organs different than skeletal muscles.

The main result of our study is that skeletal muscle StO_2 dose not estimate SvO_2 in patients with severe left heart failure and additional severe sepsis or septic shock. However, in pa-

tients with severe left heart failure without additional severe sepsis or septic shock, StO₂ values could be used for fast noninvasive SvO₂ estimation; and the trend of StO₂ may be substituted for the trend of SvO₂. The results are in concordance with our previous report of high StO₂ and slow deceleration rate of StO₂ during stagnant ischemia in septic patients.

The high StO₂/low SvO₂, seen in severe sepsis and septic shock, suggest blood flow redistribution. Thenar muscle StO₂ probably correlates with central venous oxygen saturation (ScvO₂) which is measured in mixture of blood from head and both arms. In healthy resting individuals ScvO₂ is slightly lower than SvO₂ [15]. Blood in the inferior vena cava has high oxygen content because the kidneys do not utilise much oxygen but receive a high proportion of cardiac output. As a result, inferior vena caval blood has higher oxygen content than blood from the upper body and SvO₂ is greater than ScvO₂.

StO₂ overestimated SvO₂ (bias -2.5%) in our study. This may be due to NIRS method, which does not discriminate between compartments. It provides a global assessment of oxygenation in all vascular compartments (arterial, venous and capillary) in sample volume of underlining tissue. This is major limitation of our study. The noninvasive measurement of only venous oxygen saturation is complicated by the fact that the isolation of the contribution of venous compartment to the noninvasive optical signal is not straightforward.

In low flow states, where there are still controversies on how to monitor these patients, it appears logic to take care of both macro- and micro-circulation parameters, to guide resuscitation. A large prospective study is being performed right now to evaluate the possibility of additional StO₂ regional monitoring for tissue oxygenation guidance on top of the early goal directed therapy.

Summary. The present review provides the foundation to understand and evaluate the potential value and limitations of NIRS as a tool in the assessment of critically ill. Despite continuing technical controversies concerning signal derivation, accuracy, precision, and quantitative ability, skeletal muscle NIRS clearly demonstrates promise in being able to monitor the balance of oxygen delivery and consumption at the end-organ level in severe heart failure or cardiogenic shock. It is also possible to estimate global oxygenation (mixed venous saturation) in low cardiac output without additional severe sepsis or septic shock.

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Atonic postpartum haemorrhage and interdisciplinary management: Case series and review of the literature

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Introduction. Haemorrhage is the leading cause of intensive care unit admission and one of the leading causes of death in the obstetric population [1, 2]. Especially postpartum haemorrhage can be an obstetric emergency that might follow vaginal or caesarean delivery. In a large study analysing data from 507,410 births an incidence ranging from 1.4% up to 4.9% were found [3].

Various definitions of postpartum haemorrhage exist, the most common one being an estimated blood loss of 500 ml after vaginal birth or of 1000 ml after caesarean section [4]. It has also been defined as a change in haematocrit of 10% from admission assessment to postpartum measurement or as the need for transfusion of red blood cells [5].

Underestimation of blood loss leading to a delay in diagnosis and deficiencies in communication and transportation infrastructure impeding transfer to a higher level of care are known to put the mother at an increased risk. Inability to stabilize a patient who is in haemorrhagic shock rapidly results in death. Thus routine use of prophylactic uterotonics, a standardized means of blood loss assessment, availability of a non-pneumatic anti-shock garment, and systemization of communication, transportation, and referral have been proposed to be part of a standard interdisciplinary management in order to lower the risk for and the complications of postpartum haemorrhage [6].

The aim of this work is to show by a case series how postpartum haemorrhage can lead to a life-threatening situation and to give an overview on the literature dealing with pathophysiology, risk-factors and management of bleeding after delivery.

Case series. We report on 3 patients who were admitted for atonic bleeding after delivery. For patients' characteristics see Table 1. Patient number 1 underwent acute caesarean section in general anaesthesia in her 35th gestational week after cardiotocography had revealed signs of fetal hypoxia. The operation was complicated by uterine rupture and massive bleeding

Table 1. Patient's characteristics

	Patient 1	Patient 2	Patient 3
Age (years)	41	37	34
Number of pregnancies*	7	8	6
Number of deliveries*	3	4	5

*Including the reported pregnancy/delivery.

in consequence of uterine atonia. Patient number 2 underwent delivery by acute caesarean section in general anaesthesia for the same reason 4 days after the expected date of delivery. As the atonic bleeding could not be controlled medicamentously, the obstetrician had to perform hysterectomy. In patient number 3 an elective caesarean section was done for twin pregnancy in her 40th gestational week. As spinal anaesthesia did not work properly, general anaesthesia had to be performed.

Prostaglandin F2alpha (Minprostin®) was administered directly into the myometrium to all 3 patients during caesarean section. Immediately after caesarean section, all 3 patients were admitted to an intensive care unit. Apart from erythrocyte concentrates, fresh-frozen plasma and antibiotics as listed in Table 2, patients were in need for analgesic therapy, heparins, furosemid, substitution with human albumin and other various medications. Continuous admission of uterotonics was necessary for all of them. They had to stay at the intensive care unit for 1 day (patients 2 and 3) and 2 days (patient 1). After normalization of haemoglobin, haematocrit and clinical stabilization, the patients were transferred to obstetric wards.

Discussion. Prevention of maternal deaths has gained in importance: Reducing the maternal mortality ratio by three quarters between 1990 and 2015 is the 6th target of the UN Millennium Project [7]. The leading cause of maternal mortality is haemorrhage, generally occurring in the postpartum period [6]. Most bleedings appear as atonic haemorrhages, showing an incidence of up to 1:20, after delivery [8]. Risk factors of atonic haemorrhage are pluriparity, fetal macrosomia, fast course of birth, high doses of oxytocin, status post caesarean section and status post atonic bleeding [9].

General risk factors for bleeding during pregnancy are hereditary diseases of the coagulation system, smoking, prior preterm birth, advanced maternal age, passive smoking exposure and multiple prior spontaneous abortions or multiple prior induced abortions [9]. The patients reported here show several of these factors: 2 miscarriages and 2 interruptions of pregnancy were reported by both patient number 1 and 2. They both were at advanced age. Patient number 3 has had 1 late miscarriage and 1 induced abortion. Interestingly our 3 patients showed atonic bleeding in the course of caesarean section in general anaesthesia. However, to our knowledge general anaesthesia has never been reported to be a risk factor for uterine atonia.

In general the coagulation system shows a state of hypercoagulability during pregnancy. In pregnant women increases in a number of clotting factors (I, II, VII, VIII, IX and XII), a decrease in protein S and C levels and inhibition of fibrinolysis

are found [10]. Usually, the platelet count shows no distinct alterations during pregnancy, although it may show 10% decline due to physiologic prepatal haemodilution [11].

Furthermore pregnancy leads to increases in platelet turnover, clotting, and fibrinolysis [12]. However, in the course of preeclamptic and eclamptic disease may lead to a lack of up-regulation of the fibrinolytic system. This results in an increased risk for disseminated intravascular coagulopathy.

Uterine blood flow has been estimated to be as high as 600–900 ml/min which explains the intensity of peripartur haemorrhage [13]. Furthermore, one tends to underestimate the loss of blood. Our 3 patients showed dramatic, life-threatening courses during caesarean section. Heavy bleeding led to the need for administration of several erythrocyte concentrates and to admission to an intensive care unit for stabilization and postoperative monitoring.

In case of atonic postpartur bleeding, interdisciplinary management including intensivists and obstetricians is the key point. Ultimate ambition is the early and target-orientated intervention. The gynaecologic therapy includes uterotonics (oxytocin, methylergotamine, prostaglandins such as sulproston) as well as local cooling and manual compression (Fritsch's manoeuvre, Zweifel's manoeuvre). As for all heavy bleedings, the intensivist has to treat the lethal triad of hypothermia, acidosis and coagulopathy in order to minimize effects on the coagulation system. A state of hyperfibrinolysis has to be diagnostically excluded. Substitution with red blood cells, platelets and fibrinogen, eventually rescue-therapy with recombinant Factor VIIa are important therapeutic options [14].

Close cooperation between obstetricians and intensivists are the basis for appropriate therapy in the emergency case of atonic postpartum bleeding in order to provide optimal care.

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Table 2. Treatment: During caesarean section and stay at the Intensive Care Unit

	Patient 1	Patient 2	Patient 3
Total number of erythrocyte concentrates	6	13	6
Total number of fresh-frozen plasma	0	2	5
Antibiotics	Cefuroxim	Mezlocillin	Amoxicillin + Clavulanic acid

HELLP syndrome requiring intensive care – A case report

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Introduction. Complications requiring admission to an intensive care unit (ICU) are rare events for pregnant women. Retrospective analyses have revealed rates of 0.11% up to 0.89% [1–3]. However, despite this low percentages, high overall maternal mortality rates from up to 21% in ICUs have been reported [4]. Obstetric haemorrhage, preeclampsia/eclampsia – often complicated by HELLP syndrome – are the most frequent obstetrical reasons for admission to an ICU with most of the patients being admitted postpartum [5–7].

HELLP syndrome is defined as a preeclamptic or eclamptic disorder showing haemolysis, elevated liver enzymes (serum LDH ≥ 600 IU/L or total bilirubin ≥ 1.2 mg/dL) and low platelet count (≤ 100.000 cells/ μ L). It develops in approximately 0.1% of pregnancies, normally during the third trimester, and progresses until delivery. The reported maternal mortality due to HELLP syndrome ranges from 0% up to 24% [8].

We report the case of a patient who had to be admitted to the ICU for escalated HELLP syndrome after caesarean section.

Case report. A 23-year-old woman had one HELLP syndrome induced preterm caesarean delivery in the 25th gestational week. 10 months after this event she got pregnant and had an uncomplicated pregnancy until the 31st gestational week (Table 1). In the 32nd gestational week, the patient was admitted to our obstetrical department for upper abdominal pain and high blood pressure. The clinical symptoms were accompanied by abnormal serum parameters LDH (1231 U/L), AST (272 U/L), ALT (158 U/L), uric acid (6.5 mg/dL), CRP (4.6 mg/dL) and decreased platelet count ($32 \times 10^3/\mu$ L). Urine analysis revealed heavy proteinuria. At admission she showed an elevated blood pressure of 204/106.

The patient was given urapidil to decrease blood pressure and magnesium sulphate to prevent convulsions, both were applied intravenously by perfusion pump. In order to achieve fetal lung maturity and to increase platelet count, corticosteroids were applied intravenously and intramuscularly to the patient.

However, blood pressure remained high, a lowest level of 150/97 was achieved after 6 hours. The clinical status of the patient with regard to abdominal pain worsened. Furthermore, a marked decrease in platelet count ($29 \times 10^3/\mu$ L) was seen 8 hours after admission. Therefore prompt delivery by caesarean section in general anaesthesia was performed. Intraoperatively, the patient was given 2 platelet transfusions. A female fetus with 1-/5-/10-minutes APGAR score of 7/9/9, respectively, was delivered and immediately admitted to the neonatal ICU. Immediately after surgery, the mother was awake and orientated and did not need further intubation.

She was admitted to the ICU and observed for 2 days. After the intraoperative administration of platelet transfusions an increased platelet count of $70 \times 10^3/\mu$ L was seen on the first postoperative day. Liver enzymes and blood pressure levels decreased constantly during intensive care management, allowing transferring the patient to the normal peripartur ward at the 3rd day after caesarean section. As a minor complication the patient showed wound haematoma beginning on the 3rd postoperative day requiring erythrocyte concentrates. However, this complication could be managed without reoperation. After normalization of the serum parameters the patient could be dismissed on the 10th postoperative day.

Discussion. Maternal morbidity and mortality have been decreasing since the beginning of the last century [9, 10]. However, with regard to the fact that most of the obstetric patients are younger as compared to other patients requiring ICU, ob-

stetric complications such as HELLP syndrome remain a topic of interest. Furthermore it has been demonstrated that obstetric ICU patients show much lower APACHE (Acute Physiology And Chronic Health Evaluation) scores than other ICU patients [11].

In our case, the standard protocol according to the institutional guidelines for the management of a critical HELLP syndrome was administered, involving an interdisciplinary team of obstetricians, intensivists and neonatologists from the beginning of treatment: Worsening of the clinical symptoms and laboratory values required immediate delivery. As in many critically ill patients suffering from HELLP syndrome, caesarean section was performed, in literature rates of up to 85% have been reported [12]. Caesarean delivery has been mentioned to be a contributory factor to the rate of successful perinatal outcomes [13]. However, as evaluated by Deruelle et al. [14], caesarean section combined with severity of preeclampsia or HELLP syndrome increases the risk for post-partum complications. Some of these effects may be due to the operative risk as caesarean section leads to an increased rate of post-partum infections [15] and of venous thromboembolic events [16]. Furthermore, in the study of Osmanagaoglu et al. [13], immediate caesarean delivery did not prevent maternal death for all patients. Therefore after confirmation of the diagnosis, assessment of the fetal situation and stabilization of the mother are essential steps in the management and should precede caesarean section. Prompt delivery without preoperative stabilization is indicated for pregnancies ≥ 34 weeks of gestation, in case of non-reassuring tests of the fetal status and presence of severe maternal disease as multiorgan dysfunction, disseminated intravascular coagulation, liver infarction or haemorrhage, renal failure or abruption placentae [17].

In literature, a common reason for admission of an obstetric patient to the ICU is the necessity for mechanical ventilation. Other frequent indications are postpartum haemorrhage, pregnancy induced hypertension and its complications such as renal failure, placental abruption, coagulopathies and HELLP syndrome [6]. The admission to the ICU after delivery for critical HELLP syndrome is beneficial, if not mandatory, for various reasons. Most obstetricians do not encounter sufficient number of cases and thus cannot have enough expertise to deal with such situations. Furthermore, as mentioned above, caesarean section does not prevent from maternal death and life-threatening situations may arise shortly.

In the study of Isler et al. [18], such events associated with maternal deaths among women with HELLP syndrome included cerebral haemorrhage (45%), cardiopulmonary arrest (40%), disseminated intravascular coagulopathy (39%), adult respiratory distress syndrome (28%), renal failure (28%), sepsis (23%), hepatic hemorrhage (20%), and hypoxic ischemic encephalopathy (16%).

In order to provide optimal intensive care for a critically ill patient, a team approach ensuring cooperation of the intensivist, the obstetrician and the neonatologist is essential, especially when the patient is admitted to the ICU before delivery. Physiologic changes occurring with the parturient state as well as conditions specific to or exacerbated by pregnancy or post-

Table 1. Patient's characteristics. Medication at admission to the outpatient's department

Age at admission	23 years
Number of pregnancies	2
Number of births	1
Other diseases	left cirrhotic kidney, right floating kidney, hypothyroidism
Medication at admission	Levothyroxin-Natrium (T ₄) 0.1 mg/day, low-molecular weight heparin 40 mg/day, Pantoprazol-Sodium 40 mg/day

partum state require special knowledge and have extensively been reviewed by A. Ernst [19]. Data from the Western world show maternal mortality rates of about 10% due to preeclampsia and of 3% up to 5% due to HELLP syndrome [9, 10]. As higher percentages have been found in medically less developed countries, standardized antenatal care has been mentioned to be an important tool to improve maternal outcome in complicated pregnancies [13]. Care for obstetric patients with complicated pregnancies, such as patients suffering from preeclampsia, eclampsia or HELLP syndrome, has to meet the highest requirements and should take place in specialized centers in order to reduce maternal morbidity and mortality.

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Community-Acquired Methicillin-Resistant *Staphylococcus aureus* CA MRSA infections in Czech Republic

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Introduction. Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major human pathogen. Invasive infections due to MRSA are common in Czech hospitals. During last 10 years is evident increasing trend in incidence MRSA infections in Czech Republic from 4% in 2000 to 12.8% in 2005. The number of Czech hospitals with positive occurrence of MRSA isolates increased from 11 hospitals in 2000 to 51 hospitals in 2005. MRSA infections occurred especially in hospital setting (predominantly in intensive care units) followed by subsequent outbreak into the other hospital departments and finally out of hospitals. During 2007 were detected also in Czech Republic community-acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) isolates.

CA-MRSA differs from hospital-acquired MRSA (HA-MRSA) in several important ways [1]. These include the lack of traditional risk factors associated with MRSA among patients, a bacterial susceptibility pattern with resistance to fewer classes of antimicrobial drugs, and the inclusion of specific virulence factors. CA-MRSA strains typically carry the Panton-Valentine leukocidin (PVL) genes, which produce cytotoxins that can cause tissue necrosis and leukocyte destruction. CA-MRSA infections are predominantly associated with community-associated staphylococcal skin infections and necrotizing pneumonia. CA-MRSA strains can be highly virulent, and have been documented to cause life-threatening necrotizing infections especially if lung tissue is infected. Severe necrotizing CA-MRSA pneumonia has been documented in healthy individuals and is associated with high mortality rates because there is a high risk for inadequate and delayed antibiotic treatment.

The principal question regarding to treatment of severe sepsis or septic shock is focused on choice and timing of treatment with proper antibiotics [2].

Case report. 41-year-old woman admitted in half of December 2007 to peripheral hospital had had a history rapid progression of low back pain with maximum during inspiration but without fever and any other alteration. There was a dramatic change in her status with development of dyspnoea and altered consciousness during 2 days. Chest X-ray confirmed bilateral multilobar pneumonia. MRSA strains were isolated from the sputum cultures. Due to MRSA invasive infection developed septic shock with multiple organ dysfunction syndrome and respiratory failure. She was intubated, mechani-

cally ventilated and transferred to our ICU. Computed tomography confirmed severe bilateral necrotizing pneumonia and exact analysis of MRSA revealed CA-MRSA isolate. The optimal therapy for CA-MRSA infections has not been fully elucidated but antibiotic therapy should be considered on the basis of location, extent of disease and penetration of antibiotic. This CA-MRSA detection is the first outbreak of CA-MRSA invasive infection in our institution. From the beginning antibiotic treatment was changed from vancomycin and gentamicin to combination of linezolid, gentamicin, rifampicin after consultation with microbiologists. The reason why we changed antibiotic therapy was based on better penetration of linezolid into infected tissue compared to vancomycin. Hospitalization of the patient in the ICU was complicated by repeated bilateral pneumothorax with need for bilateral thorax long-lasting drainage. The prolonged combined antibiotic treatment (linezolid 43 days) led to gradual improvement of her status, and after 33 days she was successfully weaned from the ventilator. She was discharged from the ICU after 43 days. Functional lung status was assessed by spirometry 2 months later and showed us significant reduction in vital capacity (VC) 1,96 L (57%) and forced expired volume (FEV₁) 1,75 L (60%). The next control 3 months later proved substantial improvement in functional status: VC 2,74 L (80%) and FEV₁ 2, 22 (77%). Nowadays she is able to tolerate routine physical activity.

Conclusion. CA-MRSA pneumonia should be suspected in patients with severe pneumonia and rapid progression especially during the influenza season, in those with cavitory or necrotizing infiltrates, and in those with a prior history of MRSA infections or with prior contact with MRSA positive patients or relatives. New emerging diagnostics directly from positive blood culture (RT-PCR) may improve early identification of MRSA and tight cooperation with microbiologists. The basic problem is: there are no documented community-onset healthcare risk factors. On the other hand treatment of patients with severe pneumonia should consider CA-MRSA as a potential causative pathogen and initiate efficient anti-MRSA antimicrobial therapy.

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Haemodynamic monitoring – Cost-effectiveness vs. invasiveness

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Quality of critical care and improvement of outcome, both in survival and quality of life thereafter is the primary goal of critical care physicians and is closely related to adequate diagnosis, monitoring and therapeutic strategies in accordance with best evidence.

Haemodynamic monitoring plays a pivotal role in the care of patients with potentially severe physiological derangements

or instabilities, requiring advanced artificial life support during their ICU stay. Adequate haemodynamic monitoring not only helps with the early identification of patients at risk of developing organ dysfunction syndromes due to macrocirculatory failure or more regional disturbances, but should also allow the recognition of changes in physiological parameters after any given intervention to prevent further progress from dysfunction to manifest organ failure.

Until the publication by Connors et al. in 1996 “invasive” pulmonary artery catheterization (PAC) was the gold standard in the measurement of cardiac performance, and considered a cornerstone in the management of perioperative and critically ill patients. However, besides complications resulting from catheter-related bloodstream infections, PAC can also lead to disastrous consequences – at worst – heart valvular injury or rupture of the pulmonary artery [1]. Furthermore PAC technology has failed to prove patients’ benefit in terms of survival, summarizing potential risks against outcome.

With regard to the ongoing criticism of invasive technologies for haemodynamic evaluation and management, several less invasive techniques using central venous lines and arterial lines, transesophageal Doppler monitoring, pulse contour analysis with transpulmonary thermo- or dye-dilution have evolved recently [2]. At first glance, due to a better safety profile non-invasive monitoring appears to be superior to the invasive techniques such as the PAC, however it has to be considered that the absence of invasive haemodynamic monitoring may increase inaccuracy in the evaluation and compromise the optimal treatment of the critically ill – therefore posing a threat to the patient’s safety.

Technological progress, development of new but costly therapies and a greying of the population lead to highly the increased cost of ICUs in recent years, and this trend is very likely to continue. Although ICUs usually account only for 5–10% of total beds in a hospital, they are responsible for a quarter to almost a third of total hospital costs and place a heavy burden on the healthcare budget of industrialized nations.

To be fair, the expenses concerning haemodynamic monitoring are relatively small compared to other factors like personnel costs, which could contribute up to 50% of an ICUs budget [3]. However, it must also be emphasized that the ICU is one part of the hospital as a whole, sharing the same objective, to allow patients to convalesce at the lowest possible cost. Inadequate observation and evaluation of the patient could potentially lead to erroneous therapies resulting in increased length of stays and additional cost.

Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action. In its most common form, CEA compares a new strategy with a current practice and the result is presented as a ratio [4]. Taking CEA from the literature to the bedside can be problematic for several reasons. The evidence of the effectiveness of a critical care intervention is often lacking. The various treatment modalities in an ICU are often supportive rather than curative. ICU resuscitation endpoints are usually not suitable for a CEA. Moreover the patient population is usually not homogenous at any ICU. Furthermore, typically required outcomes in CEA such as quality of life and utility assessment are difficult to determine in a critically ill population and are very often not assessed on routine basis [5].

On the other hand budgeting restrictions and limited funding of health care costs has made the implementation of basic economic management techniques fundamental for health care professionals and as a result conflicts with hospital administration or other regulatory bodies often arise. We have to question and find arguments for or against the use of specific haemodynamic devices and whether a new, and probably more costly, alternative is worth implementing in the daily routine. In particular we have to focus on two issues: is there a benefit (e.g. additional information, lower rate of false results

or complications) of the new and more costly technique or the other way round: can the same results be achieved with a cheaper or less risky alternative.

In fact – although these may appear to be simple questions – they are not always easy to answer and depend on several factors often not taken into account, such as level of care, capabilities of staff, and frequency of patients admitted to the ward.

A recent report by the UK's National Health Service and Health Technology Assessment (HTA) concerning clinical and cost effectiveness haemodynamic monitoring and the use of PAC, is adding to the debate (Health Technol Assess. 2006 Aug; 10 (29): iii–iv, ix–xi, 1–133). The HTA report includes evidence from all available randomised controlled trials concerning the effect of clinical management of critically ill patients with a PAC both on mortality and the costs of care. Summing up, the HTA report comes to the conclusion that due to given pre-existing evidence that the use of these devices does not benefit patients, a withdrawal of PAC may reduce mortality at the cost of 4446 euro per quality adjusted life year. The report draws its conclusion from a decision science perspective.

Decision analysis seeks to determine what is most likely to happen if a particular course of action is taken, in contrast to traditional hypothesis testing, which tries to detect differences that are not likely to have arisen by chance. Until now it is however unclear if the lack of benefit from measuring haemodynamics is specific to the PAC or whether it also applies to other devices and methods measuring CO and advanced haemodynamics. There is evidence of benefit for some less invasive devices but studies are scarce and populations investigated small. Furthermore conclusions drawn are often based on benefits in a specific subgroup and transferred into general. Manufacturers of other haemodynamic monitors are now required to prove clinical usefulness and cost effectiveness of their devices, since showing that their device is as good as PAC, which has no proven benefit, will not be sufficient in the future.

Further research is required to prove that advanced haemodynamic monitoring is superior to manipulation of haemodynamics by simple parameters like clinical examination, heart rate, blood pressure, urine output and peripheral perfusion. It may also be that we simply do not know the correct usage of advanced haemodynamic variables to improve the outcome of critically ill patients. Although monitoring devices do not alter mortality and only treatment alters mortality, due to the ever increasing financial burden of ICUs in a modern healthcare system, the place of invasive as well as non-invasive monitoring devices in the treatment of critically ill patients will have to be justified [6].

In summary, this article outlines that, despite decades of implementing various new haemodynamic monitoring devices in clinical practice, from an economic point of view, we still lack justification of a personal benefit for each patient. Several actions should thus be combined such as limiting the variety and quantity of different monitoring devices available on a ward, improving knowledge, as well as carrying out a systematic assessment of cost/benefits ratios to prove the cost effectiveness of what is claimed by industry to “improve” patient safety and outcome.

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Management of intracranial pressure

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The physiologic principles of increased intracranial pressure (ICP) in patients with acute brain injury are known, but many of the feedbacks and couplings remain unexplored. Studies have begun to clarify the ways in which modulating therapies act on ICP and cerebral perfusion pressure (CPP). With the introduction of fiber-optic probes, the monitoring of ICP has improved technically. The availability of reliable ICP monitoring devices has facilitated management and often dictates therapies that may become potentially harmful if used indiscriminately and not directed by measurements. For example, uncontrolled use of hyperventilation and osmotic diuretics without laboratory or pressure monitoring may potentially compromise cerebral blood flow and possibly produce cerebral ischemia.

The bony skull does not allow for expansion; therefore, one compartmental increase in volume invariably means a decrease in another. If not, ICP rises quickly, resulting in both brain stem displacement and herniation of brain tissue. Eventually, when ICP exceeds mean arterial pressure, cerebral perfusion ceases, and brain necrosis ensues.

The introduction of an additional volume in brain parenchyma (e.g. a mass from an intracranial hematoma or swollen, infarcted brain tissue) must, by necessity, be compensated for by changes in the blood or CSF compartment for intracranial volume to remain constant. There are many causes of raised intracranial pressure, the following being the most important (Table 1).

On the whole, the major mechanisms that compensate for an increased in ICP are movement of CSF into the spinal subarachnoid space and removal of blood from the cerebral venous vessels. Cerebrospinal fluid volume may also decrease from increased CSF absorption, largely caused by the low outflow resistance of the arachnoid villi.

Table 1. Causes of intracranial hypertension

Intracranial mass
Cerebral edema
Cytotoxic (intracellular)
Vasogenic (extracellular)
Cerebrospinal fluid hypervolemia
Decreased absorption
Obstructed venous outflow
Overproduction of cerebrospinal fluid
Increased intracranial blood volume
Cerebral vasodilatation (hypoxia, hypercapnia)
Obstructed venous outflow

If the limits of these compensatory mechanisms are exceeded, the ICP begins to rise, and only a few millilitres in volume may increase the ICP. Autoregulation is often impaired in patients with acute brain injury, but impairment is highly variable in different regions of the brain. Diffuse head injury, aneurysmal subarachnoid hemorrhage, and any type of global bihemispheric brain damage may virtually abolish autoregulation. In other clinical situations, focal edema surrounding masses or increased ICP alone may impair the normal regulation between cerebral blood flow and CPP. Further reduction in cerebral blood flow leads to ischemia and infarction.

Management of increased intracranial pressure. The indications for monitoring intracranial pressure are listed in Table 2. In managing of increased intracranial pressure, cerebral perfusion pressure must be considered another important guide for further titration of treatment. Cerebral perfusion pressure is calculated: $CPP = MAP - ICP$.

The reduction of increased ICP is achieved by reduction of the total intracranial volume:

1. CSF withdrawal by ventricular drain
2. Reduction of the cerebral tissue volume (e.g. osmotic dehydration)
3. Reduction of the cerebral blood volume by reduction of the cerebral blood flow or by enhancement of cerebral venous drainage and
4. Removal or decompression of a mass.

General management of increased ICP. Every patient should be adequately oxygenated, and normal mean arterial blood pressure should be maintained, mechanical ventilation frequently being necessary. Fortunately, the mode of mechanical ventilation does not significantly influence ICP. High levels of positive end-expiratory pressure (15 to 20 cm H₂O) may not markedly influence cerebral venous return.

Fever, after being investigated thoroughly, should be treated aggressively with pharmacological and physical means.

Head position should be neutral to reduce any possible compression of the jugular veins that could lead to a decrease in intracranial venous outflow. Whether the head should be elevated remains somewhat controversial, but many intensive care neurologists consider head elevation of 30° standard. This position is further supported by a careful study in 22 patients with head injury, most of whom had marked reduction in ICP. Elevation of the head, however, may cause a reduction in arterial pressure, particularly if the patient has orthostatic hypotension from diabetes mellitus or has marked hypovolemia.

One should identify possible, seemingly trivial, triggers in the intensive care unit that may increase ICP. Pain and frequent stimulation by such manoeuvres as washing and change of position are factors that may contribute to increased ICP.

In patients with increased ICP, a euvolemic state is preferred. Fluid restriction is not a recognized treatment of increased ICP. Moreover, dehydration associated with fluid restriction causes hypotension and hemoconcentrations with increased viscosity and may for that reason have a deleterious effect.

Specific ICP treatment options. *Cerebrospinal fluid drainage:* Ventricular drainage remains a very rational solution to increased ICP and is perhaps the best option. Its use is predominantly focused on patients with acute obstructive hydrocephalus after aneurysmal subarachnoid hemorrhage or acute expanding cerebellar masses. In traumatic brain injury, however, its use is very controversial, but some trauma centres almost routinely insert ventricular catheters. In patients with head injury, drainage can be significantly compromised by a large volume of intraventricular blood and compression of the frontal horns to slit like proportions from surrounding edema.

Hyperventilation: Use of hyperventilation after any insult to the central nervous system and particularly after severe closed head injury has been criticized for its potential long-term adverse effects and is not recommended.

Osmotic diuresis: The basic principle of osmotherapy is decrease of brain water. For osmotic agents to work, an osmotic gradient and intact blood-brain barrier are needed. Consequently, osmotic agents shrink mostly brain tissue that has not been damaged. Brain water filters from a compartment with low osmolality into the compartment with high osmolality. The available diuretic agents for treatment of increased ICP are mannitol, hypertonic saline, albumin, glycerol, urea, and furosemide. In most institutions, either mannitol or hypertonic saline is used to decrease ICP.

Tromethamine (THAM) has been introduced as an agent to control increased ICP; however larger studies in traumatic brain injury patients have not shown an improvement in outcome, it may be used in patients in whom mannitol may be contraindicated (e.g. renal failure).

Barbiturates: Have no place anymore to treat increased intracranial pressure mainly due to the wide range of harmful, potentially life-threatening side effects (hypotension, sepsis).

Hypothermia: A possible adjunctive measure to reduce ICP is moderate hypothermia (core temperature 33–34°C) for 24 hours. In an elegant study, ICP was reduced (mean, 10 mm Hg) and CPP increased (mean, 14 mm Hg) in 16 patients. No increase in bacterial infection was found, but premature ventricular contractions occurred in 40% of the hypothermic patients. Moreover, one patient had hypovolemic shock and another had a rapid increase in ICP during rewarming.

Moderate hypothermia has been studied in traumatic brain injury. In one study (the largest) it has not been effective in improving outcome, however more than 10 other studies showed improvement in outcome, therefore moderate hypothermia may be considered as a therapeutic option even in patients with increased intracranial pressure due to traumatic brain injury, requiring, however, close monitoring for systemic complications such as pneumonia, sepsis, leucocytopenia, thrombocytopenia, hyponatremia, hypokalemia.

Dexamethason: Corticosteroids may be helpful in patients with malignant brain tumor, or metastasis, reducing increased intracranial pressure in these patients; in addition it has been useful in patients with pneumococcal meningitis. However, it proved deleterious in TBI patients.

Little is known about the proposed ICP management strategies with propofol, or indomethacin, although single cases and little case series have shown promising results.

Surgical management: Surgical management of increased ICP has come into vogue, especially in patients with swelling from large middle cerebral artery infarcts. Interest in decom-

Table 2. Guidelines for monitoring intracranial pressure

Disorder	Specific indications
Traumatic brain injury	Any patient with GCS ≤ 8 and pathological cCT Bifrontal lobe contusion and edema Temporal lobe contusion and edema Polytrauma and need for neuromuscular blockade
Intracranial hemorrhage	Lobar or ganglionic hemorrhage with GCS ≤ 8 or shift on cCT
Middle cerebral artery territory stroke	Brain swelling with shift on cCT
Herpes simplex encephalitis	GCS ≤ 8 , necrotic mass
Aneurysmal subarachnoid hemorrhage	Acute hydrocephalus
Cerebellar stroke	Acute hydrocephalus

pressive craniotomy in traumatic brain injury has been recently rekindled. The procedure may reduce ICP and reopen compressed basal cisterns, and some early data suggest improved outcome and increased compensatory reserve. Suboccipital decompressive craniotomy and ventriculostomy for hydrocephalus are both highly effective therapies for mass lesions in the posterior fossa.

Echocardiography in intensive care unit – A practical approach

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Introduction. Echocardiography has become an essential diagnostic tool in intensive and emergency medicine [1]. It is a rapid, non-invasive bedside imaging method that is used to diagnose not only patient's cardiac disease but also to assess his/her haemodynamic condition, often substituting invasive monitoring, and to perform several procedures more safely. In addition, echocardiographic machine can be effectively used for examination of other anatomic regions, particularly abdomen and thorax.

While experience is important in echocardiography, physicians with limited training are already able to obtain valuable information that improve treatment [2]. In most patients, transthoracic echocardiography (TTE) is satisfactory, however a significant proportion of patients require transoesophageal echocardiography (TEE).

Indications for echocardiography. Indications for emergency echocardiography include, but are not limited to, certain symptoms, signs and clinical circumstances:

Unexplained hypotension (considered an indication also by The American College of Cardiology and American Heart Association) [3],

- acute dyspnoea,
- acute chest pain,
- heart murmur of recent onset,
- suspected endocarditis,
- suspected acute aortic syndrome,
- blunt or penetrating chest trauma,
- suspected cardiac source of systemic emboli,
- failure to wean from artificial ventilation,
- any condition that requires rapid haemodynamic assessment.

Some emergency procedures are performed with sonographic monitoring:

- pericardiocentesis,
- placement of arterial and venous catheters,
- placement of intraaortic balloon catheter,
- cardiopulmonary resuscitation.

Hypotension, dyspnoea and chest pain often appear in combinations and may be caused by several emergency conditions, most often by acute coronary syndrome, pulmonary embolism, cardiac tamponade, acute aortic disease and pneumothorax. Echocardiographically is useful for diagnosis of each of these conditions.

Hypotension and circulatory shock. In patients with unexplained hypotension, particularly in those in shock, echocardiography is the most valuable tool to rapidly determine the mechanism of hypotension [4]. Echocardiographically, aetiology of shock can be classified as either due to heart failure, reduced filling (or increased capacitance) of the circulation, reduced afterload in the systemic circulation, obstruction to blood flow, or a combination of these haemodynamic changes. Echocardiographically determined haemodynamic profile at admission is also important as guidance for emergency haemodynamic treatment with fluids, inotropic and vasoactive drugs.

Haemodynamic changes can be diagnosed by echocardiography far more accurately than by clinical examination. The most severe cases of shock have the most typical echocardiographic features that are easiest to interpret. TEE is rarely needed for initial haemodynamic assessment.

Dyspnoea and weaning failure. Dyspnoea in spontaneously breathing patients as well as weaning failure in artificially ventilated is caused by respiratory or circulatory dysfunction. Echocardiography can help the clinician to distinguish between these two causes. Echocardiography is particularly useful in rapid diagnosis of massive pulmonary embolism.

Pulmonary embolism: Echocardiographic diagnosis of pulmonary embolism is mostly indirect: Increased diameter of left and decreased diameter of right heart cavities, paradoxical septal movement and increased pulmonary artery pressure are signs of right ventricular overload, that may be caused by pulmonary embolism. Additionally, a free-floating thrombus in the right heart, seen with TTE, as well as thrombi in pulmonary artery branches, that may be seen with TEE, may definitely confirm a suspected pulmonary embolism.

Echocardiography is not a useful screening method for patients with non-massive pulmonary embolism, but in these patients a short delay in diagnosis does not significantly affect the prognosis, since a suspected diagnosis is already an indication for anticoagulation. Conversely, patients with severe acute pulmonary embolism benefit from TTE, because the diagnosis is established immediately, which results in rapid treatment. Early diagnosis and treatment is particularly important in patients with heart arrest due to obstructive shock who are unable to produce any medical history [5]. The effect of treatment can be assessed echocardiographically by observation of morphologic and haemodynamic changes, pulmonary artery pressure and cardiac output.

Acute chest pain. Spontaneous acute chest pain is often a diagnostic challenge. Most frequent emergency conditions causing chest pain are acute coronary syndrome, acute aortic syndrome, pulmonary embolism and pneumothorax; there are also several non-emergency conditions that may cause chest pain.

Acute coronary syndrome: TTE may diagnose acute coronary syndrome, which is particularly useful in patients with non-specific chest pain and non-diagnostic EKG [3]. If during chest pain there is no regional wall motion abnormality seen echocardiographically, then either the patient has no coronary artery disease, or the target coronary artery is very small and emergency reperfusion treatment is probably neither required nor feasible. In patients with myocardial infarction, echocardiography is indispensable for diagnosis of mechanical complications. In patients with heart rupture and haematopericardium, echocardiography guides emergency pericardiocentesis. Finally, TTE is used to detect and quantify left ventricular function and ischemic mitral regurgitation, which are important short and long term prognostic parameters.

Acute aortic syndrome: Acute aortic syndrome includes aortic dissection, intramural haematoma of the aorta, rupture of aortic aneurysm, penetrating atherosclerotic plaque, and aortic trauma. Patients with suspected acute aortic syndrome are usually screened by TTE and final diagnosis is made by CT angiography; however, if CT angiography is not feasible or if a CT angiography is suspected to be false-negative, TEE is the method of choice. TEE establishes the diagnosis, extent of the disease and most complications, including bleeding, rupture of the aortic valve and tamponade [3].

Severe infection and sepsis. In sepsis echocardiography is of particular use to an experienced operator. TTE and TEE can detect hyperdynamic circulation, contributing to the diagnosis of sepsis, and changes in left and right ventricular function [6]. Cor pulmonale due to pulmonary embolism or ARDS and

inflow obstruction due to pericardial effusion can be diagnosed. Echocardiography is the most useful imaging technique in suspected endocarditis. Echocardiographic machine can be used to screen for the abdominal source of infection. Thoracic sonography can reveal pleural effusion and consolidated lung in pneumonia [7], and guide a diagnostic or therapeutic thoracocentesis.

Suspected endocarditis: TTE can detect endocarditis in approximately 60% of patients, demonstrating anatomic and functional valve changes, caused by endocarditis: vegetations, abscesses and valve regurgitation. However, the most sensitive and specific imaging method in diagnosis of endocarditis is TEE. TEE evaluates more accurately the extent of the disease, predicts the possibility of complications, and is crucial for planning of surgical treatment of endocarditis.

Blunt and penetrating chest trauma. Chest trauma represents an indication for echocardiography whenever a blunt or penetrating injury of the heart is suspected [8]. With TTE, pericardial effusion and wall contraction irregularities may be seen. In rare cases, a ruptured valve or interventricular septum may result from a chest trauma. Aortic trauma is better assessed by CT angiography and TEE.

Haemodynamic assessment. Whereas established catheter-related methods for haemodynamic assessment measure pressures, flow and oxygen saturation of the blood, Doppler echocardiography measures dimensions and flow velocities [9]. From catheter and echocardiographic measurements, right and left heart preload, pulmonary artery pressure, heart function and cardiac output are evaluated [10]. Catheter as well as echocardiographic measurements have important limitations for assessment of preload, whereas pulmonary pressures and cardiac output can be reliably measured with both techniques.

Right heart preload is usually assessed from inferior vena cava diameter and inspiratory collapse in spontaneously breathing patients. Since right heart chambers have large compliance, dimensions of right heart chambers also reflect their transmural pressure. Left heart preload is more difficult to assess and many methods have been proposed that are either time-consuming, or unreliable, or can only be used in a small proportion of patients. The most useful method for assessment of left ventricular preload appears to be from Doppler measurements of mitral valve flow and movement of mitral valve ring [11].

Pulmonary artery systolic pressure can be calculated from maximal tricuspid regurgitant flow velocity, while pulmonary artery diastolic pressure can be calculated from end-diastolic pulmonary artery regurgitant flow velocity. From both velocities gradients are calculated and added to estimated or measured central venous pressure.

Echocardiographically, cardiac output is calculated from stroke volume and heart rate. Stroke volume can be measured from two- or three-dimensional measurements of left ventricular systolic and diastolic volumes. However, the fastest procedure is to multiply velocity time integral (VTI) from the left ventricular outflow tract, measured by pulse Doppler, and cross-sectional area (CSA) of the outflow tract. To obtain stroke volume, VTI and CSA can also be measured on mitral valve ring, in the right ventricular outflow tract and in pulmonary artery.

In addition to cardiac output, echocardiography gives valuable information about contraction abnormalities and reserve, valve dysfunction and pericardial disease.

Emergency procedures. Some procedures in critically ill are performed more safely with sonographic guidance, whereas others can not be safely performed without it, particularly emergency pericardiocentesis. In general, placement of catheters, electrodes and intraaortic balloon pump catheter, diagnostic and therapeutic evacuation of fluid, and cardiopulmonary resuscitation may be carried out with echocardiographic guidance and/or control [12].

Pericardiocentesis: Pericardiocentesis without echocardiography is nowadays inconceivable. Echocardiography is used to choose the optimal site for pericardiocentesis. When the catheter is placed, direct visualisation or contrast imaging may be used to confirm the correct position of the catheter. At the end of the procedure, the amount of fluid remaining in the pericardium can be verified [12].

Cardiopulmonary resuscitation: During resuscitation, TTE can be used to establish the cause of heart arrest, which is particularly important in patients with pulseless electric activity. In patients with heart arrest due to tamponade and pulmonary embolism, TTE is the only diagnostic method that gives an instantaneous indication for emergency pericardiocentesis and emergency thrombolysis. Echocardiography is a much better method for evaluation of spontaneous circulation than palpation of arterial pulse. TTE or TEE can be used to monitor patient's haemodynamic condition during resuscitation and immediately after restoration of spontaneous circulation [5, 13].

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Bone marrow derived stem cells – new treatment approaches in myocardial infarction patients

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Summary. Stem cell research still remains one of the most controversial fields of science today on the basis of cell plasticity and its capability of transdifferentiation or de-differentiations to certain tissue types, as well as the clinical application of this scientific concept. Stem cells derived from bone marrow, peripheral blood or umbilical cord is common therapeutic approach for treatment of haematological malignancies as part of established transplant procedures (allogeneic, autologous, syngenic stem cell transplantation). But recent clinical data revealed the potential role of stem cells in the treatment of other nonhematological diseases, degenerative disorders, cardiovascular diseases and autoimmune diseases. The experience with stem cells transplantation in hematological malignancies at the Department of hematology, Skopje has been established since 7 years ago, with more than 130 patients undergoing transplant procedures (87 autologous and 43 allogeneic recipients). Encouraging results were also reported from Cardiology clinic Skopje, in the field of intra-coronary application of bone marrow derived stem cells for the treatment of patients with acute myocardial infarction. According to Mystar project criteria we have treated 2 patients (21–42 days) after acute myocardial infarct. But still these new pathways of tissue regeneration should be further extended and evaluated in clinically randomized studies that will confirm the therapeutic potential of stem cell.

Ultrasound-Guided Procedures in ICU

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Ultrasound imaging is widely available, portable, relatively inexpensive, practical, pain and risk free. For this reasons ultrasound-guided intervention is becoming an increasingly popular tool in the ICU setting. The main areas of ultrasound guided intervention in critically ill patients are the nerve blocks, vascular access, ultrasound guided management of post-catheterization pseudoaneurysms, ultrasound guided thoracocentesis and pleural drainage, pericardiocentesis, enteral feeding tube placement, drainage of wide variety of abscess and collections, percutaneous nephrostomy, percutaneous cholecystostomy, inferior vena cava filter placement and ultrasound guided percutaneous tracheostomy.

In first part of lecture article I describe three basic techniques of the ultrasound-guided procedures (one or two operators): ultrasound-landmarks technique, ultrasound-guided free-hand technique (in-line technique and cross-sectional technique) and ultrasound-guided (“servo”) technique with adapter and guide-line. Also, in this part the most common modes (or accesses) of the ultrasound-guided procedures in the critically ill patients are presented. In the second part of lecture the technique of ultrasound guided percutaneous tracheostomy, advantages of this technique vs. endoscopy-guided as well as the possible role of ultrasound in the confirmation of correct tracheostomy tube position is described.

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Acute stroke management experiences in Slovenia – Short report

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Introduction. Acute ischemic stroke accounts for ~80% of all strokes and is a major cause of disability and other adverse long-term sequel [1]. For patients seen within 3 hours after stroke onset, intravenous thrombolysis (iv) with recombinant tissue-type plasminogen activator (rtPA) is the only Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved treatment option [2, 3]. Yet the vast majority (>95%) of patients with acute ischemic stroke do not receive such treatment. No other therapy for acute ischemic stroke is of proven clinical utility in enhancing long-term outcomes [4]. The main focus of recent ischemic stroke endeavours has been to try and realise the benefits apparent in the National Institute of Neurological Disorders (NINDS) and Stroke rtPA trial [5] in a broader stroke care setting. This requires professional awareness of the precise requirements of emergency stroke management. In the NINDS trial, carefully selected patients without CT evidence of intracerebral haemorrhage (ICH) who received rtPA thrombolysis were ≥30% more likely to be free of (or have minimal) disability at 3 months compared with placebo controls. Aside from protocol deviations, including the difficulty in treating most patients within 3 hours after stroke onset, hemorrhagic complications and the heterogeneity of clinical outcomes by thrombus dimensions and anatomic distributions are outstanding issues with thrombolysis. For instance, clot lysis/recanalisation with thrombolysis may be less effective for large internal carotid artery thrombi compared with associated proximal middle cerebral artery thrombi. The rate of symptomatic ICH ≤36 hours after stroke onset in NINDS was an order of magnitude (~10 times) higher in rtPA patients (6.4%) than in placebo controls (0.6%; $P < .001$), although 3-month mortality rates were similar in these two treatment arms (17% vs 21%, respectively; $p = 0.30$) [5]. Symptomatic ICH occurred in 8.8% of those randomized to intravenous thrombolysis compared with 3.4% of controls in the European Cooperative Acute Stroke Study (ECASS-II) involving 800 patients without major (multilobar) infarcts according to screening CT who received treatment (or placebo) within 6 hours after stroke onset [6]. Certain subgroups may be less likely to experience favourable long-term outcomes with rtPA iv therapy, including patients with more severe strokes (higher baseline National Institute for Health – Stroke Scale (NIH – SS) scores), diabetes, and/or advanced age. Studies involving fibrinolytic regimens apart from i.v. rtPA have shown no benefit (unfavourable effects) and are thus not approved. The interpretation of the some latest studies may also lead to more widespread implementation of thrombolysis, however, careful documentation and evaluation of the risk/benefit ratio of such a policy is of paramount importance [7]. One of such registers is an academic-driven, non-profit, international register, initiated by the medical profession (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register – SITS-ISTR) as an internet-based interactive thrombolysis register, to serve as an instrument for clinical centres to follow their own treatment results and compare with other centres in their countries. As well, recent project – SITS-EAST, supported by EU public health, was launched during Warsaw Stroke Experts Workshop in September 2007 [8]. Slovenia has implemented SITS-ISTR in daily stroke service in 2003.

Newer approaches to acute stroke treatment, such as intra-venous/intra-arterial (ia) approach to recanalisation is promising, showing superiority to standard iv rt-PA alone when initiated within 3 hours of stroke onset (The Interventional Management of Stroke III trial is under way).

Table 1. Demographic data and severity of stroke on admission and after treatment in patients treated in University Medical Centre Ljubljana since 1997

	Age average (range) years	Hospital stay average (range) days	NIH – SS prior to rtPA	NIH – SS 2 hours after rtPA	NIH – SS 24 hours after rtPA	NIH – SS 7 days after rtPA
iv rtPA	62.1 (27–86)	17.6 (2–92)	17.4 (5–28)	12.0 (0–28)	12.5 (0–41)	8.1 (1–26)
ia rtPA	59.2 (40–76)	23.5 (2–104)	31.3 (3–41)	27.2 (5–41)	31.3 (3–41)	14.4 (0–34)
All	61.8 (27–86)	18.2 (2–104)	18.9 (3–41)	13.6 (0–41)	14.4 (0–41)	8.3 (0–34)

iv rtPA Intra-venous recombinant tissue plasminogen activator; *ia rtPA* intra-arterial recombinant tissue plasminogen activator; *NIH – SS* National Institute for Health Stroke Scale

There are also attempts to improve mechanical devices for endovascular mechanical thrombectomy, which is a newly available modality for acute stroke therapy, specially in case if iv thrombolysis failed or there is a contraindication for iv rt-PA treatment [9]. Another treatment option is also intracranial angioplasty and stenting, combined with emergency administration of thrombolytic agents in patients with occlusions in the vertebrobasilar circulation [10].

In this short report we would like to present our experiences with the acute stroke treatment.

Intra-venous and intra-arterial thrombolysis in University Medical Centre Ljubljana. In Slovenia, thrombolytic treatment with rtPA was introduced in 1997 in University Medical Centre Ljubljana and approved for treatment in eligible acute ischemic stroke patients in other hospitals in 2000 (actually first thrombolytic treatment in other hospitals was performed in 2003). The protocols for the prehospital and hospital settings were implemented (since 2003 according to SITS-ISTR) and also a helicopter prehospital emergency unit was set-up for acute stroke patients (and also major trauma and acute coronary syndrome patients) from the regions not to be reached by ground transportation within an acceptable time window. Although rtPA has clearly been shown to benefit stroke patients, a limited number of patients receive this treatment. The majority of patients with acute ischemic stroke are not being treated with rtPA because they arrive at the emergency department after the 3-hour time window.

The stroke incidence rate is approximately 200/100.000 population (all types of stroke and subarachnoid haemorrhage) with the mortality rate around 20% within first month after stroke onset. Among all stroke victims around 78% are ischemic stroke patients [11].

Since 1997 up to April 15th 201 patients were treated with rtPA in our center. (186 iv due to stroke in anterior circulation and 15 ia – 2 due to stroke in anterior circulation, 13 due to stroke in basilar artery territory), among them 61.2% were men. Data are shown in Table 1.

The outcome according to modified Rankin scale is shown in Fig. 1. The major haemorrhage (worsening according to National Institute of Health Stroke Score (NIH-SS) for more than 4 points) was not the only reason for the worst outcome (death) as shown in Fig. 2.

Massive intracerebral haemorrhage was the major reason for death in ia treated group, where an event-to-needle time was very long (in one case even more than 24 hours), which is an obvious and most important protocol violation and in one case also the use of other drug than rtPA (intergrilin). In iv treated group where intracerebral haemorrhage occurred after rtPA treatment, there was no protocol violation except in one case where NIH – SS before the treatment was 28. No early signs of stroke on CT scan, performed before the drug application was seen in this group of patients.

The event-to-door time is the marker of prehospital organisation (Fig. 3) in the so called “stroke-code” protocol which was introduced to improve the acute stroke management and the door-to-needle time is the marker of in-hospital delay in stroke management. The event-to-needle time is showing that there is still a delay in treating the eligible acute stroke patients with rtPA. One of the reasons is that the patients are not aware of signs and symptoms of stroke. However, door-to-needle time is also very long, since the treating physician is usually waiting for lab results which is, at least in my opinion, unnecessary (ex-

Fig. 1. Outcome after 3 months according to modified Rankin scale. *ivrtPA* intra-venous recombinant tissue plasminogen activator; *iartPA* intra-arterial recombinant tissue plasminogen activator

Fig. 2. Reasons for death in our rtPA treated stroke patients. Symptomatic haemorrhage was found in 8.4% of patients (4.7% in iv treated group and 38.5% in ia treated group). *ivrtPA* intra-venous recombinant tissue plasminogen activator; *iartPA* intra-arterial recombinant tissue plasminogen activator

Fig. 3. Event-to-door, door-to-needle and event-to-needle time in both groups of stroke patients (iv and ia treated). *ivrtPA* intra-venous recombinant tissue plasminogen activator; *iartPA* intra-arterial recombinant tissue plasminogen activator

Fig. 4. Digital subtraction angiography before clot extraction from the left vertebral artery (A) and after removal of clot with the Catch device (B) (RVA right vertebral artery; LVA left vertebral artery; BA basilar artery)

cept in case the patient is heavy alcohol consumer or taking medication prior to treatment which could influence the rtPA action, such as heparin or warfarin) and therefore the application of rtPA is delayed. The average time our lab in University Medical Centre Ljubljana needs to perform that examination is usually more than half an hour.

Clot extraction In the following case we present a 69 years old patient with more than one week history of dizziness, vertigo and vomiting and acute onset of dysphagia and intranuclear bulbomotor paresis. CT angiography revealed occluded left vertebral artery with thrombus extension into proximal part of basilar artery. He was then transferred to our tertiary center for the purpose of the ia thrombolytic treatment. We decided to perform a clot extraction with the Catch device. After two attempts, the clot was completely removed as seen on DSA (Fig. 4) and the clinical picture improved (still intranuclear bulbomotor paresis, but less severe, no swallowing problem).

Conclusion. An aggressive campaign to educate the public about stroke symptoms and the importance of rapid evaluation is the most important work at the moment in our country. Intravenous thrombolytic therapy for acute stroke is now generally accepted, however new treatment options are also promising. We believe that we could improve the stroke management and that immediate stroke treatment can save people's lives as well as enhance their chances for successful recovery.

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Procalcitonin and C-reactive protein in ventilator-associated pneumonia (VAP)

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Introduction. Procalcitonin (PCT) plays a key role in the systemic inflammatory response syndrome caused by bacterial, fungal and protozoal infections [1]. The aim of the study was to assess the PCT and C-reactive protein (CRP) serum levels as markers of ventilator-associated pneumonia (VAP).

Methods. The prospective study included 38 consecutive patients aged 18–70 years, with microbiologically confirmed VAP, divided into 2 groups: I. VAP induced by multiresistant pathogens, II. VAP without isolation of multiresistant pathogens. PCT (VIDAS BRAHMS PCT) and CRP (turbidimetry assay) serum levels were assessed on the 1st and 6th day of VAP therapy. The length of stay (LOS) and mortality were compared. A microbiological analysis of material taken from the lower respiratory tract was also performed.

Results. No significant differences were found between the groups with regard to demographic data. The following pathogens were isolated in group I (n = 15): Meropenem and Imipenem resistant *Pseudomonas aeruginosa*, ESBL Gram-negative bacteria, MRSA, MRCNS; and in group II (n = 23): MSSA, MSCNS, Gram-negative bacteria, *Candida albicans*. The PCT serum level in group I was significantly higher than in group II ($p < 0.05$). The difference in CRP serum levels was statistically insignificant. Mortality and LOS were significantly higher in group I than in group II ($p < 0.05$). Among patients included in the study, 12 patients had unfavourable outcomes. The PCT serum levels were significantly higher from day 1st to day 6th in patients with unfavourable outcomes. Respective changes in CRP serum levels were found to be insignificant.

Conclusion. PCT is a better prognostic marker than CRP in the assessment of severity of VAP. The presence of multiresistant pathogens increases the PCT serum level in VAP.

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Current concept of delirium in the ICU

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Recent advances in critical care medicine have improved survival in patients cared for in intensive care units (ICU) worldwide. Critical care clinicians historically focus to pulmonary, cardiac, and renal dysfunction but have underestimated the impact of brain dysfunction.

Delirium is defined as a disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time. Delirium can be categorized into subtypes according to psychomotor behavior, and the high prevalence of hypoactive delirium in critically ill patients probably contributes to clinicians' lack of recognition of delirium. Hypoactive delirium is characterized by decreased responsiveness, withdrawal, and apathy, whereas hyperactive delirium is characterized by agitation, restlessness, and emotional lability. Delirium is a common manifestation of acute brain dysfunction in critically ill patients, occurring in up to 80% of the sickest intensive care unit (ICU) populations. Pa-

tients with delirium have longer hospital stays and lower 6-month survival than do patients without delirium, and delirium may be associated with cognitive impairment that persists months to years after discharge.

The pathophysiology of delirium is poorly understood but some promising hypotheses are subjects of ongoing research. Delirium is considered to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of neurotransmitters that normally control cognitive function, behavior, and mood. Derangements of multiple neurotransmitter systems may play a role with the greatest focus being given to dopamine and acetylcholine. An imbalance in one or both of these neurotransmitters results in neuronal instability and unpredictable neurotransmission. Inflammation plays a significant role in the dysfunction of multiple organs caused by critical illness, and inflammatory abnormalities induced by endotoxin and cytokines probably contribute to the development of ICU delirium

Risk factors for delirium can be divided into predisposing factors (host factors) and precipitating factors. Precipitating factors occur during the course of critical illness. They may involve factors of the acute illness or be iatrogenic; these factors represent areas of risk that are potentially modifiable by preventive or therapeutic intervention. Host factors: age (older), alcoholism, APOE4 polymorphism, cognitive impairment, depression, hypertension, smoking, vision/hearing impairment. Factors of critical illness: acidosis, anemia, fever/infection/sepsis, hypotension, metabolic disturbances, respiratory disease, high severity of illness. Iatrogenic factors: immobilization, medications (for example, opioids, benzodiazepines), sleep disturbances.

Because of potentially serious sequels all patients in ICU should be routinely screened for delirium. Delirium assessment instruments, such as the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the ICU (CAM-ICU) allow nonpsychiatric physicians and other ICU personnel to diagnose delirium in ICU patients rapidly and reliably, even when the patient cannot speak because of endotracheal intubation. Using the CAM-ICU, delirium is diagnosed in two steps. Level of consciousness is first assessed using a standardized sedation scale. Richmond Agitation-Sedation Scale (RASS), a 10-point scale ranging from +4 to –5, with a RASS score of 0 denoting a calm and alert patient, can be used. By convention, RASS scores of –4 and –5 identify coma; a comatose patient cannot be assessed for delirium. All other patients, (moderately sedated or more alert), should be evaluated for delirium. The CAM-ICU assesses patients for four features of delirium; three out of four features are required for a diagnosis of delirium.

The Richmond Agitation and Sedation Scale: The RASS

+4 Combative.	Overtly combative, violent, immediate danger to staff
+3 Very agitated.	Pulls or removes tube(s) or catheter(s); aggressive
+2 Agitated.	Frequent non-purposeful movement, fights ventilator
+1 Restless.	Anxious but movements not aggressive vigorous
0 Alert and calm	
–1 Drowsy.	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
–2 Light sedation.	Briefly awakens with eye contact to voice (<10 seconds)
–3 Moderate sedation.	Movement or eye opening to voice (but no eye contact)
–4 Deep sedation.	No response to voice, but movement or eye opening to physical stimulation
–5 Unarousable.	No response to voice or physical stimulation

Assessment of delirium (CAM ICU)

Prevention and treatment. Nonpharmacological interventions: repeated reorientation of the patient and provision of cognitively stimulating activities; a nonpharmacologic sleep protocol; early mobilization; timely removal of catheters and physical restraints; use of eyeglasses, magnifying lenses, and hearing aids; early correction of dehydration; electrolyte abnormalities and infection, and careful exposure to sedative and analgesic medications. These drugs play a vital role in maintaining patient comfort, and adequate pain control is likely to reduce the risk for delirium, but we must avoid oversedation.

Pharmacological interventions: After using the multicomponent prevention strategies and correcting life-threatening complications of critical illness that may lead to delirium (e.g. hypoglycemia, hypoxia, hypercapnia, and shock), pharmacologic intervention for the prevention and treatment of delirium should be considered. Clinicians should be aware that any drug intended to improve cognition may have adverse psychoactive effects, including exacerbation of delirium. All psychoactive drugs should therefore be used with caution in critically ill patients, in the smallest effective dose and for the shortest time necessary. Haloperidol is recommended as the drug of choice for the treatment of ICU delirium. Patients with hyperactive delirium should be treated with 2 mg IV, followed by repeated doses (doubling the previous dose) every 15 to 20 minutes while agitation persists. Common doses for ICU patients range from 4 to 20 mg/day, but higher doses are frequently used for the treatment of acute agitation. Atypical antipsychotics (e.g., risperidone, quetiapine, olanzapine and ziprasidone,) may also be helpful in the treatment of delirium. These medications target dopamine receptors as well as receptors for other neurotransmitters, including serotonin, acetylcholine, and noradrenaline.

Conclusion. Delirium is a common manifestation of acute brain dysfunction in critically ill patients that is associated with poor short-term outcomes and may result in adverse sequelae years after ICU discharge. Every ICU clinician should be aware of these strategies, institute routine screening for delirium in the ICU, reduce the impact of risk factors for delirium, and use treatment options when necessary.

Patient safety in Intensive Care Units: the multinational Sentinel Events Evaluation (SEE)

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Patient safety has garnered increasing interest in several medical areas since serious concerns were brought to the public by the Institute of Medicine's report "To err is human" and other similar investigations. Thus, the Research Group on

Quality Improvement of the European Society of Intensive Care Medicine conducted two multinational studies focusing on patient safety in Intensive Care Units. The results of these studies are presented on behalf of the Research Group on Quality Improvement of the European Society of Intensive Care Medicine and the SEE study investigators. The SEE studies were supported and funded by the Austrian Center for Documentation and Quality Assurance in Intensive Care Medicine (ASDI) and endorsed by the European Society of Intensive Care Medicine.

a) SEE I

Patient safety in intensive care: results from the multinational Sentinel Events Evaluation (SEE) study

Andreas Valentin, Maurizia Capuzzo, Bertrand Guidet, Rui Moreno, Lorenz Dolanski, Peter Bauer, Philipp Metnitz

Objective. To assess on a multinational level the prevalence and corresponding factors of selected unintended events that compromise patient safety (sentinel events) in intensive care units (ICUs).

Design. An observational, 24-hour cross-sectional study of incidents in five representative categories.

Setting 205 ICUs worldwide

Measurements Events were reported by ICU staff members with the use of a structured questionnaire. Both ICU- and patient-related factors were assessed.

Results. In 1,913 adult patients a total of 584 events affecting 391 patients were reported. During 24 hours multiple errors related to medication occurred in 136 patients; unplanned dislodgement or inappropriate disconnection of lines, catheters, and drains in 158; equipment failure in 112; loss, obstruction or leakage of artificial airway in 47; and inappropriate turn-off of alarms in 17. Per 100 patient days, 38.8 (95% confidence interval [CI], 34.7–42.9) events were observed. In a multiple logistic regression with ICU as a random component, the following were associated with elevated odds for experiencing a sentinel event: any organ failure (odds ratio [OR], 1.13 [95% CI, 1.00–1.28]), a higher intensity in level of care (OR, 1.62 [95% CI, 1.18–2.22]), and time of exposure (OR, 1.06 [95% CI, 1.04–1.08]).

Conclusions. Sentinel events related to medication, indwelling lines, airway, and equipment failure in ICUs occur with considerable frequency. Although patient safety is recognized as a serious issue in many ICUs, there is an urgent need for development and implementation of error prevention and early detection strategies.

b) SEE II

Parenteral medication errors – an urgent safety issue in intensive care units. Results from the multinational Sentinel Events Evaluation (SEE) study

Andreas Valentin, Maurizia Capuzzo, Bertrand Guidet, Rui Moreno, Barbara Metnitz, Peter Bauer, Philipp Metnitz

Background. Serious concerns about medication safety in intensive care units (ICUs) have been raised, mostly in single-centre studies. We aimed to assess on a multinational level the frequency, characteristics, contributing factors, and preventative measures of parenteral medication errors at the administration stage in ICUs.

Methods. We undertook an observational, prospective, 24-h cross-sectional study of sentinel events in the context of the administration of parenteral medications in 113 ICUs worldwide. Events were reported anonymously by ICU staff members with the use of a structured questionnaire.

Findings. In 1328 adult patients, 897 events affecting 441 patients were reported. In total, 77.6 (95% confidence interval [CI], 72.5–82.7) events per 100 patient days were observed. Sixteen patients (1.2% of the study population) were reported to

have suffered permanent harm or death related to a medication error at the administration stage. In a multiple logistic regression, elevated odds for the occurrence of a parenteral medication error were found with (i) increased number of organ failures (odds ratio [OR], 1.19 [95% CI, 1.05–1.35]), (ii) use of any intravenous medication (OR, 2.78 [95% CI, 1.42–5.47]), (iii) increased number of parenteral administrations (OR, 1.06 [95% CI, 1.04–1.08]), (iv) specific interventions (OR, 1.48 [95% CI, 1.13–1.94]), (v) larger ICU (more beds) (OR, 1.01 [95% CI, 1.00–1.02]), (vi) increased number of beds per nurse (OR, 1.27 [95% CI, 1.03–1.56]), and (vii) an increased occupancy rate (OR, 1.04 [95% CI, 1.01–1.06]). Decreased odds for the occurrence of parenteral medication errors were found with (i) basic monitoring in place (OR, 0.18 [95% CI, 0.07–0.47]), (ii) a critical incident reporting system in place (OR, 0.69 [95% CI, 0.53–0.90]), (iii) an established routine of checks at nurses' shift change (OR, 0.70 [95% CI, 0.53–0.91]), and (iv) an increased ratio of patient turnover to ICU size (OR, 0.75 [95% CI, 0.59–0.95]).

Interpretation. Parenteral medication errors at the administration stage occur with alarming frequency and are a serious safety problem in ICUs. With the increasing complexity of care in critically ill patients, organisational factors such as error reporting systems and routine checks can reduce the risk for such errors in ICUs.

VAC Abdominal Dressing – a retrospective study in the treatment of the open abdomen following secondary peritonitis

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Introduction. Treatment of an open abdomen following secondary peritonitis is a challenge for surgery and intensive care units (ICU). The goal of this study was to compare three different treatment strategies for the open abdomen: V.A.C. Abdominal Dressing (AD), conventional V.A.C. therapy (CV) and conventional open therapy (OP).

Methods. All patients suffering from an open abdomen following surgery for secondary peritonitis between 2001 and 2006 at 5 different surgical departments in Austria were retrospectively analyzed. Parameters that were analyzed: duration of open abdomen, incidence of multi-organ failure, need for surgical revisions, length of stay (LOS) in ICU, nursing requirements (change of dressing/day), survival and integrity of abdominal wall after discharge. Treatment strategies included: open packing (OP), classic vacuum assisted closure (VAC®)-therapy with silicone net protection for the intestines (CV) and VAC® therapy with "Abdominal Dressing" a newly developed dressing containing an encapsulated foam with non-adherent layer (AD).

Results. In total 239 patients were analyzed: 62 patients were treated with OP, 102 patients with CV and 75 patients with AD. Mortality rates were 47/62 (76%) for OP vs. 38/102 (37%) for CV vs. 27/75 (36%) for AD ($p < 0.01$)

There was no difference in age and in mean ICU LOS; 38.6 days for OP, 30 days for CV and 36.4 days for AD ($p = 0.25$ Kruskal Wallis Test). The APACHE II scores were higher in the AD group, AD: 19.3; OP: 18.9 and CV: 16.8 ($p < 0.002$) and there were no significant differences in age between the groups.

Conclusion. We found in our study that VAC Therapy could significantly reduce mortality. The VAC "abdominal dressing"-therapy appeared to be a more efficient treatment option in patients suffering from open abdomen following secondary peritonitis. The results from this retrospective study indicate the need for further prospective evaluation of VAC therapy using the VAC Abdominal Dressing to determine whether the intervention has set a new standard for managing the open abdomen.

Adverse events in intensive care unit

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Summary. Numerous studies report that iatrogenic complications are the cause of long-term hospitalization, many deaths and unnecessary expense. Critically ill patients may be more vulnerable to errors in care, and therefore more susceptible to injury. The aim of this study was to analyze the characteristics and frequency of adverse events (AE) detected in patients admitted to the intensive care unit (ICU).

Prospective study included all patients admitted to ICU during one month of observation. AE were defined as incident events in which patients were harmed or at risk of harm due to medical care. A total of 113 patients were included, 62 male and 51 female. In 53 patients, 97 incidents were detected, 14 (17,6%) of which were classified as severe, 5 (6,25%) as potentially fatal and 2 (2,25%) as contributing to the cause of death. The main types of AE were: a) nosocomial infections – 12 (nosocomial pneumonia – 3, surgical wounds – 8), b) complications of invasive procedures – 7, c) complications of surgery – 11, d) line tubes – 22 (peripheral lines – 13, central venous catheter – 3, arterial catheter – 5, urinary catheter – 5, nasogastric tube – 3, thoracic drainage – 1), e) medication errors – 22 (drug prescription – 11, drug administration – 7, adverse reaction – 4), f) others – 16 (pressure ulcer – 7, airways obstruction – 6, medical devices – 3). 82% of these AE were predictable or potentially avoidable. The incidence of adverse events in critically ill patients is high, but in most cases preventable.

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Pleural pressure estimation by using vascular pressures

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Introduction. Pleural pressure changes are transmitted into thorax vessels. We speculated that pressure changes in pulmonary artery and vena cava superior during respiratory cycle reflect pleural pressure swings and can therefore replace standard method used in this respect – oesophageal pressure measurement.

Methods. Study was approved by local EC. Patients with pulmonary catheter in place on mandatory mechanical ventilation could be recruited. Oesophageal balloon catheter was introduced and correct position verified according to Teboul [1]. Pulmonary artery pressures (PAP, diastolic pressure used

Fig. 1. Respiratory swings of central venous pressure (dCVP) and esophageal pressure (dPes)

Fig. 2. Respiratory swings of pulmonary artery occlusive pressure (dPAOP) and esophageal pressure (dPes)

for calculation – DPAP), central venous pressure (CVP) and oesophageal pressure (Pes) were recorded continuously together with distal airway pressure measured by catheter introduced above carina.

In patients a set of 10 volume control breaths in range 350–800ml was randomly applied.

Analysis of pressure tracings was performed by special software (Scopewin) and peak inspiratory – expiratory differences were calculated for every following pressure: dCVP, dDPAP, dPAOP (pulmonary artery occlusive pressure) and dPes.

We calculated Pearson r for correlations of studied parameters with dPes, means and $1.96 \times \text{SD}$ (bias) of the following differences: dPes–dCVP (ddCVP), dPes–dDPAP (ddDPAP) and dPes–dPAOP (ddPAOP).

Results. In 11 patients 200 measurements were done.

Mean and bias of differences were: ddCVP $1.5 (\pm 3.7)$, ddDPAP $-3.2 (\pm 4.5)$, ddPAOP $-3.7 (\pm 6.0)$ cm H₂O.

Coefficient r : dPes vs dCVP 0.73, dPes vs dDPAP 0.67, dPes vs dPAOP 0.61.

Plot of dPes vs dCVP and dPAOP are shown in Figs. 1 and 2.

Discussion. Our results suggest that pleural pressures are best reflected in changes of CVP and both dDPAP and dPAOP overestimate dPes. This is in contradiction with recently published study of Bellamere [2] which was done during spontane-

ous inspiratory efforts. Speculatively, our results gained from PAC can be explained by eventual position of PAC in West 1 zone of the lungs. More probable explanation seems to be that Pes underestimates a real pleural pressure around the heart [3].

Conclusion. Usage of PAC in pleural pressure estimation cannot be so far recommended.

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In honour of the 140th anniversary of Nobel Laureate Dr. Karl Landsteiner – collected abstracts of institutes of the Karl Landsteiner Society

Age-related increase of kynurenic acid in canine cerebrospinal fluid

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Introduction. Kynurenic acid (KYNA) is a well known endogenous antagonist of the glutamate ionotropic excitatory amino acid (EAA) receptors NMDA, AMPA and kainate [1] and of the nicotine cholinergic subtype 7α receptors [2]. KYNA's neuroprotective and anticonvulsive activities have been demonstrated in animal models of neurodegenerative diseases [1, 3]. In the ageing process KYNA metabolism in the brain and in the cerebrospinal fluid (CSF) of rats and also of sheep shows a characteristic pattern of changes throughout the life span. A marked increase of the KYNA content in the CNS occurs before the birth, accompanied by a dramatic decline on the day of birth [4, 5] and significant increase during maturation and ageing [6, 7]. Increase of L-kynurenine, a substrate for KYNA synthesis, with age has been also shown [8]. In human CSF significant increase of KYNA levels with age progression has been found, too [9]. This remarkable profile of KYNA metabolism alterations in mammalian brain has been suggested to result from the development of the organisation of neuronal connections and synaptic plasticity, development of receptor recognition sites, maturation and ageing [1, 7, 10]. There is significant evidence that KYNA can improve cognition and memory [11], but it has also been demonstrated that it interferes with memory [12]. This study was designed to find out whether KYNA levels in the CSF of canines (dogs) also increase with advancing age.

Materials and methods. *Subjects:* Samples of CSF of 19 dogs at the age of 2.5 months to 16.7 years which were clinically examined and then euthanized or died because of progressed diseases (e.g. malignoma) at the Veterinary University of Vienna were used for investigation. None of these dogs had shown neurological symptoms.

Measurement of KYNA: Measurement of KYNA was performed according to method described by Kepplinger et al., 2005 [8]. Briefly, CSF samples were mixed with 0.2 M HCl (vol/vol) and centrifuged (20 min, 14,000 rpm). The supernatant was applied to a Dowex 50W cation exchange column pre-washed with 0.1 M HCl. Subsequently, the column was washed with 1 ml 0.1 M HCl and 1 ml distilled water. KYNA was eluted with 2 ml distilled water and was quantitated by high performance liquid chromatography (HPLC) system coupled with fluorescence detection.

Statistical analysis: All mean values are given $\pm$ SEM. For statistical significance the one-way ANOVA and the Student's t-test were applied. For statistical significance a P value of <0.05 was considered significant.

Results. The KYNA-concentrations in CSF of dogs are within the low nanomolar range, as it has been described in human, though higher concentrations than in human CSF were detected here (dog CSF = 58,21 fmol/ μ l vs. human CSF = 3,30 fmol/ μ l). Another finding was that the mean value of the group of dogs older than 10 years was much higher than the mean value of the group with the age of 10 years and below ($81,20 \pm 79,69$ fmol/ μ l vs. $26,59 \pm 22,19$ fmol/ μ l). These results suggest that in CSF of dogs, KYNA-concentrations seem to increase with age as it has been shown in CSF of humans before.

Discussion. KYNA's neuromodulatory character has been demonstrated and its involvement has been speculatively linked to the pathogenesis of a number of neurological conditions including those in the ageing process [1, 9]. The increase of KYNA metabolism in CNS with ageing in various species such as rat, sheep, dog and human could suggest long lasting blockade of glutamatergic and cholinergic neurotransmission, events that are involved in the pathogenesis of memory and cognitive impairments. Therefore, the activation of tryptophan/kynurenine metabolism in older patients of different species may result in a negative response. An alteration of receptor activities due to an ageing process [13] may involve changes in KYNA metabolism and probably both processes could reciprocate. Further studies need to be accomplished in order to provide more evidence for mechanism(s) of direct and/or indirect KYNA action and its involvement in the memory and cognition impairment during ageing.

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Reduced Kynurenine Aminotransferase I and II and Glutamic Acid Decarboxylase and Choline Acetyltransferase Activities in the Central Nervous System of Multiple Sclerosis Patients

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Introduction. Multiple Sclerosis (MS), an autoimmune disease, is characterized by demyelination in the Central Nervous System accompanied by the disappearance of oligodendrocytes, neuronal/axonal degeneration, proliferation of astrocytes and plaques formation [1]. Kynurenic acid (KYNA) is a well known endogenous antagonist of the glutamate ionotropic excitatory amino acid receptors and of the nicotine cholinergic subtype α -7 receptor and has anticonvulsive and neuroprotective properties [2, 3]. Kynurenine aminotransferase I and II (KAT I and KAT II) catalyze the biosynthesis of KYNA from L-kynurenine and the formation of KYNA takes place preferentially in astrocytes [4]. Choline acetyltransferase (ChAT) and glutamate decarboxylase (GAD) are well known neurotransmitter markers for the excitatory cholinergic- and the inhibitory GABAergic systems in the mammalian and human CNS, respectively. The aim of present study was to investigate the activity of KAT I and KAT II and of neuronal markers

of the GABA- and cholinergic systems in plaques of post mortem tissue from MS patients and compared with controls (CO).

Material and methods. *Material:* Post-mortem samples of white and gray matter and of plaques from Frontal lobe, Occipital lobe, Pons and cervical, thoracic and lumbar Spinal cord from MS patients and anatomically corresponding samples from normal control subjects were obtained from NeuroResource Tissue Bank, University College London, England.

Determination of KAT I and KAT II activities: The activities of the KAT I and II were assayed as described by Baran et al. 1995 [6]. The reaction mixture contained the homogenate, 3 mM L-KYN, 1 mM pyruvate, 70 μ M pyridoxal 5'-phosphate and 150 mM AMP buffer, pH 9.6 (for KAT I) or 150 mM Tris-acetate buffer, pH 7.4 (for KAT II), in a total volume of 0.2 ml. After incubation for 16 hrs at 37°C formed KYNA was separated using Dowex 50 W cation exchange column and quantitated by HPLC method (Results Table 1). In other experiment for KAT I and II determinations we used the same condition of KAT assay and 100 μ M 1.175 μ Ci/ μ mol [³H]L-kynurenine and the synthesised [³H]KYNA was quantified by liquid scintillation spectrometry (Results Table 2).

Determination of GAD activity: GAD activity, as a marker for GABAergic neurons, was measured by trapping [¹⁴C]CO₂ formed from L-1[¹⁴C]glutamic acid (Amersham) as described by Roberts and Simonsen (1963) [7] with some modification by Baran et al. (2004) [8].

Determination of ChAT activity: ChAT activity, as a marker for cholinergic neurons, was determined by the rate of formation of [¹⁴C]acetylcholine from choline and [¹⁴C]-labelled coenzyme-A according to the procedure described by Fonnum, (1969) [9] with some modification by Baran et al. (2004) [8].

Protein determination: Protein was measured according to the method of Bradford (1976) using a commercially available kit (BIO-RAD) and bovine serum albumin as a standard.

Statistical analysis: Each sample (number of sample are given in parenthesis) was determined in triplicate. Results were expressed as a single value and/or as a means $\pm$ SEM. For statistical significance the Student's t-test were applied. For statistical significance a P value of < 0.05 was considered significant.

Results. Determinations of all enzyme activities in MS and CO samples were blind performed. KAT I and KAT II activities were significantly reduced in grey/white matter of Frontal lobe, Occipital lobe, and also in Pons and Spinal cord in MS patients comparing to control values (Table 1).

Marked reduction of KAT I, KAT II, GAD and ChAT activities was seen in active MS plaques in Frontal lobe. In chronic MS plaque KAT II and ChAT activities were comparable to control values (Table 2).

Table 1. Kynurenine aminotransferase I and II (KAT I and II) activities in Multiple Sclerosis (MS) and Control (CO)

Group	ORO/CAFFING SCORES	Frontal lobe white/matter		Occipital lobe white/matter		Pons		Spinal cord	
		KAT I	KAT II	KAT I	KAT II	KAT I	KAT II	KAT I	KAT II
CO.1	(NC)	84.7	133.6	75.6	150.4	96.3	133.9		
CO.2	(NC)							45.6 (L)	57.0 (L)
MS 1	(3/4)	17.3	56.7						
MS 2	(4/3)	14.7	26.3						
MS 3	(0/1)			32.1	87.2				
MS 4	(2/1)					24.1	64.4		
MS 5	(3/3)					24.7	86.9		
MS 6	(2/1)							14.1 (C)	21.1 (C)
MS 7	3/2)							22.7 (TH)	42.4 (TH)
MS 8	(2/4)							26.7 (L)	64.2 (L)

KAT I and II activities represent single results and are expressed in [pmol/mg protein/h]. C cervical; TH thoracic; L lumbar

Table 2. Kynurenine aminotransferase I and II (KAT I and II), glutamic acid decarboxylase (GAD) and choline acetyltransferase (ChAT) activities in white/grey matter of Frontal lobe of MS and CO patients

Group	KAT I	KAT II	GAD	ChAT
CO	7.08 ± 0.88 (2)	2.94 ± 0.43 (2)	269.75 ± 118.0 (2)	245.16 ± 66.92 (2)
Active MS plaque	3.28 ± 0.28 (2)	1.86 ± 0.02 (2)	35.83 ± 1.66 (2)	99.85 ± 17.35 (2)
Chronic MS plaque	3.80 ± 0.21 (2)	2.67 ± 0.66 (2)	69.92 ± 9.74 (2)	236.54 ± 32.2 (2)

KAT I, KAT II, GAD, ChAT activities are expressed in [pmol/mg wet tissue weight/h].

Moderate alterations of kynurenic acid levels were seen in Pons of MS (2) = 5.1/8.1 vs. CO (1) = 6.6 [pmol/mg protein]; Spinal cord of MS (1) = 2.0(C), 1.4(TH), 1.1(L) vs. CO (1) = 1.3 (L) [pmol/mg protein]; Frontal lobe MS (2) = 7.3/20.2 vs. CO (1) 11.8 [pmol/mg protein], respectively.

Discussion. Our data indicate markedly lowered activities of KYNA synthesizing enzymes and reduction of GABAergic and cholinergic activities in MS plaques. Decreased KAT I, KAT II and GAD activities of enzymes which synthesize potentially neuroprotective molecules, may contribute to axonal degeneration and cell loss in MS. An increased glutamate excitotoxicity might play a role as has been suggested in a model of MS [10]. These alterations may lead to the induction of epileptic activities and dementia conditions in patients with progressed MS.

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Strengthening of spontaneous reporting from Health Care Professionals

M. Gantschacher

Improvement of Drug Safety, Academy of Pharmacovigilance and Research Law of the Karl Landsteiner Institute for Quality Management and Patient Safety

Based on the research activities of the Institute and the Academy for Pharmacovigilance and Research Law, an innovative System named “Patient & Consumer Safety Services” will be created by the team and realized by the associated partners and in cooperation with international universities, authorities, organisations and pharmaceutical companies.

Background. Actually there is only minor willingness of health care professionals to report adverse reactions, which have appeared during medical treatment to the competent authorities. Very similar is the current situation concerning medical device, haemo- and tissue-vigilance. This fact can be attributed to the widespread lack of knowledge in pharmacovigilance and reporting. On the other hand there is only low compliance of health care professionals to fill in lots of downloaded forms and to post them. If they do report, these forms very often are unreadable, incomplete and do not show the real situation of the adverse event. Numerous further inquiries due to this lack of report-quality are even counterproductive.

According to “Pharmacovigilance-Planning (Vol. 9a of the European Eudralex and the Guideline E2E of the International Conference on Harmonization), even more activities have to be done by the market authorisation holders of medicinal products to identify safety risks and information. The raising formal complexity causes lots of problems for health care professionals and industry to realize that duties. Increased activities have to overcome the existing “Non-Compliance” to fill in additional documentation records during routine work has to be done.

In Addition it is important to provide a valid patient- and consumer-reporting. Patients that like to report a therapy-experience or adverse reaction as a result of a prescribed medication do not have the opportunity to do so in all member states of the European Community. Especially there is a problem to collect safety data of OTC-products, because they are sold without prescription and very often handed over to other persons. Consumer-reporting has to be strengthened, but also medically confirmed. Therefore it should be transparently documented if there is any report, but on the other hand only medically confirmed reactions should fulfil the minimum criteria of a report. To provide patients with the right to report adverse events means that education activities have to be taken into account. Information has to be easily understood and user-friendly methods have to be found to avoid mistakes, double-reporting and failed reports. Furthermore there has to be found a way to reach consumers of herbal or homeopathic medicines.

Drug safety research. First pilot studies have shown that a new and innovative System, ARTS (Adverse Reaction Tele-report-System) can be very easily used by all stakeholders and combines reporting of adverse reactions and signals via telephone with the possibility to alert health care professionals and especially patients in cases of lack of quality or hazard. All activities are documented and stored in a validated database that corresponds with authorities.

Using that interface to authorities, even off label use data can be collected. The special tools for patients and industry makes the system a complete public health network with pharmacovigilance, risk-management and patient safety functions.

Big confirmation-trials are now planned within Austria and after evaluation also in cooperation with Eastern European Universities.

Patient Safety and Quality Improvement by standardized Training in Hospitals – best practice from a Harmonization-Project within Central and Eastern Europe

On the occasion of the WHO-Congress in Vienna, organized by the Karl Landsteiner Institute of Quality Management and Patient Safety, the Academy of Pharmacovigilance and Research Law presented a review of studies that showed the importance of that quality indicator. The trained cognition of adverse reactions and signals as well as an appropriate trained stress-induced behaviour of the reporter showed improvement of the risk-management in hospitals. Based on this knowledge, the Academy developed educational strategies and a new standard on pharmacovigilance training. This curriculum covers training and education for industry members (such as the qualified person of pharmacovigilance), health care professionals, members of ethics committees, consultants, study groups and even regulatory departments and was certified by the TÜV Austria.

The Academy of Pharmacovigilance and Research-Law is a main department of the Karl Landsteiner Institute of Quality Assurance and Patient Safety (IQMS). It assures most and highly effective training standards in the pharmacovigilance and research field, that are main interfaces between health care professionals and pharmaceutical industry. Based on the current pharmaceutical and research law, qualification requirements were created, which with unique training do not find the sufficiency any more. Therefore the concept of the new academy is based on the creation of a solid basic training, followed from regular revitalization training courses, distance learning and consultation. To attain a far-reaching acceptance of the education, the institute cooperates with national and international governmental bodies, institutions, organizations and universities. Teaching contents are accredited by Austrian institutions. By the cooperation with the TÜV Austria for the first time a certifying possibility for qualified Persons of Pharmacovigilance and their established Pharmacovigilance-System was created.

Prevalence of polyneuropathy in uremic predialytic or dialyzed patients with or without diabetes

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Background. Besides diabetes and alcohol abuse, uremia is the most frequent cause of peripheral polyneuropathy (PNP) in the western world. PNP affects sensorimotor as well as autonomic nerve fibers in patients with end-stage renal disease. There is evidence, that short-term dialysis could halt the progression of non-diabetic uremic PNP, but in long-term dialysis, PNP usually worsens. About every third patient undergoing dialysis treatment is suffering from diabetes – sensorimotor and autonomic neuropathy is even more frequent in these subjects.

The aim of the present cross-sectional study was to assess the prevalence and severity of PNP in diabetic or non-diabetic uremic patients who were or were not receiving dialysis treatment. The frequency of PNP in predialytic patients was of particular interest, and whether predialytic patients are less frequently affected, or suffer milder forms of PNP, than dialyzed subjects.

Subjects and methods. Fifty-five predialytic (27 suffering diabetes) with a serum creatinine level of at least 2 mg/dl and 43 (21 diabetic) subjects with hemodialysis or chronic ambulatory peritoneal dialysis were investigated.

PNP was assessed by standard procedures as follows: Symptoms of PNP were recorded on a modified questionnaire fol-

lowing the Michigan Neuropathy Screening Instrument. The individual questions were summarized and subjects with ≥ 2 positive answers were classified as suffering symptomatic neuropathy.

The clinical neurological evaluation included simple bedside tests on sensory deficits and reflex and muscle strength tests, and the Michigan Diabetic Neuropathy Score (MDNS) was calculated.

Vibration Perception Threshold (VPT) was measured with a Biothesiometer (Horwell, London, UK) at the tips of both great toes. Current perception threshold (CPT) of the peroneal nerve was tested with a Neurometer (Neurotron Inc., Baltimore, MD, USA), a neuroselective device to electrically stimulate different nerve fiber types ($A\beta - A\delta - C$) by different frequencies (2000 – 250 – 5 Hz).

Motor and sensory nerves conduction studies were done by standard procedures (Cantata, Dantec, Dk). Conduction velocities as well as the sensory nerve action potential (SNAP) and motor compound muscle action potential (CMAP) were determined from the ulnar and peroneal nerve.

Autonomic nerve function was assessed via the cardio-respiratory reflexes during resting and deep breathing (Vagus 2000, Sigma Medizintechnik, D). The mean heart rate and coefficient of variance during resting and the expiration/inspiration ratio and mean circular resultant during deep breathing were calculated.

Statistical analysis. Normally distributed data were compared between two groups using an unpaired t-test and non-normally distributed data were compared with a Mann-Whitney U or Wilcoxon test. To analyze the results between the four different groups, a one-way ANOVA with a Tukey post-hoc test (parametric data) or a Kruskal Wallis analysis with a Dunn post-hoc test (non-parametric data) were used. Frequencies were compared between groups with a Chi-Square test.

Results. The groups were well comparable in regard to patient's characteristics, but predialytic non-diabetic patients were significant older than patients with dialysis treatment, as was the serum creatinine level significantly higher among dialyzed than predialytic subjects.

Independent of the presence of diabetes, VPT was higher in non-dialyzed than in dialyzed patients and was significantly ($p < 0.01$) elevated in non-dialyzed diabetic subjects (33.8 ± 12.6 volts) compared to dialyzed non-diabetic patients (Table 1).

The total score of the MDNS was significantly elevated ($p < 0.05$) in diabetic patients, but did not differ between non-dialyzed and dialyzed subjects within the diabetic or the non-diabetic cohort. Non-diabetic patients had significantly less neuropathic symptoms (about one symptom, each) than diabetic patients (about 3 positive symptoms) (Table 1).

CPT was generally elevated in diabetic patients. The highest thresholds were found in diabetic non-dialyzed subjects but were in the normal range in diabetic dialyzed patients. The majority of non-diabetic subjects had a completely normal CPT, which was reflected by a prevalence of hypoesthesia of less than 5 percent (Table 1).

The age-corrected mean peroneal motor NCV was reduced to an abnormal level in 3 groups, was lowest in non-dialyzed diabetic patients with $36.8 \pm 5.8 \text{ m} \cdot \text{sec}^{-1}$ but was in the normal range in non-diabetic patients without dialysis treatment. The mean amplitude of the CMAP was lowered in both diabetic groups, and 41% of predialytic and 64% of dialyzed diabetic patients had an abnormal CMAP. The percentages of an abnormal CMAP in non-diabetic patients were found to be 17% in predialytic and 24% in dialytic ones.

Ulnar sensory NCV was in the normal range in the three groups but was lowered to $40.1 \pm 4.7 \text{ m} \cdot \text{sec}^{-1}$ in diabetic patients on dialysis therapy. The ulnar SNAP was generally lower among diabetic patients and dialyzed diabetic subjects had the lowest SNAP with $5.0 \pm 3.2 \mu\text{V}$ (Table 1).

The heart rate variability was generally lower in diabetic than in non-diabetic patients but differences between groups

Table 1. Neurological evaluation in uremic patients

	Uremic non-diabetic				Uremic diabetic				p-value	
	non-dialyzed		dialyzed		non-dialyzed		dialyzed		overall	between groups ^a
Sign & Symptoms										
Pin-prick abnormal	9 (32)	15–49	5 (23)	5–40	14 (52)	33–71	13 (62)	41–83	0.048	
10g-monofilament abnormal	14 (50)	32–69	8 (36)	16–57	18 (67)	49–84	15 (71)	52–91	0.09	
ATR abnormal	15 (54)	35–72	9 (41)	20–62	22 (81)	67–96	17 (81)	64–98	0.012	
MDNS (max. 46 points)	12.4 ± 9.7	8.6–16.1	11 ± 10.7	6.2–15.7	18.9 ± 6.9	16.1–21.6	19.5 ± 9.3	15.3–23.8	0.002	1/3, 1/4, 2/3, 2/4
Symptoms (max. 12)	1.3 ± 1.5	0.7–1.9	0.9 ± 0.9	0.5–1.3	3.2 ± 2	2.4–4.0	3.4 ± 2.2	2.3–4.4	<0.0001	1/3*, 1/4*, 2/3*, 2/4*
Quantitative sensory tests										
VPT (volts)	28.0 ± 15.8	21.9–34.1	20.6 ± 12.0	15.3–26.0	33.8 ± 12.6	28.9–38.8	28.5 ± 9.8	23.9–33.1	0.008	2/3*
CPT / 2000 Hz (mA)	325 ± 126	247–376	352 ± 147	287–417	536 ± 271	428–643	398 ± 248	281–514	0.002	1/3*, 2/3
CPT / 250 Hz (mA)	96 ± 49	75–116	111 ± 56	86–135	264 ± 271	157–371	191 ± 233	82–300	0.003	1/3*
CPT / 5 Hz (mA)	65 ± 40	49–81	78 ± 67	48–108	283 ± 339	149–418	182 ± 233	73–291	0.0004	1/3*, 2/3
Nerve conduction studies										
Ulnar SNAP (µV)	11.1 ± 8.2	5.6–16.7	13.6 ± 5.1	10.7–16.6	8.2 ± 4.5	4.1–12.4	5.0 ± 3.2	1.0–8.9	0.006	2/4*
Ulnar SNCV (m*sec ⁻¹)	47.5 ± 6.1	43.7–51.4	45.9 ± 7.0	41.9–50.0	48.8 ± 4.1	45.4–52.1	40.1 ± 4.7	34.2–45.9	0.051	3/4
Peroneal CMAP (mV)	3.3 ± 2.1	2.4–4.2	4.1 ± 2.7	2.9–5.3	1.9 ± 1.3	1.2–2.6	1.7 ± 1.1	1.0–2.3	0.005	2/3, 2/4
Peroneal MNCV (m*sec ⁻¹)	42.5 ± 5.7	40.1–44.9	38.6 ± 4.7	36.5–40.7	36.8 ± 5.8	34.0–39.7	37.6 ± 4.4	35.0–40.1	0.01	1/3
Cardiorespiratory reflexes										
Heart rate (BpM)	80 ± 12	68–91	75 ± 12	66–84	75 ± 11	67–82	84 ± 9	79–89	0.11	
Coefficient of variance (%)	10.5 ± 22.7	0–29.5	4.4 ± 4.0	1.5–7.2	3.0 ± 2.3	1.5–4.4	2.6 ± 3.6	0.5–4.7	0.32	
Expiration/Inspiration (ratio)	1.4 ± 0.1	1.2–1.4	1.4 ± 0.3	1.2–1.6	1.3 ± 0.3	1.2–1.5	1.1 ± 0.2	1.0–1.2	0.06	
Mean circular resultant	5.4 ± 8.7	0–12.7	8.3 ± 6.9	3.4–13.2	5.6 ± 7.7	0.7–10.6	2.1 ± 2.9	0.4–3.8	0.16	

Values are mean ± SD or count (percentage) and 95% confidence interval of the mean or proportion. ^a ANOVA or Kruskal Wallis post hoc tests: 1/3 denotes a significant difference between group 1 vs. group 3 at a level of $p < 0.05$. * Denotes a level of $p < 0.01$. ATR Achilles tendon reflex; MDNS Michigan Diabetic Neuropathy Score; CPT current perception threshold; VPT vibration perception threshold; SNAP sensory nerve action potential; S / MNCV sensory / motor nerve conduction velocity; CMAP (distal) compound muscle action potential.

were not statistically significant. However, the expiration-in-spiration ratio, mainly reflecting parasympathetic activity, was abnormally reduced in dialyzed diabetic patients with 1.1 ± 0.2 (Table 1).

Conclusions. The aim of this cross-sectional study in diabetic and non-diabetic patients was to investigate whether uremic predialytic patients suffer from less frequent and/or milder forms of PNP than patients treated with dialysis.

The effect of dialysis therapy itself on the development and progression of peripheral PNP is controversially discussed. PNP seems to progress in long-term dialysis, as was shown in patients who experienced more than 10 years of dialysis therapy. **Patients would benefit by normalization of renal function by kidney transplantation only.** Improvements of peripheral and autonomic nerve dysfunction were seen in non-diabetic kidney recipients even within 1 year after renal transplantation. In contrast, a renal transplantation seemed to have only a brief effect on nerve function in diabetic patients; only a simultaneous pancreas and kidney transplantation could significantly increase nerve dysfunction in diabetic uremic neuropathy.

To summarize, predialytic patients suffer from comparable nerve deficits than dialyzed patients indicating an early developing deficit of peripheral nerve function. Short-term dialysis therapy seems to halt the progression of uremic neuropathy even in the presence of diabetes as demonstrated by only minor differences in the degree of nerve dysfunction between investigated predialytic and dialyzed patients.

Computer aided detection of lung nodules in the view of patient safety

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The best chance to detect bronchial carcinoma at the earliest stage is given by low dose Computed Tomography, however a rising operation rate of histologically benign lesions must be avoided. Radiation dose to the public must also be controlled very strictly. The recent development in the use of CT (Computer Tomography) offers the possibility of 64-slices of CT in 1 scan, so new possibilities to detect small lesions have been established.

In order to exclude carcinoma of the lung in the patient-group of smokers Low dose CT should possibly be preferred in comparison to conventional thorax X-ray films.

We have developed a program called "L3 LungCAD" that allows the automatic detection of RH (Round Herds) inside the lung (Fig. 1). In order to get decisive information, the nodules (RHs) may also be visualized in a 3-dimensional MIPs (Maximum Intensity projection) representation (Fig. 2).

Fig. 1. Round lesion detected by the software

L3 LungCAD by these possibilities is a good example for the application of 3-dimensional CAD-methods. The differentiation between benign and malign lesions is simplified and the rate of detection is improved in comparison to the standard 2-dimensional images. One of the most important signs of malignancy is the growth of a round herd (RH) within a defined time interval (200–300 days) (Fig. 3).

A precise volumetric estimation of the growth of a RH is extremely difficult at this 2 dimensional base. Therefore the volumetric information of a nodule is provided by the software.

The Volume of a RH is calculated by the software and linear as well as logarithmic TDR (Tumor Doubling Rate) is calculated as shown below (Fig. 4).

The resulting values are:

- Tumor first acquisition
- tumor_volume = 12.360
- Tumor second acquisition

- tumor_volume = 34.315
- tumor_growth = 278%
- tumor_doubling_time_in_days_linear = 292
- tumor_doubling_time_in_days_Logarithmic = 352

In order to detect RHs as early as possible, it must be assured that the software's detection rate of RHs is tuned to the maximum sensitivity with highest specificity. The manual analysis requires highest skills of the radiologist and a maximum of experience and concentration during the analysis, especially in the case of smaller RHs. L3 LungCAD gives the maximum support in the daily routine and increases the results of the radiological examination, especially if it is used in combination with and following the manual inspection.

The comparison may also be used in the case of treatment monitoring during chemotherapy, showing the rate of tumor-regression due to treatment.

A survey of all the detected lesions is given in an overview picture of the lung like below (Fig. 5).

Fig. 2. Round lesion detected by the software – shown in MIPs

Fig. 3. Comparison of a nodule after 200 days in 2D axial projections only

Fig. 4. Tumor doubling rate calculated by the software

Advantages of the L3 LungCAD Software in the daily routine:

- Automatic CAD method
- Increased efficiency
- Minimized time of analysis for radiologist
- Increased sensitivity of RH-recognition
- Standardized interpretation
- Comparison, tumor doubling time

Features of L3 LungCAD are:

- Automatic Lungdetection
- “One-click” automatic RH detection (CAD)
 - 2 mm to 45 mm diameter of RH
- Automatic display of RH in MPR and 3D-MIPs representation
- Automatic anatomic sorting of the RHs (right/left – head to feet)
- Automatic quantitative analysis:
 - Lungvolume (right, left, both)
 - Volume of RH
 - Tumor doubling time
 - Comparison with previous series
 - Complete tumormass
- Automatic Reporting (MS Word)

Fig. 5. Overview of detected lesions

Table 1

Lesion Nr.:	2
Min.Scan:	28
Max.Scan:	31
Central.Scan: ...	30
Center:	(104, 272)
VOLUME (mm ³):	55.859
Min.Size in mm ² : ...	3.182
Max. Size in mm ² : ...	5.000
Average HU: ...	355.818
Max. HU:	1305

By its "One-Click-Technology" the L3 LungCAD Software gives the possibility for an automatic detection of lesions inside the lung. Also the L3 LungCAD Software gives the possibility to compare series differing in aquisitiontime by 200 to 300 days fastly, as all results of the investigation are stored together with the series.

Alternatively studies in inspiration and expiration may be compared.

The 3rd generation L3 LungCAD Software uses a newly developed 3-dimensional detection algorithm, thus giving a higher detection rate than the purely visual investigation.

The L3 LungCAD Software presents a "second opinion" to the radiologist. The automatic display, numbering and ordering of the lesions in the axial, coronal and sagittal plane greatly facilitates the analysis.

The L3 LungCAD Software not only detects RHs small as 2 mm but also gives the possibility of therapy-monitoring of RHs up to the size of 45 mm.

The L3 LungCAD Software is able to detect RHs close to the pleura wall, also by its specially designed algorithm, in short time, normally less than 2 minutes.

In order to facilitate radiological documentation the RHs are ordered for the right and left lung as well as inside these from head to feet.

The documentation of a single acquisition is automatically done in the form of an MS-Word report like here (Table 1).

Conclusion. We tried to compare the results of the software with other vendors. The result was that it is until now still too difficult to get the correct information about the differences in the algorithms used in the detection. However to maximize the benefit from the point of view of patient safety we must get these informations to understand potential volumetric differences or differencies in sensitivity among different vendors. It seems that a nationwide comparison of CAD-results in this field is now necessary in order to have equal and adequate possibilities to detect lung cancer in the earliest stage for all patients in Austria.

Dental planning and patient safety

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Dental planning at the state of the art must be based on a highly sophisticated teamwork between the radiologist and the dentist. For example disturbances in tooth eruption and tooth impactions make great demands on radiographic diagnostics. The quality of its outcome has a direct effect on patient safety, as injuries of the mandibular nerve may be a direct consequence of inaccuracies hidden in the necessary actions due to planning of implants. Older methods exclusively based on panorama X-ray are not state of the art anymore as life-size measurements may not be done by this technique and also re-formatted projections in various panoramic planes as well as in orthoradial projections may never be done in such technique.

If a dental or maxillo-facial surgeon is very experienced in implantology and if there is no doubt relating bone quality and quantity, a panoramic X-ray will be sufficient for the decision to implant.

These conditions are the essential requirements to forgo computer tomography (CT) or digital bone volume tomography (DVT).

But in case of complications we should be aware, that patients intend to take legal action against the dentist.

Therefore we have to be prepared to be confronted with difficult questions so that adequate justification will be necessary.

In accordance to avoid any forensic problems, the further comments should be considered.

To estimate, if enough bone is existing, a plaster mould can be helpful in many cases too.

Of course, the highest level of safety about bone availability is attainable by CT or DVT.

But, as mentioned above, not in every case CT or DVT is necessarily to be carried out.

Depending on clinical experience, each dentist or surgeon is responsible for his doing to patient.

Certainly in not a few cases costs as well as exposition to radiation can be kept on a low level.

Fig. 1. Panoramaprojection done by 3dwk-Dental planner

Fig. 2. Orthoradial projections calculated by 3dwk-Dental Planner

Today's dental planning of implants in many cases requires the use of a CT (Computer Tomograph) or the use of Digital volume tomography (DVT) as these 2 methods are the only ones that allow 1:1 printouts. However more enough a specific dental planning software is necessary to further process the CT- or DVT-images and to give panoramic and orthoradial reconstructions, where it is possible to assess the mandibular nerve in such a way that the shortest distance between alveolar ridge and the surface of the nerve may be measured. Many software packages call themselves dental planners but are unable to give the undoubtedly necessary information, localizing hard tissue structures such as bone and teeth on various planes. Moreover this makes a three-dimensional image of the teeth, jaws and the viscerocranium impossible.

From an orthodontic point of view, CT- or DVT-based dental planning is indicated to detect impacted and ectopic teeth and to demonstrate the amount of bone available for successful implantation. In patients with cleft lip and palate, it can be used to visualize the size of the alveolar cleft and to evaluate the position and development of multiple teeth, as these patients often suffer from disturbances in tooth eruption.

We have developed a software "3dwk-Dental planner" that can fulfill all these requirements. Panoramic and orthoradial projections are calculated in real time. The mandibular nerve may be drawn in semiautomatic mode, where correction that may only be seen in orthoradial projections, may be done manually by the radiologist or dentist (Figs. 1 and 2).

They may be printed in lifesize 1:1 on film or paper, the bone quality around the implant may be estimated and the software allows its reproduction together with the dataset of Dicom-images (Digital Imaging and Communications) so that the dentist can use all the information given by the radiologist,

Fig. 3. Panoramic X-ray after 3dwk-planning and insertion of implants

together with the position of the mandibular nerve and the shortest distance between alveolar ridge and nerve. The dentist just simply inserts a CD into his PC and he can simulate himself all implants in any projection without having to buy an extra software.

The European certification CE is already passed by the software. Furthermore a study how it will fulfill the requirements of the FDA (Food and Drugs Administration) was already done in conjunction with DUK (Donau University Krems)¹. The software will be submitted to pass also the certi-

1 R. Fischer, W. Kallinger; DUK 2008; "Analyse für den Softwareentwicklungsprozeß der Dentalplanungssoftware gemäß Richtlinien der FDA (Food and Drug Administration USA), Validierung am Patienten nach mit 'Dentalplanner' geplanter Implantation, Validierung am Phantom, Dicomcompliance".

fication procedure in the US. Main efforts must be put on the patient safety, demonstrated by phantom measurements and clinical data.

For the reason to demonstrate the accuracy of any dental planning system, we have developed a perspexphantom, which may be placed in the CT or DVT and hence dental planning on the phantom may be done. It could be shown that the accuracies below 0.5 mm may well be reached in the panoramic and orthoradial projections. Furthermore patients have been planned with the software and after the insertion of several implants panoramic X-rays have been made, showing the quality if the implantation (Fig. 3). (500)

Differences to other systems are encountered in the following way

- several systems just simply are unable to show more than 1 panoramic reformation
- Some systems only allow the use of their own sets of implants to be simulated
- some systems require special software to see the outcome results.
- The Siemens software "Magic View Danube 2008" seems to be unable to show the mandibular nerve in the orthoradial projection. As the mandibular nerve many times may better be visualized on the orthoradial projections this has the consequence of an increased patient risk during the implantation.
- If a dental planning software like the Siemens software "Magic View Danube 2008" cannot correlate all positions together in the different projections it is by far more difficult to give the correct diagnosis by the radiologist, thus increasing the potential risk for the patient again.

Result. We strongly emphasize that all dental planning systems that are currently and in the future in use in Austria shall be evaluated at the "Karl Landsteiner Institut für Qualitätsmanagement und Patientensicherheit" with respect to patient safety. All systems that are unable to prepare all the information shown above in sufficient quality shall be taken off from the Austrian market in order to assure adequate patient safety during dental implantation.

Long term effects of clinical in-vitro endothelialization on synthetic vascular grafts

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In humans, synthetic small diameter vascular grafts do not spontaneously endothelialize even after long-term implantation. This lack of an endothelium makes prosthetic grafts more prone to thrombotic occlusions than vein grafts [1]. In vitro lining of synthetic grafts with cultured autologous endothelial cells overcomes this physiological deficiency by creating a confluent monolayer of autologous intima cells prior to implantation. In a step-by-step approach we developed reliable mass culture techniques for autologous endothelial cells [1] as well as precoating [2] and lining techniques which resulted in shear stress resistance of the endothelium [3]. After the preclinical proof of this concept in a non-human primate model was obtained [4] we performed a randomised clinical study involving 49 patients between 1989 and 1991. Based on the encouraging three-year results [5] and on the histological proof of an endothelium on a 5 week explant [6] and a central graft segment after 41 months of implantation [7] we commenced a clinical program of routine implantation of *in-vitro* endothelialized grafts. We report here on the seven year follow-up of the initial clinical study as well as the 15 year results of routine clinical endothelialization.

Patients and methods. Randomised Trial (Phase 1): Between June 1989 and December 1991 forty-nine patients (29 male and 20 female; mean age 65.0 ± 9.8 years) entered this initial study. Details of this study were previously reported [5]. In brief, assignment to the endothelialized group (33 patients) and the control group (16 patients) followed a 1:2 ratio. The selection criterion was the unavailability of a suitable saphenous vein graft. Indications for surgery were disabling claudication in 37 patients (grade I chronic limb ischemia) and chronic limb ischemia in 12 patients (grade II in 6 patients and grade III in 6 patients). In patients assigned to the endothelialized group the right external jugular vein was excised under local anaesthesia, using a no-touch dissection and *in-situ* cannulation [1]. Endothelial cells were cultured in medium containing 20% autologous serum. The mass culture of first passage endothelial cells in two 165 cm² culture flasks was continued until the required cell number of 16×10^6 endothelial cells was confirmed by *in-situ* counting [1]. After reinforced 6mm ePTFE grafts (W. L. Gore, Flagstaff, AZ) were precoated with clinically approved, fibrinolytically inhibited fibrin glue (Immuno, Vienna, Austria). Seeding of endothelial cells onto the graft surface ($8.1 \pm 4.2 \times 10^5$ EC/ml cell suspension) was performed in an automated, temperature and pH controlled rotation device (Microplan, Vienna, Austria). Subsequently, grafts were incubated for another 11.6 ± 3.0 days to allow the maturation of the cytoskeleton [8]. Immediately after the seeding procedure and shortly before implantation, graft specimens were taken for scanning electron microscopy (SEM) and light microscopy. During implantation grafts were not clamped and the culture medium was kept inside the prosthesis by gravity adjustment of the operating table. After nine patients were excluded from the study due to growth failure of the autologous endothelial cells, twenty-four patients received twenty-seven successfully endothelialized grafts (three had a bilateral procedure) and sixteen patients received a unilateral untreated control prosthesis. In both groups three grafts were implanted below the knee. Follow up studies were performed after 9 days, 3 months, 6 months, 1 year and on an annual basis thereafter. Patency was determined by the ankle brachial index (ABI) and duplex sonography at each time interval. Angiography was performed annually and in patients with suspected graft occlusion. Graft occlusion was suspected if a deterioration of the clinical status of the limb was confirmed by a significant drop in the ABI or a lack of flow signal on duplex sonography. Only primary graft patency was considered. During the entire observation period none of the patients were lost to follow up. One patient in the control group and five patients in the endothelialized group

Fig. 1

died during follow up for reasons other than peripheral vascular problems.

Routine Clinical Application (Phase 2): From June 1993 onwards, *in-vitro* endothelialization was offered to all patients undergoing bypass operations for peripheral arterial occlusion. The selection criterion was again the lack of a suitable saphenous vein. Over a period of 15 years 310 consecutive patients (age 64.7 ± 8.6) received 341 endothelialized ePTFE grafts (308 femoro-popliteal: 153 above knee [AK] and 155 below knee [BK] and 33 femoro-distal). Autologous endothelial cells were harvested from short segments (3.9 ± 1.1 cm) of subcutaneous veins (80.0% cephalic; 11.0% basilic; 1.8% external jugular and 7.2% saphenous) grown to mass cultures within 20.3 ± 7.2 days and confluent lined onto fibrin glue-coated ePTFE grafts. The graft diameter was 6 mm [73.6%] or 7mm [34.4%]. The procedure-related delay for graft implantation was 28.1 ± 7.7 days. Growth failure prevented 2.6% of patients from receiving an endothelialized graft. Mean observation period was 9.6 years. Primary patencies were obtained from Kaplan-Meier survivorship functions. Explants for morphological analysis were obtained from 7 patients.

Results and discussion. In our phase 1 randomised trial the Kaplan-Meier survivorship analysis showed a primary 3 year patency rate of 84.7% for endothelialized grafts and 55.4% for control grafts [5]. After 5 years it was 73.8% for the endothelialized group and 20.8% for the controls. At the end of the follow-up period which lasted 6.5 years, the primary patency rate for endothelialized grafts remained high at 73.8% whereas that for control grafts dropped to zero. Performance differences between the two groups were statistically significant (log-rank test; $p = 0.00098$ and Wilcoxon test; $p = 0.0025$).

In our clinical routine application the overall primary patency rate of femoro-popliteal grafts was 68.8% at 5 years (68.0% [AK] vs 70.5% [BK]) and 60.5% at 10 years (59% [AK] vs 64% [BK]) (Fig. 1). Primary patency of 7mm vs 6mm grafts was 78%/62% at 5 years and 71%/55% at 10 years. The difference between the two groups was statistically significant (log rank test $p = 0.023$; Breslow test $p = 0.017$). Stage I versus II/III patients showed 5 year patencies of 67% vs 73% (N.S.) and 10 year patencies of 61% vs 53% (N.S.). The primary patency of femoro-distal grafts was 52.2% at 5 years and 35.9% at 10 years. The limb salvage rate was 94% (fem-pop) vs 86% (fem-distal) at 5 years and 89% vs 71% at 10 years. All retrieved samples showed the presence of an endothelium after 38.9 ± 17.8 months.

These data even suggest that *in-vitro* endothelialization makes prosthetic grafts an equal choice to saphenous vein grafts. In Veith's multi-center study [9] the patency rate for all reversed saphenous veins was 75% at 3 years and 68% at 5 years. Taylor et al. [11] equally reported primary patency rates of 78% at 3 years and 75% at 5 years for all reversed saphenous vein grafts in femoro-popliteal position. Furthermore, even the trend towards higher patency rates in below-the-knee positions – which Veith et al. describe for saphenous vein grafts – coincides with our findings in endothelialized prostheses.

In summary, clinical *in-vitro* endothelialization were able to prove two hypotheses: autologous endothelial cell lining significantly improves the patency of prosthetic small diameter vascular grafts and a cell-culture dependent procedure can be easily carried over into clinical routine.

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Atrial fibrillation therapy through preventive pacing with a dual chamber pacemaker

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Summary. In a retrospective analysis we investigated if in patients with atrial fibrillations who received a dual chamber pacemaker therapy could be optimised by means of reading out the atrial arrhythmia data recorded by the pacemaker.

Methods. A retrospective data analysis was carried out for 53 patients.

Results. An AF burden distribution curve with two maxima was found: The first group had 0 to 5% AF burden ($n = 30$), while the other group had 95 to 100% AF burden ($n = 7$). 76.7% of the patients were successfully treated using a hybrid therapy consisting of pacemaker and drugs. Drug therapy and the preventive pacing algorithms were complemented by the arrhythmia data recorded by the pacemaker and the stored AF onset mechanisms. This therapy was optimised and adapted during each follow-up. A significant difference between the low AF burden versus high AF burden group lay in the age and in the type of atrial fibrillation.

Conclusion. The investigated pacing system is especially effective in older patients with known paroxysmal AF.

Introduction. Atrial fibrillation (AF) is the most frequent rhythm disorder leading to hospitalisation. Hospitalisation because of atrial fibrillation doubled to tripled in the USA from 1985 to 1999 [1]. In the early eighties, the Framingham Heart Study proved that mortality doubled in patients with atrial fibrillation compared to patients without this rhythm disorder [2]. Pharmacological AF therapy is often ineffective and problematic because of frequent side effects [3]. In addition to this, monitoring the efficacy of drug therapy is only possible to a limited degree using conventional means. Recently, attempts are made to treat atrial fibrillation with hybrid therapy consisting of a dual chamber pacemaker with preventive pacing algorithms combined with antiarrhythmic drugs [3, 4].

We evaluated patients who received such a pacemaker (Vitatron™) in our institution. The goal of this study was to overview the experience gained and to record statistically various parameters to achieve further improvement in the quality of treatment for atrial fibrillation. The aim of evaluating patient data was to find a possible predictive parameter, which would enable us to identify patients benefiting from a pacemaker with preventive pacing algorithms.

Methods. During the observation period 53 patients received Vitatron AF pacemakers in our centre. Data of 46 patients were included in the further analysis. 7 patients had to be excluded from the evaluation because of sensing artefacts or inadequate observation periods (<3 months).

The diagnostic memory of the Vitatron PreventAF™ DDDR and Vitatron Selection 9000 DDDR™ (Vitatron B.V., NL) dual chamber pacemaker systems helped to establish the time the patient suffered from atrial fibrillation during the follow-up period (AF burden), the number of atrial fibrillation episodes, the number of premature atrial contractions (PACs) and up to 16 detailed onset reports (DORs) [5]. Drug therapy was documented at each individual follow-up. In addition to classical antibradycardiac pacing therapies, a total of four pacing algorithms are available for the prevention of paroxysmal atrial fibrillation.

These special preventive pacing algorithms react immediately to the occurrence of possible trigger mechanisms of atrial fibrillation and can be combined in any way. The maximally achievable pacing rate for these pacing functions is determined by a programmable maximum therapy rate.

AF burden was defined as the percentage of time the patient is in atrial fibrillation during a follow-up period. Accordingly, sinus rhythm duration was defined by the duration of the follow-up period minus the time in atrial fibrillation. Sinus rhythm time was standardised to a one year period to enable data comparability. Paroxysmal atrial fibrillation was defined as atrial fibrillation lasting for less than seven days and terminating spontaneously [6]. Persistent atrial fibrillation was defined as atrial fibrillation that does not terminate spontaneously and that lasts for over seven days [6]. Brady-

Table 2. Recorded days, days in sinus rhythm (SR) in relationship to recorded time, atrial fibrillation (AF) burden, frequency of atrial stimulation

	Group A	Group B	
Memory (days)	181.1 (±98.4)	208 (±144.9)	n.s.
Days in SR/ recorded time	180.4 (±98.4)	1.24 (±1.6)	P<0.001
AF burden (%)	0.57 (±1.0)	99.07 (±1.3)	P<0.001
Atrial pacing (%)	89.7 (±22.1)	17.0 (±15.1)	P<0.001

cardia-tachycardia syndrome was defined as bradycardiac sinus rhythm and tachycardiac atrial fibrillation.

The Mann-Whitney U test was used for the statistical evaluation. A P<0.05 was considered to be significant.

Results. Data of 46 patients were recorded in an observation period. All patients had a pacemaker indication, and atrial fibrillation had been documented at least once before implantation. Patients attended follow-ups at our centre after three and six months and once a year thereafter.

Distribution of AF burden of all patients was not normally distributed, showing one peak with an AF burden of ≤5 % and a second maximum with an AF burden ≥95% (Table 1). The patients were divided into three groups accordingly: Group A (n = 30) AF burden of ≤5 % with a high benefit, Group B ≥95% (n = 7) with a low benefit, and Group C (n = 9) with an AF burden between 6 and 94%.

In order to find a parameter which would indicate a high probability for success for the preventive pacing algorithms, Groups A and B were compared.

Demographic data are listed in Table 1. Results from the AF memory in the pacemaker are recorded in Table 2.

The distributions of diagnoses leading to pacemaker implantation have a different distribution pattern for each group. In Group A paroxysmal atrial fibrillation prevails, while in Group B tachycardia-bradycardia syndrome and persistent atrial fibrillation (higher number of cardioversions) prevail. Paroxysmal atrial fibrillation is significantly more frequent in Group A (p < 0.001).

For 76.7% of patients, a combination of drug therapy and individually adapted pacemaker therapy resulted in a reduction and/or stabilisation of atrial fibrillation and thus therapeutic success of, on average, 1.4 atrial fibrillation days per year.

Discussion. The retrospective evaluation of our data showed significantly improved efficacy of the tested system for patients with paroxysmal atrial fibrillation compared to patients with bradycardia-tachycardia syndrome or persistent atrial fibrillation. Consequently, we can recommend the application of a pacemaker with a preventive function for patients with paroxysmal atrial fibrillation and a pacemaker indication, while further investigations are required for other indications.

Analysis of these differences is difficult due to the small size of our sample. However, a significant difference in age between the two groups (76.8 vs. 62 years) is noticeable, indicating that younger patients with tachycardia-bradycardia syndrome or persistent atrial fibrillation benefit less from AF preventive pacing. Patients with sudden onset from a high intrinsic heart rate, in particular, are difficult to treat. This seems to play a considerable role in the Group B, where we failed to decrease intrinsic activity.

It is remarkable that sinus rhythm can be extremely well maintained in some patients, whilst others cannot be treated adequately. This might be due to the influence of coronary heart disease, as this was diagnosed in 30.3% of patients in Group A, but only in 1 patient of Group B. Possibly the trigger for atrial fibrillation due to ischaemia can be treated better with a pacemaker both by drugs and through atrial pacing.

Table 1. Demographic data and concomitant diseases, Coronary heart disease (CHD), frequency of beta-blocker therapy and Sedacoron therapy (including combinations)

	Group A	Group B	
Age (years)	76.8 (±8.1)	62 (±8.7)	P<0.001
Sex f/m	18/12	2/5	
Cardioversions (%)	16.7	85.7	P<0.001
CHD (%)	30.3	0	n.s.
Hypertension (%)	63.3	85.7	n.s.
Beta-blocker therapy (%)	63.3	71.4	n.s.
Sedacoron therapy (%)	14.3	14.3	n.s.

The advantage of the pacemaker used is that the system documents atrial arrhythmias precisely. Onset mechanisms through intracardiac ECG markers and possible sensing problems become apparent.

In summary the majority of our patients have been clearly less symptomatic with regard to atrial fibrillation since pacemaker implantation and have shown satisfactory rate control. Paroxysmal atrial fibrillation can be satisfactorily treated with hybrid therapy. In the other two diagnosis groups, further studies are necessary to be able to carry out optimised patient selection.

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Teleconsultation in image guided dental implantology

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Introduction. Telemedicine encourages the separation of highly knowledge-based, diagnosis/consultation-oriented activities from skill-centred activities such as surgical patient treatment. Teleconsultation is defined as consultation, evaluation and management services provided to patients via telecommunication systems without personal face-to-face interaction between the patient and healthcare provider. The increasing clinical relevance of computer assisted navigation technology promoted new perspectives in telemedicine utilizing live sensor data to enhance remote visualisation [1–2]. Any “digital” content, i.e. digital images from imaging modalities (most frequently computed tomography (CT) and magnetic resonance imaging (MRI)) as well as navigation data (e.g. intraoperative coordinates of surgical instruments relatively to pre-planned pathways and target-points at the patient, implant positions etc.), can be transferred without any loss of information. This means that remote experts can be involved in surgical interventions or preoperative planning sessions while being supplied with identical information as the “local” staff.

The augmented reality principle. Our approach is based on “augmented reality”. In contrast to “virtual reality”, which stands for completely computer generated information content (as known from computer games or flight simulators), “augmented reality” expands the “real world” (i.e. the actual view onto anatomical structures or the OR-site etc.) by means of the integration of additional computer generated information [3]. This computer generated information are usually com-

puter graphics illustrating surgical pathways, implant positions or target structures inside the patient’s tissue. They are superimposed with the surgeon’s original view and therefore build a kind of “augmented world”. Spatial awareness during image guided surgery [4] is only recently the focus of research but absolutely mandatory in teleconsultation. The visual display of data in context with the patient’s anatomy as 3D computer graphic enables a more comprehensive judgment of the situation almost in real time [5].

Computer assisted dental implantology and telecommunication. So far for all the different concepts of guided dental implant positioning (e.g. common surgical drilling templates, intraoperative navigation, templates manufactured with rapid prototyping etc.), CT data are the base for preoperative treatment planning. This CT data set can easily be transmitted from the radiologist to an experienced implant planning centre, either on CD-ROMs via “snail-mail”, or via Internet. In such a centre the experts use special software that allows for comprehensive evaluation of the anatomical situation in order to accomplish a planning that optimises the dental prosthetic restoration considering the available bone as well as all prosthetic, aesthetical and functional aspects. This is a complex process that requires a high level of experience and routine.

A major difference to image guided navigation in other medical segments is that the prosthetic planning mandates the position of the implants. An intraoperative adaptation of the simulated implant position can only be successfully accomplished if the consequence for the suprastructure is visualized immediately. With CT data only the surgeon has insufficient visual clues about the correct placement of dental implants during surgery. Therefore we not only superimpose the planned implant position during surgery, but also the complete CAD/CAM designed suprastructure registered to the patient. This decision-making based on “shape information” instead of image guided navigation information alone helps the surgeon to maintain spatial awareness. We focus on tasks in dental implantology with exemplary spread between highly knowledge-based and skill-centred activities, because here research and development activities merging image guided navigation with teleconsultation have an immediate impact on patient treatment outcome. We show that 3D telenavigation can be utilized to transfer the design of bone-anchored epithesis for congenital ear malformations and consult intra-operatively an expert connected via Internet for second opinion.

Case study microtia epithesis. A 21-year old university student with microtia came to the Department of Oral and Maxillofacial Surgery Department of OMS, Faculty of Medicine, Keio University, Japan hoping to make an ear-epithesis because he had to let his long hair cut for his examination of employment after the graduation of school. The patient had no chance to receive plastic and reconstructive surgery in his younger age due to asthma. Because maxillofacial implant placement surgery is necessary to make ear-epithesis, we planned navigation implant surgery, which is becoming the standard in intraoral dental implant surgery. So far the placement of osseointegrated implants in the temporal bone has been guided with CT images and anatomical knowledge in order to avoid intracranial perforation during surgery. This time, we used an implant navigation system (Virtual Implant System). In addition, we planned the surgery using Internet communication with Vienna. The initial implant position simulation was defined relative to the 3D reconstruction of the bone, based on the CT. Mirroring the data from the other intact ear generated the initial 3D data for the ear epithesis (Figs. 1, 2). The insertion points for the implants were then modified according to the shape of the pinna. Finally, the synthetic pinna was produced by rapid prototyping. During surgery the surgeon had the patient’s anatomy and the virtual pinna superimposed on the computer screen. After teleconsultation with the experts two implants (Ankylos® extraoral implant, Friadent, Germany) were placed in the temporal bone with image guide navigation [6].

Fig. 1. Microtomia

Fig. 2. Simulated ear epithesis

Perspective: Surgical training by means of a telenavigation-client. To reduce the spread between highly knowledge-based and skill-centred activities the Karl Landsteiner Institute for Biotelematics Vienna developed the so called "telenavigation client". This software (Free and Open Source Software license, FOSS) allows a real-time transmission of data from the position-tracking unit of a navigation system to

an unlimited number of "clients", i.e. computers that are connected to the internet. Before the beginning of an operation CAD/CAM surface and CT data of the (anonymised) patient are downloaded at these clients. During the operation each client-computer performs as an independent navigation system, therefore the user can arbitrarily select 2- and 3-dimensional views (Fig. 3) and cutting planes. Consequently, he/she

Fig. 3. Telenavigation client screenshot (Free and Open Source Software license, FOSS)

can de facto participate in the operation without affecting the performance of the navigation computer in the operating room.

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Connexin 26 is up regulated in non seminomatous germ cell tumours – A preliminary report

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Summary. Immunostaining of Cx26 and Cx43 was performed in the testicles of 12 patients with non seminomatous germ cell tumours. Seminiferous tubules were screened for expression of connexins, spermatogenetic activity and tumour cells. Overexpression of Cx26 and loss of Cx43 immunostaining was observed in all seminiferous tubules of all radical orchidectomy specimens exhibiting spermatogenetic arrest and/or tumour cells. Cx26 was found to be up regulated in focal areas of seminiferous tubules in the contralateral testicle irrespective of normal or impaired spermatogenesis. This finding indicated early dysfunction in intercellular communication in the contralateral testicles.

Introduction. Cx43 is the most abundant connexin in the normal testicle and is responsible for differentiation of Sertoli cells and spermatogenesis [1].

Down regulation of Cx43 was reported in various pathological conditions including CIS and germ cell tumours [2–4]. Seminiferous tubules presenting with spermatogenetic arrest and/or infiltration of CIS only were reported to exhibited down regulation in Cx43 and strong up regulation in Cx26. Hypothetical, dysfunction in intercellular communication may promote proliferation of CIS and progress to invasive malignancy.

These reports gave rise to further analyse testicular immunostaining of connexin 43 and 26 in patients with non semi-

Cx 26

Cx 43

Fig. 1. Expression of Cx 26 and Cx 43 contralateral testicle (intact spermatogenesis)

nomatous germ cell tumours in radical orchidectomy specimens and biopsies of contralateral testicles.

Patients and methods. Cx43 and Cx26 expression was analyzed in 12 patients (age: 21–44 years) with non seminomatous germ cell tumours (stages: pT 1–3). Testicular biopsies of 11 azoospermic males with ductal obstruction served as controls.

Testis tissue was fixed by immersion in 4% buffered formaldehyde solution and embedded in paraffin wax. Immunostaining of Cx26 and Cx43 was performed on deparaffinized sections using monoclonal antibodies against Cx43 (Chemicon, UK) and Cx26 (Zymed, USA). The Labvision polymersystem and Chromogen DAB were administered for detection.

Seminiferous tubules were screened for immunostaining of Cx43 and Cx26, spermatogenetic disorder and infiltration by malignant cells.

Results. All control samples were positive for Cx43 immunostaining between Sertoli cells and between Leydig cells. Expression of Cx26 was found to be weak or negative.

In patients with germ cell tumours immunostaining of Cx43 was positive in the majority of seminiferous tubules uninvolved by the neoplastic process. In contrast, Cx43 was found down regulated and Cx26 strongly overexpressed in tubules exhibiting infiltration by tumour cells and/or spermatogenetic arrest at the spermatogonial stage.

Seminiferous tubules in the contralateral testicles were positive for Cx43. However, in focal areas seminiferous tubules yielded a shift in the expression of Cx43 towards Cx26 independent of spermatogenetic activity (Fig. 1).

Discussion. Cx43 is expressed intratubular between Sertoli cells and Sertoli-spermatocyte gap junctions and between Leydig cells. Gap junctional intercellular communication is important for growth control and the role of connexins to act as tumour suppressor has been accepted.

Connexins are essential for fertility. Replacement of Cx43 by Cx26 in transgenic mice prevented maturation of germ cells beyond the stage of primary spermatocytes [5, 6]. Hypospermatogenesis revealed a staining pattern of Cx43 similar to that of normal adult testicles. Seminiferous tubules exhibiting spermatogenetic arrest at the level of spermatogonia or Sertoli cell only syndrome were found to be completely immunonegative of Cx43 [7].

There is further evidence that germ cell tumours are associated with changes in connexin expression. Down regulation of Cx43 and up regulation of Cx26 were previously reported in men with CIS or classical seminomas indicating a

disruption of intercellular communications. These changes are discussed in the view of promotion of proliferation of CIS and progress to invasive malignancy [4].

A shift of Cx43 towards Cx26 expression was found in the ipsi- and contralateral testicles of patients with non seminomatous germ cell tumours. Obviously, a focal up regulation of Cx26 and down regulation of Cx43 independent from spermatogenetic activity reveals evidence of early dysfunction in intercellular communication in the contralateral testicle.

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Bacterial colonization of two different antiseptic-impregnated central venous catheters (CVC) in a rabbit model

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Purpose of the investigation: Central venous catheters (CVC) are indispensable in modern-day medical practice, particularly in intensive care units (ICUs). Their use puts patients at risk for local and systemic infectious complications. Catheter-related bloodstream infections (CRBSI) are most commonly caused by coagulase-negative staphylococci. Catheters coated with chlorhexidine/silversulfadiazine (CSS) on the external luminal surface have been studied as a means to reduce CRBSI. The latest development is a CVC coated with the antiseptic agent polyhexamethylene-biguanide (PHMB)

In this study, we compared the bacterial colonization rates of a standard CSS-CVC with a novel PHMB-CVC in an in-vivo rabbit model.

Basic procedures: 24 standard, single lumen CSS-CVC (Arrowguard blue®, Arrow Inc, Reading, USA) and 23 novel

PHMB-CVC were tested in an in-vivo model using implantation of catheters into the internal jugular veins of rabbits. The bacterial inocula were prepared by culture of *Staphylococcus epidermidis* DSM 3269. Before insertion, the CVC were incubated for 14 hours in the inocula.

A total of 47 male rabbits were used in this study. The study protocol was approved by the local government. The animals were randomly allocated to receive an impregnated CSS-CVC or PHMB-CVC. Under anaesthesia, the catheter was implanted into the jugular vein. The catheters were flushed with 1 ml of the bacterial inocula. The external end of the catheters were locked and fixed in a subcutaneous tunnel.

At day seven after surgery, the animals were sacrificed under anaesthesia. The catheters were removed. The bacterial colonisation to catheter segments was determined by the quantitative culture technique.

Main findings: The mean bacterial colonization of the CSS-CVC was $5,63 \times 10^3$ CFU / 2 cm (colony forming units per 2 cm). In comparison, the mean colonization of the PHMB-CVC was considerably larger ($2,68 \times 10^4$ CFU / 2 cm). The results were also statistically significant (Mann-Whitney-U-Test, $p < 0.05$).

Principal conclusions: PHMB-CVC showed a lower intravascular antimicrobial effect against *Staphylococcus epidermidis* in the rabbit model in comparison to CSS-CVC.