Monitoring in the Intensive Care Unit: Its Past, Present, and Future

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Editorial

Monitoring in the Intensive Care Unit: Its Past, Present, and Future

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Received 27 June 2012; Accepted 27 June 2012

Monitoring in the critical care setting has dramatically improved during the past 50 years and has contributed significantly to improve patients’ safety and outcome [1–3]. New technologies have allowed the transfer of advances in biology, physiology, and bioengineering to the bedside to support data driven decision making and continuous monitoring of the vulnerable critically ill patients. The most striking advances include the continuous and noninvasive measurement of oxygen saturation by pulse oximeters and of end tidal CO2 and the real-time displays of flow, volume, pressure time curves, and derived measures by modern ventilators as well as the development invasive and more recently noninvasive devices that provide beat-to-beat arterial pressure, stroke volume, and cardiac output monitoring.

Despite these advances and the apparent impact made on patients’ outcome, there are still a lot of progress to be made to bring monitoring to the level of safety and reliability achieved by industries such as aviation [3, 4].

The future of monitoring in the critical care setting probably relies less on global appraisal of descriptive variables and more on functional monitoring of organs. Ultimately monitoring complex organ function is more informative and will likely be more important than global and/or regional physiological parameters such as organs perfusion and oxygenation. Metabolic monitoring, reflecting the biologic functions of the organs, starts to emerge [5]. Noninvasive monitors and trend analysis will obviously continue to grow. In addition, more advanced monitoring of pain, sleep, wakefulness, and delirium are very much needed. At the end of the day, decision support systems and automated system will become instrumental and central in daily monitoring when such system can provide the high level of accuracy needed to allow health care providers to rely on them [6, 7]. In addition, decision support systems will only make sense if they improve clinicians’ decision making, not if they just synthesize clinical algorithms. We expect that decision support software that integrates monitoring signals to raise the safety, reliability, and efficiency bar and not to fully replace human being. Finally, there is still a lot to be learned regarding identifying which variables should be monitored to impact outcome and what constitute an appropriate as oppose to pathological harmful one to critical illnesses. Without such understanding, enhanced monitoring has the potential to lead to costly and counterproductive interventions.

Finally, one has to ask whether new monitoring technologies must be evaluated and clearly demonstrate a positive impact on outcome before being used. There is no easy and universal answer to this question, we believe. Most hospital administrators may require outcome data before purchasing any new and potentially expensive technologies. This approach could, however, delay the implementation of useful technologies. It is indeed possible and likely that initial studies, even when well conducted, could only show no impact on outcome [8]. As an example, the pulse oximeter has been shown to have no impact on patients outcome [9, 10] despite the fact that this is considered standard of care. While some in the medical community are still wondering...
whether pulse oximeters do improve outcome since the data is lacking, in other industries such as aviation evidence-based data before implementing new technologies (monitors, autopilot, simulation) is not required and this industry has now reached an unmatched level of safety. On the other end, a more thoughtful assessment of clinical indication and physician education of physicians regarding Swan-Ganz catheter and hemodynamic management would have prevented many unhelpful right heart catheter placement over decades and possible harm. Clearly, there is not a single simple answer for every technology and/or problem at hand.

In conclusion, monitoring in our specialty has come a long way. We are, however, still facing difficult challenges and the future holds great promises for our patient [3], particularly if, as an scientific community, we can learn from our past mistakes. This special issue on monitoring of critical patients illustrates some of the current and future challenges we are facing.

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References


Review Article

Monitoring in the Intensive Care

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Received 7 May 2012; Accepted 21 June 2012

Academic Editor: Daniel De Backer

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In critical care, the monitoring is essential to the daily care of ICU patients, as the optimization of patient’s hemodynamic, ventilation, temperature, nutrition, and metabolism is the key to improve patients’ survival. Indeed, the decisive endpoint is the supply of oxygen to tissues according to their metabolic needs in order to fuel mitochondrial respiration and, therefore, life. In this sense, both oxygenation and perfusion must be monitored in the implementation of any resuscitation strategy. The emerging concept has been the enhancement of macrocirculation through sequential optimization of heart function and then judging the adequacy of perfusion/oxygenation on specific parameters in a strategy which was aptly coined “goal directed therapy.”

On the other hand, the maintenance of normal temperature is critical and should be regularly monitored. Regarding respiratory monitoring of ventilated ICU patients, it includes serial assessment of gas exchange, of respiratory system mechanics, and of patients’ readiness for liberation from invasive positive pressure ventilation. Also, the monitoring of nutritional and metabolic care should allow controlling nutrients delivery, adequation between energy needs and delivery, and blood glucose. The present paper will describe the physiological basis, interpretation of, and clinical use of the major endpoints of perfusion/oxygenation adequacy and of temperature, respiratory, nutritional, and metabolic monitorings.

1. Central Hemodynamic Monitoring

1.1. Introduction. In critical care, the optimization of patient’s hemodynamic and temperature is the key to improve patient morbidity and mortality. The goal of hemodynamic monitoring is to provide data that aids in the optimization of end organ tissue oxygenation and effectively combats global tissue hypoxia, shock, and multiorgan failure. Traditional, noninvasive methods of hemodynamic monitoring pertained solely to physical examination, and invasive methods included central venous and pulmonary artery catheterization mostly. These pressure-derived preload values have been used extensively in the management of fluid resuscitation and titration. However, numerous studies of various patient populations (sepsis, cardiovascular surgery, trauma, and other critical illnesses) have challenged the notion that these indicators accurately predict volume status [1–7]. These “static” pressure-derived values do not accurately identify a position on the Starling curve and, therefore, poorly predict whether volume will improve hemodynamics. In fact a recent meta analysis showed no positive association between PAC use for fluid management and survival [8].

Recently, however, technologic advancements in this area have introduced new methods of noninvasive and less invasive hemodynamic monitoring. Generally, this data provides insight into the fluid status of the patient by indicating where the patient is on the Frank-Starling curve (preload) and may also provide insight into cardiac output,
myocardial contractility, systemic vascular resistance, and more novel parameters related to the pulmonary vascular system. This chapter seeks to provide an overview of these new technologies and its implication in the critical care setting.

1.2. Macrocirculation Monitoring. Identification of patients who are on the steep part of frank starling curve and therefore are fluid responsive is a core principle of hemodynamic monitoring and aids in the determination of the extent that circulatory homeostasis can be maintained with fluids alone, versus the need for inotropes or vasopressors. Similarly the continuous assessment of cardiac output, myocardial contractility, and vascular tone is crucial to the diagnosis and management of critically ill patients, and this has long been solely provided by the PAC catheter. Recently, however there are new technologies that may provide this information in a less invasive or completely noninvasive manner.

1.2.1. Pulse Contour Analysis. The concept of pulse contour analysis is a method of ascertaining the cardiac output from analyzing of the pulse pressure waveform. It is known that the pulse pressure is directly proportional to stroke volume and inversely related to vascular compliance. Also it is known that the pulse pressure waveform depicts the changes in stroke volume that occur with positive pressure ventilation. Specifically, during the inspiratory phase of positive pressure ventilation, intrathoracic pressure increases passively, increasing right atrial pressure and causing venous return to decrease, decreasing right ventricular output, and after two or three heart beats affecting left ventricular output. Monitoring this stroke volume variation has shown to accurately predict patients who are fluid responsive [9]. A large pulse pressure/stroke volume variation (10% to 15%) is indicative of hypervolemia and predictive of volume responsiveness.

There are several technologies that use pulse contour analysis; these include the FloTrac, PiCCO, and LiDCO plus systems. These systems differ in their modality to assess for vascular tone their requirements for invasive monitoring and need for external calibration for CO measurements. A short discussion of each of these devices is in the following.

1.2.2. The Vigileo/FloTrac System. The FloTrac has a proprietary software algorithm that analyzes characteristics of the arterial pressure waveform and uses this analysis, along with patient-specific demographic information, to determine continuous CO, systemic vascular resistance, and the dynamic parameter of stroke volume variation. It carries the advantage of being able to be used for any arterial catheter in any arterial location. In addition, the device self-calibrates were based on patient demographics and waveform analysis. Differences in patient populations, study environments (intraoperative, postoperative, nonsurgical), FloTrac software versions, ventilatory settings, medical interventions, and reference standard(s) used (intermittent thermodilution CO, continuous thermodilution CO, esophageal Doppler, PiCCO), combined with the relatively small single center studies, are all central to this issue. Newer FloTrac software versions have improved the accuracy of the system’s ability to determine CO.

1.2.3. LiDCO Plus System. This system also uses analysis of pulse contour from an arterial line to determine stroke volume and CO. However, the main difference is that this system uses a lithium-based dye-dilution technique to calibrate its pulse contour analysis algorithm, referred to as Pulse CO. After calibration, the LiDCO plus system can generate CO measurements using pulse contour analysis; however recalibration is recommended every 8 hours.

1.2.4. The PiCCO System. Like the LiDCO and FloTrac systems, this device provides CO through pulse contour analysis of the arterial waveform. It also requires an external calibration (cold saline) for this analysis. The PiCCO monitor provides several other measurements as well including global end-diastolic volume measurements of all four heart chambers as well as extravascular lung water measurements. One of the limitations of this technology is the requirement for proximal artery catheterization with a thermistor-tipped catheter [10]. As with the other pulse contour technologies previously described, periods of significant hemodynamic instability result in potentially intolerable inaccuracies in CO measurement requiring frequent recalibration [11]. Once again, small single center studies, different settings, and different standards of reference make generalizations difficult.

1.2.5. Esophageal Doppler. The esophageal Doppler is a flexible probe that has a Doppler transducer (4 MHz continuous wave or 5 MHz pulsed wave, according to manufacturers) at the tip that is placed in the esophagus to obtain an aortic velocity signal in the descending aorta. The technology allows one to gain insight into preload by looking at the flow time of the velocity time integral (VTI) of the aortic flow (normal = 330–360 msec), with states of decreased preload shortening the flow time. Also it quantifies myocardial contractility by assessing the peak velocity of the aortic VTI signal (normal > 70 cm/sec). Finally, this technology derives vascular tone by analysis of the VTI waveform. A meta-analysis Dark and Singer demonstrated an 86% correlation between cardiac output as determined by esophageal Doppler and PAC [12]. Clinical studies comparing TED guided protocols to conventional approaches of volume replacement (guided by clinical assessment and/or central venous pressure) conclusively report beneficial effects in the Doppler-optimized groups, including a reduced risk of postoperative morbidity and a shorter length of hospital or ICU stay [13–20]. However, the resulting waveform is highly dependent on correct positioning and requires frequent adjustments in depth, orientation, and gain to optimize the signal [21]. Therefore, while esophageal Doppler has some utility in aiding in the assessment of the hemodynamic status of critically ill patients, this technology has been slow to be adopted. This is likely secondary to high amount continuous user involvement needed to produce accurate data.
1.2.6. Thoracic Electrical Bioimpedance. Using low voltage, electrical impedance (or resistance) across the chest is measured. The higher the fluid content, the lower the impedance since fluid conducts electricity. As the volume of blood in the thorax changes during the heart cycles through systole and diastole, these variations can be measured electrically [22]. Many of the problems associated with TEB have been overcome with newer generation devices. Recently, a number of investigators have reported a good correlation between TEB and thermodilution in patients following cardiac surgery using these improved devices [23–28]. There are limited data on the use of TEB in critically ill ICU patients; however, the improved TEB technology does hold promise in this group of patients.

1.2.7. Echocardiography. Recent advances in point of care ultrasound devices have tremendously increased the utility of echocardiography in the critical care setting. The benefit of echocardiography lies in the fact that it allows the clinician to directly visualize the cardiac anatomy as well assess flow dynamics and thus rapidly assess structural abnormalities, contractility, and intravascular volume. While historically echocardiography has required extensive specialty training, recent literature supports the ability to train noncardiologist to perform and interpret a limited transthoracic echocardiography exam [29, 30]. Recently, guidelines have been published for POC cardiac ultrasound by noncardiologists for the intensive care setting [30]. Some of key points from these guidelines include (1) CVP estimate via inferior vena cava (IVC) diameter and its response to respirations, (2) estimation of preload via right and left ventricular end diastolic diameters, (3) assessment of RV/LV function via fractional area change and detection of regional wall motion abnormalities, (4) recognition of pericardial effusion and tamponade, and (5) global assessment of valvular function via color Doppler interrogation.

In summary, no device stands out as being better than another and although not perfectly accurate, all the devices are able to detect alterations in cardiac output. Therefore, the true benefit lies with correct application of these devices by understanding the technology as well as the limitations for each device.

2. Peripheral Hemodynamic-Tissue Perfusion Monitoring

Shock is defined as “inadequate tissue oxygen for aerobic cellular respiration.” Therein lie the issues of shock management: the relationship between oxygen delivery and perfusion, the issues of mitochondrial dysfunction and lactate, and the issue of inadequate delivery to demand. Shock results from varying macrocirculatory and microcirculatory failure leading to hypoperfusion. Additionally, mitochondrial dysfunction may result in cellular oxygen misuse. Furthermore, stress and physiological compensation increase oxygen demand in situations of poor delivery. This oxygen delivery and demand inadequacy compound organ failure and can ultimately result in death despite optimal management.

Shock management has included “restoring” or “maximizing” oxygen delivery and tissue oxygenation, albeit with varying results. A meta-analysis [31] showed that mortality decreased and oxygen delivery increased when management was guided by endpoints such as central venous pressure (CVP), mean arterial pressure (MAP), cardiac output (CO), cardiac index (CI), oxygen transport (TO2), and central or mixed venous oxygen saturation (ScvO2 or SvO2).

Rather than a “holy grail” endpoint, the past decade has been marked by the early goal directed therapy (EGDT) approach of Rivers [32]. EGDT is based upon sequential endpoints: CVP >8 mmHg, subsequent norepinephrine management to MAP >65 mmHg, followed by a global endpoint, ScvO2, to assess oxygen delivery adequacy. A >5% drop in ScvO2 led to Hb level assessment/transfusion, CO assessment/inotropes, or intubation, ventilation, and sedation to decrease O2 demand. Interestingly, EGDT led to increased fluid loading, blood transfusion, and inotropes. Regardless of controversies [33], EGDT has been integrated into many studies, recommendations, and other settings such as high-risk surgery [34–36].

However, impaired oxygen extraction in sepsis and altered flow impede the use of ScvO2 to assess adequate tissue perfusion/oxygenation [37], and high ScvO2 can coexist with hypoperfusion [38]. Therefore, beyond restoring ScvO2 >70%, judging tissue perfusion may require other parameters such as lactate clearance or venoarterial PCO2 gradient and/or the visualization of microcirculation.

2.1. Microcirculation Monitoring. An important subject characterizing critically ill patients is that capillary circulation cannot be predicted by macrohemodynamic parameters. As depicted in situations like septic shock [39, 40] or heart failure [41], despite an optimal macroperfusion (blood pressure, cardiac output, etc.), microcirculatory perfusion could be inadequate [42] and capillary flow severely altered and responsible for a persistent tissue ischemia. Using Sidestream dark-field (SDF) imaging [43], microcirculatory flow can be visualised at the bedside, noninvasively, in different tissue regions (sublingual, rectal mucosa, etc.). Hence, microcirculatory assessment becomes a part of the global hemodynamic evaluation in critically ill patients, since patient standard of care could be influenced. However, it is important to highlight that microcirculatory monitoring with SDF could be difficult as it has its own limitations regarding measurement errors [44]. As example, different recordings of 20 seconds should be performed in different locations and microcirculatory quantification should be based on the average of multiple recordings, each being performed by two independent investigators. Indeed, sometimes the result presented (MFI, capillary density, etc.) must be taken with caution for the present semiquantitative technique. Optimistically, in the future, new technology and measurement method should be developed to allow rapid, accurate, and reproducible assessment of capillary perfusion at the bedside.

2.2. Gastric Tonometry and Sublingual Capnography. It is a known phenomenon that early on in hemodynamic
stressed states there is a flow distribution away from the gastrointestinal tract, resulting in an increase in the PCO₂ of the stomach wall. It is assumed that the increased gastric mucosal CO₂ leading to gastric mucosal acidosis is a result of anaerobic metabolism consequent to splanchnic hypoperfusion. Previous studies indicate that gastric tonometry is a highly sensitive predictor of outcome in patients undergoing cardiac surgery [45], admitted to the ICU [46], in sepsis [47], or with acute circulatory failure [48]. However, the widespread application of gastric tonometry has proven to be practically difficult. While these studies support the importance of assessing gastrointestinal perfusion, there are several limitations to gastric tonometry that impede its clinical implementation. First gastric tonometry relies on the concept that intraluminal gut CO₂ will be elevated when local perfusion is compromised secondary to resulting anaerobic cellular metabolism from reduced oxygen delivery. In addition, the concept has yielded a very poor specificity secondary to multiple confounders such as inappropriate measurement of stomach content PCO₂, temperature (Haldane effect) buffering of gastric acid by duodenal/esophageal reflux, difference in arterial supply, and enteral feeding.

Recently sublingual capnometry has been introduced as a method of resolving many of these difficulties associated with gastric tonometry. Sublingual capnometry is a technically simple, noninvasive, inexpensive technology that has been shown to provide insight into the adequacy of tissue perfusion during both hemorrhagic and septic shock [37, 49, 50]. Further studies with this technology, however, are needed that demonstrate the clinical utility of PsICO₂ monitoring.

2.3. Tissue Oximetry. The assessment of end organ oxygenation may be of value when caring for the critically ill patient. Previous studies have shown that impaired tissue oxygenation events are not easily detected by usual monitoring of heart rate, urine output, central venous pressure (CVP), cardiac output (CO), and blood pressure (BP) [51, 52] secondary to compensatory autonomic mechanisms, such as regional vasoconstriction. Based on this concept one may be able to detect these compensatory stress states by assessing the microcirculatory status, such as the noninvasive measurement of tissue oxygen saturation (StO₂) when coupled with a functional hemodynamic monitoring test, such as the vascular occlusion test (VOT). Noninvasive measurement of StO₂ using near infrared spectroscopy (NIRS) has been shown as a valid method to assess the microcirculation status, especially in septic and trauma patients [53]. The addition of dynamic ischemic challenge in which VOT is utilized has shown to improve the predictability of StO₂ to identify tissue hypoperfusion [54].

Similarly, the ability to continuously assess oxygen delivery to organs supplied by the splanchic circulation may be of critical importance since blood flow abnormalities to this region are associated with a range of morbidities, perhaps most notably multiple organ failure that can lead to death [51]. Markers such as mixed venous saturation (SvO₂) and serum lactate levels are markers of global oxygen supply and demand and may be a poor reflection of splanchnic regional oxygen delivery and regional tissue viability [51, 55–57]. One can postulate that detection of decreased splanchnic circulation by monitoring oxygen delivery to an organ system supplied by the splanchic circulation would allow treatment of the causative physiologic state before more systemic measures (SvO₂, lactate, HR, UOP, BP, CVP) are affected. Preliminary data with an esophageal probe T-STAT 303 (Spectros Corporation, Portola Valley, CA, USA) utilizing visible light spectroscopy (VLS) has shown positive results with its ability to detect ischemia to the splanchic bed [58, 59].

2.4. Mixed Venous or Central Venous Oxygen Saturation (SvO₂/ScvO₂)

2.4.1. SvO₂ and Oxygen Extraction. In normal SaO₂ and Hb conditions, SvO₂ should be >70%. During effort, oxygen uptake increases with transport. The oxygen transport (TO₂) and uptake (VO₂) relationship is defined by the extraction ratio of oxygen (ERO₂):

$$\text{ERO}_2 = \frac{\text{VO}_2}{\text{TO}_2}$$

(1)

Through transformations

$$\text{ERO}_2 = \frac{\text{CO} \times (\text{CaO}_2 - \text{CvO}_2)}{\text{TO}_2},$$

$$\text{ERO}_2 = \frac{\text{CO} \times (\text{CaO}_2 - \text{CvO}_2)}{(\text{CO} \times \text{CaO}_2)},$$

$$\text{ERO}_2 = \frac{(\text{CaO}_2 - \text{CvO}_2)}{\text{CaO}_2},$$

$$\text{ERO}_2 = 1 - \frac{\text{CvO}_2}{\text{CaO}_2},$$

$$\text{ERO}_2 = 1 - \frac{\text{SvO}_2}{\text{SaO}_2},$$

$$\text{ERO}_2 = \frac{1}{\text{SaO}_2} - \text{SvO}_2.$$ (2)

The resulting equation is

$$\text{SvO}_2 = \frac{1}{\text{SaO}_2} - \frac{\text{ERO}_2}{\text{SaO}_2}.$$ (3)

When arterial oxygenation is achieved, SaO₂ is 100%:

$$\text{SvO}_2 = 1 - \text{ERO}_2.$$ (4)

Thus, normal SvO₂ values of 70–75% correspond to normal ERO₂ of 25–30% delivered oxygen. Oxygen extraction depends on activity, tissue, and mitochondrial function. During effort, increased oxygen demand leads to increased extraction and decreased SvO₂. While SvO₂ normally drops to 60% through ERO₂ increase to 40%, SvO₂ may drop to 40% with ERO₂ reaching up to a maximum of 60%. If this ERO₂MAX is reached, any further demand leads to anaerobic lactate production. This maximal “critical ERO₂” corresponds to a “critical SvO₂” of 40% below which inadequate transport-to-demand, and therefore shock, is inevitable [60].
2.4.2. Interpreting SvO2. SvO2 is the net result of pathophysiological processes and therapeutic compensations of VO2 and TO2 (Table 1). Before ascribing ScvO2 decrease to VO2 increase and decreasing it, all causes of TO2 increase (decreased SaO2, Hb, or CO) must be considered and managed. Conversely, before ascribing a decrease in SvO2 to decreased TO2 and increasing it, causes of increased VO2 (pain, stress, and fever) should be considered and managed. Of note, ScvO2 is more easily obtainable from a central line placed in the superior vena cava (rather than a right cardiac catheter for SvO2) and correlates well with SvO2 [61]. Thus, decreased ScvO2 in shock, once increased VO2 has been managed, reflects increased ERO2 compensating for decreased TO2, which must be explored. These are the principles underlying EGDT [32].

Increased ScvO2 may reflect two situations: either an increase in TO2 relative to VO2, in a successfully optimized, stabilized, or recovering patient, or a decrease in VO2 relative to TO2, due to mitochondrial dysfunction [62].

These issues highlight that (1) decreased ScvO2 is a marker of inadequate global oxygenation which can only be interpreted by taking into account factors related to VO2 increase on one hand and TO2 decrease on the other and (2) “normal” ScvO2 is not a reliable marker of adequate oxygen transport-to-demand when oxygen uptake may be impaired.

2.4.3. ScvO2 and Perfusion. Oxygenation cannot be dissociated from perfusion. Indeed, when global perfusion is decreased due to decreased CO, all circulations have low flow and decreased TO2 relative to VO2 resulting in decreased ScvO2. However, while ScvO2-guided therapy reduced mortality in septic shock, 30% mortality remained, due to multiorgan failure with hypopuffer[32]. The most likely reason for this discrepancy is the inability of ScvO2 to explore locoregional or microcirculatory perfusion. Indeed, perfusion heterogeneity, such as in septic shock [63], will lead to hypoxia in tissue surrounding nonperfused capillaries [64]. However, capillaries remaining perfused will receive additional shunted flow from nonperfused capillaries, and, since surrounding oxygen consumption is unchanged, resulting net venous capillary oxygen saturation will be a mix of highly saturated from open capillaries and low saturations from closed capillaries (Figure 2), with a normal net ScvO2.

This also occurs locally with some circulations hypoperfused while contributing little desaturated blood to venous return, and others maintained through macrocirculatory optimization contributing much overly saturated venous blood, again resulting in a net normal ScvO2 despite overt or occult hypopuffer[32].

Therefore, ScvO2 cannot see local/microcirculatory hypopuffer[32], and normal ScvO2 should not be considered the ultimate endpoint [65].

2.5. Lactate Clearance. Glycolysis produces pyruvate, which either enters aerobic mitochondrial respiration requiring oxygen or, in tissue hypoxia, is transformed into lactate metabolized by the liver, kidneys, and skeletal muscle. In low flow, increased lactate is related to tissue hypoxia by hypopuffer[66, 67]. In sepsis, increased glycolysis and increased production by the gut, lung or even white blood cells are thought to participate in nonhypoxic lactate increase [68]. Regardless of metabolism [68] and catecholamine effects on lactate metabolism [69], lactate clearance seems a useful endpoint.

De Backer et al. studying local sublingual capillary perfusion in patients with septic shock showed that lactate clearance was correlated to capillary reperfusion following dobutamine independently of cardiac index, arterial pressure, systemic vascular resistance, or VO2 [70]. Lactate clearance may therefore reflect occult hypopuffer[32]. Indeed, persistent hyperlactatemia has been considered to reflect occult hypopuffer[32] in studies showing associated with poor prognosis and hypopufferation-related complications in trauma [71, 72], cardiac arrest [73, 74], septic shock [75, 76], and high-risk surgery [77]. Therefore, lactate clearance has repeatedly been proposed as a resuscitation endpoint, additional or alternative to ScvO2.

Simultaneous ScvO2 and lactate clearance were also measured in a study of 203 patients with septic shock in which reaching only the ScvO2 goal was inferior to reaching only the lactate clearance goal [78]. This suggests that ScvO2 and lactate clearance must be used hierarchically. Interestingly, Rivers participated in a noncomparative study prior to EGDT in which both ScvO2 and lactate clearance were used as subsequent endpoints and allowed a low mortality rate of 14% [79].

In the largest RCT comparing two EGDTs in septic shock, Jones et al. showed that ScvO2 or lactate clearance performed similarly and concluded that lactate clearance could be used instead of ScvO2 [80].

However the real question is not whether lactate clearance should replace ScvO2, but if it should be an additional endpoint. Strikingly, while Jones et al. did not find any difference when replacing ScvO2 by lactate clearance, Nguyen et al., in a study of sepsis bundles, showed that by adding lactate clearance to ScvO2, mortality decreased even further from 24.5% to 17.9% [75].

2.6. Venous-to-Arterial CO2 Gradient

2.6.1. CO2 Production and Transport Physiology. CO2 is a byproduct of oxidative metabolism. Tissue production of CO2 (VCO2) is related to oxygen uptake:

\[ VCO_2 = R \times VO_2 \]  (5)

in which R is the respiratory quotient which ranges from 0.7, for pure fat, to 1.0, for pure carbohydrate, as is usually the case in patients with shock; therefore,

\[ VCO_2 = VO_2 \]  (6)

\[ VCO_2 = CO \times (CaCO_2 - CvCO_2) \]  (7)

\[ VCO_2 = CO \times k \times P(v-a)CO_2 \]  (8)

in which P(v-a)CO2 is the venoarterial PCO2 gradient and k the coefficient between CO2 concentrations and partial pressures.
Table 1: ScvO2 variations related to causes of TO2 and/or VO2 variations.

<table>
<thead>
<tr>
<th>Increased VO2</th>
<th>ScvO2 &lt; 70%</th>
<th>Decreased TO2</th>
<th>Decreased VO2</th>
<th>ScvO2 &gt; 75%</th>
<th>Increased TO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Pain</td>
<td>(i) Anemia</td>
<td>(i) Analgesia, sedation, anesthesia</td>
<td>(i) High Hb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) Anxiety</td>
<td>(ii) Hypoxemia</td>
<td>(ii) Anxiolytics</td>
<td>(ii) Supplemental oxygen ventilation/high FiO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) Fever</td>
<td>(iii) Low CO</td>
<td>(iii) Hypothermia</td>
<td>(iii) High CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iv) Shivering</td>
<td>(iv) Hypovolemia</td>
<td>(iv) Muscle paralysis</td>
<td>(iv) Mitochondrial dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(v) Polypnea</td>
<td>(a) Relative</td>
<td>(v) Mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(vi) Respiratory distress</td>
<td>(b) Absolute</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(vii) Increased work of breathing</td>
<td>(2) Vasoplegia</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

ScvO2: central venous oxygen saturation; VO2: oxygen consumption; TO2: oxygen transport; CO: cardiac output; Hb: hemoglobin; FiO2: inspired oxygen fraction.

Figure 1: Capillary SvO2 and perfusion. (a) Schematic representation of the circulation (arterial in red, venous in blue, R.A: right atrium, L.A: left atrium, R.V: right ventricle, L.V: left ventricle, I: intestine, L: liver) and a generic capillary bed. (b) Schematic representation of both a hypoperfused capillary (lower dashed line) and normally perfused capillary (upper continuous line) receiving increased perfusion redistributed from the hypoperfused capillary. Following normal oxygen consumption by the tissues adjacent to the capillaries, SvO2 in each capillary is specified as is the resulting SvO2 downstream of the heterogeneously perfused capillaries.
2.6.2. Determinants of $P(v-a)CO_2$. The previously mentioned Equation (a) can be transformed:

$$P(v-a)CO_2 = \frac{VCO_2}{(CO \times k)} .$$  

(b)

Therefore, the venoarterial PCO$_2$ gradient is proportional to VCO$_2$, itself inversely proportional to the CO$_2$ clearance from tissues (washout), Given its diffusible nature CO$_2$ washout depends mainly on cardiac output (CO) and tissue perfusion. The determinants of P(v-a)CO$_2$ are therefore VCO$_2$, CO, and tissue perfusion (Figure 1(c)).

CO$_2$ washout is so dependent upon flow that any situation of local or regional low flow due to decreased local perfusion (Figure 1(a)) eventually compounded by decreased cardiac output will (1) increase tissue stagnation of CO$_2$ (Figure 1(b)), and (2) increase diffusion of CO$_2$ from hypoperfused tissue to venous capillaries with residual minimal flow (Figure 1(b)), leading to an increase in P(v-a)CO$_2$ $>6$ mmHg (Figure 1(c)).

Teboul et al. demonstrated the role of cardiac output in CO$_2$ clearance in patients with chronic heart failure and low cardiac output in whom P(v-a)CO$_2$ $>6$ mmHg decreased to normal following dobutamine [81]. Vallet et al. demonstrated, in isolated-perfused canine hindlegs, that P(v-a)CO$_2$ increased in conditions of perfusion dependency [82]. This has also been shown through tissue-to-arterial PCO$_2$ differences correlated to hypoperfusion [83].

The relationship between P(v-a)CO$_2$ and cardiac output is curvilinear, with asymptotic VCO$_2$ isopleths (Figure 1(c)): increases in P(v-a)CO$_2$ occur when cardiac output decreases, and P(v-a)CO$_2$ remains normal when cardiac output is normal or increased. These are major issues for interpretation: (1) decreased cardiac output will increase P(v-a)CO$_2$ $>6$ mmHg independently of underlying hypoperfusion (pink area, Figure 1(c)); (2) increase in P(v-a)CO$_2$ $>6$ mmHg may unmask occult hypoperfusion only if cardiac output is normal or increased (orange area, Figure 1(c)). This second situation arises in resuscitated septic shock in which fluid loading and vasopressors have increased cardiac output without treating underlying septic hypoperfusion [84].

2.6.3. P(v-a)CO$_2$ Increase and Clinical Hypoperfusion. Mekontso-Dessap et al. studied 89 critically ill patients with normal cardiac index (IC = 3.65 ± 1.65 L/min/m²) seeking to discriminate patients with or without hypoperfusion defined as blood lactate $>2$ mmol/L. Neither SvO$_2$ nor mixed venous PaCO$_2$ was discriminant. However, increased P(v-a)CO$_2$ was correlated to increased blood lactate levels with an optimal cutoff at 6 mmHg [85].

This was also shown, by Creteur et al., in patients with resuscitated septic shock and normal cardiac index (IC = 3.6 ± 0.6 L/min/m²) using in vivo sublingual microcirculation imaging and sublingual tonometric assessment of PCO$_2$, in which sublingual PCO$_2$-PaCO$_2$ difference was correlated to hypoperfusion and decreased with reperfusion following low-dose dobutamine [37]. Vallee et al. studied 56 patients with EGDT-resuscitated septic shock further resuscitated to decrease hyperlactatemia while maintaining ScvO$_2$ $>70\%$ [86]. Despite normal cardiac index, patients with increased P(v-a)CO$_2$ $>6$ mmHg had slower and lower lactate clearance and increasing organ failure than patients with normal P(v-a)CO$_2$.

This prognostic value of P(v-a)CO$_2$ was tested in high-risk surgery EGDT showing that ScvO$_2$ and P(v-a)CO$_2$ were correlated to postoperative complications [87]. Interestingly, complications undetected by “normal” ScvO$_2$ ($>70\%$) were detected by increased P(v-a)CO$_2$.

It appears that increased P(cv-a)CO$_2$ in resuscitated septic shock or high-risk surgical states may (1) reflect inadequate cardiac output, and, (2) in patients with normal/increased cardiac output, increased P(cv-a)CO$_2$ may reflect underlying occult hypoperfusion; (3) targeting P(cv-a)CO$_2$ $<6$ mmHg might be of benefit although it remains unclear how best to achieve this [84].

The future of perfusion monitoring may be comprehensive EGDT-like approaches integrating endpoints of global oxygenation such as ScvO$_2$, adequacy of cardiac output to perfusion such as P(cv-a)CO$_2$, global perfusion such as lactate clearance and local perfusion indices. All the clinical tools already exist; however, while some can be monitored continuously such as ScvO$_2$, others such as P(cv-a)CO$_2$ and blood lactate require repeated sampling and blood gas analysis. What remains in order to encourage development of tools for continuous perfusion monitoring through these parameters is to design and carry out studies implementing comprehensive, stepwise, multiple-endpoint, EGDT-like approaches.

3. Temperature Monitoring

Maintenance of normal body temperature is critical in the intensive care setting and should be regularly monitored. While assessment of core temperature is ideal, there are other sites that can be used in critically ill patients, and understanding the limitations of any device and the site monitored is essential for clinical decision making.

Indeed, numerous trials have shown that even mild hypothermia causes numerous adverse outcomes [88] including morbid myocardial outcomes [89] secondary to sympathetic nervous system activation [90], surgical wound infection [91, 92], coagulopathy [93, 94], delayed wound healing [91], delayed post-anesthetic recovery, prolonged hospitalization [47], shivering [95], and patient discomfort [96]. In this sense, it is also known that all general anesthetics produce a profound dose-dependent reduction in the core temperature secondary to impairment of normal thermoregulatory mechanisms, the largest culprit being core-to-peripheral redistribution of body heat.

Core temperature relates to the compartment that is composed of highly perfused tissues whose temperature is uniform. This fact makes that accurate measurement of this temperature has been shown in the pulmonary artery, distal esophagus, tympanic membrane, or nasopharynx [97, 98]. However each of these modalities has its limitations. Esophageal monitoring requires correct positioning at or
Figure 2: Venoarterial PCO2 gradient: relationship to cardiac output and capillary hypoperfusion. (a) Schematic representation of the circulation (arterial in red, venous in blue, R.A: right atrium, L.A: left atrium, R.V: right ventricle, L.V: left ventricle, I: intestine, L: liver) and a generic capillary bed. (b) Schematic representation of both a hypoperfused capillaries (dashed lines) and normally perfused capillaries (continuous lines) receiving increased perfusion redistributed from the hypoperfused capillary. CO2 builds up in the tissue adjacent to hypoperfused capillaries (gray cylinders). Due to its highly diffusible nature, accumulated CO2 from hypoperfused tissue diffuses to tissue adjacent to perfused capillaries which successfully “washout” this increased amount of CO2 leading to higher venous PCO2 than normal and therefore a vеноarterial PCO2 gradient, P(v-a)CO2, higher than the upper norm of 6 mmHg. (c) Relationship between P(v-a)CO2 and cardiac output (CO). P(v-a)CO2 decreases along an isopleth for a given metabolic production of CO2 (VCO2). For “normal” cardiac outputs over 4 L/min and normal VCO2 (green area), P(v-a)CO2 remains under the upper threshold of 6 mmHg. Decreased cardiac output below 4 L/min leads to increased P(v-a)CO2 due to insufficient “washout” regardless of capillary perfusion. P(v-a)CO2 increases over 6 mmHg in conditions of adequate cardiac output, and normal VCO2 is pathological and reflects capillary hypoperfusion (off-isopleth orange area).

below the position of maximal heart sounds if esophageal stethoscope is used. Nasopharynx (correctly placed a few cm past the nares) requires obstruction of airflow to prevent the air currents from cooling the thermocouple. Correct tympanic membrane monitoring may be difficult secondary to tortuous aural canal and also requires obstruction of airflow [88]. Finally pulmonary artery catheterization is a highly invasive procedure.

Since these sites are always available or convenient, a variety of “near-core” sites are also used clinically. These include the mouth, axilla, bladder, rectum, and skin surface, all of which have their own limitations. Oral temperature can be inaccurate secondary to recent PO intake and airflow. Axillary temperature may be accurate with correct positioning (over the axillary artery with the patients arm kept by their side) [99]. However difficulty with maintaining this position has limited its use [100]. Rectal temperature has shown to lag behind the core temperature sites and has shown to fail to increase appropriately during certain hyperthermic crises [88, 101–103]. Bladder temperature is strongly affected by urine flow, and it has shown to be equal to rectal temperature when urine flow is low, but equal to pulmonary artery temperature (and thus core) when flow is high [104]. Finally, skin temperature is considerably lower than core temperature [105]. For instance, forehead skin temperature is typically 2°C cooler than core [62], and this gradient may be increased in case of hypoperfusion.

4. Respiratory Monitoring of the Ventilated ICU Patients

4.1. Introduction. Monitoring of the respiratory system is integral to the daily ICU care of all ventilated patients. Such monitoring in its broader sense includes serial assessment of gas exchange, of respiratory system mechanics, and of patients’ readiness for liberation from invasive positive pressure ventilation. Tracking respiratory system changes over time may help minimize ventilator-associated complications, optimize patient-ventilator synchrony, and provide important clues regarding possible causes for alarm sounding
and/or changes in patients’ conditions. A prerequisite for such an approach is a good understanding of the physiology behind the variables being monitored.

Despite the importance of respiratory monitoring in ventilated ICU patients, this is not always performed as often or interpreted accurately particularly by some residents and younger colleagues. This is probably due to the general prejudice that some measurements are cumbersome to obtain and/or to interpret in part due to increased role of protocols and to the decreased understanding of physiology specifically at the bedside. Other measurements are taken for granted (e.g., pulse oximetry), and the limitations of the methods are not always taken into consideration. In this paper, our goal is to give a brief overview of key basic readily available parameters and the principles underlying their alterations. These parameters related to respiratory mechanics and gas exchange should be obtained at initiation of mechanical ventilation and at regular interval thereafter particularly in patients who are difficult to ventilate and oxygenate and require heavy sedation and paralysis. These patients have a higher risk of complications, and adequate monitoring becomes even more critical.

4.2. Basic Respiratory System Mechanics. While certain measures require an active patient (e.g., measure of respiratory muscle strength), most bedside measures and estimations of the respiratory system (RS) mechanics require a passive patient. Modern ventilators display real time pressure, volume, and flow time curves. Reviewing these curves daily is essential to assess whether the ventilator settings are safe and adapted to the patients’ conditions.

Partitioning the contribution of the lung from that of the chest wall to the RS mechanics would require measuring pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. Although this measure is not done routinely, understanding pleural pressures and placement of an esophageal probe. 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FRC and to decrease at high lung volume if the system becomes overdistended or at low lung volume with the loss of aerated unit (derecruitment). Changes in $C_{RS}$ may thus reflect change in the position of tidal ventilation relative to inflection points on the pressure volume curve and/or shift of curve. In conclusion, $C_{RS}$ therefore is helpful to size the tidal volume relative to the size of the baby lung and to track if recruitment, derecruitment, or overdistension may occur over time. The stress index proposed to monitor ARDS patients ventilated with constant flow using the shape of the pressure time curve applies the same principle to detect tidal recruitment and overdistension [109].

For a practical standpoint, measuring $C_{RS}$ can provide useful information to set tidal volume relative to the size of the lung. Tracking its change over time is helpful to alert the possibility that derecruitment, overdistension (decreasing $C_{RS}$), or recruitment (increased $C_{RS}$) is taking place. Everything else being equal, this can be done as often as needed by monitoring $P_{plat}$ as long as the patient remains passive and the ventilator settings are the same. $P_{plat}$ is an important variable that reflects alveolar pressure and is often used at the bedside to estimate the risk of ventilator-associated lung injury. $P_{plat}$ has been found to be associated with outcome in ARDS [110, 111]. Any significant change in $P_{plat}$ therefore warrants a thorough assessment of the patients using the principles outlined previously, and one has to incorporate in this process consideration for the pleural pressure.

4.4. Resistance of the Respiratory System. Flow ($Q$) and Pressure Drop ($AP$) across the airways are used to calculate the resistance $R_{RS} = Q/AP$. Since flow occurs during inspiration and expiration, resistance can be defined as $R_{RSI}$ and $R_{RSE}$.

By applying an inspiratory pause as indicated previously, airway pressure drops from its peak value ($P_{peak}$) to $P_{plat}$, and $P_{peak} - P_{plat}$ tracks the resistive pressure that must be overcome to deliver $V_T$ at a given flow. If flow during inspiration is known, $R_{RSI}$ can be easily calculated. More pragmatically, it is important at initiation of ventilation to measure $P_{peak}$ and $P_{plat}$ and to make note of the pressure difference between those two pressures to assess whether the patient may have abnormal airway resistance (large $P_{peak}$ to $P_{plat}$ difference), keeping in mind that an inappropriately high set flow rate or a small endotracheal tube may both increase this pressure difference. The initially recorded $P_{peak}$ and $P_{plat}$ difference will then allow one to monitor for any change in $C_{RS}$ and $R_{RSI}$ and to establish when facing a $P_{peak}$ pressure alarm (during volume controlled ventilation), if a $P_{peak}$ change is due to a compliance or resistance alteration. For instance, a sudden increase in peak pressures associated with a larger $P_{peak}$ to $P_{plat}$ difference is most consistent with an increase in resistance secondary to the native airway problem (e.g., bronchospasm) or partial obstruction of the artificial airways (e.g., ET tube kinked or obstructed by secretions.) In contrast, an unchanged $P_{peak}$ to $P_{plat}$ difference strongly supports a change in static $C_{RS}$ (e.g., tension pneumothorax, right main bronchus intubation, atelectasis, or pulmonary edema) as the cause of the $P_{peak}$ pressure alarm.

Expiratory flow and airway resistance vary with lung volume and flow decays exponentially in normal circumstances. The endotracheal tube, exhalation valve, heat moisture exchangers—when present—as well as the native airways all contribute to the expiratory resistance ($R_{RSE}$). A first important step is thus to identify the site responsible for any abnormal airway resistance. $R_{RSE}$ is a parameter that is neither easy nor necessary to measure routinely. What is always needed, however, is to recognize the presence of an abnormally high resistance, to identify and treat its cause, and to monitor and minimize its consequences. Consequence could be dynamic hyperinflation and auto-PEEP, which increases the work of breathing and the risk of barotraumas and/or hypotension [112]. Abnormally high expiratory flow resistance can easily be recognized by observing that the shape of flow time curve becomes biexponential (flow limitation) and that the expiratory phase is prolonged, and flow does not reach zero before the next tidal breath is delivered by the ventilator or initiated by the patient. The leads to dynamic hyperinflation auto-PEEP and commonly wasted inspiratory effort and asynchrony.

4.5. Dynamic Hyperinflation. As discussed previously, dynamic hyperinflation is important to monitor and recognize. Measuring auto-PEEP and $P_{plat}$ at the initiation of the ventilation and at regular intervals helps with the detection of dynamic hyperinflation. The pressure measured at the end of expiration when airflow is interrupted is termed total PEEP. Auto-PEEP is then calculated as the difference between total PEEP and extrinsic PEEP (PEEP set on the ventilator). Most modern ventilators have the capacity to measure auto-PEEP semiautomatically. Auto-PEEP may develop for a variety of reasons (e.g., airflow obstruction, high lung compliance, high minute ventilation, and whenever the ventilatory settings are such that expiratory time is insufficient for lung volume to return to its relaxed FRC).

Auto-PEEP does not necessarily mean that dynamic hyperinflation is present. It is thus not synonymous with dynamic hyperinflation. If a patient is actively expiring, the calculated auto-PEEP may merely reflect active expiration and not necessarily the degree of hyperinflation, if any. This can be detected by observing the patient and by placing a hand on the patient’s abdomen to feel for contraction of the abdominal muscle during expiration and the measurement.

In addition, even in a passive patient, auto-PEEP may underestimate the degree of hyperinflation. Auto-PEEP is a measure of the average positive pressure present in the system at the end of expiration. Some lung regions with high auto-PEEP may not contribute to the average auto-PEEP measured due to airway closure (hidden PEEP) [113]. This prevents accurate assessment of alveolar pressure at the end expiration in all lung regions. When hidden PEEP is present, the overall degree of hyperinflation present will be reflected during tidal ventilation and thus in the $P_{plat}$, and the tidal volume is delivered on top of the trapped gas. It is therefore important to monitor both auto-PEEP and $P_{plat}$ in patients with obstructive physiology and to adjust the ventilator to minimize dynamic hyperinflation.
and address its cause. This often requires decreasing minute ventilation and accepting some degree of respiratory acidosis (permissive hypercapnia). Sometimes increasing the external PEEP helps reduce airway collapse during expiration and reduce the work needed to trigger the ventilation. When PEEP is used in this setting, it is typically set at a level below the measured total PEEP but one subsequently measures the resulting changes in $P_{\text{plat}}$ and trapped volume, as the effects of external PEEP on $P_{\text{plat}}$ are difficult to predict [114].

4.6. Gas Exchange

4.6.1. Monitoring Oxygenation. The adequacy of tissue oxygen delivery and utilization cannot be measured directly, and the oxygenation status of vital organ is typically inferred and monitored by using data from different sources.

Arterial Oximetry. Oximetry is a widely used monitoring technique in ICU. Despite its accepted utility, it is not a substitute for arterial blood gas monitoring as it provides no information about the ventilatory status and has several other limitations. Probe placement is important as both high and low values could be seen with partial alignment of the probe electrodes [115], presence of the blood pressure cuff on the same side as the oximetry probe [116], excessive motion (e.g., shivering or seizures) [117, 118], and having electromagnetic fields such as those created by MRI machines, cellular phones, and electrocautery [119, 120].

Erroneous readings may also be caused by hypotension [121] and hypoperfusion due to hemodynamic instability and use of vasoconstrictor medications [122, 123]. Forehead sensors may be more accurate in those circumstances. Abnormal hemoglobin moieties such as methemoglobin [117, 124, 125] and carboxyhemoglobin [115, 117, 126, 127] could result in overestimation of oxyhemoglobin. False readings are also seen in severe anemia (Hb < 5 g/dL) [128], in presence of excessive skin pigmentation [115, 129], nail polish [119], or dyes. It is thus important to question the reading when the latter does not seem to fit the clinical picture.

Efficacy of Oxygen Exchange. Oximetry is not a sensitive guide to gas exchange in patients with high baseline PaO$_2$ because of the shape of the oxygen dissociation curve. On the upper horizontal portion of the curve large changes in PaO$_2$ may occur with little change in pulse oximetry (SpO$_2$) [130] till the PaO$_2$ is in the mid sixty range. It is thus wise to adjust the inspired O$_2$ to keep the hemoglobin saturation below 100 percent. Numbers of indices have been used to assess the efficiency of oxygen exchange including venous admixture and shunt fraction. The calculation of these indices involves mixed venous blood sampling with a PA catheter, which are not commonly used anymore in most centers. These indices are thus more helpful for research than for daily care.

Alveolar-arterial oxygen tension difference has been used in the past but it is limited, and it changes unpredictably with FiO$_2$ changes in critically ill patients with combination of etiologies of hypoxia.

Conditions encountered in the ICU associated with a low PaO$_2$ include (1) hypoventilation, (2) impaired diffusion, (3) ventilation/perfusion mismatching, and (4) shunting. Significant shunting as opposed to ventilation/perfusion mismatching is likely present if 60% or greater FiO$_2$ is required to keep the arterial O$_2$ saturation above 90%. Since PaO$_2$ is loosely related to gas exchange efficiency unless the FiO$_2$ is also taken into consideration, the PaO$_2$ : FiO$_2$ ratio is thus generally used to quantify the degree of pulmonary gas exchange dysfunction and lung injury. Indeed, this ratio is integral to the definition of ALI and ARDS [131]. PaO$_2$ : FiO$_2$ ratio in the 500–300 range is consistent with normal-to-mild impaired oxygen exchange; values less than 300 indicates moderately impaired gas exchange as seen in ALI, and values of less than 200 are supportive of significant shunt physiology as encountered in ARDS. The ratio can also be used to assess the response to therapeutic interventions [132, 133].

Although in one study [134] PaO$_2$ : FiO$_2$ ratio exhibited stability at FiO$_2$ values of ≥0.5 and PaO$_2$ values of ≤100 torr (≤13.3 kPa), others have found the PaO$_2$ : FiO$_2$ ratio to have poor association with pulmonary shunt [135] and that alteration in the PaO$_2$ : FiO$_2$ occurred when the FiO$_2$ is changed [136]. Such variability makes this parameter dependent on the management style: for example, aiming to keep the arterial O$_2$ saturation on the high side (e.g close to 99%) as opposed to the low side (e.g., close to 90%) may cause certain patients to have to be reclassified from ARDS to ALI. Another important limitation of the PaO$_2$ : FiO$_2$ ratio to assess the gas exchange function is that it is also affected by the ventilatory strategy such as the size of the tidal volume used [110], the PEEP level and presence of recruitable lung regions [137], and the hemodynamic conditions. PaO$_2$ : FiO$_2$ ratio has not been shown to correlate with the mortality in ARDS/ALI [138]. Despite its limitation, when used in combination with other hemodynamic and respiratory mechanics measures, monitoring PaO$_2$ : FiO$_2$ ratio is easy to obtain at the bedside to track cardiorespiratory changes. It is important to keep in mind the above limitations, its lack of correlation with outcome, and that the overall goal of mechanical ventilation is to achieve acceptable gas exchange with minimal stress and not to achieve the highest PaO$_2$ : FiO$_2$ ratio as such strategy has the potential to be counterproductive.

4.6.2. Monitoring Carbon Dioxide. Arterial PCO$_2$ depends on CO$_2$ production relative to its elimination by the lungs. In sedated and passively ventilated patients who have a fixed imposed minute ventilation, PCO$_2$ may rise due to increased metabolic rates such as seen, for instance, with fever, a high carbohydrate load, and/or overfeeding. Blood PCO$_2$ level is also governed by acid-base fluctuations and perfusion adequacy. Finally, PCO$_2$ may rise if alveolar ventilation decreases as dead space increases. We shall now briefly discuss monitoring of PCO$_2$ and dead space.

Assessment of PaCO$_2$. Traditionally in the ICU, gas exchange is assessed on the arterial side by measurement of PaO$_2$, PaCO$_2$, and pH. There has been a long-standing interest in alternate methods for measurement of PaCO$_2$. 
PaCO₂ can be continuously monitored using miniaturized electrochemical or optical sensors. End-tidal CO₂ (etCO₂) and transcutaneous PCO₂ (tcPCO₂) are commonly used in operative rooms and sleep centers. tcPCO₂ measurement uses a sensor to detect CO₂ that is diffusing out through the body tissues and skin and could be a helpful alternative to blood gas measurement. The tcPCO₂ measured by this technique measures tissue CO₂ that is slightly higher than the arterial value requiring corrective algorithms. tcPCO₂ can be used to estimate and to trend PaCO₂ in different settings such as adult critical care [139, 140], mechanically ventilated patients [141, 142], and pediatric and neonatal ICU [141, 143]. However, the accuracy of tcPCO₂ measurement is limited during severe vasoconstriction or presence of skin edema. Other limitations include the need for periodically changing the membrane and calibrating the sensor when using electrochemical measurement technique.

Recent publications [144, 145] have evaluated the role of measurement of PaCO₂, PaO₂, pH in peripheral and central venous blood instead of arterial blood. In the studies venous PCO₂ and pH were a reasonable surrogate of arterial PCO₂ and pH. In normal conditions venous PCO₂ is 3–4 mmHg higher than the arterial blood that leads to an increase in bicarbonate levels (1–1.5 mmol per liter) and a simultaneous decrease in a pH by 0.03–0.05 pH units. However, in the presence of shock or cardiac arrest the arterial-to-venous PCO₂ and pH difference increases. Such an increase in difference may be an important clue that tissue hypoperfusion is present, and the case has been made that in cardiac arrest patient venous blood gas may better reflect tissue acid-base status and oxygenation than arterial blood gas [146].

**Dead Space Ventilation and PCO₂ in ICU**

The physiologic dead space (VD) refers to the portion of tidal breath, which fails to participate in effective CO₂ exchange and is made of the sum of the “anatomic” and the “alveolar” dead space. The dead space fraction can be estimated by simultaneous measurement of arterial PCO₂ and partial pressure of exhaled gas CO₂:

\[
\frac{V_D}{V_T} = \frac{(PaCO_2 - PeCO_2)}{PaCO_2}.
\]  

(9)

In ventilated patients, the ventilator circuit increases, and a tracheostomy decreases, the anatomic dead space. Modest decreases in the dead space can also be seen with extended breath holding [147, 148] and decelerating inspiratory flow pattern ventilation [149, 150]. Other common ICU conditions associated with an increased VD include low cardiac output states, pulmonary embolism, pulmonary vasoconstriction, and mechanical ventilation with excessive tidal volume or PEEP particularly when blood volume is low [151].

In critically ill patients, it is not exceptional for the VD/V_T to rise to values that exceed 0.65 (normal 0.35) [152, 153]. Dead space accounts for most of the increase in V_f requirements and CO₂ retention seen in lung injury and hypoxic respiratory failure. Overdistention leading to increased dead space should be suspected when under controlled constant inspiratory flow ventilation, examination of the pressure time curve demonstrates concavity or an upward inflection. It should be considered in the differential when associated with an elevated P_plat. In these situations, reducing the tidal volume or PEEP could help reduce VD/V_T.

In patients with ARDS, increased dead space, rather than a decrease in PaO₂:FiO₂ (oxygenation), has been shown to be associated with alteration of the lung structure [108] and increased mortality [153–156]. It is not known if therapy or ventilatory strategy aiming at reducing dead space would improve ARDS patient’s outcome.

In ARDS, hypercapnia could result from lung protective ventilation (permissive hypercapnia), due to increased dead space due to damaged lung or a combination of both. It is important to differentiate respiratory acidosis due to increased dead space associated with an elevated minute ventilation and mortality from the one that results from a lung protective strategy (permissive hypercapnia) associated with lower mortality [157] and deliberately low tidal volume. Although respiratory acidosis per se may have a lung protective effect in experimental ventilator-induced lung injury model [158] and in patients exposed to high mechanical stress [159], respiratory acidosis has complex biological effects and is not without potential hazards, as reviewed elsewhere [160, 161]. In the absence of contraindication, respiratory acidosis is currently justified only to limit injurious mechanical stress or dynamic hyperinflation.

In summary, monitoring of oxygenation and ventilation is important but before attempting to adjust the ventilator to correct the PaO₂ and/or PaCO₂ to normal levels, the underlying alteration in the respiratory physiology and mechanics needs to be understood and its cause addressed whenever possible. It is also essential to weigh the risk benefits specifically in regard to mechanical stress on the lungs before attempting to correct abnormal blood gas values. Monitoring in the ICU should aim to keep the patients within a safety zone and does not imply we need to act on all abnormal values. First do no harm.

**5. The Monitoring of the Nutritional and Metabolic Care in the Intensive Care Unit (ICU)**

The monitoring of nutritional and metabolic care in the ICU has three main goals: first, the control of macronutrients (glucose, protein, fat) and micronutrients (vitamins and trace-elements) delivery, second, the assessment of the adequation between energy needs and delivery, and, finally, the glycaemic control. This issue is of high relevance, since a plenty of evidence indicates that an insufficient coverage of protein and energy needs and an impaired glycaemic control are both related to a worse clinical outcome in the ICU. Several studies have demonstrated that computer-assisted systems allow an accurate monitoring of nutrition and metabolic parameters and contribute to optimize protein-energy delivery and glycaemic control. Therefore,
Nutrition support in the ICU

**Enteral nutrition alone**
- Insufficient coverage of nutritional needs: protein-energy deficit

**Parenteral nutrition**
- Overfeeding
- Dysregulation of glucose metabolism: hypoglycaemia, hyperglycaemia

**Negative impact on clinical outcome**
- Infections
- Complications
- Mortality
- Liver steatosis and dysfunction
- Mortality

**Optimization of protein and energy delivery**
- Better adherence to guidelines
- Improved clinical outcome
- Optimized glycaemic control

**Computerized monitoring of:**
- Protein and energy delivery
- Glycaemia/insulinotherapy

**Figure 3:** Conceptualization of the expected impact of the computerized monitoring of the nutritional and metabolic care in the intensive care unit (ICU). Although it is the recommended nutrition support, early enteral nutrition (EN) is associated with an insufficient coverage of energy and protein needs, leading to a protein-energy deficit, itself associated with an increased risk of infections and complications and increased mortality. The use of parenteral nutrition (PN) could be associated with overfeeding, and especially hyperglycaemia, which is associated with an increased risk of infections and liver metabolic complications and increased mortality. By allowing an early and tight adaptation of protein and energy delivery to nutritional targets and an optimization of glycaemic control, the computerized monitoring of the nutritional and metabolic care could improve the adherence to clinical guidelines and the clinical outcome of ICU patients.

5.1. Monitoring of Protein and Energy Delivery for the Prevention of Protein-Energy Deficit

5.1.1. Rationale. In the ICU, the first line recommended nutrition support is the early enteral nutrition (EN) [162, 163], since it reduces infectious risk and mortality in comparison with late EN [164] and early parenteral nutrition (PN) [165]. Yet, several observational studies have shown that the use of EN during the first week of the ICU stay is associated with a protein and energy deficit [166, 167], which is, in turn, related to an increased risk of infections [166–169] and complications [167], as well as increased mortality [170]. Delivering too much energy regarding the needs, that is, overfeeding, favors the onset of hyperglycaemia and its related complications [171]. Reaching an adequacy between nutritional needs and delivery is mandatory in all ICU patients to avoid protein-energy deficit, overfeeding and hyperglycaemia, and the onset of their related complications.

5.1.2. How Can Protein and Energy Delivery Be Monitored in Clinical Practice? Current guidelines recommend the use of indirect calorimetry to measure energy needs [162, 163]. In the situations where indirect calorimetry is not available, which is the case in most ICUs, the use of predictive formula, that is, 20–25 kcal/kg/day at the acute phase, and 25–30 kcal/kg/day at the postacute phase, is advised [162, 163]. Because of the absence of measurement methods, protein needs should be evaluated according to the 1.2–1.5 kcal/kg ideal body weight/day formula. Once the energy target is established, energy and protein delivery has to be monitored to prevent the onset of energy deficit. Several studies have shown that the use of computerized systems for the prescription and the monitoring of nutrition support allows decreasing time for prescription and improving the adequacy between delivery and needs of energy, glucose, protein, and fat [172–176]. Recent clinical studies have demonstrated that the computer-assisted optimization of nutrition delivery could improve the clinical outcome of ICU patients [177, 178]. Singer et al. have shown that the computer-assisted targeting of energy delivery according to indirect calorimetry could reduce mortality in comparison with targeting energy delivery according to the 25 kcal/kg/day formula [177]. Also, a study published in
an abstract form has suggested that the computer-assisted full coverage of energy target by supplemental PN from the fourth day of ICU stay could reduce the number of infections and the duration of mechanical ventilation in ICU patients covering only 60% of their energy target by EN alone within the three first days of stay [178]. In addition, computerized monitoring systems allow registering gastric residual volumes and could be helpful for the prescription of prokinetics and antioxidant micronutrients. Nevertheless, computerized monitoring alone is not sufficient for an optimal coverage of nutritional needs. It represents a clinical tool helping at implementing the nutritional recommendations in the context of a global educational and interdisciplinary program of nutritional care [175]. One study has shown that, in addition to a computer-assisted global nutritional program, the presence of an ICU-dedicated dietician further improves protein-energy delivery in the ICU [175].

5.2. Monitoring of Glycaemia and Insulinotherapy for Optimized Glycaemic Control

5.2.1. Rationale. In the past 20 years, it was extensively demonstrated that PN could induce metabolic disorders, such as hyperglycaemia, hypertriglyceridemia, liver steatosis, endocrine dysfunction, impairment of immunity, infections, and increased mortality [171]. PN-related infectious complications have been related to hyperglycaemia [171]. Large randomized, controlled, prospective studies have shown that an optimized glycaemic control with the aim to obtain a glycaemia less than 10 mmol/L and avoid hyperglycaemia reduces mortality [179, 180]. Therefore, it is now established that, through a daily monitoring of glycaemia and insulin doses, optimized glycaemic control allows improving the clinical outcome of ICU patients.

5.2.2. How Can Glycaemia and Insulinotherapy Be Monitored in Clinical Practice? Computerized systems have to be used for the constitution of insulin algorithms that have been shown to improve the glycaemic control in comparison with manual protocols [172]. In addition, computerized systems allow reducing nurses and physicians work time, time to reach the targeted glycaemia and the onset of hypo- and hyperglycaemia [172, 181]. For example, a pilot study suggests that nurse-centered computer-assisted glycaemia regulation during stepwise increases of PN according to a predefined protocol resulted in adequate caloric intake within 24 hours together with an adequate glycaemic control [182]. Recent articles develop physiological and practical mathematical models for intensive insulin therapy and tight glycaemic control [183, 184]. Moreover, new devices continuously measuring glycaemia using intravascular catheters have been produced recently. This kind of advanced metabolic monitoring technology could be of great help in the future. Further research is needed to identify the most sensitive models for optimal insulinotherapy and glycaemic control.

In summary, the monitoring of the nutritional and metabolic care is part of the management of the ICU patient. The use of a computer-based monitoring system of nutrients delivery and glycaemic control contributes to reinforce the adherence of clinical practice to guidelines. In addition, computer-based monitoring systems, by preventing protein-energy deficit and overfeeding and optimizing glycaemic control, should contribute to improve the clinical outcome of ICU patients. The medicoeconomic impact of computer-based monitoring systems remains to be evaluated.

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Critical Care Research and Practice


Clinical Study
Increased Extravascular Lung Water Reduces the Efficacy of Alveolar Recruitment Maneuver in Acute Respiratory Distress Syndrome

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Received 13 October 2011; Accepted 20 February 2012

Academic Editor: Alain Broccard

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Introduction. In acute respiratory distress syndrome (ARDS) the recruitment maneuver (RM) is used to reexpand atelectatic areas of the lungs aiming to improve arterial oxygenation. The goal of our paper was to evaluate the response to RM, as assessed by measurements of extravascular lung water index (EVLWI) in ARDS patients. Materials and Methods. Seventeen adult ARDS patients were enrolled into a prospective study. Patients received protective ventilation. The RM was performed by applying a continuous positive airway pressure of 40 cm H2O for 40 sec. The efficacy of the RM was assessed 5 min later. Patients were identified as responders if PaO2/FiO2 increased by >20% above the baseline. EVLWI was assessed by transpulmonary thermodilution before the RM, and patients were divided into groups of low EVLWI (<10 mL/kg) and high EVLWI (≥10 mL/kg).

Results. EVLWI was increased in 12 patients. Following RM, PaO2/FiO2 increased by 33 (4–65)% in the patients with low EVLWI, whereas those in the high EVLWI group experienced a change by only −1(−13)–(+5)% (P = 0.035). Conclusion. In ARDS, the response to a recruitment maneuver might be related to the severity of pulmonary edema. In patients with increased EVLWI, the recruitment maneuver is less effective.

1. Introduction

The consolidation of pulmonary tissue and, in particular, the formation of atelectases is a key component in the pathogenesis of acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS) [1]. Loss of pulmonary tissue aeration resulting from decreased production of surfactant, evolution of lung edema, and denudation of alveolar basal membrane, is one of the crucial mechanisms of intrapulmonary shunting and arterial hypoxemia [2]. The formation of atelectases can also be triggered by gravity forces related to the increased weight of the edematous parts of the lungs resulting in a fall in functional residual capacity and compression of dependent lung areas in the supine patient [1].

The accumulation of interstitial, alveolar, and migrating cellular fluid in the lungs may also play an important role in the pathogenesis of ARDS, although its importance is often underestimated [3, 4]. Obviously, in severe lung edema the lung fluid content, which is reflected by extravascular lung water, can increase 2-3-fold prior to a significant decrease in arterial oxygenation [5]. Increments in extravascular lung water content of 500–700 mL up to 1000–1800 mL, corresponding to increments in extravascular lung water index (EVLWI) of from 7–10 mL/kg to 14–25 mL/kg may be seen. An experimental study from our group demonstrated that...
such an increase in EVLWI is not necessarily accompanied by a substantial expansion of the pulmonary parenchyma, as assessed by spiral computer tomography (CT) [6]. The expansion of the extravascular fluid volume may take place at the expense of a compression in the conducting airways and alveoli and, to a minor extent, of the vascular bed, since severe pulmonary hypertension is not a prerequisite for the evolvement of ARDS [7]. Most likely accumulation of extravascular lung water in the early exudative phase of ARDS may result in destabilization of alveolar tissue requiring higher PEEP values to counteract gravity-related lung collapse and consolidation.

The aim of the alveolar recruitment maneuver (RM) is to expand and reopen collapsed lung tissue by intermittent short-acting increase in airway pressure. In the general ICU population, RM may improve the oxygenation ratio (PaO₂/FiO₂) by 29–50% of ARDS patients [8–10]. However, this method also has a number of side-effects and complications, the most severe being barotrauma and compromised cardiac preload [11, 12]. Notably, these adverse effects are more pronounced in nonresponders with a considerable decrease in the individual benefit-to-risk ratio [13].

Therefore, an active search for predicting an individual’s response to RM seems to be reasonable. Assuming there is a potential propensity of edematous pulmonary tissue to consolidate, or vice versa, a resistance of injured parenchyma to reopen, we hypothesized that EVLWI may influence the efficacy of the recruitment maneuver in ARDS patients. Thus, the aim of our study was to evaluate the response to RM, as assessed by EVLWI, in patients with ARDS.

2. Materials and Methods

The study was approved by the Medical Ethics Committee of Northern State Medical University, Arkhangelsk, Russian Federation. Written informed consent was obtained from every patient or his/her next of kin.

This prospective pilot study was performed in a 900-bed university hospital. From 2007 to 2010, we enrolled 17 adult patients who met the ALI/ARDS criteria according to the American European Consensus Conference [14]. Exclusion criteria were duration of ALI/ARDS >24 hrs, hypovolemia, severe COPD, and/or severe cerebral or cardiac diseases.

Patients were sedated with fentanyl (1 mcg/kg/hr) and midazolam (0.05 mg/kg/hr) and ventilated using pressure-controlled ventilation (PCV) (Avea, Viasys, USA) with the following initial settings: FiO₂: 0.5, positive end-expiratory pressure (PEEP) 5 cm H₂O, driving pressure to a targeted tidal volume of 7 mL/kg of predicted body weight (PBW), and a respiratory rate providing a PaCO₂ of 35–45 mm Hg. For males, PBW (kg) was calculated as \( \frac{50 + 2.3 \times \text{height (cm)}}{2.54-60} \), and correspondingly for females PBW (kg) = 45 + 2.3 (height (cm)/2.54–60). If the initial ventilator settings did not result in a \( \text{SaO}_2 \geq 94\% \) and/or \( \text{PaO}_2 \geq 70 \text{ mm Hg} \), FiO₂ was increased in steps of 0.1 up to 0.8 and remained unchanged during the study.

Hemodynamic monitoring was performed using the single transpulmonary thermodilution technique. In all patients the femoral artery was cannulated with a 5F thermodilution artery catheter (Pulsicath PV2015L20, Pulsion). The catheter was connected to a PiCCOplus (Pulsion Medical Systems, Germany) monitor for measurements of cardiac index (CI), extravascular lung water index (EVLWI, which was adjusted to PBW), global end-diastolic volume index (GEDVI), systemic vascular resistance index (SVRI), mean systemic arterial pressure (MAP), and heart rate (HR). The thermodilution measurements were performed in triplicate with injections of ice-cold (<8°C) 5% dextrose solution via a preinserted jugular central venous catheter (8.5F triple-lumen 20 cm catheter).

After initial measurements and muscular relaxation with pipercuronium (0.06 mg/kg), RM was performed by subjecting the patients to a continuous positive airway pressure of 40 cm H₂O for a period of 40 seconds [10]. The RM was discontinued in case of hypotension (MAP <50 mm Hg or a decrease in MAP of more than 30 mm Hg from the initial value), or hypoxemia (\( \text{SpO}_2 <85\% \) or a decrease of more than 10%). Then PCV was resumed with the same settings as before the RM. PEEP was set at 2 cm H₂O above the lower inflection point (LIP) of the pressure-volume (P-V) curve determined by an inflection point maneuver by the ventilator (Avea, Viasys, USA). The efficacy of the recruitment maneuver was assessed by registering the change in \( \text{PaO}_2/\text{FiO}_2 \) five minutes later. Patients were identified as responders if \( \text{PaO}_2/\text{FiO}_2 \) increased by at least 20% [8, 10, 13]. The stability of RM was assessed by following changes in \( \text{PaO}_2/\text{FiO}_2 \) at 40–60 min after the return to PCV.

For additional analysis of the efficacy of RM, patients were divided by the baseline EVLWI values as low EVLWI (\(<10 \text{ mL/kg}\)) and high EVLWI (\(\geq10 \text{ mL/kg}\)) groups [4, 15].

Hemodynamic parameters were evaluated at baseline. Blood gases, lung mechanics, and parameters of mechanical ventilation were registered before RM and at 5 min and 40–60 min after RM.

2.1. Statistical Analysis. For data collection and analysis we used SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). Power analysis was not performed because of the pilot design of the study. The data distribution was assessed with Shapiro-Wilk’s test. Quantitative data were presented as mean ± standard deviation or median (25th–75th percentile) depending on the data distribution. Discrete data were expressed as absolute values or percentages. In case of normal distribution, we used two-tailed Student’s t-test for comparisons between the groups and repeated measures t-test for assessment of intragroup changes. Nonparametrically distributed data were assessed by two-tailed Mann-Whitney’s U-test and Wilcoxon’s test for comparisons between and within the groups, respectively. Discrete data were evaluated using Fisher’s exact test. For all tests a \( P \) value <0.05 was considered significant.

3. Results

Fourteen male and three female patients were enrolled into the study. The mean age of the patients was 47 ± 2 yrs.
Table 1: General characteristics of responders and nonresponders to lung recruitment maneuver.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n = 5)</th>
<th>Nonresponders (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.2 ± 16.7</td>
<td>47.6 ± 17.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>5/0</td>
<td>9/3</td>
<td>0.50</td>
</tr>
<tr>
<td>Height, cm</td>
<td>178 ± 4</td>
<td>172 ± 8</td>
<td>0.11</td>
</tr>
<tr>
<td>Actual body weight, kg</td>
<td>84.6 ± 20.8</td>
<td>77.0 ± 12.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Predicted body weight, kg</td>
<td>73.3 ± 3.2</td>
<td>66.5 ± 7.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Type of ARDS, direct/indirect</td>
<td>4/1</td>
<td>8/4</td>
<td>1.00</td>
</tr>
<tr>
<td>SAPS II, points</td>
<td>40.0 ± 12.4</td>
<td>44.6 ± 14.9</td>
<td>0.56</td>
</tr>
<tr>
<td>SOFA, points</td>
<td>9.0 ± 3.2</td>
<td>7.9 ± 2.6</td>
<td>0.47</td>
</tr>
<tr>
<td>Murray score, points</td>
<td>2.50 (2.25–3.08)</td>
<td>2.25 (2.06–2.75)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, absolute values or median (25th–75th percentile).

Table 2: Arterial blood gases, hemodynamics and parameters of mechanical ventilation in responders and nonresponders to lung recruitment maneuver.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n = 5)</th>
<th>Nonresponders (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2 baseline, mm Hg</td>
<td>127 ± 50</td>
<td>155 ± 45</td>
<td>0.27</td>
</tr>
<tr>
<td>PaO2/FiO2 after RM, mm Hg</td>
<td>158 (136–311)</td>
<td>152 (116–161)</td>
<td>0.29</td>
</tr>
<tr>
<td>PaO2/FiO2 stability of RM, mm Hg</td>
<td>152 ± 63</td>
<td>141 ± 44</td>
<td>0.71</td>
</tr>
<tr>
<td>PaCO2, baseline, mm Hg</td>
<td>45 ± 8</td>
<td>45 ± 8</td>
<td>0.98</td>
</tr>
<tr>
<td>PaCO2 after RM, mm Hg</td>
<td>45 ± 12</td>
<td>49 ± 8</td>
<td>0.25</td>
</tr>
<tr>
<td>PaCO2 stability of RM, mm Hg</td>
<td>43 ± 7</td>
<td>48 ± 8</td>
<td>0.27</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.17 ± 0.90</td>
<td>3.84 ± 1.29</td>
<td>0.31</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>71 ± 7</td>
<td>96 ± 26</td>
<td>0.06</td>
</tr>
<tr>
<td>SVRI, dyn sec cm⁻¹/m²</td>
<td>1717 (1089–1994)</td>
<td>1662 (1285–2271)</td>
<td>0.46</td>
</tr>
<tr>
<td>HR, beat/min</td>
<td>95 ± 8</td>
<td>112 ± 29</td>
<td>0.22</td>
</tr>
<tr>
<td>GEDVI, mL/m²</td>
<td>702 ± 136</td>
<td>695 ± 130</td>
<td>0.92</td>
</tr>
<tr>
<td>EVLWI, mL/kg</td>
<td>11.6 ± 5.5</td>
<td>13.1 ± 4.4</td>
<td>0.55</td>
</tr>
<tr>
<td>FiO2, %</td>
<td>50 (50–80)</td>
<td>50 (50–60)</td>
<td>0.51</td>
</tr>
<tr>
<td>Tidal volume, mL</td>
<td>494 ± 58</td>
<td>444 ± 55</td>
<td>0.14</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>11.6 ± 4.2</td>
<td>10.3 ± 1.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Dynamic respiratory compliance, mL/cm H₂O</td>
<td>29 (26–62)</td>
<td>28 (24–35)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or median (25th–75th percentile).

RM: recruitment maneuver; CI: cardiac index; MAP: mean arterial pressure; SVRI: systemic vascular resistance index; HR: heart rate; GEDVI: global end-diastolic volume index; EVLWI: extravascular lung water index.

In most cases (94%), the baseline PaO2/FiO2 was less than 200 mm Hg.

3.1. The Efficacy of the Recruitment Maneuver: Responders and Nonresponders. The recruitment maneuver was accompanied by an increase in PaO2/FiO2 of more than 20% of the baseline value in 5 patients (responders) and did not affect oxygenation significantly in 12 patients (nonresponders). The demographic characteristics of responders and nonresponders are presented in Table 1. The groups did not differ regarding age, weight and height, type of ARDS, and the severity of lung injury or other organ dysfunctions. Baseline PaO2/FiO2 values were similar in both groups (Table 2).

The RM increased PaO2/FiO2 by a median of 62 (32–91) % in the responders, whereas the nonresponders demonstrated no changes or even decreased PaO2/FiO2 compared to the baseline value: 1((−13)–(+4))% (P = 0.002). Despite improvement in PaO2/FiO2 after RM in the responders, the PaO2/FiO2 did not differ significantly between responders and nonresponders (Table 2).

The stability of the RM was evaluated in 12 patients including 4 responders and 8 nonresponders. A decrease in PaO2/FiO2 of more than 15% compared with values yielded immediately after recruitment was found in 58% of patients including 75% of the responders and 38% of the nonresponders. The average decreases in PaO2/FiO2 were 61 (6–102) % and 14 (4–22) % in responders and nonresponders, respectively (P = 0.19). Hemodynamics and ventilatory variables did not differ significantly between responders and nonresponders (Table 2).

3.2. Association between the Efficacy of the Recruitment Maneuver and Extravascular Lung Water. Increased EVLWI
Table 3: General characteristics of patients with low and increased extravascular lung water index.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EVLWI &lt;10 mL/kg (n = 5)</th>
<th>EVLWI ≥10 mL/kg (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40.4 ± 14.9</td>
<td>49.2 ± 17.2</td>
<td>0.34</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>5/0</td>
<td>9/3</td>
<td>0.52</td>
</tr>
<tr>
<td>Type of ARDS, direct/indirect</td>
<td>3/2</td>
<td>9/3</td>
<td>0.60</td>
</tr>
<tr>
<td>SAPS II, points</td>
<td>38 ± 7</td>
<td>46 ± 16</td>
<td>0.29</td>
</tr>
<tr>
<td>SOFA, points</td>
<td>10.4 ± 2.7</td>
<td>7.3 ± 2.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Murray score, points</td>
<td>2.50 (2.38–2.75)</td>
<td>2.25 (2.06–3.12)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, absolute values or median (25th–75th percentile).

(≥10 mL/kg) was found in 12 patients including two responders (40% of all responders) and 10 nonresponders (83% of all nonresponders). EVLWI did not differ between patients with direct and indirect ARDS.

The general characteristics of patients with low and high EVLWI are presented in Table 3. Patients with low EVLWI had higher SOFA score values (Table 3).

The baseline PaO2/FiO2 did not differ between patients with low and high EVLWI. In response to the RM patients in the low EVLWI group demonstrated a 33 (4–65) % increase in PaO2/FiO2. In contrast patients with EVLWI ≥10 mL/kg showed no substantial changes in PaO2/FiO2: −1(−13)−(+5) (P = 0.035 compared with the low EVLWI group) (Figure 1).

During the assessment of recruitment stability, PaO2/FiO2, PaCO2, and hemodynamic parameters were similar in patients with low and increased EVLWI (Table 4). Baseline tidal volume was higher in the low compared to the high EVLWI group.

4. Discussion

Our study demonstrates that during ALI and ARDS the efficacy of alveolar recruitment depends, at least partly, on the content of extravascular lung water. Pulmonary edema is associated with a reduced capability of 40 cm H2O × 40 sec RM to improve arterial oxygenation, thus, necessitating a search for other interventions to counteract hypoxemia during ARDS.

Alveolar RM is an important component of the open lung strategy in patients with ALI/ARDS of different etiologies. There are multiple modifications of the RM technique with individual adverse effects and benefits [16–18]. One extensively used principle is to increase pressure in the airways related to the consolidated areas over the level of the re-opening pressure [19]. A short-term sustained inflation pressure of up to 40 cm H2O for 40 seconds is the simplest and most well-studied version of RM, commonly used in ARDS patients.

Our study showed that 40 cm H2O × 40 sec RM resulted in a substantial improvement in PaO2/FiO2 in 29% of the patients. This is consistent with the findings of other recent investigators who reported the percentage of responders as 29–50% [8–10]. It is intriguing that the PaO2/FiO2 in responders and nonresponders was similar after the RM but the difference in response can be explained by the tendency to lower baseline PaO2/FiO2 in responders. In 75% of the responders and 38% of the nonresponders PaO2/FiO2 decreased within 40–60 minutes following the RM despite having identified and set an optimal individual PEEP value (2 cm H2O above LIP of the P-V curve). Indeed, the effect of alveolar recruitment is unstable; PaO2/FiO2 may decrease to baseline values as quickly as 30–45 minutes after PEEP has been adjusted [20, 21]. The stability of the alveolar reexpansion may be limited by the technique used to detect the optimal PEEP. The adjustment of an optimal PEEP using the pressure-volume (P-V) curve, as used in this study, is probably one of the most widespread and preferable methods for use at the bedside [22]. However, particularly in patients with “stiff” lungs resulting from severe ARDS, the lower inflection point of the P-V curve may be hard to discern [23].

The response to an RM may be affected by a wide range of factors, including the origin of ALI (direct or indirect), the technique used for the recruitment and the PEEP level used...
Reexpansion [24]. However, the effects are still controversial. Several studies demonstrate that indirect ALI/ARDS may be associated with a decreased response to RM [25, 26], while others disagree with these assumptions [10, 27]. In the present study no association was found between the type of ARDS and the response to RM.

Increased interstitial hydrostatic pressure and pulmonary weight have been suggested to be among the key mechanisms of atelectasis formation in ALI/ARDS according to the “sponge theory,” postulating a fall in lung compliance combined with compression and collapse of dependent small airways [24, 28, 29]. Studies carried out with the use of spiral CT have revealed that RM can lead to overdistension of intact or minimally injured areas located adjacent to the consolidated foci of lung tissue, resulting in volume- and/or biaxial changes of atelectasis according to the “sponge theory” [32]. In addition, according to the above definition, EVLWI measurement might be influenced by pulmonary vascular obstruction and prevalence of focal or regional pulmonary injury [34]. In the absence of lung edema, the atelectatic areas might be more compliant to the transiently increased airway pressure, similar to compression atelectasis where gas remains in the occluded acinar compartment [35].

In this study, patients with low EVLWI (<10 mL/kg) showed a significant increase in PaO2/FiO2 following RM. In contrast, those with pulmonary edema failed to respond with an improvement in arterial oxygenation. However, we found no significant correlation between EVLWI and the percentage of positive response to RM. The cut-off value for EVLWI of 10 mL/kg was selected according to the results obtained by Chung and coauthors, who demonstrated that EVLWI ≥10 mL/kg predicts mortality with a sensitivity of 94.7% and a specificity of 66.7% [4]. In our study, EVLWI was above 10 mL/kg PBW in 71% of patients. This is in agreement with previously published data from our group [32]. In addition, according to the above definition, EVLWI was increased in 40% of the responders and 83% of the nonresponders. Indeed, pulmonary edema and aeration of lung parenchyma are closely associated. Extravascular lung water index correlates with the CT-reconstructed volume of pulmonary tissue of aqueous density, both in experimental [6] and clinical settings [33]. However, the accuracy of EVLWI measurement might be influenced by pulmonary vascular obstruction and prevalence of focal or regional pulmonary injury [34]. In the absence of lung edema, the atelectatic areas might be more compliant to the transiently increased airway pressure, similar to compression atelectasis where gas remains in the occluded acinar compartment [35].

Our study has several limitations, first of all, a small sample size. Thus, further larger studies of extravascular lung water and alveolar recruitment are warranted. The numerical differences in mean tidal volumes between the groups may be explained by different predicted body weights and dynamic ventilatory properties of the edematous and nonedematous lungs. Surprisingly, in this population of critically ill patients, the SOFA score was higher in the group with low EVLWI. This finding may confirm our assumption that the severity of pulmonary edema rather than dysfunction of other organs is a key factor that might affect the efficacy of the RM in ARDS patients.

### 5. Conclusions

In ALI and ARDS responses to the lung recruitment maneuver (40 cm H2O × 40 sec) may depend on the severity of
pulmonary edema. In patients with EVLWI above 10 mL/kg, the recruitment maneuver may be less effective and may even be considered as contraindicated.

Conflict of Interests

Mikhail Kirov is a member of the medical advisory board of Pulsion Medical Systems.

References


Research Article

Critical Care Nurses Inadequately Assess SAPS II Scores of Very Ill Patients in Real Life

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Received 12 September 2011; Revised 24 December 2011; Accepted 13 January 2012

Academic Editor: Benoit Vallet

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Background. Reliable ICU severity scores have been achieved by various healthcare workers but nothing is known regarding the accuracy in real life of severity scores registered by untrained nurses.

Methods. In this retrospective multicentre audit, three reviewers independently reasessed 120 SAPS II scores. Correlation and agreement of the sum-scores/variables among reviewers and between nurses and the reviewers’ gold standard were assessed globally and for tertiles. Bland and Altman (gold standard—nurses) of sum scores and regression of the difference were determined. A logistic regression model identifying risk factors for erroneous assessments was calculated.

Results. Correlation for sum scores among reviewers was almost perfect (mean ICC = 0.985). The mean (±SD) nurse-registered SAPS II sum score was 40.3 ± 20.2 versus 44.2 ± 24.9 of the gold standard (P < 0.002 for difference) with a lower ICC (0.81). Bland and Altman assay was +3.8 ± 27.0 with a significant regression between the difference and the gold standard, indicating overall an overestimation (underestimation) of lower (higher; >32 points) scores. The lowest agreement was found in high SAPS II tertiles for haemodynamics (κ = 0.45–0.51).

Conclusions. In real life, nurse-registered SAPS II scores of very ill patients are inaccurate. Accuracy of scores was not associated with nurses’ characteristics.

1. Introduction

The simplified acute physiology score II (SAPS II) [1] is probably still the most commonly used score in Europe to compare a critically ill patient’s severity and—by its expanded form[2]—to evaluate clinical course and outcome [3, 4]. In addition, SAPS II has become a key-component for defining the degree of hospital reimbursement in Germany [5], and an analogous procedure is scheduled in Switzerland for the beginning of 2012 [6]. Considering the various implications, accuracy in the assessment of SAPS II scores is of the upmost importance.

Adequate interrater reliability of SAPS II has been reported in few studies [7, 8] and small differences in values of some SAPS II variables between observers have determined important differences in scores [8]. The Acute Physiology and Chronic Health Evaluation II scoring system (APACHE II) [9] has been more extensively studied, and reliable overall APACHE II scores have been achieved by various healthcare workers (trained hospital abstractors, nurses, resident physicians, and intensivists) [10–16]. Reliability was demonstrated to further increase by training [15] as well as by a multifaceted, multidisciplinary quality improvement intervention [16]. However, these results all refer to well defined study settings with specifically trained observers, and just one study [8] has so far measured the accuracy of physician registered severity scores in real life.

In our intensive care units (ICU) the SAPS II score is manually assessed by specialized critical care nurses. This procedure is required exactly 24 hrs after admission or our electronic medical record system inhibits any further use for the patient in question. Assessment by nurses was chosen in order to comply with medical and organisational deficiencies (small ICUs with inexperienced junior doctors on short-term rotation and contemporaneous extra tasks about all during night shifts, no permanent ICU specialist) and because specialized nurses are present in ICUs at all hours and days and are accustomed to personally handle most of the SAPS
II variables (retrieval of physiologic data and laboratory tests with their recording in the patients’ charts).

The aim of our study was (1) to assess the reliability of nurse registered SAPS II scores in real life, (2) to recognize error-prone variables, and (3) to conceive an appropriate improvement intervention.

2. Methods

2.1. Patients and Setting. This is a retrospective multicentre study, conducted within the Department of Intensive Care Medicine of the Ente Ospedaliero Cantonale, Ticino, Switzerland. Our department groups the mixed ICUs from 4 regional teaching hospitals (Bellinzona, Locarno, Lugano, and Mendrisio), has a total of 34 beds and cares for about 3,200 adult patients per year. Among the 159 nurses (with varying degrees of occupation), 70% are critical-care registered, whereas the remaining are registered nurses with ongoing specific training. Nurse/patient ratio is usually 1 : 1.5. No structured training program regarding SAPS II is offered to the nurses.

Scoring SAPS II is performed in a semiautomatic manner: (1) manual acquisition of data: for the diagnostic information (type of admission, underlying disease variables) the nurses have complete access to the medical charts. Physiologic data (heart rate, systolic arterial pressure, urinary rate, body temperature, oxygenation status, and Glasgow Coma Scale) and laboratory findings (complete access to all variables on the electronic medical record system) are consecutively documented by nurses on the daily patient survey charts, from which they are ultimately retrieved for registration of the SAPS II score. (2) For every variable the nurse has to select the most pondered option (among the lowest and highest value), that is eventually entered in the electronic medical record system. Consecutively, this system automatically calculates the final score. Identification of the nurse-recorder is assured by means of a personal code.

Patients ≥ 18 years of age, admitted to our ICUs between January 2010 and October 2010, were eligible. Considering the retrospective, noninterventional design of this quality assurance study, no informed consent was required by the Cantonal Ethics Committee.

2.2. Study Protocol. Among 2386 eligible patients the primary investigator randomly selected 30 patients per ICU presenting with the following principal discharge diagnostics (number of patients): septic shock (5), acute ischemic stroke (3), acute myocardial infarction (3), cardiopulmonary arrest (3), acute heart failure (3), acute respiratory failure due to pneumonia (3), chronic obstructive pulmonary disease (2), acute pancreatitis (2), polytrauma (2), arrhythmias (2), and patients with an ICU stay less than 24 hrs (2). Patients’ charts were then obtained by employees of the corresponding local quality control services and collocated for the review “in loco.”

Two experienced, board-registered intensivists and one critical-care registered nurse specifically trained for the use of SAPS II created a structured form for review that was principally based on the original definitions of the variables necessary for SAPS II [1]. The following issues were more accurately specified in order to correctly reflect organ dysfunction: (1) in case of uninterrupted vasopressor therapy for haemodynamic instability during the first day, the definitions were adapted according to elements proposed in the SOFA score [17], (2) cardiac arrest leading to ICU admission was deemed equal to cardiac arrest within ICU in order to ponder the increased mortality; (3) utilisation of laboratory tests performed immediately prior to ICU admission was permitted, as follow-up tests within our ICUs are generally executed by a careful and selective approach; (4) sensory and motor aphasia due to acute ischemic stroke in a patient with otherwise adequate mentation were disregarded for the calculation of the Glasgow Coma Scale.

2.3. Data Collection and Evaluation. The analysis was done by the three investigators by means of the above-mentioned template. The review process was performed in two steps. During the first stage the investigators independently examined the charts from all 30 patients and assessed the SAPS II scores. The results were evaluated, differences between the reviewers’ judgments were eventually resolved by discussion, and a final consensus (gold standard) was achieved. The second step served for assessment of agreement between the nurse-registered SAPS II scores (retrieved from the electronic medical record system by the primary investigator) and the gold standard.

This procedure was repeated in all four ICUs for a total of 120 patients. For each patient the following data were registered: (1) SAPS II sum score, (2) every item of the SAPS II score, (3) differences in the reviewers’ judgements and (4) differences between the nurse registered SAPS II score and the gold standard. The following variables were retrieved for the nurses that did the SAPS II scoring: centre, gender, certification, and duration of specific professional experience.

2.4. Statistical Analysis. Variables are expressed as mean ± standard deviation (SD) if not specified otherwise. A P < 0.05 was considered statistically significant. All analyses were performed with Stata statistical software, release 11.0 (Stata Corporation, College Station, TX, USA) and Statview (SAS institute Inc., Cary, NC, USA).

2.4.1. Validation of the Gold Standard. Agreement between reviewers was assessed by average measure interclass correlation coefficient (ICC) (Spearman-Brown correction) for continuous variables (sum scores) and with weighted kappa statistics (and 95% confidence interval) for analysis of the different SAPS II items. Kappas were calculated only for items where more than 20% of the values differed from baseline [18]. Mean agreement for the sum scores and for items between reviewers was assessed by calculating their mean percentage of identical classifications among a pair of reviewers. Perfect agreement was defined as identical categorization of sum scores and items. Differences between the reviewers were analyzed according to the SAPS II tertile (low, medium, and high) and according to their mechanism.
2.4.2. Comparison of the Nurse-Assessed SAPS II Scores and the Gold Standard. Differences in the sum-scores were assessed by a paired t-test. The mean difference (with 95% CI) and the mean absolute difference (i.e., the mean of the value of the difference) between SAPS II sum scores (gold standard minus nurses) were calculated.

Agreement between nurses and the gold standard was assessed as between the reviewers. Agreement was defined as identical categorization of sum scores and items. Kappas and the agreement were analyzed according to the SAPS II tertile (low, medium, and high) and the ICC of the sum scores were analyzed according to the SAPS II tertile and to the center. Concerning the SAPS II sum score a modified Bland Altman analysis with on the x-axis the gold standard and on the y-axis the difference between the two sum scores (gold standard minus nurse value) was performed, completed by a regression analysis between the SAPS II gold standard and the SAPS II gold standard minus the nurse value sum score. A scatter plot between the difference in the predicted mortality calculated with the SAPS II gold-standard sum-score minus the mortality predicted by the SAPS II nurse-registered sum score on the y-axis and the SAPS II gold standard sum score on the x-axis was performed. The difference between the predicted mortalities (deriving from SAPS II sum-scores: gold-standards minus nurse-assessed values) was modelized, using the formula identified in the regression analysis described above.

A univariate analysis was done to define risk factors for the occurrence of an error in items or sum scores, including centers and nurse characteristics (gender, professional experience, and certification). Results are shown as odds ratios (OR; 95% CI) in order to estimate the effect size of risk factors associated with an erroneous estimation. A multivariate logistic regression was performed in order to obtain adjusted estimates of the ORs and to identify factors independently associated with errors, including for the model always the 3 nurse variables and the 4 centers. The multivariate analysis was performed only for those items with sufficient errors enabling the analysis: assuming that for each of the 6 considered predictor variables (centres and nurse characteristics) about 5–10 events should be available, we needed a minimum of 30 and a maximum of 90 events.

3. Results

3.1. Gold Standard Created by Reviewers. A total of 120 different SAPS II scores (1800 variables) were assessed and for 171 cases of divergence (9% of all variables) a gold standard had to be defined by consensus. The minimum-maximum (median) gold standard SAPS II score overall, of low, medium, and high SAPS II tertiles was 6–111 (38), 6–31 (22), 32–47 (38), and 48–111 (70), respectively. Agreement for sum scores among reviewers was almost perfect (mean ICC = 0.985; significant correlation \( P < 0.0001 \); \( P \) for significant difference > 0.05). Table 1 shows the reviewers’ reliability regarding the single variables assessed; accuracy was highest for temperature and bilirubin (perfect agreement = 1.0 and 0.99, resp.) and lowest for systolic blood pressure (perfect agreement = 0.75). Errors in reviewers’ assessment (Table 2) were most frequently observed in the high SAPS II tertile (79 errors), followed by the medium (52) and low tertiles (40). Occurrence of errors was basically due to negligence (49% of cases), followed by a problem related to the definition of the variable (22%), incorrect calculation (16%), and others (13%). Table 2 lists the differences between the reviewers’ judgments according to the kind of error.

3.2. Accuracy of Nurse-Registered SAPS II Scores. The mean (±SD) nurse registered SAPS II sum-score was 40.34 ± 20.19 points versus 44.17 ± 24.86 points of the gold standard (\( P = 0.002 \)). About 90% of the SAPS II sum-scores (112/120) were erroneous in at least one variable (87.5% (35/40) in the low, 97.5% (39/40) in the medium, and 95% (38/40) in the high SAPS II tertiles). Table 3 shows the accuracy in assessment of the single variables when compared to the gold standard. Overall, there was good agreement in the variables sodium, temperature, age, chronic diseases, leucocytes, potassium, and bilirubin (0.83–0.97); the lowest agreement was found in heart rate and systolic pressure (0.45–0.51). Calculated kappas were best for age and lowest for heart rate and systolic pressure (0.32–0.37). Generally, agreement and Kappas were worst in the high SAPS II tertile.

Although SAPS II sum scores were underscored throughout the whole range, there were considerable differences among SAPS II tertiles, in bias and bias dispersion of the difference (SD of difference) and minimum and maximum differences (Table 4). Differences (absolute differences) changed also depending on the SAPS II tertile. Table 5 shows the origin of the over- and underestimation of the low and high SAPS II sum score tertiles. Figure 1 confirms a general trend to overestimate low (≤ 32 points) and underestimate higher sum scores, by highlighting a significant regression between the difference and the gold standard SAPS II sum score (regression of the Bland Altman analysis: \( y = −10.183 + 0.317 \times x; R^2 = 0.34, P < 0.0001 \)). The cut-off point between over- and underestimation was at 32 SAPS II gold standard points.

The mean nurse-predicted mortality rate was 29.11 ± 28.65% versus 35.39 ± 33.59% of the gold standard (\( P = 0.002 \)). The mean difference between the predicted mortality by the gold standard and the predicted mortality by nurses was 6.28% (CI –3.29 to 45.5%, range –50.7 to 56.9%) and a mean absolute difference of 13.8% (CI 0.0 to 30.6%, range 0 to 56.9%). Figures 2(a) (scatter plot) and 2(b) (provisional modelization) illustrates the over- and underestimation of the predicted mortality depending on the SAPS II (golden standard) sum-score values. Considerable differences were found in bias and bias dispersion of the difference (SD of difference) and minimum and maximum differences among the different centers (Table 4).

Table 5 illustrates the variables that induce the overestimation of lower SAPS scores (oxygenation, urinary output, urea, bicarbonate, and bilirubin) and underestimation of the highest SAPS II scores (heart rate, systolic blood pressure, urea, and Glasgow Coma Scale).
Table 1: Reliability across reviewers for the single variables of the SAPS II score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kappa (95% CI)</th>
<th>Mean agreement</th>
<th>Perfect agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.84 (0.79–0.89)</td>
<td>0.88</td>
<td>0.83</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.76 (0.68–0.84)</td>
<td>0.83</td>
<td>0.75</td>
</tr>
<tr>
<td>Temperature</td>
<td>NA</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>0.84 (0.80–0.88)</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td>Urinary output</td>
<td>0.76 (0.72–0.80)</td>
<td>0.90</td>
<td>0.86</td>
</tr>
<tr>
<td>Urea</td>
<td>0.94 (0.91–0.97)</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>NA</td>
<td>—</td>
<td>0.96</td>
</tr>
<tr>
<td>Potassium</td>
<td>NA</td>
<td>—</td>
<td>0.88</td>
</tr>
<tr>
<td>Sodium</td>
<td>NA</td>
<td>—</td>
<td>0.98</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.84 (0.81–0.87)</td>
<td>0.93</td>
<td>0.89</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>NA</td>
<td>—</td>
<td>0.99</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.74 (0.69–0.79)</td>
<td>0.88</td>
<td>0.82</td>
</tr>
<tr>
<td>Age</td>
<td>0.94 (0.92–0.96)</td>
<td>0.95</td>
<td>0.93</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>NA</td>
<td>—</td>
<td>0.94</td>
</tr>
<tr>
<td>Type of admission</td>
<td>NA</td>
<td>—</td>
<td>0.94</td>
</tr>
</tbody>
</table>

a Mean weighted Kappa (95% confidence interval) of the 3 reviewer.
bMean proportions of agreement among the 3 reviewers versus gold standard.
cPercentage of total agreement among the 3 reviewers versus gold standard.
NA: not applicable; no reliable Kappa statistics (≤20% of results differ from norm).

Lower absolute errors were performed in the higher scores. Overall haemodynamics were the most error-prone variables and mistaken assessment was independent of the nurses’ characteristics. However, in the higher SAPS II tertiles, haemodynamics as well as urea and the Glasgow Coma Scale contributed to the underestimation whereas in the lower SAPS II tertile errors in the oxygenation status, urinary output, urea, bicarbonates, and the bilirubin concentration contributed to overestimation of the SAPS II sum scores.

Astonishingly, the agreement of haemodynamic variables—although apparently simple—was inadequate. Our results are comparable to those from Strand et al. [7], who reported similar difficulties for Norway junior doctors in assessing heart rate and systolic blood pressure. A mathematical explanation of this problem could be that five (four) choices are given for scoring of systolic blood pressure (heart rate) whereas the rating of the other physiological variables is generally less demanding. Another explication may be that there it is not only to chose the quantity of deviation (from the normal value) but also the direction of highest ponderation (lowest versus highest value).

With this retrospective audit we were not able to disclose by which mechanisms nurses created mistakes in assessing the SAPS II scores. However, we could show that professional experience and certification had no impact on the occurrence of errors, neither was there a general centre effect. The analysis of the three reviewers’ most frequent sources of problems in defining the gold standard might give some insight (Table 2). In this sense, negligence was the most common source of erroneous assessment. Problems related to the definition of the variables and incorrect calculation of data (oxygenation ratio, urinary output, age) as well as lacking interest in scoring should also be considered. It is

A total of 78 nurses registered the 120 SAPS II scores. No association was found by univariate and multivariate analysis between nurses’ characteristics (experience, certification, gender, and centres) and erroneous scoring of the total SAPS II score or its variables.

4. Discussion

Our study shows that nurse-registered SAPS II sum scores are quite inaccurate. Overall, there was a clear overestimation of lower SAPS II scores and an underestimation of higher SAPS II scores with a center-tendency trend (one fits all tendency). Larger absolute errors were performed in the higher scores.

Figure 1: Linear regression between the difference (gold standard–nurse value) of the SAPS II sum-score and the gold-standard SAPS II sum-score. SAPS II tertiles are illustrated.
Table 2: Differences among the reviewers' judgments for the different items according to the SAPS II tertile and the mechanism of error.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Mechanism of error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Low SAPS (6–31 points)</td>
</tr>
<tr>
<td></td>
<td>N = 120</td>
<td>N = 40</td>
</tr>
<tr>
<td>N, % of differences,</td>
<td>N, (%/%)</td>
<td>N, (%/%)</td>
</tr>
<tr>
<td>% of scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>21 (12/17.5)</td>
<td>8 (20/20)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>30 (18/20)</td>
<td>9 (22.5/22.5)</td>
</tr>
<tr>
<td>Temperature</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>16 (9/13)</td>
<td>2 (5/5)</td>
</tr>
<tr>
<td>Urinary output</td>
<td>17 (10/14)</td>
<td>4 (10/10)</td>
</tr>
<tr>
<td>Urea</td>
<td>6 (4/5)</td>
<td>1 (2.5/2.5)</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>5 (3/4)</td>
<td>0</td>
</tr>
<tr>
<td>Potassium</td>
<td>14 (8/12)</td>
<td>2 (5/5)</td>
</tr>
<tr>
<td>Sodium</td>
<td>3 (2/2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>13 (8/11)</td>
<td>2 (5/5)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1 (0.5/1)</td>
<td>1 (2.5/2.5)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>22 (13/18)</td>
<td>7 (17.5/17.5)</td>
</tr>
<tr>
<td>Age</td>
<td>9 (5/7.5)</td>
<td>2 (5/5)</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>7 (4/6)</td>
<td>1 (2.5/2.5)</td>
</tr>
<tr>
<td>Type of admission</td>
<td>7 (4/6)</td>
<td>1 (2.5/2.5)</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total of differences</td>
<td>171 (100)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Total of scores with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>differences</td>
<td>94 (78)</td>
<td>29 (72.5)</td>
</tr>
</tbody>
</table>

\(^a\) Problem related to the definition of variables and its application (e.g., chronic diseases, type of admission, sustained haemodynamics, GCS in aphasic stroke).

\(^b\) Mathematical problem (e.g., oxygenation ratio, age, daily urinary output).

\(^c\) Insufficient examination of the charts (e.g., erroneous exclusion of laboratory results).

\(^d\) Other mechanism (e.g., insufficient available data in the chart).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Kappa (95% CI)</th>
<th>Low SAPS II (6–31 points) Kappa (95% CI)</th>
<th>Medium SAPS II (32–47 points) Kappa (95% CI)</th>
<th>High SAPS II (48–111 points) Kappa (95% CI)</th>
<th>Agreement Overall Agreement Low SAPS II Agreement Medium SAPS II Agreement High SAPS II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0.32 (0.16–0.48)</td>
<td>0.28 (0.12–0.44)</td>
<td>0.32 (0.15–0.49)</td>
<td>0.22 (0.08–0.36)</td>
<td>0.45</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.37 (0.24–0.50)</td>
<td>NA</td>
<td>0.22 (0.06–0.38)</td>
<td>0.20 (0.08–0.32)</td>
<td>0.51</td>
</tr>
<tr>
<td>Temperature</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.95</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>0.66 (0.56–0.76)</td>
<td>0.33 (0.16–0.50)</td>
<td>0.72 (0.60–0.84)</td>
<td>0.54 (0.40–0.68)</td>
<td>0.71</td>
</tr>
<tr>
<td>Urinary output</td>
<td>0.77 (0.70–0.84)</td>
<td>0.73 (0.63–0.83)</td>
<td>0.80 (0.70–0.90)</td>
<td>0.73 (0.64–0.82)</td>
<td>0.58</td>
</tr>
<tr>
<td>Urea</td>
<td>0.71 (0.64–0.78)</td>
<td>0.70 (0.62–0.78)</td>
<td>0.71 (0.62–0.80)</td>
<td>0.71 (0.63–0.79)</td>
<td>0.67</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.40 (0.29–0.51)</td>
<td>0.83</td>
</tr>
<tr>
<td>Potassium</td>
<td>NA</td>
<td>NA</td>
<td>0.39 (0.24–0.54)</td>
<td>0.32 (0.19–0.45)</td>
<td>0.83</td>
</tr>
<tr>
<td>Sodium</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.81 (0.76–0.86)</td>
<td>0.77 (0.70–0.84)</td>
<td>0.77 (0.69–0.85)</td>
<td>0.76 (0.65–0.87)</td>
<td>0.68</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.80 (0.71–0.89)</td>
<td>0.48 (0.19–0.77)</td>
<td>0.68 (0.43–0.92)</td>
<td>0.89 (0.80–0.98)</td>
<td>0.78</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.97–0.99)</td>
<td>0.98 (0.96–1.00)</td>
<td>0.99 (0.97–1.00)</td>
<td>0.97 (0.94–1.00)</td>
<td>0.93</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.93</td>
</tr>
<tr>
<td>Type of admission</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Table 3: Reliability of nurses versus gold standard SAPS II items in overall SAPS II and SAPS II tertiles.

*aMean weighted Kappa of the 120 nurse-registered SAPS II scores versus the gold standard.

*bMean proportions of agreement of the nurses versus the gold standard.

NA: not applicable; no reliable Kappa statistics (≤20% of results differ from norm).
important to emphasize that our nurse-registered SAPS II scores are based on manual acquisition of data. The nurses rely on previously registered physiological data from the daily patient survey charts and administrative data from the physician charts. They eventually insert manually the variables in the electronic medical record system that automatically calculates the final score. SAPS II being a severity score concerning the first 24 hrs after ICU admission, several care givers are involved in the collection of the different variables and each of them is prone to errors.

Both, reviewers and nurses, globally underestimated SAPS II scores. Most interestingly, we found a negative relationship between the height of the nurse registered sum-scores and their reliability, when compared to the gold standard: the higher the sum scores the more they were underestimated. Exclusion of critical pre-ICU data (e.g., cardiac arrest) may seriously affect SAPS II scores and predicted mortality, as much as some pathologic data goes unconsidered (11 points for heart rate; 13 and 26 points for systolic blood pressure and Glasgow Coma Scale, resp.). The same might apply, although to a smaller extent, for mistaken omission of pathologic laboratory findings, obtained immediately prior to ICU admission (e.g., in the emergency room, on the ward).

The analysis of the correlation and agreements between the nurse-assessed SAPS II scores and the gold standards, calculated without considering the pre-ICU data, showed only slightly better results (not shown). The impact of the differences in scoring (over- and underestimations) may be important. Indeed, we can identify at least 3 areas of concern. First, the stratification or adjustments for research purposes on the basis of routinely (nurse-) assessed SAPS II scores (particularly in multicenter studies with the support of different systems) could be misleading. Secondly, benchmarking across ICUs may be heavily biased. Finally, reimbursements based primarily or secondarily on the SAPS II score as in Germany or Switzerland [5, 6] may seriously suffer from the inaccuracy of the SAPS assessment, especially by the underestimation of higher SAPS II scores. Indeed, in an European study 10% (12%) of respondents reported that their reimbursement relied primarily (secondarily) on severity scores [19].
It has been shown that automatic retrieval of variables may increase scores through a higher sampling rate [20]. Such an approach would probably also decrease the number of missing components who otherwise may lead to an underestimation of sum scores and predicted mortality [21]. A correct transmission of pertinent data, if properly validated, could also increase reliability. In this sense we are adapting our electronic medical record system in order to automatically prepopulate the SAPS II scores with laboratory results and age. Furthermore, by means of a data management system, achievement of haemodynamic and respiratory variables could be automatized. This system, however, is also prone to different problems. First, importation of incoherent data may occur if the information is not manually verified. Second, as severity scores were developed and calibrated with manually acquired data, computer-assisted extraction of data may alter outcome prediction [22]. Accurate acquisition and correct transmission of related data are definitely essential, but without adequate knowledge of the definitions and their exact application, SAPS II scores will hardly become very reliable. Thus, a structured training program will be implemented in our department in order to increase understanding and motivation. Furthermore, the introduction of an interactive program asking in detail the highest and lowest value of a variable (maybe also requiring the exact data) may optimize the SAPS II assessment reducing some of the errors called “negligence.”

Our study presents some strengths and/or limitations: (1) scoring is a difficult task, even for specifically trained reviewers. By consequence, one might question our gold standard. Actually, we believe that this point represents a strength. The way we did this audit (see Section 2) actually excluded any bias regarding professional background, specific training for SAPS II, and assessment practice. Ultimately, there was excellent agreement among reviewers regarding the sum scores. Analysis of the different subscores revealed almost perfect agreement for most of the variables and still substantial agreement for systolic blood pressure, urinary output and the Glasgow Coma Scale. Moreover, the multicentre design of this study permits a certain generalization of the results. (2) The introduction of adapted definitions regarding haemodynamic instability (see Section 2) might have influenced our results. However, exact analysis of the variable systolic blood pressure revealed that only in about 30% of cases there was an underscoring due to disregarding of continuous vasopressor therapy. Moreover, we believe that the definition of this variable should be changed. In order to detect an increased risk of mortality it seems not adequate to score patients with normal systolic blood pressures under huge amounts of vasopressors as “regular.” (3) One might also criticize our real-life situation, where nurses do the assessment of SAPS II scores. However, there are no unequivocal data in the literature able to confute our method. In the unique study directly comparing residents with nurses there was no significant difference between mean APACHE II scores or mean predicted mortality rates [10]. On the other hand, accuracy of scoring among physicians was reported to depend rather on instruction [15] than on the professional experience [23]. (4) Finally, generalization of our results might be further limited inasmuch they refer to SAPS II, whereas the most frequently used ICU severity score worldwide is the Acute Physiology and Chronic Health Evaluation (APACHE) II score [9]. However, we would like to emphasize that the two severity scores diverge principally in the attribution of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean difference (gold standard – nurse value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Heart rate</td>
<td>2.0</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>2.8</td>
</tr>
<tr>
<td>Temperature</td>
<td>0.1</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>−0.2</td>
</tr>
<tr>
<td>Urinary output</td>
<td>−1.3</td>
</tr>
<tr>
<td>Urea</td>
<td>−0.1</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>0.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.4</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.0</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>−0.6</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>1.2</td>
</tr>
<tr>
<td>Age</td>
<td>0.0</td>
</tr>
<tr>
<td>Chronic diseases</td>
<td>−0.1</td>
</tr>
<tr>
<td>Type of admission</td>
<td>−0.4</td>
</tr>
<tr>
<td>ΔSAPS II sum scores</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Table 5: Mean differences between the gold standards and nurse-assessed SAPS II scores concerning the values of the different items composing the SAPS II score, overall, and by tertiles.
A. W. Holt, L. K. Bury, A. D. Bersten, G. A. Skowronski, and that reliability was not influenced by different backgrounds, levels of training and gender. Higher SAPS II sum scores are underestimated and lower scores overestimated. These differences may severely impact on benchmarking, research results, and ICU reimbursement. A multifaceted improvement intervention [16], based on automatic (computer-based) retrieval of most physiological data and implementation of a structured training program, is warranted. Whether these observations may apply also to other severity scores or other healthcare professionals remains an interesting question to be answered.

**Disclosure**

This work was performed at the four regional teaching hospitals of Southern Switzerland: Bellinzona, Locarno, Lugano and Mendrisio.

**References**


Clinical Study
Consecutive Daily Measurements of Luminal Concentrations of Lactate in the Rectum in Septic Shock Patients

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Received 23 August 2011; Revised 31 October 2011; Accepted 29 November 2011

1. Introduction

Resuscitation of patients with septic shock is most often guided by only global parameters such as mean arterial pressure (MAP), central venous pressure (CVP), central venous oxygen saturation (ScvO2), and arterial lactate [1, 2]. However, patients who appears initially to be adequately resuscitated as judged by global parameters may later develop multiple organ failure with fatal outcome [3]. Inability of splanchnic blood flow to meet metabolic demands has been proposed to be one factor in the development and persistence of multiple organ failure in such patients [3, 4]. Therefore, different techniques have been used to assess splanchnic blood flow and metabolism [5–8].

Equilibrium dialysis is a simple, minimally invasive method for the estimation of the concentration of lactate luminally in the rectum and the method was first used to show differences in electrolyte transport and production of inflammatory markers in patients with inflammatory bowel disease [9–11]. Using this method in patients with severe sepsis and septic shock persisting for more than 24 h we have previously shown that luminal concentrations of lactate in the rectum correlate with large bowel permeability [12] and disease severity and outcome [13] indicating pathophysiological relevance. However, in a larger study of patients with septic shock for less than 24 h we observed low luminal rectal concentrations and no relation between concentrations of lactate in the rectal lumen and mortality [14]. Taken together, we have found higher concentrations of lactate in the rectal lumen in patients with septic shock for more than 24 h than in those patients with septic shock for less than 24 h. These observations suggested that the rectal lactate concentration could change over time in some patients and potentially be a marker of outcome.

Therefore, the aim of the present study was to perform daily rectal equilibrium dialysis for the first three days in patients with septic shock to investigate if the concentration of lactate in the rectal lumen changed during this period of time.

2. Materials and Methods

The 22 patients were enrolled at the general intensive care units of Rigshospitalet and Herlev Hospital, University of Copenhagen, Denmark and the population included both surgical and medical patients. The regional ethics committee
approved the study protocol and informed written consent was obtained from the patient or the next of kin. The investigation was registered at http://www.clinicaltrials.gov/ (no. NCT00197938).

2.1. Design. This was a prospective, observational, pilot study with daily consecutive measurements of luminal rectal lactate concentrations in patients on the first 3 days of septic shock.

Patients were enrolled consecutively when meeting the following inclusion criteria: (a) septic shock according to consensus criteria [15] and (b) infusion of vasopressors for 6–24 h. By not including patients in the first 6 h of vasopressor treatment the aim was to exclude patients needing only a short (<6 h) period of vasopressor support during initial resuscitation. All patients were resuscitated according to the principles of the Surviving Sepsis Campaign Guidelines and early goal-directed therapy. Thus, the first rectal equilibrium dialysis was performed 6–24 h after onset of shock (day 1) and repeated 24 h (day 2) and 48 h (day 3) after the initial dialysis.

Exclusion criteria were age less than 18 years, vasopressor treatment for more than 24 h, rectal bleeding or pathology, cardiac arrest during the current episode of sepsis, previous episode of septic shock within current ICU admission or limitations or impending withdrawal of active therapy of the episode of septic shock (day 1) and repeated 24 h (day 2) and 48 h (day 3) after the initial dialysis.

2.2. Data Registration. The following data were registered in all patients: arterial lactate, mean arterial blood pressure (MAP), central venous oxygen saturation (ScvO2), nora-drenaline dose, and intra-abdominal pressure (IAP). To calculate the group medians of parameters other than concentrations of rectal lactate the mean of the registrations done before and after the 4 h of rectal dialysis in individual patients were used. Simplified acute physiology scores (SAPS) II were calculated based on values of the first 24 h after ICU admission and sequential organ failure assessment (SOFA) scores were calculated at inclusion and daily thereafter until either death or discharge from the ICU. Thirty-day mortality was obtained from hospital registries.

2.3. Rectal Equilibrium Dialysis. Measurement of rectal luminal lactate was done as previously described [16, 17]. In brief, a 12 cm long bag of dialysis tubing (semipermeable cellulose, molecular weight cut-off 12 kDa, Sigma, St. Louis, MO, USA) was filled with 4 mL of 6% dextran 70 in saline (Macrodex, MEDA Group, Solna, Sweden) and closed over 5 cm of Tygon tube (Cole-Parmer Instruments Company, Vernon Hills, IL, USA) with a three-way stopcock at the distal end to allow sampling. Once filled, the bag is firm and can be easily inserted into the rectal lumen after digital exploration. Part of the Tygon tube and the three-way stopcock will then protrude from the anus. The dialysate was sampled after 4 h of dialysis, since 90–95% equilibrium with the lactate concentration in the surrounding medium is obtained at this time point [17]. Dialysates were analysed immediately at the study sites using standard blood gas autoanalysers (ABL 725, Radiometer, Copenhagen, Denmark), which were calibrated according to the manufacturer’s instructions. This analyser is stereospecific and measures only concentrations of L-lactate.

2.4. Statistics. Continuous variables are presented as medians (25th–75th percentiles) unless stated otherwise. The Mann-Whitney test or Fisher’s exact test were performed where appropriate. The Friedman test (repeated measures) was used when analysing three paired groups (e.g., changes in concentrations of luminal rectal lactate over 3 days) and Wilcoxon’s signed rank test was used when analysing two paired groups of observations (e.g., changes in concentrations of luminal rectal lactate over 2 days in those patients with only 2 dialysis periods). All analyses were done using GraphPad Prism v. 4.00 (GraphPad Software, San Diego, CA, USA). Values of $P < 0.05$ (two-tailed) were considered significant.

3. Results

The overall 30-day mortality of the study population was 23% (5 nonsurvivors and 17 survivors). The characteristics of the 22 patients are shown in Table 1. All patients underwent rectal equilibrium dialysis in 2 consecutive days, but only 15 patients underwent rectal equilibrium dialysis in all 3 days (3 patients were discharged or transferred to another ICU, 1 patient died, and 3 patients had profuse diarrhoea on the 3rd day, so that the dialysis bag slipped out of the rectum).

3.1. Nonsurvivors and Survivors. There were no differences in the concentrations of lactate in the rectal lumen between nonsurvivors and survivors on any day. On day 1 the concentration of rectal lactate was 2.4 (1.3–7.5) mmol/L in nonsurvivors and 2.1 (1.2–4.4) mmol/L in survivors ($P = 0.58$) see Table 2. On day 2 the rectal concentrations of lactate were 3.2 (1.7–4.2) mmol/L and 2.1 (1.1–3.4) mmol/L ($P = 0.39$) and on day 3 the concentrations were 2.9 (1.5–3.0) mmol/L and 2.3 (0.9–3.0) mmol/L ($P = 0.61$), respectively, (Table 2).

Neither were there any changes in the actual concentrations of lactate in the rectal lumen over the 3 days in neither nonsurvivors nor survivors; see Figure 1.

Similarly, there were no difference in arterial values of lactate between the groups of nonsurvivors or survivors or within the groups over the days; see Table 2 and Figure 1.

3.2. Changes in Luminal Rectal Lactate over Time. Data were stratified according to patients with an increase or a decrease/no change in the concentration of lactate in the rectal lumen from day 1 to day 2 and/or from day 2 to day 3; see Table 3. Eleven patients had an increase in the concentration of luminal rectal lactate from day 1 to day 2 with a median increase of 0.7 (0.1–1.7) mmol/L and 7 patients had an increase from day 2 to day 3 (1.0 (0.1–1.2) mmol/L). Eleven patients had a decrease in the concentration of rectal lactate
Table 1: Characteristics of 22 septic shock patients. Medians (25th–75th percentiles) or numbers (percentage).

<table>
<thead>
<tr>
<th></th>
<th>Nonsurvivors $(n = 5)$</th>
<th>Survivors $(n = 17)$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68 (51–75)</td>
<td>65 (49–68)</td>
<td>0.43$^a$</td>
</tr>
<tr>
<td>Male/female</td>
<td>3/2</td>
<td>12/5</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>Focus of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (20%)</td>
<td>7 (41%)</td>
<td>0.61$^b$</td>
</tr>
<tr>
<td>Abdominal</td>
<td>1 (20%)</td>
<td>3 (18%)</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>3 (60%)</td>
<td>3 (18%)</td>
<td>0.10$^b$</td>
</tr>
<tr>
<td>Infectious agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative</td>
<td>1 (20%)</td>
<td>2 (12%)</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>Gram-positive</td>
<td>3 (60%)</td>
<td>10 (59%)</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>Both</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>Fungi, virus or unknown</td>
<td>1 (20%)</td>
<td>3 (18%)</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>SAPS II</td>
<td>64 (56–75)</td>
<td>48 (39–70)</td>
<td>0.15$^a$</td>
</tr>
<tr>
<td>SOFA score at inclusion</td>
<td>12 (9–16)</td>
<td>12 (9–14)</td>
<td>0.78$^a$</td>
</tr>
<tr>
<td>Shock duration at inclusion (hours)</td>
<td>11 (8–17)</td>
<td>12 (9–18)</td>
<td>0.61$^a$</td>
</tr>
</tbody>
</table>

$^a$Mann-Whitney test  
$^b$Fisher’s exact test.

from day 1 to day 2 ($−1.0 (−0.3–−4.8)$ mmol/L) and 8 patients a decrease from day 2 to day 3 ($−0.5 (−0.2–−1.7)$ mmol/L). There were no difference in SAPS II, SOFA score at inclusion or day 5 between the groups with an increase or a decrease/no change in rectal lactate either from day 1 to day 2 or from day 2 to day 3.

3.3. Rectal versus Arterial Concentration of Lactate. The luminal rectal and arterial concentrations of lactate did not differ significantly on any day in any group, see Figure 2.

The rectal-arterial gradient (delta-lactate) was not different in nonsurvivors on any day and did not change over the days in either group; see Table 2. There was no correlation between MAP, noradrenaline dose, intraabdominal pressure or ScvO2, and rectal lactate concentrations in any group at any time.

Ninety-day mortality was 41% (9 nonsurvivors and 13 survivors). Results were unchanged when data were analysed according to 90-day mortality (data not shown).

4. Discussion

There were four main findings of this study. Firstly, the concentrations of lactate in the rectal lumen did not change over the first 3 days in patients with septic shock. Secondly, there was no difference in the rectal lactate concentrations between nonsurvivors and survivors. Thirdly, there were no differences in SAPS II and SOFA scores at inclusion or day 5 in those patients with increasing concentrations of lactate in the rectal lumen compared with those patients with a decrease/no change and fourthly, there was no significant difference between luminal rectal and arterial concentrations of lactate.

These findings raise some important questions. Why this discrepancy of the observations of these later studies and the previous study regarding an association between concentrations of lactate in the rectal lumen and outcome? Mortality is a “hard” outcome parameter often requiring larger populations to establish a significant difference, so it is perhaps not surprising that we did not observe any difference between nonsurvivors and survivors in the present small population. However, in the study of early septic shock we investigated 130 patients [14] and significant differences in mortality have been seen before in patient populations of this smaller size, both by ourselves and others [13, 18].

In the previous cohort [13], in which the mortality was 48% (11 of 23 patients), we observed significantly higher concentrations of lactate in the rectal lumen in nonsurvivors compared to survivors of severe sepsis or septic shock. In that study the lactate concentrations in the rectal lumen were also higher than arterial concentrations and the difference were more pronounced (5.0 (0.9–11.8) versus 2.2 (0.4–4.9) mmol/L; $P < 0.0001$) than the difference in the arterial concentrations (3.8 (1.7–7.0) versus 1.6 (0.5–3.6) mmol/L; $P < 0.01$) between nonsurvivors and survivors. These findings suggested that the concentration of lactate in the rectal lumen could be an important marker of regional metabolic dysfunction of the gut and distinctly different than arterial concentrations of lactate. Therefore that study was followed by the study of patients with early (6–24 h) septic shock [14], which was designed to investigate this apparent association between rectal lactate concentrations and mortality. However, the observations could not be reproduced in patients with septic shock for less than 24 h and the concentrations of lactate in the rectal lumen and arterial lactate were both lower than in the previous study [13]. One possible explanation for this discrepancy could
Table 2: Daily parameters in 22 patients with septic shock stratified by survival.

<table>
<thead>
<tr>
<th></th>
<th>Nonsurvivors (n = 5)</th>
<th>Survivors (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>(88–114)</td>
<td>(80–125)</td>
<td>(70–95)*</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>5/5</td>
<td>4/5</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0/5</td>
<td>1/5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td>Noradrenaline dose</td>
<td>0.34</td>
<td>0.04</td>
</tr>
<tr>
<td>(μg/kg/min)</td>
<td>(0.12–0.49)</td>
<td>(0.01–0.09)</td>
</tr>
<tr>
<td>ScvO2 (%)</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>IAP (mmHg)</td>
<td>14</td>
<td>16*</td>
</tr>
<tr>
<td>Lactate, arterial</td>
<td>1.9</td>
<td>1.5</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>(1.6–8.2)</td>
<td>(1.2–3.7)</td>
</tr>
<tr>
<td>Lactate, rectal lumen</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>(1.3–7.5)</td>
<td>(1.7–4.2)</td>
</tr>
<tr>
<td>Delta-lactate</td>
<td>0.25</td>
<td>0.60</td>
</tr>
<tr>
<td>(rectal-arterial (mmol/L))</td>
<td>(−0.1−0.3)</td>
<td>(−0.4–0.2)</td>
</tr>
</tbody>
</table>

Values are medians (25th–75th percentiles). *P = 0.02 compared with IAP day 2 in survivors. No other significant differences were found using the Mann-Whitney test (comparing values between groups on specific days) or Wilcoxon’s signed rank test or Friedmans’s test (comparing paired values within groups over 2 or 3 days, resp.). Range since n = 3.

Table 3: SAPS II score, SOFA score at inclusion and day 5 of patients with an increase or decrease/no change in luminal rectal lactate from day 1 to day 2 or from day 2 to day 3, respectively.

<table>
<thead>
<tr>
<th></th>
<th>From day 1 to day 2</th>
<th>P</th>
<th>From day 2 to day 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase in rectal lactate</td>
<td>(n = 11)</td>
<td>Decrease in rectal lactate</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>64</td>
<td>46</td>
<td>0.07</td>
<td>53</td>
</tr>
<tr>
<td>(48–74)</td>
<td>(28–53)</td>
<td></td>
<td></td>
<td>(46–74)</td>
</tr>
<tr>
<td>SOFA (at inclusion)</td>
<td>12</td>
<td>10</td>
<td>0.14</td>
<td>13</td>
</tr>
<tr>
<td>(11–15)</td>
<td>(8–13)</td>
<td></td>
<td></td>
<td>(10–14)</td>
</tr>
<tr>
<td>SOFA (day 5)</td>
<td>8</td>
<td>8</td>
<td>0.67</td>
<td>8</td>
</tr>
<tr>
<td>(4–13)</td>
<td>(6–11)</td>
<td></td>
<td></td>
<td>(8–13)</td>
</tr>
</tbody>
</table>

Values are medians (25th–75th percentiles). Statistical analysis comparing values between patients with an increase or a decrease/no change in rectal luminal lactate were done using the Mann-Whitney test.

be that in the first study [13] most patients had their rectal equilibrium dialysis when they had had septic shock for 48–72 h. It could be speculated that there is a “delay” in time in the development or change in the concentrations of rectal lactate. Interestingly, Poeze et al. [18] did an excellent study in 28 critically ill patients where they found that regional variables (gastric mucosal pH and indocyanine green clearance) were better to predict outcome than global hemodynamic parameters, but only after initial stabilisation, typically at least 12 hours.

However, the data of this present study cannot support such a time-dependent change or development in the concentrations of lactate in the rectal lumen in patients with septic shock.

Were the patients in this present study less severely ill? It seems unlikely since the SAPS II and SOFA scores were high, but they did have arterial concentrations of lactate in the lower range compared to other studies [13, 19–21]. However, such lower concentrations of arterial lactate have been observed by others in both nonsurviving and surviving patients.
patients with sepsis [18]. Also, we did not see the difference in the arterial lactate concentrations between nonsurvivors and survivors, which have been observed in other studies [18–21], but our study was not specifically designed to investigate arterial lactate concentrations. An important difference could be that the values of arterial lactate reported in our data is not strictly admission values or 24 h values but the corresponding arterial lactate concentrations at the time of rectal equilibrium dialysis which was performed at any time from 6–24 h after onset of shock.

Because we did not observe any change in the rectal concentrations of lactate in neither the group of nonsurvivors or survivors we analysed if there were any difference in disease severity between the individual groups of patients with increasing or decreasing/no change concentrations of luminal lactate in the rectum. No such difference were found regarding SAPS II score, SOFA score at inclusion or day 5, but the actual increases or decreases in rectal lactate concentrations were small.

Perhaps most importantly, we did not observe any difference in the concentrations of lactate in the rectal lumen compared with the arterial concentrations, a finding which also contrasts our earlier observations in septic patients [12, 13, 16]. If the concentrations of lactate in the rectal lumen are no different than arterial concentrations of lactate, no more information is gained by using this method trying to assess metabolic dysfunction of the gut.

Are luminal concentrations of lactate a valid marker of metabolic dysfunction? Animal studies indicates this as concentrations of lactate in the intestinal lumen has been studied in animal models of occlusive gut ischaemia [22–25] and was found to be a more sensitive marker of hypoperfusion-induced intestinal metabolic dysfunction compared to lactate levels in blood or intestinal serosa or mucosa.

There are many different techniques available for assessing blood flow and the metabolic state of the gut [5–8]. We believe our method of assessing luminal lactate in the rectal lumen is valid based on our previous studies in septic shock [12, 13, 16, 17], cardiac surgery [26], and the earlier studies by others on inflammatory bowel disease [9–11]. Thus, Perner and coworkers [26] found a 2- to
Figure 2: Rectal and arterial concentrations of lactate in nonsurvivors and survivors of septic shock. There were no differences using Wilcoxon’s signed rank test.

3-fold increase in concentrations of lactate in the rectal lumen in patients during coronary artery bypass grafting (CABG) with cardiopulmonary bypass as compared to off-pump CABG and healthy subjects. Similar results have been obtained by others. Using a microdialysis catheter Solligård and coworkers found a 10-fold increase in luminal rectal lactate in patients during cardiopulmonary bypass [27]. In our opinion these observations support the notion that luminal concentrations of lactate in the rectum could be a marker of ischaemia or metabolic dysfunction.

So, could our results reflect that the patients in both our study in early septic shock [14] and the present study did not have hypoperfusion or metabolic dysfunction of the gut and that the patients in our earlier studies did have detectable metabolic dysfunction or hypoperfusion? Unfortunately neither of the studies were designed to evaluate this...
issue further, since we opted for a more simple study design in order to better facilitate enrolment of patients. But this should be an important question to address in future studies.

5. Conclusion

Our study showed no change or development in the concentrations of lactate in the rectal lumen over the first 3 days in patients with septic shock or any difference between nonsurvivors and survivors. We found no difference between luminal rectal and arterial concentrations of lactate at any point. At present, the role of rectal equilbrium dialysis outside experimental trials is not defined and needs further investigation, ideally in studies also evaluating other methods of assessing gut metabolic function or blood flow.

Conflict of Interests

The authors declare that they have no conflict of interests.

Disclosure

Parts of this study were presented at the 30th Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine 2009.

References


Clinical Study

The Impact of a Pulmonary-Artery-Catheter-Based Protocol on Fluid and Catecholamine Administration in Early Sepsis

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Received 21 July 2011; Revised 6 October 2011; Accepted 2 December 2011

Academic Editor: Maxime Cannesson

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Objective. The pulmonary artery catheter (PAC) remains topic of debate. Despite abundant data, it is of note that many trials did not incorporate a treatment protocol.

Methods. We retrospectively evaluated fluid balances and catecholamine doses in septic patients after the introduction of a PAC-based treatment protocol in comparison to historic controls.

Results. 2 × 70 patients were included. The first day the PAC group had a significantly higher positive fluid balance in comparison to controls (6.1 ± 2.6 versus 3.8 ± 2.4 litre, P < 0.001). After 7 days the cumulative fluid balance in the PAC group was significantly lower than in controls (9.4 ± 7.4 versus 13 ± 7.6 litre, P = 0.001). Maximum dose of norepinephrine was significantly higher in the PAC group. Compared to controls this was associated with a significant reduction in ventilator and ICU days.

Conclusions. Introduction of a PAC-based treatment protocol in sepsis changed the administration of fluid and vasopressors significantly.

1. Introduction

The pulmonary artery catheter (PAC) by Swan and Ganz, in the setting of critically ill patients, was originally introduced to “apply physiologic principles to the understanding of the circulatory abnormalities characterizing an illness in an individual patient, and to provide a rational basis for selection of therapy with objective, quantitative assessment of patient response” [1, 2]. In the following decades, this mechanistic perspective on the clinical relevance of PAC and other monitoring devices was gradually abandoned and replaced by “evidence-based medicine,” with emphasis on its potential value to reduce morbidity and mortality. Ever since, multiple randomised controlled trials in different subsets of ICU patients have been performed, to evaluate the use of PAC to improve outcome [3–7]. Lack of consistency in the results of these trials have led many to believe that the use of PAC should be done with great restraint [8]. Others, however, have stressed the potential methodological drawbacks of these trials, that may obscure underlying beneficial effects of the use of PAC; correct measurement, correct interpretation, and correct application of PAC-derived data are all essential to the final result [9, 10]. Today, many aspects of such methodological flaws have been acknowledged. Errors in measurements [11, 12], delay in insertion of PAC in acutely ill patients [13], misinterpretation of static filling pressures as a marker of preload [14], absence of therapeutic strategies [6, 7], as well as faulty supranormal endpoints [15] have all been reported. Furthermore, over the years the use of PAC has shifted from intermittently measuring static filling pressures towards a continuous indicator of (dis)balance between oxygen supply (cardiac output) and consumption
(mixed venous oxygen saturation, SvO₂). Furthermore it has now become a tool for the assessment of functional hemodynamic parameters, such as fluid responsiveness. To our knowledge, data on the effect of a PAC-based protocol, that integrates most of these aspects seem to be lacking.

In the present study we aimed to evaluate the influence of a PAC-based protocol on fluid administration and catecholamine use of well-trained intensivists in the specific setting of critically ill patients with early-phase severe sepsis/septic shock. We chose this particular group of patients, under the assumption that (a change in) hemodynamic management might have considerable potential impact on patient morbidity. Primary endpoints were the fluid balance after 24 hours and 7 days and maximum dose of dopamine and norepinephrine within the first 24 hours. Secondary outcome variables were days on the ventilator and length of stay (LOS) ICU.

2. Material and Methods

2.1. Patients. The study was performed in a closed-format 22-bed mixed ICU in a tertiary teaching hospital. After the introduction of a PAC-based protocol for hemodynamic management as standard treatment for patients with sepsis as primary reason for ICU admittance, all patients ≥18 years with severe sepsis and septic shock, according to international criteria [16], were included in the study during an 18-month period in 2007-2008. The historic control group was recruited from our database in a 2-year period in 2005-2006 and matched for sepsis criteria in a 1:1 ratio from a consecutive period prior to implementation of the protocol. The experiment was conducted with the understanding and the consent of the human subject. According to applicable laws the need for ethical approval or individual consent was waived.

2.2. Protocol. During the study period hemodynamic assessment in patients with severe sepsis or septic shock was achieved through continuous invasive monitoring of arterial blood pressure and right heart catheterisation with continuous cardiac output and SvO₂ measurement (Vigilance, Edwards Lifesciences, Saint-Prex, Switzerland) within 4 hours after ICU admittance. Until a PAC was in place, the use of fluids and vasoactive drugs was at the discretion of the attending physician, aiming at a minimal mean arterial pressure (MAP) of 60 mmHg. After insertion and calibration of the PAC, treatment of circulatory failure was aimed at a MAP ≥60 mmHg in combination with a cardiac index (CI) ≥2.5 L/m²/min and an SvO₂ ≥70%. Achievement of these endpoints was performed in the following strict hierarchical order. (1) Exclusion of fluid responsiveness by repeated infusions of at least 250 mL crystalloids, colloids, or blood products, until the increase in left ventricular stroke volume was less than 10% or until the pulmonary artery wedge pressure exceeded 18 mmHg. Fluid administration was also stopped in case hemodynamic endpoints were fulfilled. (2) Treatment of inadequate systemic oxygen supply, defined as a cardiac index <2.5 L/m²/min or central venous oxygen saturation <70%, with dopamine administered at up to 10 μg/kg/min and additional enoximone in the event of an inadequate response to dopamine. (3) Reversal of hypoten-son with norepinephrine in case of MAP <60 mmHg despite the aforementioned steps (Figure 1). Feedback on adequacy of PAC measurements and compliance with the protocol was given to the attending intensivists on a daily basis by an independent observer.

In the control group hemodynamic monitoring consisted of an indwelling arterial catheter and central venous line. Treatment was aimed at a MAP ≥60 mmHg and central venous pressure (CVP) between 8 and 12 mmHg. A closed-format setting, as well as protocols for the use of antibiotics (including selective decontamination of the digestive tract), tight glucose regulation, low tidal volume ventilation, weaning, (enteral) nutrition, activated protein C and steroid administration, and a general red blood cell transfusion trigger (hematocrit <25%) were unaltered during the study and control period.

2.3. Data Collection. The following data were recorded at baseline: demographic characteristics; severity of illness and predicted mortality consistent with APACHE IV [17], SOFA [18] (calculated over the first 24 hours following ICU admission), and RIFLE [19] scores; hemodynamic data including fluid balance and dose of vasoactive drugs; results of standard laboratory tests, including blood gases, arterial lactate concentrations, blood cultures, and cultures of specimens sampled from each presumed site of infection. Daily routine recordings consisted of hemodynamic data, fluid balance, dose of vasoactive drugs, arterial lactate concentrations, and blood gases; SOFA and RIFLE scores were calculated daily during each patient’s ICU stay. The presence of ARDS was retrospectively established by an independent observer by chest X-ray assessment in combination with gas exchange criteria [20]. Survival status was confirmed for each subject at the end of their hospitalisation.

2.4. Statistical Analysis. For continuous variables, data are presented as mean ± SD or as medians and interquartile ranges (IQRs) in case of nonnormal distribution. Differences in baseline values and outcome parameters between groups were compared using an independent sample t-test, or Mann-Whitney test in case of nonnormal distribution. Comparison of mortality rates across different treatment strategies was performed using the χ² test. A two-sided P value of <0.05 was considered statistically significant. Confounding of the group effect on the primary endpoint was analysed using multiple regression analyses. Variables with significant group differences at baseline were entered individually and in combination in the regression model to detect significant confounding effects. The Statistical Package for Social Sciences (SPSS 15.1 for Windows, Chicago, IL, USA) was used for statistical analyses. Sample size was based on the following assumptions. According to a random sample of 20 protocol-treated patients we estimated the fluid balance after 24 hours 5.7 ± 2.5 litres. With an alpha of 0.05 and a power of 0.9, it would require a sample size of 2 × 66 patients to detect a difference of at least 1 litre.
3. Results

In 2007 and 2008 70 patients fulfilling the criteria for severe sepsis or septic shock were included in the study; 70 matched control patients were recruited from 2004 to 2006. Protocolized resuscitation and pulmonary artery catheterisation was performed successfully in all patients within 4 hours of ICU admittance. No PAC-related complications, including pneumothorax, line-related sepsis, or knotting were reported; median duration of PA catheterisation was 4 days. Baseline characteristics were balanced between groups with the exception of a significantly higher age, lactate, and RIFLE score in the control group and higher SOFA score in the PAC group (Table 1).

**Primary Outcome.** During the first 24 hours patients in the PAC group had a significantly higher positive fluid balance in comparison to controls (6.1 ± 2.6 versus 3.8 ± 2.4 litre, \(P < 0.001\)). However, after 7 days the cumulative fluid balance in the PAC group was significantly lower than in controls (9.4 ± 7.4 versus 13 ± 7.6 litre, \(P = 0.001\); Table 2, Figure 2). Use of norepinephrine was significantly higher in the PAC group, both in dose and number of patients, but no difference in the use of dopamine between groups was observed (Table 2). Multiple linear regression analyses showed that the statistically significant difference in fluid balance after day 1 between the groups was not altered after correction for age, lactate, and RIFLE score in the control group and higher SOFA score in the PAC group (Table 1).

**Secondary Outcome.** Median number of days on the ventilator was significantly lower in the PAC group in comparison to controls: 7 (5–11) versus 10 (6–18) days, \(P = 0.01\) (Table 3). This was accompanied by a significantly
Table 1: Baseline characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PAC (n = 70)</th>
<th>Control (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>42 (61)</td>
<td>39 (56)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age</td>
<td>62 ± 16</td>
<td>67 ± 13</td>
<td>0.02</td>
</tr>
<tr>
<td>APACHE IV</td>
<td>90 ± 47</td>
<td>88 ± 29</td>
<td>0.73</td>
</tr>
<tr>
<td>Predicted mortality APACHE IV (%)</td>
<td>43 ± 21</td>
<td>39 ± 16</td>
<td>0.36</td>
</tr>
<tr>
<td>SOFA</td>
<td>10 ± 3</td>
<td>8 ± 3</td>
<td>0.03</td>
</tr>
<tr>
<td>Source of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>19</td>
<td>16</td>
<td>0.19</td>
</tr>
<tr>
<td>Abdominal</td>
<td>34</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>ARDS (n)</td>
<td>4</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>71 ± 12</td>
<td>68 ± 15</td>
<td>0.18</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>110 ± 17</td>
<td>109 ± 20</td>
<td>0.82</td>
</tr>
<tr>
<td>Central venous pressure, mmHg</td>
<td>13 ± 5</td>
<td>12 ± 5</td>
<td>0.84</td>
</tr>
<tr>
<td>Ventilator, use of, n (%)</td>
<td>69 (99)</td>
<td>69 (99)</td>
<td>1.00</td>
</tr>
<tr>
<td>PEEP, cm H₂O</td>
<td>13 ± 3</td>
<td>13 ± 3</td>
<td>0.88</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>2.4 (1.4–4.3)</td>
<td>3.5 (2.7–5.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>RIFLE score on admission</td>
<td>0 (0–1)</td>
<td>0 (0–2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

PAC: pulmonary artery catheter. APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, PEEP: positive end expiratory pressure, RIFLE: risk injury failure loss and endstage. Data are presented as mean ± SD, median (IQR) or as numbers (%).

Table 2: Primary outcome variables: fluid balance and use of vasoactive drugs.

<table>
<thead>
<tr>
<th></th>
<th>PAC (n = 70)</th>
<th>Control (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid balance day 0–4 hours (L)</td>
<td>2.0 ± 1.4</td>
<td>1.9 ± 1.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Fluid balance day 1</td>
<td>6.1 ± 2.6</td>
<td>3.8 ± 2.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluid balance day 2</td>
<td>3.7 ± 2.0</td>
<td>4.8 ± 2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Fluid balance day 3</td>
<td>1.6 ± 1.9</td>
<td>3.2 ± 2.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluid balance day 4</td>
<td>−0.1 ± 2.1</td>
<td>1.4 ± 2.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Fluid balance day 5</td>
<td>−0.3 ± 1.7</td>
<td>0.1 ± 2.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Fluid balance day 6</td>
<td>−0.7 ± 1.4</td>
<td>−0.5 ± 2.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Fluid balance day 7</td>
<td>−0.7 ± 1.6</td>
<td>0.1 ± 2.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Fluid balance day 1–7</td>
<td>9.4 ± 7.4</td>
<td>13 ± 7.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Maximum dose norepinephrine (μg/kg/min, n)</td>
<td>0.12 (0.03–0.19), 59</td>
<td>0.02 (0–0.17), 39</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum dose dopamine (μg/kg/min, n)</td>
<td>7.02 (4.7–9.8), 65</td>
<td>7.7 (4.7–9.6), 66</td>
<td>0.79</td>
</tr>
</tbody>
</table>

PAC: pulmonary artery catheter. Data are presented as mean ± SD, median (IQR) or as numbers.

shorter LOS ICU for patients in the PAC group, as compared to controls: 9 (6–13) versus 14 (7–28) days, P < 0.001. Post hoc univariate analysis revealed a significant correlation between the cumulative fluid balance after 7 days and both number of days on the ventilator (r_s = 0.47, P < 0.001) as well as LOS ICU (r_s = 0.43, P < 0.001). However, there was no correlation between the fluid balance on day 1 and number of days on the ventilator or LOS ICU (r_s = 0.17, P = 0.06, and r_s = 0.13, P = 0.12, resp.; Figure 3).

4. Discussion

In the present study implementation of a PAC-based protocol for the hemodynamic management of patients with severe sepsis and septic shock was associated with a considerable impact on the use of volume resuscitation and vasopressors, both in timing and total volume. In comparison to historic controls, the PAC group received significantly more fluids during the first 24 hours. Interestingly this was accompanied
Critical Care Research and Practice

Figure 2: Fluid balances in the first week.

Table 3: Secondary outcome variables: morbidity and mortality.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PAC (n = 70)</th>
<th>Control (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on ventilator</td>
<td>7 (5–11)</td>
<td>10 (6–18)</td>
<td>0.01</td>
</tr>
<tr>
<td>PO$_2$/FiO$_2$ ratio, worst (mmHg)</td>
<td>196 ± 81</td>
<td>158 ± 64</td>
<td>0.003</td>
</tr>
<tr>
<td>CVVH, n</td>
<td>28</td>
<td>35</td>
<td>0.24</td>
</tr>
<tr>
<td>CVVH, days</td>
<td>0 (–5)</td>
<td>0 (0–8)</td>
<td>0.08</td>
</tr>
<tr>
<td>RIFLE score, highest</td>
<td>2 (0–3)</td>
<td>3 (1–3)</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS ICU (days)</td>
<td>9 (6–13)</td>
<td>14 (7–28)</td>
<td>0.001</td>
</tr>
<tr>
<td>LOS hospital</td>
<td>24 (14–40)</td>
<td>30 (17–51)</td>
<td>0.16</td>
</tr>
<tr>
<td>Cumulative SOFA score day 1–5</td>
<td>39 ± 15</td>
<td>40 ± 16</td>
<td>0.67</td>
</tr>
<tr>
<td>Cumulative SOFA score day 1–5 survivors</td>
<td>39 ± 12</td>
<td>38 ± 16</td>
<td>0.63</td>
</tr>
<tr>
<td>Mortality ICU (n, %)</td>
<td>15 (21)</td>
<td>21 (30)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mortality hospital (%)</td>
<td>17 (24)</td>
<td>27 (39)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

PAC: pulmonary artery catheter, FiO$_2$: inspiratory oxygen fraction, CVVH: continuous veno venous hemofiltration, RIFLE: risk injury failure loss and endstage, LOS: length of stay, SOFA: sequential organ failure assessment. Data are presented as mean ± SD, median (IQR) or as numbers (%).

by a significant reduction in total fluid administration in the first 7 days. These differences were not only statistically significant, but also associated with clinically relevant endpoints: reduction of days on the ventilator and LOS ICU.

In this respect, the setting in which the PAC-based protocol was tested seems to be of great importance. We specifically selected patients with assumed perfusion abnormalities. In this setting of patients with severe sepsis or septic shock, we anticipated a high likelihood to detect differences in the early management of fluids and vasoactive drugs between conventional and PAC-based hemodynamic treatment. This is in contrast to other groups of patients, in which hemodynamic management may not be of equal importance, for example, in routine noncardiac surgery [21].

Despite an overwhelming number of trials, addressing the use of PAC in different clinical subsets, there are not many data specifically focused on (differences) in the use of fluids, inotropes, and vasopressors, as a result of a PAC-based treatment algorithm. The vast majority of studies did not incorporate hemodynamic endpoints and/or treatment protocols and failed to report how the use of PAC changed therapeutic behaviour [7, 22]. Other studies aimed for supranormal endpoints (CI, SvO$_2$) generally considered faulty in hindsight; interestingly in these trials only a minority of patients fulfilled endpoints [3, 15]. Furthermore, many protocols were based on the incorrect assumption that static filling pressures could predict cardiac response to volume infusion [14] or formation of pulmonary oedema [23].
The presented dynamics in fluid administration (more fluids in the early phase, less fluids later) show similarities with previous data from hemodynamic endpoint-driven treatment protocols in sepsis. After a $S_{O2}$-based protocol differences in the use of fluids in comparison to conventional treatment were observed after 6 hours, rather than after 3 days [24]. In a retrospective study in patients with septic shock and ARDS, both initial fluid frontloading and subsequent fluid restriction were identified as markers of morbidity and mortality [25]. In accordance with our data, this was associated with increased use of norepinephrine, but not dopamine. The importance of timing was illustrated by the fact that the use of PAC in ARDS, after a mean period of admittance to the ICU of >40 hours and a fluid intake >4900 mL, was not associated with improvement in outcome [13]. Interestingly, we observed an association between LOS ICU/number of days on the ventilator and the cumulative fluid balance after 7 days, but not after 24 hours. This may be explained by the fact that pulmonary oedema formation in sepsis may not occur during (early) volume loading in the steep part of the cardiac function curve, as opposed to (late) volume loading in the horizontal part of the curve [26].

It seems unlikely that the observed changes in fluid dynamics and vasopressor administration are restricted to the use of the PAC itself. Guidance by other physiologic variables, derived from pulse contour analysis or oesophageal Doppler monitoring, were also associated with a change in therapeutic behaviour [27–29].

Several limitations of the study need to be addressed. Comparison between an intervention group and historic controls may be biased by unknown changes in patient management over time. The imbalance in lactate at baseline between groups might reflect significant differences in level of resuscitation or case mix and, therefore, create a bias in interpretation of the fluid balances. To “correct” this to some extent we performed a multiple linear regression analysis that included the difference in baseline lactate between groups, and its potential influence in fluid balance after day 1. After correction for age, RIFLE score, lactate, and SOFA score, the impact of the protocol remained highly significant for the primary endpoints ($P < 0.001$). Similar considerations need to be taken into account with respect to the imbalance in RIFLE score at baseline. The presence of acute renal failure at baseline is likely to be associated with LOS ICU and mortality. Alternatively, a positive fluid balance itself has also been identified as an independent risk factor for the occurrence of acute renal failure [30].

A single centre setup determines both skills in insertion of PAC and correct measurements, as well as the use of fluids and vasoactive drugs “according to the discretion of the attending physician.” Extrapolation to other settings should therefore be done with great restraint. Although the relation between primary and secondary outcome variables appear to be relevant, one should realize that the number of days on the ventilator and LOS ICU is surrogate endpoint for ICU treatment. However, the number of patients in this study was not adequate to detect potential differences in hospital mortality. At best, our results can be considered as hypothesis generating, rather than conclusive. Nevertheless, the data seem to indicate that a PAC-based treatment protocol, applied to a very early phase of a disease state with a high a priori chance on hemodynamic-related morbidity and mortality, has considerable impact on fluid and vasopressor management in comparison to nonprotocolized treatment, both in absolute numbers and dynamics. Future studies with adequate design are necessary to establish its potential for mortality reduction.

**Conflict of Interests**

The authors declare no conflict of interests.
References


Research Article

Sepsis and AKI in ICU Patients: The Role of Plasma Biomarkers

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Received 3 August 2011; Revised 6 October 2011; Accepted 22 November 2011

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Given the higher mortality rate of ICU patients with sepsis and AKI, we decided to investigate the possible correlation between serum biomarkers of organ damage, such as neutrophil gelatinase-associated lipocalin (NGAL), advanced oxidation protein products (AOPP), and brain natriuretic peptide (BNP) and endotoxin activity in ICU septic patients. Ninety-eight consecutive adult patients were enrolled in this study. Patients were divided in two groups depending on the presence of sepsis. Fifty-six patients had sepsis, while forty-two patients were nonseptic. Among septic patients, twenty-four subjects developed AKI, while thirty-two did not. AKI occurred in fourteen patients without sepsis as well. The levels of NGAL, BNP, and AOPP were significantly higher among septic patients compared with nonseptic subjects ($P < 0.001$). Among septic patients, subjects who developed AKI showed significant higher levels of NGAL and AOPP ($P = 0.0425$) and BNP ($P = 0.0327$). Among patients who developed AKI, a significant difference was found only in terms of AOPP levels between septic and nonseptic patients. The correlation between endotoxin activity and BNP in septic patients and the increase in the levels of NGAL, BNP, and AOPP in case of sepsis and AKI, in particular if they are associated, indicate a multiorgan involvement in these two conditions.

1. Introduction

Sepsis, defined as a systemic inflammatory response syndrome (SIRS) associated with an infectious disease [1, 2], is a primary cause of morbidity and mortality in ICU [3] and critically ill patients. Mortality rates range from 20% for sepsis, to 40% for severe sepsis, to 60% for septic shock in ICU patients [4].

Gram-negative bacteria are implicated in 50–60% of sepsis, with Gram-positive bacteria accounting for a further 35–40% of cases. The remainder of causes are due to the less common causes of fungi, viruses, and protozoa [5].

The heat-stable toxic component of Gram-negative bacteria, identified for the first time by Pfeiffer at the end of the 19th century [6, 7] and called “endotoxin”, is considered to play an important role in the pathogenesis of septic shock [8]. It causes the release of different cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), and interacts with the complement pathway and the coagulation system [8, 9].

Sepsis is also a contributing factor in more than 20% of cases of acute kidney injury (AKI) in ICU patients, with cases severe enough to require renal replacement therapy [10–12]. AKI occurs in 35–65% of ICU admissions, and most studies show a threefold to fivefold increase in the risk of death among patients with AKI compared to patients without AKI.

Given the higher mortality rate of ICU patients with sepsis and AKI, we decided to investigate the possible correlation between serum biochemical markers of organ damage, such as neutrophil gelatinase-associated lipocalin (NGAL), advanced oxidation protein products (AOPP), and brain natriuretic peptide (BNP) and endotoxin activity in ICU septic patients. Moreover, comparisons of the levels of these biomarkers were made between septic and nonseptic patients, septic patients with or without AKI, and between patients who developed AKI with or without sepsis.

2. Material and Methods

2.1. Study Population. Ninety-eight consecutive adult patients, admitted to ICU of San Bortolo Hospital, Vicenza, Italy, between October 2008 and August 2010, were enrolled in this study. Patients were divided in two groups depending...
on the presence of sepsis, defined as systemic inflammatory response syndrome (SIRS) associated with an infectious process. SIRS was considered to be present when at least two of the following criteria were present: temperature above 38 °C or below 36 °C, heart rate above 90 beats/min, respiratory rate above 20 breaths/min or partial pressure of carbon dioxide below 32 mmHg, and white blood cell count above 12,000 mm$^3$ or below 4,000 mm$^3$. Fifty-six patients had sepsis, while forty-two patients were nonseptic. Clinical and biochemical characteristic of septic patients are summarized in Table 1.

Among septic patients, twenty-four subjects developed AKI, defined by RIFLE criteria, while thirty-two did not. AKI occurred in fourteen patients without sepsis as well.

Within four hours after admission blood samples were taken for EAA (endotoxin activity assay), NGAL, and BNP measurement. EDTA was used as an anticoagulant. Heparinized blood samples were collected for AOPP evaluation.

Correlation between NGAL, AOPP, BNP and endotoxin activity in septic patients was evaluated. Moreover, comparisons of the levels of these biomarkers were made between septic and non septic patients, septic patients with or without AKI, and between patients who developed AKI with or without sepsis.

2.2. Endotoxin Activity Assay (EAA). Serum endotoxin activity was measured by the EAA$^{tm}$ which measures the degree of chemiluminescence of the circulating neutrophil population induced by the exposure to endotoxin.

The test is based on the interaction between the endotoxin and a specific antiendotoxin antibody. Complement components opsonize the endotoxin-antibody complex. The opsonized immune complex primes neutrophils in the blood to enhance their respiratory burst in response to zymosan. The respiratory burst of the neutrophils yields oxidants that react with luminal in the reaction mixture to emit chemiluminescence.

The chemiluminescence can then be detected in a photon-counting luminometer (SmartLine TL, Berthold Detection Systems, Pforzheim, Germany).

A basal activity measurement (Tube 1) in the absence of the specific antiendotoxin antibody measures the nonspecific oxidative burst of the patient's neutrophils. An additional control measurement including the specific antiendotoxin antibody and an excess of exogenous endotoxin (Tube 3) measures the maximum oxidative burst of the patient's neutrophils. The test measurement (Tube 2) includes the specific antibody to measure the net level of endotoxin activity. The EAA$^{tm}$ level is calculated by normalizing the chemiluminescence in the test sample (Tube 2) against the maximum chemiluminescence (Tube 3), correcting both measurements for the basal activity chemiluminescence (Tube 1).

Endotoxin activity levels are expressed as units on a scale ranging from 0 to 1

- 0.00–0.39: EAA$^{tm}$ units: low endotoxin activity level,
- 0.40–0.59: EAA$^{tm}$ units: intermediate endotoxin activity level,
- ≥0.60: EAA$^{tm}$ units: high endotoxin activity level.

2.3. NGAL and BNP Measurement. Plasma samples for NGAL and BNP measurement were stored at minus 80 degrees Celsius to be analyzed subsequently. Plasma NGAL and BNP were measured with fluorescence-based immunoassay with the Triage point-of-care analyzer (Biosite Inc., San Diego, CA, USA), which allows a rapid quantitative measurement of NGAL and BNP concentration in EDTA-anticoagulated whole blood or plasma. NGAL and BNP concentrations were expressed as nanograms per millilitre (ng/mL) and pictograms per millilitre (pg/mL), respectively.

2.4. AOPP Measurement. AOPP levels were measured by spectrophotometry and calibrated with Chloramine-T solutions (Sigma Chemical Co., St. Louis, MO, USA), which adsorb at 340 nm in presence of potassium iodide. Two hundred microliters of plasma diluted 1/5 in PBS, and 20 μL of acetic acid were mixed and calibrated versus the standard reference of 200 μL Chloramine-T solution (0–100 μmol/L) with 20 μL of acetic acid and 10 μL of potassium iodide.

The absorbance of the reaction mixture was read at 340 nm against a blank containing 200 μL of PBS, 10 μL of potassium iodide, and 20 μL of acetic acid. AOPP concentrations were expressed as micromoles per liter of chloramine-T equivalents (μmol/L).

2.5. Statistical Analysis. Statistical analysis was performed with the use of SPSS software version 15.0. Categorical variables were expressed as percentages; continuous variables were expressed as means ± standard deviation (parametric variables) or median (interquartile range; nonparametric variable). Differences between groups were analyzed using Student t-test and Mann-Whitney test as appropriate. Correlation was performed with the use of the Spearman rank coefficient. Two-tailed probability values of <0.05 were considered statistically significant.
### Table 2: Comparison of biochemical markers between septic patients and nonseptic patients.

<table>
<thead>
<tr>
<th></th>
<th>Septic pts (N = 56)</th>
<th>Nonseptic pts (N = 42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>33.9</td>
<td>66.7</td>
<td>0.0013</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 (48.7 to 74.2)</td>
<td>67 (59 to 75)</td>
<td>0.83</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.64 (1.04 to 2.97)</td>
<td>1.0 (0.8 to 1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td>459 (213 to 744)</td>
<td>120 (79 to 174)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AOPP (μmol/L)</td>
<td>505.1 (307.6 to 643.5)</td>
<td>115.7 (79.2 to 181.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>409 (212 to 673)</td>
<td>135 (61 to 275)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sofa score</td>
<td>10 (8 to 12)</td>
<td>5 (4 to 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died (%)</td>
<td>32.1</td>
<td>16.7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

NGAL: neutrophil gelatinase-associated lipocalin; AOPP: advanced oxidation protein products; BNP: brain natriuretic peptide; SOFA score: sequential organ failure assessment.

### Table 3: Comparison of biochemical markers between AKI and No-AKI septic patients.

<table>
<thead>
<tr>
<th></th>
<th>AKI septic pts (N = 24)</th>
<th>No-AKI septic pts (N = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>29.2</td>
<td>37.5</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 (50 to 71)</td>
<td>69 (45 to 76)</td>
<td>0.63</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.3 (1.5 to 3.4)</td>
<td>1.2 (0.8 to 1.9)</td>
<td>0.0065</td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td>572 (308 to 819)</td>
<td>321 (154 to 573)</td>
<td>0.0425</td>
</tr>
<tr>
<td>AOPP (μmol/L)</td>
<td>554.0 (366.8 to 717.6)</td>
<td>419.5 (286.8 to 607.4)</td>
<td>0.0425</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>576 (291 to 1723)</td>
<td>348 (174 to 538)</td>
<td>0.0327</td>
</tr>
<tr>
<td>Sofa score</td>
<td>11 (8 to 13)</td>
<td>9 (7 to 12)</td>
<td>0.28</td>
</tr>
<tr>
<td>Died (%)</td>
<td>45.8</td>
<td>21.9</td>
<td>0.0575</td>
</tr>
</tbody>
</table>

NGAL: neutrophil gelatinase-associated lipocalin; AOPP: advanced oxidation protein products; BNP: brain natriuretic peptide; SOFA score: sequential organ failure assessment.

### 3. Results

Septic patients were divided in three groups depending on EAA levels. EAA < 40: 8 patients; EAA 40–60: 17 patients; EAA > 60: 31 patients.

A significant correlation ($P = 0.02$) was found only between endotoxin activity and BNP levels of septic patients (Figure 1). The levels of NGAL, BNP, and AOPP were significantly higher among septic patients compared with nonseptic subjects ($P < 0.001$) (Table 2). Among septic patients, subjects who developed AKI showed significant higher levels of NGAL and AOPP ($P = 0.0425$) and BNP ($P = 0.0327$) (Table 3). Among patients who developed AKI, a significant difference was found only in terms of AOPP levels between septic and non septic patients (Table 4).

### 4. Discussion

As reported by Marshall et al., intermediate and high levels of endotoxin activity are often found in ICU septic patients [13], and they seem to correlate with the severity of the disease, in particular with the hemodynamic alterations [14]. Sepsis, indeed, frequently causes cardiac abnormalities and kidney dysfunction [15, 16] and, for this reason, can be considered as an important cause of type 5 cardiorenal syndrome [17].

In this study we investigated the possible correlation between endotoxin activity in septic ICU patients and biochemical markers of organ damage, such as NGAL, AOPP, and BNP.

As shown in Figure 1, a significant correlation was found only between endotoxin activity and BNP levels of septic patients ($P = 0.02$). BNP is considered to be a good diagnostic and prognostic biomarker, especially among patients with congestive heart failure [18]. Elevated levels of BNP are independent predictors of cardiovascular morbidity and mortality, both in patients with normal and impaired renal function, thus emphasizing the value of BNP in the assessment of cardiorenal syndrome [19]. In our study, intermediate and higher levels of endotoxin activity, which predict an elevated risk for developing severe sepsis, were associated with higher levels of BNP, which result from cardiac dysfunction induced by sepsis.

We also compared the levels of NGAL, AOPP, and BNP between septic and non septic patients, septic patients with or without AKI, and between patients who developed AKI with or without sepsis.

Serum NGAL has been shown to increase before serum creatinine in case of acute kidney injury [20] and has therefore become a novel early biomarker of acute renal damage [21]. Moreover, it was found to rise in patients with congestive heart failure, thus indicating a link between cardiac dysfunction and renal injury [18, 22, 23].

Critically ill patients also present increased levels of AOPP, induced by the overproduction of reactive oxygen species (ROS) and the subsequent depletion of the antioxidant endogenous stores. AOPP levels were demonstrated to
Table 4: Comparison of biochemical markers between AKI septic patients and AKI nonseptic patients.

<table>
<thead>
<tr>
<th></th>
<th>AKI septic pts (N = 24)</th>
<th>AKI nonseptic pts (N = 14)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>29.2</td>
<td>78.6</td>
<td>0.0033</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 (50 to 71)</td>
<td>76 (69 to 80)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.3 (1.5 to 3.4)</td>
<td>1.0 (0.8 to 1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td>572 (308 to 819)</td>
<td>312 (141 to 633)</td>
<td>0.15</td>
</tr>
<tr>
<td>AOPP (( \mu )mol/L)</td>
<td>554.0 (366.8 to 717.6)</td>
<td>118.9 (90.1 to 152.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>576 (291 to 1723)</td>
<td>305 (134 to 559)</td>
<td>0.1055</td>
</tr>
<tr>
<td>Sofia score</td>
<td>11 (8 to 13)</td>
<td>5 (5 to 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died (%)</td>
<td>45.8</td>
<td>42.9</td>
<td>0.85</td>
</tr>
</tbody>
</table>

NGAL: neutrophil gelatinase-associated lipocalin; AOPP: advanced oxidation protein products; BNP: brain natriuretic peptide; SOFA score: sequential organ failure assessment.

correlate with the risk to develop severe sepsis and with the severity of AKI in ICU patients [19, 24].

In our study, the levels of NGAL, BNP, and AOPP were significantly higher among septic patients compared with non septic subjects \( (P < 0.001) \), as shown in Table 2. Among septic patients, subjects who developed AKI showed significant higher levels of NGAL and AOPP \( (P = 0.0425) \) and BNP \( (P = 0.0327) \) (Table 3). Among patients who developed AKI, a significant difference was found only in terms of AOPP levels between septic and non septic patients (Table 4).

These data suggest that sepsis and AKI are responsible for the increase in the level of the three biomarkers, in particular if they are associated. When limiting to the AKI patients, there was no significant difference in terms of NGAL and BNP levels between septic and non septic patients. The reason for this finding remains to be clarified. A possible explanation could be that renal damage alone can cause a similar increase in the level of the two biomarkers, independently on the presence of sepsis.

5. Conclusions

In septic ICU patients endotoxin activity correlates with BNP levels. NGAL, AOPP, and BNP levels seem to be higher in patients with sepsis and AKI, in particular if they are associated. In case of AKI, a significant difference between septic and nonseptic patients was found only for AOPP levels.

NGAL, AOPP, and BNP increase in case of sepsis, thus indicating both cardiac and renal impairment. For this reason, the rise in their levels in this condition can allow clinicians to individualize patients at higher risk for developing severe sepsis and therefore at higher risk of death.

References


Research Article

Characterization of Bacterial Etiologic Agents of Biofilm Formation in Medical Devices in Critical Care Setup

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Received 1 July 2011; Revised 22 September 2011; Accepted 21 October 2011

Abstract

Background. Biofilms contaminate catheters, ventilators, and medical implants; they act as a source of disease for humans, animals, and plants. Aim. Critical care units of any healthcare institute follow various interventional strategies with use of medical devices for the management of critical cases. Bacteria contaminate medical devices and form biofilms. Material and Methods. The study was carried out on 100 positive bacteriological cultures of medical devices which were inserted in hospitalized patients. The bacterial isolates were processed as per microtitre plate. All the isolates were subjected to antibiotic susceptibility testing by VITEK 2 compact automated systems.

Results. Out of the total 100 bacterial isolates tested, 88 of them were biofilm formers. A 16–20-hour incubation period was found to be optimum for biofilm development. 85% isolates were multidrug resistants and different mechanisms of bacterial drug resistance like ESBL, carbapenemase, and MRSA were found among isolates.

Conclusion. Availability of nutrition in the form of glucose enhances the biofilm formation by bacteria. Time and availability of glucose are important factors for assessment of biofilm progress. It is an alarm for those who are associated with invasive procedures and indwelling medical devices especially in patients with low immunity.

1. Introduction

Microorganisms universally attach to surfaces and produce extracellular polysaccharides, resulting in the formation of a biofilm. Biofilms pose a serious problem for public health because of the increased resistance of biofilm-associated organisms to antimicrobial agents and the potential for these organisms to cause infections in patients with indwelling medical devices. An appreciation of the role of biofilms in infection should enhance the clinical decision-making process. Many bloodstream infections and urinary tract infections are associated with indwelling medical devices and, therefore, are (in most cases) biofilm associated. The most effective strategy for treating these infections may be removal of the biofilm contaminated device [1].

When an indwelling medical device is contaminated with microorganisms, several variables determine whether a biofilm develops. First the microorganisms must adhere to the exposed surfaces of the device long enough to become irreversibly attached. The rate of cell attachment depends on the number and types of cells in the liquid to which the device is exposed, the flow rate of liquid through the device, and the physicochemical characteristics of the surface. Components in the liquid may alter the surface properties and also affect the rate of attachment. Once these cells irreversibly attach and produce extracellular polysaccharides to develop a biofilm, rate of growth is influenced by flow rate, nutrient composition of the medium, antimicrobial-drug concentration, and ambient temperature [2].

There are many works that discuss some features of biofilm-positive bacteria, but there is no consistency in the conditions which are feasible for biofilm formation among authors [3–7]. The only agreement is in the culture temperature, 37°C seems to be appropriate. Other conditions,
for example, presence of nutrition and time of cultivation, vary in many publications. In our study we paid attention to those culture conditions that differ in most authors. We investigated the potential relationship between colonization of different medical devices by various clinical bacterial isolates and to determine the differences in biofilm formation in different conditions and to determine the minimum time and conditions necessary for the development of a homogenous and mature biofilm layer [3].

2. Materials and Methods

Approval was obtained from our institutional review board. The study was carried out on 100 positive bacteriological cultures of medical devices which were inserted in hospitalized patients.

Catheter Culture Technique. All catheters/devices submitted to the clinical laboratory for culture during a 3-year period were studied. Each catheter coming to the clinical laboratory for culture was directly cultured by roll plate method then placed in 10 mL of tryptic soya broth (Himedia, Mumbai, India), incubated for 2 hrs at 37 °C and then vortexed for 15 seconds. Broth was then surface-plated by using a wire loop on Blood agar, Chocolate agar, and MacConkey agar (Himedia, Mumbai, India) [8].

Isolates derived later from the clinical laboratory for the purpose of our study were frozen in nutrient broth with 15% glycerol at −20 °C. Samples retrieved for the study were grown on blood agar plates and were processed as described below.

Cultures retrieved from the frozen material retained the same biochemical reactions, confirming that no alteration had occurred in bacterial isolate because of storage and processing.

3. Biofilm Formation and Quantification of Activity against Biofilms

Preparation of Inoculum. 3 different media were taken: tryptic soya broth, tryptic soya broth with 0.25% glucose, and tryptic soya broth with 0.5% glucose for culture. Isolated colonies were inoculated and incubated for 24 hrs in these media then cultures were diluted 1 : 200 with respective fresh media.

Control. Biofilm-producing reference strains of Acinetobacter baumannii (ATCC 19606) and Pseudomonas aeruginosa (ATCC 27853) and nonbiofilm forming reference strains of Staphylococcus aureus (ATCC 25923) and E. coli (ATCC 25922) were used [9].

Microtitre Plate Assay. Biofilm formation was induced in 96-well flat-bottomed polystyrene microtitre plates. An aliquot of 200 µL of diluted bacterial suspension was added to each well and incubated for 16 h, 20 h, and 24 h at 37 °C. At the end of incubation period, the wells were carefully aspirated and washed twice with 300 µL of phosphate-buffered saline (PBS, pH, 7.2) to remove planktonic bacteria. Wells were emptied and dried before biomass quantification of the biofilms was performed by staining. The staining was done with 200 µL of 0.1% safranine and 0.1% crystal violet into respective wells for 45 minutes. At the end of time, the wells were carefully washed twice with distilled water to remove excess stain. After staining, 200 µL of ethanol/acetone (90 : 10) was added to each well to dissolve remaining stain from the wells. The optical density was then recorded at 492 nm with 630 nm reference filter using an ELISA reader [3, 10–13]. Wells originally containing uninoculated medium, non-biofilm producing bacteria and known biofilm producing bacteria were used as controls for cutoff, negative controls, and positive controls, respectively. The test was carried out in quadruplicate, results were averaged and standard deviations were calculated.

The cutoff was defined as three standard deviations above the mean ODc [14]. Each isolate was classified as follows: weak biofilm producer OD = 2 × ODc, moderate biofilm producer 2 × ODc < OD = 4 × ODc, or strong biofilm producer OD > 4 × ODc [9, 15].

Antimicrobial susceptibility testing was performed by using VITEK 2 compact automated system according to the norms of Clinical Laboratory Standards Institute (CLSI). Relevant statistical analysis was done.

4. Results

The demographic profile of the patients under study indicates 41% female and 59% male patients with bacteriological positive culture. Medical ICU: 36 (44%) was the predominant source of specimen followed by surgery ward: 18 (22%) and neonatal ICU: 16 (20%), least from obstetrics.
Table 1: Relation of clinical bacterial isolates and the type of device inserted.

<table>
<thead>
<tr>
<th></th>
<th>Acinetobacter baumannii</th>
<th>Pseudomonas aeruginosa</th>
<th>Klebsiella pneumonia sub spp. Pneumonia</th>
<th>E. coli</th>
<th>Enterobacter cloacae</th>
<th>Coagulase negative staphylococci</th>
<th>Enterococci</th>
<th>Staphylococcus aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal tube</td>
<td>16</td>
<td>17</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CVP tip</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Foley’s catheter tip</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal drain tube</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephrostomy tube</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tracheostomy tube</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D.J. stent tip</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SPC tip</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>23</strong></td>
<td><strong>20</strong></td>
<td><strong>16</strong></td>
<td><strong>4</strong></td>
<td><strong>9</strong></td>
<td><strong>3</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

Table 2: Quantitative analysis of biofilm production by clinical bacterial isolates as evaluated by microtitre plate method.

<table>
<thead>
<tr>
<th></th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>1</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Klebsiella pneumonia sub spp. Pneumonia</td>
<td>1</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Coagulase negative staphylococci</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Enterococci</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5</strong></td>
<td><strong>44</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>

and gynecology ward and pediatrics ward: 6 (7% each). 59 endotracheal tubes (ETT), 11 CVC (central vascular catheter) tips, 10 Foley’s catheter tips, 7 abdominal drain tubes, 5 nephrostomy tubes, 4 tracheostomy tubes, 3 D. J. (Double J) stent tip, and 1 SPC (supra pubic catheter) tip were found bacteriologically positive under study group. Bacteriologic profile of group showed 23% Acinetobacter baumannii, 23% Pseudomonas aeruginosa, 20% Klebsiella pneumonia sub spp. pneumonia, 16% E. coli, 9% coagulase negative Staphylococci, 4% Enterobacter cloacae, 3% Enterococci, and 2% Staphylococcus aureus isolates. Table 1 shows that in endotracheal tube colonization by Acinetobacter, Pseudomonas and Klebsiella as prevalent bacterial isolates, followed by E. coli. Present study showed that frequently isolated bacteria in central venous line (CVP tip) were Coagulase negative staphylococci (46%) followed by Acinetobacter (18%), P. aeruginosa (18%), Enterococci species (9%), and S. aureus (9%). Enterococci are more commonly associated with colonization of central venous lines and Foley’s catheter.

Out of 100 clinical isolates tested, 88 were found to be biofilm formers by micro titer plate method. Out of two different staining methods; 0.1% safranine had detected 88 biofilm producers while 0.1% crystal violet had detected 69 biofilm producers (See Figure 1).

Biofilm formation in response to different concentrations of glucose was studied. Tryptic soya broth without glucose showed biofilm formation in 75 (85%) isolates. Out of 75, 2 were strong and 28 were moderate biofilm formers as shown in Table 3. In tryptic soya broth with 0.25% glucose; 81 (92%) were found positive, of which 3 were strong and 30 were moderate biofilm formers. In tryptic soya broth with 0.5% glucose; 67 (76%) were found positive, out of which 4 were strong and 28 were moderate biofilm formers.

Biofilm formation at different incubation time periods was studied. At 16 hr incubation period; 88 (100%) were found to be positive, out of it, 3 were strong and 28 were moderate biofilm formers. At 20 hr incubation period, 81 (92%) found positive, 2 were strong and 36 were moderate biofilm formers. At 24 hr incubation period; 76 (86%) found positive, 4 were strong, and 29 were moderate biofilm formers.

Table 4 shows antimicrobial drug resistance profile of bacterial isolates suggesting majority as multiple drug resistant. Phenotypic evaluation showing expression of different drug-resistance mechanisms includes ESBL production (23%), carbapenemase production (34%), AmpC production (7%), carbapenem impermeability (41%), and modification of PBP (13%) responsible for resistance among betalactam antibiotics tested. Drug resistance by Van A (35%), Van B (35%), and TEC (50%) was seen among glycopeptides antibiotics. For MLSB (macrolide lincosamide streptogramin B) group; constitutive (87%) and inducible (1%) have both mechanisms worked for resistance.

5. Discussion

Indwelling medical devices are frequently used in all health setup while critical care units of hospitals use multiple medical devices for treatment and intervention in patient care. Endotracheal tube amounted to more than 50% of our specimen; these may be due to more specimens from patients admitted in critical care which were either intubated or needing ventilator support in multispecialty hospital.
Table 3: Screening of 100 bacterial isolates for biofilm formation by microtitre plate method in different media and at 16, 20, and 24 hr incubation periods.

<table>
<thead>
<tr>
<th>Biofilm formation (OD_{492-630 mm})</th>
<th>TSB</th>
<th>TSB, 0.25% glucose</th>
<th>TSB, 0.5% glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 hr</td>
<td>20 hr</td>
<td>24 hr</td>
</tr>
<tr>
<td>High (ODc &lt; OD &gt; 2 × ODc)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moderate (2 × ODc &lt; OD = 4 × ODc)</td>
<td>17</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Weak (ODc &lt; OD &gt; 2 × ODc)</td>
<td>39</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

Experiment was done in quadruplet and repeated two times. All OD_{492-630 mm} values were expressed as average with standard deviation.

Table 4: Different mechanisms of drug resistance in isolates of indwelling medical devices.

<table>
<thead>
<tr>
<th>Name of bacteria</th>
<th>ESBL</th>
<th>Carbapenemase</th>
<th>Alteration of PBP</th>
<th>Van A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>15</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>25</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae sub spp. Pneumoniae</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase negative Staphylococci</td>
<td></td>
<td></td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococci spp.</td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>60</td>
<td>55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Second most common specimen for investigation was central venous catheters that amounted to 12% of total specimen volume under study. Central venous catheters (CVCs) pose a greater risk of device-related infection than does any other indwelling medical device, with infection rates of 3 to 5%. Catheters may be inserted for administration of fluids, blood products, medications, nutritional solutions, and hemodynamic monitoring. 12% of the specimen was urinary catheter for our study. Urinary catheters were used for many indications in hospital like to measure urine output, collect urine during surgery, prevent urinary retention, or control urinary incontinence.

These organisms isolated in this study may originate from the skin of patients or healthcare workers, tap water to which entry ports are exposed, or other sources in the environment [2]. Acinetobacter, Pseudomonas, Klebsiella, Staphylococcus, Enterobacter, and E. coli are the most common causes of nosocomial infections, and that may be common cause of colonization in indwelling medical devices even responsible for biofilm production [10, 11]. These microorganisms survive in hospital environments despite unfavorable conditions such as desiccation, nutrient starvation, and antimicrobial treatments. It is hypothesized that their ability to persist in these environments, as well as their virulence, is a result of their capacity to colonize medical devices [8].

In a study by Feldman et al. [16], it was documented that the interior of the ETT of patients undergoing mechanical ventilation rapidly became colonized with gram-negative microorganisms which commonly appeared to survive within a biofilm. While it appears that colonization of the ETT may begin from as early as 12 h, it is most abundant at 96 h.

Colonization of the ETT with microorganisms commonly causing nosocomial pneumonia appears to persist in many cases despite apparently successful treatment of the previous pneumonia. A study by Donlan et al. showed that the organisms most commonly isolated from central venous catheter biofilms are Staphylococcus epidermidis, S. aureus, Candida albicans, P. aeruginosa, K. pneumoniae, and Enterococcus faecalis [9, 10]. Stickler et al. [17] showed that the organisms commonly contaminating this urinary catheter and developing biofilms are S. epidermidis, Enterococcus faecalis, E. coli, Proteus mirabilis, P. aeruginosa, K. pneumoniae, and other gram-negative organisms [2, 9–11]. The study of different mechanisms of drug resistance showed isolates commonly found positive for ESBL, carbapenemase production in gram-negative organism and MRSA, vancomycin resistance among gram-positive organisms. Resistant strains are circulating in the environment of the hospital and are responsible for contamination/colonization of different indwelling medical devices used for patient management and complicate the course of treatment.

Indwelling medical devices are frequently used in all health setup while critical care units of hospitals use multiple medical devices for treatment and intervention in patient care. Endotracheal tube amounting to more than 50% of our specimen; may be due to the fact that more specimens are from patients admitted in critical care which were either incubated or needing ventilator support in multispecialty hospital. The second most common specimen for investigation was central venous catheters amounting 12% of total specimen volume under study. Central venous catheters (CVCs) pose a greater risk of device-related infection than does any other indwelling medical device, with infection rates of 3% to 5%. Catheters may be inserted
for administration of fluids, blood products, medications, nutritional solutions, and hemodynamic monitoring. 12% specimen was of urinary catheter for our study. Urinary catheter were used for many indications in the hospital like to measure urine output, collect urine during surgery, prevent urinary retention, or control urinary incontinence.

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### 6. Conclusion

Out of the two different staining methods, safranine 0.1% and crystal violet 0.1%, safranine staining gave more positive, stable, and accurate results in terms of reproducibility, for both, gram-positive as well as gram-negative bacteria. 20 hr incubation time was found to be optimum for detection of biofilms produced by bacteria. Moderate to weak biofilm producing bacteria although do attach to the surfaces, but detachment occurs early because of weak binding. Strong biofilm producers can be detected even at 24 hours of incubation period. Availability of nutrition favors biofilm formation by bacteria so glucose enhances biofilm forming ability of bacteria, but effect of osmolarity and pH cannot be ruled out on biofilm formation.

ESKAPE’ group (Enterococci, *Staphylococcus aureus*, Klebsiella, *Acinetobacter*, *Pseudomonas*, and *Enterobacter cloacae*) of bacteria that are important nosocomial treats in ICUs; which are biofilm producers and responsible for chronic and multidrug-resistant infections. There is presence of multidrug-resistant isolates in the environment of hospital and majority of them were biofilm producers, so it is an alarm for those who are associated with invasive procedures and indwelling medical devices especially in patients with low immunity. They are responsible for increased morbidity and mortality under hospital environment and impacts are major on patient outcome. Biofilm bacteria exhibit various mechanisms of drug resistance transfer so spread of drug resistance among ICU infection is a major threat to patient care in critical care units of health care institutes.

### Disclosure

This paper was supported by the government of Gujarat. Ethical committee approval letter no. MCS/STU/Ethics/5523/2009, 7th March ’09, was obtained.

### Authors Contributions

The paper has been read and approved by both the authors and each author believes that the paper represents honest work and authors alone are responsible for the content and writing of the paper.

### References


Clinical Study
Cardiac Output Measurements in Septic Patients: Comparing the Accuracy of USCOM to PiCCO

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Received 4 July 2011; Accepted 10 October 2011

Academic Editor: Karim Bendjelid

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USCOM is an ultrasound-based method which has been accepted for noninvasive hemodynamic monitoring in various clinical conditions (USCOM, Ultrasonic cardiac output monitoring). The present study aimed at comparing the accuracy of the USCOM device with that of the thermodilution technique in patients with septicemia. We conducted a prospective observational study in a medical but noncardiological ICU of a university hospital. Septic adult patients (median age 55 years, median SAPS-II-Score 43 points) on mechanical ventilation and catecholamine support were monitored with USCOM and PiCCO (\( n = 70 \)). Seventy paired left-sided CO measurements (transaortic access = \( \text{CO}_{\text{US-A}} \)) were obtained. The mean \( \text{CO}_{\text{US-A}} \) were 6.55 l/min (\( \pm 2.19 \)) versus \( \text{CO}_{\text{PiCCO}} \) 6.5 l/min (\( \pm 2.18 \)). The correlation coefficient was \( r = 0.89 \). Comparison by Bland-Altman analysis revealed a bias of \( -0.36 \text{l/min} (\pm 0.99 \text{l/min}) \) leading to a mean percentage error of 29%. USCOM is a feasible and rapid method to evaluate CO in septic patients. USCOM does reliably represent CO values as compared to the reference technique based on thermodilution (PiCCO). It seems to be appropriate in situations where CO measurements are most pertinent to patient management.

1. Introduction

Thermodilution cardiac output measurements have been routinely performed as part of intensive care practice since the introduction of the balloon-directed, thermistor-tipped pulmonary artery catheter in the 1970s [1–3]. Introduced by Swan and Ganz, the pulmonary artery catheter (PAC) became to be the gold standard for more than two decades [1, 2]. However, arrhythmia, infection, and possible pulmonary artery disruption have always been concerns related to the use of a PAC and led to a growing interest in the development of noninvasive hemodynamic monitoring devices [4–6]. One less invasive thermodilution-based technique consists of the pulse-induced cardiac output device (PiCCO) but exclusively ultrasound-based devices as the USCOM monitor are entirely non-invasive methods for measuring CO [7–13]. Besides accuracy and the method-related risks, another crucial criterion consists of the time required for the determination of CO [14]. USCOM is a feasible, continuous-wave Doppler-based method which noninvasively measures CO in a fast and economical way.

The present study aimed at comparing the accuracy of the USCOM device with that of the thermodilution technique (PiCCO) in septic patients.
2. Materials and Methods

Seventy adult, predominantly and mechanically ventilated, patients were investigated in this observational study. All patients suffered from septic infections and required catecholamine support. The study protocol was approved by the institutional ethics committee. As the protocol was the considered part of the routine practice, informed consent was waived.

All patients were measured by PiCCO and USCOM (COUS-A left-sided aortal access n = 70). With the assistance of a nurse, CO measurements (COUSCOM, COPiCCO) were carried out simultaneously. All measurements were undertaken during patients were hemodynamically stable throughout the time of CO measurements. The PiCCO device was recalibrated immediately prior to any measurements by USCOM. To exclude an interindividual observer variability, all CO measurements by USCOM and PiCCO were undertaken by the same investigator.

2.1. USCOM. The USCOM device (USCOM Ltd., Sydney, Australia) is a non-invasive bedside method to evaluate cardiac output basing on continuous-wave Doppler ultrasound. After starting the USCOM device, the left-sided transaortic (COUS-A) or right-sided transpulmonary access has to be chosen before the patients data like height, weight, and gender are typed in. The flow profile is obtained by commonly using a 2.2 MHz transducer placed on the chest in either the left parasternal position to measure transpulmonary blood flow (right-sided access, 3rd to 5th parasternal intercostal space) or the suprasternal position to measure transaortic blood flow (left-sided access, suprasternal notch). The operator registries a Doppler flow curve with maximal blood flow which is characterized by a sharp, well-defined waveform with the clearest audible sound. The flow profile is displayed as a time velocity curve at the monitor (VTI: velocity time integral). Once the optimal flow profile is obtained, the trace is frozen. The USCOM device calculates CO by the product of stroke volume (SV) and heart rate (HR) where the SV is the product of the velocity time integral (VTI) and the cross-sectional area of the chosen valve (CSA). The chosen valve cross-sectional area is given by the USCOM internal algorithm based on the formerly typed in patients data (height and gender) [15, 16].

2.2. PiCCO. Continuous cardiac output using pulse contour analysis was measured by the PiCCO plus system (Pulsion Medical Systems, Munich, Germany). Cardiac output was measured discontinuously by thermodilution using a triplicate injection of 15 mL ice-cold 0.9% saline administered through a temperature detecting inline sensor central vein catheter [17]. A femoral or brachial artery catheter (4-F aortic catheter with an integrated thermistor) registers the time until the bolus attains and identifies the alteration of temperature [18].

2.3. Statistical Analysis. The Bland-Altman Plot was used to estimate the bias and limits of agreement between measurements by the two methods [19]. According to the recommendations by L. A. H. Critchley and J. A. H. Critchley, we quoted the mean CO (μ), the bias, the limits of agreement (95% CI), and the percentage error (±2 SD/μ) [20]. Bland-Altman plots and correlation curves were performed using GraphPad for Windows (Version 5.01, GraphPad Software, San Diego, California, USA).

For statistical calculations (Pearsons’ correlation coefficient) SPSS for Windows was used (Version 15.0, SPSS Institute, Chicago, Ill, USA).

3. Results

3.1. Patient Characteristics. Seventy mechanically ventilated patients with a catecholamine support (median norepinephrine 0.55 mg/h c.i., range 0.1–3.0) at a median age of 45 years and a median SAPS Score of 43 points were enrolled. The majorities of the patients suffered from hematological (n = 38) or hepatological diseases (n = 16). In 9 cases, patients had received prior chemotherapy for solid tumors (n = 9), and 7 patients suffered from other diseases. All patients fulfilled the criteria for sepsis. In most cases sepsis was related to chemotherapy-induced neutropenia. Detailed patients’ characteristics are given in Table 1.

3.2. Detection Ability: USCOM. In total, 70 left-sided, transaortic CO measures from 70 subjects were acquired. High-quality, left-sided transaortic doppler signals could not be obtained in two patients due to anatomic variability (short neck and tracheostoma). The detection ability rate was COUS-A 98.4%.

3.3. USCOM versus PiCCO

3.3.1. Transaortic Analysis: COUS-A. The CO values of seventy patients were measured by PiCCO and left-sided transaortic USCOM (126 paired measurements).

The median CO was 6.5 l/min (±2.18) for PiCCO device and 6.55 l/min (±2.19) for the transaortic measurements with USCOM. The Pearsons’ correlation coefficient was r = 0.89 (P < 0.01) (Figure 1).

The bias, using the Bland-Altman analysis, was −0.36 l/min (±0.99 l/min) with 95% limits of agreement from −2.34 to 1.62 (Figure 2). The mean percentage error according to Critchley L. A. H. and J. A. H. Critchley amounts to 29%.

3.3.2. Time Requirement: tCOUS-A versus tCOPiCCO. The time requirements for each single method of CO measurements were recorded (starting the device: first admissible result) on the following preconditions.

PiCCO artery and central venous line were already in situ. The PiCCO device was recalibrated immediately prior to measurements.

Mean measurement time of PiCCO (tCOPiCCO) was 8.46 minutes (min) (±2.15; min/max 4.0/20.0 min) and of transaortic USCOM (tCOUS-A) analysis 3.69 min (±1.59; min/max 1.0/10.0 min).
Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Value/median range</th>
<th>Standard deviation (±/−SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45 years</td>
<td>23–78</td>
</tr>
<tr>
<td>Gender</td>
<td>45 m/25 f</td>
<td></td>
</tr>
<tr>
<td><strong>ICU characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II score</td>
<td>43</td>
<td>23–60</td>
</tr>
<tr>
<td>BP (systolic)</td>
<td>124 mmHg</td>
<td>94–170</td>
</tr>
<tr>
<td>BP (diastolic)</td>
<td>58 mmHg</td>
<td>37–70</td>
</tr>
<tr>
<td>HR</td>
<td>97 bpm</td>
<td>53–142</td>
</tr>
<tr>
<td>CVP</td>
<td>10 mbar</td>
<td>3–17</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.5 mg/h</td>
<td>0.1–3.0</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
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<td></td>
</tr>
<tr>
<td>fiO2</td>
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<td>0.3–1.0</td>
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<tr>
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</tr>
<tr>
<td>Liver cirrhosis</td>
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<td></td>
</tr>
<tr>
<td>SBP</td>
<td>5</td>
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</tr>
<tr>
<td>Hepatitis</td>
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<tr>
<td>GI bleeding</td>
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<tr>
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<tr>
<td>HCC</td>
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<tr>
<td>Acute liver failure</td>
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<tr>
<td>Liver transplantation</td>
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<tr>
<td><strong>Haematological disease</strong></td>
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<tr>
<td>Acute leukaemia</td>
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<tr>
<td>SCT</td>
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<tr>
<td>Chronic leukaemia</td>
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<tr>
<td>Solid tumors</td>
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<tr>
<td>Other</td>
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</table>

**Abbreviations:** BP: blood pressure, HR: heart rate, CVP: central vein pressure, SBP: spontaneous bacterial peritonitis, HCC: hepatocellular carcinoma, SCT: stem cell transplantation, and GI: gastrointestinal.

4. Discussion

This study aimed to compare the accuracy of CO measurements between the noninvasive continuous-wave Doppler-based monitoring system USCOM and a thermodilution-based technique (PiCCO).

USCOM is a noninvasive cardiac output monitor based on the transthoracic measurement of Doppler flow velocity over the aortic and pulmonary outflow tract. It is easy to operate, and CO is displayed “beat by beat”. Following a short booting time, the device can be used immediately. Moreover, the technique is reported to be easily learned after a short learning period by nonphysicians [21, 22].

In contrast to previously reported trials which investigated USCOM in predominantly cardiac surgical patients’ collectives, we analyzed patients with sepsis. A former pilot study indicated a comparable accuracy of USCOM and the PiCCO device in a similar patients subset [23]. According to these data, the present study indicated also an acceptable agreement between the USCOM CO measurements and those determined by a thermodilution-based method.

For analyzing the accuracy, the Bland-Altman method was used because it measures the extent of deviation from the line of complete agreement (no bias) between the methods. This is different from the correlation coefficient which measures how close to a straight line the pairs of measurements lie, but that line need not to be the one of complete agreement. Moreover, in addition to reporting the mean cardiac output (μ), the bias, and the limits of agreement (95%CI), we quoted the percentage error as recommended by, L. A. H. Critchley and J. A. H. Critchley [20].

Analysing the accuracy of COUS and COPiCCO, the Pearson’s correlation coefficient was 0.89 which seems comparable to that reported in the study of Knobloch and coworkers.
They investigated 36 patients by PAC and USCOM and obtained a comparable correlation coefficient of $r = 0.87$ ($P < 0.01$) [12]. By analyzing our data with the Bland-Altman method, the mean percentage error according to L. A. H. Critchley and J. A. H. Critchley was 29% for the transaortic access. Since the accepted threshold is <30% one can conclude that transaortic CO measurements by USCOM do reliably reflect the measurements by PiCCO.

In contrast to these data, an inferior accuracy for USCOM was reported by other authors who found that CO measurements by USCOM do not reliably represent absolute values as compared to pulmonary artery catheter thermodilution technique [16, 24]. Possible explanations for such incoherent findings are as follows.

1. Parts of reported examinations were done during cardiac surgery by placing the probe directly on the right ventricular outflow tract. Patients in our study, for instance, were ventilated mechanically which contributes to difficulties in CO measurements by an ultrasound-based device.

2. In cases of relatively high cardiac output, USCOM tends to underestimate the real CO value when it is relatively high [9–11]. On the contrary, such a difference does not appear in Su et al’s research [10, 11]. They investigated patients with liver cirrhosis because of their unique hyperdynamic status with high CO values ranging up to 13.6 L/min. They found that even at high CO values, USCOM still reliably measures CO [10, 11].

3. The accuracy of the USCOM depends on obtaining accurate VTI and valve diameter measurements. An accurate VTI measurement requires a good flow signal. An inadequate beam alignment with the blood flow direction will lead to suboptimal Doppler signal.

4. The cross-sectional area of the chosen valve contributes to the estimated CO ($CO = HR \times SV; SV = VTI \times CSA$). The valve area is given by the height-based algorithm built into the device. Knirsch et al. studied twenty-four pediatric patients with congenital heart disease without shunt undergoing cardiac catheterization under general anesthesia [16]. Interpreting the moderate accuracy of USCOM in their study, it has to be considered that the USCOM algorithm which determinates the valve cross-sectional area based on the data of healthy volunteers [15]. Despite the opportunity to correct the valve cross-sectional area manually in cases of known cardiac valve anomalies after exact evaluation by transthoracic or transeophageal echocardiography, the first examination by USCOM can be misleadingly too low or too high.

5. The PiCCO device may be not as accurate as reference technique in this setting (septicemic patients). Any bias and limits of agreement observed in this study could therefore be explained by the inaccuracy of the PiCCO system. The accepted clinical standard is still the intermittent thermodilution technique which in has its own inherent variability [25–27].

Early goal-directed therapy (EGDT) has become regarded as the standard of care for the management of patients with severe sepsis and septic shock [14, 28, 29]. However, it is critical to discuss that the concept of EGDT is still an issue of controversy [30]. Nevertheless, USCOM is attractive in many ways. It is easy to use, and as an ultrasound technique is safe so it can be used repeatedly to measure the trend over time. It avoids the problems of an esophageal probe and is tolerated by awaken patients. Moreover, by using the USCOM device the physician will obtain a result in an unbeatable period of time. The role of USCOM is evolving but USCOM is limited to CO measurements and does not provide variables as pressure measurements or ScvO2. Thus, USCOM does not replace invasive methods as PiCCO or PAC. But USCOM seems to be appropriate in situations where CO measurement is most pertinent to patient management.

**Author’s Contribution**

Sophia Horster and Sandra Geiger contributed equally to this work.

**Disclosure**

This original paper is part of the dissertation of Florian Bretter, which has been conducted at the Ludwig-Maximilians University, Campus Großhadern, Munich, Germany.

**References**


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