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About the cover: the cover shows the trends of rSO₂ and PbtO₂ for patient n. 4 in the prospective, observational, unblinded study about the assessment of cerebral oxygenation in neurocritical care patients. Data show the inability of rSO₂ to detect ongoing brain death. For more information, see the article by Esnault P. et al. beginning on page 876.
Videolaryngoscopy: may the force be with you!

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Since John Pacey, a surgeon, introduced the GlideScope® into clinical practice in 2001, videolaryngoscopes (VLS) have become increasingly successful. Similar to the use of ultrasound guided techniques for vascular puncture and nerve blocks, VLS have very quickly gained popularity among anesthesiologists. They are becoming more and more indispensable tools for teaching purposes, for the management of difficult airways and as documentation tools for everyday cases. Many different VLS are available and their number keeps steadily increasing. Prior to marketing, all these devices lack evidence of efficacy or safety. Hence, without academic guidance, the choice to use and to buy one particular VLS will depend on marketing strategies of the companies. The British Difficult Airway Society has addressed this problem in an article that defines “a minimum level of evidence needed to make a pragmatic decision about the purchase or selection of an airway device”. In this issue of Minerva Anestesiologica, Pieters et al. provide some of the necessary evidence about efficacy and safety of three VLS. From everyday clinical practice we know that the force necessary to obtain a good view of laryngeal structures is markedly decreased with VLS. This has also been shown by Goto et al. Pieters and the study group led by André van Zundert present more data enforcing this knowledge. They confirm their previously published finding that the force exerted on the maxillary incisors is lower with the use of VLS compared to the use of the Macintosh laryngoscope. We cannot directly deduce that the incidence of dental lesions is reduced by using VLS, but it is difficult to study the incidence of dental lesions because they occur in only about 1/2000 (0.05%) of anesthesia cases. The force exerted on the teeth appears to be an acceptable surrogate parameter. Importantly, those findings apply to the non-difficult airway, not the non-anticipated difficult airway: the title of the study might be misleading.

VLS can be divided into devices without a guiding channel for the tracheal tube (such as the three devices evaluated by Pieters et al.) and devices with a guiding channel. Additionally, VLS blades may resemble the standard Macintosh blade (e.g. the C-MAC® blades evaluated in the study) or may feature a more pronounced curve (e.g. the MacGrath® series 5 and the GlideScope® evaluated by Pieters et al., or the C-MAC “D-blade”). Curved blades are primarily designed for the difficult airway and direct comparisons with Macintosh blades are difficult. The more curved the blade, the more essential it is to introduce a stylet into the tracheal tube for guidance. If a stylet is not used, tracheal intubation will be more difficult, as shown by Pieters et al. who did not use stylets in their study. Most likely, this is why the GlideScope® seemed to perform inferiorly.

Facing the emerging importance of VLS, a crucial question becomes whether we should abandon the 80-year old standard Macintosh blade in favor of VLS. While superiority has been claimed for VLS in the ICU setting and evidence shows that in normal airways, laryngoscopy becomes even easier when using videolaryngoscopes, there are important advantages...
of direct laryngoscopy using the Macintosh blades. The most obvious one is the fact that one drop of blood or mucus may be sufficient to completely obstruct the view obtained by videolaryngoscopes. Also, equipment failure remains a problem. The Macintosh laryngoscope is a simple, reliable tool that is difficult to break. It is cheap, transportable, available in all sizes and usable in all settings, even in the pre-hospital setting in bright sunlight. Of note, VLS have so far not been incorporated into difficult airway algorithms, although this may change in the near future. While VLS seem to be very valuable assets to the airway tool library, we risk losing our skills with two important techniques by more and more using VLS: intubation with the ubiquitously available Macintosh laryngoscope and fibreoptic intubation. Several studies on VLS in the simulated difficult airway situation using manual inline stabilization have been conducted, mostly demonstrating a better visibility of the vocal cords and some showing a higher intubation success rate with VLS compared to the Macintosh laryngoscope. Despite that, it is also known that even with a good view obtained by the VLS, there still might be problems to actually intubate the trachea (“you see that you fail”). Therefore, alternative techniques like the flexible fibreoptic intubation must continue to be taught and used on a regular basis. To secure the airway in the spontaneously breathing patient (awake intubation) remains the gold-standard in the management of the anticipated difficult airway, especially when difficult face-mask ventilation is suspected, and should not be abandoned. Videolaryngoscopes are additions, not replacements to our airway tool library. Their role in securing patients’ airways is increasingly being supported by evidence like the study by Pieters et al. More evidence will have to follow in the future, especially about the role of VLS in the setting of difficult airway management.

References

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Measuring (and interpreting) the esophageal pressure: a challenge for the intensivist

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In a mechanically ventilated passive patient a portion of the positive pressure applied at the airway opening (P_{AO}) does not distend the lung but works to “move” the chest wall. As a consequence, the pleural pressure (P_{PL}) increases above its end-expiratory level, proportionally to chest wall stiffness. What actually distends the lung is the increase in trans-pulmonary pressure (P_{L}) above its end-expiratory level, i.e. P_{AO} minus P_{PL}. The straightforward implication is that P_{L} is always lower than the applied P_{AO}. In patients with acute respiratory distress syndrome (ARDS), in the attempt to minimize alveolar hyperinflation, we limit the end-inspiratory airway opening plateau pressure (P_{AO,PLAT}) to 30 cmH_{2}O. In the most severe ARDS forms, in the attempt to increase lung aeration, we use lung-recruiting maneuvers (LRM) followed by high positive end-expiratory pressure (PEEP). Indeed, alveolar recruitment may change the clinical course of severe ARDS: a non “recruiting” patient is candidate to “rescue” strategies, for example extracorporeal membrane oxygenation (ECMO). For P_{AO,PLAT}, LRM and PEEP we reason in terms of pressure applied at the airway opening, assuming that the chest wall stiffness is normal. Unfortunately, this is not the case in a relevant portion of patients. Several pathologic conditions, for example deformities, pleural effusions and increased abdominal pressure may impair chest wall compliance. If the chest wall is stiff, a relevant portion of P_{AO} is dissipated to move it, generating higher P_{PL} and lower P_{L}. When this happens, the P_{AO}-based lung protective and/or lung-recruiting strategies often fail, regardless the potential for alveolar recruitment. Studies have shown that titrating mechanical ventilation on P_{L} rather than on P_{AO} significantly improves gas exchange and lung mechanics and may reverse refractory hypoxemia.

In the assisted ventilation modes, the patient actively contracts his or her inspiratory muscles and P_{L} results by the interplay between the ventilator that pushes (positive P_{AO}) and the patients that pulls (negative P_{PL}). Think to a patient with mild ARDS non-invasively ventilated with a pressure support of 15 cmH_{2}O. If this patient generates a substantial inspiratory effort (P_{PL} minus 20 cmH_{2}O), the end-inspiratory P_{L} will be 35 cmH_{2}O, a figure compatible with ventilator induced lung injury (VILI). Indeed, P_{L} is of paramount importance to estimate work of breathing and patient-ventilator interactions during assisted ventilation.

Despite its importance, we rarely measure P_{L} in clinical practice or, even worst, take the P_{L} “concept” into account in our clinical reasoning. There are at least four reasons to explain this paradox:

A) Measuring P_{PL} is virtually impossible in the...
clinical setting. We have a surrogate, the esophageal pressure (PES), measured through a catheter positioned in the lower esophageal third. Since the esophageal lumen is a virtual space, to sense the pressure acting on the esophageal wall, the catheter tip must be inserted in an air filled balloon. The air volume put in the balloon needs careful titration: if the balloon collapses on the catheter tip, PES is underestimated. On the other hand, if the balloon is overinflated, the stretch on the balloon wall generates positive pressure by itself, and PES is overestimated. In adjunct, the PES reading is influenced by patient posture and the esophageal muscular tone and contractions.1

B) The correct catheter positioning in the lower esophageal third requires expertise. There are several methods to check the catheter position:14 some of them require active patients inspiration against the occluded airway.15 Unfortunately few ventilators are equipped with airway opening occlusion devices.

C) We lack of devices to measure PES. For a correct reading PES should be showed together with PAO, Flow and Volume, in real time. Few ventilators and multi-parametric monitors are equipped with an auxiliary port to measure PES.

D) After years of debates, we yet don’t know how to interpret PES.16, 17 Some authors maintain that the absolute PES value is just the “right” PPL value.10, 14, 18 Others do not trust on absolute PES and just trust on the PAO and PPL swings for partitioning the respiratory system elastance (ERS) into its lung and chest wall components (E′L and E′CW).2 This is reasonable since: a) the EL/E′CW ratio defines the partitioning of PAO in PPL and P′L during positive pressure lung inflation; and b) a single “real” absolute PPL virtually does not exist. In healthy subjects PPL is slightly negative at functional residual capacity (FRC), varies with gravity and body posture and is occasionally frankly positive in the dependent lung regions, for example in patients with abdominal hypertension.14

In summary, while the experts recommend measuring P′L, several problems wait a solution. The paper by Mojoli et al. published in the present issue of Minerva Anestesiologica is a step in this direction.19 It is an elegant and rigorous in vitro study testing six second-generation PES catheters at different balloon filling volumes and surrounding pressures to define the catheter-specific range of “appropriate” balloon filling volumes. Rather surprisingly, it shows that this range may be different from the one recommended by catheters manufacturers. Most importantly, the study establishes a “gold standard” in vitro approach to test PES catheters. We urgently need preclinical and clinical studies like this one.13 Our challenge is to quickly go from theory to practice. Measuring and interpreting P′L is complex, requires considerable expertise and technological improvements. Nevertheless, we should wonder if it is challenging like measuring and interpreting the electrocardiogram. Cardiologists won this challenge several years ago. Will the intensivists do the same in the near future?

References


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The use of esophageal manometry has become increasingly important for the management of the most critically ill mechanically ventilated patients. When performed properly, esophageal pressure measurement provides an estimate of pleural pressure and its measurement has advanced our understanding of the pathophysiology of critically ill patients and has increasingly assisted in the management of the most complex patients. Esophageal pressure measurement is useful in guiding the setting of positive end-expiratory pressure (PEEP) in severe adult respiratory distress syndrome (ARDS), the determination of maximum plateau pressure without undue risk of induced lung injury in patients with altered chest wall mechanics or marked obesity, and for the determination of autoPEEP and work of breathing in spontaneously breathing patients receiving assisted ventilation. Scientific interest in the exploration of possible applications of esophageal pressure guided ventilation has been recently highlighted by the PLUG working group.

The use of esophageal manometry to describe intrathoracic pressure changes during spontaneous breathing dates back to 1878. The estimation of pleural pressure through esophageal manometry allows the determination of transpulmonary pressures (end inspiratory plateau pressure minus pleural pressure), i.e. the distending pressure of the lungs. The assessment of how much pressure is spent for the passive inflation of the thorax is particularly helpful in any clinical condition characterized by increased pleural pressure and/or chest wall elastic abnormalities, including but not limited to ARDS, obesity or surgical pneumoperitoneum. This differentiation allows the clinician to better understand whether it is reasonably safe and feasible to increase airway pressures to better customize mechanical ventilation in different pathophysiological settings. Specifically, to be able to identify those situations where plateau pressure can exceed 28 cmH2O without increased risk of lung injury. End expiratory transpulmonary pressure has been proposed as the optimal method of determining optimal PEEP. The goal, is to insure end expiratory transpulmonary pressure in positive and thus to avoid end expiratory collapse. Additionally, the measurement of esophageal pressure has proven useful in hemodynamic interpretation (as it allows the calculation of transmural filling pressures). Monitoring of patient-ventilator synchrony, measurement of auto-PEEP during spontaneous breathing and estimation of work-of-breathing through measurement of the pressure-time product has been shown to be particularly useful in patients difficult to wean from ventilator support.

Since the introduction of esophageal manometry, there has been debate whether esophageal pressure faithfully reflected pleural pressure. The main issue with esophageal pressure measurements is its geometrically limited validity. As pleural pressure is characterized by different values, following a gravity-vecored gradient, the pleural pressure estimated through esophageal manometry is valid only for structures in close

Comment on p. 855.
proximity of the balloon itself. For the same reason, balloon positioning at different depths yields different pleural pressure estimates. As a result positioning and functioning of the balloon is critical. Proper positioning is at the mid-esophageal level identified by the presence of cardiac artifact and a matching of esophageal pressure change with airway pressure change during active inspiration determined by an occlusion test. Therefore, the esophageal pressure and airway pressure change during inspiration and expiration should be equivalent. Similarly during controlled ventilation, airway and esophageal pressure should change equivalently. Additionally, the volume of air used for balloon inflation influences the reliability of esophageal manometry. Balloon pressure increases with balloon volume, as a result of tension of the balloon itself and the surrounding structures, as shown in 1964 by Milic-Emili et al. These authors concluded that esophageal pressure best estimates pleural pressure at near-zero balloon volume. More recently Walterspacher et al. and Mojoli et al. published interesting papers that address the issue of esophageal balloon filling volumes. Specifically, in this issue of Minerva Anestesioligica, Mojoli et al. studied in vitro the minimum and maximum volume at which different catheters accurately measure the surrounding pressure. It is interesting to note that the minimum volume to be injected for proper pressure measurement was greater than recommended by each of the four manufacturers of the catheters tested, and the best balloon working volume did vary considerably among catheters. Clinicians, in addition, should be aware that the pressure-volume curve of the balloon changes after the first inflation, suggesting that some inflation/deflation cycles should be performed before placement. The authors emphasize that in the case of an unsuccessful occlusion test evaluation of balloon filling volume should occur before repositioning of the balloon. According to their data, some balloons require working filling volumes of up to 7.5 mL considerably more that has been traditionally recommended (0.5 to 1.0 mL). However, these studies were performed exclusively in vitro and on a single catheter per brand; adoption of the suggested filling volumes is still debated. Furthermore, the findings of these two studies have yet to be validated in an in vivo setting.

Esophageal manometry is an increasingly important tool in the management of complex, refractory respiratory failure, allowing the evaluation of the true amount of airway pressure used for lung inflation and the minimum level of PEEP required to avoid cyclic inflation and deflation. It is also useful for the assessment of autoPEEP, and work of breathing in the spontaneously breathing patient failing ventilator discontinuation trials. However, esophageal balloon manometry is still flawed by methodological issues. Mojoli et al. have filled one of the gaps that afflict measurement. Future clinical studies however are needed to validate their results.

References

Passing through a critically illness and facing the Intensive Care Unit (ICU) scenario are experiences that frequently brings uncomfortable physical, cognitive and psychological sequelae for patients and family members. In contrast, a smaller proportion of patients deal with surviving ICU as a victory in their life and, so, a source of energy and a life changing opportunity.

Concurrently, the multidisciplinary staff involved in the care of critically ill patients also receive many inputs during the workday apart of technical issues: from happiness of recovering patients and gratefulness of family members to stressful situations, dealing with life threatening conditions, death, and impotence feelings.

Nowadays, the proportion of ICU survivors is increasing and new challenges caused to the health care system, health care workers and population. Indeed, the suffering of recovering patients and relatives can be high and negatively affects their quality of life.

Furthermore, the burden of ICU survivors is enormous and needs special attention. In this issue of Minerva Anestesiologica, Dettling-Ihnenfeldt et al. reported a pilot experience in conducting two Post-ICU Clinics in Netherlands.

Post-ICU clinics are specialized units with the main aim to help ICU survivors and was first described in UK in 1985. Several centres around the world have implemented these clinics; however, there are questions around their implementation.

What are the aims of the Post-ICU Clinic?

This is a crucial point in the topic and has changed over time. Post-ICU Clinics can be facilities for screening ICU survivors and their families sometime after hospital discharge. The rational is to identify patients who are not recovering or presented with new problems. Post-ICU Clinics can also be focused on physical and psychological rehabilitation, manned by staff specializing in the care of ICU survivors, who have different demands from routine patients, such as hallucinations related to their ICU stay. However, the ideal goal of Post-ICU Clinics should be an advanced facility that allows continuity of care. Indeed, initiatives beginning as early as possible (sometimes inside the ICU) could decrease the incidence of problems after hospital discharge.

The context of each centre should be understood, since the cost-effectiveness of these models must be discussed. In a national survey in the UK, financial constraints was the main reason for not having a Post-ICU Clinic. Other point raised by Dettling-Ihnenfeldt et al. is the existence of other services within the health system, which already provide rehabilitation and support, sometimes close to the patients’ home or familiar to them because of previous attendance. The ICU-rehabilitation
team should be aware of all other possibilities of referral and support. In this context, Post-ICU Clinics could be a referral point for ICU survivors and caregivers.

Should we offer and refer to the Post-ICU Clinic every ICU survivor or should we identify high-risk patients? Should family members be asked to visit?

In the study by Dettling-Ihnenfeldt et al., patients who were mechanical ventilated ≥48 h and were discharged to their own home were invited to attend the Post-ICU Clinic. The authors reported that an average 15% of ICU patients, from the two hospitals, were invited to the clinic. Although there is a rational for this criteria, it can includes a myriad of patients, from surgical patients to patients with acute respiratory distress syndrome, one of the populations most affected and studied after ICU discharge. Other studies included all patients who stayed some time in ICU (i.e. 5 days) or included every patient who received high-level of care. Although some risk factors for poor outcomes are known, there is no consensus on how select patients, since the recovery process is subject to the influence of individual characteristics. Furthermore, as discussed by the authors, 18% of selected patients did not attended because of having “no complaints”. This could be a matter of concern, since it is possible they did not attended because of avoidance behavior as a symptoms of post traumatic stress disorder and, so, are vulnerable to long-term problems. There is no consensus whether active recruitment for this situation is advisable or whether telephone follow-up could be an alternative. Certainly early contact with the patient and respective family whilst still hospitalized, can decrease the need for long-term follow-up and allows the recognition of those patients who may need ongoing physiotherapy or psychological support.

Another interesting point reported by the authors is how to care for family members and caregivers. The authors assessed the close relatives and informal caregivers, finding high level of burden and stressful conditions in approximately 10-15%. This approach with close relatives should be integrated into the design of Post-ICU Clinics because they are fundamental actors in the process of care and suffering. Although not reported in this study, family members of patients who died in ICU should also be evaluated, similar to palliative care teams supporting relatives in the grief period. Whether close relatives should visit separately from patients is a question that still needs to be addressed.

What staff should compose the Post-ICU Clinic?

Another question about Post-ICU Clinics is what professions or services should be available. In the study by Dettling-Ihnenfeldt et al., each centre have different profile. One centre was nurses-led, a common finding in the literature and in the other centre, nurses, physiotherapists, psychologists and physicians were present. We believe that a multidisciplinary team is advisable and the inclusion of staff from the ICU is desirable. Indeed, patients and family members may have close relationship to the ICU staff who attended them during critical illness and this could enhance the coping in stressful situations. Furthermore, the ICU staff will have a chance to face different challenges, observe good results, or feedback to other staff on practices that have had a positive or negative impact on the patients’ recovery. Indeed, outcomes from critically ill patients should be assessed sometime after ICU discharge.

Challenges and promising approaches

As reported by the authors, patients from hospitals of different levels of care deserves care after critical illness. When planning the introduction of a Post-ICU Clinic, health care workers and policy makers should consider all the above aspects. The risks and features of the patients following ICU admission is dynamic over time. ICU and hospital discharge are moments of great anxiety and carry important care level changes. Therefore, focusing on each moment of this time frame is essential: the im-
plementation of light sedation and early rehabilitation,16 ICU diaries,10 manualise rehabilitation programmes such as the ICU Recovery Manual,17 home-based programmes18 and new approaches to optimize an effective communication between teams from ICU and ward, ward and outpatient services are fundamental.

The introduction of a Post-ICU Clinic is desirable and might be very useful, but has several challenges.9, 12, 19 Based on the balance between benefits and costs, we should discuss whether it is better to guarantee inpatient rehabilitation and discharge facilities first and only then introduce a Post-ICU Clinic; or whether is suitable conduct both strategies at the same time.

References

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Near-infrared spectroscopy for monitoring brain oxygenation: to trust or not to trust?

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Near-infrared spectroscopy (NIRS) is increasingly used in anesthesia to monitor brain regional saturation in oxygen (rSO2). In cardiac surgical patients, rSO2 monitoring has shown interesting results suggesting an improvement in brain morbidity in some situations.1, 2 Large changes in brain oxygenation may be expected during cardiac surgery due to cannula malposition or during carotid endarterectomy after carotid artery clamping, for example. Still, definitive demonstration of the usefulness of this monitoring technique for improving patient outcome is lacking. In the neurointensive care unit, the main objective is to avoid or limit cerebral ischemia, especially after traumatic brain injury. Changes in brain oxygenation may guide our treatments for this purpose. However, the amplitude of brain oxygenation changes is usually small, needing accurate monitoring methods. Spurious brain oxygenation values may lead to inappropriate therapeutic interventions and inadequate patient management. Observational studies using brain interstitial tissue pressure in oxygen (PbtO2) have shown promising results. Compared to historical control groups, patients managed with PbtO2-guided management had better outcomes.3, 4 However, this monitoring is invasive, limiting its use only to sedated severe brain injured patients. It would certainly be a real monitoring breakthrough if intensivists could obtain reliable information on brain oxygenation using a non-invasive device like NIRS, as it is used in the operating room.

In the past, a few studies have shown important limitations of NIRS to monitor brain oxygenation.3 In normal subjects NIRS monitoring can be adversely affected by extra-cranial contamination of the signal after routine physiological tests, like Valsalva maneuver, hyper-ventilation and head-up tilt.6 It was confirmed in volunteers with no difference between three NIRS devices.7 In anesthetized patients in beach-chair position for arthroscopic shoulder surgery, there was no agreement between SjO2 and rSO2 values, and rSO2 was not reliable in detecting a low SjO2. In anesthetized children, NIRS devices demonstrated a correlation with SjO2, but the agreement between rSO2 and SjO2 was poor.8 In brain-injured patients, Ter Minnassian et al. used a carbon dioxide (CO2) and blood pressure challenge with norepinephrine to compare changes in rSO2 and SjO2. They demonstrated that changes in rSO2 were positively correlated with changes in SjO2 during a CO2 challenge but negatively during the blood pressure challenge. This suggested that extracerebral vasoconstriction influenced rSO2 values making it unreliable for clinical monitoring in the ICU. One can argue that NIRS not only measures venous blood oxygenation but both arterial and venous saturation. In fact, NIRS devices use a fixed proportion of arterial (30%), capillary and venous (70%) blood within brain tissue. This is also a limitation in brain-injured patients because this proportion may change over time.

Recently, new devices have appeared on the market and all manufacturers claim the algo-
rithms have been improved in order to limit extracerebral contamination of the signal. Thus, it is important to test these devices to assess their value for clinical monitoring. The study by Esnault et al., published in this issue of *Minerva Anestesiologica* compared one new NIRS device with brain tissue oxygen pressure in oxygen (PbtO₂). Strength of this study was to use an accurate measurement method of regional cerebral oxygenation in the same area than rSO₂ measurement. Of course, one can argue again that PbtO₂ and rSO₂ are not the same measures of brain oxygenation. However, the results were straightforward: like the other monitors (INNOS™, CEROX™) rSO₂ measured by the EQUANOX™ monitor could not detect most ischemic episodes detected by PbtO₂.

This does not mean that NIRS monitoring is useless. For example, NIRS has been validated as an acceptable method for continuous assessment of cerebral autoregulation. However, only changes over time were taken into account and not absolute values of brain oxygenation. At this time, we have to follow recent guidelines telling us NIRS is not currently indicated for routine monitoring of neurointensive care patients. Undoubtedly, NIRS will still be used for research purposes, but at this time we have to take the information provided by NIRS devices cautiously.

**References**


Acute painful stimulation induces modification of the autonomic nervous system (ANS) modulation through activation of the sympathetic nerve activity directed to the heart and vessels.\(^1\,\2\) During general anesthesia the conscious perception of pain is abolished, thus the assessment of nociception is difficult. Traditionally, patients’ movements or autonomic mediated reflexes like tachycardia, hypertension and tearing are used by anesthesiologists to assess the adequacy of antinociception. Unfortunately, these clinical signs have been proven to carry low specificity and sensitivity as indicators of nociception in anaesthetized patients.\(^3\,\6\) Recently the Surgical Pleth Index (SPI), a novel pulse plethysmograph-derived index has been proposed as a tool to predict the nociception-anti-nociception balance during general anesthesia.\(^7\) The SPI seems to be related to the remifentanil effect-site concentration, is unrelated to the

**ABSTRACT**

**Background.** Surgical noxious stimuli generate a stress response with an increased sympathetic activity, potentially affecting the perioperative outcome. Surgical Pleth Index (SPI), derived from the pulse plethysmogram, has been proposed as a tool to assess nociception-antinociception balance. The relationship between SPI and autonomic nervous system (ANS) during general anesthesia is poorly understood and it is doubtful if SPI-guided analgesia may offer advantages over the standard clinical practice. The study was designed to evaluate if SPI-guided analgesia leads to a lower sympathetic modulation compared with standard clinical practice.

**Methods.** Electrocardiographic wave, non-invasive blood pressure and SPI were recorded in ASA I-II patients undergoing elective laparoscopic cholecystectomy, randomized to receive SPI-guided analgesia or standard analgesia. Hemodynamic parameters, SPI, mean and variance of heart rate, low (LF) and high frequency (HF) spectral components of heart rate variability were measured at four time points: (T0) baseline, (T1) after induction of general anesthesia, (T2) after pneumoperitoneum insufflation and (T3) after pneumoperitoneum withdrawal.

**Results.** SPI, hemodynamic and ANS parameters changed significantly in both groups during the study period (\(P<0.0001\)). At T2 SPI and markers of sympathetic modulation were significantly lower in SPI group (mean [SD] SPI 38.1 [15.3] vs. 48.1 [16.2] normalized units, \(P<0.05\); LF 38 [8.6] vs. 56.2 [20.6] normalized units, \(P<0.01\); LF/HF 1.01 [1.1] vs. 2.68 [2.07], \(P<0.01\)). There was no difference in remifentanil consumption, recovery time from anesthesia, or postoperative pain and complications.

**Conclusion.** SPI-guided analgesia led to a more stable sympathetic modulation but didn’t seem to offer clinically relevant advantages over the standard clinical practice for laparoscopic cholecystectomy. (Minerva Anestesiol 2015;81:837-45)

**Key words:** Autonomic nervous system - Nociception - Heart Rate.
propofol effect-site concentration during general anaesthesia, and it predicts the probability of movements at skin incision more accurately than commonly used clinical parameters. High SPI values are considered indicators of a prevalence of the nociception over the antinociception.

To date, it is unclear if a SPI-guided analgesia offers some advantages in terms of ANS activation during general anaesthesia. Direct measurement of ANS activity is not feasible in a clinical context. Heart rate variability (HRV) analysis in the frequency domain provides an indirect measurement of sympathetic and vagal modulation directed to the heart. We conducted a prospective randomized controlled trial to investigate if SPI-guided analgesia results in a lower sympathetic activity measured by means of the HRV analysis compared to a standard clinical practice in patients undergoing laparoscopic cholecystectomy.

Materials and methods

Patients selection

This is a single centre, prospective, randomized, double blinded study, conducted at the Luigi Sacco Hospital in Milan, Italy, from February 2010 to March 2011. Eligible participants were adults aged between 18 and 50 years old, American Society of Anaesthesiologists status I and II who were scheduled for elective laparoscopic cholecystectomy under general anesthesia. Exclusion criteria were comprised of: a history of diabetes, hypertension requiring pharmacological treatment, chronic cardiovascular or neurological disease, obesity, history of alcohol or drug abuse, arrhythmic cardiac disease (atrial fibrillation, atrial flutter, ectopic beats >5% of normal sinus beats), endocrine pathology (thyroidal or adrenal), peripheral neuropathy, and any known autonomic dysfunction. The study was previously approved by the local Ethics Committee and all patients provided written informed consent.

Study protocol

The eligible patients were randomized into one of the two study groups: SPI-guided analgesia group (SPI group) and standard practice analgesia group (control group). All patients were asked to fast eight hours preoperatively, and no vagolytic drugs (i.e. atropine, scopolamine) or benzodiazepines were administered as premedication. Ten milligrams of oxycodone was administered orally 1 hour before the surgery. Upon arrival at the operating theatre, patients were placed in a supine position and connected to a S/5 Advance Monitor provided with SPI (General Electric, Helsinki, Finland). Monitoring consisted of continuous electrocardiogram (ECG), non-invasive blood pressure every 2.5 min, pulse oximetry, respiratory gas analysis, end-tidal carbon dioxide (EtCO2), electroencephalographic rest (RE) and state (SE) entropy, pulse photoplethysmography, cutaneous temperature at the tenar eminence of the left hand, and SPI. The SPI ranges from 0 to 100 and may be calculated as SPI=100-(0.33xPBI_norm + 0.67xPPGA_norm), where PBI and PPGA are the normalized pulse beat interval and pulse plethysmographic amplitude, derived from the photo plethysmographic probe. Normalization algorithm is a property of the manufacturer and it is undisclosed. All data were recorded continuously and were exported to a laptop computer provided with the S/5 Collect software and real time SPI measurement (General Electric, Helsinki, Finland). All variables were analysed at four main time points: 1) T0, baseline before induction of general anesthesia; 2) T1, after the tracheal intubation and five min after starting of mechanical ventilation; 3) T2, five min after the insufflation of pneumoperitoneum; 4) T3, five min after the removal of pneumoperitoneum.

Induction and maintenance of anesthesia

In all patients, anesthesia was induced with propofol and remifentanil via target-controlled infusion pumps (Asena Alaris; Cardinal Health, Basingstoke, United Kingdom). The pharmacokinetic models used were Schnider’s and Minto’s for propofol and remifentanil respectively. The predicted effect-site concentration of propofol (CE_prop) initially was set at 4 µg·mL⁻¹ and remifentanil (CE_rem) at 4 ng·mL⁻¹. After loss of consciousness, oxygen was given by facemask.
and muscle relaxation was induced with cis-atracurium bolus (0.2 mg x kg⁻¹). After tracheal tube placement, mechanical ventilation was started at 15 breaths min⁻¹ with a volume targeted to get an EtCO₂ between 35-38 mmHg. The respiratory rate was increased if the EtCO₂ exceeded 38 mmHg with a tidal volume of 10 mL x kg⁻¹ and/or an airway plateau pressure exceeding 35 cm-H₂O. A respiratory rate <15 breaths x min⁻¹ was not allowed during the study period.

The CEₚᵢᵢ was adjusted by step of 1 µg x mL⁻¹ every min to maintain an electroencephalographic state entropy (SE) level between 40-60 (the minimum allowed CEₚᵢᵢ was 3 µg x mL⁻¹). A rescue dose of cis-atracurium (0.08 mg x kg⁻¹) was administrated 40 min after the induction of general anesthesia if needed. In the SPI group, the remifentanil infusion rate was adjusted by step of 1 ng x mL⁻¹ every 1 min to maintain SPI below 50 (the allowed range CEᵣₑᵣᵣᵢ was 2-15 ng x mL⁻¹). In the control group the SPI was unavailable to the anesthesiologist while it continued to be acquired by the researchers to a laptop computer. In the control group, the anesthesiologist adjusted the remifentanil infusion rate based on the clinical signs of inadequate analgesia (systolic blood pressure above +20% from the baseline or mean blood pressure >100 mmHg, heart rate >90 bpm, coughing, chewing, grimacing, midriasis, tears) or excessive analgesia (heart rate <50 bpm, systolic blood pressure below -20% from the baseline or mean blood pressure <55 mmHg in absence of active bleeding). A pneumoperitoneum was surgically induced and maintained between 12-14 mmHg.

Severe bradycardia (<45 bpm) was treated with atropine 0.01 mg x kg⁻¹ i.v. and hypotension (systolic blood pressure <90 mmHg or mean blood pressure <50 mmHg) unresponsive to fluid challenge of ringer’s acetate 500 mL was treated with ephedrine boluses 5 mg i.v. The patients were considered drop-outs and the data were excluded from the analysis if atropine or vasopressors were needed at any time before the conclusion on the study protocol, blood loss was >200 mL, laparoscopy was converted into laparotomic surgery, or cutaneous temperature dropped >1 °C from baseline.

Non-invasive blood pressure was measured every 2.5 min. Cutaneous temperature, SE, RE, and SPI values represented the mean of values recorded every 15 seconds during the ECG acquisition. The heart rate is displayed as R-to-R mean interval of ECG (msec). Beats per minute are calculated with the equation: HR=(60/RR_mean) x 10³.

After the withdrawal of the gallbladder, tramadol 100 mg and acetaminophen 1 g were administered intravenously. Propofol and remifentanil were stopped at the time of trocar withdrawal.

Recovery time was calculated as the time elapsed from the stop of propofol and remifentanil infusion to tracheal extubation.

Postoperative pain was measured with Numerical Rating Scale (NRS) 6 and 24 hours after the surgery.

Heart rate variability analysis

At each study time point, the ECG was sampled at 300 Hz for HRV analysis according to the recommendations of the European Society of Cardiology Task Force. HRV analysis was performed offline by a semi-automatic tachogram identifier (R-to-R interval identification made by a derivative/threshold method taken from the ECG). After detecting the QRS complex on the ECG and locating the R-apex, the interval between two consecutive R was computed as heart period. Postoperatively, the tachogram was extracted from the recorded ECG and reviewed by an investigator to avoid erroneous detections or missed beats. If isolated ectopic beats occurred, they were removed and linearly interpolated using the closest values unaffected by ectopic beats.

The power spectrum was estimated using an autoregressive model. Sequences of 300 consecutive heart beats were selected inside each experimental step. The mean and the variance of heart period are expressed in msec and ms² respectively. Autoregressive spectral density was factorized into components each of them characterized by a central frequency. A spectral component was labeled as LF if its central frequency was between 0.04 and 0.15 Hz, while it was classified as HF if its central frequency
was between 0.15 and 0.5 Hz. The LF and HF powers are defined as the sum of the powers of all LF and HF spectral components respectively. The HF power was considered to represent respiration-driven vagal heart rate modulation. The LF may reflect vasomotor activity, which is an indirect index of sympathetic nerve activity and partially affected by parasympathetic activity. Spectral values were expressed in normalized units (nu) to remove the effect of changes in total power spectrum densities on LF and HF components. Normalization consists of dividing the power of a given spectral component by the total power minus the power below 0.04 Hz (Very Low Frequency spectral component), and multiplying the ratio by 100. The ratio of the LF power to the HF (LF/HF) was considered an indicator of the balance between sympathetic and vagal modulation directed to the heart.

The investigator who analysed the heart rate variability data was blinded to SPI value.

Outcomes

Primary endpoint: to evaluate if SPI-guided analgesia leads to a lower sympathetic modulation compared to standard clinical practice during laparoscopic cholecystectomy.

Secondary endpoints: to identify if the two groups have a difference in intraoperative hemodynamic variables, consumption of remifentanil, recovery time from anesthesia or postoperative pain.

Statistics

Randomization was based on computer generated list balanced in block of six. Sample size was calculated with PS Power and Sample Size Calculator Software for Windows (http://bio-stat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). There is a wide range in size of ANS variables reported in literature. A previous study found that opiate administration to healthy volunteers during a paced spontaneous breathing trial led to a significant reduction of LF/HF (1.6 vs. 0.92, P=0.013). A minimum of 30 subjects in each study group was required to detect a difference of 0.8 (SD 1.1) in the means of LF/HF between groups at the time of maximal visceral stimulation (pneumoperitoneum insufflation), with a probability of 0.8 and alpha error of 0.05 with two tails test for unpaired groups.

Continuous variables are expressed as mean ±SD, or median (25-75th percentiles) when not normally distributed. The D’Agostino-Pearson’s test was used to check for normal distribution. Student’s t test for independent samples was used to compare the means (or Mann-Whitney U when not normally distributed) between groups of non-repeated measures. Repeated measures were analysed with two way ANOVA followed by Bonferroni’s post hoc test for the comparison between groups. The categorical variables differences in proportions were compared using the χ² test or Fisher’s exact test, as appropriate. The recovery time from general anesthesia were analysed using Kaplan–Meier log-rank survival analysis (calculating the cumulative probability of patients remaining intubated after discontinuation of the anesthetic drugs).

Two tailed P values <0.05 were considered statistically significant. GraphPad Prism 5 was used for statistical analysis.

Results

During the study, 64 patients were recruited. Two patients in the SPI-group and one patient in the control group were excluded because of intraoperatively atropine administration. One patient in the control group was excluded because of conversion to open laparotomy. A total of 60 patients (30 in each group) were analysed (Figure 1).

Patient characteristics are summarized in Table I. Hemodynamic variations and ANS variables during the study protocol are summarized in Figure 2. The SPI showed significant variation during the study protocol with group (P=0.009) and time (P<0.0001) accounting for the total variance. During the maximal visceral stimulation corresponding to the induction of pneumoperitoneum, SPI was significantly higher in the control group than in SPI group (48.1±16.2 vs. 38.1±15.3, P<0.05). Heart rate, systolic and mean arterial pressures, and all HRV indexes changed significantly during the study
protocol, with time accounting for the total variance (P<0.0001). At time of the induction of pneumoperitoneum the power of variability in the low frequency spectrum and the LF/HF ratio were significantly higher in the control group than in SPI group (LF 56.2±20.6 vs. 38±18.6, P<0.01; LF/HF 2.68±2.07 vs. 1.01±1.1, P<0.01). The heart rate, expressed as R-to-R interval on ECG, was also different between groups (control group 0.944±0.139 s vs. SPI group 1.045±0.139 s, P<0.05). There were no significant differences in the CE remifentanil consumption between control and SPI group during study protocol (T1 3.84±0.51 vs. 4.03±1.05 ng x mL⁻¹, T2 4.61±1.69 vs. 5.17±1.23 ng x mL⁻¹, and T3 4.23±2.18 vs. 4.56±1.65 ng x mL⁻¹). There was no significant differences in the total remifentanil consumption between control and SPI group (1056.1±440.5 µg vs. 1036.7±420.6 µg, P=0.5) or indexed remifentanil consumption
COLOMBO

SURGICAL PLETH INDEX HELPS TO PREVENT SYMPATHETIC STRESS

Discussion

Our findings contribute significantly to understanding of the autonomic nervous system modulation changes that occur during general anesthesia for laparoscopic surgery. Although it is commonly believed that laparoscopic surgery is a “minimally invasive” surgery, actually it is “maximally perturbing” surgery because of the changes in intra-abdominal pressure, intra-thoracic pressure, diaphragm shift, right and left atrial pressure, vascular resistances, cardiac

Figure 2.—Grey columns represent control group, white columns represent the SPI group. *P<0.05, **P<0.01 between groups. SPI: Surgical Pleth Index; LF: low frequency component of power spectrum of HRV expressed in normalized units; HF: high frequency component of power spectrum of HRV expressed in normalized units; R-to-R: mean interval between QRS peaks on ECG expressed in sec; SAP: systolic arterial pressure; MAP: mean arterial pressure.

Figure 3.—Kaplan-Meier curves represent the percentage of remaining intubated patients after stopping the infusion of remifentanil and propofol (P=0.66).
output and carbon dioxide overload. Moreover, it is well known that noception induces a sympathetic activation, generating a stress response of increased heart rate, blood pressure, catecholamine and corticosteroid release, and it has been supposed to influence postoperative outcome. Unfortunately, it is difficult to assess the surgical stress during general anesthesia. Previously we found that changes in SPI correlate with changes in ANS modulation during general anesthesia. Nowadays it was unknown if titrating analgesia according to a low SPI might reduce the intraoperative autonomic stress. This study found that SPI-guided analgesia aimed at maintain SPI below 50 leads to lower sympathetic activity than the standard clinical practice. Some Authors found that SPI-guided analgesia, with the index kept between 20 and 50 compared to standard clinical practice, resulted in lower remifentanil and propofol consumption, more stable hemodynamic, faster recovery but with contradictory results on incidence of unwanted events. This study did not find a difference in remifentanil consumption, hemodynamic, or recovery time from anesthesia between groups. This might be due to the different surgery type and patient population.

There has been uncertainty about neurally mediated hemodynamic distress elicited by pneumoperitoneum during laparoscopic surgery. An anecdotal vagal hypertone or sympathetic hyperactivity caused by insufflation of pneumoperitoneum has been alternatively advocated as a cause of hemodynamic changes. This study provides additional evidence that pneumoperitoneum insufflation increases the sympathetic modulation during a standard clinical practice anesthesia, as stated by high LF/HF ratio due to high LF spectral component whereas the vagal component remained unchanged in the control group.

The relationship between SPI and LF/HF may be explained by considering the physiologic bases of SPI. It is calculated from the pulse plethysmographic amplitude that reflects pulsatile changes of arteriolar blood volume into the tissue. This is related to the arteriolar wall distensibility and influenced both by intravascular volume status and by sympathetic-mediated vasoconstriction of the arterioles. It is well demonstrated that different types of sympathetic stimuli (painful, orthostatic, lower body negative pressure) increase the firing rates of sympathetic muscular fibers resulting in vessels constriction. These changes ultimately affect the PPGA and SPI. Furthermore, SPI is affected by several confounding factors (atropine administration, level of sedation, spinal anesthesia, intravascular volume status and patient’s position), all influencing ANS activity. We believe that this point is the core of the misunderstanding about pulse plethysmographic-derived indexes as a measure of nociception-antinociception balance: during general anesthesia, altered homeostasis and autonomic response can be induced by several factors, not just nociceptive. The results of this study suggest that SPI reflects the sympathetic mediated vasoconstriction. Other monitoring systems based on HRV analysis have been proposed to measure adequacy of anti-nociception under general anesthesia. The Autonomic Nociceptive Index (ANI) is derived from the automatic analysis of the HRV using a wavelets transformation algorithm in order to keep only HF variations, and then the oscillations’ amplitude are normalized and displayed as absolute number. ANI is based on the assumption that noception causes a reduction of vagal activity that is reciprocal to increased sympathetic activity. This is not true in all cases. Vagal and sympathetic modulation can show quite different oscillations in amplitude and are not always reciprocal to each other. For example, in this study we found a stable HF component and a marked different LF component after pneumoperitoneum insufflation. Thus, any heart rate variability or pulse plethysmographic based index should be considered for their physiological meanings: they measure only the modulation of ANS on cardiovascular system in response to a multitude of affences, not only noception.

Changes in HRV during general anesthesia likely result from the interaction of hypnosis, surgical stimulation, antinociception, and direct cardiovascular effects of drugs. In this study we kept a stable level of hypnosis measured with electroencephalographic state entropy in order to rule out the effect of the depth of hypnosis on SPI and ANS activity.
Commonly, it is believed that high surgical stress is equal to high blood pressure and high heart rate, and vice-versa in the case of low surgical stress. This is true in the majority of cases, but these clinical modifications are late signs of unbalanced or overbalanced sympathetic outflow. Assessing the ANS modulation by means of heart rate variability or pulse plethysmographic analysis might give anesthesiologists more detailed information about the ANS activity under general anesthesia. If these indexes could be complementary and could help to better titrate the hypnotic and analgesics drugs during anesthesia should be an interesting subject for future research.

This study has few limitations. We studied almost healthy subjects. Among these patients we did not found clinically relevant advantages over the standard clinical practice. It should be further investigated if SPI-guided analgesia can allow the anesthesiologists to achieve better control of intraoperative stress, more stable hemodynamic, and prevent perioperative morbidity in moderate-to-high risk patients or in high risk surgery. Although there is no evidence of the optimal SPI value to be maintained during general anesthesia, this study chose values below 50 in the SPI group. Unlike other studies, this study did not set a lower limit of SPI in the SPI group. Although there was no difference between groups in remifentanil consumption or CErem at the three intraoperative study points, mean SPI was lower than 50 in both groups. At the time of abdominal distension by pneumoperitoneum, SPI increased significantly only in the control group. We hypothesize that SPI-guided analgesia may help the anesthesiologist to better titrate analgesia during major surgical stress and decrease opioid infusion during less stressful phases.

Conclusions

In conclusion, this study found that pneumoperitoneum insufflation induces a sympathetic activation of ANS and SPI guided analgesia reduces the sympathetic response during laparoscopic cholecystectomy. However, there are no clinically relevant advantages over standard clinical practice in healthy subjects. Furthermore, these data suggest that SPI seems to reflect sympathetic cardiovascular modulation under general anesthesia.

Key messages

— Pneumoperitoneum represents a stressful stimulus inducing a marked sympathetic activation.
— A target controlled opioid infusion based on Surgical Pleth Index values below 50 reduces the sympathetic response during laparoscopic cholecystectomy.
— Surgical Pleth Index appears to reflect changes in sympathetic modulation during general anesthesia for laparoscopic surgery.

References

Surgical Pleth Index Helps to Prevent Sympathetic Stress

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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34. Burton AC. Relation of structure to function of the tissues of the wall of blood vessels. Physiol Rev 1954;34:619-42.


During endotracheal intubation the anesthesiologist has to avoid using the maxillary incisors as a fulcrum to lever the soft tissues upwards. This may otherwise result in dental trauma. It is obvious that contact with teeth and even worse the incidence of accidental dental trauma, are directly related to the difficulty of the intubation.1

Indirect videolaryngoscopy using Macintosh blades in patients with non-anticipated difficult airways results in significantly lower forces exerted on teeth relative to classic direct laryngoscopy: a randomized crossover trial

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ABSTRACT

Background. Videolaryngoscopy has proven advantageous over direct laryngoscopy for a variety of outcome variables, most importantly, making laryngoscopy more successful. We tested whether three videolaryngoscopes (VLS), McGrath® series 5 (Aircraft Medical Ltd, Edinburgh, UK), C-MAC® (Karl Storz, Tuttingen, Germany) and GlideScope® Cobalt (Verathon Medical, Bothell, WA, USA) exert reduced forces on maxillary incisors and lower teeth, and compared them with a classic Macintosh MAC 3 laryngoscope blade during laryngoscopy.

Methods. In this randomized crossover trial, we included 141 patients (ASA I-III) with non-anticipated difficult airways. They were randomly allocated to undergo direct laryngoscopy and videolaryngoscopy performed with one of three VLS. Primary outcome was the magnitude of forces applied to the maxillary incisors during laryngoscopy. Secondary outcomes were the frequency with which forces were applied, and the magnitude of forces applied to the lower teeth.

Results. Forces applied to the maxillary incisors during direct classic laryngoscopy were on average higher than forces applied during videolaryngoscopy. Among the VLS the average force applied was significantly lower for the C-MAC® as compared to the McGrath® and the GlideScope® VLS. The frequency with which a force was applied to the maxillary incisors was significantly lower for the C-MAC®, compared to the other VLS and classic Macintosh laryngoscope. The number of cases in which force was applied to the lower teeth was smallest for the McGrath VLS.

Conclusion. Forces exerted on maxillary incisors are lower using video-assisted Macintosh blade laryngoscopy compared to classic direct laryngoscopy. The number and magnitude of forces applied to maxillary incisors also differ substantially between different VLS. (Minerva Anestesiol 2015;81:846-54)

Key words: Laryngoscopes - Pressure - Dentition.
Videolaryngoscopy has proven advantageous over direct laryngoscopy using a classic Macintosh blade, for improved viewing of the glottis, with subsequent more successful intubations, and a shorter effective airway time both in patients with non-anticipated difficult and anticipated difficult airways.², ³ Previously, it has been demonstrated that the forces applied to the patient's maxillary incisors are reduced when using a VLS, compared to a classic Macintosh laryngoscope. However, in these studies only one type of VLS (V-MAC®, Karl Storz, Tuttingen, Germany) or Airtraq® (Prodol Meditec, Guecho, Spain) was used.⁴, ⁵ In the other, different types of VLS than the ones used in this study were investigated, and forces on lower teeth were not investigated.⁶

We tested whether three different brands of VLS, i.e. McGrath® series 5 (Aircraft Medical Ltd, Edinburgh, UK), C-MAC® (Karl Storz, Tuttingen, Germany) and GlideScope® Cobalt (Verathon Medical, Bothell, WA, USA) apply similar reduced forces on both maxillary incisors and lower teeth, and compared them with a classic Macintosh MAC 3 laryngoscope.

The primary outcome was the magnitude of forces applied to the maxillary incisors.

Secondary outcomes were the frequency with which forces were applied and the magnitude of the forces applied to the lower teeth.

Materials and methods

After obtaining Institutional Review Board approval (Catharina Hospital Eindhoven, The Netherlands (Chairman: dr. R. Grouls), registration M12-1217), CCMO registration (NL39915.06012) and registration at Clinical Trials (NCT01599312), written informed patient consent was obtained. In total, 150 consecutive patients (ASA I-III) with non-anticipated difficult airways, undergoing a variety of surgical interventions, for which endotracheal intubation was indicated, were enrolled in this randomized crossover trial between May and September 2012 at the Catharina Hospital Eindhoven. The patients were randomly allocated, using computer-generated tables, to receive direct laryngoscopy (classic Macintosh laryngoscope [MAC 3 blade]) and one of three VLS: McGrath®, C-MAC® or GlideScope®. The C-MAC® was used with indirect (monitor) viewing throughout the experiment. Exclusion criteria were no informed patient consent, patients younger than 18 years, patients requiring other than size 3 blade Macintosh laryngoscope, patients with preoperative predictors of a difficult airway (Mallampati score IV, restricted neck movement, thyromental distance <65 mm, interincisor/interdental distance <35 mm), patients with ASA class ≥IV, emergency surgery, surgery of head and/or throat, locoregional anaesthesia, patients fasted <6 hours, bad dentition, dental crowns and/or fixed partial denture. Patients were enrolled during the preanesthetic visit of the patient (performed by anesthesiologists not involved in this study). During this visit, patient characteristics mentioned above (with respect to exclusion criteria) were recorded.

When the patients arrived in the OR, they were connected to standard monitoring devices. Patients were placed in the supine position with the patient's head resting on a pillow 8 cm in height. After three minutes of oxygen administration, IV induction of anesthesia was performed with 1 μg/kg fentanyl, 3 mg/kg propofol, and rocuronium 0.7 mg/kg, followed by manual ventilation via a facemask using sevoflurane in oxygen. The laryngoscope was inserted at least 90 seconds after completion of induction, and only when the anesthesiologist considered the level of anesthesia adequate for intubation and the end-tidal sevoflurane concentration was ≥1.5%. Muscle paralysis was measured using the train-of-four-ratio.

The patients had the classic Macintosh laryngoscope placed in their mouth. The anesthesiologist subsequently determined the best possible view of the glottic opening and an endotracheal tube (7.5 mm endotracheal tube for men, 7.0 mm for women) was brought into position in front of the glottic opening. After the Macintosh laryngoscope was removed, one of three VLS was placed in their mouth and the procedure was repeated. Actual intubation was only performed with the VLS. Three anesthesiologists, familiar with the tested VLS (minimum 100 uses on actual patients) and classical intubation,
participated in the study. They were specifically instructed in avoiding any contact with the teeth. We chose to instruct anesthesiologists in this way because we could not blind them for the sensors placed on the laryngoscope blade. The participating anesthesiologists did know the purpose of the study and therefore may have taken extra care in avoiding dental trauma.

Effective airway time was measured as the time between picking up the endotracheal tube and placing it in front of the glottic opening (in case of the classic Macintosh laryngoscope) or insertion between the vocal cords (in case of the VLS). Each approach towards the glottic opening was counted as an intubation attempt. After two unsuccessful attempts a stylet was inserted into the endotracheal tube to facilitate intubation.

Patient characteristics (i.e. weight, age, gender, height, BMI), specific metrics of intubation difficulty (i.e. Mallampati grade, thyromental distance, neck movement, mouth opening, dentition, Cormack-Lehane grade, number of intubation attempts), and any complication were recorded.

The method used to measure the forces applied to the teeth (dependent parameter) for the duration of insertion of each laryngoscope was the same as used by Lee et al., using Flexiforce® sensors (A201-25, Tekscan, MA, USA). These were fixed to the blade of the laryngoscope at the possible area of contact with the teeth. Three sensors were mounted on top of the blade (the site of the blade directed at the maxillary incisors during intubation) along its length and three at the bottom of the blade (the site of the blade directed towards the tongue during intubation) (Figure 1).4 6 This configuration completely covers the possible contact points between the blade and the teeth. The sensors are rated to 110 N. Calibration was performed by applying a known mass (from 1 to 12 kg, in steps of 1 kg) using a flat-headed screwdriver (as geometrical approximation of the contact with the teeth) to the sensors mounted upon the blade. The sensors were invariant to the contact point of the applied load. Each of the sensors was individually calibrated in situ. The sensors were cleaned and sterilized between each use by submersion of the blade in chlorhexidine 0.5% in alcohol 70%. The sensors were assumed to work reliably, as the forces were an order of magnitude lower than required to permanently damage the sensor. This assumption was tested by calibration tests at the end of the experiments, whereby none of the sensors indicated degradation.

Data acquisition was achieved with a National Instruments® (DAQ6009 (National Instruments Corporation, TX, USA) card at 500 Hz, using Labview® 7.0 (National Instruments Corporation, TX, USA) on a laptop computer (Hewlett Packard Company, CA). Peak forces were subsequently noted for each of the patients. Because drift and noise in the sensors could result in very low but incorrectly detected contact forces between the teeth and the blade we used a threshold of 2N to determine whether a force was applied to the teeth or not. All registrations of forces applied to the maxillary incisors or lower teeth were registered on the laptop computer in such a way that these were completely blinded for the anesthesiologist who intubated the patient’s trachea. The results of these measurements were only available to an engineer (JVD) of the Technical University Delft, The Netherlands.

Prior to the experiment we performed a power analysis to estimate the required sample size of patients required for finding differences between the magnitudes of used forces. We were interested in finding a difference between the laryngoscopes of at least 20N as, based on earlier results by Lee et al., we assumed that such a difference would have a significant clinical value.4 6 Fur-
Corrections were made for multiple hypothesis tested using Bonferroni ($t.e.$ alpha/k=0.05/6).

Results

All 150 patients were successfully intubated in the study. However, in nine patients in the VLS group and in one patient in the direct laryngoscopy group, registration of forces was not realized due to technical problems.

The actual sample size was larger than initially calculated by the power analysis, because during the study it was not directly clear how many measurements were lost due to the technical problems. Therefore the study included the results of 141 patients (63 males and 78 females), all intubated with one of the three VLS. Patient characteristics are given in Table I, results obtained during laryngoscopy in Table II. No differences were seen between the groups regarding patient characteristics, the objective metrics

Table I.—Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Classic N=141</th>
<th>McGrath® N=48</th>
<th>C-MAC® N=47</th>
<th>GlideScope® N=46</th>
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<tr>
<td>Age; years</td>
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<td>55.5±15.0</td>
<td>51.9±15.0</td>
<td>54.2±16.6</td>
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<td>Height; cm</td>
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<td>172.4±9.4</td>
<td>171.3±9.0</td>
<td>171.0±8.5</td>
</tr>
<tr>
<td>Weight; kg</td>
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<td>80.1±15.6</td>
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<td>BMI; kg.m⁻²</td>
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<td>27.0±6.2</td>
<td>27.4±7.1</td>
<td>28.9±7.4</td>
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<tr>
<td>Thyromental distance; mm</td>
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<td>84.3±9.9</td>
<td>84.1±8.4</td>
<td>82.4±3.5</td>
</tr>
<tr>
<td>Intercisor/interdental distance; mm</td>
<td>43.4±6.6</td>
<td>44.0±6.4</td>
<td>43.5±6.1</td>
<td>43.2±7.2</td>
</tr>
<tr>
<td>Adequate neck movement; yes/no, N.</td>
<td>141:0</td>
<td>48:0</td>
<td>47:0</td>
<td>46:0</td>
</tr>
</tbody>
</table>

Values are numbers, or mean±SD.

Table II.—Results obtained during laryngoscopy using three videolaryngoscopes (McGrath®, C-MAC®, GlideScope®) and the classic Macintosh laryngoscope.

<table>
<thead>
<tr>
<th></th>
<th>Classic N=141</th>
<th>McGrath® N=48</th>
<th>C-MAC® N=47</th>
<th>GlideScope® N=46</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cormack Lehane grade</td>
<td>77:52:10:2*</td>
<td>47:1:0:0</td>
<td>43:4:0:0</td>
<td>41:5:0:0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Effective airway time, s</td>
<td>22±13</td>
<td>28±12</td>
<td>11±6*</td>
<td>27±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intubation attempts; N/A</td>
<td>7:11:18:12</td>
<td>36:10:1:0*</td>
<td>6:12:19:9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Use of sylet; yes:no; N.</td>
<td>N/A</td>
<td>1:46</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are numbers (%), or mean±SD. NS: not significant; N/A: not applicable.

*Significant difference between * and the other groups.
with the classic laryngoscope (30.2±33.9 N) was on average higher than the force applied with the VLS (16.2±17.4 N, McGrath® (NS); 9.31±11.3 N, GlideScope® (P<0.004)) and that the average force applied was lowest for the C-MAC® VLS (1.18±4.73 N (P<0.001)). Post Hoc testing revealed that the average force applied for the C-

of intubation difficulty, and Cormack-Lehane grade, although the latter differed significantly between direct and indirect laryngoscopy.

Figures 2, 3 display the peak force per laryngoscope for the maxillary incisors and lower teeth, respectively, averaged across all measurements. Figure 2 shows that the force applied with the classic laryngoscope (30.2±33.9 N) was on average higher than the force applied with the VLS (16.2±17.4 N, McGrath® (NS); 9.31±11.3 N, GlideScope® (P<0.004)) and that the average force applied was lowest for the C-MAC® VLS (1.18±4.73 N (P<0.001)). Post Hoc testing revealed that the average force applied for the C-

Figure 2.—Peak force for the maxillary incisors per laryngoscope, averaged across all measurements.

Figure 3.—Peak force for the lower teeth per laryngoscope, averaged across all measurements.
in which force (>2N) was applied to the maxillary incisors, before computing the averages. The results are displayed in Figure 4. Figure 4 shows that the peak force applied to the maxillary incisors with the classic laryngoscope (44.6±30.8 N) was on average higher than the force applied with the VLS and that the average force was lowest for the C-MAC® VLS (11.5±8.1 N).

Post hoc testing revealed that there was a significant difference between the average peak force found for the classic Macintosh laryngoscope and the average values found for the VLS. The difference between the C-MAC® and the other VLS did, however, not reach significance. For the lower teeth (Figure 5), the peak force found for the different laryngoscopes was low, the median being 1.5 N. The mean forces applied to the lower teeth were significantly lower for the McGrath® compared to the classic Macintosh laryngoscope (P<0.001). Of the other

MAC® VLS is significantly lower than the average forces found for the McGrath® (P<0.001) and the GlideScope® VLS (P=0.001). Table III displays the median and IQR for the forces applied to the maxillary incisors, across all measurements. Figure 3 proves that hardly any force was exerted on the lower teeth with any of the laryngoscopes. The differences between median forces for the classic laryngoscope (2.5N [IQR 7.5N]) and the C-MAC® VLS (2.6N [IQR 8.2N]) were very small. For the GlideScope® (<0N [IQR 4.3N]) and McGrath® VLS (<0N [IQR 1.1N]), median forces were negligible.

The results displayed in Figures 2, 3 also incorporate the cases in which no contact was made between the teeth and the blade, effectively lowering the average peak force. To determine whether the applied force differs among the various laryngoscopes we selected the cases in which contact was made between the teeth and the blade, and

Table III.—Forces (Newton) applied per laryngoscope for the maxillary incisors (across all measurements).

<table>
<thead>
<tr>
<th>Laryngoscope</th>
<th>Median Force</th>
<th>IQR Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>17.1</td>
<td>54.5*</td>
</tr>
<tr>
<td>McGrath</td>
<td>16.5</td>
<td>24.6</td>
</tr>
<tr>
<td>C-MAC®</td>
<td>5.0</td>
<td>2.2</td>
</tr>
<tr>
<td>GlideScope® VLS</td>
<td>16.0</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*Significant difference between * and the other groups.

Figure 4.—Average peak force for the maxillary incisors per laryngoscope. Averages are based on the selection of cases in which contact was made between teeth and blade.
Discussion

This study confirms that when using videolaryngoscopy, the forces applied to the patient's maxillary incisors are reduced when compared with the classic Macintosh laryngoscope, while there are no differences in the forces exerted on the lower teeth.

The number of contacts made with the maxillary incisors was lowest with the C-MAC® VLS, whereas there were no differences in number of contacts between the other VLS studied and the classic laryngoscope. The difference in average peak force between the C-MAC® and the other VLS was not statistically significant. However, when unexpectedly, intubation averages, none were significantly different from each other.

Tables IV, V summarize the proportion of cases where contact was made with the upper and lower teeth, respectively.

The mean effective airway time was 8.6±5.6 s for the patients in the direct laryngoscopy group, compared to 18±11 s in the McGrath® group (P<0.001); 23±16 s in the GlideScope® group (P<0.001) and 11±10 s in the C-MAC® group (NS). In the latter group significantly more first attempt successful intubations were realized compared to the other two VLS groups. In only 2/47 (4%) of the patients in the C-MAC group a stylet was needed to intubate the trachea, which was significantly lower than in the McGrath (29/48, i.e. 60%) and GlideScope® (28/46, i.e. 61%) groups.

Table IV.—Proportion of cases in which contact was made between the maxillary incisors and the blade and a force was applied (>2N).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Contact</th>
<th>Percentage</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macintosh laryngoscope</td>
<td>141</td>
<td>93</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>McGrath® videolaryngoscope</td>
<td>48</td>
<td>34</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>C-MAC® videolaryngoscope</td>
<td>47</td>
<td>9</td>
<td>19*</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>GlideScope® videolaryngoscope</td>
<td>46</td>
<td>28</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>282</td>
<td>164</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference between * and the other groups.
was more difficult than anticipated (Cormack Lehan grade III/IV), and for example the BURP maneuver had to be used or the help of an assistant was required, this did not result in differences between VLS concerning forces applied to the maxillary incisors.

When intubation could only be realized after multiple attempts, differences between numbers of contacts at each intubation attempt did exist. The trend seemed to be that providers made more contact at subsequent attempts. However, there was no clear increase in magnitude of forces applied to teeth.

The design of the C-MAC® laryngoscope blade is similar to a classic Macintosh blade, but differs from the blades of the McGrath® and GlideScope® VLS. The fact that a VLS with a Macintosh blade creates more room for intubation compared to other VLS, makes intubation not only easier (more room to direct/manipulate the tube and less use of stylets), but also faster (shorter effective airway time because the laryngeal and pharyngeal axes are more in one line compared to a VLS with a curved blade, making the route, which the tube has to follow, more direct) and with less frequent contacts with maxillary incisors.

When using a classic direct laryngoscope with a Macintosh blade, all three axes (laryngeal, pharyngeal and especially oral) need to be positioned in one line. Often this requires the anesthesiologist to use more force and so frequently more force is applied to the maxillary incisors.

The results of this study show a large difference between forces applied during direct and indirect laryngoscopy, with the mean force applied to the maxillary incisors being lowest for all measurements in the C-MAC® group (i.e. 1.18±4.73 N), which is comparable to the results of Lee et al.4–6

Patients were not intubated using the classic laryngoscope, and this could have affected the effective airway time realized by direct laryngoscopy. The results on the forces obtained with the classic Macintosh laryngoscope may have been greater than the ones recorded. Actually passing the tube through the vocal cords could have turned out to be more difficult than just positioning it in front of the vocal cords, requiring more force to be used.

Limitations of the study include: 1) the restricted number of different brands of VLS in this study, since the amount of available brands of VLS seems to increase daily; 2) this study only included patients with non-anticipated difficult airways, and hence nothing can be deduced for patients with difficult airways. One could argue if patients with a Mallampati Score III can be considered as having a non-anticipated difficult airway. Indeed, this is often associated with a difficult airway. However, sometimes even a patient with a Mallampati I turns out to be difficult to intubate because of a high-anterior positioned glottis. The combination of exclusion criteria mentioned earlier and a cut-off value of Mallampati III is valid to exclude the majority of patients with a difficult airway. This was confirmed by the fact that all patients were successfully intubated; 3) we considered 2N as the lower range for determination of any force, which means that the actual number of contacts might be higher; and 4) actual intubation was only performed with the VLS, and hence intubation time could have been influenced for direct laryngoscopy. Also, additional pressure may be applied and a higher number of contacts with the teeth may be experienced during actual passing of the ETT between the vocal cords. This could have resulted in more contacts with teeth and greater force being applied to the teeth for the classic Macintosh laryngoscope; 5) a stylet was inserted into the endotracheal

| Table V.—Proportion of cases in which contact was made between the lower teeth and the blade and a force was applied (>2N). |
|---|---|---|---|
| N. | Contact | Percentage | P value |
| Macintosh laryngoscope | 141 | 73 | 52 |  |
| McGrath® videolaryngoscope | 48 | 4 | 8* | <0.001 |
| C-MAC® videolaryngoscope | 47 | 24 | 51 |  |
| GlideScope® videolaryngoscope | 46 | 14 | 30 |  |
| Total | 282 | 115 | 41 |  |

*Significant difference between * and the other groups.
We strongly recommend considering using VLS in patients with poor dentition, dental crowns and/or fixed partial denture, needing intubation. When choosing a videolaryngoscope for this category of patients, the anesthesiologist has to be aware of differences between VLS concerning risk of dental trauma.

**Key messages**

— Compared to classic direct intubation, intubating with VLS results in reduced forces exerted on the maxillary incisors.

— VLS differ in the magnitude of forces applied to maxillary incisors during intubation. Forces are lowest when VLS with Macintosh shaped blades are used.

— Forces applied to lower teeth seem clinically insignificant.

**References**

In 1878 Luciani 1 was the first to publish esophageal pressure measurements and in 1949 Buytendijk 2 proposed an esophageal pressure measurement technique with a balloon in the esophagus to estimate pleural pressure. Subsequently, several studies demonstrated the possibility of applying esophageal pressure as an adequate surrogate of pleural pressure in the clinical practice.3 The most widely applied technique consists of an esophageal balloon filled

**ABSTRACT**

**Background.** The aim of this study was to evaluate in vitro the accuracy of second generation esophageal catheters at different surrounding pressures and filling volumes and to suggest appropriate catheter management in clinical practice.

**Methods.** Six different esophageal catheters were placed in an experimental chamber at four chamber pressures (0, 10, 20 and 30 cmH₂O) and at filling volumes ranging from 0 to 10 mL. The working volume was defined as the volume range between the maximum (Vmax) and minimum (Vmin) volumes achieving acceptable accuracy (defined by a balloon transmural pressure ± 1 cmH₂O). Accuracy was evaluated for a standard volume of 0.5 mL and for volumes recommended by manufacturers. Data are shown as median and interquartile range.

**Results.** In the four conditions of chamber pressure Vmin, Vmax and working volume were 1.0 (0.5, 1.5), 5.3 (3.8, 7.1), and 3.5 (2.9, 7.1) mL. Increasing chamber pressure increased Vmin (rho=0.9; P<0.0001), that reached 2.0 mL (1.6-2.0) at 30 cmH₂O. Vmax and working volumes differed among catheters, whereas Vmin did not. By injecting 0.5 mL and the minimum recommended volume by manufacturer, balloon transmural pressure was <-1 cmH₂O in 71% and 53% of cases, it was negatively related to chamber pressure (rho=-0.97 and -0.71; P<0.0001) and reached values of -10.4 (-12.4, -9.7) and -9.8 (-10.6, -3.4) at 30 cmH₂O.

**Conclusion.** Measuring positive esophageal pressures needs higher injected volumes than usually recommended. The range of appropriate filling volumes is catheter-specific. Both absolute values and respiratory changes of esophageal pressure can be underestimated by an underfilled balloon. (Minerva Anestesiol 2015;81:855-64)

**Key words:** Esophagus - Catheters - Lung - Pressure - Pleura.

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**ORIGINAL ARTICLE**

**Esophageal pressure measurements under different conditions of intrathoracic pressure. An in vitro study of second generation balloon catheters**

F. MOJOLI 1, D. CHIUMELLO 2, M. POZZI 1, I. ALGIERI 3, S. BIANZINA 1

S. LUONI 1, C. A. VOLTA 4, A. BRASCHI 1, L. BROCHARD 5

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Comment in p. 827 and p. 830.
with air, connected to a long thin catheter for pressure transmission.\textsuperscript{3, 4} The length, diameter and filling volume of these esophageal balloon catheters significantly affected the accuracy of esophageal pressure measurements.\textsuperscript{5-7} In particular, based on the experience on spontaneous breathing patients, a very small filling volume of about 0.5 mL was considered mandatory to avoid both balloon overdistention and esophageal artifacts.\textsuperscript{5, 8} This first generation of catheters was mainly applied in research, but scarcely in the clinical practice.

In the last years clinicians have reassessed this technique, mainly in the light of several studies showing the utility of esophageal pressure monitoring for correct management of patients with acute respiratory distress syndrome,\textsuperscript{9, 12} and due to the availability of a second generation of esophageal balloon catheters.\textsuperscript{3, 13} The technique is now considered to estimate the role of the chest wall in airway pressures or to adjust ventilator pressures based on the absolute values measured in the thorax with the balloon. Technical information concerning these new catheters is still very limited.\textsuperscript{3} A recent study found that pressure recorded may be influenced by artifacts caused by material adhesion and may depend on the balloon design and filling volumes, underlining the risk of balloon overfilling, which might lead to overestimation of esophageal pressure.\textsuperscript{14} We also reported that, under positive pressure conditions, esophageal pressure can be under-

![Figure 1.—Esophageal balloon catheters. Esophageal balloon’s material is polyethylene for Cooper, NutriVent, SmartCath and SmartCathG and latex for Marquat and Microtek catheters. Balloon's length is 100 mm for Microtek, NutriVent, SmartCath and SmartCathG, 95 mm for Cooper and 80 mm for Marquat. Catheter's diameter (Fr) and length (cm) are 5/85 (Cooper), 6/78 (Marquat), 8/100 (Microtek), 14/91 (NutriVent), 8/101 (SmartCath) and 16/114 (SmartCathG).]
transmitted when too low inflation volumes are used.\textsuperscript{15}

The aim of this \textit{in vitro} study was thus to evaluate the accuracy of common commercial esophageal balloon catheters at different filling volumes and surrounding pressures, in order to suggest clinicians how to properly manage this second generation catheters under different intrathoracic conditions.

**Materials and methods**

\textit{Esophageal catheters}

Six different commercially available esophageal balloon catheters were evaluated (Figure 1): SmartCath (Avea SmartCath Carefusion, San Diego, CA, USA), SmartCathG (Avea SmartCath nasogastric pressure, Carefusion, San Diego, CA, USA), Nutrivent (NutriVent, Sidam, San Giacomo Roncole, Mirandola, Modena, Italy), Marquat (Marquat Genie Biomedical, Boissy-Saint-Léger Cedex, France), Cooper (Cooper Surgical, Trumbull, CT, USA) and Microtek (Microtek, Zutphen, The Netherlands). SmartCath, SmartCathG, Marquat, Cooper and Microtek are equipped with an esophageal balloon. Nutrivent is equipped with both an esophageal and a gastric balloon. SmartCathG and Nutrivent have also an internal line for feeding and stomach aspiration. Inflating air volumes recommended by the manufacturer are 1-2 mL (Cooper), 0.5-3 mL (Marquat), 4 mL (NutriVent) and 0.5-2.5 mL (SmartCath and SmartCathG). To our knowledge, no manufacturer's indications are available for Microtek, therefore we considered 0.5-1.0 mL as previously reported for this catheter.\textsuperscript{16}

For each catheter type, five samples were visually inspected and fully inflated at ambient pressure, in order to exclude different behavior among samples due to manufacturing defects.

\textit{Experimental setup}

The experimental setup (Figure 2) consisted of an experimental chamber and a data acquisition system (OptiVent, Sidam, Italy). The experimental chamber consisted of a rigid plastic cylinder (inner volume 2 liters) connected to a 100 mL syringe and to the data acquisition system by a 3-way stopcock and a 120 cm tube line. The esophageal balloon catheters were introduced into the experimental chamber through a small opening, that was subsequently sealed. Esophageal catheters were connected to a 10 mL syringe for balloon inflation and to the data acquisition system by a 3-way stopcock and a 80 cm tube line.

\textit{Measurements}

Simultaneous measurement of chamber and balloon pressure were provided by pressure sensors (26PCAFA6G, Honeywell Micro Switch Sensing and Control, USA) located in the OptiVent system; data were sampled at 100 Hz and processed on this dedicated data acquisition system.
Experimental protocol

To simulate a wide range of “pleural” pressures surrounding the esophageal balloons, the pressure in the chamber was set at 4 different levels: 0, 10, 20 and 30 cmH₂O. The chamber pressure was returned to ambient by disconnecting the 100 mL syringe. Positive values of chamber pressure were obtained by the injection and pressurization of different volumes of air in the cylinder by the 100 mL syringe. Different esophageal catheters were introduced in the experimental chamber in a random order. At each level of chamber pressure, the esophageal balloon catheters were progressively inflated by 0.5 mL steps, from 0 up to a maximum inflating air volume of 10 mL or a maximum of balloon pressure of 50 cmH₂O, whatever came first. For each step, before the injection of the desired volume by the 10 mL syringe, the esophageal balloon catheter was deflated with generation of negative pressure and then equilibrated at zero pressure by disconnecting the 10 mL syringe for at least 10 seconds. After that, the catheter was inflated up to the maximum level in order to distend the balloon’s wall and then deflated to the desired one. Since the increase of balloon volume could, in theory, slightly modify the chamber pressure, this was rechecked and eventually adjusted at the desired level.

In all the tested conditions the balloon and chamber pressures were obtained in duplicate. Balloon transmural pressure was calculated as the difference between the balloon and the chamber pressure. Acceptable accuracy was defined by a transmural pressure between -1 and +1 cmH₂O. For each esophageal balloon catheter the working volume (Vworking) was defined by the difference between the maximum (Vmax) and minimum (Vmin) injected air volume above zero which provided an acceptable accuracy. The balloon underfilling, appropriate filling and overfilling were defined by all the injected air volumes respectively below Vmin, between Vmin and Vmax and above Vmax. The overlap range of appropriate volumes (Voverlap) was defined by the maximum value of Vmin and the minimum value of Vmax observed at the four different levels of chamber pressure. Because the esophagus can be considered a liquid milieu, Vmin and Vmax were systematically verified by submerging all the catheters under a 10, 20 and 30 cm water column.

A single catheter (NutriVent, Sidam, Italy) was also studied at negative (-10 cmH₂O) chamber pressure; in this case, after the catheter had been equilibrated with ambient pressure, both volume injection into and volume removal from the catheter were evaluated, up to 10 mL or 50 cmH₂O or down to -10 mL or -50 cmH₂O, respectively.

Statistical analysis

Data are given as median (interquartile range). Agreement and correlation between measurements obtained in the experimental chamber and those obtained in the water column were evaluated by Bland-Altman analysis and Spearman’s test. Vmin, Vmax and Vworking were compared among catheters by Kruskal Wallis test. Correlation between Vmin, Vmax and chamber pressure was evaluated by Spearman’s test. Balloon transmural pressures associated to a standard volume of 0.5 mL and to volumes recommended by manufacturers were computed and correlation with chamber pressure evaluated by Spearman’s test.

MedCalc®, version 13.0.6.0 (MedCalc Software, Belgium) was used for statistics. A P value<0.05 was considered significant.

Results

Considering both balloon and chamber pressure, the difference between two repeated measurements was always smaller than 0.2 cmH₂O. Appropriate injected volumes were determined for each esophageal balloon catheter in all conditions (Figure 3). Considering all catheters and conditions the median and interquartile range for the Vmin, Vmax and Vworking were 1.0 (0.5, 1.5), 5.3 (3.8, 7.1) and 3.5 (2.9, 6.1) mL, respectively. In Table I are shown Vmin, Vmax, Vworking and Voverlap for each type of esophageal balloon catheter. Vmax differed among catheters (P<0.002), whereas Vmin did not. Marquat and NutriVent had the highest
Vmax, while Cooper the lowest one (P<0.05).
The working volumes differed among catheters
(P=0.001): the greatest were observed with Mar-
quat and NutriVent (P<0.05 vs. all the other
catheters), whereas Cooper showed the smallest
one (P<0.05 vs. all the other catheters).

By increasing chamber pressure, Vmin sig-
ificantly increased (rho=0.88, CI 0.75-0.95;
Values of $V_{\text{min}}$ and $V_{\text{max}}$ obtained in the water column agreed (mean difference $-0.1\pm0.2$ mL and $0.1\pm0.4$ mL, respectively) and were strictly correlated ($\rho=0.98$, CI 0.94-0.99, $P<0.0001$ and $\rho=0.99$, CI 0.96-0.99, $P<0.0001$, respectively) with those obtained in the experimental chamber.

In 15/24 cases (63%), the volume ranges recommended by manufacturers included inappropriate values. The minimum recommended volumes of Marquat, Microtek, SmartCath and SmartCathG were associated with balloon underfilling ($P<0.0001$), being 0.5 mL (0.5-0.5) at 0 cmH$_2$O, 1.0 mL (1.0-1.0) at 10 cmH$_2$O, 1.5 mL (1.1-1.5) at 20 cmH$_2$O and 2.0 mL (1.6-2.0) at 30 cmH$_2$O.

Values of $V_{\text{min}}$ and $V_{\text{max}}$ obtained in the water column agreed (mean difference $-0.1\pm0.2$ mL and $0.1\pm0.4$ mL, respectively) and were strictly correlated ($\rho=0.98$, CI 0.94-0.99, $P<0.0001$ and $\rho=0.99$, CI 0.96-0.99, $P<0.0001$, respectively) with those obtained in the experimental chamber.

In 15/24 cases (63%), the volume ranges recommended by manufacturers included not appropriate values. The minimum recommended volumes of Marquat, Microtek, SmartCath and SmartCathG were associated with balloon underfilling ($P<0.0001$), being 0.5 mL (0.5-0.5) at 0 cmH$_2$O, 1.0 mL (1.0-1.0) at 10 cmH$_2$O, 1.5 mL (1.1-1.5) at 20 cmH$_2$O and 2.0 mL (1.6-2.0) at 30 cmH$_2$O. Marquat, NutriVent, SmartCath and SmartCathG showed an overlap among the appropriate volumes observed at the four different chamber pressures (Figure 3); thus, for these four catheters it was possible to identify a range of volumes ($V_{\text{overlap}}$) providing acceptable accuracy throughout the 0-30 cmH$_2$O external pressure range (Table I).

Table I.—Appropriate and recommended filling volumes in the tested esophageal balloon catheters.

<table>
<thead>
<tr>
<th></th>
<th>$V_{\text{min}}$ (mL)</th>
<th>$V_{\text{max}}$ (mL)</th>
<th>$V_{\text{working}}$ (mL)</th>
<th>$V_{\text{overlap}}$ (mL)</th>
<th>$V_{\text{rec}}$ (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper</td>
<td>0.8 (0.4-1.1)</td>
<td>1.8 (1.4-2.1)$^*$</td>
<td>1.0 (1.0-1.0)$^*$</td>
<td>/</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Marquat</td>
<td>1.3 (0.8-1.6)</td>
<td>8.3 (7.5-9.3)$^*$</td>
<td>7.5 (7.3-7.6)$^*$</td>
<td>2.0-7.5</td>
<td>0.5-3.0</td>
</tr>
<tr>
<td>Microtek</td>
<td>2.0 (1.1-2.6)</td>
<td>5.3 (4.0-6.1)</td>
<td>3.3 (2.9-3.5)</td>
<td>/</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>NutriVent</td>
<td>1.3 (0.8-1.6)</td>
<td>7.5 (6.8-8.1)$^*$</td>
<td>6.3 (6.0-6.5)$^*$</td>
<td>2.0-6.0</td>
<td>4.0</td>
</tr>
<tr>
<td>SmartCath</td>
<td>1.3 (0.8-1.6)</td>
<td>4.3 (4.0-4.6)</td>
<td>3.0 (3.0-3.5)</td>
<td>2.0-4.0</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>SmartCathG</td>
<td>1.0 (0.8-1.1)</td>
<td>4.8 (3.8-5.5)</td>
<td>3.5 (3.0-4.1)</td>
<td>1.5-3.0</td>
<td>0.5-2.5</td>
</tr>
</tbody>
</table>

$V_{\text{min}}$ and $V_{\text{max}}$: minimum and maximum volumes providing appropriate balloon filling; $V_{\text{working}}$: $V_{\text{max}}$-$V_{\text{min}}$ difference; $V_{\text{overlap}}$: overlap range of appropriate volumes; $V_{\text{rec}}$: volumes recommended by manufacturers.

$^*$P<0.05 vs. all others catheters.
$^\#P<0.05$ vs. Marquat, Microtek, Nutrivent, SmartCath, SmartCathG.
$^\ddaggerP<0.05$ vs. Marquat, Microtek, Nutrivent.
$^\astP<0.05$ vs. Cooper, SmartCath, SmartCathG.

Figure 4.—Balloon transmural pressure as a function of chamber pressure (injected volume 0.5 mL).
In case of negative surrounding chamber pressure, the equilibration of the catheter with ambient pressure led to balloon overinflation (positive transbalance pressure) and therefore to overestimation of the external pressure, despite no volume injected in the catheter (Figure 5). The removal of some air volume from the catheter was effective in restoring the appropriate filling of the balloon and allowing an accurate transmission of the external pressure, with negligible balloon transmural pressure.

**Discussion**

The major findings of this study are: 1) all the esophageal balloon catheters showed a good accuracy in transmitting the external pressure when inflated with appropriate filling volumes; 2) un-
nder positive pressure conditions, the minimum appropriate filling volume was greater than 0.5 mL in most cases and was directly dependent on the external pressure, and 3) the range of appropriate filling volumes differed among the esophageal balloon catheters and in most cases did not completely correspond with manufacturer’s recommendations.

The most common indications for measuring esophageal pressure are the assessment of elastic properties of the lung, the optimization of the ventilator setting like the settings of positive end-expiratory pressure (PEEP) and the measurement of work of breathing.3 Reliability of esophageal pressure measurements depends on a proper positioning in the esophagus,4,5,7,17,18 but also on the amount of volume injected in the balloon catheter.6 An underfilled balloon cannot properly transmit the surrounding pressure,8 whereas an overfilled and overdistended one can generate a significant recoil pressure by itself and overestimate.3,5–7 The injected volumes required to avoid both the underfilling and overfilling of the balloon, i.e., the range of appropriate volumes, depend on both balloon and catheter length, diameter and compliance.6–7 Thus, appropriate filling volumes may significantly differ among the various esophageal catheters available on the market.3,8

In the present study, appropriate filling volumes were identified for all the catheters at all the chamber pressure tested. Importantly, these volumes did not differ when a liquid instead of a gas environment for the balloon catheters was set up. The minimum volume to avoid underfilling (Vmin) was very similar among the esophageal balloon catheters. Median value of Vmin was 1 mL, but accordingly to our preliminary report15 it clearly rose with the increase of the external pressure and reached values as high as 3 mL. Our experimental observations are only apparently in contrast with the assumption that a minimal volume, i.e., more or less 0.5 mL, is necessary for the balloon to accurately transmit pressure.8 When a certain amount of volume is injected in the catheter by a syringe, this leads to a corresponding inflation of the balloon only in the case of atmospheric pressure surrounding the balloon. Instead, when this pressure is positive, the injection of a volume of air actually translates into a pressurization of the gas contained in the catheter, until the inner pressure reaches the one surrounding the balloon. At this point, the balloon’s transmural pressure is no more negative and the balloon starts inflating (Figure 4). Therefore, the more positive the external pressure, the higher the volume that has to be injected in the catheter to avoid the underfilling of the balloon.

Balloon overinflation can also occur. At low filling volumes, esophageal balloons show a non-elastic behaviour, i.e., they can increase their volume without generation of elastic recoil pressure.3,7 Above a critical value, any further air volume injection produces a steep increase of pressure, i.e., the balloon starts being overdistended, thus leading to a progressive and significant increase of the balloon transmural pressure with overestimation of the real external pressure. Despite very similar balloon lengths, the volume at which overinflation started (Vmax) varied significantly among the different catheters, ranging from 1 to 7.5 mL at ambient pressure. Recently, it was observed that a sustained overinflation of an esophageal balloon can stretch its wall and increase the volume at which overdistention occurs, thus slightly prolonging the range of appropriate volumes.14 Higher volumes of overinflation lead to larger working volumes and allow an overlap of the appropriate volumes observed at different external pressure levels. In 4 of the 6 catheters tested we could identify a range of volumes (Voverlap) that gave accurate transmission of the surrounding pressures in the whole 0–30 cmH₂O range. The possibility to inject in the esophageal catheter the same volume for almost all intrathoracic conditions simplifies the clinical practice and allows good accuracy also in case of great respiratory variations of pleural pressure. Interestingly, these volume ranges only partially corresponded to the volumes suggested by literature and by manufacturers. In particular, the conventional and widely accepted volume of 0.5 mL and the minimum recommended volume by single manufacturers led to balloon underfilling in more than 70% and 50% of the cases, respectively.

Conventional small volumes (0.5–1.0 mL) seem to be appropriate for measuring near-atmospheric intrathoracic pressures in upright sponta-
neously breathing subjects, but are prone to underestimate the more positive pleural pressures generally observed in ICU patients undergoing positive pressure mechanical ventilation while lying in supine position. Moreover, the more positive the external pressure, the greater the underestimation: this means that end-inspiratory values of esophageal pressure will be more affected than end-expiratory ones. Therefore, both absolute values and respiratory oscillations of esophageal pressure may be under-transmitted by an underfilled balloon.

Any time esophageal pressure is considered for clinical or research purposes, accuracy of the measurement should be checked by performing an airway occlusion test. Our data suggest that, in case of incomplete transmission of pleural pressure to the esophageal balloon during this test, the risk of balloon underfilling should be considered before attempting the repositioning of the catheter. Accordingly, an injected volume among those in vitro validated as appropriate under positive pressure conditions should be tried out. Alternatively, the volume could be in vivo titrated up to the actual $V_{\text{min}}$, that is the volume at which balloon pressure stabilizes and the balloon pressure-volume relationship becomes roughly flat.

When negative intrathoracic pressures were simulated, the risk of balloon overfilling also for small injected volumes (or even no injection at all) was clearly demonstrated. In theory, in case of negative surrounding pressures, the removal of some volume from the esophageal catheter could restore the appropriate balloon filling volume and the accuracy of esophageal pressure measurement (Figure 4). Anyway, it seems more reasonable to avoid equilibrating the esophageal catheter with ambient pressure during patient’s inspiratory efforts that may lead to negative intrathoracic pressures. For this purpose, the patient could be asked for a respiratory pause or a Valsalva maneuver.

Study limitations

This study has some limitations. Our experimental setup, conceived to evaluate the accuracy of esophageal balloon catheters in transmitting the surrounding pressure, was clearly a simplistic model. Actually, the difference between pleural and esophageal balloon pressures have been attributed to both the elastic properties of the balloon and the elastance of the esophageal wall. We decided not to simulate the esophageal reaction to balloon inflation because it was considered not technically feasible and reliable. Moreover, we applied a constant and uniform pressure in our experimental chamber, but pleural pressure is not homogeneous along the lung surface and a vertical gradient is normally present. Therefore, beneficial effects on esophageal pressure measurements provided by titrating balloon filling volume up to an appropriate value as suggested by our in vitro experience should be confirmed by further in vivo studies.

Conclusions

In conclusion, all the esophageal catheters tested in this in vitro study allow accurate transmission of the external pressure when properly filled, being the range of appropriate filling volumes different among catheters. The minimum volume that has to be injected is greater than those usually recommended and is directly dependent on the external pressure surrounding the balloons. Under and overfilling of esophageal balloons can lead to significant errors in the assessment of both absolute values and respiratory changes of esophageal pressure.

Key messages

— The range of appropriate filling volumes differs among the second-generation esophageal balloon catheters.
— Under and overfilling of esophageal balloons can lead to significant errors in the assessment of esophageal pressure-based parameters.
— Under positive pressure conditions the minimum volume that has to be injected may be greater than those usually recommended.
— In case of unsatisfactory occlusion test, before attempting catheter repositioning consider the possibility of balloon underfilling and try to achieve the appropriate volume range by further volume injection.
References


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A. Braschi participated in the development of Nutrivent, and he is involved in a University research spin-off and he received a honorarium as member of the advisory board. He did not receive any payment for writing or contributing to the report.

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Feasibility of Post-Intensive Care Unit Clinics: an observational cohort study of two different approaches

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ABSTRACT

Background. Post-ICU clinics have been advocated to reduce long-term physical and psychological impairments among ICU survivors. A format for optimal structure, timing, and care content has not yet been established. We developed and implemented two post-ICU clinics in different hospital settings and evaluated the feasibility.

Methods. In this prospective cohort study ICU-survivors of a university hospital (AMC) and a general hospital (TG), who were mechanically ventilated ≥2 days and discharged to their homes, were invited to the post-ICU clinic one month after hospital discharge (AMC) or three months after ICU discharge (TG). Feasibility was evaluated as 1) the number of eligible ICU-survivors and the proportion that attended; 2) the prevalence of ICU-related abnormalities, that required referral for further treatment; and 3) patient satisfaction.

Results. Forty-five of 629 AMC-patients and 70 of 142 TG-patients were eligible for the post-ICU clinic. Of these, 49% and 67% respectively, visited the outpatient clinic (P=0.026). The majority of all screened patients had functional restrictions, and 68% required referral for further diagnosis and treatment. Patient satisfaction was high.

Conclusion. This study provides valuable information to support the implementation of post-ICU clinics. The use of validated screening instruments facilitates the identification of patients with need for further treatment. Early in-hospital screening and recruiting patients at highest risk for adverse outcome could be a more targeted approach to achieve greater benefit. (Minerva Anestesiol 2015;81:865-75)

Key words: Intensive care - Rehabilitation - Feasibility studies - Outpatient clinics, hospital.

Each year about 80,000 adults are admitted to intensive care units (ICUs) in the Netherlands and, due to progress in critical care, survival rates have increased. A significant proportion of survivors have long-term physical, psychological, and cognitive impairments that negatively affect daily function, employment, and health related quality of life (HRQOL).1-5 The complexity and magnitude of these ICU-related consequences, recently denoted as Post Intensive Care Syndrome (PICS), require comprehensive multidisciplinary care.6 However, ICU survivors experience inadequate and disjointed multidisciplinary care after hospital discharge, with inconsistent service provision.7 Particularly for ICU survivors who are discharged to their homes, PICS may not be reliably and promptly recognized, resulting in incomplete or late referral to the appropriate care.

Post-ICU clinics have been advocated to manage ICU-related problems in survivors,8-10 but to date such clinics are scarce, their organization varies, and their optimal structure, timing, and care content has not been established yet. Furthermore, there is no direction or consensus on how to implement it. We developed and im-
plemented a post-ICU clinic in a large tertiary university hospital and in a general hospital in the Netherlands, based on the recommendations from the National Institute for Health and Clinical Excellence (NICE) guidelines. The aim of this post-ICU clinic according to the NICE guideline, is to 'screen and detect' patients “that recover at a slower rate than anticipated, and to identify patients that has developed new physical and/or psychological morbidity, that was not previously identified”, and to initiate tailored treatment, if required. We assumed that patients of a university hospital would have more complex and serious illnesses, resulting in longer ICU and hospital stays and a greater need for the post-ICU clinic than ICU survivors of a general hospital would have. Also, we expected that the programmatic evaluation of both approaches would provide important practical information for further improvement of post-ICU clinics.

The purpose of this study was to evaluate the feasibility of the post-ICU clinic in each hospital setting by determining: 1) the number of eligible ICU survivors and the proportion that attends the post-ICU clinic; 2) the prevalence of physical and psychological impairments and functional restrictions that require referral for further diagnosis and treatment; and 3) the level of patient satisfaction with the post-ICU clinic.

Materials and methods

Study design, setting and participants

This prospective cohort study was undertaken in the Academic Medical Center (AMC) in Amsterdam and the Tergooi (TG) in Hilversum. The AMC is a 1000-bed university hospital with a 34-bed mixed medical and surgical closed-format ICU and TG is a 633-bed general hospital with a 10-bed mixed medical and surgical closed-format ICU.

All consecutive adult (age ≥18 years) ICU patients admitted in a 20 months period (2010-2012) in the AMC and TG were screened for participation in the study. Critically ill patients mechanically ventilated for ≥2 days and discharged to their homes from the hospital were considered eligible. Patients with insufficient knowledge of the Dutch language or comorbidity that would impair completing questionnaires or visiting the outpatient clinic (e.g. mental retardation, mechanical ventilation at home, terminal disease, etc.) were excluded. Considering their limited physical resilience and mobility range, AMC patients living beyond the service area of the hospital (a travel distance of more than 15 km) were also excluded. The Ethical Review Board of the AMC waived the need for informed consent because of the non-interventional nature of this study.

Description of the post-ICU clinics

The main purposes of our post-ICU clinics were 1) to screen patients for physical and psychological impairments, functional restrictions, and HRQOL; 2) to identify caregiver strain and symptoms of post-traumatic stress disorder (PTSD) in close relatives; 3) to refer patients or close relatives with unanticipated ICU-related sequelae for further treatment; and 4) to inform patients and their close relatives about short and long-term ICU-related consequences. As part of the standard clinical care, in both hospitals physical therapy interventions started early on the ICU, and were continued on the wards until hospital discharge.

Although the purposes of the post-ICU clinic were similar in the two hospitals, the approach differed with respect to the involved professionals, the timing, and the used satisfaction questionnaires because of the differences in existing care approaches. In the AMC, the post-ICU clinic was implemented in May 2010 by the department of rehabilitation medicine and carried out by a senior physical therapist specialized in critical care. Patients and relatives were invited one month after hospital discharge to enable early identification of ICU-related problems and referral to other practitioners. In October 2010, a similar post-ICU clinic was implemented in the general hospital under the responsibility of the ICU, led by nursing staff. Patients and their relatives were invited three months after ICU discharge to evaluate recovery and initiate additional care if necessary.

In both hospitals, two weeks prior to the visit
to the post-ICU clinic, patients completed the Dutch-translated and validated versions of the following questionnaires:

1) The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) was used to measure HRQOL. The domains “physical function” and “role limitation due to physical problems” were used to screen patients for physical impairments and functional restrictions.

2) The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression. Sub-scale scores (0-21) of ≥8 indicate anxiety or depressive symptoms.

3) The 10-item Trauma Screening Questionnaire (TSQ) was used to identify patients at risk for PTSD. A cut-off score of 6 has found to be optimal.

4) Health care utilization, a self-composed list on which patients had to mark all health care professionals that they received care from.

Information on socio-demographics (age, height, body weight, living situation, and employment [number of working hours] before and after the ICU admission) was recorded, and clinical data were retrieved from medical records.

In close relatives, PTSD and potential care giving concerns were assessed before their visit to the post-ICU clinic, using the TSQ and Caregiver Strain Index (CSI). The CSI is a validated 13 item questionnaire with a score of >7 indicating a higher risk for strain. In addition, socio-demographic characteristics (age, gender, relationship to the patient, work situation before and after patient’s hospital admission) were recorded.

At the post-ICU clinic, a shortened version of the International Classification of Functioning, Disability, and Health (ICF) checklist (Part 1a: impairments of body functions and Part 2: activity limitations and participation restrictions), and the Malnutrition Universal Screening Tool (MUST) were completed for the screening of ICU-related impairments or functional restrictions. The ICF checklist of the World Health Organization is a practical tool to identify and classify information on the functioning and disability of an individual. The MUST is used in hospitals to identify patients at risk for undernourishment. A MUST score of 2 implies a high risk of malnutrition.

Patients with clinically meaningful ICU-related physical or psychological impairments according to the questionnaires and screening tools were referred for further treatment. Close relatives with high burden of care and/or symptoms of PTSD were advised to contact their general practitioner for support or additional care.

AMC patients were asked to rate their satisfaction with the post-ICU clinic on an ordinal 5-item scale (4=very satisfied, 3=satisfied, 2=not satisfied/nor dissatisfied, 1=dissatisfied, 0=very dissatisfied). At TG, a 10-point scale, with higher scores indicating more satisfaction (1=very dissatisfied, 10=very satisfied) was used.

ICU survivors who declined the invitation to visit the post-ICU clinic were contacted by phone to ascertain their reasons for not attending.

**Feasibility**

The feasibility of each post-ICU clinic was evaluated as: 1) the number of eligible ICU survivors and the proportion that attended one month after hospital discharge for AMC, and three months after ICU discharge for TG; 2) the prevalence of physical and psychological impairments, and functional restrictions that required referral for further diagnosis and treatment; and 3) patient satisfaction.

**Statistical analysis**

Demographic and clinical data of ICU patients, including age, gender, Body Mass Index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II), ICU admission diagnosis, duration of mechanical ventilation, length of ICU and hospital stay, and working hours prior to ICU admission, were compared both between the two hospital settings, and between patients that attended the post-ICU clinic and patients who declined or who were lived beyond the service area of the hospital. Also, physical and psychological impairments, and functional restrictions after hospital discharge were compared between the two hospitals, as well as the demographic data of close relatives, caregiver strain, and post-traumatic stress. Comparisons were performed with the independent t-test.
(continuous data), the Mann-Whitney U-test (ordinal data), and the Chi-square test (categorical and dichotomous data) or Fisher’s exact test. A P-value less than 0.05 was considered statistically significant. For descriptive analysis, mean values were presented with standard deviation (±SD), median values with interquartile range (IQR) and proportions with percentages and total numbers. All analyses were performed in IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, USA).

Results

Number of eligible patients

Of the patients who were mechanically ventilated ≥2 days (AMC: N.=629, TG: N.=142), 45 patients from the AMC and 70 from TG met the inclusion criteria and were discharged home (Figure 1). The baseline characteristics of the 60 AMC-patients who were excluded because of travel distance >15 km, did not differ from those of included AMC-patients, except for age (median [IQR] age 57 [42-66.8] in excluded patients vs. 61 [54-69.5] in included patients, P=0.041).

Of all eligible patients, 22 AMC patients (49%) and 47 TG patients (67%) visited the post-ICU clinic (P=0.026). AMC patients visited the outpatient clinic at a mean of 5.5 weeks (SD 2.6) after hospital discharge and TG patients at 12.1 weeks (SD 3.7) after ICU discharge.

Reasons for not attending (N.=23) the post-ICU clinic in the AMC were: good health (N.=2) or participation in a cardiac rehabilitation program (N.=8), no need (N.=6), health-related difficulties (N.=4), and re-admission to the hospital (N.=2); one patient could not be traced. At TG, the reasons for not attending (N.=23) were: impossible to contact (N.=12), health-related difficulties (N.=6), and no need (N.=5).

The demographic and clinical data of the study participants in the two hospitals were comparable (Table I), except for gender (42% men in AMC vs. 76% in TG, P=0.008). Patient characteristics between ICU survivors who visited the post-ICU clinic and who declined did not differ (P>0.05) (Table II). Three AMC patients and one TG patient were excluded from the analysis because of incomplete questionnaires (Figure 1).

Functional status and referral

There were no statistical differences in functional status of ICU survivors in the two hospitals (Table III). Out of all SF-36 domain scores, only “bodily pain” and “mental health” scores were comparable to the normative values of the general Dutch population. All other SF-36

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>AMC</th>
<th>Tergooi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of patients</td>
<td>19</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>58.1 (14.2)</td>
<td>63.4 (11.5)</td>
<td>0.118</td>
</tr>
<tr>
<td>Gender (male), N. (%)</td>
<td>8 (42.1)</td>
<td>35 (76.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>24.9 (22.5-31.2)</td>
<td>27.4 (23.5-29.8)</td>
<td>0.478</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30), N. (%)</td>
<td>5 (26.3)</td>
<td>10 (21.7)</td>
<td></td>
</tr>
<tr>
<td>ICU admission diagnosis, N. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>16 (84.2)</td>
<td>36 (78.3)</td>
<td>0.077</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>1 (5.3)</td>
<td>4 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Non-elective surgery</td>
<td>2 (10.5)</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>APACHE II Score, median (IQR)</td>
<td>21 (16-24)</td>
<td>18 (15-24.5)</td>
<td>0.891</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days), median (IQR)</td>
<td>6 (4-7)</td>
<td>4.15 (2.9-7.3)</td>
<td>0.155</td>
</tr>
<tr>
<td>LOS in ICU (days), median (IQR)</td>
<td>7 (5-8)</td>
<td>6.85 (5-10)</td>
<td>0.840</td>
</tr>
<tr>
<td>LOS in hospital after ICU-discharge (days), median (IQR)</td>
<td>11 (8-14)</td>
<td>12 (6.8-17.3)</td>
<td>0.817</td>
</tr>
<tr>
<td>Remunerative employment, N. (%)</td>
<td>6 (31.6)</td>
<td>13 (28.3)</td>
<td>0.160</td>
</tr>
<tr>
<td>Working hours per week, median (IQR)</td>
<td>36 (27-40)</td>
<td>36 (31-39)</td>
<td></td>
</tr>
<tr>
<td>Voluntary work, N. (%)</td>
<td>2 (10.5)</td>
<td>8 (17.4)</td>
<td>0.485</td>
</tr>
<tr>
<td>Hours per week</td>
<td>3-5</td>
<td>2-20</td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range (25th and 75th percentile); N.: number; BMI: Body Mass Index (kg/m2); ICU: intensive care unit; APACHE II: Acute Physiology and Chronic Health Evaluation; LOS: length of stay.
Table II.—Comparison of patient characteristics between intensive care unit survivors who visited the post-ICU clinic, and who did not.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Participants post-ICU clinic</th>
<th>Non-participants post-ICU clinic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of patients</td>
<td>65</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.8 (14.7)</td>
<td>61.8 (12.5)</td>
<td>0.247</td>
</tr>
<tr>
<td>Gender (male), N. (%)</td>
<td>43 (66.2)</td>
<td>27 (58.7)</td>
<td>0.423</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>26.8 (23.3-30.2)</td>
<td>28.4 (25.3-23.9)</td>
<td>0.151</td>
</tr>
<tr>
<td>ICU admission diagnosis, N. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>52 (80.0)</td>
<td>35 (76.1)</td>
<td>0.799</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>5 (7.7)</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Non-elective surgery</td>
<td>8 (12.3)</td>
<td>8 (17.4)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score, median (IQR)</td>
<td>18 (15.5-24)</td>
<td>19 (15-23.25)</td>
<td>0.838</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days), median (IQR)</td>
<td>5 (3-7)</td>
<td>8 (3-10)</td>
<td>0.078</td>
</tr>
<tr>
<td>LOS in ICU (days), median (IQR)</td>
<td>6.9 (5-10)</td>
<td>8.6 (4.7-12.4)</td>
<td>0.481</td>
</tr>
<tr>
<td>LOS in hospital after ICU-discharge (days), median (IQR)</td>
<td>12 (7.5-16.5)</td>
<td>11 (6-20)</td>
<td>0.808</td>
</tr>
<tr>
<td>Remunerative employment, N. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working hours per week, median (IQR)</td>
<td>22 (33.8)</td>
<td>NO</td>
<td>-</td>
</tr>
<tr>
<td>Voluntary work, N. (%)</td>
<td>10 (15.4)</td>
<td>NO</td>
<td>-</td>
</tr>
<tr>
<td>Hours per week, range</td>
<td>2-20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range (25th and 75th percentile); N.: number; BMI: Body Mass Index (kg/m²); ICU: intensive care unit; APACHE II: Acute Physiology and Chronic Health Evaluation; LOS: length of stay; NO: not available.

Figure 1.—Study patient recruitment diagram.
and 54% of the TG patients received physical therapy. Signs of PTSD were found in 19% of the 65 participants and symptoms of anxiety and depression were present in 29% and 20%, respectively. Of the patients with psychological domain scores were lower in our study population. Figure 2 shows the ten most frequently reported impairments and restrictions according to the ICF checklist. For these, predominantly physical impairments, 47% of the AMC patients and 54% of the TG patients received physical therapy. Signs of PTSD were found in 19% of the 65 participants and symptoms of anxiety and depression were present in 29% and 20%, respectively. Of the patients with psychological

![Figure 2](image-url)
symptoms, 41% received treatment from a psychologist, psychiatrist, or social worker. Thirty-seven percent of all patients had signs of malnutrition of which 16% received treatment from a dietician.

No patient had returned to paid work, but four out of ten patients had resumed the volunteer work they did prior to ICU admission.

In the AMC post-ICU clinic, 15 patients were referred to other specialties: physical therapist (N.=6), psychologist/psychiatrist (N.=3), and dietician (N.=8). In addition, 2 patients with physical impairments were referred back to their physical therapist with specific training instructions. In TG, 27 patients were referred to a physical therapist (N.=8), psychologist/psychiatrist (N.=7), and dietician (N.=12), and 12 patients were referred back to their physical therapist with additional training instructions.

Close relatives

In the AMC 11 and in TG 41 close relatives completed the questionnaires. The median age of the close relatives and the reported hours per week spent on care were significantly higher for the TG than for the AMC patients (median age: 58 vs. 63 [P=0.023]; care assignment: 3.8 vs. 10 hours per week [P=0.025]). Burden of care was high (CSI≥7) in 9% of the close relatives in the AMC and 18% in the TG. Signs of PTSD were not found in the AMC population, but were present in 16% of close relatives of TG patients. High scores on TSQ and CSI were particularly found in partners and children.

Patient satisfaction

AMC patients were “very satisfied” (65%) and “satisfied” (35%) with the post-ICU clinic. For the TG patients, the median (IQR) satisfaction score was 8 (8-9).

Discussion

The results of our study show that post-ICU clinics are useful in identifying potential problems in daily functioning in survivors of critical illness. Although, the number of eligible patients and the follow-up rates of ICU survivors were limited in our study, the programmatic evaluation of the two post-ICU clinics in a university and a general hospital provides important information on different formats of post-ICU clinics.

We found that a limited proportion of the AMC survivors were discharged to their homes, 17%, versus 49% of the TG survivors. This can be explained by the fact that a tertiary university hospital has a large catchment area and many patients were transferred back to a general hospital near their residential area early after specialized medical treatment. Additionally, the majority

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>AMC</th>
<th>Tergooi</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of close relatives</td>
<td>11</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>58 (52-59)</td>
<td>63 (57-69)</td>
<td>0.023</td>
</tr>
<tr>
<td>Gender (female), N. (%)</td>
<td>7 (63.6)</td>
<td>30 (73.2)</td>
<td>0.535</td>
</tr>
<tr>
<td>Relationship to patient, N. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>9 (81.8)</td>
<td>32 (78)</td>
<td>0.576</td>
</tr>
<tr>
<td>Family (other than partner)</td>
<td>1 (9.1)</td>
<td>7 (17.1)</td>
<td></td>
</tr>
<tr>
<td>No family</td>
<td>1 (9.1)</td>
<td>2 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Remunerative employment, N. (%)</td>
<td>5 (45.5)</td>
<td>15 (36.6)</td>
<td>0.436</td>
</tr>
<tr>
<td>Working hours/week baseline, median (IQR)</td>
<td>36 (26-40)</td>
<td>32 (21.3–40)</td>
<td>0.158</td>
</tr>
<tr>
<td>Working hours/week after ICU discharge, median (IQR)</td>
<td>32 (10-40)</td>
<td>29 (16-40)</td>
<td>0.329</td>
</tr>
<tr>
<td>Relatives working less hours after ICU, N. (%)</td>
<td>4 (9.1)</td>
<td>4 (26.7)</td>
<td>0.781</td>
</tr>
<tr>
<td>Care assignment, N. (%)</td>
<td>8 (72.7)</td>
<td>19 (55.8)</td>
<td>0.025</td>
</tr>
<tr>
<td>Hours/week, median (IQR)</td>
<td>3.8 (1-5)</td>
<td>10 (3-18)</td>
<td></td>
</tr>
<tr>
<td>CSI≥7</td>
<td>1 (9.1)</td>
<td>7 (17.9)</td>
<td>N.=39</td>
</tr>
<tr>
<td>TSQ≥6</td>
<td>0</td>
<td>6 (15.8)</td>
<td>N.=38</td>
</tr>
</tbody>
</table>

CSI: Caregiver Strain Index (sum score ≥7 indicating higher risk for strain); IQR: interquartile range; no: number; TSQ: Trauma Screening Questionnaire (sum score ≥ 6 indicating risk for post-traumatic stress disease).
of AMC-patients lived beyond the service area of the hospital, which resulted also in a small number of eligible patients for the post-ICU clinic.

Of all eligible patients 49% of the AMC and 67% of the TG patients visited the outpatient clinic. This result was in line with comparable studies from Schandl and Cutler with attendance rates of 66% and 32% three months after ICU discharge. Ten eligible AMC patients (22%) did not attend the post-ICU clinic, because they had no complaints, or were already involved in a rehabilitation program. These patients may be assumed to have received care tailored to their individual needs. However, of greater concern was the group of eligible patients (13% at AMC and 23% at TG) that reported no need for ICU follow-up, because these patients may be suffering serious psychological problems, such as anxiety or PTSD, and consequently avoiding hospital contact.

With respect to the limited physical and psychological resilience of ICU survivors, also the timing of the post-ICU clinic seems important. One month after hospital discharge, 29% of the eligible AMC patients were not able to visit the outpatient clinic due to poor health. For that reason, 16% of the AMC patients visited the post-ICU clinic later, between 5 and 12 weeks after hospital discharge. Of the TG patients, only 9% did not attend the post-ICU clinic at three months after ICU discharge because of poor health. Based on these findings, we suppose that a post-ICU clinic three months after ICU discharge would be more feasible for ICU-survivors. With the purpose of screening in mind, this timing enables patients to reflect on their recovery process and to determine any physical, mental or cognitive impairments, that were not present during hospital stay. This is also in line with the recommendation in the NICE guideline. However, early identification of functional impairments is essential to initiate rehabilitation treatment as soon as possible, to improve recovery and to prevent chronic complaints. In addition, several studies emphasize the importance of early support because of the many difficulties patients face shortly after hospital discharge. Therefore, early in-hospital screening and risk stratification, followed by an assessment in a post-ICU clinic could be a more targeted approach to identify ICU patients at highest risk for adverse outcome.

We expected that patients of a university hospital (AMC) would have more complex and serious illnesses, resulting in longer ICU and hospital stays and a greater need for the post-ICU clinic than ICU survivors of a general hospital (TG). However, we found no significant differences between patient and clinical characteristics, functional status, and indications for referral between the two hospitals. These results should be taken cautiously, given the small study-population and the several differences in approach of the post-ICU clinics. Given the fact that TG patients visited the clinic two months later than AMC patients, we expected that they would have been further in their recovery process and perceive better HRQOL. Nevertheless, this was not the case in our study. Although, it is not possible to draw firm conclusions on the basis of the small numbers involved, these results show that patients experienced similar restrictions and HRQOL, regardless of type of ICU, severity of illness, demographic characteristics and time after ICU discharge. Despite the exclusion of patients who were transferred to a long-term care facility, we found severe physical and psychological impairments and functional restrictions in the majority of screened patients, both one month and three months after ICU discharge. This finding is in line with previous studies and underlines the importance of a continued chain of care for ICU survivors who are discharged home.

As expected, our study also demonstrated that close relatives, such as the partners and children of ICU survivors, were at risk for PTSD or a high burden of care, which is in line with other studies that found a high prevalence of anxiety and depressive conditions. Therefore, we recommend the assessment of close relatives for symptoms of stress, anxiety, depression, and care giver strain as a regular part of the post-ICU clinic.

With the screening instruments used in this study, problems in different health domains were identified. Subsequently, patients were referred to different health care providers based on the
available cut-off scores. The validity of these criteria for referral purposes was not assessed in this study and should be evaluated in future research.

Besides the identification of ICU-related problems and referral to other professionals, providing information about the ICU period and the physical and psychological recovery was an integral part of the post-ICU clinic. A better understanding of what had happened and how to recognize and to deal with ICU-related consequences appears to be very valuable for patients and their close relatives, and contributed to an overall high satisfaction with the post-ICU clinic. It is not convincing that the use of different questionnaires has affected this result, because on both instruments the responses ranged between the highest scores. Nevertheless, the 5-item scale might be more feasible, because 5 different response options are more easily to rate than 10.

Our study has some limitations that should be considered in the interpretation of the results. Due to the small number of patients and the selection of ICU survivors who were discharged to their homes, our study results might be biased and not generalizable to other ICU survivors. Furthermore, a significant proportion of eligible patients was unable or not willing to participate in follow-up. Developing strategies to offer post-ICU clinics to all ICU survivors who might benefit, would be an important improvement in this. Additionally, an appropriate comparison between the two post-ICU clinic approaches was limited, because of the differences in hospital settings. Finally, this study does not provide long-term outcome data of the patients to control for efficacy and treatment success. In future work, patient relevant outcome data should be collected in longitudinal studies to evaluate the effectiveness of post-ICU clinics and to further improve the care of ICU survivors after hospital discharge. Despite the restrictions of this study, it provides useful information to support the implementation of post-ICU clinics.

Based on the results of this study and current developments we recommend the following longitudinal approach to improve the care for ICU survivors. First of all, a systematic early screening for patients at risk for post ICU physical and psychological impairments should be performed repeatedly during hospital admission. With this, patients can be referred directly to outpatient rehabilitation services or be scheduled for a follow-up in a post-ICU clinic. Three months after ICU discharge, patients and their next relatives should be invited to administer questionnaires, to screen for remaining or new ICU-related problems in daily functioning, and to evaluate whether the offered care is sufficient or that additional care is needed. The use of computerized questionnaires and tele-medicine applications could be useful to facilitate this process. With the use of electronic surveys, it would be possible to assess more patients, also those who are physically or practically unable to return to a clinic, or those with avoidant behaviors. We assume that this could improve the recruitment of ICU survivors. Furthermore, appropriate use of technology may also enhance the cost-effectiveness of post-ICU clinics, another concern of post-ICU clinics. Tele-medicine as an alternative to face-to-face consultation serves clients, clinicians, and systems by minimizing the barriers of distance, time, and costs. Based on this “electronic” reassessment, patients and relatives with symptoms of PICS could be invited for a post-ICU clinic visit or could be directly referred for further diagnosis and targeted treatment. Additionally, we suppose that the development of a network with predefined arrangements with other allied health and medical specialists will improve the continuity of care. With such an integrated, stepped care program, the continuum of care for the transition from the hospital can be ensured for critically ill patients at risk for PICS.

**Conclusions**

Post-ICU clinics are important to facilitate the continuity of care for critically ill patients who are discharged to their homes. Validated screening instruments should be used for the identification of physical and psychological impairments and for referral to medical and allied health professionals. To increase the proportion of patients that can take advantage of post-ICU services, an early in-hospital screening to identify patients at risk for long-term ICU-related
Key messages

— The pragmatic evaluation of post-ICU clinics in two different settings provides useful information to support the implementation of post-ICU clinics.

— A post-ICU clinic is feasible for the identification of patients with ICU-related sequelae, and to refer these patients for further diagnosis and treatment.

— Early in-hospital risk stratification, followed by a post-ICU clinic evaluation 3 months after ICU discharge might be a beneficial approach to improve the continuum of targeted care after critical illness.

References

33. Brennan DM, Mawson S, Brownss S. Telehabilitation:


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Assessment of cerebral oxygenation in neurocritical care patients: comparison of a new four wavelengths forehead regional saturation in oxygen sensor (EQUANOX®) with brain tissue oxygenation. A prospective observational study

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ABSTRACT

Background. Because of restricted information given by monitoring solely intracranial pressure and cerebral perfusion pressure, assessment of the cerebral oxygenation in neurocritical care patients would be of interest. The aim of this study was to determine the correlation between the non-invasive measure regional saturation in oxygen (rSO2) with a third generation NIRS monitor and an invasive measure of brain tissue oxygenation tension (PbtO2).

Methods. We conducted a prospective, observational, unblinded study including neurocritical care patients requiring a PbtO2 monitoring. Concomitant measurements of rSO2 were performed with a four wavelengths forehead sensor (EQUANOX Advance®) of the EQUANOX® 7600 System. We determined the correlation between rSO2 and PbtO2, and the ability of the rSO2 to detect ischemic episodes defined by a PbtO2 less than 15 mmHg. The rSO2 ischemic threshold was 60%.

Results. During 2 months, 8 consecutive patients, including 275 measurements, were studied. There was no correlation between rSO2 and PbtO2 (r=0.016 [-0.103-0.134], r²=0.0003, P=0.8). On the 86 ischemic episodes detected by PbtO2, only 13 were also detected by rSO2. ROC curve showed the inability for rSO2 to detect cerebral hypoxia episodes (AUC=0.54).

Conclusion. rSO2 cannot be used as a substitute for PbtO2 to monitor cerebral oxygenation in neurocritical care patients. (Minerva Anestesiologica 2015;81:876-84)

Key words: Brain - Cell respiration - Hypoxia, brain - Spectroscopy, near-infrared

It has been established that monitoring of cerebral perfusion pressure (CPP) is the cornerstone parameters in brain-injured patients in neurocritical care unit.1 However, intracranial pressure (ICP) and CPP monitoring alone are unable to indicate whether the chosen threshold is efficient to maintain an optimal cerebral oxygenation.2 Moreover, deleterious hypocapnia remains undetected by the sole measurement of CPP. For these reasons, advanced cerebral monitoring has been used increasingly to measure brain oxygenation and/or cerebral blood flow.

Comment in p. 835.
Some monitors are invasive (brain tissue oxygen tension [PbtO2]) catheter or jugular bulb venous oxygen saturation [SjvO2]), and others are non-invasive as the regional saturation in oxygen (rSO2) measured with near-infrared spectroscopy (NIRS). NIRS is a recent attractive monitor, easy to use, accessible anywhere and provides continuous real-time assessment of cerebral oxygenation. However, a recent study suggested that rSO2 measured with the INVOS 5100® (NIRS monitor, Somanetics INVOS® system, Somanetics Inc., MI, USA) is poorly correlated with PbtO2 and did not represent a substitute for PbtO2 values after traumatic brain injury (TBI). This system only used two wavelengths of near-infrared light to measure rSO2. The NONIN Medical® society has developed a new sensor with 4 wavelengths and 2 emitters (EQUANOX Advance®, Nonin Medical®, Inc, Plymouth, MN, USA) in order to determine more accurately cerebral saturation. The main objective of this study was to compare this third generation NIRS monitoring with measure of cerebral oxygenation by PbtO2 in brain-injured patients.

Material and methods

Study design and patients selection

After approval of the institutional review board, we conducted a prospective, observational, single-center study at the Sainte Anne Military Teaching Hospital of Toulon (France). Between November 2011 and January 2012, brain-injured patients admitted to the neurocritical care unit and requiring advanced multimodal neuromonitoring (ICP and PbtO2 at least) were eligible. Inclusion criteria were patients with age over 18 and a Glasgow Coma Scale (GCS) Score of ≤9 on admission with severe injury requiring multimodal monitoring. Patients suffering from forehead or skull lesions, and those with deficient signals measured by NIRS or PbtO2 were excluded from the study. Informed consent was obtained from patient’s family and relatives. Intracranial pressure was monitored continuously by using an intraparenchymal sensor (Codman®, Randolph, MA, USA). Patients were sedated, intubated and mechanically ventilated in accordance with the international guidelines and with the following objectives: head elevation (30°), PaO2>85 mmHg, PaCO2 between 35 mmHg and 45 mmHg, natremia between 140 mEq/L and 145 mEq/L, targeted temperature <37.5 °C, ICP <20 mmHg, and CPP>60 mmHg initially then threshold adapted daily to PbtO2. If ICP increased, the protocol included moderate hypocapnia (PaCO2 between 30 mmHg and 35 mmHg), increase of sedation with propofol, muscle paralysis with cisatracurium and moderate hypothermia (33-35 °C). Third line treatment included barbiturates and/or unilateral craniectomy.

Regional saturation in oxygen monitoring (rSO2)

rSO2 was measured using the EQUANOX® 7600 monitor (Nonin Medical®, Inc, Plymouth, MN, USA) associated with its specific sensor (EQUANOX Advance®) placed on the skin in the frontal region. The sensor was placed ipsilaterally to PbtO2 probe in all patients. The EQUANOX® system uses NIRS technology to allow estimation of grey matter oxygen. rSO2 is a composite value based on the expected relative proportion of arterial (30%), capillary and venous (70%) blood within brain tissue. The EQUANOX® uses dual emitters alternately creating pairs of reflected light paths through surface tissue to the shallow receiver and through the cerebral cortex to the far receiver. The algorithm is supposed to remove surface effects that modulate light amplitude, resulting in a measurement of rSO2 of cortical grey matter in the anterior and middle cerebral arteries territories. The EQUANOX Advance® sensor uses 4 wavelengths ranging from 730 nm to 880 nm to measure equilibrium between oxy- and deoxyhemoglobin. The manufacturer claims that doubling of the LED light sources allows the device to compare rSO2 measurements in adjacent tissues to confirm accuracy of a measurement. A recent study confirmed this hypothesis. The EQUANOX® system demonstrated less degree of extracranial contamination than the INVOS® system. The ischemic threshold from manufacturer and given by some studies is under 60%.
The EQUANOX® system did not play a role in the medical management of the patients.

**Brain tissue oxygen tension monitoring (PbtO₂)**

A PbtO₂ probe (LICOX®, Integra Neurosciences, USA) was inserted into the frontal lobe of the most injured hemisphere through the same screw of ICP probe (Bolt system, IM2, Integra Neurosciences, USA). The correct location of the monitor was confirmed by CT-scan and manipulation of oxygen inspired fraction (FiO₂). As recommended, values were taken into account only after an initial in vivo equilibration period of 2 hours. In accordance with preliminary clinical studies, the ischemic threshold is 15 mmHg and below.¹¹ ¹²

**Data collected**

Patient characteristics, nature of brain injury, CT-scan classifications according to the National Institutes of Health Traumatic Coma Data Bank (TCDB), surgical procedures and Glasgow Outcome Scale (GOS) were collected.¹³ ¹⁴

Every 3 hours during all the monitoring phase, the following variables were simultaneously recorded: rSO₂ (%), PbtO₂ (mmHg), CPP (mmHg), ICP (mmHg), End-tidal CO₂ (EtCO₂) (mmHg), SpO₂, FiO₂ and bladder temperature (°C). Temperature is particularly relevant because, at identical partial pressure in oxygen, hemoglobin saturation is physiologically increased by hypothermia.¹⁵ All PbtO₂ and rSO₂ values were adjusted to patient bladder temperature. PbtO₂ values were adjusted by means of a computer (LICOX® system). rSO₂ values were adjusted a posteriori with equations given elsewhere.¹⁵ PbtO₂ and rSO₂ values were paired measurements simultaneously obtained from the software of the both monitors.

**Endpoints**

The primary endpoint of this study was to assess a correlation between rSO₂ and PbtO₂. Secondary endpoints were to assess a correlation between rSO₂ and the others data recorded (CPP, ICP, SpO₂, FiO₂ and EtCO₂), and to establish the ability of rSO₂ to detect ischemic events.

**Statistical analysis**

Statistical analysis was performed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous data were reported as the mean±standard deviation or median with interquartile ranges (25-75th) when not normally distributed. Nominal variables are reported as numbers and proportions (%). A univariate analysis was conducted using the χ² test or Fisher’s exact test to compare categorical variables and the Mann-Whitney test or Student’s t-tests to compare groups for continuous variables (respectively for comparison of medians and comparison of means). The correlation between rSO₂ and relevant parameters were evaluated by Pearson correlation test. A receiver-operator characteristic (ROC) curve analysis was performed to evaluate the ability of ipsilateral rSO₂ to detect ischemic events. We determined 3 levels of cerebral hypoxia: moderate (defined by a PbtO₂≤15 mmHg), severe (PbtO₂≤10 mmHg) and critical (PbtO₂≤5 mmHg). The sensitivity, specificity, predictive values of rSO₂ thresholds were determined for each level of brain hypoxia. For all tests, P<0.05 was considered statistically significant.

**Results**

**Patient characteristics and brain hypoxia episodes**

We included consecutively 8 brain-injured patients (5 male and 3 female). No patients were excluded. Patient characteristics are presented in Table I. The mean age was 49.6±15.6 years, the median Simplified Acute Physiology Score (SAPS II) was 42,³⁴ ⁶² and the median GCS on admission was 6 (range 3-9). The median patient temperature during monitoring was 35.1 (34.5-36 °C. The type of surgical intervention (if applicable) and the location of monitors are detailed in Table I. The brain tissue oxygen probe was placed in the most-injured hemisphere. In this cohort, no complication was attributed to the PbtO₂ probe (no intracranial hemorrhage or infection). The PbtO₂ probe of patient number 4 was placed ipsilaterally to the internal carotid artery dissection. The PbtO₂ probe for patient number 7 was inserted in the edema surround-
No correlation was found between the rSO2 and the PbtO2 (r=0.016 [-0.103 – 0.134], r²=0.0003, P=0.8) (Figure 1). Figure 2 showed the care of the patient number 4. When the patient evolved into brain death with a PbtO2 falling to 0 mmHg, rSO2 was still showing normal values with no variation.

Concerning the temporal correlation of rSO2 and the PbtO2 changes over time, the values followed the same trends in only 58.9% of cases.

Correlation between rSO2 and PbtO2

The ROC curve demonstrated that rSO2 had low accuracy to detect moderate cerebral hypoxia (PbtO2≤15 mmHg) with an area under curve (AUC) with 95% confidence interval (95% CI) of 0.54 (0.43-0.65) (Figure 3). The recom
The image contains two figures and a table. The first figure is labeled as Figure 1, showing the absence of correlation between PbtO2 and rSO2 (pooled values). The second figure is labeled as Figure 2, showing trends of rSO2 and PbtO2 for patient n°4, indicating the inability of rSO2 to detect ongoing brain death.

The table, labeled as Table II, is titled "Correlation between rSO2 and physiological parameters values." It includes columns for Parameter, Coefficient of correlation, 95% CI, Lower Bound, Upper Bound, and P Value. The parameters listed are SpO2, FiO2, ICP, CPP, and EtCO2, with corresponding values for correlation and statistical significance.

The equations and values on the figures are also noted, including the equation for the line drawn in the first figure: 

\[ y = 0.014x + 18.415 \]

\[ R^2 = 0.00023 \]
By investigating the accuracy of rSO\textsubscript{2} for detecting severe cerebral hypoxia (PbtO\textsubscript{2}≤10 mmHg), we observed a minimal improvement in the AUC (0.64 [0.51-0.76], P<0.0001) and sensitivity (20%), and an LR+ of 0.89 for a threshold of rSO\textsubscript{2}<60% (Table III).

We repeated the calculations for a rSO\textsubscript{2} threshold of 50%, 55%, 65% and 70%. We found that the best rSO\textsubscript{2} threshold to predict a PbtO\textsubscript{2}≤15 mmHg was 70%, with a PPV of 41.7%, a sensitivity of 78.2% and LR+ of 1.55 (Table III).

By investigating the accuracy of rSO\textsubscript{2} for detecting severe cerebral hypoxia (PbtO\textsubscript{2}≤10 mmHg), we observed a minimal improvement in the AUC (0.64 [0.51-0.76], P<0.0001) and sensitivity (20%), and an LR+ of 0.89 for a threshold of rSO\textsubscript{2}<60% (Table III).

The accuracy of rSO\textsubscript{2} for detecting critical cer-
ebral hypoxia (PbtO$_2 \leq$5 mmHg) was moderately improved with an AUC of 0.67 (0.54-0.78) (P<0.0001) and sensitivity of 27%, and an LR+ of 1 for a threshold of rSO$_2 <$60% (Table III).

**Discussion**

To our knowledge, this study is the first assessing the validity of a third generation NIRS compared to PbtO$_2$. Our results highlighted an absence of correlation between EQUIANOX® and PbtO$_2$ measurements. This study also showed the very low ability of rSO$_2$ to detect patients with moderate cerebral hypoxia. When using a threshold of 60%, there was a high rate of false-negative (37%) and false-positive (22%) results, which could lead to miss true ischemic episode or treat unnecessary false ischemic episode. Severe and critical cerebral hypoxias were better detected by EQUIANOX® than moderate cerebral hypoxia (AUC=0.64 and 0.67 respectively).

This study confirmed limitations of rSO$_2$ to detect cerebral hypoxia in neurocritical care patients, as shown previously, in TBI and subarachnoid hemorrhage (SAH) patients.16, 17 In the study by Naidech et al. using the INVOS 5100® to monitor 6 SAH patients, the authors were unable to find a value that was associated with cerebral hypoxia.17 Likewise, information given by PbtO$_2$ and rSO$_2$ (measured by the INVOS 5100®) were compared in 22 TBI patients.3 A direct poor correlation between PbtO$_2$ and rSO$_2$ was demonstrated (r=0.179), but the ability of rSO$_2$ to identify patients with intracerebral hypoxia was moderate (AUC=0.62). Recently, Rosenthal et al. demonstrated that PbtO$_2$ was not significantly related to rSO$_2$ measured by the CerOx® 3110 monitor (Ornim Medical Ltd.) (r=0.014), indicating that these two measures of brain oxygenation are not correlated.16

Although both PbtO$_2$ and rSO$_2$ measure cerebral tissue oxygenation, they differ in the type of data that they provide. PbtO$_2$ reflects the balance between oxygen delivery and oxygen consumption. PbtO$_2$ is primarily correlated with CBF (CPP), arterial oxygen tension (FiO$_2$, PaO$_2$), cerebral oxygen diffusion, and hemoglobin levels.18-21 In contrast, rSO$_2$ depends primarily by the degree of oxygen extraction determined by the balance between oxygen delivery and utilization.16 In fact, rSO$_2$ is supposed to measure the hemoglobin saturation in 3 different compartments (venous, arterial, and capillary), but because cerebral blood volume is largely represented by venous blood, rSO$_2$ may predominantly represent the hemoglobin saturation in the venous bed.22, 23 Thereby, it is not surprising that, like in our study, rSO$_2$ is correlated with FiO$_2$, PaO$_2$, CPP and/or ICP.17, 24-26

Although rSO$_2$ was not correlated to PbtO$_2$, its use has demonstrated its interest in some situations, especially in operating room during carotid endarterectomy or pediatric cardiac surgery.27, 28 In our study, rSO$_2$ is well correlated with ICP, CPP and PaCO$_2$ (through the EtCO$_2$), three essential parameters in brain-injured patients. rSO$_2$ could be interesting in situations where invasive monitoring of ICP or PbtO$_2$ is not available: elective surgery, prehospital care, unspecialized ICU or coagulopathy. In these specific conditions, rSO$_2$ can bring useful information concerning cerebral oxygenation. NIRS monitoring might maybe also replace the SjvO$_2$ monitoring in neurocritical care patients. In fact, a recent study showed a good correlation between the SjvO$_2$ and the NIRS measure in 18 TBI patients.16 However, NIRS monitoring is noninvasive, with an excellent signal quality (100% in our study) and devoid of complications. In contrary, the continuous measure of SjvO$_2$ entails technical difficulties like the availability of good-quality signal, the need for frequent recalibration and the risks of vascular puncture.29

The recommended ischemic threshold by NONIN® company for rSO$_2$ is 60%. We found that this threshold was not efficient to detect moderate cerebral hypoxia and weakly efficient to detect severe and critical cerebral hypoxia. We found that the optimal threshold of rSO$_2$ was 70% to detect moderate cerebral hypoxia. However, this value would have a high sensitivity but a low specificity, making it of little clinical value. Moreover, it is necessary to define an ischemic threshold according to the patient’s core temperature when using NIRS with an absolute rSO$_2$ value. Indeed, it is physiologically established that hemoglobin saturations depends
Further prospective studies investigating the relationship between invasive and non-invasive assessment of cerebral hypoxia, are needed.

Key messages

— This study is the first to assess a correlation between a third generation NIRS and PbtO₂.
— Our results highlighted an absence of correlation between EQUANOX® and PbtO₂ measurements.
— This study also showed the very low ability of rSO₂ to detect patients with cerebral hypoxia.
— rSO₂ values were also indirectly related to ICP and weakly directly correlated to CPP.

References


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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Blood acidosis is a recognized factor underlying coagulopathy and bleeding in different conditions. The main clinical environment where a low blood pH has been found as a determinant of severe bleeding is the traumatic coagulopathy, where coagulopathy, acidosis, and hypothermia concur in increasing the patients’ risk of ongoing bleeding and death.1-4

Cardiac surgery-associated coagulopathy in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) is a complex syndrome, including dilution/consumption of coagulation factors, thrombocytopenia, platelet dysfunction, decreased fibrinogen levels, hyperfibrinolysis, and residual heparin/protamine effects.5

During cardiac operations, different mechanisms may lead to acidosis: ischemia-reperfusion of the heart and lung during CPB; cooling-re-warming associated ischemia-reperfusion; inadequate oxygen delivery during CPB; low cardiac output before and after CPB. All these factors are determinants of metabolic acidosis, whose marker is an increased lactate (LAC) formation. As a matter of fact, hyperlactatemia (HL) is common during CPB and after cardiac sur-
and is the most typical mechanism leading to bicarbonate buffer consumption and metabolic acidosis. Conversely, considering that all the patients are mechanically ventilated, other forms of acidosis (respiratory acidosis) are rare in cardiac surgery patients during and early after surgery.

Despite the relatively common finding of HL and metabolic acidosis immediately after cardiac surgery, and the equally common finding of postoperative bleeding in the first 12 hours after surgery, no reports have investigated the possible role of acidosis as a determinant of postoperative bleeding.

The present study is a retrospective analysis exploring the hypothesis that postoperative acidosis may be an independent risk factor for postoperative bleeding in patients undergone cardiac surgery with CPB.

Materials and methods

Study design

Two-center, retrospective cohort study based on data prospectively collected at the two participating institutions (IRCCS Policlinico San Donato and University Hospital of Siena). The study was approved by the Local Ethics Committee of the IRCCS Policlinico San Donato, and the need for an informed consent from the patients was waived. At the hospital admission all the patients gave written approval to the treatment of their data in an anonymous form and for scientific purposes.

Patients

We analyzed data routinely collected in the institutional databases of the two participating institutions from January 2010 through December 2013. The databases include all the patients receiving a cardiac surgery operation, with the exclusion of transplant operations. Both institutions are routinely using the same database, where specific fields contain the blood gas analysis values at the arrival in the Intensive Care Unit (ICU) immediately after surgery. Patients aged <18 years, patients operated without CPB, and patients with missing data in the fields of interest were excluded from the study population. The final study population included 4251 patients (3824 at the IRCCS Policlinico San Donato and 427 at the University Hospital of Siena).

Data collection and definitions

For each patient, the following data were collected and were available: 1) preoperative: demographics; left ventricular ejection fraction (%); preoperative HCT (%); recent (within 30 days prior to surgery) myocardial infarction; congestive heart failure; active endocarditis; unstable angina; serum creatinine value (mg/dL); chronic obstructive pulmonary disease; diabetes (on medication); previous cerebrovascular accident; previous cardiac surgery; urgent/emergent procedure; use of anticoagulants (warfarin), low-molecular weight heparin, anti-platelet agents (aspirin and/or thienopyridines). 2) Operative: type of operation; CPB duration (minutes). 3) Postoperative: moderate-high dose catecholamines at the arrival in the ICU (defined as dopamine >5 µg/kg/min or epinephrine/norepinephrine >0.03 µg/kg/min); postoperative bleeding (drain blood collected in the first 12 postoperative hours); rate of surgical revision due to bleeding; arterial blood gas analysis data at the arrival in the ICU (pH, PaCO₂, HCO₃⁻, LAC concentration [mMol/L]).

CPB and surgery

CPB was generally conducted under moderate (32 °C) hypothermia and alpha-stat management, unless for specific operations. The priming volume consisted of a mixture of 80% gelatin and 20% tromethamine (THAM) solution (4236 patients) or crystalloid solution (15 patients).

The cardioplegic arrest was achieved with antegrade administration of cold crystalloid cardioplegia and, in a minority of the cases, with antegrade cold blood cardioplegia. Anticoagulation was achieved with unfractionated heparin according to the standard institution protocols, and heparin reversal was achieved with adequate doses of protamine sulphate. All the patients re-
received tranexamic acid at a dose of 15 mg/kg before CPB and 15 mg/kg after protamine administration. No patient received aprotinin during the period of observation.

Statistical analysis

All data are presented as number with percentage for categorical variables, mean with standard deviation for continuous, normally distributed variables, and median with interquartile range for non-normally distributed variables. Normality of distribution was checked with the Kolgomorov-Smirnov test. The association between pH values, LAC values, and postoperative bleeding was investigated using polynomial regression analyses. Postoperative acidosis was defined as a pH value <7.35; the pH values distribution was analyzed according to deciles of distribution, with the first decile arbitrarily settled at a level of pH<7.35. HL was defined as a blood LAC value >4.0 mMol/L. LAC values distribution was analyzed according to deciles of distribution, with the last decile corresponding to a LAC value >4.0 mMol/L. Differences in postoperative bleeding at the various deciles of pH and LAC distribution were analyzed with an Analysis of Variance (ANOVA) with post-hoc Bonferroni’s test and adjustment for multiple comparisons.

Multivariable analyses included regression analyses having postoperative bleeding as the dependent variable, the values of pH and LAC at the arrival in the ICU, and a number of possible confounders included as covariates. To be considered as a possible covariate, pre and intra-operative factors should be univariately associated with postoperative bleeding at a P level <0.1; intercorrelation was checked; a multivariable regression model with stepwise forward procedure was applied.

No patient with missing data was admitted to the study.

All tests were two-sided. A P value <0.05 was considered to be significant for all statistical tests. Statistical calculations were performed using computerized statistical programs (SPSS 13.0, Chicago, IL, and GraphPad Prism 6, San Diego, CA, USA).

Results

The general characteristics of our patient population are shown in Table I. At a univariate analysis, there was a significant (P=0.001) negative association between the pH values and postoperative bleeding, according to a polynomial (cubic) regression analysis. The association between the pH values and postoperative bleeding according to the decile distribution of the pH values is shown in Figure 1. An ANOVA analysis of the between-groups difference demonstrated that only the value of postoperative bleeding in patients with a pH value <7.35 (540±460 mL) at

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (60-76)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (65-82)</td>
</tr>
<tr>
<td>Gender male</td>
<td>2848 (67)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55 (49-61)</td>
</tr>
<tr>
<td>Previous (30 days) myocardial infarction</td>
<td>217 (5.1)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>53 (2.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>393 (8.7)</td>
</tr>
<tr>
<td>Active endocarditis</td>
<td>95 (2.1)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>127 (3.0)</td>
</tr>
<tr>
<td>Diabetes on medication</td>
<td>823 (18.2)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>375 (8.3)</td>
</tr>
<tr>
<td>Preoperative hematocrit (%)</td>
<td>39 (36-42)</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>316 (7.0)</td>
</tr>
<tr>
<td>Anti-thrombotic therapy</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>50 (1.1)</td>
</tr>
<tr>
<td>Low molecular weight heparin</td>
<td>624 (13.8)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>881 (19.5)</td>
</tr>
<tr>
<td>Isolated coronary surgery</td>
<td>1447 (34.0)</td>
</tr>
<tr>
<td>Isolated valve surgery</td>
<td>1343 (31.6)</td>
</tr>
<tr>
<td>Double valve or valve+coronary surgery</td>
<td>1062 (25.0)</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>57 (1.4)</td>
</tr>
<tr>
<td>Others</td>
<td>392 (8.0)</td>
</tr>
<tr>
<td>Non-elective procedure</td>
<td>466 (10.3)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass duration (min)</td>
<td>80 (60-111)</td>
</tr>
<tr>
<td>Moderate-high dose of catecholamines</td>
<td>563 (13.2)</td>
</tr>
<tr>
<td>Acid-base balance at the arrival in intensive care unit</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.5 (7.46-7.53)</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>34 (31-37.3)</td>
</tr>
<tr>
<td>HCO3− (mEq/L)</td>
<td>25.8 (23.7-27.1)</td>
</tr>
<tr>
<td>Lactates (mMol/L)</td>
<td>1.4 (1.0-2.1)</td>
</tr>
<tr>
<td>Acidosis (pH&lt;7.35)</td>
<td>156 (3.4)</td>
</tr>
<tr>
<td>Hyperlactatemia (lactates &gt;4.0 mMol/L)</td>
<td>436 (9.6)</td>
</tr>
<tr>
<td>Postoperative bleeding (mL/12 h)</td>
<td>350 (200-525)</td>
</tr>
</tbody>
</table>

Table I.—Demographics, risk profile, operative details and acid-base balance at the arrival in the intensive care unit (N.=4251). Data are number (%) or median (interquartile range).
A multivariable regression analysis (Table II) confirmed a pH value <7.35 as an independent determinant of postoperative bleeding, after correction for the other confounders, including the use of moderate-high dose catecholamines.

The LAC values demonstrated a significant (P=0.001) association with postoperative bleeding according to a polynomial (cubic) regression analysis. At the analysis per deciles of distribution (Figure 2), only patients in the upper decile (HL, LAC value at the arrival in the ICU>4.0 mMol/L) demonstrated a significantly higher bleeding rate (513±417 mL) with respect to all the other deciles (overall, 408±297 mL).

At the multivariable analysis, HL remained independently associated with postoperative bleeding (Table III) after correction for the other

Table II.—Multivariable analysis for pH and other postoperative bleeding determinants

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression coefficient</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>130</td>
<td>109-150</td>
<td>0.001</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>0.88</td>
<td>0.64-1.13</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate-high dose catecholamines</td>
<td>50</td>
<td>20.8-78.5</td>
<td>0.001</td>
</tr>
<tr>
<td>pH at the arrival in intensive care unit &lt;7.35</td>
<td>61</td>
<td>5.4-117</td>
<td>0.032</td>
</tr>
<tr>
<td>Constant</td>
<td>252</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval.
sated (576±489 mL/12h) metabolic acidosis vs. no acidosis/HL (406±293 mL/12 h). Patients with respiratory acidosis had a higher bleeding, but due to the limited number (1.7% of the patient population) the difference did not reach statistical significance. However, a linear relationship between PaCO₂ at the arrival in the ICU and postoperative bleeding was found significant (P=0.001).

Surgical revision due to bleeding was significantly (P=0.001) higher in patients with any kind of acidosis and HL without acidosis (7.2% and 7% respectively) with respect to patients without acidosis and HL (2%).

Postoperative bleeding in cardiac surgery patients is a multi-factorial event. The bleeding confounders, including the use of moderate-high dose catecholamines.

This analysis was conducted separately from the previous one, due to intercorrelation between pH and LAC values.

To investigate the relative role of acidosis and HL in the determinism of postoperative bleeding, a sensitivity analysis was undertaken. The patients were divided into 4 groups: 1) no acidosis and no HL (N.=3740); 2) no acidosis and HL (compensated metabolic acidosis), N.=355; 3) acidosis and no HL (respiratory acidosis), N.=74; 4) acidosis and HL (decompensated metabolic acidosis) N.=82.

Postoperative bleeding in the 4 groups is depicted in Figure 3. Overall, there was a significantly (P=0.001) higher bleeding in the groups with compensated (493±393 mL/12 h) and decompensated (576±489 mL/12 h) metabolic acidosis vs. no acidosis/HL (406±293 mL/12 h). Patients with respiratory acidosis had a higher bleeding, but due to the limited number (1.7% of the patient population) the difference did not reach statistical significance. However, a linear relationship between PaCO₂ at the arrival in the ICU and postoperative bleeding was found significant (P=0.001).

Surgical revision due to bleeding was significantly (P=0.001) higher in patients with any kind of acidosis and HL without acidosis (7.2% and 7% respectively) with respect to patients without acidosis and HL (2%).

**Discussion**

Postoperative bleeding in cardiac surgery patients is a multi-factorial event. The bleeding

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**Table III.—Multivariable analysis for lactate value and other postoperative bleeding determinants.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Regression coefficient</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>130</td>
<td>110-151</td>
<td>0.001</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>0.83</td>
<td>0.58-1.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Moderate-high dose catecholamine</td>
<td>37</td>
<td>7.1-67.3</td>
<td>0.015</td>
</tr>
<tr>
<td>Lactate level at the arrival in the ICU &gt;4.0 mMol/L</td>
<td>63</td>
<td>26-99</td>
<td>0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>254</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; ICU: intensive care unit.
Other determinants of bleeding have been identified in our study. These are patient-related (gender male, serum creatinine levels), drug-related (preoperative use of heparin) and procedure-related (CPB duration, complex surgery, redo surgery) factors. The above factors are well-known determinants of bleeding, and after adjustment for these confounders, both acidosis and HL remained independently associated with postoperative bleeding. Additionally, the use of moderate-high degree catecholamines was found associated with postoperative bleeding, acidosis, and HL.

The effects of acidosis on the different coagulation steps have been elucidated by various animal studies. Severe acidosis (pH=7.1) moderately inhibits the initiation phase of thrombin generation, and greatly inhibits the propagation phase. This indicates an inhibitory effect on factors V, VIII, IX and X. Other studies highlighted that severe acidosis induces a decrease in fibrinogen levels and platelet count. Platelet activation is downregulated by extracellular acidosis. Finally, fibrinolysis is enhanced by acidosis. Overall, the acidosis-induced coagulopathy involves thrombin generation, clot firmness...
ACIDOSIS AND BLEEDING IN CARDIAC SURGERY

In charge for intraoperative assistance usually introduce a number of measures to increase the oxygen delivery; simultaneously, it is common to correct the pH values intraoperatively (and especially during CPB) with variable doses of bicarbonates or other buffering agents. Unfortunately, we are lacking data on the pharmacologic measures applied during and after CPB. Conversely, we have the information related to the use of catecholamines at the arrival in the ICU. Metabolic acidosis and HL are very likely to be ascribed to an intraoperative poor oxygen delivery, due to a low cardiac output. Of notice, the use of moderate-high degree of catecholamines is strongly associated with both these conditions, being a marker of the therapeutic approach to a cardiac-related low output syndrome. However, even after correction for the use of catecholamines, both acidosis and HL maintains an independent association with postoperative bleeding.

The final pattern is that of a “corrected metabolic acidosis” where the pH goes back to normal, unless it is possible that the hemodynamic conditions leading to HL continue to deteriorate. The process of buffering acid lactic leads to CO₂ formation, and the relationship between arterial PaCO₂ and postoperative bleeding is confirmative of this interpretation.

In light of this observation, the interpretation of the conditions leading to HL with normal pH (about 9% of our patient population) is that these patients experienced an exposure to metabolic acidosis during surgery, whose effects on the pH were subsequently corrected.

Despite this, these patients demonstrate an increased bleeding tendency, without significant differences with respect to those with both acidosis and HL. Therefore, correction of the acidosis with bicarbonates does not seem to limit the acidosis-induced impairment of coagulation and hemostasis.

From this perspective, it is useful to underline that previous animal studies on the effects of bicarbonate correction of acidosis gave similar results. Martini et al. performed a study based on viscoelastic tests in acidic swines, before and after correction of the acidosis with bicarbonate infusion. After recovery of a normal (7.4) pH value, there was no recovery of the coagula-
tion function in terms of clotting time and clot firmness. The same results were obtained using alternative measures of buffering. Additionally, fibrinogen levels and platelet count remained at depleted levels after pH neutralization. The authors hypothesize that this depletion of substrates is the main reason for acidosis-induced coagulation disturbance.

From the clinical perspective, this piece of information leads to the concept that, in presence of intra or postoperative acidosis, neutralization of pH by bicarbonates or other buffers is not effective for preventing acidosis-induced bleeding. However, the clinicians should be aware that the effects of acidosis and HL are not clinically irrelevant, leading to a considerable increase in surgical revision rate, that is, per se, a cause of morbidity and mortality. Possible measures to treat acidosis-related bleeding should therefore rely more on substrate supplementation (basically, fibrinogen and platelets).

**Study limitations**

There are limitations in our study. The first one is the retrospective nature of the data analysis, that is based on our institutional databases. This allowed us to include a large series of patients, but inevitably led to some missing information: basically, we are lacking data on intraoperative pH, LAC levels, and administration of bicarbonates. Additionally, we do not have available data on viscoelastic tests after surgery, platelet counts, and fibrinogen levels at the arrival in the ICU. This does not allow us to clearly demonstrate on which part(s) of the coagulation system acidosis exerts the most detrimental effects. Due to these factors, the interpretation of our data is at least in part speculative.

Nevertheless, our study adds an additional interpretation to the factors leading to postoperative bleeding and surgical revision rate in cardiac surgery, which certainly deserves further studies to be fully elucidated.

**Conclusions**

The final interpretation of our data should be that, besides a number of well recognized factors, moderate acidosis and HL play an independent role in determining postoperative bleeding in cardiac surgery patients.

**Key messages**

— In cardiac surgery patients, a moderate degree of early postoperative acidosis (pH<7.35) is associated with an increased postoperative bleeding.
— Early HL (blood lactates >4 mMol/L) is associated with an increased postoperative bleeding.
— HL is associated with increased postoperative bleeding even in absence of acidosis.
— Intraoperative acidosis/HL are the most likely determinants of early acidosis/HL at the arrival in the intensive care unit.

**References**


Acknowledgments.—M. R conceived the experimental design, analyzed the data, and wrote the draft manuscript; E. B collected the data and participated in data interpretation; F. S collected the data and reviewed the manuscript; M. R (Matteo Ranucci) participated in data analysis and interpretation; S. S analyzed the data and reviewed the manuscript.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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OPRM1 receptor as new biomarker to help the prediction of post mastectomy pain and recurrence in breast cancer

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ABSTRACT
Breast cancer is the most common type of cancer among women worldwide. Short-term postsurgical recovery is complicated by many factors, including imbalanced inflammatory and immune response, acute pain associated with functional impairment, and chronic postmastectomy pain (CPMP), developed by about 25-60% of patients. Opioids, most common drugs used for treatment of cancer pain, are immunosuppressive, and therefore, they might directly and/or indirectly influence long-term cancer recurrence. Moreover, they also produce endocrinopathy, which consists primarily of hypothalamic-pituitary-gonadal axis or hypothalamic-pituitary-adrenal axis dysfunction. The interindividual variability in both CPMP and opioid response is believed to be largely underlined by genetic variability in the gene locus for μ-opioid receptor (OPRM1) that modulates opioid pharmacodynamics. For this reason, OPRM1 genotype may play a key role both in short-term postmastectomy outcome and in long-term follow-up, becoming a new biomarker for breast cancer recurrence in patients suffering from chronic postmastectomy pain managed by opioid therapy. Hence OPRM1 might be used in near future to customize the opioid therapy, avoiding not only opioid side effects but also the disease progression. In this review we evaluate the literature state of the art on this topic and possible steps towards obtaining the safest individualized postmastectomy analgesic therapy. Therefore, a personalized pain treatment strategy might be useful to both manage pain and control cancer disease progression.

(Key words: Genetics - Pain - Breast neoplasms - Mastectomy.)

Breast cancer (BC) is one of the most common types of cancer among women worldwide with high social direct and indirect costs. More than 205,000 BC diagnoses are made only in USA per year, with 40,230 annual deaths. Surgery is one step of multidisciplinary approach to cure BC and to ensure oncologic radicalness and preservation of femininity through oncoplastic techniques. Mastectomy with reconstructive surgery provides restored body symmetry to patients, improving their satisfaction and quality of life. However, women after breast surgery are susceptible to severe postoperative pain and chronic postmastectomy pain (CPMP), regardless of the type of surgery. CPMP includes phantom breast pain, scar pain (“iron bra”), or neuroma pain caused by damage to cutaneous nerves entrapped in scar tissue. Moreover, pain associated with breast reconstruction following mastectomy could be related to capsule formation, to the compression of lateral and medial pectoral nerves under the pectoralis muscle and to the detachment of the serratus anterior muscle re-
sulting from pressure exerted on the muscle by the implant.6

Wallace et al. reported that over half of the patients who have undergone mastectomy with reconstruction suffered from pain for at least one year, compared to one-third after mastectomy alone (53% vs. 30%).7 In a recent meta-analysis the prevalence of pain patients with a probable/definite neuropathic component has been estimated approximately 67%.8

There is still debate about the clinical determinants of CPMP: young age and lymphadenectomy are major risk factors,9, 10 however, it is possible that neural (brain morphology, activity and connectivity) or psychosocial factors may also predispose to CPMP.11 Genetic factors also have been reported as influencing the susceptibility to CPMP.12

In turn, pain worsens quality of life, increasing emotional stress and disability;13 it represents an important social and clinical concern, also because of its complex causes (including psychosocial factors such as anxiety and catastrophizing) and manifestations.11, 13

Uncontrolled perioperative pain can severely affect patients' long-term outcome both as it could act as important immunodepressant factor and as it is one of the most important risk factors of chronic postoperative pain. Hence, an adequate pain perioperative treatment is mandatory to reduce immunodepression pain related and the risk of chronic persistent pain. At biological level, pain is a mediator of surgery-induced immune suppression, and then anesthesia and analgesia techniques, by reducing postoperative pain, would also impact the long-term postoperative outcome.14

Opioids, alone or associated with non-opioid drugs, such as NSAIDS and acetaminophen, are currently the main used drugs to control postoperative and chronic pain (both nociceptive and neuropathic) in these patients, even if both paravertebral blocks and intrawound continuous infusion of local anesthetics could be promising in guaranteeing a better control of acute and chronic pain.15

There is a substantial variability in acute and chronic response to opioids, whose sources have not yet been fully elucidated at molecular, neurophysiologic and clinical level.

Opioids are known to be immunosuppressive, although their actions are complicated, often indirect, and not well understood.16 Some authors argue that they could both directly and indirectly influence cancer growth, facilitating recurrence through modulation of cell proliferation and/or apoptosis;17 these drugs may also modulate neoplastic cell proliferation and/or apoptosis, suppressing immune function affected by surgical stress and volatile anesthetics.18, 19 Immunomodulation is due to the interaction between opioid receptors and several molecules involved in the complex immune response, such as transcription factors and receptors of both myeloid and lymphoid cells.20 They also decrease the concentrations of circulating natural killer (NK) cells, and can have a dose-dependent effect on NK cell cytotoxicity.21

Gupta and collaborators showed that morphine stimulates human microvascular endothelial cell proliferation and angiogenesis in vitro and in vivo, and at clinically relevant doses, it may promote tumor neovascularization.22 At high concentrations, the disruption of the endothelial barrier occurs, and this might be harmful in angiogenesis-dependent cancers. Nevertheless, further studies examining the direct association between opioids and cancer are warranted.

The mu-opioid receptor (OPRM1) is the main site of action for opioid analgesia.23 Gene encoding this receptor, OPRM1, has a number of functional variants and, as demonstrated by Klepstad et al., its polymorphisms could be involved in modulating the morphine clinical efficacy in cancer pain.24 The most common and well known genetic variant is the single nucleotide polymorphism (SNP) A118G (rs1799971), with 30% frequency of minor allele G in Caucasians and 7% in African Americans (HapMap data; http://hapmap.ncbi.nlm.nih.gov/). It seems that this variant influences the immunomodulation caused by exogenous opiates, with a protective effect of G allele;25 moreover, it decreased response to a social stressor by means of suppression of the hypothalamic–pituitary–adrenal (HPA) axis activation.26 Larger studies, aimed to delineate the effect of AG and GG genotypes on immunosuppression and endocrine response, are needed.
As also immunosuppression and endocrine alterations are related to OPRM1,27, 28 a deeper knowledge about the effects of the genetic variation in this receptor might be useful not only in predicting acute and chronic postoperative pain, but also in optimizing the analgesic therapy with a long-term perspective, that is BC recurrence.

As cancer patients homozygous for the G allele of A118G variant required higher doses of oral morphine for long-term treatment,24 the genotype might be considered as a potential biomarker of therapeutic intervention in oncologic surgery setting.

Therefore, pharmacogenetics, by detecting the patients who need to receive more morphine to achieve the same level of analgesia, might identify the patients at major risk to develop cancer progression due to morphine treatment. It would be suitable, for this group of patients, to administer analgesic drugs without immunosuppressive effects as good alternative to opioids.

Material and methods and results

Analyses of OPRM1 polymorphisms associated with opioid response and BC recurrence

Firstly, we analyzed the literature data about OPRM1 gene, its polymorphisms, and the interindividual variability of opioid pharmacodynamics. By using the key words: “OPRM1, polymorphisms, opioids”, we found 122 results on PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), from 2002 to 2014: 15 clinical trials and 28 reviews.

We found some consistent data that genetic variants of OPRM1, the primary site of action for the most commonly used opioids, play a key role in the interindividual variability of opioid pharmacodynamics.29 One of the most frequent polymorphisms reported corresponds to the mentioned above SNP rs1799971, in exon 1, which causes nucleotide substitution from an adenine to guanine at position 118 (A118G), in turn producing the amino acid exchange at position 40 of the corresponding protein from asparagine to aspartic acid (N40D), and the consequent loss of a N-glycosylation site in the extracellular region of the receptor.30 This variant has been already associated with decreased potency of morphine and morphine-6-glucuronide,31 and could act as a potential marker to predict adequate opioid dosages in individualized pain treatment,32 nevertheless, in postoperative setting, its role is not always confirmed.33, 34 Another functional OPRM1 SNP, rs563649, located within a structurally conserved internal ribosome entry site (IRES) in the 5-UTR of a recently discovered exon 13-containing OPRM1 isoforms (MOR-1K), affects both mRNA levels and translation efficiency (Figure 1).35-37 This SNP has been already associated with individual variations in pain perception and differences in morphine responses.36

By using the keywords: “mu opioid receptor, breast cancer”, we found 25 papers. Bortsov et al. reported the first study examining the association between genetic polymorphisms and the function of opioid pathways and cancer survival: they suggested a protective effect of A118G polymorphism in patients with invasive BC.38 Women with at least one copy of G allele may experience significant reduction in BC-specific mortality, however, further research is needed to verify this hypothesis.

Lastly, we focused on opioid-induced endocrinopathy (by using the keyword “opioid-in-
duced endocrinopathy" we found 16 items) that is one of the most common, even if least often diagnosed, consequences of prolonged opioid therapy. Opioids inhibit the luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Consequently, hormone substitution could be indicated to treat symptoms, and the decrease/termination of opioid treatment reverses endocrine dysfunction. Nevertheless, the inhibition of the hormones by opioids might be an advantage for the BC patients: antiestrogens and aromatase inhibitors are clinically used to arrest the estrogen-dependent BC recurrence. Therefore, to optimize the postmastectomy outcome, physicians should realize the challenges associated with opioids, recognizing the balance between their positive effects and the possible risks for each patient, also defined by the genetic background.

**Discussion**

Even if opioids continue to be one of the most commonly prescribed medications (together with non steroidal anti-inflammatory drugs), there are still important open questions related to their efficacy, safety and predictability of patient’s response.

OPRM1 polymorphism and CPMP could be evaluated as possible prognostic biological and clinical factors in BC patients. Research on opioid effects on cancer is still an emerging field, and combination of basic and clinical new knowledge would provide insights for postmastectomy patient care. Even though in animal models morphine-based analgesia reduces the number of pulmonary metastases after surgery, in humans recent evidence suggests that opioid-based perioperative analgesia is associated with reduced recurrence-free survival, when compared with regional techniques, such as paravertebral blocks and intrawound continuous infusion of local anesthetics, for breast surgery.

Future clinical and basic studies that seek to identify the functional genetic variants within OPRM1 locus, and associated molecular mechanisms, will result in a better understanding of individual responses to opioid therapy and ultimately to the development of new diagnostic tools. As high interindividual variability of opioid response is mostly due to OPRM1 polymorphisms, and since opioids, mediating immunosuppression might facilitate tumor recurrence, the OPRM1 genotype could play a key role also in long-term follow-up in target BC patients, assuming a great importance as new biomarker for breast cancer recurrence, overall in patients suffering from CPMP under opioid therapy. In fact, OPRM1 genotype could be related not only to interindividual safety and effectiveness of opioid therapy, but also to a different immune and endocrine response to the same opioid.

In the near future, genetics-based opioid pain therapy could solve CPMP symptoms, also be-

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**Table I.**—Effects of A118G polymorphism in different clinical settings.

<table>
<thead>
<tr>
<th>A118G effect</th>
<th>Setting</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased morphine requirements</td>
<td>Malignant disease</td>
<td>Klepstad P et al. 23</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>Opiate users</td>
<td>Hajj A et al. 46</td>
</tr>
<tr>
<td>Suppression of the hypothalamic–pituitary–adrenal (HPA) axis activation</td>
<td>Health volunteers</td>
<td>Mao J 47</td>
</tr>
<tr>
<td>Increased amount of morphine and highest pain scores</td>
<td>Post-hysterectomy pain</td>
<td>Sia AT et al. 32</td>
</tr>
<tr>
<td>Protective effect</td>
<td>Breast cancer survival</td>
<td>Bortsov AV et al. 37</td>
</tr>
</tbody>
</table>
coming a treatment for the oncological disease at reasonable cost. A multidisciplinary approach would obtain this innovative role, through a network involving different professionals ranging from clinicians (surgeons and anesthesiologists) to pharmacologists and biologists, with a “from bench to bedside” approach. The analysis might be feasible on a large scale because the sequencing cost per base is falling dramatically”.

The authors of this review already reported, in 12 publications from 2009 to 2014, the importance of OPRM1 variability (used as search criteria in PubMed: each of the 4 surnames followed by OPRM1, A118G, or mu opioid receptor) (Table II).28, 33-54

### Conclusions

Development of translational approaches for BC pain therapy treatment involving genotypic analysis of OPRM1 gene locus, would contribute to better-customized short-term and long-term postoperative BC outcomes.

These new biomarkers of opioid pharmacodynamics will help to stratify patients’ risk of CPMP and cancer recurrence, increasing the role of pain therapy all the way from the patient care focused on pain relief to cancer recovery.

### Key messages

— Postmastectomy patients often report severe acute postoperative pain and chronic postmastectomy pain, which are usually treated with opioids.

— Breast cancer recurrence is potentially related to opioid consumption, as opioids modulate neoplastic cell proliferation and/or apoptosis and suppress immune function, already affected by surgical stress and volatile anesthetics.

— OPRM1 variability, influencing pharmacodynamics, can potentially help predicting short- and long-term postoperative outcomes, such as opioid requirement, analgesic response to opioids, and breast cancer recurrence.

### References

3. Goldfarb Y, Ben-Eliyahu S. Surgery as a risk factor for breast cancer recurrence and metastasis: mediating mecha-

### Table II.—Publications by the authors about the role of OPRM1 variability, in chronologic order.

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal, year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dever 48</td>
<td>AIDS 2014</td>
<td>Differential expression of the alternatively spliced OPRM1 isoform μ-opioid receptor-1K in HIV-infected individuals</td>
</tr>
<tr>
<td>Kolesnikov 49</td>
<td>Mol Pain 2013</td>
<td>Chronic pain after lower abdominal surgery: do catechol-O-methyl transferase/opioid receptor μ-1 polymorphisms contribute?</td>
</tr>
<tr>
<td>De Gregori 33</td>
<td>Eur J Clin Pharmacol 2013</td>
<td>Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain</td>
</tr>
<tr>
<td>Mura 50</td>
<td>J Pain Res 2013</td>
<td>Consequences of the 118A&amp;ggr;G polymorphism in the OPRM1 gene: translation from bench to bedside?</td>
</tr>
<tr>
<td>De Gregori 51</td>
<td>Metab Brain Dis 2012</td>
<td>Morphine metabolism, transport and brain disposition.</td>
</tr>
<tr>
<td>Serohijos 52</td>
<td>Structure 2011</td>
<td>Structural basis for μ-opioid receptor binding and activation</td>
</tr>
<tr>
<td>Gris 53</td>
<td>Methods Mol Biol 2010</td>
<td>Molecular assays for characterization of alternatively spliced isoforms of the u opioid receptor (MOR)</td>
</tr>
<tr>
<td>Max 54</td>
<td>Mol Pain 2006</td>
<td>A clinical genetic method to identify mechanisms by which pain causes depression and anxiety.</td>
</tr>
</tbody>
</table>


The authors received comments on a draft of this paper from the following members of the SIMPAR group: Dr. Adele Sgarella (Pavia, Italy), Dr. Virginia Gallo (Pavia, Italy), Dr. Lorenzo Cobianchi (Pavia, Italy), Dr. Christian Compagnone (Parma, Italy).

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Recent publications on epidural steroid injections (ESIs) focused on epidural route, epidural steroid injectate composition, optimal steroid dose, cost effectiveness, impact on healthcare utilization, prevention of surgery, safety, and alternatives to steroid as the injectate. There have been reports of central nervous system (CNS) injuries after transforaminal (TF) ESIs prompting a Working Group, under the sponsorship of the Food and Drug Administration (FDA) Safe Use Initiative, to issue recommendations to improve the safety of ESIs. Non-particulate steroids were recently shown to be as effective as and long lasting as particulate steroids. The efficacy of disease modifying anti-rheumatic drugs (DMARDs) has been studied as an alternative to steroid. In this review, we will update the reader on these topics.

We performed a Medline/PubMed search on the topics discussed in our review, including the following: 1) safety of ESIs; 2) ESIs and need for surgery; and 3) tumor necrosis factor alpha inhibitors. In view of word limitations, the list of publications related to these topics can be requested from one of the authors (HTB).

Injection route

Differences in epidural injection route, vertebral level, control group, injectate composition and spinal pathology make drawing conclusions regarding the efficacy of epidural steroid injec-
tions difficult. Several studies have attempted to compare the ESI routes including interlaminar (IL), transforaminal (TF), and caudal with mixed findings. Each route has its advantages and disadvantages in terms of proximity to pain pathology and the potential risks of dural puncture, intravascular injection or neurologic injury.1

Some of the studies on the efficacy of the TF compared with the IL approach were retrospective or retrospective case-control studies.2-5 Other studies compared different injectates in the transforaminal technique, i.e. methylprednisolone-bupivacaine versus saline,6 bupivacaine with betamethasone versus bupivacaine alone,7 or triamcinolone versus saline;8 TL injection versus trigger point injection;9 or, ganglionic versus preganglionic TF injection.10

Several studies directly compared the TF with the IL approach in a prospective randomized manner (Table I). One study showed epidural perineural injections to be more effective than conventional posterior epidural injections or paravertebral local anesthetic.8 In this study, the transforaminal technique is not the typical TF technique that we use today. In their TF approach, the authors inserted their needle contralaterally, passing through the ligamentum flavum with the needle tip ending at the lateral aspect of the anterior epidural space.8 Another study compared nerve root injection with IL injections and noted no difference between the two techniques.11 In this study, the glucocorticoid cortivazol was used, a steroid that is not used in the United States or Canada.

In a randomized study, patients with S1 radiculopathy from herniated nucleus pulposus received epidural steroid injections via TF, caudal or IL route with the TF approach resulting in better pain relief than either IL or caudal injection route.12 Furthermore, the patients who were observed to have ventral epidural spread on fluoroscopy during injection corresponded to a better outcome and this was most common in patients who received TF epidural steroid injection. These findings were confirmed in two studies.13, 14 In a study of patients with axial back

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design; Subjects</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kraemer et al.18 1997</td>
<td>R; 93 patients</td>
<td>Perineural vs. IL vs. paravertebral local anesthetic</td>
<td>Better results with perineural compared to IL; both groups better than paravertebral</td>
<td>Doses not stated; perineural technique not classic TF approach</td>
</tr>
<tr>
<td>Ackerman &amp; Ahmad 12 2007</td>
<td>R, evaluator blinded; 90 with L5-S1 disc herniation and radicular pain</td>
<td>C, 40 mg TA + 19 mL PF saline; IL, 40 mg TA + 4 mL NS; TF, 40 mg TA + 4 mL NS</td>
<td>At 24 weeks, pain relief was greatest for TF followed by IL and C</td>
<td>Patients with ventral epidural spread reported greater pain relief</td>
</tr>
<tr>
<td>Lee et al.13 2009</td>
<td>R, evaluator blinded; 192 patients with HNP or SS</td>
<td>TF, 20 mg TA + lidocaine per side; IL, 40 mg TA + lidocaine</td>
<td>At 4m, there was greater relief with TF than with IL in patients with SS</td>
<td>TF injections were done bilaterally</td>
</tr>
<tr>
<td>Gharibo et al.14 2011</td>
<td>R, DB; 38 patients</td>
<td>TF, 40 mg TA + B; IL, 40 mg TA + B</td>
<td>Better pain relief with TF injection</td>
<td>No difference in terms of disability, function, depression, and opioid use</td>
</tr>
<tr>
<td>Candido et al.15 2008</td>
<td>R; 60 patients with unilateral radiculopathy from HNP or degenerated disc</td>
<td>TF, 80 mg MP + NS + lidocaine; Parasagittal IL, 80 mg MP + NS + lidocaine</td>
<td>No difference in VAS scores between TF and parasagittal IL groups up to 6 months</td>
<td></td>
</tr>
<tr>
<td>Rados et al.16 2011</td>
<td>R; 64 patients with unilateral radiculopathy from HNP</td>
<td>TF, 40 mg MP + lidocaine; IL, 80 mg MP + lidocaine</td>
<td>No difference in pain relief or function at 6m</td>
<td>Steroid dose in TF was half the dose compared to IL approach</td>
</tr>
</tbody>
</table>

B: bupivacaine; C: caudal; D: dexamethasone; DB: double-blind; HNP: herniated nucleus pulposus; IL: interlaminar; MP: methylprednisolone; NS: normal saline; PF: preservative free; R: randomized; TA: triamcinolone; TF: transforaminal; SS: spinal stenosis.

Study by Kolsi et al.11 is not included since the steroid used, cortivazol, is not commonly used for epidural steroid injections.
pain from herniated nucleus pulposus or spinal stenosis, either IL or bilateral TF epidural steroid injections were performed. Patients who received TF epidural steroid injections had better outcomes than those who received IL injection for up to four months follow-up. In the other study, patients with radicular leg pain who received TF steroid injections had better pain relief than those who had IL injections. However, the improvements in secondary outcomes including the Oswestry Disability Index, Depression Scale, and walking tolerance were not different between the two techniques.

In contrast, a study found no difference in analgesia between TF and parasagittal IL epidural steroid injections for up to 6 months. The IL approach was associated with better spread of the contrast in the anterior epidural space. Additionally, the lack of difference in efficacy between the TF and IL approach was noted in another trial. In this study, different doses were given in the two approaches: 80 mg methylprednisolone in the IL approach and 40 mg methylprednisolone in the TF approach.

Overall, the results of randomized studies are not uniform (Table I). However, there is moderate support for the TF route given its association with a greater incidence of ventral epidural spread. This must be balanced with an increased risk profile when compared to the IL or caudal approach.

Steroid injectate composition, optimal dose of steroid

The type of steroid and the optimal steroid dose has been the subject of recent research. When comparing different types of steroids, particulate to non-particulate, the results again are mixed. An older study comparing non-particulate with particulate steroid in interlaminar injections showed better efficacy of the particulate steroid. A recent study where equipotent doses of methylprednisolone (80 mg) and dexamethasone (15 mg) were used, the authors noted that dexamethasone approached the safety and effectiveness of methylprednisolone although there was a non-significant trend toward less pain relief and shorter duration of action of the non-particulate steroid. For transforaminal injections, older studies showed less efficacy and shorter duration of pain relief of non-particulate steroids. One randomized study showed increased benefit with respect to pain reduction after TF injection of the particulate steroid triamcinolone compared to dexamethasone.

More recent studies, however, showed the efficacy of non-particulate steroids to approach that of the particulate steroids in transforaminal injections. A retrospective study of patients with cervical radiculopathy showed no difference in pain score between patients receiving non-particulate versus participate steroid. However, the dose of dexamethasone and triamcinolone used in this study were not equipotent, possibly confounding the results. Another retrospective observational study found the non-particulate steroid dexamethasone to be non-inferior to particulate steroids triamcinolone or betamethasone in terms of pain relief and functional improvement. The study however was retrospective and follow-up was only for two months. Moreover, the non-particulate dexamethasone was injected after 2010 while the particulate steroids triamcinolone and betamethasone were injected from 2006 to 2010. A more recent randomized multicenter trial showed lumbar TF dexamethasone to be as effective as triamcinolone at 6 months follow-up although there was a slight increase in the number of patients requiring three injections. It now appears that the efficacy of the non-particulate steroid closely approximates the efficacy of particulate steroid steroids in transforaminal injections. This is important because of the potential neurologic injuries resulting from TF particulate steroid injection.

Studies attempted to address the optimal steroid dose. A study randomized patients with newly exacerbated lumbar radicular pain to receive one lumbar interlaminar ESI with either 40mg or 80mg of methylprednisolone. Comparable improvements in VAS scores were observed in both groups at both two weeks and three months post injection. Additionally a non-statistically significant reduction in post-injection flares, flushing and hyperglycemia was observed among patients who received low dose versus high dose steroid. Another study looked at the
Epidural steroid injections and the need for surgery

In a study of patients who were considered to be operative candidates, 55 patients were randomized to receive a selective nerve root injection of either bupivacaine with or without betamethasone.7 Twenty of 28 patients who received the steroid injection decided not to have surgery. In contrast, only 9 of 27 patients who were injected with bupivacaine opted not to have the operation (P<0.004). A follow-up of the 29 patients who did not have surgery showed that 21 still did not have surgery at 5 years.30 There was no difference between the patients who received bupivacaine (1/9) and those who had the bupivacaine and dexamethasone (3/12, P=0.422). Interestingly, there was no difference between the patients who had HNP (1/7) and those with spinal stenosis (3/14). The authors concluded that the relief by the ESI was long enough for the symptoms including pain to resolve naturally. A subgroup analysis of a randomized controlled trial noted that at one year follow-up, TF methylprednisolone-bupivacaine injection prevented operations for contained herniations but not in the patients with extruded discs.31

Two retrospective studies showed a surgery-sparing effect of the ESIs. In one study, 26 of 30 patients had rapid regression of their pain after periradicular injection of triamcinolone, 60% of which had permanent resolution of their pain allowing avoidance of surgery for an average of 16 months.32 In another study, 51 of 90 patients with sciatica from lumbar disc herniation avoided surgery after TF epidural triamcinolone.33 Studies with need for surgery as a primary outcome demonstrated the strongest evidence for epidural steroid injection, correlating with a reduced incidence of surgical intervention. However, the benefit appears to be greatest in the short-term rather than in the long-term.

The limited number of patients in one study,7 30 the subgroup analysis nature in another study,31 and the retrospective nature in two other publications 32, 33 make one hesitate to conclude a surgery-sparing effect of ESIs. Also, other studies where the incidence of surgery was analyzed as a secondary end point, showed no
dose-response after two TF ESIs with 5 mg, 10 mg, 20 mg or 40 mg of triamcinolone, given one week apart.26 The number of patients reporting considerable pain relief was significantly lower at one week after the first epidural injection among the patients who received the 5 mg dose. However, pain scores improved in all the groups at one week after the second epidural injection. Given these findings the authors recommended a minimal effective dose of 10 mg triamcinolone for immediate pain relief in patients with lumbar radicular pain.26 Although the number of studies is small, the literature appears to favor the ability of a reduced steroid dose to provide similar pain relief with possibly less steroid associated side effect. The reduced dose has implications in patients with diabetes mellitus because of the hyperglycemic effect of steroids.27 As these findings are contrary to usual dose used in clinical practice, additional larger studies are needed.

Epidural steroid versus non-steroid injections

A recent systematic review and meta-analysis evaluated the “control” injections, mainly local anesthetic, in randomized control trials.28 The authors determined whether epidural non-steroid injections constituted treatment or true placebo in comparison with non-epidural injections. Indirect comparisons suggested that epidural non-steroid injections were more likely than non-epidural injections to attain a positive outcome and provide greater reduction of pain. In very limited direct comparisons, no significant difference in outcome was observed between epidural non-steroid and non-epidural injections. The authors concluded that epidural non-steroid injections may provide benefit beyond placebo but that further research is needed to determine the potential role of epidural non-steroid injections in patients with lumbar pain in whom steroid use may be considered high risk.

The efficacy of local anesthetic as control was recently highlighted in a recent publication that showed no significant difference between lidocaine and steroid in lumbar spinal stenosis.29 The lack of superiority of steroid in the study may also be due to the etiology of the back pain, i.e. canal stenosis.
difference between epidural steroid and placebo.34-36

Cost effectiveness and healthcare utilization

A cost utility analysis was performed using direct payment data for 480 patients over a 2 year period from four previously published randomized control trials assessing the clinical effectiveness of caudal epidural injections with or without steroid for pain related to lumbar disc herniation, lumbar degenerative disc, lumbar spinal stenosis and post lumbar surgery syndrome.37 All patients showed clinical improvement and positive cost utility analysis results. The cost per one-year quality-adjusted-life-year was $2,172.50 for all patients and $1,966.03 for patients judged to be successful. Although the study showed a better cost utility of managing chronic lumbar pain with caudal epidural injections than non-interventional therapy, this study was limited to a single center. Another study assessed cost effectiveness by looking at mean quality-adjusted-life-year gains of patients receiving epidural steroid injections in an outpatient setting in England.38 Epidural steroid injections were noted to provide short-term but cost-effective means of managing chronic back pain.

Safety of epidural steroid injections

Paraplegia has been reported after TF ESIs, with the cause ascribed to embolism of the particulate steroid. Animal studies showed death or cerebral hemorrhage after injection of particulate steroid into the vertebral artery of pigs or into the cerebral artery of rats.40 In contrast, these complications were not noted after non-particulate steroids. The routes of embolism include the segmental radicular artery, ascending cervical and deep cervical arteries, artery of Adamkiewicz, and lateral sacral arteries which anastomose with the sacral radicular arteries and the ansa communications at the conus. A Working Group, under the sponsorship of the Food and Drug Administration, made recommendations to decrease the complications. Some of their recommendations include the use of image guidance and injection of contrast for ESIs, interlaminar over the transforminal approach in cervical ESIs, transforminal over interlaminar approach in lumbar ESIs, the preferred use of non-particulate steroid in cervical transforminal injections and the initial use of non-particulate steroids in lumbar TF ESIs.41

To better detect intravascular placement of the needle in lumbar TF injection of particulate

Figure 1.—Fluoroscopy images showing epidural contrast pattern with no visible intravascular injection after injection of contrast (A) and simultaneous epidural and clear intravascular pattern with DSA. From Lee MH et al.42
though modest, the risk was statistically significant. However, it should be noted that the study did not control for other variables that may also contribute to fracture risk such as smoking, level of exercise, or Body Mass Index.

Radiation exposure to both the patient and clinician is a concern with fluoroscopy-guided ESI. A prospective, randomized single blind clinical study by found no statistical difference in terms of pain score or Oswestry Disability Index in patients receiving ultrasound-guided versus fluoroscopy-guided caudal epidural steroid injection for unilateral lumbar radicular pain.48 Although this study has a number of limitations in terms of blinding, practitioner experience, patient number and selection, it highlights potential benefits of ultrasound guidance that can be explored in larger trials.

**Epidural anti-inflammatory non-steroid injections**

The role of inflammation in the causation of low back and radicular pain led to the use of disease modifying anti-rheumatic drugs for this condition. Of these drugs, only etanercept and tocilizumab were investigated epidurally (Table III). Two trials showed greater efficacy of epidural etanercept compared to placebo. A study of 24 patients showed better efficacy of three doses of etanercept (2, 4, 6 mg) compared to sa-

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects or injections</th>
<th>Number of positive intravascular injections</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLean et al.43 (Subjects)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast injection under real-time fluoroscopy</td>
<td>67</td>
<td>12 (17.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSA</td>
<td>67</td>
<td>22 (32.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al.42</td>
<td>87 injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast injection under real-time fluoroscopy after aspiration</td>
<td>5</td>
<td>25%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>DSA</td>
<td>12</td>
<td>60%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Hong et al.44</td>
<td>249 injections</td>
<td>22 of 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular uptake on real-time fluoroscopy</td>
<td>31 of 31</td>
<td>71%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

*Table III.—Incidence of Intravascular Injection with and without digital subtraction angiography.*


P value between contrast injection and DSA, McLean et al. study: 0.0471.43

P value between real-time fluoroscopy and DSA, Hong et al. study: 0.007.44
equal efficacy will probably result in increased use of non-particulate steroid TF injections in unilateral radicular pain, thereby reducing the incidence of CNS injury. Studies evaluating TF injection at the triangle of Kambin, instead of the “safe triangle” should be pursued. The evidence appears to favor a steroid ceiling effect so for patients in whom steroid use is high risk, a lower steroid dose, non-particulate steroid or non-steroid epidural injection should be considered. Studies that look at the need for surgery as a primary outcome showed a reduced need for surgery in the short term. Research studies on epidural anti-inflammatory non-steroid injections are preliminary and recommendations on their future clinical applicability cannot be made at this time.

Conclusions

In this review, we discussed current issues associated with ESI. The TF route appears to be more effective than the IL route, however, this must be balanced with the higher risk of vascular injection or neurologic injury with this technique. More recent studies demonstrated the efficacy and duration of TF non-particulate steroid to approach that of particulate steroids. This equal efficacy will probably result in increased use of non-particulate steroid TF injections in unilateral radicular pain, thereby reducing the incidence of CNS injury. Studies evaluating TF injection at the triangle of Kambin, instead of the “safe triangle” should be pursued. The evidence appears to favor a steroid ceiling effect so for patients in whom steroid use is high risk, a lower steroid dose, non-particulate steroid or non-steroid epidural injection should be considered. Studies that look at the need for surgery as a primary outcome showed a reduced need for surgery in the short term. Research studies on epidural anti-inflammatory non-steroid injections are preliminary and recommendations on their future clinical applicability cannot be made at this time.

Key Messages

— There is moderate support for the greater efficacy of transforaminal injection when compared with interlaminar and caudal injection approaches, due to greater in-

Table III.—Results of studies on epidural injections of disease modifying anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Study, drug</th>
<th>Study design</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al.⁴⁸, etanercept</td>
<td>Double-blind placebo-controlled, dose-response; 24 patients</td>
<td>Transforaminal injection of 2, 4, or 6 mg etanercept vs. saline</td>
<td>Improvement in etanercept but not in saline</td>
<td>Small number of patients (24), short-term follow-up</td>
</tr>
<tr>
<td>Freeman et al.⁵⁰, etanercept</td>
<td>Randomized, double-blind, placebo-controlled, 49 patients</td>
<td>Transforaminal epidural etanercept (0.5, 2.5, 12.5) vs. placebo</td>
<td>Superiority of 0.5 mg etanercept over placebo in terms of leg pain, Oswestry</td>
<td>Lowest dose of etanercept noted to be the most effective</td>
</tr>
<tr>
<td>Ohtori et al.⁵¹, etanercept</td>
<td>Prospective, randomized; 80 patients</td>
<td>Transforaminal epidural etanercept (10 mg) and lidocaine vs. dexamethasone (3.3 mg) and lidocaine</td>
<td>Etanercept more effective for low back and leg pain, and leg numbness</td>
<td>Dose of dexamethasone low; follow-up short (1 month)</td>
</tr>
<tr>
<td>Cohen et al.⁵², etanercept</td>
<td>Multicenter, 3-group, randomized placebo-controlled trial; 84 patients</td>
<td>Transforaminal epidural methylprednisolone (60 mg) vs. etanercept (4 mg) vs. saline</td>
<td>Epidural steroid resulted in better relief of leg pain and improvement in functional capacity than etanercept</td>
<td></td>
</tr>
<tr>
<td>Ohtori et al.⁵³, tocilizumab</td>
<td>Prospective, 60 patients</td>
<td>Transforaminal epidural tocilizumab (80 mg) and lidocaine vs. dexamethasone (3.3 mg) and lidocaine</td>
<td>Tocilizumab more effective in relieving back and leg pain and numbness</td>
<td>One month follow-up; dexamethasone dose low (3.3 mg)</td>
</tr>
</tbody>
</table>
Epidural steroid injections may potentially reduce healthcare costs by reducing healthcare utilization and/or the need for surgical intervention.

Future areas of research should focus on improving the safety and efficacy of epidural injections by examining the role of diagnostic aids (digital subtraction angiography), needle position (safe triangle versus triangle of Kambin), injectate (non-particulate steroid or non-steroid epidural injections by examining the role of diagnostic aids (digital subtraction angiography), needle position (safe triangle versus triangle of Kambin), injectate (non-particulate steroid or non-steroid epidural injections, and new approaches (ultrasound versus fluoroscopic guidance).

References
Preoxygenation and general anesthesia: a review

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ABSTRACT
Because intubation can potentially become a lengthy procedure, the risk of arterial oxygen (O₂) desaturation during intubation must be considered. Preoxygenation should be routine, as oxygen reserves are not always sufficient to cover the duration of intubation. Three minutes of spontaneous breathing at FiO₂=1 allows denitrogenation with FAO₂ close to 95% in patients with normal lung function. Tolerable apnea time, defined as the delay until the SpO₂ reaches 90%, can be extended up to almost 10 minutes after 3 minutes of classic preoxygenation. Eight deep breaths within 60 seconds allow a comparable increase in O₂ reserves. For effectiveness, the equipment must be adapted and tightly fitted. Inadequate preoxygenation (FeO₂ <90% after three minutes tidal volume breathing) is frequently observed. Predictive risk factors for inadequate pre-oxygenation share overlap with criteria predictive of difficult mask ventilation. In cases of respiratory failure, oxygenation can be improved by positive end expiration pressure or by pressure support. In morbidly obese patients, preoxygenation is enhanced in a seated position (25°) and by use of positive pressure ventilation. O₂ can also be administered during the intubation procedure; techniques include pharyngeal O₂, special oxygen mask, or even pressure support ventilation for patients with spontaneous ventilation or positive pressure ventilation to the facial mask for apneic patients. Clinicians (especially anesthesiologists trained in ENT and traumatology) must be prepared to handle life-threatening emergency situations by alternate methods including trans-tracheal ventilation. The availability of equipment and training are two essential components of adequate preparation. (Minerva Anestesiol 2015;81:910-20)

Key words: Intubation, intratracheal - Cell respiration - Laryngeal masks - Ventilation - Anesthesia.
The partial fraction of \( O_2 \) (\( FAO_2 \)) is close to 0.95 and the reserve increases as follows: 0.95x3000=2850 mL. These theoretical figures are maximal values; the \( FAO_2 \) is lower in practice because the ventilation/perfusion ratio is heterogeneous.

The plasma \( O_2 \) reserve of a subject breathing in ambient air (\( PaO_2=80 \text{ mmHg} \)) with a plasma volume of 3 L is calculated as 0.003x80x3x10=7 mL. At a \( PaO_2 \) of 500 mmHg, this plasma reserve amounts to 45 mL. The hemoglobin \( O_2 \) reserve is calculated as follows for a concentration of hemoglobin of 12 g. 100 mL-1 and a total blood volume of 5 L: 1.34x0.98x12x10x5=788 mL in ambient air (saturation=98%). The value increases to 804 mL with a \( FiO_2 \) of 1 (saturation=100%). In cases of anemia, hyperoxic ventilation increases the utilizable \( O_2 \) by augmenting the dissolved \( O_2 \).

Considering the three main physiological \( O_2 \) reserves, the total \( O_2 \) reserve is about 1450 mL when breathing in ambient air and it rises to approximately 3700 mL when breathing pure \( O_2 \). This increase (approximately 2250 mL) is mainly due to the rise \( FAO_2 \) in FRC. The theoretical values were confirmed experimentally by measurement of oxygen uptake breath-by-breath in healthy volunteers during preoxygenation. The mean expired fraction of \( O_2 \) (\( FEO_2 \)) after 3 minutes of breathing \( O_2 \) was 0.92±0.01, and the mean additional oxygen taken up was 2.23±0.85 L. This value closely agrees with the physiological model.

Several factors influence \( O_2 \) availability: the initial rise in \( PaCO_2 \) (Haldane effect), FRC, \( FAO_2 \), fraction of shunt, \( VO_2 \), hemoglobin concentration, and cardiac output. Replacement of nitrogen by \( O_2 \) in the lung reservoir during preoxygenation obeys an exponential law. The change in \( O_2 \) reserve over time is linear in both blood and tissue compartments.

### \( O_2 \) consumption

The \( O_2 \) consumption of an awake subject is about 300 mL per min and it falls about 15% in the elderly. After ventilation in ambient air, \( O_2 \) reserves allow, at maximum, 3 minutes of apnea without serious impact on \( O_2 \) transport. This time can be doubled by correctly performed preoxygenation. The duration of apnea tolerated is additionally decreased if \( O_2 \) reserves are low due to decreased FRC, low \( PAO_2 \), and/or high \( VO_2 \).

### Ventilation/perfusion mismatch

Preoxygenation leads to increased shunt and micro-atelectasis after anesthetic induction. High \( FiO_2 \) is not the only mechanism responsible because atelectasis has also been observed when a \( FiO_2 \) 0.4 is used. The use of a \( FiO_2 \) of 0.8 does not prevent the appearance of micro-atelectasis, and it results in a considerably shortened margin of time before unacceptable desaturation compared with the use of 100% oxygen. Microatelectasis are reversible by application of an alveolar recruitment maneuver (tracheal pressure >30 cm \( H_2O \) for 15 seconds) and they can be prevented by the addition of a positive end expiration pressure (PEEP) of 10 cm \( H_2O \). In morbidly obese patients and in parturients, shunt can exceed 20% and even increasing \( FiO_2 \) to 1 does not provide correction of the hypoxemia. Implementation of a microatelectasis prevention strategy of alveolar recruitment maneuvers and PEEP limits the extent in elderly and obese patients.

### Epidemiology of arterial desaturation during induction and intubation

#### Anesthetic induction

Before upper airway control, arterial \( O_2 \) desaturation occurs when the \( O_2 \) reserves are insufficient to support the \( O_2 \) consumption during the apnea period. There are three mechanisms responsible (Figure 1): quantitative decrease in reserves (decrease in FRC, impairment of gas exchange), increase in \( VO_2 \) (parturient, fever), and prolonged apnea. Four high-risk situations deserve special mention:

- rapid induction sequence in which mask ventilation increases the risk of inhalation of gastric fluid (although this has never been demonstrated to occur);
- predicted difficulty with face mask ventilation;
- predicted difficulty with intubation due
The durations in minutes were estimated from the literature for a rapid sequence induction data and have shown in timeline with pre-oxygenation conditions and duration of apnea up to $\text{SpO}_2 < 90\%$. In some cases the apnea time will be less than the duration of action of anesthetic agents and that an alternative method for oxygenation will become necessary.

to anatomical abnormality or specific technical considerations (e.g., double lumen tube);
— obesity or pregnancy.

After rapid sequence induction, the resumption of spontaneous ventilation does not occur fast enough to allow recovery after a failed intubation procedure, and saturation falls below 90\% in 11\% of patients (Figure 2).\(^{11}\) After induction by propofol (2 mg.kg\(^{-1}\)) and fentanyl (2 µg.kg\(^{-1}\)), the administration of succinylcholine (0.56 mg.kg\(^{-1}\) and 1 mg.kg\(^{-1}\)) increases the risk of desaturation and apnea duration compared to placebo.\(^{12}\) In a pharmacodynamic study of succinylcholine (from 0.3 to 1 mg.kg\(^{-1}\), intubation conditions were found to be excellent at dosages above 0.5 mg.kg\(^{-1}\) (Table I), but the delay in resumption of spontaneous breathing rose from 4.0 to 6.16 minutes after administration.
Infection of the upper respiratory tract is noted to increase the risk of desaturation during induction.\(^{18}\)

Resuscitation and prehospital emergency

Variability exists among published incidences of desaturation in various studies \(^{22, 23}\) but it is reported to reach 60\% during prehospital intubation.\(^{22}\) In emergency medicine, desaturation occurs frequently, even in patients who are not difficult to intubate and for whom the intubation process is relatively rapid. Decreased FRC related to lung pathology (pulmonary edema, pneumonia, pulmonary contusion) is a determining factor. Pulmonary aspiration and esophageal intubation are responsible for some cases of severe desaturation during the intubation process.\(^{24}\) In a prospective study, preoxygenation was found to be effective (achieved PaO\(_2\)>100 mmHg) in 7 of 8 cases in which the indication was the protection of the airway (coma) and in 5 of 34 cases (15\%) in which intubation was indicated due to respiratory or cardiac failure.\(^{23}\)

**Preoxygenation**

In cases in which there is a potential risk of desaturation before securing the airway by endotracheal intubation, pre-oxygenation is highly recommended during induction of anesthesia. In its absence, the risk of desaturation is increased.

**Preoxygenation techniques**

The equipment must be adapted and tightly fitted to the patient, particularly the face mask. A morphological mismatch between the mask and the face of the patient (e.g., inappropriate mask size, presence of beards or moustaches)
The mask must be applied securely on the face of the patient; 20% dilution of O₂ by ambient air occurs when the mask is not tightly applied, and 40% dilution occurs when it is held close to the face. The circle system with fresh gas flow (5 L·min⁻¹) is used as the standard for comparison in anesthesia studies evaluating the effectiveness of different circuits because it allows higher inspiratory flow rates. Some open circuit (Bain or Magill) systems have been shown to be much less effective. Before preoxygenation, the circuit and the reservoir should be filled with O₂. Three preoxygenation techniques are used: spontaneous breathing at FiO₂ of 1 for 2 to 5 minutes, the “four vital capacities” method, and deep breaths (Table II).

Spontaneous breathing at FiO₂ of 1

The following technique of pre-oxygenation that was initially proposed by Hamilton in 1955 is still the reference standard: 3 minutes of spontaneous breathing at FiO₂ of 1. In patients with normal lung function, this provides denitrogenation with an FAO₂ of close to 95%. The denitrogenation is effective from the first minute of the preoxygenation; nevertheless, circuit leakage cancels these effects by a rapid decrease of the FiO₂. Breathing pure O₂ for longer than a minute appears to have little benefit in terms of SpO₂ or denitrogenation alveolar, but positively influences the duration of apnea before arterial desaturation. In experiments performed with healthy subjects, apnea time (with the exception of an insufflation to verify tracheal intubation) that is maintained until the SpO₂ reaches over 90%, can be extended to almost 10 minutes after 3 minutes of classic pre-oxygenation. The apnea time can be increased by an additional two minutes by application of positive pressure during the preoxygenation and by ventilation to the mask after induction.

VITAL CAPACITY MANEUVERS

The four vital capacities method is used in cases in which patient cooperation is lacking. The duration of apnea without desaturation is shorter after four capacities maneuvers than with spontaneous breathing. Technical requirements are responsible for the limitations of this technique: bag capacity, inspiratory flow and room gas inspiration. They are partly resolved by the addition of an additional 2 liter bag and a non-rebreathing “Ambu” valve. The vital capacity maneuver preferably begins with a forced expiration to optimize the elevation of FeO₂. To be fully effective, the inspiratory O₂ flow should be greater than the peak inspiratory flow, which is attained by activating the O₂ system “by-pass” during inspiration; or 4 or 5 forced breaths of pure O₂ were found to be as efficient as conventional pre-oxygenation assessed on the FeO₂. However, these results were not confirmed when PaO₂ was used for comparison; PaO₂ was observed to

Table II.—Comparison of the different techniques of pre-oxygenation in normal subjects.

<table>
<thead>
<tr>
<th>Study</th>
<th>N.</th>
<th>Endpoint</th>
<th>Preoxygenation technique used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambee AM</td>
<td>12</td>
<td>DAWD to 90% min</td>
<td>TVB 4 DB 30s 8 DB 60s TVB with AI + PEEP</td>
</tr>
<tr>
<td>Fleureaux O</td>
<td>17</td>
<td>DAWD to 95% min</td>
<td>8.9±10* 6.8±1.8</td>
</tr>
<tr>
<td>Baraka AS</td>
<td>24</td>
<td>Pa O₂ mmHg</td>
<td>9.9±3±10* 9.8±1.83</td>
</tr>
<tr>
<td>Herriger A</td>
<td>40</td>
<td>DAWD to 90% min</td>
<td>3.73±0.76 2.78±0.39 5.21±0.96*</td>
</tr>
<tr>
<td>Gold M</td>
<td>22</td>
<td>Pa O₂ mmHg 350.4±35.8 339±33.9</td>
<td>7.83±2.63</td>
</tr>
<tr>
<td>Rooney MJ</td>
<td>24</td>
<td>FeO₂ % 91.9±3</td>
<td>90.8±3</td>
</tr>
<tr>
<td>Nimmagadda U</td>
<td>24</td>
<td>FeO₂ % 88±5*</td>
<td>80±5 87±3*</td>
</tr>
<tr>
<td>Pandit JI</td>
<td>5</td>
<td>FeO₂ % 92±1*</td>
<td>83±9 91±4*</td>
</tr>
<tr>
<td>Gagnon C</td>
<td>20</td>
<td>FeO₂ % 89±3*</td>
<td>76±7</td>
</tr>
<tr>
<td>Tanouhi I</td>
<td>20</td>
<td>FeO₂ % 89±6</td>
<td>94±4*</td>
</tr>
</tbody>
</table>

TVB: tidal volume breathing; DB: deep breaths; DAWD: duration of apnea without desaturation.
be lower after the four vital capacity maneuver (293±86 mmHg) than after spontaneous ventilation in pure O2 (397±48 mmHg). The voluntary hyperventilation technique (1 minute at FiO2 1 followed by 2 minutes of voluntary hyperventilation) has been proposed to prevent post-apneic hypercapnia. PaCO2 after intubation was similar, compared to a control, when either hyperventilation before induction or 3 min normal breathing was used as the pre-oxygenation technique.

Deep breathing method

Eight deep breaths within 60 seconds at an oxygen flow of 10 L per min constitutes a simple method of preoxygenation. This technique results in a mean arterial oxygen tension of 369±69 mmHg, which is not significantly different from the value achieved by 3 minutes of tidal volume breathing at an oxygen flow of 5 L per minute. The voluntary hyperventilation technique has been proposed to prevent post-apneic hypercapnia. PaCO2 after intubation was similar, compared to a control, when either hyperventilation before induction or 3 min normal breathing was used as the pre-oxygenation technique.

Pressure support ventilation

In healthy volunteers, PSV has been shown to improve the quality of pre-oxygenation by two mechanisms: acceleration of nitrogen washout and better contact between the mask and the face. In a healthy volunteer study, FEO2 after 3 minutes of preoxygenation was higher (p<0.001) with PSV 4 cm H2O/PEEP 4 (94±3%) and PSV 6 cm H2O/PEEP 4 (94±4%) than with the standard technique (89±6%). One hundred percent and 90% of the participants reached 90% FEO2 with PSV 4 and 6 cmH2O respectively vs. 65% with spontaneous breathing at FiO2 of 1 (P=0.0013). Clinical tolerance was impaired at the highest level of pressure tested.

Preoxygenation failure

Inadequate preoxygenation, defined as an FEO2<90% after three minutes of tidal volume breathing, is seen frequently in practice (6% in a sample of 1050 patients). The effective FiO2 delivered was observed to be lower in patients with a FEO2<90%. Risk factors for inadequate preoxygenation were determined to be bearded male, beardless male, ASA>1, lack of teeth, and age >55 years. These predictive factors overlap with those previously associated with difficult mask ventilation.

While SpO2 measurement is not informative regarding the quality of pre-oxygenation maneuvers, it is essential to identify oxygenation problems. The FeO2 depends on the tidal volume; small tidal volumes increase the difference between FeO2 and FAO2, leading to overestimation of FAO2. The CO2 wave shape is informative regarding the quality of the ventilation and the tightness of the circuit. FeO2 of <90% indicates incomplete denitrogenation at the FRC level. In a study of 40 volunteers, 9 subjects were unable to attain FeO2>90%. Even if the mechanisms that cause incomplete denitrogenation are not identified, this monitoring method has utility in routine practice. If the FeO2 cannot be increased above 90%, PSV may be proposed to improve preoxygenation quality. In emergency medicine, the monitoring of preoxygenation is typically based on SpO2 measurement and pre-oxygenation duration, as the FeO2 is not usually available.

Morbidly obese patients

In the obese, the decrease in FRC, increase in O2 consumption, and heterogeneity of the ventilation/perfusion (V/Q) ratio result in a decrease in the time required for alveolar denitrogenation and a decrease in O2 stores, which in turn reduce the duration of apnea tolerance. After 3 minutes of classic preoxygenation, obese patients can tolerate apnea of 3 minutes duration while maintaining SpO2 higher than 90%, and the time required to increase saturation above 96% after desaturation is 37 seconds, which is longer than the 22 seconds required in healthy subjects. Pulmonary abnormalities are correlated to Body Mass Index and are responsible for early desaturation, before complete muscle relaxation and intubation. The effectiveness of spontaneous ventilation and eight deep breaths as preoxygenation methods are comparable in the obese when regarding FeO2 and the duration of apnea before the SpO2 reaches 95%. Continuous Positive Airway Pressure (CPAP) (7.5 cm H2O versus Mapleson
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104±30 seconds between 13-26 weeks of pregnancy, 80±20 seconds between 26-42 weeks, and 130±30 seconds in controls, due to the reduction in the FRC during pregnancy. Spontaneous ventilation in FiO2 of 1 for 3 minutes and the four vital capacities method for 30 seconds give comparable results, whether judged by PaO2 or apnea duration. Some women were observed to have a tolerable apnea duration of only approximately 60 seconds; this short delay carries obvious risk. The shortening of the time to FeO2 of 90% (average 107 seconds) is a good argument supporting recommendation of the 8 deep breaths technique during obstetric emergencies.

Preoxygenation and chronic obstructive pulmonary disease

In patients with chronic obstructive pulmonary disease, the time needed to decrease the alveolar fraction of nitrogen (FAN2) from 78% to 2% can exceed 30 minutes, as it is inversely proportional to the peak expiratory flow rate. FetO2 monitoring is used to evaluate the time necessary for preoxygenation in such patients.

Preoxygenation in pediatrics

In pediatrics, the respiratory physiology of young children is particularly age-specific. The inhibition of intercostal tonus by general anesthesia is responsible for a reduction in FRC. Hypoxemia arises more quickly in children because of a higher VA/FRC ratio, a higher O2 consumption, and lower O2 reserves. Children exhibit a delay before reaching FeO2 close to 90% of approximately 60 seconds; this short delay carries obvious risk. The shortening of the time to FeO2 of 90% (average 107 seconds) is a good argument supporting recommendation of the 8 deep breaths technique during obstetric emergencies.

Preoxygenation in pregnancy

In the parturient, the time required for complete denitrogenation (FeN2=2%) is shorter than in non-parturient young women as follows:
been reported. The duration of apnea required to reach a SpO$_2$ of 98%, 95%, or 90%, is significantly increased when the preoxygenation is extended for 1 to 2 minutes, but no benefit was found by extension past 3 minutes. When the gas mixture used during pre-oxygenation passes from an average FiO$_2$ of approximately 93% to 39%, the duration of apnea until a 95% SpO$_2$ decreases from 210 to 71 seconds.

**Intensive care patients and emergency medicine**

In emergency medicine, all of the patients can be considered to be at risk for desaturation during airway control and thus preoxygenation should be recommended as part of routine practice. In emergency nonsurgical intubation, pre-oxygenation is difficult to achieve. The benefit of the pre-oxygenation is probably greater in patients who do not have respiratory illness at the time of intubation. Thus, all patients who are intubated for neurological distress should benefit from a careful preoxygenation of at least 3 minutes in duration, even if a lack of patient cooperation limits its effectiveness. During intubation of hypoxemic patients, pre-oxygenation using PSV is more effective at reducing arterial desaturation than the usual method. At the end of the preoxygenation period, SpO$_2$ was higher in the PSV group than in the control group (98±2 vs. 93±6%, P<0.001). During the intubation procedure, lower SpO$_2$ values were observed in the control group (81±15 vs. 93±8%, P<0.001). Twelve (46%) of the patients in the control group and two (7%) in the PSV group had a SpO$_2$ below 80% (P<0.01).

**Apneic oxygenation**

It is possible to maintain oxygenation during a long period of apnea by administering 10 to 15 L per min of continuous oxygen into the pharynx. However, this method is only effective following a complete preoxygenation. Apnea of longer than 30 minutes in duration has been reported to result in severe hypercapnia (>150 mmHg) without damage to the patient. Apneic oxygenation failures are related to failure of the preoxygenation procedure and to reduced FRC. An indirect method of apneic oxygenation is the administration of O$_2$ during intubation attempts, and the administration of O$_2$ at a rate of 3 L per min by a naso- or oro-pharyngeal catheter can significantly delay the onset of arterial O$_2$ desaturation. Similar results have been reported more recently in ASA 1-2 patients after preoxygenation. This method is easy to apply and it confers a definite advantage in patients without respiratory pathology and probably in morbidly obese patients as well.

**Management of failures of preoxygenation and oxygenation**

As the risk factors for pre-oxygenation failures and difficult mask ventilation are similar, such at-risk patients should be identified and carefully monitored. If FeO$_2$ is lower than 0.9 after pre-oxygenation, alternative methods of oxygenation should be immediately available. Knowing that none of techniques is 100% reliable, it is essential to be able to provide several methods. The equipment must be immediately available and the team must be familiar with its use. The most popular device is the intubating laryngeal mask airway (ILMA). The ventilation is of good quality in the vast majority of cases and oxygenation failures are rare when using this device. However, only the No. 3 size exists for use with child patients, and little data are available about ILMA use in pediatrics. For patients of less than 30 kg, the standard laryngeal mask is used, with the awareness that implementation is more difficult and not always successful.

In the event of ventilation failure with the facial or laryngeal mask, rescue trans-tracheal oxygenation is to be considered. Inter-crico-thyroid membrane puncture is straightforward in 98% of non-emergency cases. Because the use of transtracheal ventilation in emergency medicine is very rare, studies on this subject include only very few patients. The success rate of the emergency puncture procedure is unknown. Jet ventilation is administered using a manual injector with operator control or using a jet ventilator with control of the driving pressure. The major risk is the possibility of pulmonary barotrauma by lung overdistension, the impact
of which can be serious in this context. It is important to closely monitor the quality of expiration and keep in mind that the outflow of a 14 gauge catheter to a driving pressure of 3 bars is approximately 600 mL per second. With O₂ consumption being approximately 300 mL per minute, the injection duration and respiratory rate are limited to a minimum.

Conclusions

It is of particular importance to consider the issues related to oxygenation because O₂ reserves are low and the difficulties of intubating the patient and providing adequate ventilation are often associated. The situation becomes critical when O₂ reserves are insufficient. Efficient technique and FeO₂ monitoring can improve the effectiveness of the pre-oxygenation and thereby increase the margin of safety. After pre-oxygenation, supplemental O₂ increases the duration of tolerable apnea in most cases, and this very simple measure should not be neglected. Failures of pre-oxygenation must be identified and alternative methods of oxygenation should be available for rapid and facile implementation. To this end, these methods should be taught and practiced on models or during simulation courses, so teams are prepared if the need arises.

Key messages

— Effective preoxygenation (FeO₂ >90%) is essential to avoid hypoxemia during airway management.
— Preoxygenation can be improved by use of a seated position (20° to 30°), PSV, and/or PEEP, especially in obese patients.
— Some induction situations present higher risk: pregnancy, obesity, rapid induction sequence and require special attention.
— Those situations at risk may be anticipated by identifying risk factors.

References

44. Matsumura M, Yamao T, Komiyama T, Tsurumi H, Soejima T, Matsuda T et al. Preoxygenation is more effective in the
54. Teller LE, Alexander CM, Frumin MJ, Gross JB, Pharyn-
58. Altermatt FR, Munoz HR, Delfino AE, Cortinez LI. Preoxygenation in the obese patient: effects of position on toler-
59. Byrne F, O’Duro-Dominia A, Kipling R. The effect of pregnancy on pulmonary nitrogen washout. A study of pre-
61. Teller LE, Alexander CM, Frumin MJ, Gross JB, Pharyn-
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Mortality rate related to severe sepsis and septic shock has decreased significantly as a result of aggressive intravenous fluid management, appropriate and early broad spectrum antibiotics and early removal of the source of infection. Nonetheless, mortality of sepsis remains high despite these improvements in clinical management and new therapies are still needed. Despite a better understanding of the mechanisms involved in septic response, targeted immunotherapies have not improved survival rates. Statins have antioxidant and antiapoptotic effects and have demonstrated the ability to reduce the production of pro-inflammatory cytokines known to be detrimental in the development and progression of sepsis. To date, numerous observational studies on the interest of statins in sepsis have been published. Meta-analyses suggest potential beneficial effect of statins on mortality. More recent meta-analyses have also pooled data from randomized studies. However, those studies were conducted in patients with variable severity of sepsis. Several, randomized controlled trials...
als of statins *versus* placebo, have been recently conducted in patients with severe sepsis,8 with ventilator-associated pneumonia 9 and with acute respiratory distress syndrome.10, 11 The aim of this review was to perform a meta-analysis of randomized controlled studies conducted in this population and summarize the literature on the role of statins in improving outcome of sepsis in critically-ill adult patients.

**Rationale for statin therapy in sepsis**

Statins inhibit the conversion of hydroxy-methyl-glutaryl-coenzyme A to mevalonate, an early rate-limiting step in cholesterol biosynthesis, thereby reducing total cholesterol.2 Beyond their lipid-lowering effect, statins also have pleiotropic properties including anti-inflammatory, antioxidant, immunomodulatory and antithrombotic effects 12-14 which could prevent or curtail sepsis. Traditionally, the host immune response to sepsis has been described as an overly exuberant immunization response for endothelial dysfunction and injury leading to organ failures.15 The concept of sepsis as a cytokine storm emerged, as several trials described increased concentration of various cytokines in patients with sepsis.16, 17 Later, Bone et al. advanced the idea that the initial inflammatory response gave way to a subsequent "compensatory anti-inflammatory response syndrome".18 However, recent studies have shown that infection triggers a much more complex and prolonged host response where both pro-inflammatory and anti-inflammatory responses occur early and simultaneously.19, 20 Although a large part of septic patients die from multiorgan failure, a persistent deficiency of both innate and adaptive immunity leads a marked immunosuppressive state,21 resulting in deaths from inability to clear primary infections and/or development of secondary infections. A persistent activation of innate immunity which results in prolonged hyperinflammation is responsible for organ injury and late deaths.22 Therapies with immunomodulatory properties such as statins may favorably influence the evolution of sepsis. First, an improvement in endothelial dysfunction and apoptosis, which play a crucial role in the pathogenesis of sepsis,23 has been shown with statins (Table I). Second, statins have various immunomodulatory effects. Although these properties could reduce ability to clear infection, they have been associated with an improvement of prognosis in animal models of sepsis.24, 25 Statins reduce geranylpyrophosphate and farnesylpyrophosphate availability, by interacting in cholesterol biosynthesis pathway, which are major components of subcellular binding sites for small GTP-binding protein. GTP-binding proteins have crucial roles in intracellular inflammatory signaling.2 Moreover, statins reduce the expression of pro-inflammatory cytokines 26, 27 and also reduce C-reactive protein level (CRP), which is associated with organ dysfunction and death in critically ill patients.28, 29 Third, statins inhibit leucocyte movement by reducing adhesions molecules expression.30 Statins could finally modulate adaptive immunity through the direct inhibition of MHC-II expression by monocytes and macrophages.31 Whether some statins have more anti-inflammatory power than others is unclear since they have rarely been compared. However, simvastatin has been used for a majority of experimental studies and has exhibited the largest range of effects and in vivo properties.2 Different statins may have sometimes opposing effects. For exam-

**Table I.—Main immunomodulatory and therapeutic actions of statins.**

<table>
<thead>
<tr>
<th>Improvement in endothelial dysfunction and apoptosis23</th>
<th>Reduction of components of subcellular binding sites for small GTP-binding protein, affecting intracellular inflammatory signaling2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of the expression of proinflammatory cytokines (IL-1, IL-6 and TNF alpha) 24, 25</td>
<td>Inhibition of leucocyte movement by reducing adhesions molecules expression 28</td>
</tr>
<tr>
<td>Inhibition of MHC-II expression by monocytes and macrophages29</td>
<td>Modulation of coagulation by blunting monocyte tissue factor expression and reducing plasminogen activator inhibitor (PAI)-1 (cross-talk with inflammation)</td>
</tr>
<tr>
<td>Promotion of a favorable balance between constitutive and inducible NOS leading to improved hemodynamic stability23</td>
<td></td>
</tr>
</tbody>
</table>

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ple, simvastatin reduced, whereas atorvastatin enhanced superantigen-mediated T-cell activation in healthy volunteers.30

During sepsis, significant alteration of both coagulation system and cells that regulate this system also occur.33, 34 Statins have been shown to modulate coagulation by blunting monocyte tissue factor expression and reducing plasminogen activator inhibitor (PAI)-1 which interact with the fibrinolytic system.2 The main mediators of inflammation-induced activation of coagulation are pro-inflammatory cytokines.35, 37 There is increasing evidence that extensive crosstalk between inflammation and coagulation exists, whereby inflammation leads to activation of coagulation and components of the coagulation system may modulate the inflammatory response.34 Therefore, the ubiquitous effects of statins both on inflammation and coagulation may be synergistic in sepsis.

Finally, during sepsis, endothelial constitutive nitric oxide synthase (NOS) activity decreases, while a delayed increase in inducible NOS leads to an overproduction of nitric oxide, which is responsible for vasodilatation, loss of vascular resistance and vascular leak.38 Statin could contribute to a favorable balance between constitutive and inducible NOS leading to improved hemodynamic stability.23

Clinical applications

Statins for prevention of severe sepsis

Observational studies of acute ward patients suggest a preventive role for statins in sepsis. The first published work was a prospective observational cohort study, in which all consecutive patients admitted to a medicine ward with a known or presumed bacterial infection were included and divided into two groups on the basis of whether they were taking statins for at least one month before admission or not.39 Of the 361 patients enrolled, 82 (22.7%) were treated with statins. Severity scores were similar between groups. The primary outcomes were the development of severe sepsis, which was significantly lower in the statin group than in the non-statin group (2.4% vs. 19% respectively, P<0.001), and admission to an intensive care unit (ICU), which was 3.7% in the statin group versus 12.2% in the group without statins (P=0.025).39 The same authors conducted a prospective observational population-based study to evaluate the infection-related mortality in 11,362 patients with atherosclerotic disease.40 Patients were divided into two groups on the basis of whether they were taking statins or not. Infection-related mortality, defined as death due to an acute infection occurring within 30 days of admission, was significantly lower in the statin compared with the non-statin group (0.9% vs. 4.1%) with a relative risk of 0.22 (95% confidence interval, 0.17-0.28).36

Several studies have also been performed in critically-ill patients. In a two-center, randomized, open-label trial, Makris et al.41 compared pravastatin (40 mg/d) with a placebo in ICU patients without infection but receiving mechanical ventilation. Six patients (8.4%) in the pravastatin group and 16 (19.8%) in the control group died during the 30-day treatment period (P=0.06). In a cross-sectional analysis of a prospective cohort, O’Neal et al.42 evaluated the impact of statins received before ICU admission in critically-ill patients. Of 575 patients, 149 (26%) were on statin therapy prior to hospitalization. In a multivariable logistic regression model including age, gender, race, current tobacco use, prehospital aspirin use, and APACHE II score, prehospital statin use was significantly associated with a lower rate of diagnosis of severe sepsis (OR 0.62, 95% CI 0.40-0.96, P=0.03).42

Harbi et al.43 conducted a nested cohort study within two randomized controlled trials unrelated to statins. Of the 763 patients enrolled in the study, 107 (14%) received statins during their ICU stay, and 656 (86%) did not. In the statin group, patients were older (69±11 years vs. 49±22 years, P<0.0001) and presented higher APACHE II score than in the non-statin group (27±7 vs. 23±8 P<0.0001). There was no significant association between statin use and the development of sepsis or severe sepsis.43 Fernandez et al.44 retrospectively reviewed the ICU charts of patients receiving mechanical ventilation for more than 96 hours. Patients were classified into statin group, which consisted of patients taking...
statins before ICU admission and continuing on statin therapy throughout the course of hospitalization, or the non-statin group. Of the 438 patients included, the 38 statin-treated patients were older (71±8 years vs. 61±18 years P=0.001) and tended to have a higher median APACHE II Score (21 vs. 17, P=0.07). The ICU-acquired infection rate in statin-treated patients was not significantly lower (29% vs. 38%, P=0.3) nor delayed (median 12 vs. 10 days, P=0.6).44 No differences were found regarding the source of infections.44 Finally, a recent meta-analysis made from 11 randomized controlled trials totaling 30,947 patients showed no effect of statins on the risk of infections (RR=1.00, 95% CI 0.96-1.05) or on infection related deaths (0.97, 0.83 to 1.13).45 Thus, the effect of statin in preventing severe sepsis remains uncertain especially in critically-ill patients.

Continuation of statin therapy in sepsis

In ambulatory settings, elevated hepatic transaminases generally occur in 0.5% to 2.0% of cases and are dose-dependent.45 Another untoward effect is myopathy but little is known about the fundamental mechanisms of statin-associated myopathy. Severe myopathy is rare and its incidence is reported to be 0.08% with lovastatin and simvastatin.46 Current prescribing guidelines suggest caution in the continued use of statins in critically-ill patients because of concern regarding serious side effects and toxicity that might be greater than in the general population. However, should statins influence the inflammatory response to sepsis, cessation may cause an inflammatory rebound leading to worse outcomes. Very few studies have explored this topic and particularly in critically-ill patients. Mekontso-Dessap et al.47 conducted a retrospective cohort study among patients admitted for severe sepsis and septic shock in the ICU and with ongoing statin therapy (initiated at least one month before ICU admission and continued with no interruption until ICU admission). Of 76 patients included in the final analysis, 44 had statin therapy continued and 32 had not. After propensity-matching or multivariable adjustment, there was no association of statin continuation with organ failure-free days (beta coefficients with 95% CI of 2.37 [-0.96 to 5.70], P=0.20 and 2.24 [-0.43 to 4.91], P=0.11 respectively).47 Another observational study suggested a better outcome in prior statin users presenting with ventilator-associated pneumonia who continued statin therapy in the ICU compared with those who stopped statin therapy.48

Kruger et al. conducted the only prospective randomized double-blind placebo-controlled trial on this subject.29 They randomized atorvastatin (20 mg) or matched placebo in 150 patients on preexisting statin therapy requiring hospital admission for infection. The primary end point was the progression to severe sepsis. Severe sepsis was present at baseline in 32% (24 of 75) of patients in both groups. Presence of severe sepsis significantly decreased over time (P<0.01) in each group with no significant difference between treatment groups at each follow-up time point (day 3, 5, 10, 14) (overall P=0.6). Twenty-four patients (16%) of the cohort required ICU admission (atorvastatin group 13/75, placebo group 11/75). Investigators also explored inflammatory markers (IL-6 and CRP) for both groups at baseline and follow-up time-points. Median IL-6 for the cohort at baseline was 43.8 pg/mL (interquartile range 16.9-100.5), with no significant difference between the groups. IL-6 level decreased in both groups over time (P<0.01) with no significant difference between groups at any follow-up time-point (overall P=0.7).29 Finally, in a trial which randomized patients to receive atorvastatin 20mg per day or placebo, the subgroup of prior statin users with continued atorvastatin therapy had a significantly lower 28-day mortality (5% vs. 28%; P=0.01). However, the difference was not statistically significant at day 90 (11% vs. 28%; P=0.06).8

Statins to improve outcome of sepsis

Most studies that evaluated the role of statins in patients with sepsis are retrospective cohort trials and few focused on critically-ill patients. Wan et al.7 performed a meta-analysis of 5 randomized and controlled trials and of 27 observational studies. Among randomized controlled trials, statins did not improve 28-day mortality.
(RR, 0.93; 95% CI, 0.46 to 1.89) while observational studies indicated a significant decrease in morality with adjusted data (RR, 0.65; 95% CI, 0.57 to 0.75). Janda et al. conducted another meta-analysis of 20 studies whose 18 were cohort studies. Pooled odds ratios were all in favor of statin versus non-statin use: 0.61 (95% CI, 0.48 to 0.73) for 30-day mortality (N. = 7) and 0.40 (95% CI, 0.23 to 0.57) for sepsis-related mortality. These results suggested a protective effect of statins in patients with sepsis. However, these meta-analyses are limited by the cohort design of the selected studies and the high heterogeneity among them regarding the type and severity of patients, dosage and duration of statin administration, and type of infection. Since randomized controlled trials have been recently conducted to evaluate the potential interest of statins in treating patients with severe infections requiring ICU admission, we performed a meta-analysis limited to this type of trial.

Methods for meta-analysis

We performed an electronic article search through Pubmed. We used combinations of keywords related to statins (“hydroxymethylglutaryl-CoA Reductase Inhibitor” or “statin” or “simvastatin” or “rosuvastatin” or “pravastatin” or “atorvastatin” or “fluvastatin” or “cerivastatin” or “pitavastatin” or “lovastatin”) AND the associated disease (“infection” or “sepsis” or “severe sepsis” or “septic shock”) AND the type of patients (“Intensive care” or “critical care” or “critically ill”). All searches were limited to “English language” and “humans”. Only randomized controlled trials were included and must have met the following criteria: adult patients admitted to ICU, experienced severe sepsis at study enrollment, statins compared with a control and data available on the mortality. Abstracted data included: characteristics of the studies, characteristics of the included patients and outcomes of the studies. The endpoint was mortality (60-day mortality or in-hospital mortality at 60-day and 28-day mortality). Authors were contacted to obtain data and results that were not in the manuscript. The methodological quality of studies was evaluated using the Jadad Scale, which is a 0 to 5 point scale used to independently assess the methodological quality of a clinical trial.

In examining the associations between statins and infection/sepsis mortality, results were expressed as risk ratios with 95% confidence intervals (CIs). Heterogeneity across trials was assessed by means of the I² statistic, with significance being set at I² > 50%. Random effects models were used for statistical analysis.

Results

The flowchart of included studies and selection progress is presented in Figure 1. Eight randomized studies were identified. Among them 3 were not retained for analysis because they included only or mainly ward patients and one since it did not include patients with sepsis. Finally, 4 studies were retained for analysis (Table II).

Figure 2 shows the pooled results from random effects models combining the risk ratios for mortality. Overall analysis including 1818 patients total from 4 studies showed that there was no significant difference between statins (223/903) and placebo (233/899) in terms of 60-day mortality (risk ratio, 0.930; 95% CI, 0.722 to 1.198), with moderate heterogeneity among the studies (I² = 52%, P = 0.09). Similarly, no 28-day mortality difference was observed between groups (statins 191/907, placebo 199/911; risk ratio 0.953; 95% CI, 0.715 to 1.271) with moderate heterogeneity among the studies (I² = 54%, P = 0.09).

The first prospective randomized double blind, placebo controlled was a phase II trial designed to assess the biological and clinical effect of atorvastatin therapy in critically-ill patients with severe sepsis (Table II). A total of 250 patients admitted in 21 ICUs underwent randomization. Seventy seven patients (30.8% of the cohort) were on prior statin therapy (37 randomized to treatment, 40 to placebo). Mean APACHE II Score was 22.1 and 23.5 and SOFA score was 8.3 and 8.0 in statin and placebo group respectively. For the entire cohort, as for de novo therapy, there was no statistically significant difference in ICU, hospital, 28-day or 90-day mortality and in length of stay between groups.
Papazian et al. conducted a multicenter prospective randomized double-blind placebo-controlled trial evaluating simvastatin (60 mg/day) versus placebo in critically-ill patients who underwent ventilator-associated pneumonia. Patients were free of statin therapy at the mo-

![Figure 1.—Flowchart of included studies and selection progress.](image)

**Table II.—Outcome data of randomized controlled trials included in the meta-analysis of statin for sepsis in critically ill patients.**

<table>
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<tr>
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<th>Inclusion criteria</th>
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<td>Prospective, randomized, double blind placebo-controlled, phase II, multicenter trial (21 ICU)</td>
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<td>Suspected or proven infection and severe sepsis</td>
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<td>Prior statin users (N.=77)</td>
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<td>Papazian et al. (2013)</td>
<td>Prospective, randomized, placebo-controlled, double blind, parallel-group, multicenter trial (26 ICU)</td>
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<td>5</td>
<td>Mechanical ventilation &gt;48 hours and suspected ventilator-associated pneumonia (CPIS &gt;5)</td>
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<td>Prior statin users (N.=26)</td>
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<tr>
<td>NHLBI ARDS clinical trial Network (2014)</td>
<td>Prospective, randomized, double blind placebo-controlled, multicenter trial (44 hospitals)</td>
<td>March 2010-September 2013</td>
<td>5</td>
<td>Mechanical ventilation and PaO2 to FiO2 ratio &lt;300 mmHg and known or suspected infection</td>
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<td>Prior statin users (N.=109)</td>
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<tr>
<td>McAuley et al. (2014)</td>
<td>Prospective, randomized, double blind placebo-controlled, multicenter trial (40 hospitals)</td>
<td>December 2010-March 2014</td>
<td>5</td>
<td>Mechanical ventilation and ARDS &lt;48 hours (PaO2 to FiO2 ratio &lt;300 mmHg)</td>
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<td></td>
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<td></td>
<td>Prior statin users (N.=0, exclusion criteria)</td>
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</table>
ment of intubation. Mean overall SOFA Score on day 1, was 7.0. The trial was stopped for futility at the first scheduled interim analysis. Three hundred patients were enrolled, and 284 were analyzed, 146 in the simvastatin group and 138 in placebo group. 28-day mortality was not dif-
The Acute Respiratory Distress Syndrome (ARDS) Network recently conducted a multicenter trial in patients with sepsis-associated ARDS. They randomly assigned patients to receive rosuvastatin or placebo in a double-blind way. The study was stopped because of futility after enrollment of 745 patients (379 in rosuvastatin group and 366 in placebo group). Mortality at day 60, ventilator-free days and ICU free days to day 28 did not differ significantly between the two groups. One hundred and nine patients had used statins previously (54 in rosuvastatin group and 55 in placebo group). Rosuvastatin therapy had no effect on mortality in this subgroup (17/54 deaths in rosuvastatin group, 11/55 deaths in placebo group, P=0.14).

Finally, McAuley et al. published the results of a multicenter trial which randomized 540 ARDS patients to receive either simvastatin (80 mg/day) or placebo. Patients having received a statin within 2 weeks of meeting ARDS criteria were excluded. There was no significant difference between the study groups in the number of ventilator-free days (12.6±9.9 with simvastatin and 11.5±10.4 with placebo, P=0.21), in 28-day mortality (22% and 26.8% respectively, p=0.23) or in mortality before discharge from hospital (25.9% and 32.1% respectively, P=0.13). Although 404 of included patients presented with sepsis (189/259 in simvastatin group and 218/280 in placebo group), there was no interaction between outcome and presence or absence of sepsis. Therefore, the results of the whole population have been included in the present meta-analysis.

Regarding adverse effects of statins (alanine aminotransferase or creatine kinase elevation during the study period), there were no significant differences between statin and placebo groups in three trials. However, one trial reported fewer days free of hepatic failure or renal failure in the statin group. The rate of adverse events in the most recent study was higher in the simvastatin group than in the placebo group (OR 2.2 [1.1-4.2], P=0.02). The majority of the adverse events were related to elevated creatine kinase and hepatic aminotransferase levels.

Implications for clinical practice

In numerous cohort trials, statins have been suggested to decrease mortality or the risk of infection in septic patients. Four prospective randomized double-blind placebo-controlled trials in the ICU have failed to demonstrate benefit with statins in patients with severe sepsis. Two of them were stopped for futility. A trend in higher 28-day mortality in the statin group in one study and in 60-day mortality in the statin group in another one prompted our desire to perform a meta-analysis of available randomized trials. Our results confirm the lack of beneficial effects but do not exhibit any significant detrimental effect of statins on mortality.

A limitation of this meta-analysis is that trials had different inclusion criteria, respectively severe sepsis, ventilator-associated pneumonia and sepsis-associated ARDS. However, populations had similar severity scores and mortalities, ranging from 14% to 24%. Another limitation is that these trials tested 3 different statins, respectively atorvastatin, simvastatin and rosuvastatin. These molecules had been chosen by investigators since immunomodulatory effects had been described with each molecule and since they had a safety profile compatible with administration in critically-ill patients. Nevertheless, the results of the three studies were similar with 3 different molecules, reinforcing the idea that statin lack of effect on the course of sepsis is not molecule dependent.

Like previous observational studies, a very recent large cohort study suggested that patients treated with high regimens of statins at least one month before the occurrence of sepsis had lower hospital and one-year mortality. This result supports the concept that statin premedication may confer additional protection in community-acquired sepsis that is not related to atherosclerotic diseases. This preventive potential has not been evaluated in recent trials. Moreover, the potential of statins as the part of a multimodal approach to improve prognosis of sepsis remains to be evaluated.
Conclusions

In conclusion, the results of this meta-analysis confirm that the use of statin therapy should not be recommended in the management of severe sepsis in critically ill patients. Since one study reported less hepatic and renal failure free days in the statin group, statins should be continued with caution at ICU admission only if considered as necessary.

Key messages
— The use of statin therapy should not be recommended in the management of severe sepsis in critically ill patients.
— Statins should be continued with caution at ICU admission only if considered as necessary.
— The potential of statins given for a long time before sepsis remains to be clarified.

References


Association between steroid particle sizes and serious complications during epidural injections

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Dear Editor,

I have read with curiosity the intriguing article entitled “Epidural steroid injections: update on efficacy, safety, and newer medications for injection” published in this issue of Minerva Anestesiologica. 1 Kozlov et al. skillfully reviewed the literature on efficacy, safety, and newer medications for epidural steroid injections (ESIs). This review is a helpful article for resolving the interpretations about safety and efficacy of using ESIs during the management of radicular pain. However, I would like to add some additional points about association between steroids particle sizes and serious complications, which are evident in the results discussed below.

It was showed that larger particle sizes of steroids might have a higher risk for small vessels occlusion of arterial tree as a potential sequel after incidental steroid injection in radiculomedullary artery. Notably, infarction of the spinal cord, cerebellum, and the brainstem may occur. One might contemplate that particles of steroid smaller than an erythrocyte diameter are safer. 2 Injectable preparations including betamethasone sodium phosphate, triamcinolone acetonide, betamethasone acetate, methylprednisolone acetate, and dexamethasone sodium phosphate were analyzed by light microscopy in vitro. Derby et al. 2 have revealed that triamcinolone acetonide particles were greater than median-sized erythrocytes. Betamethasone and triamcinolone particles were packed with an extensive particle aggregation. Methylprednisolone in a mixture with lidocaine and iodinated contrast media and alone showed that particles with their aggregations were smaller than red blood cells. Nevertheless, methylprednisolone particles were packed, signifying the potency to form emboli with following occlusion of small arterioles. Sodium phosphate dexamethasone particles without the tendency of particle aggregation were smaller than erythrocytes. A mixture of dexamethasone, iodinated contrast media, lidocaine showed the same properties 2 and did not precipitate.

On the other hand, MacMahon et al. 3 evaluated dexamethasone sodium phosphate, triamcinolone acetonide, and methylprednisolone acetate nondilute injectable particle sizes and after mixing with human plasma and local anesthetic. Again, corticosteroids in a mixture with local anesthetics did not change their properties. Additional plasma showed significant reduction in the aggregate sizes eventually related to repulsion effects and coating effects of albumin; however, the insoluble corticosteroid particle sizes was unchanged. 3 Consequently, the steroid aggregates might play the role of potential embolization agents within spinal cord arterioles.

As is obvious from the above discussion, after incidental intra-arterial injection, soluble dexamethasone is less likely to cause capillary or arterial occlusion. Interestingly, more studies are required for a deeper understanding of the association between steroids particle sizes and serious complications.

References


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Dear Editor,

The interesting study from Pieters et al.1 about the forces applied by the laryngoscope on patients’ teeth opens the discussion on some issues that, in our opinion, need to be specified.

The authors suggest in the discussion that the Mac blades create more room for intubation compared to other videolaryngoscopes (VLS), making intubation easier and faster. While time is a continuous variable that was measured, the ease of laryngoscopy is a subjective element which does not find any reference in the results and is therefore an inference.

We have recently published a study on the activation of the upper limb muscles recorded through surface electromyography (SEMG) during laryngoscopy in manikins, which included also the assessment of workload with the NASA Task Load Index to compare direct laryngoscopy and Glidescope® (GLS).1

Our results showed that the force used by the muscles of the left upper limb during videolaryngoscopy is much lower than during direct laryngoscopy and the workload showed the same trend. Unfortunately, this paper is not mentioned by Pieters et al.

Furthermore, the differences in the results are the consequence of the decision not to use the stylet with both McGrath® and GLS and of the lack of expertise with the two VLS.

While with direct laryngoscopy it is crucial to create a wide room by only pushing the soft tissue for passing the tube, this is not necessary with the angulated blades as it is the shape of the malleable stylet that adapts the tube to the pharyngeal anatomy and allows its progression with respect of the soft palate and the tonsillar pillars.

The required bimanual task to accomplish videolaryngoscopic intubation needs a long training to reach expertise and the abandonment of the stylet for fear of soft tissue injury is the proof that the expertise was not yet reached with either GLS or with McGrath® before the study began, and this bias affected the results and the conclusions of the study.

In further support of this argument, we would like to point out that in the methods the three investigators were defined as “experts” because they have done at least 100 intubations with each of the three VLS.

Therefore, before the study started each operator would have had at least 300 intubations done for a total of 900 consecutive intubations.

However, only 150 consecutive patients were enrolled in a 5 months period (May-September 2012).

This means that each operator would have taken at least 10 months to reach the expertise, for a total of 30 months for the three operators, and the training would have started in 2009.

Even considering this likely, the authors should have provided at least the total number of intubations and the training period for supporting their expertise with the three VLS, as suggested by Behringer in 2012 2 and by Cortellazzi in the 2014.3

In our opinion, the authors should have also taken into consideration the evidences from the recent literature that are missing.

References

LETTER TO THE EDITOR

Videolaryngoscopy offers us more than classic direct laryngoscopy

A. A. J. VAN ZUNDERT¹, B. M. A. PIETERS²

¹Department of Anesthesia and Perioperative Medicine, Royal Brisbane and Women’s Hospital, Brisbane, Queensland, Australia; ²Department of Anaesthesiology, University Hospital of Leuven, Leuven, Belgium

Dear Editor,

Thank you for allowing me the privilege to respond to the questions posed by Drs. Caldiroli and Orena ¹ in relation to our recent publication ² in this journal.

While authors should do their utmost to provide the latest literature, this is not always possible due to the delay between submission and publication dates. Hence, at the time of acceptance of our paper, the cited publication ³ was not yet available, and we considered another cited publication ⁴ of no additional value to our paper.

We thank Caldiroli et al.⁵ for demonstrating less muscular activity and perceived workload with the use of the GlideScope® compared to classic direct laryngoscope. However, we regret that only one videolaryngoscope was used. The results of their current study do not surprise us, since the oral, pharyngeal and laryngeal axes have to be brought in one line when performing direct laryngoscopy using a Macintosh blade, requiring more force. Having to bring these axes in one line has a bigger implication than “only pushing the soft tissue for passing the tube”.¹ With videolaryngoscopy these axes do not need to be brought into one line, and so significantly less force is applied to the maxillary incisors.²

We fully agree with Drs. Caldiroli and Orena¹ that only experienced clinicians with equal expertise should execute studies. The three clinicians involved in our study ² have been using the three videolaryngoscopes (C-MAC®, GlideScope®, McGrath®) extensively on a daily basis. The authors’ experience with videolaryngoscopy ranges from 1000 to >4000 clinical cases in the operating theatre plus regular practice and studies on manikins.

We disagree with Drs. Caldiroli and Orena¹ that the abandonment of the stylet for fear of soft tissue injury is the proof that the expertise was not yet reached with either the GlideScope® or McGrath® videolaryngoscopes. We based our decision precisely on our long-time experience with both videolaryngoscopes and, more importantly, proved that even without stylet, endotracheal intubation with both GlideScope® (39%) and McGrath® (40%) is possible.²

The reasons why it took several months to complete our study² were not due to a lack of expertise but merely to its particular setting (special equipment to measure pressure exerted), the availability of the correct team (experienced staff member, research nurse and specialised technician), and the availability of the videolaryngoscopes for research.

We agree with Cortellazzi et al.³ that frequent practice is essential to maintain expertise. We therefore plea for routine use of videolaryngoscopy for endotracheal intubation in all cases.

It is time to discourage the use of less successful - potentially blind - direct laryngoscopy. The anesthesia community now has to prove which blade design is most optimal. Indeed, all videolaryngoscopes provide a better laryngeal view, but this does not necessarily result in an easy and successful intubation. In our opinion, anesthetists would benefit from blades designed so that they provide sufficient illumination for good visualization at the distal end of the blade (e.g. Macintosh design) and which create more room, necessary for intubation and use of adjuncts (e.g. Magill forceps, bougie).

References


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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## TOP 50 MINERVA ANESTESIOLOGICA REVIEWERS

Most active reviewers between January 2015-June 2015

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