Survival in out-of-hospital cardiac arrest

Survival

Public/other
Place of residence

Days after cardiac arrest

P<0.001
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EDITORIAL

Hemadsorption in cardiac surgery: myth against reality

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Cardiopulmonary bypass (CPB) surgery determines an unpredictable activation of a systemic inflammatory response induced by extrinsic and intrinsic factors.1, 2 Once activated by the extracorporeal circuit, this may lead to a dysregulation of inflammatory homeostasis, with increased levels of both pro-inflammatory — interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α) — and anti-inflammatory — IL-6, IL-8, IL-10 — plasma mediators.3-7 Both an excessive increase of pro-inflammatory plasma cytokines and an imbalance of pro- and anti-inflammatory mediators seem predictive for postoperative organ dysfunction and major complications, such as postoperative infection rates, mechanical ventilation need, prolonged postoperative course, thus for an unfavorable outcome.4, 8

The elimination of both pro- and anti-inflammatory cytokine is supposed to reduce not only the inflammatory response but also the eventual immune imbalance; indeed, small molecules as cytokines may be eliminated by adsorption depending on their plasma concentration using the hemadsorption technique,9 with a possible improvement of cardiovascular function. The imbalance between pro- and anti-inflammatory mediators derived from on-pump surgery has been the target of various studies evaluating the effects of blood purification; these therapies include endotoxin adsorption, ultrafiltration and lipopolysaccharide adsorption but, despite safe and well tolerated, no consistent results on mediator removal or outcome were demonstrated.10-12 Among the proposed strategies, extracorporeal sorbent hemadsorption (HA) is approved in the European Union and indicated for various clinical situations with elevated cytokine levels, having demonstrated to be technically feasible and effective for cytokine absorption.13-15 HA is supposed to reduce the inflammatory response, as molecules smaller than 55 kDa, such as cytokines, are adsorbed depending on their plasma concentration. In this way, the Cytosorb® adsorber (Cytosorbents Europe GmbH, Berlin, Germany) eliminates most of the released cytokines.9 HA on CPB is feasible and safe; beside experimental and clinical data in sepsis, limited data is available on its effects on the inflammatory response after cardiac surgery.15-21 Except for some positive case reports,22, 23 the first randomized study on CPB by Bernardi et al. showed no differences of pro-inflammatory cytokine levels when HA was compared to the standard of care, despite a noticeable reduction of absolute levels within the first 24 hours.24 Nevertheless, this study lacked both hemodynamic monitoring and any goal-directed intraoperative management, making it unfeasible to objectively assess procedure-related volume and hemodynamic variations.25
Several uncertainties thus remained not only on the impact of blood purification on the cardiovascular (CV) system and outcome patients submitted to CPB, but also, on the optimal technique to be used (intensity of therapeutic support and effects). As far as HA is considered, a large prospective ongoing study (RECCAS) will hopefully provide new insights on this topic in the near future. In this issue of Minerva Anestesiologica, Garau et al. present the results of an exploratory single-center, randomized controlled trial which prospectively evaluated the effects of HA on CPB on IL-6, IL-8, and TNF-α levels and hemodynamic status during elective on-pump cardiac surgery patients. The authors found that after a cytokine increase during and at the end of surgery, IL-8 and TNF-α levels were significantly lower after weaning from bypass, compared to the control group, with a difference within the time trend. They proposed that HA could support CV recovery as it was associated with an increased cardiac index immediately after surgery. Being the first study showing a reduced pro-inflammatory response with HA on CPB, the authors suggest that HA could be a relevant therapeutic option to temporarily reduce the inflammatory imbalance and to improve CV performance after CPB. The authors’ approach may be of interest for the scientific community, as they used a 300-ml/min perfusion rate of the CytoSorb™ cartridge compared to the previously-adopted 200 ml/min and as they performed a goal-directed fluid/volume therapy via a pulse-contour and transpulmonary thermodilution technique to objectively and individually optimize patient’s fluid/volume balance to minimize confounders on the hemodynamic effects of HA or hemodilution of cytokines.

However, some important issues need to be discussed to better understand the impact of such exploratory findings in the clinical management of cardiac surgery patients. First of all, it is difficult to merely conclude that these data support a routine use of HA in this context, because of the objective technical limitations of the study design. The authors chose a population submitted to medium complex cardio-surgical interventions with an estimated CPB time of 120 minutes, which may be too short to allow a significant reduction of cytokine levels and could explain the short-term effect; indeed, in all previous conducted studies and case reports the treatment time was at least four hours up to four days. If on the one hand, their target population represents a frequent one, on the other hand, the study does not allow to draw conclusions on the efficacy of HA in extended cardio-surgical procedures. Furthermore, during HA cytokines are supposed to be eliminated depending on their plasma concentration; the pro-inflammatory cytokine load in patients with septic shock is above those of elective cardiac surgical patients and HA was performed for longer (days) and not just hours; thus patient category selection and HA duration might encounter for differences which were observed only in the first hours after CPB weaning. Last, no measurement was performed for anti-inflammatory mediators as IL-10, allowing no comparison with previous trials on this topic. Second, despite randomization, caution should be taken with respect to all the possible confounding factors: those risk factors which are not evaluated with the EuroSCORE II and those related to the single blinded character of the study, being the medical team aware of the treatment allocation. Furthermore, the Authors did not monitor the preoperative use of non-steroidal anti-inflammatory drugs (e.g. aspirin), statins or metformin which may have anti-inflammatory effects.

Third, only 40 patients were subjected to the analysis of primary and secondary outcome, with all the limitations related to the small sample size, mostly the impossibility to detect minimal changes and to evaluate the procedural influence on morbidity and mortality. Indeed, both this study and the one by Bernardi et al. were not powered to assess the effect of HA on clinical outcome.

Fourth, some substances which may be eliminated by HA were not measured: free hemoglobin and myoglobin, whose increased levels may contribute to the pathogenesis of cardiac surgery-associated acute kidney injury and damaged endothelia glycocalyx products, such as syndecan-1, hyaluronan and heparan-sulphate.
This information could have been of interest, mostly for organ dysfunction assessment.

Last, when evaluating CV function and outcome, HA patients needed less vasopressor support for achieving the target mean arterial pressure, had a significantly higher Cardiac Index and lower Extravascular Lung Water Index after CPB weaning. Despite the absence of statistical significance, patients allocated in the study group received more fluid (both crystalloids and colloids) in the intraoperative period and remained longer in the ICU, compared to the control group (76±42.6 vs 51.1±21.1 hours, respectively). What is more, despite the pulse contour and transpulmonary thermodilution management, which was carried out before and after cardiac arrest, little information is provided about the precise CPB hemodynamic monitoring and management.

Thus, Garau et al.27 have contributed new findings on the clinical effects of blood purification strategies on the management of cardiac surgery patients. Future prospective research should aim to better understand the potential mechanisms and effects of hemadsorption during CPB and to clearly identify which patients and interventions would benefit more from such therapeutic option. Also, the impact of a standardized protocol of hemodynamic optimization on the effectiveness of this kind of blood purification and the occurrence of organ dysfunction should be further characterized.

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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Predictive models in clinical practice: useful tools to be used with caution

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Diagnostic and prognostic predictive models, aimed at calculating the probability of occurrence of a certain event (disease or its evolution), are frequent in biomedical literature 1 and in clinical guidelines for formal risk assessment. So, the necessity of their systematic reviews led to the formation of the Cochrane Collaboration Prognosis Reviews Methods Group, 2 which developed and validated search strategies for identifying prediction model studies. 3

Then, a Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) 1 has been designed, followed by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines. 4, 5

A search for “predictive” or “prognosis” or “risk factors” or “diagnosis” in the title of the original articles published on Minerva Anestesiologica from 2013 to 2017 returned 38 papers on building and eight papers about the validation of a predictive model. Furthermore, a review on the design, statistics, interpretation, and validation of the predictive models for postoperative pulmonary complications has been recently published 6 with an editorial 7 emphasizing their clinical impact.

Indeed, the actual question is: how much can these predictive models be considered as useful tools for the clinical practice? For an overview of the statistical methodology the readers are referred to a Tutorial in Biostatistics by Harrell et al. 8 and to four British Medical Journal papers mainly tackling the general methodology of these studies. 9–12

First of all, predictive models must come from properly planned ad-hoc studies (prospective “multivariable” cohort observational studies, being randomized trials affected by the presence of the treatment although not statistically significant). Then, patients have to be consecutively selected according to well defined inclusion/exclusion criteria for having a sample with the best possible representativeness of the target population, which must also be as wide as possible by including broad clinical scenarios. Furthermore, the recorded variables must be able to best characterize the phenomenon of interest and have to be used the best validated methods of measurement for which the properties of accuracy, precision, repeatability and reproducibility have to be fulfilled. Finally, “hard” (i.e., objective) variables should be preferred to “soft” (i.e., subjective) variables.

The requirement of an adequate sample size is a particularly relevant aspect taking into account that problems arising from data-dependent
selection, goodness of fitting, validation, etc. can be exacerbated by small sample sizes. The frequently used criterion of at least ten events per variable (EPV) to be included into the predictive model has indeed to be considered as a very lowest threshold and, actually, not satisfactory.

Harrell et al.\(^{13}\) concluded that for regression modelling the EPV should be at least ten times the number of potential prognostic variables that could be included in the model. Peduzzi et al.\(^{14}\) showed that an EPV equal to 10 has to be considered a minimum. Finally, Feinstein\(^{15}\) suggested that an EPV of 20 is safer. It must to be pointed out that most published studies do not meet the above criteria.

Many statistical procedures can be used to build a predictive model: from the traditional regression models (multiple linear, logistic, Cox’s proportional hazard regression) to the recent methods of regression trees (CART), neural networks, machine learning techniques that, however, seem to not bring any consistent advantage.

It is not possible to consider here the pros and the cons of these statistical methods: each of them has its strengths and weaknesses, but, generally, all can be useful and usable if the prediction obtained is accurate for groups of patients or for individual patient. Indeed, according to Burstein,\(^{16}\) “Usefulness is determined by how well a model works in practice, not by how many zeros there are in the associated P values.”

It has to be pointed out that predictive models have to pass two steps. Firstly, the internal validity is assessed on the same dataset used to develop the model by obtaining the “apparent performance,” which obviously tends to be overestimated, and consequently biased. Secondly, and more relevant, the external validity has to be assessed on different validation samples. To these aims, a number of predictive performance measures and statistics have to be evaluated graphically and/or by formal statistical tests: goodness of fitting, calibration (“how well the predicted risks compare to the observed outcomes”), discrimination (“how well the model differentiates between those with and without the outcome”), classification measures (notably, sensitivity and specificity), and reclassification measures (such as net reclassification improvement).

In this issue of *Minerva Anestesiologica*, Ranucci et al.\(^{17}\) present a retrospective analysis of hemodynamic data to assess discrimination and calibration properties of the Hypotension Probability Indicator (HPI) for prediction of hypotensive events in 23 patients undergoing vascular and cardiac surgery. Cardiovascular patients are quite often expose to intraoperative hemodynamic derangements (e.g., cardiac arrhythmias, impaired myocardial contractility, changes in preload and afterload due to blood loss or systemic inflammatory reaction), which occur with arterial hypotension and potential postoperative complications.

HPI is obtained by a machine-learning approach and its development and external validation has been recently published by Hatib et al.\(^{18}\) These authors declared that HPI has a very satisfactorily performance, but they did not explain the statistical details for calculating the coefficients (unknown for patent reasons) of the variables. On the contrary, Ranucci et al.\(^{17}\) in the validation part of their paper reported that the HPI algorithm had a poor calibration performance not even satisfying the first step of the goodness of fitting assessment of a prediction model.

A fundamental point is that without an external validation, a predictive model should be used very cautiously in clinical practice and, particularly, in different institutions. So validation studies are mandatory and, even if sample size rules are not well established, they have to be carried out with a minimum of 100 events and ideally 200 (or more) events,\(^{19}\) or a minimum of 100 events and 100 non-events and 20 participants per predictor in the case of continuous outcomes.

More challenging than the usual statistical methods are the frequentistic and Bayesian procedures aimed to build a prognostic model from repeatedly measured independent variables as predictors and a fixed outcome.\(^{20}\) Of course, repeated measurements would provide more information about the variable’s trajectory over the time than just a single measurement. However, among other things, it has to be taken into account the correlation among the measures and the fixing of a time lag between the measurements and the event of interest.

Sophisticated statistical techniques together
with the involvement of a professional statistician are also required for jointly considering, as in Ranucci et al.17 paper, repeated measures of a predictor and the possible occurrence of multiple events per subject (hypotensive episode) in which both assumptions of independence of the predictor and of the events are not fulfilled.

Readers have to be well aware that the application of sophisticated statistical techniques is not sufficient to confer validity to a predictive model; indeed, we may, rather provocatively, state that the (mis)use of the statistical methods would allow one to demonstrate almost everything.

A rule of thumb to suggest to readers for disregarding a paper about a predictive model is when the above outlined criteria for assessing the internal/external validity are missing. An even more definitive/external negative judgement is when sensitivity or specificity confidence intervals have the lower limit less than 0.5 or when it is not reported, to avoid showing that a predictive model is equal to the toss of a coin.

Indeed, it is precisely in this area that the statistical and clinical aspects should play an integrative role, requiring that a predictive model is valid only if it has passed tests of statistical validation and of utility in clinical practice.

The limited sample size of patients enrolled in the study by Ranucci et al.,17 even if the number of events is similar to the one recommended for independent events,19 allows to stress the fact that building and validating predictive models have to be carried out with large sample sizes, without being satisfied with the lower values reported in the statistical literature. Finally, it has to stress the obvious fact that 100 events occurring on the same subject cannot be a satisfactory basis for validating a predictive model at the same way as 100 events occurring on 100 subjects.

In conclusion, Ranucci et al.17 are to be commended for having focused on the value of HPI in cardiovascular surgery patients, in whom intraoperative hypotension is frequently observed due to bleeding, reduced ventricular function, and systemic vasodilation. However, as the authors stated in their article, a homogenous approach to the statistical methodology is strongly recommended, especially in HPI validation studies. We agree with that statement. Indeed, the question about HPI is still open and requires further validation studies.

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The unresolved problem of how to improve the prognosis of out of hospital cardiac arrest at place of residence

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Investigating the outcomes of cardiac arrest (CA) remains the only available way to assess the clinical significance and weight of each ring of the cardiopulmonary resuscitation (CPR) chain. The paper by Andréll et al.1 published in this issue of Minerva Anestesiologica includes a post-hoc analysis of the Targeted Temperature Management after cardiac arrest trial (TTM trial) and it aims at analyzing whether location of arrest was associated with outcome in a selected group of initial survivors admitted to intensive care. Place of residence was a common location of out of hospital cardiac arrest (OHCA) and it was independently associated with poor outcome.2

One feature that should be considered to correctly interpret the results of the investigation by Andréll et al.1 concerns the sample of selected OHCA patients, which represents about one-fourth of the entire population, which could not be completely characterized since the full Charlson Comorbidity Index was not calculated.

However, this topic has not been extensively investigated to date3,4 though Utstein gives great importance to the setting of cardiac arrest5-7 being able to influence the timing of initiation of the CPR maneuvers, that is the low flow period.

The place of residence of OHCA has pathophysiological and organizational implications.8,9 It is intuitive that if the system effectively holds the timing and modalities of CA onset, it is possible to more accurately determine the usefulness of the “new indicators” of perfusion, such as the trend of CO2 during CPR and the evaluation of lactates in the reperfusion phase and this can only be achieved by maintaining, as controlled, a perfusion pressure and then by taking care of emergency medical personnel. Over the years the most unexplored rings of CPR chain have been those related to the alerting of the emergency system and overall to the prehospital phase. The place of residence is in most cases a closed place hardly accessible to emergency services.

According to the study by Andréll et al.1 patients with cardiac arrest at home in whom the causes of OHCA are not known receive significantly less bystander-CPR than OHCA in public or other places. This finding qualifies a critical initial condition characterized by a phase of no-flow certainly more prolonged and, more importantly, by all prehospital time intervals significantly longer.8,9

This is an apparently unsolvable problem if not foreseeing its possible mitigation in metropolitan areas where the arrival times of services are faster, and this is an aspect that should probably be explored better. In this perspective a useful indication to act more on other aspects that provide, in non-metropolitan areas, interventions which aim mainly to identify subjects with CA risk factors, train citizens and bystanders and guarantee the implementation of systems of anticipation and prevention of cardiac arrest, use of telemetry systems and transfer of critical data that can be processed and anticipated.

Moreover, the implementation of specific training programs targeting bystanders may rep-
represent a promising tool for ameliorating the prognosis of place of residence OHCA. Overall research on the prehospital phase of OHCA should gain renewed interest from the scientific community, specifically in terms of assessing epidemiological differences in outcomes between metropolitan and rural areas.

Also from an ethical point of view the emergency systems cannot ignore many of the findings of the study by Andrèll et al.:² prehospital time intervals were significantly longer in patients arrested at a place of residence and all crucial time intervals (no-flow, low-flow, time to ALS, time to ROSC) were all significantly longer. ROSC was one of the significant predictors in the multivariable regression analysis. It is therefore undoubted that OHCA location influences the final outcomes regardless of the correct application of the CPR. Consequently, the key problem is related to the time of first contact between emergency professionals and OHCA setting. Interestingly most of the at home cases are recorded in the range from 6 pm to 6 am and associated with a longer intervention time at night compared to daylight hours, prefiguring an organizational problem. Finally, OHCA patients at residence place were less frequently submitted to coronary angiography, and it cannot be ruled out that this factor may have contributed to the poor prognosis of this subset of patients. The post resuscitation care of OHCA includes coronary angiography, which was associated with improved survival, as recently reported in large cohort series as well as in meta-analysis.¹⁰⁻¹³

The CPR chain continues to be poorly explored by the Registries but it is evident that bystander-CPR and emergency care can severely condition post-CA therapeutic strategies, such as patients’ eligibility for angiography procedures and in addition, opening new perspectives in the maintenance of organ perfusion, in the absence of ROSC, potentially useful also in the context of organ procurement.

References
Pain in trauma patients at the emergency department: expert operators should take care of it

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Acute pain management of patients with musculoskeletal trauma at the emergency department (ED) represents a challenge for the anesthesiologist. There is indeed uncertainty about how and when to start the treatment of pain after major trauma because patients may be clinically unstable and incapable of describing the degree of their pain due to impaired consciousness (e.g. brain injury, intoxication) or clinical conditions (e.g. orotracheal intubation).

Acute musculoskeletal pain is a vital sign, but it is often undertreated in pre-hospital settings and at EDs. The “chaos” of the rescue scene and the need to stabilize and optimize the clinical conditions of these patients at the ED in the shortest possible time are the main reasons leading to the postponement of pain treatment. It has been shown that less than 50% of the trauma patients receive a treatment for acute pain in ED, and even less in the prehospital. Hodynamically unstable patients are less likely to receive pain treatment than stable ones. This is not surprising, since the opioids are the most used drugs for pain treatment in trauma patients at ED, and in some circumstances, they can affect hemodynamics and worsen oxygenation.

In addition, in patients presenting with head injury and hemodynamic instability, opioid-related arterial hypotension and low cardiac output may be responsible for cerebral hypoperfusion, especially in the ED, where advanced neuromonitoring tools are not available. Following stabilization at ED, trauma patients are transferred to a given department (e.g. orthopedic ward), to intensive care unit (ICU), or operating room (OR) to undergo urgent surgery. In intubated patients requiring general anesthesia or admitted to ICU, analgesia with opioids alone or in combination with other drugs can abolish the pain, improve the discomfort, and may modulate intracranial pressure in traumatic brain-injured patients.

The Italian Intersociety Recommendations on pain management in the emergency setting suggest minimizing the use of opioids in favor of their association with non-opioid analgesic drugs. On the other hand, non-opioid analgesics (e.g. non-steroidal anti-inflammatory drugs) may expose the patient to other risks, such as bleeding. Conversely, the regional anesthesia (RA) technique represents a safe anesthetic approach to this end, as it is gaining popularity as a component of multimodal approach for pain management in injured patients.

RA is particularly important when patients with musculoskeletal trauma are transferred from ED to other departments than ICU, where the unavailability of advanced cardiovascular and respiratory monitoring and the lack of an anesthesiologist may expose the patient to opioid-induced adverse effects (e.g. respiratory depression, arterial hypotension).

In this issue of Minerva Anestesiologica, Sa
ranteas et al.\textsuperscript{12} emphasize the role of RA as a component of the multimodal pain treatment in traumatic patients. The authors are to be commended because they reviewed the RA techniques employed in musculoskeletal trauma and provide a useful iconography and video clip of echography of peripheral nerve block techniques that can be employed in trauma patients. Also, they analyzed the principal controversies regarding RA in managing acute pain of trauma patients and highlighted echography as a useful tool for this type of anesthesia. From our point of view, there are some issues about this topic that deserve to be further highlighted.

Firstly, the incidence of opioids-related adverse events leads to a significant increase in morbidity and mortality. Conversely, RA represents a key component of multimodal analgesia that guarantees excellent pain control, reduces the use and dose of opioids and is associated to a better outcome.\textsuperscript{4, 10, 13} In particular, the modern RA techniques are performed with special percutaneous catheters that allow obtaining a continuous peripheral nerve block and an opioid-sparing pain management.\textsuperscript{1, 14, 15} These RA techniques allow exploiting the analgic effects of RA throughout the clinical pathways of the patients, from the ED to any department, including OR, while paying attention to potential complications such as infections or anesthetic toxicity, as described by Saranteas et al.\textsuperscript{12} Although RA can potentially be performed anywhere, that is, outside the operating room, its main limitation is the need for an expert operator to perform it.

Secondly, the role of ultrasound in RA deserves particular comments. Studies on ultrasound-guided RA to control the pain in trauma patients, including those admitted to ED, are very scarce. A meta-analysis including 13 randomized controlled studies conducted on different types of nerve blocks showed a higher rate of block success, a faster onset and progression of block, and a procedural time saving using ultrasound rather than peripheral nerve stimulator (PNS) as guidance to RA.\textsuperscript{16} Complications, such as vascular puncture during block performance, are lower using ultrasound technique.\textsuperscript{16} Conversely, it seems to be more difficult to compare ultrasound and PNS as guidance to RA in terms of major adverse effects (\textit{i.e.} persistent neurological injury or systemic local anesthetic toxicity) because these have a very low incidence rate.

Indeed, Auroy et al. in mixed cases of RA reported an incidence rate of major complications related to anesthetic technique of 0.035%,\textsuperscript{17} and similar findings were reported by others.\textsuperscript{16} As a consequence, it is very difficult to prove that ultrasound-guided RA is associated with fewer complications compared with other techniques of nerve identification. However, the advantage of direct visualization of the nerve makes the use of ultrasound increasingly appreciated in the era of the modern anesthesia.\textsuperscript{17, 18}

Finally, two categories of trauma patients deserve some special considerations: 1) sedated or unconscious patients, and 2) the ones with rib fractures. Regarding the first category, as stated by Saranteas et al., there are no adult randomized studies comparing the effects of RA in anesthetized or awake patients.\textsuperscript{18} However, some data are available from pediatric registries. In a prospective study including 100,000 nerve blocks of various types in children under general anesthesia, no major complications related to RA have been reported. The incidences of neurologic deficit and local anesthetic toxicity after RA were 2.4 per 10,000 and 0.76 per 10,000, respectively.\textsuperscript{19} The authors also showed that the use of ultrasound-guided RA increased over the years, with a decrease of neurologic complications.\textsuperscript{19} Considering that the nerve structures are more vulnerable and that the anatomic spaces are smaller in children, there is no reason to think that in adults, the findings would be different. Patients with rib fractures are at an increased risk of respiratory failure.\textsuperscript{20} Malekpour et al., in a propensity matching study involving 194,766 patients with rib fractures (1073 epidural analgesia, 1110 paravertebral blocks, 192,583 having neither procedure) showed no differences in outcome between the two groups of patients undergoing different RA techniques. Conversely, the patients who did not undergo RA had increased odds of mortality (OR=2.25).\textsuperscript{21} This underscores the pivotal role the anesthesiologist has in managing pain in patients with musculoskeletal trauma since admission to ED.

In summary, pain is a vital sign that the an-
esthesiologist should monitor and manage, starting when the trauma patient presents to the emergency department. It would be desirable for anesthesiologists to increase education and training around pain management in trauma within the multidisciplinary team at the emergency department, as well as playing an early active role at patient admittance. Analgesia, especially in trauma patients, is one of the typical examples of precision medicine in which the anesthesiologist is an expert tailor who has to sew the most suitable dress for “covering the pain” of a given patient.

References


The importance of getting death by neurological criteria right

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There is a broad (though not unanimous) international consensus that brain function is the essence of human life. Therefore, a patient who has irreversibly lost neurological function (usually defined as areflexic apneic coma — which does not demand the loss of pituitary/hypothalamic function nor the loss of every cortical neuron) is dead. In this construct, neurological function is the only essence of human life, so that a patient who has lost circulation and/or respiration is only dead when that loss of circulation/respiration results in the irreversible loss of neurological function. This concept is commonly referred to as “brain death,” but more accurately termed “death by neurological criteria” (DNC). In their paper published in this issue of Minerva Anestesiologica, Robba et al. have quite impressively summarized the current literature and provided state of the art guidance in making accurate determinations of DNC.1

The determination of irreversible loss of function includes two elements: documentation of loss of function, and determination of irreversibility. In considering how to best assure irreversibility and loss of function, it is useful to keep in mind that patients who present in what may be irreversible coma are pathophysiologically diverse. For example, a patient may have overwhelming supratentorial swelling resulting in intracranial pressure (ICP) equal to mean arterial pressure (MAP). In this patient, the loss of function proceeds from supratentorial to infratentorial, so great attention needs to be paid to the apnea and lower cranial nerve testing, as these would be the last functions to be lost. A patient with primary brainstem pathology and relatively preserved cerebral hemispheres on imaging would require EEG testing to assure the absence of organized activity that might imply the presence of consciousness. The documentation of loss of function is but one snapshot in time, and judgement is needed to determine irreversibility. If the amount of parenchymal damage on the imaging is not overwhelming and/or the history is not consistent with an overwhelming likelihood of irreversibility, further examinations are needed to rule out possible return of function. As noted in the paper, those losing function due to hypoxia should be re-examined over time to rule out global ischemic penumbra.5
The choice of ancillary testing needs to be matched to the patient’s pathology. While in the ideal situation no ancillary testing should be needed, testing can compensate for errors in judgment as well as eliminate erroneous determinations that might have been made without it. As noted above (and in the paper), EEG is needed to rule out subclinical cerebral activity in patients where pathology and imaging suggest it may be present. The absence of cerebral blood flow (assuming that there isn’t a reason to expect the blood flow to be rapidly re-established) contributes powerful certainty to the irreversible nature of the clinical determination. It is this author’s opinion that ideally cerebral blood flow (CBF) testing should be done on every patient being considered for DNC.

Combined with the clinical impression of irreversibility and the clinical determination of lack of function, the lack of CBF provides confirmation of irreversibility and the determination of DNC. It should be emphasized that the presence of CBF is not proof of the presence of function nor of reversibility. Patients can have irreversible loss of function (which is due to neuronal damage), yet the rise in ICP (cerebral edema being primarily due to glial cell damage) does not overtake the MAP, and therefore some CBF is preserved. The presence of CBF should be seen not as proof that the patient is not DNC, but as an impetus to re-evaluate the clinical assessments of both the loss of function and determination of irreversibility, and in some cases result in further assessments or testing. If, after being certain of irreversible loss of function despite the presence of CBF, the patient is obviously dead.

This article provides excellent guidance for the determination of DNC. There are some who oppose DNC on philosophical or religious grounds. These are matters primarily of belief, either in some alternate concept of human life or a particular interpretation of foundational religious texts. The space here is not adequate to address the issue in depth, and in matters of belief, appeals to rational arguments are not usually effective. For the purposes here, it is sufficient to note that DNC is accepted by essentially every major medical society that is relevant to DNC, and, perhaps more importantly, I am not aware of any that explicitly reject DNC. Furthermore, DNC is accepted by many traditionalists (and even more of those who interpret their fundamental texts less literally) in the three major Abrahamic religions (Christianity, Judaism, and Islam) as well as Eastern (Buddhism, Hinduism) and other religions. For those who choose to use it (and I would encourage all to do so), this article provides the practitioner with all the practical tools needed for determining if patient is alive or dead based on the concept of DNC.

References

End stage liver disease: a delicate balance of bleeding and thrombosis

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It is well known that the coagulation processes may be seriously altered in end-stage liver disease (ESLD). Historically, hepatatopathic patient has always been considered auto-anti-coagulated; however, recent acquisitions have led to considering this patient “rebalanced” towards a condition of labile and delicate hemostatic balance, due to a concomitant decrease of procoagulative and anticoagulative factors.1, 2 These problems become more relevant in the case of surgical procedures and, even more, during liver transplantation (LT), a procedure that may be associated with large fluid shifts, huge blood losses and major hemodynamic changes.3, 4

The introduction in the clinical practice of the policy of prioritization of MELD as concerns the allocation of organs (sickest first) has made these problems more evident due to the need to treat increasingly serious patients.

The recent presentation of the position paper by the LICAGE group published in this issue of Minerva Anestesiologica is, therefore, particularly indicated and useful in providing updated recommendations concerning the perioperative hemostatic management of cirrhotic patient.5 Unfortunately, at present, few recommendations reach a highly convincing evidence according to the “evidence based medicine”, a phenomenon, however, quite frequent in medical disciplines. The paper covers the most important topics of coagulation in the cirrhotic patient, presenting new laboratory coagulation tests and illustrating the limits of the currently used ones, both conventional and viscoelastic.

While traditional coagulation tests are inaccurate in predicting the likelihood of bleeding in liver failure patients, the viscoelastic ones have emerged as an important means of analyzing clotting function in real time using whole blood; this type of test can overcome some limits of conventional coagulation ones, taking into consideration also some anticoagulation factors; moreover, viscoelastic-guided transfusion algorithms may allow a reduction in blood product administration.4, 6 In addition to a “point of care” evaluation, viscoelastic tests allow to rule out the principle according to which an altered coagulation test (PT, INR or aPTT) necessarily corresponds to a greater risk of bleeding.6 On the other hand, randomized clinical trials involving patients with chronic liver disease have shown that procoagulant agents fail to control bleeding during liver transplantation, even though the postinfusion prothrombin time is considerably shortened.7
It is obvious that while representing this position paper a decisive step towards a more rational management of the blood coagulation process in the cirrhotic patient, further developments are to be expected. In particular, the improvement of the pathophysiological knowledge of hemostasis may lead to the definition of new coagulation tests more adherent to the patient’s clinical reality, limiting the risk of bleeding as well as of thromboembolic events.\textsuperscript{8, 9} Indeed, as pointed out by the LICAGE group, the bleeding risk of the cirrhotic patient is not only linked to hemostatic problems, but is also related to the surgical techniques adopted (temporary portocaval shunt, piggyback technique, venovenous bypass and so on), as well as to anesthesiological management, with particular reference to the fluid therapy management and the adequate use of vasoactive drugs. In this connection, an unrestricted volume load can increase the splanchnic and portal pressure, and, at the same time, the tendency to bleeding by activating a dangerous vicious circle.\textsuperscript{11} Indeed, the need for transfusions during LT has declined considerably over time, not because of any substantial change in medication, but rather because of improved surgical procedures and anesthesiological management of the patients.\textsuperscript{3, 4} Furthermore, the continuous aging of the liver transplant patient population has led to new clinical problems, such as the need to treat patients with cardiovascular diseases undergoing anticoagulation and/or antiplatelet therapy. Cardiovascular disease remains one of the major causes of morbidity and mortality in end-stage liver disease; recent evidence has proved a coronary artery disease (CAD) prevalence of up to 27\% in patients with cirrhosis, and it continues to increase with age. Listing for LT in patients with known CAD remains a challenge. However, as demonstrated by Satapathy \textit{et al.}, post-transplant survival in LT recipients with revascularized CAD is independent of the number of vessels with CAD or severity of CAD. These patients, if appropriately revascularized, can safely undergo LT and have post-transplant survival comparable to non-CAD patients.\textsuperscript{12}

Finally, even if the development of new laboratory tests is highly desirable to better define the coagulative pattern of the cirrhotic patient, the clinical evaluation and a careful anesthesiological management always remain fundamental in order to avoid from one side the bleeding risk and from the other side the occurrence of a thrombosis.\textsuperscript{1}

Currently, a watchful waiting approach seems to be optimal in non-bleeding patients, since the risk of thrombosis can be considered as dangerous as bleeding in these patients, and therefore, the maintenance of the newly formed balance in the hemostatic process is of significant importance.\textsuperscript{1, 3}

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Hemadsorption during cardiopulmonary bypass reduces interleukin 8 and tumor necrosis factor α serum levels in cardiac surgery: a randomized controlled trial

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ABSTRACT
BACKGROUND: Surgical trauma and cardiopulmonary bypass (CPB) are associated with the liberation of pro-inflammatory cytokines. With hemadsorption (Cytosorb®) during CPB, pro-inflammatory cytokines may be reduced and the inflammatory response may be decreased.

METHODS: In this prospective, randomized single center study, serum cytokine levels of interleukin 8 (Il-8), interleukin 6 (Il-6) and tumor-necrosis-factor α (TNFα) were assessed in elective on-pump cardiac surgery patients with hemadsorption on CPB (study group [SG], N.=20) and without (control group [CG], N.=20). Cytokine levels were assessed prior to CPB, at the end of CPB, and 6 hours (h) and 24 h after the end of CPB, together with a hemodynamic assessment. Cardiac-Index (CI) was assessed with transcardiopulmonary thermodilution.

RESULTS: For Il-8, significantly lower serum levels were observed in the SG compared to the CG at the end of CPB (P=0.008). In the SG, TNFα levels were also below those in the CG at both the end of CPB (P=0.034). After 24 hours, TNFα levels were at baseline in both groups. No significant differences were found for Il-6. The CI was significantly higher in the SG at the end of CPB (P=0.025). However, there was no difference between both groups 6 h after CPB.

CONCLUSIONS: This prospective study shows a significant reduction in pro-inflammatory cytokine levels of Il-8 and TNFα with hemadsorption in on-pump cardiac surgery whilst also demonstrating safety in its applications. However, the differences in cytokine levels and CI between patients treated with hemadsorption and those without were minor and of short duration.


Key words: Cardiac surgical procedures; Cardiopulmonary bypass; Hemadsorption; Cytokines; Inflammation.

Cardiac surgery is associated with the liberation of pro-inflammatory and anti-inflammatory cytokines and activation of the complement, endothelium and cellular immune systems.1, 2 Pro-inflammatory cytokines that increase immediately after surgery are II-1β and TNFα. II-8 and II-6 increase later in the postoperative period and peak between three h to 24 h after surgery.1, 2 In cardio-
Thoracic surgery, IL-6 is related to the degree of the surgical trauma, whereas IL-8 seems to be specifically expressed following cardiac surgery. An excessive increase of pro-inflammatory plasma cytokines is associated with an unfavorable outcome. For example, increased postoperative infection rates were observed in patients with high IL-6 levels. Not only the increase in pro-inflammatory cytokines but also an imbalance of pro- and anti-inflammatory cytokines seems predictive for unfavorable outcomes in cardiac surgery.

Hemadsorption (the eliminating of pro- and anti-inflammatory cytokines) is supposed to reduce the inflammatory response, as molecules smaller than 55 kDa, such as cytokines, are adsorbed depending on their plasma concentration. In this way, the Cytosorb® adsorber (CytoSorbents Europe, GmbH, Berlin, Germany) eliminates most of the cytokines released in cardiac surgery and sepsis. There are many case reports on the use of hemadsorption in septic patients and postcardiopulmonary bypass systemic-inflammatory-response-syndrome (SIRS), in which plasma cytokine levels and cardiovascular function improved following hemadsorption. First reports on the use of this therapy in combination with extracorporeal membrane oxygenation (ECMO) were also positive, however, the first randomized study in elective on-pump cardiac surgery observed no superiority of hemadsorption during cardiopulmonary bypass (CPB) compared to standard care.

Therefore, this single-center, randomized controlled pilot-study investigated whether pro-inflammatory cytokines (primary endpoint) were reduced by hemadsorption with a Cytosorb® adsorber in patients undergoing elective cardiac surgery using CPB compared to a control group (CG) without hemadsorption. Cardiovascular function during goal-directed fluid management was the secondary endpoint.

Materials and methods

Study design and study population

This study was performed as a single-center randomized, controlled trial. After approval by the local government ethics committee (Ethics Committee Hamburg Medical Board, protocol-number PV4420, date of approval 08.07.2013) and after obtaining written informed consent, 43 patients scheduled for either coronary artery bypass grafting, aortic valve replacement or a combined procedure, with an expected CPB time of more than 120 min, were prospectively recruited. Twenty-two patients were randomized into the CG without the hemadsorption device and twenty-one patients were allocated to the study group (SG) in which hemadsorption was performed during CPB. Randomization was performed on the day of the surgery. A sealed envelope was drawn to determine which group the patient would be assigned to (Table I).

Exclusion criteria were an age of less than 18 years, a Body Mass Index (BMI) of less than 18 kg/m², pregnancy, atrial fibrillation, use of immunosuppressive medication, leukopenia, emergency and urgent surgery, rethoracotomy, serum creatinine of more than 2 mg/dL, transplant surgery and refusal of written informed consent. The study began in September 2013 and ended in June 2015.

The EuroSCORE II (European System for Cardiac Operative Risk Evaluation) was documented. It is a model for calculating the peri-operative mortality risk in cardiac surgery. Pre-existing illnesses and the planned operation are included in the calculation and evaluated by means of a logistic regression analysis.

Anesthesia and hemodynamic management

According to institutional guidelines, each patient received 30 mg of flurazepam p.o. on the evening before surgery and 7.5 mg of midazolam p.o.
minutes before induction of anesthesia. Standard monitoring and an arterial line were established and anesthesia was induced with 0.7 µg/kg ideal body weight (IBW) sufentanil, 1 mg/kg IBW propofol and 0.1 mg/kg IBW pancuronium. All patients were intubated and mechanically ventilated with a combination of pressure controlled and volume-controlled modes (Volume-Auto-Flow®) using a Zeus® anesthetics machine (Dräger, Lübeck, Germany) with a tidal volume of 7 mL/kg IBW, and a positive end-expiratory airway pressure (PEEP) of 5 mbar. Oxygen concentration and ventilation frequency were adjusted to maintain normoxemia (>90 mmHg) and normocapnia (35-45 mmHg). Anesthesia was maintained with sevoflurane (end-tidal concentration 1.3 Vol%) and the continuous infusion of sufentanil 0.7 µg/kg/h. Furthermore, a 5-French thermistor-tipped catheter (PV2015 L20, Pulsiocath; Pulsion Medical Systems, Munich, Germany) was inserted into a femoral artery for transcardiopulmonary thermodilution (TCPTD) and arterial pulse-contour analysis (PiCCO; Pulsion Medical Systems). A 7-French triple lumen central venous catheter (CVC) was inserted into the right jugular vein.

CPB was performed using non-pulsatile flow at 2.5 L · min⁻¹ · m⁻², a body temperature of 32 degrees Celsius, a non-heparin-coated circuit, and a membrane oxygenator (LivaNova, Sorin-Group, London, UK). Cardiac arrest was induced by blood-cardioplegia.

Fluid therapy using a balanced crystalloid solution (Sterofundin® Iso, B.Braun, Melsungen, Germany) was guided by stroke-volume-variation (SVV) to target a SVV≤10% intraoperatively. Mean-arterial-pressure (MAP) was maintained above 60 mmHg with norepinephrine. Inotropic support with epinephrine was used during CPB weaning.

After surgery, patients were transferred to the Intensive Care Unit (ICU), where they were extubated following institutional criteria. Procedural times such as duration of surgery, CPB time, time in ICU and hospital discharge time were recorded.

Hemadsorption

For hemadsorption on CPB, a CytoSorb® adsorber (CytoSorbents Europe GmbH, Berlin, Germany) was installed into a parallel arm of the extracorporeal circuit and a blood flow of 300 mL/min was maintained over the period of the CPB time. Safety of this device has been tested prior to this study in an in-vitro experiment showing no relevant thrombocyte or heparin elimination in a CPB system filled with human blood. The heparin concentration was 1.86 U mL⁻¹ at 0 min, 1.82 U mL⁻¹ at 60 min and 1.21 U mL⁻¹ at 120 min bypass time. Previous studies have shown that there is no elimination of physiological blood components by CytoSorb hemadsorption.7, 9, 11

Primary endpoint: cytokine measurements and procalcitonin

Blood samples for measurement of cytokine levels were taken from the arterial line at four time points of measurement: before (M1) and at the end (M2) of CPB, and 6 h (M3) and 24 h after CPB (M4). Serum was obtained from whole blood samples by centrifugation (10 min at 5000 rpm) and was frozen at -80 °C immediately thereafter for later laboratory analysis. IL-8 and TNFα were analyzed by an Enzyme-linked Immunosorbent Assays (ELISA) (ThermoFisher Scientific, Waltham, MA, USA) (TNF Alpha Human ELISA KIT, Ultrasensitive, KHC3013, Sensitivity <0.09 pg/mL), (IL 8 Human ELISA Kit, KAC 1301, Sensitivity 0.7 pg/mL). Serum concentrations were determined by using a multiplate spectrophotometer (MultiSkanSpectrum, Version V1.2, ThermoFisher Scientific). IL-6 and procalcitonin (PCT) were quantified by the central laboratory.

Secondary endpoints: hemodynamic measurements

Pulse-contour and thermodilution derived parameters were recorded after induction of anesthesia until six hours after CPB. Recalibration of the PiCCO-system was performed at time points M1, M2 and M3. The thermodilution derived parameters CI, extravascular lung water (ELWI), global end diastolic volume (GEDI) and systemic vascular resistance index (SVRI) were indexed to the body surface area (BSA). Furthermore, fluid and catecholamine requirements were documented throughout the study.
Statistical analysis and script preparation

Sample characteristics are given as absolute and relative frequencies or mean±standard deviation, as deemed appropriate. Based on an anticipated difference in IL-6 concentration of 25% between the SG and the CG, an α-error of 0.05 and a power of 0.9, a group size of 18 patients would be necessary to detect a significant difference. For drop out compensation, a sample size of 40 patients was finally chosen. All outcome parameters were analyzed separately; if necessary, the parameters were transformed by calculating the logarithmatized values to meet the required model assumptions. Linear mixed models were used to analyze the effect of hemadsorption in comparison to control on changes from baseline to the follow-up time points (FUs). Additionally, the interaction term between group and the FUs were included to estimate potentially different time trends. In the case of an insignificant interaction term, only the main effects group and FUs were included. This decision was met by using the likelihood ratio test for model comparison. Moreover, all models were adjusted for the baseline level of the outcome parameter, age, aortic-cross clamp time, duration of extra corporal circulation and duration of surgery. To take the cluster structure of the data into account, random intercepts for patient were included. For repeated measurements, we applied a first order autoregressive structure. The adjusted results were estimated as marginal means, which are presented in tables and graphs with 95% confidence intervals (95% CI).

All of the models presented available case analyses. A two-tailed P<0.05 was considered to be statistically significant. Nominal P values are reported without correction for multiplicity. All of the analyses were performed using StataCorp Stata 14.

The study complied in accordance with the Consort guidelines.

Results

Demographic data

Forty-three patients were included in this single center interventional study. Two patients were excluded due to extension of surgery and prolonged CPB time (N.=2). Another patient was excluded due to immediate re-operation as a result of postoperative bleeding (N.=1). Data from those patients were not included the statistical analysis. Finally, data from 20 patients randomized to the SG were analyzed (Figure 1). Demographic data and surgical data did not differ between the two groups. Furthermore, there were no differences with respect to intraoperative fluid and total catecholamine requirements (Table II). Based on the evaluation using the EuroSCORE II, the patients in both groups showed no difference in perioperative mortality risk (Table II).

Primary endpoint: cytokine measurements and PCT

In both groups, IL-6 levels increased during and after surgery, showing a peak at six hours after the end of CPB. Twenty-four hours after the end of CPB, IL-6 levels decreased again in both groups. No significant differences in the IL-6 levels either between the CG and SG time trend (P=0.384) or between the groups in general could be determined (P=0.229).

IL-8 levels also showed an increase during and after surgery in both groups, with a non-significantly different time trend (P=0.057). However, there was a difference between the two groups, with a significantly increased IL-8 level in the CG at the end of CPB (P=0.008).

For PCT, no statistically significant differ-
Discussion

In this controlled, randomized pilot study, patients treated with hemadsorption (CytoSorb®) during CPB had significantly lower serum levels of IL-8 and TNFα early after CPB compared to patients without hemadsorption. Furthermore, the use of the CytoSorb™ device was associated with a significantly increased CI after weaning from CPB in the SG compared to the CG.

The use of the adsorber in a CPB system was feasible and safe without any adverse events observed.

In this study, the laboratory analysis focused on cytokines liberated early in the postoperative period following on-pump cardiac surgery.1 Cytokines such as IL-6, IL-8 and TNFα usually peak within the first 24 h following cardiac surgery. In contrast to IL-8 and TNFα, postoperative IL-6 levels were lower only by trend, but not significantly. In summary, this study is showing for the first time a reduced pro-inflammatory response in patients with hemadsorption on CPB. However, the short duration of hemadsorption during on-pump cardiac surgery may explain the short-term effect on pro-inflammatory cytokines. Furthermore, cytokine release is triggered both by cardiopulmonary bypass and surgical trauma, the latter being an ongoing effect.

| Table II.—Demographic and surgical data, fluid and catecholamine requirements. Mean value and standard deviation are presented. BMI is the Body Mass Index. Time in ICU are the hours patients spent on the ICU. ASA class shows the classification according to the American Society of Anesthesiologists risk stratification. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Study group | Control group |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Age (years)** | 67.9 (12.7) | 72.7 (9.2) | 70.9 | 72.8 |
| **Height (cm)** | 173.2 (7.5) | 171 (9.5) | 174 | 170 |
| **Weight (kg)** | 82 (15.4) | 80.5 (18.3) | 80 | 80 |
| **BMI (kg/m²)** | 27.3 (3.8) | 27.6 (5.4) | 26.8 | 26.3 |
| **ASA class** | 3.7 (0.5) | 3.75 (0.4) | 4 | 4 |
| **EuroSCORE** | 6.1 (2.2) | 6.3 (2.9) | 6 | 6 |
| **Mortality index** | 6.6 (5.4) | 8.12 (7.5) | 5 | 5.5 |
| **Amount of norepinephrine (µg) total** | 2349.6 (1747.8) | 2704.2 (2653.7) | 1592.5 | 1834 |
| **Amount of epinephrine (µg) total** | 99.1 (51.4) | 105.2 (90.2) | 90 | 98 |
| **Amount of crystalloid (mL) intraop** | 2986.5 (901.9) | 2790 (955.81) | 3000 | 2750 |
| **Amount of colloid (mL) intraop** | 88.3 (196.5) | 75 (183.2) | 0 | 0 |
| **Duration of surgery (min)** | 259.2 (51.7) | 253 (51.44) | 255 | 242.5 |
| **Duration ECC (min)** | 141.2 (41.1) | 138.6 (40.1) | 133 | 128 |
| **Duration aortic clamping (min)** | 105 (34.4) | 102.2 (29.1) | 100 | 98.5 |
| **Days in hospital after surgery (days)** | 9 (5.2) | 8 (2.5) | 7 | 8 |
| **Time in ICU (hours)** | 76 (42.6) | 51.1 (21.1) | 66 | 47 |
Figure 2.—Changes in serum concentrations of IL6, IL8, PCT, TNFα, GEDI, ELWI, SVRI and CI at the end of cardiopulmonary bypass (CPB), 6 h and 24 after CPB.

The first four graphs show the relative change in serum levels compared to baseline values (after thoracotomy) at end of CPB, and six and 24 hours after surgery. The last four graphs show the relative changes in hemodynamic parameters compared to baseline value after thoracotomy within the study-group (dashed line) and the control-group (continuous line). The continuous line represents the control-group without adsorber and the dashed line represents the intervention-group with adsorber.

P values indicate a statistically significant difference between the both groups (“by group”) or within the group over the study period (“interaction time by group”).
into the early postoperative period. This may explain why the cytokine levels in both groups equalized later on and no difference between the SG and the CG were found after 24 h in this study.

A previous study from Bernardi et al. also investigating hemadsorption with the CytoSorb™ adsorber in elective cardiac surgery, found no significant differences in postoperative pro-inflammatory cytokines such as IL-6 and TNFα. A difference in the perfusion rate of the CytoSorb™ cartridge, 300 mL min⁻¹ in this study versus 200 mL min⁻¹ in the study of Bernardi et al., is one possible explanation for this anomaly. However, Bernardi et al. still observed a longer-lasting anti-inflammatory response of IL-10 in patients with hemadsorption on CPB. In both studies, there was a moderate beneficial effect of hemadsorption on the postoperative inflammatory response after cardiac surgery, but both studies were not powered to assess the effect of hemadsorption on clinical outcome. In spite of the moderate changes in interleukin serum levels, no major effect on clinical outcome should be expected in elective cardiac surgery.

The comparison of elective cardiac surgery patients to septic patients and patients with multiorgan failure, in which a reduction of vasopres-
sor requirement has been reported after therapy with CytoSorb™ hemadsorption in case reports and case series, is limited. Firstly, pro-inflammatory cytokine load in patients with septic shock is above those of elective cardiac surgical patients. Therefore, the CytoSorb™ absorber is supposed to be more effective, as cytokines are eliminated depending on their plasma concentration. Secondly, in these reports, hemadsorption was usually performed for days and not just for a few hours. An in-vitro study by Kellum et al. showed that a CytoSorb™ adsorber, which is perfused with a defined load of cytokines, needs two hours for complete elimination of IL-6 and even longer for other cytokines. In the clinical study presented, there was a physiologically constant liberation of cytokines both during and after the perfusion of the adsorber. This might explain why the significant differences observed were only present in the first hours after weaning from CPB. Thereafter, cytokine plasma levels adapted in the SG and the CG after 24 h.

Patients in the SG profited with respect to cardiovascular performance, which might be due to the hemadsorption therapy and the associated reduction in cytokine levels. They needed slightly less vasopressor support for achieving the target MAP and had a significantly increased CI after weaning from CPB. In all patients, fluid therapy based on functional hemodynamic monitoring, i.e. pulse-contour-derived SVV, was performed and no differences in fluid therapy were found. Therefore, patients from both groups may be considered to be volume optimized, and changes in interleukin levels and hemodynamics may be attributed to changes in the inflammatory response rather than to hemodilution. In this regard, the difference in CI might be explained by improved myocardial function and reduced left ventricular afterload. The ELWI tended to be lower in the SG, suggesting that the endothelial barrier was better preserved after hemadsorption. In a recent case report of a septic shock patient, an additional in-vitro analysis was performed with patient blood and human umbilical vein endothelial cells and a better integrity of the blood barrier function after hemadsorption therapy was found. Whether the observed short-term effect on hemodynamics is of clinical relevance or not cannot be answered from this study. In the study from Bernardi et al., no difference in vasopressor and inotropic support or CI was observed between the SG and the CG. However, in many patients from both groups, catecholamine therapy was required for longer than six hours after surgery. In our study, catecholamine support six hours after CPB was not required by any patient. Therefore, no conclusion on the long-term clinical effects of hemadsorption therapy on CPB can be drawn so far. In septic patients, a decrease in plasma cytokine levels and vasopressor requirements was observed in many case reports of the longer-term use of hemadsorption in septic patients. In a case series in eight septic patients, norepinephrine requirements decreased within 72 h of hemadsorption therapy. However, also in these patients, there was no prospective data on outcome after hemadsorption therapy.

Limitations of the study

The study population chosen for this study was medium complex cardio-surgical procedures with an estimated bypass duration of 120 min, as the release of cytokines is supposed to be related to the duration of cardiopulmonary bypass. Therefore, this study allows no conclusion on the efficacy of hemadsorption in extended cardio-surgical procedures.

The sample size was calculated assuming that there is a difference in interleukin-6 levels of 25% between the SG and the CG. Therefore, the smallest of differences in interleukin-6 would not be detected due to the small sample size. Similarly, the influence of hemadsorption on morbidity and mortality could not be assessed with this pilot study.

Though patients were randomly allocated to the study or the control-group, there might have been a difference between the two groups with respect to confounding risk factors not evaluated with the EuroSCORE II. Additionally, the study was performed as a single blinded study, with the medical team performing surgery being aware of the group allocation. However, group allocation for the ELISA measurements of the primary endpoint after surgery were not known. Therefore, the key message of this study was certainly not influenced by the study designed.
A strength of this study, and a major difference to the study of Bernardi \textit{et al.}, is the PiCCO-guided goal-directed fluid management, which is supposed to have a beneficial influence on postoperative morbidity.\textsuperscript{14}

Conclusions

In this pilot-study, a significant reduction in plasma cytokine levels of IL-8 and TNF\(\alpha\) directly after the end of CPB was observed in the SG treated with the Cytosorb\textsuperscript{TM} adsorber compared to a CG without hemadsorption therapy. Furthermore, a temporary increase in CI was observed in the SG. Further investigations are needed to evaluate the effect of hemadsorption on cardiopulmonary bypass and in emergency cardiac surgery.

What is known

- Cardiac surgery is associated with the liberation of pro-inflammatory cytokines and an excessive increase or an imbalance is associated with an unfavorable outcome.
- Hemadsorption on cardio-pulmonary bypass is feasible and safe.

What is new

- Hemadsorption on cardio-pulmonary bypass is associated with reduced plasma levels of proinflammatory cytokines such as IL-8 and TNF\(\alpha\) immediately after weaning from bypass.
- Hemadsorption on cardio-pulmonary bypass supports cardiovascular recovery and is associated with an increased cardiac index immediately after weaning from bypass.

References


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Authors' contributions.—Ingo Garau and Alexander März contributed equally.


Discrimination and calibration properties of the hypotension probability indicator during cardiac and vascular surgery

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ABSTRACT
BACKGROUND: Hypotension during surgery is linked to postoperative complications. Recently, a new hemodynamic algorithm intended to predict hypotensive events (hypotension probability indicator [HPI]) has been developed. The aim of the present study is to test the discrimination and calibration properties of the HPI.

METHODS: The intraoperative files of 23 patients undergoing cardiac and major vascular surgery receiving the HPI-based hemodynamic monitoring were retrospectively investigated for prediction of hypotensive events (mean arterial pressure <65 mmHg). The HPI was available at 20 seconds intervals; the values of HPI five to seven minutes before a hypotensive event (HPI_{5-7}) were tested for discrimination and calibration.

RESULTS: The HPI_{5-7} has a fair level of discrimination (area under the curve 0.768) and a poor calibration, due to overestimation of the hypotensive risk. At the observed prevalence, a cut-off value of 85% carries a sensitivity of 62.4% and a specificity of 77.7%, a negative predictive value (NPV) of 97.8% and a positive predictive value (PPV) of 12.6%; a value of 98% has a PPV of 64% and an NPV of 95.3%.

CONCLUSIONS: The HPI_{5-7} may offer some useful insights. Values ≤85% carry a clinically acceptable NPV for hypotensive events at the observed prevalence and may represent a “safe zone” during surgery. Values >85% do not carry enough PPV to trigger hemodynamic interventions, but represent a warning signal. Values >98% are highly suggesting a hypotensive event after 5-7 minutes. Further studies exploring the predictive ability of the HPI at different times are needed.

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Key words: Arterial pressure; Hypotension; Surgery; Hemodynamic monitoring.

Hypotension during non-cardiac surgery has been recently associated with a number of bad outcomes, including acute kidney injury, myocardial infarction, and 30-day mortality. Even if a clear definition of intraoperative hypotension is not available in the literature, the majority of the authors defined a hypotensive event as a mean arterial pressure (MAP) <65 mmHg for a least one minute in duration.

Intraoperative hypotension may result from a wide range of mechanisms: systemic vasodilation, hypovolemia due to fluid or blood loss, poor myocardial contractility, extrinsic compression of heart chambers (cardiac tamponade due to pericardial effusion or severe pneumothorax). These factors may act separately or in combination, and hemodynamic monitoring of the cardio-circulatory conditions is of paramount
importance for the prevention, diagnosis, and
treatment of hypotension.

In 2016, Edwards Lifesciences (Irvine, CA,
USA) launched a new monitoring platform in-
cclusive of an algorithm that should provide a
prediction of hypotensive events, called Acumen
Hypotension Probability Indicator (HPI) soft-
ware. This algorithm is based on a combination
of different hemodynamic signals, and provides
a predictive percentage value (range 0-100%) that
a hypotensive episode may manifest after a
non-specified period of time in the following
15-20 minutes. The optimal cut-off value was
settled at an HPI of 85%. This value is presently
presettled in the Acumen HPI platform as the
“alarm threshold” for high probability that a hy-
potensive event will occur within the following
15-20 minutes.

So far, apart from the proprietary data present-
ed at different meetings, there is only one study
presently under publication on this new technol-
y. The purpose of the present study is to assess
the discrimination and calibration properties of
the HPI in a series of patients undergoing vas-
cular and cardiac surgery. The HPI will be tested
for prediction of hypotensive events five to seven
minutes before the event (HPI_{5-7}).

Materials and methods

The present study is a retrospective analysis of
hemodynamic data in 23 patients receiving car-
diac or major vascular surgery at the IRCCS
Policlinico San Donato, a Clinical Research
Hospital partially funded by the Italian Ministry
of Health. The study was approved by the Local
Ethics Committee of the Institution, without the
need for a specific informed consent, apart from
the approval for the treatment of data for scien-
tific purposes in an anonymous form, which was
signed by all the subjects.

Patients

The patient population was constituted by 20 pa-
tients receiving cardiac surgery and three patients
major vascular surgery. This sample size was
considered adequate for a validation study, based
on the fact that the surgery time was long enough
(4-5 hours) to guarantee a number of around 700-
800 experimental points per each patient (the
HPI is produced continuously at 20-seconds in-
terval). The number of hypotensive events during
surgery was anticipated at four per each patient,
thus producing an expected number of 92 events
to predict. This number of events is close to the
minimum amount recommended for external
validation of multivariable models (100 events)7
and therefore was considered adequate for exter-
nal validation of a single variable (HPI) model.

The general characteristics of the patient pop-
ulation are shown in Table I.

Hemodynamic monitoring

All the patients were treated according to our
standard hemodynamic monitoring for major
surgical operations, which includes:

- 5-leads electrocardiographic monitoring
  and heart rate (HR);
- peripheral oxygen saturation (SpO₂);
- end-tidal carbon dioxide measurement;
- invasive systemic arterial pressure monitor-
ing through an arterial cannula placed in the ra-
dial artery, with continuous measurement of sys-
tolic, diastolic, and mean arterial pressure (MAP,
mmHg);
- three-lumen central venous catheter placed
  in the right internal jugular vein with measure-
ment of the central venous pressure (CVP,
mmHg);
- arterial pulse waveform monitoring with the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>72 (63-77)</td>
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<tr>
<td>Gender male</td>
<td>19 (82.6)</td>
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<tr>
<td>Weight (kgs)</td>
<td>70 (62-80)</td>
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<td>Height (cms)</td>
<td>170 (160-178)</td>
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<tr>
<td>Body surface area</td>
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<tr>
<td>Type of surgery</td>
<td></td>
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<tr>
<td>Cardiac</td>
<td>20 (86.9)</td>
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<tr>
<td>Major vascular</td>
<td>3 (13.1)</td>
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<tr>
<td>Duration of the surgical operation (min)</td>
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<tr>
<td>Number of hypotensive events (per each patient)</td>
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<tr>
<td>Minimum-maximum number of hypotensive events</td>
<td></td>
</tr>
<tr>
<td>Total number hypotensive events</td>
<td>77</td>
</tr>
<tr>
<td>Duration of hypotensive events (min)</td>
<td>21 (5-39)</td>
</tr>
</tbody>
</table>

Data are number (%) or median (interquartile range).
measurement of cardiac output (CO, L/min), cardiac index (CI, L min⁻¹ m⁻²), stroke volume (SV, mL) and systemic vascular resistances (SVR, dynes sec cm⁻⁵), and the fluid responsiveness indicators stroke volume variation (SVV, %) and pulse pressure variation (PPV, %);  
- cardiac surgery patients with heart valve interventions received intraoperative transesophageal echocardiographic assessment.

The above-mentioned parameters were acquired using a specific arterial pressure transducer (FloTrac IQ, Edwards Lifesciences).

The transducer was connected to the hemodynamic platform EV 1000 (Edwards Lifesciences), which provides a continuous output of the hemodynamic parameters. Additionally, the system provides some additional hemodynamic parameter: the dP/dt (mmHg/sec) and the dynamic elastance (EaDyn, ratio between PPV and SVV).

The EV 1000 – FloTrac IQ system provides an estimate of the hypotension probability (HPI, %) based on a proprietary algorithm. This algorithm is based on a retrospective series of patients and was developed using data from almost 13,000 past hypotensive events and over 12,000 non-hypotensive events. Different possible predictors of hypotension (defined as a MAP <65 mmHg) were entered in a multivariable logistic regression producing the final model. Although the exact regression coefficient of each variable included in the predictive model is presently covered by an industrial patent, it is known that the variables included in the predictive equation are: heart rate variability (changes in heart rate/changes in MAP); arterial pressure waveform complexity (approximate waveform entropy, sample waveform entropy, frequency domain measure of higher order harmonics); preload parameters (PPV and SVV); contractility parameters (slope of the ascending part of the pressure waveform above time, dP/dT); and afterload parameters (SVR, EaDyn).

The HPI is continuously measured, presented, and recorded at intervals of 20 seconds.

Patient management

Intraoperative patient management was based on our routine practice. All the patients were treated by the same anesthesiologist (LB) who was in charge for the evaluation of the product. Interventions to maintain an adequate hemodynamic profile were based on the routine hemodynamic parameters HR, MAP, CI, CVP, SVR, SVV, and echocardiographic data when available, but not on the HPI. Interventions included fluid administration and the use of vasoactive and inotropic drugs.

The definitions and adjudication of the hypotensive event are the following:
- an event is a period of hypotension (MAP <65 mmHg) lasting at least one minute (three consecutive measurements taken at 20 seconds interval). Events related to unpredictable hypotension (surgical manipulation or external compression of the heart in cardiac surgery during heart cannulation, release of aortic cross clamp in vascular surgery of the abdominal aorta) were censored. To achieve this, the anesthesia and perfusion files were retrieved and the time period around the above-mentioned events was excluded by the analysis;
- once an event was adjudicated, it was attributed to the onset time. The following measurements during the time of the event were not considered;
- the HPI measurements between five and seven minutes before the event (six measures) were tested for prediction of an event and were defined as HPI₅₋₇;
- a no-event is a period of no hypotension lasting at least one minute;
- the HPI measurements between five and seven minutes before the no-event (six measures) were tested for prediction of a no-event. This applied to the whole period of no-event;
- at the end of the event, a wash-out period of five minutes of no-event was applied. During this period, the measurements were not considered. This wash-out period was applied because during the event the HPI is usually 100% and cannot be considered as predictive of the event cessation.

An example of the event/no-event adjudication and HPI window of predictive ability is provided in Figure 1 (from a real case in our series).

For cardiac surgery patients, data recording was stopped at the onset and re-started at the end of cardiopulmonary bypass.

Statistical analysis

Data are expressed as number and percentage for dichotomous variables and median with inter-
The statistical approach of the present study aims to determine the discrimination and calibration properties of the HPI in the prediction of hypotensive events five to seven minutes before the event.

The association between HPI$_{5-7}$ (continuous variable, range 0-100) and the event (hypotension, binary variable, coded 0 for no-event and 1 for event) was tested using generalized estimating equations with binomial error and logit link function, producing odds ratios and 95% confidence intervals. Cluster robust standard errors were computed.

The discrimination properties of the HPI$_{5-7}$ were tested using a Receiver Operating Characteristics (ROC) analysis, producing the area under the curve (AUC) which represents the discrimination ability of the HPI$_{5-7}$ for prediction of the hypotensive events after five to seven minutes. Two hundred bootstrap replicates were used to evaluate optimism in AUC. The best cut-off value was identified according to the Youden Index (best match between specificity and sensitivity). This and other cut-off values were explored for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). To calculate the PPV and NPV, the prevalence of the event was considered equal to that observed in the sample population.

The goodness of fit of the HPI$_{5-7}$ model was tested with the le Cessie-van Houwelingen Test$^8$. Calibration was investigated by the creation of a calibration plot of the predicted vs. observed hypotensive events, developed according to recent statistical suggestions for developing and validating risk scores.$^9$ This plot considers predicted vs. observed hypotensive events at different levels of HPI$_{5-7}$, with a locally weighted scatterplot smoothing. Two hundred bootstrap replicates were used to evaluate optimism in calibration.

Differences between binary variables were tested with a Fisher’s exact test.

For all the tests, a P level <0.05 was considered statistically significant. All the calculations were done using computerized statistical packages (SPSS 13.0, IBM, Chicago, IL, USA; GraphPad Prism 6, San Diego, CA, USA; and MedCalc 16.2.0, Ostend, Belgium) and R software with rms package Frank E Harrell Jr (2017. rms: Regression Modeling Strategies. R package version 5.1-1).

Results

General data of the patient population are shown in Table I. The general outcome was good, with no mortality at 30-days after surgery, no stroke, myocardial infarction, acute kidney injury. Twenty-one patients were admitted to the intensive care unit after surgery. Their median mechanical ventilation time was 17 hours (interquartile range 12-20 hours), median intensive care unit stay was two days (interquartile range 1-2.2 days) and median postoperative hospital stay was seven days (interquartile range 7-7.7 days).

Overall, 8569 points in time were analyzed in 23 patients. There was a median of three hypotensive events (range 0-11 events) per each patient, for a total of 77 events adjudicated and analyzed. The median duration of each event was 21 minutes (range 1-92 minutes).

Figure 2 reports the logistic regression equation between HPI$_{5-7}$ and the observed hypotensive events. There is a significant (P<0.001) association, with an odds ratio of 1.032 (95% confidence interval 1.021-1.044). However, the goodness of
fit of the model is inadequate (P=0.033 at the le Cessie-van Houwelingen Test).

The ROC analysis of the hypotensive events prediction by the HPI_{5-7} is reported in Figure 3. The AUC demonstrated a fair discrimination (bootstrap corrected AUC =0.768, 95% confidence interval 0.758-0.778).

The calibration plot (Figure 4) between expected and observed hypotensive events confirmed the poor calibration of the model, showing an overestimation for low and high risks and an underestimation for intermediate risk.

The best cut-off value was identified at an HPI_{5-7} of 56%. This value yielded a sensitivity of 79%, a specificity of 63%, an NPV of 98.3% and a PPV of 9.8%. The suggested cut-off value of 85% carries an NPV of 97.6% and a PPV of 12.6%. At an HPI value >98%, the NPV is still high (95.3%) and the PPV climbs up to 64%.

**Discussion**

The present study deals with prediction of hypotensive events during surgery, using a new technology. It does not deal with the association between hemodynamic events and bad outcomes, which remains a matter of debate. Our sample size is mainly represented by cardiac surgery patients, and within this setting the association between intraoperative hypotension and bad outcomes was never demonstrated. The purpose of this study is to validate the predictive properties of the new algorithm. The original dataset where

the HPI algorithm was developed included cardiovascular surgery patients, and therefore our series represents an adequate surgical setting for validation purposes.

The validation of an algorithm designed to
provide a prediction of an event is a normal practice in medical statistics, based on the assessment of the discrimination and calibration properties. Usually, to every single patient a risk prediction (based on a risk score) is attributed and compared to the observed presence/absence of the event. Conversely, the validation process of the HPI algorithm carries some peculiar aspects. First of all, the event (hypotension) may appear several times within the time course of a surgical operation. Secondly, it may last for different and sometime long periods of time. Due to this dynamic aspect, a simple point-by-point ROC analysis is inadequate to address the discrimination properties of the algorithm. Specific measures should be applied to the rough dataset of 20-seconds recording of HPI and MAP, to avoid repetition of the event adjudication, and overlapping of prediction of events and no-events. Basically, every point in time should be considered as a different patient, and the HPI value at each time should be confronted with the MAP after a certain period of time (in our study, 5-7 minutes). Additionally, once an event occurs, data obtained during the event (usually HPI 100%) should not be considered, and a sufficient wash-out period of time (five minutes in our study) should be applied before re-starting the statistical assessment.

Once applied, our methodology provided a reasonable assessment of the properties of the HPI. Basically, there was a significant association between the HPI5-7 and the presence of a hypotensive event after five-seven minutes, and the discrimination carries an acceptable AUC of 0.768. However, the overall calibration of the HPI5-7 appears inadequate, with a constant overestimation of the risk of hypotension. Despite this, from a clinical perspective, the impact of the HPI may not be trivial. The best cut-off value is 56%, but this value is associated with a clinically inadequate PPV of 9.8% for hypotensive events. At the suggested value of 85% the NPV is still very strong (97.6%), so that clinicians may be reasonably confident that no hypotension will develop in the following five-seven minutes if this level is not exceeded. Conversely, the PPV is still poor (12.6%) and inadequate to prompt specific interventions to prevent a hypotensive event. However, the true risk of hypotension is rapidly raising above an HPI5-7 of 85%, and this level is reasonably to be considered as an early warning signal. Finally, for values >98% there is a 64% probability of a hypotensive event after five-seven minutes, and this may justify adequate interventions to prevent the event.

Limitations of the study

There is a possible (and probably inevitable) source of bias in our study. Even if the attending anesthesiologist did not consider the HPI as a trigger for interventions, he certainly applied a number of measures to prevent or correct an inadequate hemodynamic pattern, based on the usual parameters of HR, CI, SVV, CVP, and MAP. These interventions are likely to be successful in the hands of an experienced anesthesiologist. The HPI algorithm includes the majority of the above-mentioned variables in its equation, and therefore it is likely that in many cases, despite a high probability of hypotension, the hypotensive event may not occur due to the hemodynamic interventions. Actually, in cardiovascular surgery, there is often the need to maintain the blood pressure at a level slightly superior to a MAP of 65 mmHg. This means that under the circumstances of a MAP maintained between 66 mmHg and 70 mmHg for a long period of time (no-event time) the HPI may claim a high risk of hypotension without that any event will occur. This of course affects the PPV of the cut-off value and is the basis for the constant overestimation of the hypotensive risk observed in our series.

A second important point pertains the window of time between the prediction and the event. It must be admitted that we challenged the algorithm in a specific window of time, and that the algorithm was designed to predict an event after a larger period of time (15-20 minutes). In our study, we arbitrarily set this window within five and seven minutes; it is likely that the more the prediction is close to the event the more the HPI will be accurate and calibrated (more true positive). Of course, from a clinical perspective, a prediction too close to the event is probably not useful; however, further studies are needed to test the discrimination and calibration properties of the HPI1-3 and HPI3-5. Extension of the window of time to values between seven and 15 minutes may represent another possible field of study.
An additional limitation is that the PPV and NPV of the HPi were calculated assuming that the prevalence of the event (hypotension) was equal to what observed in the sample; in case of a different prevalence (i.e. in other types of surgery), the PPV and NPV will change.

It is not the purpose of the present study to address the clinical relevance of this new monitoring tool for the standard practice. It is possible that anticipating hypotensive events may change the behavior of the anesthesiologist from “reactive” to “proactive.” However, there is at present no evidence that this will improve the outcome of the patient, at least in the cardiovascular setting. Additionally, it could even be that this “proactivity” may lead to an increase in the hemodynamic interventions, potentially inducing the risk of an overtreatment.

Conclusions

In conclusion, this new technology deserves attention and additional studies, especially in other clinical scenarios like non-cardiovascular surgery and critical care patients. A homogeneous approach to the statistical methodology applied in HPi validation series is strongly recommended.

What is known

- Hypotension episodes during major surgery are associated with a worse outcome.

What is new

- The HPi is a new algorithm designed to anticipate hypotensive events, based on a number of hemodynamic parameters.

- HPi has acceptable discrimination power for predicting hypotensive events after five-seven minutes. However, it carries a good negative predictive value, whereas the positive predictive value is acceptable only for a HPi value of 98%.

References


Conflicts of interest.—Marco Ranucci received speaker’s honoraria from Edwards Lifesciences.

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Authors’ contributions.—Marco Ranucci conceived the experimental design, analyzed the data, and wrote the draft manuscript; Luigi Barile collected the data and participated in data interpretation; Valeria Pistuddi participated in data collection and analysis.


Postoperative pain after vitreo-retinal surgery is influenced by surgery duration and anesthesia conduction

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ABSTRACT

BACKGROUND: The control of postoperative pain (POP) is a key component of perioperative care. POP after vitreo-retinal surgery (VRS) has been under-investigated, and its incidence remains elusive.

METHODS: In order to assess POP after VRS, the associated risk factors and efficacy of the analgesic protocol in use at our institution, we made a one-year retrospective study on patients undergoing VRS. Patients aged >18 years, ASA Class I-III undergoing VRS entered the study. POP was evaluated by measuring a Numerical Rating Scale (NRS), and analgesic consumption.

RESULTS: A total of 782 patients entered the study. Patients received locoregional (LRA) or general anesthesia (GA) with supplemental block. Twenty-two percent of patients needed analgesics (acetaminophen in 97% of cases), mostly between two and six hours after surgery. The univariate analysis showed a positive association between POP and duration of surgery (P<0.0001) and glaucoma (P=0.04), and a negative association with age (P=0.008), analgesic administration at the end of surgery (P=0.005) and the intraoperative administration of remifentanil for surgery under LRA (P=0.02); sedation to execute the block for LRA did not reduce POP. Patients treated with GA with supplemental block had less pain compared to those treated with LRA with/without remifentanil (P=0.03, P=0.002, respectively). The multivariate analysis confirmed a positive correlation between POP and duration of surgery (P=0.0007) and a negative correlation with the intraoperative remifentanil administration during LRA (P=0.04), and with GA with supplemental block (P=0.01).

CONCLUSIONS: The incidence of POP after VRS is low but not absent, especially for long procedures, it does not require postoperative opioids and can be modified by anesthesiologic choices.

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KEY WORDS: Postoperative pain; Pain management; Ophthalmologic surgical procedures; Vitrectomy.
of the eye, such as retinal detachment, diabetic proliferative retinopathy, macular holes, epiretinal membrane and vitreous hemorrhage. Since these eye diseases are most prevalent in elderly patients, with the increase in the population’s average age and diseases such as diabetes, pars plana vitrectomy (PPV) and scleral buckling (SB) — two types of VRS — are now frequently carried out. When oil is used to stabilize the retina after vitreous removal, once the retina appears stable, removal of silicone oil (ROSO) is carried out. During the last 15 years there have been many technical improvements in VRS (for example the use of smaller diameter instrumentation) which have reduced surgery time, improved patients’ comfort and limited the need for general anesthesia (GA). Nowadays, most VRS is performed under loco-regional anesthesia (LRA), which is also suitable for day-case surgery, because in addition to offering optimal intraoperative conditions, patients remain conscious and breathe spontaneously, and therefore they can be discharged within a few hours. Mild intravenous sedation can be combined with LRA, however some patients still require GA, for example young or anxious people who are afraid of eye surgery, patients with psychiatric conditions or neurological impairment, or when surgeons suggest it (i.e. long or complicated operations).

There is limited literature on the extent of POP after VRS; moreover, POP is often investigated only for the first six hours after surgery.

In our hospital a protocol for POP treatment is applied for the first 12-24 hours and data collection is obtained for this period; nurses have been trained to evaluate POP as soon as patients return to the ward and at several intervals after surgery.

The main aim of this study was therefore to retrospectively observe how much pain occurs after VRS according to reported pain scores and analgesic consumption during a one-year period. We also investigated which risk factors are associated with POP and the efficacy of the analgesic protocol we have in use.

Materials and methods

We carried out a retrospective analysis of POP on patients who had undergone VRS at Careggi University Hospital, in Florence, which hosts over 1300 beds. The study was approved by the local Ethical Committee (Approval Registration No.: 11096).

Patients admitted from 1st January 2016 to 31st December 2016, aged >18 years, who underwent VRS (specifically PPV, SB, ROSO), ASA I-III, were considered eligible for the study. Data were collected from clinical records and electronic registers. A list of examined data is reported in Table I.

Patients undergoing VRS usually arrive in the preoperative room where they are immediately monitored. A peripheral vein is cannulated. Most patients receive retrobulbar LRA, which is performed by the surgeon with a 25-G needle (38-mm length). Usually two injections of 5 mL each of a solution 1% ropivacaine + 2% lidocaine plus hyaluronic acid, 300 IU, are sufficient to obtain a complete block; if this is not the case, a third injection can be carried out. Prior to the first injection an intravenous sedation is frequently given (propofol single bolus, dose calculated according to the formula of Hocking and Balmer, which is based on the patient’s weight and age). After the completion of the block, patients are taken to the operating room, where surgery is carried out. Some patients receive intraoperatively an intravenous infusion of remifentanil in a concentration

### Table I. — List of parameters analyzed.

<table>
<thead>
<tr>
<th>Demographic parameters</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td>Glaucoma</td>
<td>ASA Class</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Previous ophthalmological surgery</td>
</tr>
<tr>
<td>Surgery</td>
<td>Type of surgery</td>
<td>Duration of surgery</td>
</tr>
<tr>
<td></td>
<td>Trocar diameter (G)</td>
<td>Analgesia at the end of surgery</td>
</tr>
<tr>
<td></td>
<td>Sedation to perform LRA</td>
<td>Type of anesthesia (GA vs. LRA)</td>
</tr>
<tr>
<td>Pain evaluation</td>
<td>Intraoperative management</td>
<td>NRS 0</td>
</tr>
<tr>
<td></td>
<td>NRS at 0-2 hours interval (T2)</td>
<td>NRS at 0-2 hours interval (T2)</td>
</tr>
<tr>
<td></td>
<td>NRS at 2-6 hours interval (T6)</td>
<td>NRS at 2-6 hours interval (T6)</td>
</tr>
<tr>
<td></td>
<td>NRS at 6-12 hours interval (T12)</td>
<td>NRS at 6-12 hours interval (T12)</td>
</tr>
<tr>
<td></td>
<td>NRS at 12-24 hours interval (T24)</td>
<td>NRS at 12-24 hours interval (T24)</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologist; LRA: locoregional anesthesia; NRS: Numerical Rating Scale; T0: arrival at the ward; T2: from 0 to 2 hours after surgery; T6: from 2 to 6 hours after surgery; T12: from 6 to 12 hours after surgery; T24: from 12 to 24 hours after surgery.
of target-controlled infusion (TCI) 0.5-0.8 µg/mL. At the end of surgery patients may receive an intravenous dose of acetaminophen (0.5-1 g according to their weight and age). Patients who are given GA receive a single injection (5 mL) of the above-mentioned local anesthetic solution just before the beginning of the surgical procedure, in addition to sevoflurane (MAC=1) and remifentanil (TCI 1-2 µg/mL) with or without muscle relaxants under train-of-four (TOF) monitoring. Airway control is usually achieved with a laryngeal mask (LMA), thus possibly reducing POP due to a sore throat.\textsuperscript{10} Antiemetic prophylaxis (ondansetron and dexamethasone) is administered.

The Numerical Rating Scale (NRS) was used to assess POP, because patients might have significant visual impairment soon after ophthalmic surgery, and therefore they might not be able to use the Visual Analog Scale (VAS).\textsuperscript{11-13} The NRS rates pain using numbers from 0 to 10, where 0 means “no pain” and 10 “the worst pain possible.” Analgesics are administered if NRS≥3 according to previous studies where this threshold indicates moderate pain.\textsuperscript{14, 15} POP is treated with acetaminophen (0.5-1 g three or four times a day, depending on the weight and age of patients). If the treatment with acetaminophen is not sufficient, or if there are contraindications to its use, ketorolac (15-30 mg) or tramadol (0.5-1 mg/kg) are used. POP is measured in four time intervals: on arrival at the ward (T0), from zero to two hours after surgery (T2), from two to six hours (T6), from six to 12 hours (T12), and over 12 hours after surgery (T24).

This manuscript adheres to the applicable CONSORT guidelines.

Statistical analysis

For the descriptive analysis, qualitative data are presented as percentages while continuous data are presented as means and standard deviations.

For the explorative analysis, the associations between the principal outcome (amount of POP) and risk factors are evaluated using a simple and multiple logistic regression model. The backward selection method is used in multiple logistic regression analysis. For each association, odds ratio (OR), 95% confidence interval (CI), and P values are reported.

### Results

Data regarding 782 patients were analyzed during the study period. Their main clinical and demographic characteristics are summarized in Table II. PPV was the most frequent type of surgery carried out. Surgery lasted approximately 55 minutes (range: 40-80 minutes), with the duration of surgery intended as the time from trocar insertion to trocar removal for PPV or from opening to closing of the conjunctiva for SB. LRA was performed in almost 80% of patients; it was often associated with sedation with propofol during the first block. Intraoperative administration of remifentanil was carried out in about 35% of the patients under monitored anesthesia care with regional anesthesia. Twenty-two percent of patients received analgesics at the end of surgery (90% acetaminophen, 8% ketorolac tromethamine, 2% tramadol) (Table II).

Ninety-six percent of patients had NRS=0 on arrival in the ward (T0); at that time less than target-controlled infusion (TCI) 0.5-0.8 µg/mL. At the end of surgery patients may receive an intravenous dose of acetaminophen (0.5-1 g according to their weight and age). Patients who are given GA receive a single injection (5 mL) of the above-mentioned local anesthetic solution just before the beginning of the surgical procedure, in addition to sevoflurane (MAC=1) and remifentanil (TCI 1-2 µg/mL) with or without muscle relaxants under train-of-four (TOF) monitoring. Airway control is usually achieved with a laryngeal mask (LMA), thus possibly reducing POP due to a sore throat.\textsuperscript{10} Antiemetic prophylaxis (ondansetron and dexamethasone) is administered.

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### Table II.—Main clinical and demographic patients’ characteristics.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N. patients (%)</th>
<th>N. patients for whom data was available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>352 (45%)</td>
<td>781</td>
</tr>
<tr>
<td>Male</td>
<td>429 (55%)</td>
<td>781</td>
</tr>
<tr>
<td>Age, years*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>122 (16%)</td>
<td>766</td>
</tr>
<tr>
<td>II</td>
<td>458 (60%)</td>
<td>766</td>
</tr>
<tr>
<td>III</td>
<td>180 (24%)</td>
<td>766</td>
</tr>
<tr>
<td>ASA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>122 (16%)</td>
<td>766</td>
</tr>
<tr>
<td>II</td>
<td>458 (60%)</td>
<td>766</td>
</tr>
<tr>
<td>III</td>
<td>180 (24%)</td>
<td>766</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPP≥23 G</td>
<td>101 (12.9%)</td>
<td>781</td>
</tr>
<tr>
<td>VPP&lt;23 G</td>
<td>518 (66.3%)</td>
<td>781</td>
</tr>
<tr>
<td>SB</td>
<td>101 (12.9%)</td>
<td>781</td>
</tr>
<tr>
<td>ROSO</td>
<td>32 (4.10%)</td>
<td>32</td>
</tr>
<tr>
<td>Duration of surgery, min*</td>
<td>55 (40-80)</td>
<td>778</td>
</tr>
<tr>
<td>Previous ophthalmological surgery</td>
<td>443 (56.6%)</td>
<td>782</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>63 (8%)</td>
<td>775</td>
</tr>
<tr>
<td>Diabetes</td>
<td>135 (17.5%)</td>
<td>772</td>
</tr>
<tr>
<td>Sedation to perform LRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (5.4%)</td>
<td>731</td>
</tr>
<tr>
<td>Yes</td>
<td>527 (72%)</td>
<td>731</td>
</tr>
<tr>
<td>GA</td>
<td>164 (22.4%)</td>
<td>731</td>
</tr>
<tr>
<td>Intraoperative management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRA</td>
<td>307 (42.2%)</td>
<td>727</td>
</tr>
<tr>
<td>LRA + remifentanil</td>
<td>256 (35.2%)</td>
<td>727</td>
</tr>
<tr>
<td>GA</td>
<td>164 (22.5%)</td>
<td>727</td>
</tr>
</tbody>
</table>

ASA: America Society of Anesthesiologists; VPP: pars plana vitrectomy; SB: scleral buckling; ROSO: removal of silicon oil; LRA: locoregional anesthesia; GA: general anesthesia. "Data expressed as median (interquartile range)."
No correlation between POP and trocar diameter (25 G versus smaller diameter, i.e., 25 or 27 G) or type of surgery (PPV vs. SB vs. ROSO) was observed (Figure 2), nor between POP and sex, ASA Class and previous surgery on the same eye.

The multivariate analysis confirmed the significant positive correlation between POP and duration of surgery (P=0.0007) and negative correlation with the intraoperative opiate (remifentanil) administration during LRA (P=0.04), and with GA (with supplemental block, P=0.01).

However, despite these correlations, as shown in Figure 1, 2% had pain high enough to require analgesics (NRS≥3). At T2, 53 patients (8%) had pain. NRS≥3 was mainly reported at T6 when it was present in 128 patients (16%), while pain at T12 and T24 was present only in 1.4% and 0.6% respectively (Figure 1). The maximum pain score was NRS=8 at T12, experienced by only one patient. In more than 97% of the patients requiring analgesic treatment for POP, acetaminophen was sufficient. No side-effects due to postoperative analgesic administration nor increased intraocular pressure at the end of the surgery were reported.

The univariate analysis could be carried out only at T6 (which refers to the two- to six-hour interval) because the number of patients with pain at the other intervals was not sufficient to be statistically evaluated (Figure 1). The analysis showed a positive association between POP and duration of surgery (P<0.0001) and glaucoma (P=0.04), and a negative association with age (P=0.008), analgesic administration at the end of surgery (P=0.005) and the intraoperative administration of remifentanil for surgery under LRA (P=0.02); sedation to execute the block under LRA did not reduce POP. Patients treated with GA had less pain compared both to those treated with LRA plus remifentanil (P=0.03) and to those treated with LRA without remifentanil (P=0.002).
in Figure 3 the calculated area under the curve (AUC=0.6490) was not big enough and the model could not accurately predict POP at T6 for each single patient.

Discussion

The aim of our study was to assess how painful VRS is, how the pain can be treated, and which factors are associated with POP. According to our data, POP requiring analgesics after VRS affects about 20% of patients, it is mainly restricted to the two- to six-hour interval after surgery and is well controlled with acetaminphen. The duration of the surgical procedure is an unquestionable factor which increases POP, while anesthetic choices (i.e. the intraoperative use of remifentanil with LRA and GA with supplemental bock) can reduce it.

The control of POP is a key component of good perioperative care. Minimal residual pain is essential criteria for hospital discharge after day-case or ambulatory surgery.1,3 There is a lack of data concerning POP after VRS despite the increasing popularity of this surgery, since the published data are collected from small samples of patients or from patients who underwent highly different surgical eye procedures (from cataract surgery to evisceration).11 Even in the study of Chung et al.,16 more than 70% of the patients had undergone cataract surgery, a surgical procedure much less invasive than VRS. Thus our study is one of the largest studies evaluating POP after VRS, since it concerns about 800 patients.

The duration of the surgical procedure was found to be associated with POP. This had previously been observed both in non-ophthalmo-logical1 as well as in retinal surgery.17 In a prospective study involving 185 patients, Fekrat et al. found a cut-off of 120 minutes associated with POP.17 The reason for this might be that the longer the surgery, the higher the inflammatory response. However, in contrast to this “inflammation hypothesis,” in our study pain treatment with acetaminphen — a drug which does not show anti-inflammatory properties — resulted in a positive response in more than 97% of our patients.

We did not find any difference in POP according to the type of VRS, despite the fact that PPV, SB and ROSO are different techniques of VRS. PPV is performed by removing the vitreous body.18 SB consists in creating a buckle which allows the re-apposition of detached layers, re-storing anatomic-physiological connections;19 finally, ROSO consists in a PPV during which silicone oil is removed.20 We only had a few cases of ROSO in our sample because patients are usually discharged in less than six hours. We also failed to observe an association between trocars of a smaller diameter (25 and 27 G vs. 23 G) and less POP, although they should cause less conjunctival scarring and postoperative inflammation.

On the contrary the type of anesthesia had an impact on POP. In our study, the standardization of the anesthetic techniques is an important factor and it may partly mitigate the limit of a retrospective study. The comparison between the different types of anesthesia (LRA vs. GA) in determining ophthalmological POP has been evaluated previously by Henzler et al.,20 but only for surgery other than VRS. In our study, when LRA is administered, the intraoperative association of remifentanil reduced POP, and less pain was observed after GA with supplemental block rather than LRA. In 2016, Lesin et al.11 found that patients receiving benzodiazepines preoperatively had less POP, but in this study there were few cases of VRS. Despite it being more and more frequently reported that reducing opiate use during surgery can improve recovery after anesthesia and diminish opiate-related side effects,21 we observed that low doses of remifentanil diminished POP without side-effects. Remifentanil was turned off at the end of surgery without supplementation of long-lasting opioids and no opioids in the postoperative period were required.

Sex has been reported to influence ophthalmic POP by Henzler et al.,20 who observed more POP in women than in men but in our study, sex had no effect in the multivariate analysis. Age can also have an effect on the amount of pain perceived.22 In our univariate analysis there was a negative correlation between age and POP, in that young people were more likely to suffer pain, a result that was similar to that of Fekrat et al.,17 but that we could not confirm in the multivariate analysis.
In order to evaluate POP, we considered only NRS changes which were equal or higher than a pre-established cut-off. As the cut-off point we chose a value of 3 which is assumed to reflect moderate pain that requires analgesics.\(^{13}\) Henzler \textit{et al.}\(^{20}\) evaluated POP after ophthalmic surgery only if VAS was \(\geq 5\) which indicates severe POP. Lesin \textit{et al.},\(^{11}\) on the contrary, analyzed all variations of NRS, but NRS values \(\leq 2\) are not clinically relevant. Our choice was in line with the “no worse than mild pain” principle.\(^{14}\) Finally, there are different intervals/time points of pain assessment after eye surgery. We assessed pain at several intervals but more frequently in the first six hours after surgery, when pain is more likely.\(^{11}\)

Strengths and limitations of the study

The main strengths of this study are: 1) being one of the few studies investigating POP for VRS; 2) a high number of patients undergoing the same type of eye surgery have been included; 3) the standardized anesthetic techniques and the assessment/treatment of POP; 4) the nurses were trained and therefore their evaluation was reliable; 5) POP could be evaluated for a longer period than it generally happens in eye surgery.

Our study has some limitations as well, namely: 1) its retrospective design (some data were missing; Table II); 2) few patients with ROSO were examined because they are usually discharged after a few hours; 3) no evaluation of the psychological dimension of pain was carried out; 4) POP evaluation was performed during the first 24 hours only, and not for longer time intervals, but the number of patients who were likely to have pain after that time point was deemed negligible.

Conclusions

Despite the limitations listed above, our work has added some important data regarding the study of POP after VRS, which has been largely under-investigated so far. Patients can be reassured that POP after VRS is not absent but, if present, it occurs soon after surgery and can be treated with common analgesics; no opioids are necessary. Patients can also undergo GA supplemented with block without the fear of suffering more POP.

What is known

- The control of POP is a key component of good perioperative care.
- Literature on the extent of POP after VRS is limited and there are no guidelines on its control.

What is new

- The incidence of POP in VRS is low but should not be neglected. It occurs mostly in the first two to six hours after surgery, correlates with duration of surgery, and is influenced by anesthesia choices.
- No opioids are necessary in the postoperative period.

References

13. Myles PS, Myles DB, Galagher W, Boyd D, Chew C, MacDonald N, \textit{et al.} Measuring acute postoperative pain using the visual analog scale: the minimal clinically important...

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Congresses.—Preliminary data from this research were presented as an abstract at the FLORetina 2017 Meeting, which was held on April 28th-30th in Florence, Italy; and at the 2017 National Congress of the SIAARTI, which took place on October 18th-21st in Rimini, Italy.
Out-of-hospital cardiac arrest at place of residence is associated with worse outcomes in patients admitted to intensive care

A *post-hoc* analysis of the targeted temperature management trial

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ABSTRACT

BACKGROUND: The majority of out-of-hospital cardiac arrests (OHCA) occur at place of residence, which is associated with worse outcomes in unselected prehospital populations. Our aim was to investigate whether location of arrest was associated with outcome in a selected group of initial survivors admitted to intensive care.

METHODS: This is a *post-hoc* analysis of the Targeted Temperature Management After Cardiac Arrest (TTM) trial, a multicenter controlled trial, randomizing 950 OHCA patients to an intervention of 33 °C or 36 °C. The location of cardiac arrest was defined as place of residence versus public place or other. The outcome measures were mortality and neurological outcome, as defined by the Cerebral Performance Category Scale, at 180 days.

RESULTS: Approximately half of 938 included patients arrested at place of residence (53%). Location groups did not differ with respect to age (P=0.11) or witnessed arrests (P=0.48) but bystander CPR was less common (P=0.02) at place of residence. OHCA at place of residence was associated with higher 180-day mortality (55% vs. 38%, P<0.001) and worse neurological outcome (61% vs. 43%, P=0.001) compared with a public place or other. After adjusting for known confounders, OHCA at place of residence remained an independent predictor of mortality (P=0.007).

CONCLUSIONS: Half of all initial survivors after OHCA admitted to intensive care had an arrest at place of residence which was independently associated with poor outcomes. Actions to improve outcomes after OHCA at place of residence should be addressed in future trials.


KEY WORDS: Comorbidity; Mortality; Neurologic manifestations; Induced hypothermia; Out-of-hospital cardiac arrest.
Out-of-hospital cardiac arrest (OHCA) is an exceptionally time-critical condition\(^1,2\) and a great challenge to both society and the medical community since it depends on immediate action from bystanders, lay-rescuers and emergency medical systems (EMS).\(^3-5\) For every minute of delay to initiation of cardiopulmonary resuscitation (CPR) and/or delivery of a shock, the risk of death or permanent brain damage increases by 5-10%.\(^1,2\) The majority of OHCAs occur at place of residence, which is associated with worse outcomes compared to OHCAs in public places,\(^3,4,6-10\) and may be explained by higher age and more comorbidities in patients arresting at home.\(^6,10-13\) In addition, important factors such as initial rhythm, whether or not the arrest was witnessed, bystander CPR and time to defibrillation favour patients who arrest in public places.\(^3,4,6,7,9\) Suffering an OHCA at place of residence is a known risk factor for poor outcomes in unselected prehospital populations.\(^3,4,6,10\) No study has to our knowledge highlighted the importance of the location of arrest among initial survivors admitted to intensive care, representing a mere 20-25% of the entire prehospital OHCA population.

This is a post-hoc analysis of the Targeted Temperature Management After Cardiac Arrest (TTM) trial,\(^14\) a large international multicenter trial randomizing OHCA patients to a temperature intervention of either 33 °C or 36 °C, with no difference in outcome between intervention arms. Our first aim was to investigate the association of location of arrest and outcome at 180 days, and second, to identify independent predictors of outcome. Our hypothesis was that being admitted to intensive care after OHCA at place of residence was associated with higher mortality (primary outcome) and worse neurological outcome (secondary outcome) compared to patients suffering OHCA in a public place.

Materials and methods

Study population

This is a predefined post-hoc analysis of the TTM trial, a randomized, assessor-blinded, multi-center, investigator-initiated clinical trial, in which two temperature interventions were compared after OHCA, 33 °C versus 36 °C.\(^14\) The TTM trial was conducted in 36 ICUs in Europe and Australia between November 2010 and January 2013. The primary outcome was all-cause mortality at the end of trial, a secondary outcome was neurological function at 180 days, assessed by the Cerebral Performance Category (CPC) Scale. Main inclusion criteria were age above 18 years, presumed cardiac cause, sustained ROSC (>20 minutes) and unconsciousness (Glasgow Coma Scale [GCS] <8). Exclusion criteria included unwitnessed cardiac arrest with an initial rhythm of asystole, refractory shock and failure to randomize within 240 min from the arrest. The TTM trial randomized 950 OHCA patients with no difference in end-of-trial mortality or 180-day neurological outcome between the intervention arms.\(^14\) The TTM protocol\(^15\) was approved by ethical committees in all participating countries. In accordance with national requirements and the principles of the Declaration of Helsinki, written informed consent was waived, delayed, or obtained from a legal surrogate, depending on the circumstances, and was obtained from each patient who regained mental capacity.\(^16\)

Location of arrest

Location of OHCA was divided according to the Utstein recommendations\(^17\) into three categories, namely place of residence (home, apartment), public place (the street, city park, shopping center, sports stadium, entertainment center, airport, railway station, beach, office building), and other (hotel room, private office, long-term care nursing facility). In this post-hoc analysis, public place and other were merged and we thus compared characteristics and outcome between two groups of patients, those with an arrest at place of residence versus those arresting in public place or other (Supplementary Digital Material 1: Supplementary Figure 1).

Outcome

Primary outcome was 180-day mortality. Secondary outcome was neurological function at 180 days assessed using the five-point CPC-scale, where 1 means good cerebral performance or minor disability, 2 means moderate disability, 3 means severe disability, 4 means coma or veg-
etative state, and 5 means death.18 Neurological outcome was dichotomized, defining CPC 1-2 as good outcome and CPC 3-5 as poor outcome.

Covariates

We used the Utstein definitions17 to select variables and possible effect modifiers (e.g. bystander CPR, witnessed arrest, initial rhythm and time intervals) for the regression analysis.19 In addition, daytime (06:00-17:59) versus nighttime (18:00-05:59) OHCA was investigated.20, 21 For comorbidity, a modified Charlson Comorbidity Index (mCI) as defined by Winther-Jensen et al.22 was used to assess the potential impact of comorbidity (Supplementary Digital Material 2: Supplementary Table I).

Statistical analysis

Categorical data are presented as numbers and continuous data as percentages and medians with first and third quartile for skewed data. For univariable comparisons between location groups, Pearson’s χ² test was used for dichotomous data and Mann-Whitney U-test was used for continuous and ordinal data. A logistic regression analysis for 180-day mortality was performed reporting associations as odds ratios (OR) with 95% confidence interval (CI), for each potential predictor separately and then for all variables controlling for one another. A correlation matrix was run for all variables included in the logistic regression analysis, demonstrating that no correlations were above a Spearman correlation of 0.7.23 A Kaplan-Meier analysis was performed to display the course of mortality during the 180-day period with a log-rank test for analyzing survival differences between groups. All statistical analyses were performed with SPSS Software v. 24.0 and the significance level was set at P<0.05.

Results

Nine hundred and fifty patients were randomized in the TTM trial, 939 patients remained in the modified intention-to-treat population. One patient had missing data on location of arrest and was excluded, leaving a final sample of 938 individuals (Supplementary Figure 1). Five hundred arrests occurred at a place of residence, 385 in a public place and 53 in other. By combining public place and other, we ended up with two groups for further analysis, place of residence (N.=500, 53.3%) versus public place/other (N.=438, 46.7%).

Baseline characteristics in the two location groups are presented in Table I, missing data are presented in the table subtext. The median age of the study population was 65 years (range: 56-73 years) with no significant difference between location groups. Patients with cardiac arrest at a place of residence were more likely to be female, and cardiac arrest was less likely to occur during daytime. Bystander CPR was less common in the ‘place of residence’ group, but the proportion of witnessed arrests did not differ with any significance between groups. A shockable rhythm was more common in the ‘public place/other’ group but there was no significant difference in ST elevation myocardial infarction on the admission electrocardiogram between groups. More cardiac arrest patients in public place/other group, however, underwent coronary angiography during hospital stay.

Half of all patients did not have any pre-arrest comorbidity (Table I, Figure 1), comorbidities were statistically more common among patients arresting at a place of residence. Also, all prehospital time intervals were significantly longer in patients arresting at a place of residence (Figure 2). The overall mortality at 180 days was 47.4% (445 of 938). A Kaplan-Meier plot (Figure 3) visualizes the probability of survival in the two

![Figure 1.—Distribution of comorbidity points by modified Charlson Comorbidity Index (mCI) among patients with out-of-hospital cardiac arrest at place of residence versus public place other. Comorbidity was assessed by mCI and further categorized into four groups: 1) no comorbidity points; 2) one comorbidity point; 3) two comorbidity points; 4) three or more comorbidity points. Mann-Whitney U-test was used for comparisons.](image-url)
Table I.—Baseline characteristics stratified by location of out-of-hospital cardiac arrest in the TTM trial.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All cases (N=938)</th>
<th>Location</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Place of residence (N=500)</td>
<td>Public or other (N=438)</td>
<td></td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>65 (56-73)</td>
<td>65 (57-73)</td>
<td>64 (56-72)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>760 (81.0%)</td>
<td>392 (78.4%)</td>
<td>368 (84.0%)</td>
</tr>
<tr>
<td>Pre-arrest CPC a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPC 1</td>
<td>893 (95.8%)</td>
<td>474 (95.0%)</td>
<td>419 (96.8%)</td>
</tr>
<tr>
<td>CPC 2</td>
<td>38 (4.1%)</td>
<td>25 (5.0%)</td>
<td>13 (3.0%)</td>
</tr>
<tr>
<td>CPC 3</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity groups b</td>
<td></td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td>Group 1</td>
<td>474 (50.5%)</td>
<td>239 (47.8%)</td>
<td>235 (53.7%)</td>
</tr>
<tr>
<td>Group 2</td>
<td>274 (29.2%)</td>
<td>145 (29.0%)</td>
<td>129 (29.5%)</td>
</tr>
<tr>
<td>Group 3</td>
<td>122 (13.0%)</td>
<td>74 (14.8%)</td>
<td>48 (11.0%)</td>
</tr>
<tr>
<td>Group 4</td>
<td>68 (7.2%)</td>
<td>42 (8.4%)</td>
<td>26 (5.9%)</td>
</tr>
<tr>
<td>Time of the day</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>06:00-17:59</td>
<td>634 (68.0%)</td>
<td>283 (56.7%)</td>
<td>351 (80.9%)</td>
</tr>
<tr>
<td>18:00-05:59</td>
<td>299 (32.0%)</td>
<td>216 (43.3%)</td>
<td>83 (19.1%)</td>
</tr>
<tr>
<td>Bystander witnessed</td>
<td>838 (89.3%)</td>
<td>450 (90.0%)</td>
<td>388 (88.6%)</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>683 (72.9%)</td>
<td>348 (69.7%)</td>
<td>335 (76.5%)</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>752 (80.2%)</td>
<td>383 (76.6%)</td>
<td>369 (84.2%)</td>
</tr>
<tr>
<td><strong>EMS interventions</strong></td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>EMS chest compression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>717 (76.6%)</td>
<td>369 (74.1%)</td>
<td>348 (79.5%)</td>
</tr>
<tr>
<td>Device c</td>
<td>219 (23.4%)</td>
<td>129 (25.9%)</td>
<td>90 (20.5%)</td>
</tr>
<tr>
<td>Three or more defibrillations</td>
<td>453 (54.8%)</td>
<td>236 (55.1%)</td>
<td>217 (54.4%)</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>627 (67.8%)</td>
<td>343 (69.4%)</td>
<td>284 (65.9%)</td>
</tr>
<tr>
<td>Dose of epinephrine</td>
<td>2 (0-4)</td>
<td>2 (1-4)</td>
<td>2 (0-3)</td>
</tr>
<tr>
<td>In hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock on admission</td>
<td>137 (14.6%)</td>
<td>77 (15.4%)</td>
<td>60 (13.7%)</td>
</tr>
<tr>
<td>Lactate</td>
<td>6.0 (3.0-9.6)</td>
<td>6.2 (3.2-10.1)</td>
<td>5.6 (2.8-9.0)</td>
</tr>
<tr>
<td>TTM randomization</td>
<td></td>
<td></td>
<td>0.351</td>
</tr>
<tr>
<td>33 °C</td>
<td>473 (50.4%)</td>
<td>245 (49.0%)</td>
<td>228 (52.1%)</td>
</tr>
<tr>
<td>36 °C</td>
<td>465 (49.6%)</td>
<td>255 (51.0%)</td>
<td>210 (47.9%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>384 (41.4%)</td>
<td>211 (42.7%)</td>
<td>173 (39.9%)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>589 (62.8%)</td>
<td>296 (59.2%)</td>
<td>293 (66.9%)</td>
</tr>
<tr>
<td>Two largest sites</td>
<td>218 (23.2%)</td>
<td>124 (24.8%)</td>
<td>94 (21.5%)</td>
</tr>
</tbody>
</table>

Data presented as median (first-third interquartile) or as number of cases (percentage). Missing data: CPC (N=6), time of day (N=5), bystander CPR (N=1), EMS chest compression (N=2), three or more defibrillations (N=111), endotracheal intubation (N=13); dose of epinephrine (N=4), shock on admission (N=1), lactate (N=61), and STEMI (N=10). CPC: Cerebral Performance Category Scale; CPR: cardiopulmonary resuscitation; EMS: emergency medical system; TTM: targeted temperature management; STEMI: ST elevation myocardial infarction.

a CPC 1 = good cerebral performance or minor disability; CPC 2 = moderate cerebral disability; CPC 3 = severe cerebral disability; P value calculated for CPC 1 vs. 2-3; b comorbidity was assessed for each patient using a modified version of the Charlson Comorbidity Index and further categorized into four groups: 1) no comorbidity points; 2) one comorbidity point; 3) two comorbidity points; 4) ≥3 comorbidity points; c includes real-time feed-back compression tool or mechanical chest compression device.

groups. Mortality at 180 days was significantly higher in the “place of residence” group, 55.4% (277 of 500), compared to 38.4% (168 of 438, P<0.001) in the “public place/other” group (OR=2.00 [95% CI: 1.54-2.59], P<0.001). Neurological outcome showed similar results with poor outcome in 61.4% (306 of 498) among those arresting at a place of residence compared to 42.9% (186 of 434) in public places or other places (P<0.001).

Univariable and multivariable analyses are presented in Table II. In the multivariable analysis, place of residence was an independent predictor for 180-day mortality (P=0.007), and so were age, shockable rhythm, time to ROSC (all P<0.001), as well as shock on admission (P=0.006). While comorbidity was associated with increased mortality in the univariable analyses, no significant association remained when adjusting for confounders (Table II).
Importance of Location in Cardiac Arrest

Place of residence and their outcomes were significantly worse compared to patients suffering an arrest in public or other places. Female sex, more comorbidity, less shockable rhythm and less bystander CPR characterized patients arrestng at place of residence, while age and proportion of witnessed arrests did not differ. After adjusting for known confounders, cardiac arrest at place of residence remained a strong independent predictor of mortality.

Discussion

In this post-hoc analysis of the TTM trial, approximately half of all patients had an arrest at place of residence and their outcomes were significantly worse compared to patients suffering an arrest in public or other places. Female sex, more comorbidity, less shockable rhythm and less bystander CPR characterized patients arresting at place of residence, while age and proportion of witnessed arrests did not differ. After adjusting for known confounders, cardiac arrest at place of residence remained a strong independent predictor of mortality.

Table II.—Univariable and multivariable analysis of 180-day mortality after out-of-hospital cardiac arrest in the TTM trial.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariable a</th>
<th>Multivariable b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Location, place of residence</td>
<td>2.00 (1.54-2.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of day, 06:00-17:59</td>
<td>0.93 (0.71-1.22)</td>
<td>0.602</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.06 (1.05-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.65 (0.47-0.90)</td>
<td>0.010</td>
</tr>
<tr>
<td>Comorbidity groups a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>ref.</td>
<td>ref.</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.75 (1.30-2.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.65 (1.76-4.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 4</td>
<td>2.94 (1.73-5.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bystander witnessed</td>
<td>0.52 (0.34-0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>0.52 (0.39-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shockable rhythm</td>
<td>0.13 (0.08-0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to ALS, min</td>
<td>1.06 (1.03-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to ROSC, min</td>
<td>1.03 (1.03-1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock on admission</td>
<td>2.69 (1.83-3.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TTM 36 °C</td>
<td>0.97 (0.75-1.26)</td>
<td>0.834</td>
</tr>
</tbody>
</table>

Data provided as median (interquartile range). Missing data: time of day (N=5), bystander CPR (N=1), time to ALS (N=22), shock on admission (N=1). Comorbidity was assessed for each patient using a modified version of the Charlson Comorbidity Index and further categorized into four groups: 1) no comorbidity points; 2) one comorbidity point; 3) two comorbidity points; 4) ≥3 comorbidity points. A logistic regression was used to analyze data.

OR: odds ratio; CI: confidence interval; CPR: cardiopulmonary resuscitation; ALS: advanced life support; ROSC: return of spontaneous circulation; TTM: targeted temperature management.

a Association between each variable and mortality; b association between each variable and mortality, controlling for all other included covariates.
Our results from a large population of initial survivors admitted to intensive care after OHCA showed that place of residence was independently associated with higher mortality and worse neurological outcome compared to arresting in a public place, a finding that deserves attention. Previous studies in larger and unselected prehospital populations have shown similar results, but our findings indicate that place of residence remains strongly associated with poor outcomes among initial survivors admitted to intensive care. In the general population, the proportion of OHCA at place of residence is high, approximately seven of ten, but among initial survivors admitted to intensive care this is reduced to five of ten, as shown here. This reflects the decreased chance of ROSC when arresting at place of residence, which is due to several unfavorable factors including more comorbidity and less bystander CPR in these patients. Some of these factors probably play a role in our study population as well, but there are also differences. For example, in contrast to the results from prehospital studies, neither age nor the proportion of witnessed arrests, both independent predictors of poor outcome, differed between location groups in the present study. Bystander CPR was nevertheless less common at place of residence, more victims were female and in addition, all time intervals were longer, which might explain the higher proportion of non-shockable rhythms. Also, comorbidities were more common, but contrary to findings in prehospital populations, the burden of comorbidity in patients admitted to intensive care was not independently associated with poor outcomes, as previously reported.

The reasons why cardiac arrest at place of residence remained a strong independent predictor of poor outcomes can only be speculated on, but it might be difficult to fully adjust for the frailty associated with being unable to leave one’s house. Previous reports indicate that the frequency of bystander CPR in residential locations is lower, and we present similar findings, in spite of the fact that the proportion of witnessed arrests was similar compared to a public place. This is in line with findings from Tanaka and co-workers who showed that bystander CPR was initiated to a lesser extent by family members, compared with friends, colleagues or others, implying longer no-flow times. In addition, Takei and co-workers demonstrated that the quality of CPR differed depending on where the OHCA occurred and whether the lay-rescuer was related to the victim or not, which might translate to a lower quality of CPR, due to fatigue or lack of training.

Poor outcomes amongst those arresting at place of residence is indeed a problem that demands further attention and the present findings highlight the need to improve early interventions prior to EMS arrival. This could be achieved by intensified education of lay-rescuers, improved dispatcher-assisted CPR and by further deployment of automated external defibrillators (AEDs), reaching out to residential areas to a larger extent.

Recent findings indicate that the deployment of AEDs is skewed in favor of public locations and that their use is less frequent at place of residence compared to a public place. Hansen and co-workers showed that while bystander defibrillation increased from 1.2% to 15.3% in public places during a 12-year period and was associated with improved outcomes, the use of an AED at place of residence remained unchanged at 1.3%. The benefit of home use AEDs has, however, been questioned by others. Efforts to increase good-quality bystander CPR and shorten time to defibrillation, probably the two most important variables in order to achieve better outcomes, should thus be made for patients arresting at place of residence. One such initiative is deployment of a mobile-phone positioning system to dispatch lay volunteers, which has been shown to increase rates of bystander initiated CPR. Using unmanned aerial systems, so-called drones, carrying an AED to the location of an OHCA may be another way of reducing time to defibrillation in the near future, but their actual impact on survival numbers is less certain.

Limitations of the study

Limitations of this study include investigating selected OHCA patients of presumed cardiac
origin who were included in a randomized trial. The actual cause of cardiac arrest however was not registered, which is a potential weakness. Patients with unwitnessed cardiac arrest and initial asystole as well as patients with a non-cardiac cause were not included and our results can therefore not be generalized to the entire prehospital OHCA population. Few previous studies, however, present detailed data for selected patients with sustained ROSC in the ICU, which we consider a strength. The lack of data on all 22 relevant comorbidities did not enable us to use the full CCI,22 which is a weakness; instead we used the modified version (mCCI) as described.22 Another weakness is the limitation to fully adjust for known and unknown confounders, including the use of sedation and neuromuscular blockade. Also, patient inclusion was carried out between 2010 and 2013, and potential changes in the EMS systems since then have not been taken into account. Strengths include controlled data from a large international multicenter trial and no missing data on the primary outcome measure.

Conclusions

In conclusion, patients who suffer a cardiac arrest at place of residence and are admitted to intensive care have worse outcomes than those resuscitated at public or other places. After adjusting for known confounders, cardiac arrest at place of residence remained a strong independent predictor of mortality, which implies that other yet unknown factors contribute to poor outcomes. Actions to improve outcomes after OHCA at place of residence constitute a great challenge and should be addressed in future trials.

What is known

- A majority of out-of-hospital cardiac arrests (≈70%) occurs at the place of residence, which is associated with worse outcomes.
- This is due to higher age, more comorbidities, more unwitnessed arrests, less bystander CPR and longer response times compared to patients arresting in a public place.

What is new

- Among initial survivors admitted to intensive care, the proportion of patients arresting at place of residence was similar to that of victims in a public place, while outcomes remained worse.
- There was no difference in age or proportion of witnessed arrests between groups, but fewer patients received bystander CPR and response times were longer at place of residence.
- Cardiac arrest at place of residence remains a strong independent predictor of poor outcome among initial survivors admitted to intensive care.

References


Conflicts of interest.—Janneke Horn reports receiving lecture fees from Bard Medical. Niklas Nielsen has received speaking fees from Bard Medical and is on the Advisory Board for BrainCool AB. Hans Friberg reports receiving lecture fees from Bard Medical and is a scientific advisor for QuickCool. All of the other authors report no conflicts of interest.

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Congresses.—The early results of the study have been presented at the European Resuscitation Council Conference in Freiburg, Germany, in September 2017.


For supplementary materials, please see the HTML version of this article at www.minevamedica.it
ABSTRACT

BACKGROUND: It has been reported that noninvasive, objective tests are needed for determining the success of peripheral nerve blocks because conventional methods necessitate the cooperation of the patient. It is also known that the brachial plexus block causes vasodilatation and an increase in blood flow due to its sympathectomy effect. Our study aimed to determine whether Perfusion Index (PI) and measured regional hemodynamic changes using ultrasound were reliable parameters in evaluating the early success of an infraclavicular block.

METHODS: Forty ASA I-III patients who were administered a successful infraclavicular block were included in this study. In addition to the baseline hemodynamic measurements, PI and regional hemodynamic parameters, such as brachial artery diameter (BAD), brachial arterial area (BAA), blood flow (BF), end-diastolic velocity (EDV), Resistance Index (RI), peak systolic velocity (PSV), and time average velocity (TAV) were measured. After completing the block procedure, all values were rerecorded at the 10th, 20th, and 30th minute. Patients with a successful block during the first 10 minutes were assigned to Group A, while patients with a successful block after the 10th minute were assigned to Group B.

RESULTS: Statistically significant differences were observed for all regional hemodynamic variables and PI after 10 minutes. When the regional hemodynamic data and PI were compared between the groups, differences were identified for PI, BF, PSV, EDV, and TAV. Within the measured parameters, EDV was the parameter showing the greatest proportional change.

CONCLUSIONS: Changes in EDV, especially RI and PI, provide more effective and objective results for the assessment of early regional block success.

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KEY WORDS: Autonomic nerve block; Doppler ultrasonography; Perfusion.

Conventional methods such as detection of sensory block via cold stimulation or pin-prick test are generally used when determining the success of peripheral nerve blocks. These tests are subjective and necessitate the cooperation of the patient.1, 2 It has therefore been reported that noninvasive, objective tests are needed for an accurate determination of success.3

Many regional hemodynamic changes have been reported in the ipsilateral upper extremity following a sensory block. Sympathetic blockage related to plexus blocks and the resulting vasodilatation lead to an increased blood flow within the extremity, which could be used in the evaluation of block success. In some studies, it has been shown that regional hemodynamic parameters, such as brachial artery diameter (BAD, mm), brachial arterial area (BAA, mm²), blood flow (BF, mL/min), end-diastolic velocity (EDV, cm/s) and Resistance Index (RI), which can be
measured using spectral Doppler ultrasound, were significantly changed following the block. The Perfusion Index (PI) has been used to evaluate peripheral perfusion dynamics as a result of changes in the peripheral vascular tone. Ipsilateral PI has been demonstrated to increase subsequent to the block and can be used as a method to evaluate the success of blocks. However, thus far, we have been unable to find a comprehensive study comparing brachial artery measurements with ultrasound and PI parameters to evaluate block success.

The aim of our study was to compare the regional hemodynamic data obtained via ultrasonography and PI data observed prior to and after the block that appear as a result of the changes observed in extremity blood flow in patients undergoing infraclavicular block, and to investigate their efficacy in evaluating the early success of the block.

**Materials and methods**

This study was conducted at the Department of Anesthesiology and Reanimation, Faculty of Medicine, Bülent Ecevit University between July 15th, 2016 and July 15th, 2017, following the approval of the Clinical Research Ethical Committee (meeting No.: 2016-81-29/06) and after obtaining written informed consent from the patients.

The study included a total of 40 patients between 18 and 65 years of age with an ASA status of I-III, who underwent an infraclavicular block due to elective, unilateral carpal, or cubital operations, which was evaluated as successful. Those with a neurological deficit, ipsilateral major vascular trauma, mental retardation, alcohol or drug abuse, allergy to local anesthetic agent (LAA) including amide groups, morbid obesity, coagulopathy, chronic analgesic therapy, α and/or β blocker intake, diabetes mellitus, those who were pregnant, and those with contraindications to infraclavicular block were excluded from the study.

The demographic characteristics (age, height, weight, gender) and ASA risk groups of the patients were recorded.

The patients were taken into rooms at a temperature of 23-24 °C. Prior to the blockage, electrocardiographic data (ECG), heart rate (HR), respiratory rate (RR), noninvasive blood pressure (from the contralateral arm) (BP), and peripheral oxygen saturation (SpO₂) were monitored. Vascular access was established from the contralateral arm using a 20-gauge intracath, and a crystalloid infusion at 10 mL/kg/h was begun. The patients were administered 0.01 mg/kg of intravenous (IV) midazolam (Zolamid 5 mg/5 mL, Deferma, Turkey) and 1 µg/kg of fentanyl (Talinat 0.5 mg/10 mL, Vem Ilaç, Çerkezköy, Turkey). All patients underwent blockage and received 2-4 L/min of oxygen through a face mask throughout the operation.

In addition to the basic hemodynamic measurements, a pulse oximetry sensor was placed on the second finger of the ipsilateral upper extremity (RZ-25 adult, adhesive sensors Masimo SET® Radical™ pulse oximeters, Masimo Corp., Irvine, CA, USA) to obtain PI measurements. This was connected to a Rad-7™ Pulse CO-oximetre instrument. A 10- to 18-MHz linear probe (using an Esaote ultrasound [US] device) was used to take the patients’ Doppler US measurements.

The basal hemodynamic, US, and PI data were recorded just prior to the procedure. Doppler US measurements were obtained by sagittal monitoring of the brachial artery from a 2–4 cm proximal aspect of the ipsilateral antecubital fossa. The B mode US image was optimized, and the Doppler US mode was switched on. Sample volume measurements were set to include the whole of the brachial artery lumen. The Doppler angle between the blood flow and Doppler line was set to 30-60 °C. The image was frozen when cardiac traces were obtained in the form of spectral waves. To minimize measurement mistakes, five consecutive cardiac cycles were evaluated. The borders of the cardiac cycles were drawn. Peak systolic velocity (PSV, cm/s), EDV, time average velocity (TAV, cm/s), and RI values were recorded. In general, the BAD demonstrates a 10% difference between systolic and diastolic beats. Thus, the end-diastole of the ECG trace of the initial cardiac cycle was marked using the US device’s trackball in B mode US. End-diastolic BAD was measured as the vertical distance between two lumens of the vessel and was record-
ed. The BAA was measured automatically by the US device, and the flow rate was measured using this TAV area (FR, ml/dk) and recorded. To standardization the measurements performed after the procedure, the initial site of the brachial artery Doppler US measurements was marked using a skin marker pen. Baseline sensory examination of the patients was performed using the pinprick test and recorded.

Following the baseline data recording, the infraclavicular block procedure was begun. The patients were placed in the supine position with their heads facing the contralateral side. The injection site was cleaned using povidone iodine. Prior to the block, US gel was spread over the linear probe, and it was covered with a plastic cover. The site of the procedure was covered with sterile gel, and the longitudinal axis (in-plane) image was planned to be obtained using US.

The probe was placed 1 cm to the anterior aspect of the coracoid process to obtain the sectional image of the axillary artery passing below the pectoralis minor muscle in the sagittal plan.

For the blocking procedure, 22-gauge, 80-mm echogenic needles (Stimuplex Ultra, B. Braun, Melsungen, Germany) with electro-neurostimulation ports were used. When the axillary artery was visualized via US, 2 mL of lidocaine (Jetmonal 2%, 20 mg/mL, Adeka, Istanbul, Turkey) was injected to the planned injection site via cutaneous-subcutaneous infiltration. The stimulation needle to be used for the blockage was connected to the nerve stimulator concomitantly (Stimuplex HNS 11, B. Braun). The anode (positive pole) of the nerve stimulator was connected to the ECG electrode on the shoulder of the block side.

The stimulation needle was inserted through the skin and placed in the 6-8 o’clock direction of the axillary artery using the “in-plane” method under the guidance of the US probe. The concomitant stimulator was turned “on,” and in case of motor movement at 0.5 mA, a local anesthetic agent was injected as a single dose following a negative aspiration test (the test was repeated after each 5 mL injection of LAA. In case of a nonresponse with a sufficient current in the stimulator during the complete positioning of the needle, in case of a lack of an accurate visualized distribution of the LA solution, and in case of resistance or pain observed during injection, the needle was redirected with minimal movements. As LAA, 10 mL of 2% lidocaine (Jetmonal 2%, 20 mg/mL, Adeka) and 20 mL of 0.5% bupivacaine (Buvasin 0.5%, 20 mL, Vem Ilaç) were used. Following the complete injection of the anesthetic agent, the U-shaped distribution of the solution around the axillary artery was visualized. The chronometer was set as soon as the needle exited the skin.

All blocks were performed by the same anesthesiologist. All measurements and examination findings were performed by another anesthesiologist and were recorded.

Following the completion of the blockage (exit of the needle from the skin was accepted as minute 0), SpO2, mean arterial pressure (MAP), KAH and PI, TAV, BAD, BAA, AH, PSV, EDV, and RI were recorded at the 10th, 20th, and 30th minute.

The duration of sensory loss was evaluated using the pinprick test, and the quality of the anesthesia and blockage were evaluated using the Hollmen scale (Quality of anesthesia: 0 = normal transmission using the pinprick test; 1 = needle sensed less compared to the contralateral extremity; 2 = feeling the needle as a blunt object; 3 = loss of tactile sense; Quality of motor block: 0 = normal muscular function; 1 = reduced muscular function compared to preblockage; 2 = significantly reduced muscular function; 3 = complete motor block).

Quality of anesthesia and quality of motor block were recorded concomitantly (0, 10, 20, 30 minutes). In the pinprick test, the presence of pain in the related dermatomes was investigated using 27-G blunt dental needles. The quality of the motor block was investigated by evaluating the movements in the shoulder, elbow, wrist, and fingers of the blocked extremity.

Patients with a score of at least two from each quality of the Hollmen scale (quality of anesthesia and quality of motor block), who did not require additional anesthesia during the operation, were said to have a successful block. The data of the patients with a successful block within the first 10 minutes were assigned to Group A, and those with a successful block later than the first 10 minutes were assigned to Group B.
Statistical analysis

The findings were evaluated using the SPSS for Windows v. 19.0 program package. We examined the normality distribution of numerical variables using the Shapiro-Wilk test. Descriptive statistics were presented by means and standard deviations or by medians and interquartile ranges for numerical variables. We presented categorical variables using frequencies and percentages. Repeated means were compared by ANOVA or Friedman test prior to post-hoc comparisons. The Friedman test was also performed to explore the difference between repeated medians. Two independent means were compared using a Student’s t-test. The relationship between two categorical variables was investigated using a χ² test. The ROC curve and Youden Index method were used to understand the optimal cutoff points of independent variables. A P value <0.05 was chosen as a significance level.

Results

A total of 40 patients who underwent successful infraclavicular block for hand, wrist, ankle, arm, and elbow operations were included in the study. Procedure-related or LA injection-related complications were not observed.

Among the participants, 11 (27.5%) were female, and 29 (72.5%) were male. The mean age was 36.4 years, the mean Body Mass Index (BMI) 25.33 kg/m². According to the Holmenn Scale, a complete block was observed in 11 patients (27.5%) at the 10th minute, in 37 patients (92.5%) at the 20th minute, and in all patients at the 30th minute. There was no significant difference in demographic characteristics between the groups (P>0.05) (Table I).

It was observed in our measurements that early diastolic flow, which typically was initially negative, was elevated to positive values at the 10th minute following the block (Figure 1).

When the parameters related to success were examined, it was seen that the greatest percentage change was in EDV, BF, PI, and TAV, respectively, and the percent change in 10th minute values was statistically significant when compared to measured values at other time intervals (P<0.001) (Table II).

The baseline HR, MAP, and SpO₂ values were statistically similar to those measured at 10, 20, and 30 minutes after blockage. A significant difference was observed between the baseline of the regional hemodynamic measurements and PI and those at 10, 20, and 30 minutes (Table III).

The systemic hemodynamic data were similar between the groups at the baseline (P>0.05). Regarding the useful parameters in early successful blocks, a significant difference was observed between all parameters except for the BAD and BAA at the baseline and at the 10th minute between the groups (P<0.05). Only PI and PSV were different between the groups with regard to the initial regional hemodynamic parameters (P<0.05) (Table IV).

A ROC analysis was performed for the parameters that were found to significantly change in the first 10 minutes. Table V shows the cutoff value of these parameters.

Discussion

In our study, it was observed that regional hemodynamic data measured via PI and spectral Doppler US were effective in evaluating the success of the block. In particular, EDV, RI, and PI changes were observed to provide more ef-

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (N=40)</th>
<th>Group A (N=11)</th>
<th>Group B (N=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>36.4±13.13</td>
<td>38.9±14.6</td>
<td>35.5±12.7</td>
<td>0.464</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (27.5%)</td>
<td>5 (45.5%)</td>
<td>6 (20.7%)</td>
<td>0.137</td>
</tr>
<tr>
<td>Male</td>
<td>29 (72.5%)</td>
<td>6 (54.5%)</td>
<td>23 (79.3%)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.33±4.18</td>
<td>26.5±4.66</td>
<td>24.9±4.0</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or as number of patients (percentage).
generally assessed using cold stimulation or the pinprick test to find the sensory block level. Such tests are subjective and necessitate patient effective and objective results in the evaluation of regional blocks.

The success of peripheral nerve blocks is generally assessed using cold stimulation or the pinprick test to find the sensory block level. Such tests are subjective and necessitate patient
Table IV.—Comparison of the systemic and regional hemodynamic parameters between Group A (N=11) and Group B (N=29).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>0 minutes</th>
<th>10 minutes</th>
<th>20 minutes</th>
<th>30 minutes</th>
<th>P&lt;sub&gt;i&lt;/sub&gt; value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>Group A</td>
<td>71.7±10.6</td>
<td>70.5±12.4</td>
<td>70.9±12.6</td>
<td>71.4±12.7</td>
<td>0.214</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>77.8±15.8</td>
<td>75.8±14.5</td>
<td>75.9±15.0</td>
<td>75.5±14.8</td>
<td>0.264</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.262</td>
<td>0.296</td>
<td>0.413</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>Group A</td>
<td>88.8±18.7</td>
<td>90.4±15.2</td>
<td>89.7±18.8</td>
<td>93.6±18.2</td>
<td>0.070</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>95.1±14.2</td>
<td>90.6±10.1</td>
<td>91.8±11.4</td>
<td>92.2±12.7</td>
<td>0.032* a</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.208</td>
<td>&gt;0.999</td>
<td>0.628</td>
<td>0.820</td>
<td></td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Group A</td>
<td>97.6±0.94</td>
<td>97.2±0.99</td>
<td>97.6±1.13</td>
<td>97.3±0.91</td>
<td>0.433</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>97.7±1.50</td>
<td>97.3±1.78</td>
<td>97.1±1.68</td>
<td>97.4±1.62</td>
<td>0.009* b</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.424</td>
<td>0.412</td>
<td>0.599</td>
<td>0.400</td>
<td></td>
</tr>
<tr>
<td>TAV</td>
<td>Group A</td>
<td>14.6±12.5</td>
<td>33.0±18.4</td>
<td>33.6±19.0</td>
<td>34.1±18.8</td>
<td>&lt;0.001* a,b,c</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>8.29±6.01</td>
<td>15.6±8.82</td>
<td>21.4±12.3</td>
<td>22.4±13.2</td>
<td>&lt;0.001* a,b,c,d,e</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.087</td>
<td>0.003*</td>
<td>0.051</td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>BAD</td>
<td>Group A</td>
<td>3.81±0.49</td>
<td>4.13±0.52</td>
<td>4.25±0.44</td>
<td>4.55±0.42</td>
<td>&lt;0.001* b,c,e</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>3.89±0.61</td>
<td>4.24±0.55</td>
<td>4.46±0.55</td>
<td>4.75±0.61</td>
<td>&lt;0.001* a,b,c,c,f</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.402</td>
<td>0.659</td>
<td>0.224</td>
<td>0.280</td>
<td></td>
</tr>
<tr>
<td>BAA</td>
<td>Group A</td>
<td>11.5±3.17</td>
<td>13.6±3.30</td>
<td>14.3±2.96</td>
<td>16.3±2.89</td>
<td>&lt;0.001* c,e</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>12.3±3.83</td>
<td>14.3±3.60</td>
<td>15.9±3.79</td>
<td>17.9±4.50</td>
<td>&lt;0.001* a,b,c,c,f</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.405</td>
<td>0.650</td>
<td>0.209</td>
<td>0.282</td>
<td></td>
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<tr>
<td>AH</td>
<td>Group A</td>
<td>97.3±72.7</td>
<td>27±163</td>
<td>295±177</td>
<td>338±201</td>
<td>&lt;0.001* a,b,c,d,e,f</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>64.1±55.3</td>
<td>132±80.4</td>
<td>198±123</td>
<td>238±153</td>
<td>&lt;0.001* a,b,c,d,e,f</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.177</td>
<td>0.007*</td>
<td>0.163</td>
<td>0.108</td>
<td></td>
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<tr>
<td>PSV</td>
<td>Group A</td>
<td>56.8±34.8</td>
<td>75.9±42.1</td>
<td>74.3±40.9</td>
<td>73.0±40.6</td>
<td>0.017* a,b</td>
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<tr>
<td></td>
<td>Group B</td>
<td>33.3±21.5</td>
<td>40.6±24.3</td>
<td>47.2±27.0</td>
<td>48.0±29.2</td>
<td>&lt;0.001* a,b,c,d,e</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.04*</td>
<td>0.008*</td>
<td>0.076</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>EDV</td>
<td>Group A</td>
<td>3.75±5.82</td>
<td>21.4±13.8</td>
<td>23.4±15.1</td>
<td>25.1±14.9</td>
<td>&lt;0.001* a,b,c</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>2.25±2.72</td>
<td>8.22±4.68</td>
<td>13.9±8.52</td>
<td>15.6±9.92</td>
<td>&lt;0.001* a,b,c,d,e</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.347</td>
<td>0.01*</td>
<td>0.049*</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>Group A</td>
<td>3.83±1.92</td>
<td>9.11±2.45</td>
<td>10.9±2.70</td>
<td>11.3±3.02</td>
<td>&lt;0.001* b,c,e</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>2.39±1.41</td>
<td>6.36±2.30</td>
<td>8.73±3.00</td>
<td>10.3±3.34</td>
<td>&lt;0.001* a,b,c,d,e,f</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.010*</td>
<td>0.008*</td>
<td>0.021*</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>Group A</td>
<td>0.94±0.06</td>
<td>0.73±0.06</td>
<td>0.70±0.06</td>
<td>0.66±0.07</td>
<td>&lt;0.001* b,c,e</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>0.93±0.07</td>
<td>0.79±0.10</td>
<td>0.71±0.09</td>
<td>0.69±0.09</td>
<td>&lt;0.001* a,b,c,e</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; value</td>
<td></td>
<td>0.915</td>
<td>0.007*</td>
<td>0.671</td>
<td>0.296</td>
<td></td>
</tr>
</tbody>
</table>

HR: heart rate; MAP: mean arterial pressure; SpO<sub>2</sub>: peripheral oxygen saturation; PI: Perfusion Index; TAV: time average velocity; BAD: brachial artery diameter; BAA: brachial artery area; BF: blood flow; PSV: peak systolic velocity; EDV: end-diastolic velocity; RI: Resistance Index; P<sub>i</sub> value: within-group comparison; P<sub>i</sub> value: between-group comparison. *Statistically significant difference; a: 0-10; b: 0-20; c: 0-30; d: 10-20; e: 10-30; f: 20-30.

Table V.—Cutoff value of perfusion index and regional hemodynamic parameters and in the first 10 minutes.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV10</td>
<td>0.846</td>
<td>0.719-0.974</td>
<td>0.001</td>
<td>≥7.15</td>
<td>100%</td>
<td>55.2%</td>
</tr>
<tr>
<td>TAV10</td>
<td>0.806</td>
<td>0.653-0.959</td>
<td>0.003</td>
<td>≥24.4</td>
<td>63.6%</td>
<td>86.2%</td>
</tr>
<tr>
<td>BF10</td>
<td>0.779</td>
<td>0.616-0.952</td>
<td>0.007</td>
<td>≥112.5</td>
<td>90.9%</td>
<td>58.6%</td>
</tr>
<tr>
<td>RI10</td>
<td>0.779</td>
<td>0.639-0.919</td>
<td>0.007</td>
<td>≤0.795</td>
<td>100%</td>
<td>58.6%</td>
</tr>
<tr>
<td>PI10</td>
<td>0.776</td>
<td>0.617-0.935</td>
<td>0.008</td>
<td>≥9.2</td>
<td>54.3%</td>
<td>96.6%</td>
</tr>
<tr>
<td>PSV10</td>
<td>0.774</td>
<td>0.601-0.948</td>
<td>0.008</td>
<td>≥106.3</td>
<td>45.5%</td>
<td>100%</td>
</tr>
</tbody>
</table>

cooperation.² Regional anesthesia can be provided under general anesthesia or deep sedation in some patients, which may mask complications or the failure of the block.⁹ Therefore, noninvasive, objective, independent-observer tests are needed.³ Brachial plexus blockage leads to vasodilation in the ipsilateral upper extremity and results in increased blood flow.¹⁰ In the light of this information, in our study, we investigated the relationship between regional hemodynamic changes after the infraclavicular block and the success.
of the block. The PI, TAV, BAD, BAA, BF, PSV, EDV, and RI variables were compared to evaluate the success of the block. We observed that the PI and spectral wave-measured PSV, EDV, TAV, BF, BAD, and BAA values were increased, whereas RI was decreased.

In their study, Li et al.\textsuperscript{4} reported that there was no significant difference in systemic hemodynamic changes following an axillary block. In our study, we have obtained the same results. However, there are conflicting outcomes in the literature on the subject. We believe that these conflicting results may have arisen from many factors, such as premedications, the initial pain status of the patients, and the anxiety formed because of the procedure.

The spectral wave form is triphasic. The triphasic wave comprises a rapid forward flow during systole and a subsequent early diastolic short retro-flow (protodiastolic flow) and a forward flow for a variable period during diastole. This type of circulation with high peripheral vascular resistance is typical in the extremities.\textsuperscript{11, 12} In our study, it was observed that the disappearance of the retro-flow during early diastole and the spectral wave observed as a switch from a triphasic wave to a monophasic wave with an increased diastolic flow were the earliest changes at the 10th minute in regional hemodynamic changes following a block.

Li et al.\textsuperscript{4} showed that the most significant difference was observed in the EDV with a 3.7-fold increase following an axillary brachial plexus block. In the same study, this increase was reported at the 5th minute. In another study investigating the regional hemodynamic changes in the radial and ulnar arteries of patients undergoing primary palmar hyperhidrosis due to a thoracic sympathetic block, EDV was reported to be significantly increased.\textsuperscript{13} In our study, EDV was observed to be the parameter with the most significant change following the block at the 10th minute (3.45 times). The cutoff value of EDV was found $\geq 7.15$ for early success.

PI is a parameter that reflects the strength of tissue perfusion by calculating the relationship between pulsatile (arterial blood) and nonpulsatile (venous blood or tissue blood) light in the pulse oximeter.\textsuperscript{5, 14, 15} The output volume, skin temperature, and vasomotor tonus are the main factors that affect the PI, and the blood flow within the monitored area affects PI measurements.\textsuperscript{16} In the study evaluating the effect of infraclavicular block on regional perfusion, an infraclavicular block was shown to increase the brachial artery BF and PI, and PI significantly increased at 5 min post-blockade in the blocked limb, from 4±3 to 9±5 (2.25 times).\textsuperscript{17} In the study of Kuş et al.\textsuperscript{6} investigating the efficacy of PI in the assessment of infraclavicular block success, PI was shown to increase by 1.94 times at 10 minutes after the block. In the successful group, 10-, 20-, 30-minute percent change of the PI was statistically higher when compared with the initial value ($P<0.001$). In our study, the increase in PI was 2.56 times at 10 minutes and also percent changes of PI measured in the time interval of 0-10th min were statistically higher than the time interval of 10-20 minutes ($P<0.001$).

Abdulnasser et al.\textsuperscript{18} showed that PI at 10 min was a good measurement to predict supraclavicular block success with a cutoff value >3.3. In our study, the mean PI value measured in patients with a successful block after the 10th minute was determined to be 6.4±2.3 with a cutoff value >9.2. We believe this difference in cutoff values may be because the two studies were performed using different nerve blocks.

Iskandar et al.\textsuperscript{10} showed that brachial artery BF after 30 min. following an interscalene block increased from 32 (18-46) mL/min to 88 (59-98) mL/min (2.75 times, $P<0.01$). A similar increase was observed by Ebert et al.\textsuperscript{19} in their study following an axillary block (1.9 times). This increased BF in the ipsilateral side was said to shorten the period of improvement, especially in patients undergoing a venous fistula operation due to terminal stage renal failure, in addition to those undergoing microsurgery.\textsuperscript{20} Shemesh et al.\textsuperscript{21, 22} reported that a brachial plexus block provided venous and arterial vasodilatation and increased the success rate in AV fistula operations. In our study, the mean values of the brachial artery BF volume were found to be increased by 2.32, 3.07, and 3.62 times at the 10, 20, and 30 minutes, respectively, similar to the literature.

Previous studies have demonstrated a sig-
nificant increase in BAD and BAA following a brachial plexus blockage starting at the 10th minute.\(^4\)\(^,\)\(^19\) In our study, BAD and BAA were found to be significantly increased by the 10th minute, but BAD and BAA were not effective in revealing the early success of the block (\(P>0.05\)).

Normally, there is a 10% difference between the systolic and diastolic brachial artery diameter.\(^23\) We took the BAD measurements at the end of the diastoles. Mistakes, especially in the vessel diameter, would lead to a second-degree exponential mistake when calculating the vessel area, and a third-degree exponential mistake when calculating the flow volume.\(^23\) Furthermore, an observer-related difference may be seen in the measurements. In their study, Li et al.\(^4\) investigated regional hemodynamic changes following axillary blockage, and 1520% of the changes in BF were observed in observer-related measurements. Therefore, all measurements were performed by the same observer in our study, and the first site of measurement was marked to ensure the same measurement of each site. BF measurement, on the other hand, is not only related to the diameter but changes proportional to the flow rate and, thus, we believe it is a rather objective parameter compared to the BAD and BAA.

Li et al.\(^4\) showed that PSV was significantly increased at the 10th minute (1.36 times) but demonstrated no significant increase at the 5th minute in contrast to other parameters. In our study, PSV was observed to increase link in previous studies, and a 1.37-fold increase was observed at the 10th minute. These findings make us expand the use of PSV as an early indicator of block success.

Studies have reported significantly increased TAV starting at the 10th minute.\(^4\)\(^,\)\(^7\) In our study, TAV was the most increased parameter after EDV, PI, BF, and PSV. It increased by 1.03, 1.46, and 1.57 times at 10, 20, and 30 minutes, respectively.

As discussed previously, all parameters evaluated are susceptible to measurement and/or observer mistakes, except for the PI. However, parameters that have a rational value, such as RI, may provide more reliable data. The RI is calculated using the formula \((PSV-EDV)/PSV\).\(^24\) Fei et al.\(^13\) showed that the RI of the radial artery (RA) and ulnar artery (UA) of the patients after surgery were 0.85±0.05 and 0.97±0.07, respectively, while the RI of the RA and UA were 0.57±0.04 and 0.64±0.09, respectively, thus they had significantly decreased after surgery. The difference was statistically significant (\(P<0.01\)). In our study, similar decreases in RI were observed. During the literature search, many methods were used to evaluate the motor block, such as the Bromage Scale, the Modified Bromage scale, the Lovett rating scale, and the Holmenn scale. Loss of cold sensation, loss of vibration sense, and pinprick tests were also used to evaluate the sensory block.\(^25\)\(^,\)\(^26\) In their study, Galvin et al.\(^27\) reported the loss of cold sense as a more sensitive test than the pinprick test in the evaluation of sensory block following an axillary block. Lee et al.\(^28\) designed their durations of axillary block and sensory and motor blocks according to the Hollmen scale. In our study, both motor and sensory blocks were evaluated using the Hollmen Scale. To parallel previous studies, blocks in patients with a score of at least 2 in both motor and sensory blocks were accepted as successful.

Limitations of the study

The main limitations of the present study are the lack of an unsuccessful nerve block group and the fact that the initial value of PI was different between the groups, so more reliable values can be attained by performing studies with a larger group of patients.

Conclusions

Regional hemodynamic variables and PI showed a significant change in a successful infraclavicular block after the 10th minute. The highest change was observed in EDV using a spectral Doppler ultrasound during the evaluation of the block's success. However, we think that RI will be a more objective measurement of the success because it \(((PSV-EDV)/PSV)\) is a rational value. If ultrasound cannot be used to evaluate block success, we think the perfusion index technology is easily applicable even though it is new.

As subjective methods could be insufficient in...
evaluating block success, and there is the need for effective time usage in operating rooms, we believe that RI and PI would provide more effective and objective outcomes in the evaluation of regional blocks because they are least affected by practitioner and measurement mistakes.

What is known

- Traditional methods to evaluate the success of blocks requires patient cooperation.
- After successful peripheral nerve blockade, changes in the regional hemodynamic parameters and Perfusion Index can be seen.
- Hemodynamic parameters such as end-diastolic velocity, Resistance Index, and Perfusion Index monitoring may provide a quick evaluation of block success.
- Resistance Index and Perfusion Index appear to be more objective parameters for evaluating early block success.

What is new

- Hemodynamic parameters such as end-diastolic velocity, Resistance Index, and Perfusion Index monitoring may provide a quick evaluation of block success.
- Resistance Index and Perfusion Index appear to be more objective parameters for evaluating early block success.

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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.

LMA® Protector™ versus traditional LMA to perform endobronchial ultrasound-guided transbronchial needle aspiration: a retrospective analysis

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ABSTRACT

BACKGROUND: The aim of this study was to evaluate the use of laryngeal mask airway (LMA)® Protector™ by comparison with traditional LMA for performing endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

METHODS: This was a retrospective observational single-center study including 143 patients who underwent EBUS-TBNA for mediastinal staging of lung cancer. Patients were retrospectively divided into two groups based on whether a traditional LMA (traditional LMA group) or LMA Protector was used. Anesthesiologist outcomes, diagnostic yield of EBUS-TBNA, and complications related to the procedure were computed for each group and statistically compared.

RESULTS: LMA traditional group and LMA Protector group counted 70 and 73 patients, respectively. LMA traditional group versus LMA Protector group showed no significant difference on time of LMA insertion (120±25 vs. 118±39 s; P=0.49), reposition rates (18% vs. 16%; P=0.78); systolic pressure (140±55 vs. 118±37 mmHg; P=0.59); diastolic pressure (82±15 vs. 90±26 mmHg; P=0.39); heart rate (82±9.9 vs. 83±20 bpm; P=0.49); SpO2 values (93±21% vs. 92±14%; P=0.63); diagnostic accuracy (91.3% vs. 92%; P=0.95), and patients’ complications as nausea (4% vs. 3%; P=0.61); vomiting (3% vs. 1%; P=0.96); gastric aspiration (7% vs. 1%; P=0.08); and sore throat (7% vs. 3%; P=0.22). Conversely, LMA traditional group versus LMA Protector group presented a longer procedural time (47±23 vs. 38±17 s; P=0.02), higher number of passage to biopsy target lesion (4±0.5 vs. 3.1±0.6; P=0.01); higher rate of balloon ultrasound rupture (11% vs. 1%; P=0.01).

CONCLUSIONS: EBUS-TBNA conducted with LMA Protector is a useful strategy that reduced the procedural time and in theory ensured the comfort of patients. Our results should be confirmed by larger, prospective, randomized studies.


KEY WORDS: Laryngeal masks; Deep sedation; Bronchoscopy.

Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has become the first invasive approach for mediastinal staging in lung cancer.1 The main advantage compared to traditional TBNA is the possibility of guiding in real-time the puncture of lymph nodes.2 However, compared to traditional TBNA, EBUS-TBNA is a more time-consuming procedure
that requires adequate sedation in order to provide comfortable environment for the patient and enable the physician to obtain adequate tissue samples. Generally, EBUS-TBNA is performed under general anesthesia via an artificial airway such as laryngeal mask airway (LMA) or endotracheal tube (ETT). Even though the LMA allows the access to higher mediastinal lymph node stations that would otherwise be obscured by the ETT, however, its shape is not fully suitable for ultrasound bronchoscope. The friction due to the passage of the ultrasound bronchoscopy through the traditional LMA could damage the instrument or the EBUS distal balloon and limit the endoscopic maneuvers. The LMA® Protector™ (Teleflex Medical, Wayne, PA, USA) is a new type of laryngeal mask. Conversely to the traditional LMA, the distal end of airway tube of the LMA Protector is elliptical in cross section to facilitate insertion in patients with reduced interdental space, without increasing the resistance to breathing. The firm, anatomical shape facilitates easy insertion without placing fingers in the mouth and also helps minimize accidental rotation, once in place. Furthermore, it offers a better manageability of EBUS bronchoscope when it is introduced through it. The aim of this paper was to evaluate the use of LMA Protector by comparison with traditional LMA for performing EBUS-TBNA.

Materials and methods

Study design

It was a retrospective observational study performed at Monaldi Hospital, in Naples, Italy. All consecutive patients undergoing EBUS-TBNA for mediastinal staging of lung cancer between January 2016 and May 2018 were eligible. Patients aged >18 years with mediastinal adenopathies located in stations accessible by EBUS-TBNA and fit for ultrasound bronchoscopy were included in the study. Patients with ASA Class >III, with increased risk of aspiration, with upper airway pathology and mouth opening of less than 2 cm were excluded since in these cases EBUS-TBNA procedure was performed using endotracheal tube. From 2017, LMA Protector was routinely used for EBUS-TBNA procedure at our hospital. Patients were retrospectively divided in two groups based on whether EBUS-TBNA was performed using traditional LMA (traditional LMA group) or LMA (LMA Protector group). The intergroup differences based on anesthesiology outcomes, diagnostic yield, and complications were statistically compared to confirm the better performance of LMA Protector over traditional LMA for performing EBUS-TBNA (clinical hypothesis of the study). Data were recorded in a prospective data base and then retrospectively analyzed. All patients gave signed written informed consent and were aware that the data could be used for scientific purpose only.

Study population

A total of 230 consecutive patients with lung cancer and mediastinal adenopathies was scheduled for EBUS-TBNA in the study period. According to standard clinical recommendations, all patients underwent a contrast enhanced whole body positron emission tomography/computed tomography (PET/CT). Mediastinal LN were suspected of involvement if the short-axis diameter was >1 cm or FDG-avid on PET scan (standardized uptake value [SUV] >2.5). Demographic, clinical and pathological data were recorded.

EBUS-TBNA procedure

All procedures were performed in a dedicated endoscopic room. Midazolam 0.05 mg/kg was given as premedication. Anesthesia induction was performed with propofol 1 mg/kg and a 0.05 µg/kg/min remifentanil infusion was started. No neuromuscular blockade was used. During anesthesia, monitoring was continuous ECG, SpO₂, EtCO₂, and NIBP, according to the non-operating room anesthesia (NORA) guidelines. Once patient reached RASS 4 or less, he was placed in a semi-sniffing position and the traditional LMA or the LMA Protector was inserted in a standard manner. The tip of the device was pushed forward the hard palate and the mask was gently driven until resistance was felt. The proper position of the LMA was confirmed by the endoscopy view of vocal folds and the cuff was then inflated. Anesthesia was maintained with
propofol and remifentanil continuous infusion. LMA was connected to mechanical ventilation in CPAP mode with 5 cmH$_2$O and FiO$_2$ 0.5. After the end of the procedure, propofol infusion was stopped; the patient was oxygenated via a face mask and transferred to the recovery area before being discharged home.

Outcome measures

Anesthesiology outcomes

The time to achieve airway control, from pickup of the LMA to bronchoscopic confirm of proper positioning, were recorded. The systolic blood (SBP), diastolic blood pressure (DBP), heart rate (HR) and pulse oxygen saturation (SpO$_2$) were measured before, during, and after the examination.

EBUS-TBNA procedure

The average time to perform EBUS-TBNA, the diagnostic accuracy of the procedure, the number of passages to biopsy the target lesion, damage of the instrument and/or balloon rupture were computed.

Patients’ complications

The main complications were nausea, vomiting, gastric aspiration, sore throat were measured during the follow-up.

Statistical analysis

Data were expressed as mean and standard deviation for continuous variables or absolute number and percentage for categorical variables. The $\chi^2$ and Student’s $t$-test was used to compare categorical variables and continuous variables, respectively. Multiple comparison was made using ANOVA test. A P value <0.05 was considered significant. MedCalc Statistical Software v. 12.3 was used for the analysis.

Results

Of the 230 consecutive patients performing EBUS-TBNA in the study period; traditional LMA and LMA Protector were used in 70 and in 73 patients, respectively. Thus, our study population included a total of 143 patients. The two groups were well matched regarding demographic, histological diagnosis, lymph node station, size, and SUV value, as reported in Table I.

Outcome measures

Anesthesiology outcomes

The time for positioning traditional and LMA Protector was similar (120±25 vs. 118±39 seconds; P=0.49). Reposition of LMA was needed in 13 (18%) cases of LMA traditional group and in 12 (16%) cases of the LMA Protector group (P=0.78). No significant changes were observed between LMA traditional group and LMA Protector group during the procedure regarding systolic pressure (140±55 vs. 118±37; P=0.59); diastolic pressure (82±15 vs. 90±26; P=0.39); heart rate (82±9.9 vs. 83±20; P=0.49); and SpO$_2$ values (93±21 vs. 92±14; P=0.63). The data are summarized in Table II.

EBUS-TBNA procedure

LMA traditional group presented a longer procedural time than LMA Protector group (47±23
Patients’ complications

No significant difference was found between LMA traditional group and LMA Protector group regarding the rate of post-procedural complications including nausea (4% vs. 3%; P=0.61); vomiting (3% vs. 1%; P=0.96); gastric aspiration (7% vs. 1%; P=0.08); and sore throat (7% vs. 3%; P=0.22). The data are summarized in Table IV.

Discussion

American cancer guidelines recommended EBUS-TBNA as the initial step in mediastinal staging of lung cancer, followed by a mediastinoscopy in case of lack of a firm diagnosis.1, 6 Anesthetic management is challenging in patients undergoing EBUS-TBNA. The contact with mucosa to obtain ultrasonic images and guide the biopsy generate reflex coughing and laryngospasm that cause difficulties in obtaining an adequate view of the target lesion and increase the risk of vessel injury during the needle insertion. Thus, the ideal anesthesia should prevent any airway movement and assure an adequate ventilation to the patients who sometimes have poor respiratory function due the presence of lung cancer and COPD. Generally, the ventilation during ultrasound bronchoscopy is assured via an artificial airway (e.g. endotracheal tube or laryngeal mask). The main advantage of the LMA is that it allows access to higher mediastinal lymph node stations that would otherwise be obscured by the ETT. Yasufuku et al.7 reported that stations 2R and 2L were sometimes difficult to assess because of the presence of the endotracheal tube and this limitation has been overcome by LMA. However, the ultrasound bronchoscopy is thicker than standard fiberoptic bronchoscopic

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**Table II.**—Anesthesiology outcome measures (N.=143).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Traditional LMA group (N.=70)</th>
<th>LMA Protector group (N.=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-LMA, seconds</td>
<td>120±25</td>
<td>118±39</td>
<td>0.5</td>
</tr>
<tr>
<td>LMA repositioning</td>
<td>13 (18%)</td>
<td>12 (16%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>135±29</td>
<td>130±36</td>
<td>0.6</td>
</tr>
<tr>
<td>During procedure</td>
<td>140±55</td>
<td>118±37</td>
<td>0.02</td>
</tr>
<tr>
<td>After procedure</td>
<td>131±45</td>
<td>127±29</td>
<td>0.45</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>88±19</td>
<td>82±25</td>
<td>0.4</td>
</tr>
<tr>
<td>During procedure</td>
<td>82±15</td>
<td>90±26</td>
<td>0.4</td>
</tr>
<tr>
<td>After procedure</td>
<td>83±25</td>
<td>89±19</td>
<td>0.4</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure</td>
<td>75±12</td>
<td>77±15</td>
<td>0.6</td>
</tr>
<tr>
<td>During procedure</td>
<td>82±9.9</td>
<td>83±20</td>
<td>0.5</td>
</tr>
<tr>
<td>After procedure</td>
<td>77±10</td>
<td>80±17</td>
<td>0.6</td>
</tr>
<tr>
<td>Lymph node station</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paratracheal</td>
<td>37 (53%)</td>
<td>40 (55%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Subcarinal</td>
<td>33 (47%)</td>
<td>33 (45%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Lymph node size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paratracheal</td>
<td>1.43±0.5</td>
<td>1.35±0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Subcarinal</td>
<td>1.33±0.3</td>
<td>1.30±0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Lymph node SUV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paratracheal</td>
<td>4.9±1.4</td>
<td>5.1±1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Subcarinal</td>
<td>4.5±2.1</td>
<td>4.9±1.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or as number of patients (percentage). The P value was calculated using the $\chi^2$ test (for qualitative data) or Student’s t-test (for quantitative data).

---

**Table III.**—EBUS-TBNA outcomes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Traditional LMA group (N.=70)</th>
<th>LMA Protector group (N.=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS procedure time, minutes</td>
<td>47±23</td>
<td>38±17</td>
<td>0.02</td>
</tr>
<tr>
<td>N. of passages</td>
<td>4±0.5</td>
<td>3.1±0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>91.3%</td>
<td>92%</td>
<td>0.9</td>
</tr>
<tr>
<td>Rupture of balloon ultrasound</td>
<td>8 (11%)</td>
<td>1 (1%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or as number of patients (percentage). The P value was calculated using the $\chi^2$ (for qualitative data) or Student’s t-test (for quantitative data).

---

**Table IV.**—Patients’ complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Traditional LMA group (N.=70)</th>
<th>LMA Protector group (N.=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Gastric aspiration</td>
<td>5 (7%)</td>
<td>1 (1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5 (7%)</td>
<td>2 (3%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or as number of patients (percentage). The P value was calculated using the $\chi^2$ test.
and thus it is unfit for standard LMA. The shape of standard LMA could create a friction between the instrument and LMA that potentially limit the endoscopic maneuvers and damage the instrument. The LMA Protector, from Teleflex, has some feature of safety recommended by the international guidelines, such as gastric access and possibility to intubate through the device, with an integrated cuff pressure indicator for single-use airway management. This device enables continuous cuff pressure monitoring at a glance and facilitates easy, accurate adjustment when necessary. The internal diameter of LMA Protector size 4 and 5 has a diameter of 7.5 mm that easily allows the passage of ultrasound bronchoscopy that has an outer diameter of 6.9 mm. Thus, the larger space prevents the scope to be trapped and frictioning between the side walls of the ventilation lumen and assures the ventilation of the patient (Figure 1). In the light of these considerations, from 2017 we routinely used in our unit the LMA Protector rather than traditional LMA as an artificial airway for assuring ventilation during EBUS-TBNA procedure. The use of LMA Protector has been reported in different fields but no paper, before the present, have been investigated its role during EBUS-TBNA procedure. To evaluate the better effectiveness of LMA Protector over traditional LMA (nihil hypothesis of the study), we planned a retrospective study where, to minimize the potential bias, we included only patients undergoing mediastinal staging of lung cancer considering that EBUS-TBNA has a relatively low sensitivity for other types of mediastinal lesions as of 57-90% for lymphoma, and a diagnostic yield of 54% to 93% for sarcoidosis. Furthermore, the EBUS-TBNA procedures were performed by expert physicians that performed more than 50 EBUS-TBNA procedures every years.

We found that there were no differences between the two procedures in terms of cardiorespiratory changes during the procedure. In addition, the insertion of LMA Protector was not particularly cumbersome since the insertion time and the rate of dislocation was similar between two groups. The diagnostic accuracy of EBUS-TBNA was similar in two study groups in line with other studies supporting the hypothesis that different type of anesthesia did not affect the diagnostic yield of EBUS-TBNA. In the only prospective randomized controlled trial of EBUS-TBNA performed under general anesthesia versus moderate sedation diagnostic yield, complication rates and patient tolerance were comparable despite five patients in the moderate sedation group did not tolerate the procedure and needed generally anesthesia. These results were confirmed by other retrospective series. Öztaş et al. evaluated 152 patients underwent EBUS-TBNA under deep sedation and 122 patients received just midazolam administered by the endoscopist. The diagnostic yield was not statistically different in the two groups, no major complications were observed in either group and minor complications were similar. Ost et al. found that deep sedation and general anesthesia were associated with more lymph nodes sampled per patient, but this it was not associated with higher EBUS-TBNA diagnostic yield. Conversely, Yarmus et al. compared 163 procedures performed under deep sedation with 146 performed under moderate sedation. The diagnostic yield was higher in the deep sedation group with shorter procedure time and a higher number of nodes sampled. However, the procedures carried out in two different institutions by different operators and pathologists, and the incomplete follow-up were the main limits of this paper. On the other hand, if we considered the procedural EBUS-TBNA time and the number of passages to biopsy the target lesions, the use of LMA Protector presented a significant advan-
tage over traditional LMA. In theory, the LMA Protector allowed more easily to manage the ultrasound bronchoscopy and thus facilitated the endoscopic maneuvers as selection and biopsy of target lesions. Confirming that, LMA traditional group presented a significant higher rate of balloon rupture as result of the difficult access and movement of ultrasound bronchoscopy through the traditional LMA. There were no significant differences regarding patients’ complications between two groups. This was in line with other studies who found that anesthesia techniques do not seem to affect the frequency of complications with EBUS-TBNA. The traditional LMA group presented an higher rate of gastric aspiration compared to LMA Protector group, despite the difference was not significant. This difference could be explained with the different shape of the LMA Protector. The presence of double drainage channels, a unique feature of the LMA Protector, may reduce the risk of aspiration and regurgitation. The LMA Protector was investigated in a cadaveric study that found that it offered significant protection against aspiration. The same results were then confirmed by other studies in live patients.

Limitations of this study

Our results do not allow us to draw definitive conclusions due the following limitations: the retrospective nature of the study, the lack of patient randomization, and the limited number of cases that did not allow to apply a propensity score match analysis to limit the selection bias. Additionally, the EBUS-TBNA interventions have been performed by different skilled physicians and this could additionally affect the results.

Conclusions

EBUS-TBNA conducted with LMA Protector is a useful strategy in order to simplify the procedure. The different shape of LMA Protector over traditional LMA provides a better space for ultrasound bronchoscopic maneuvers, reducing the procedural time and ensuring in theory the comfort of patients. Due to the small sample size, our results should be confirmed by larger, prospective, randomized studies.

What is known

• EBUS-TBNA is performed under general anesthesia via an artificial airway as LMA or ETT.
• Despite LMA allows access to all lymph node stations otherwise obscured by the ETT, its shape is not fully suitable for ultrasound bronchoscope.

What is new

• The internal diameter of LMA Protector easily allows the passage of an ultrasound bronchoscope.
• EBUS-TBNA conducted with LMA Protector is a useful strategy in order to simplify the procedure.

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.

ABSTRACT

Pain is the most common complaint amongst trauma patients throughout the perioperative period. Multimodal analgesia is currently being regarded the mainstay, with regional anesthesia techniques constituting an integral part of it. Ultrasound imaging techniques display a plethora of advantages that have pervaded regional anesthesia practice. In this review, we set out to provide several examples of injuries, to elucidate the precise anatomy of fractured bones (osteotomes), and to elaborate on certain peripheral nerve blocks employed in pain management of trauma patients. Controversies/special considerations pertaining to peripheral nerve blocks also dictate thorough analysis: as such, acute compartment syndrome, acute peripheral nerve injuries, regional anesthesia in awake or anesthetized patients, continuous peripheral nerve blocks, positioning limitations and, finally, ultrasound imaging versus neurostimulation techniques are extensively reviewed.


KEY WORDS: Wounds and injuries; Nerve block; Pain; Analgesia.

From emergency departments and theaters to intensive care units (ICU) and hospital wards, patients experiencing severe trauma are often undertreated and suboptimal pain therapy is frequently employed. The broad range of complications pertaining to opioids pharmacotherapy has compelled physicians to adopt other pain management therapies. More specifically, in trauma, the modern pain treatment mandates multimodal approach encompassing different techniques and drugs.

Regional anesthesia (RA) exhibits traits of a supreme analgesic technique. Superior analgesia, reduction of stress response, less opioid systemic side-effects, protection against chronic pain and increased quality of life are its major benefits. Additionally, new, innovative techniques, such as ultrasound imaging, have rekindled the interest in RA.

In this review, we set out to elucidate the precise anatomy (osteotomes) of fractured bones and to provide examples of injuries where certain types of peripheral nerve blocks can be implemented. Additionally, in the context of RA, ultrasound imaging techniques as well as specific considerations and controversies will be discussed.
Upper limb trauma

RA of the upper limb can be achieved by blocking the brachial plexus at different locations along the course of its roots (C5-T1 nerve roots), trunks, divisions, cords, and terminal branches. The anatomy of the brachial plexus as well as its anatomic variations are of fundamental clinical importance and both should be understood by all clinicians who perform RA.

Brachial plexus anatomic variations

At the level of brachial plexus nerve roots, the C4 ventral ramus often contributes to the C5 nerve root, and the T2 ventral ramus usually contributes to the T1 nerve root. Moreover, variations have been described where the brachial plexus roots run within the anterior scalene muscle; cases where the C5 ventral ramus descends anterior to the anterior scalene muscle have also been documented.

Conventionally, at the infraclavicular region the three cords of the brachial plexus exhibit a perivascular distribution around the axillary artery. Nevertheless, in some cases all three cords of the brachial plexus lie lateral to the axillary artery or they are fused to a single cord which is also arranged lateral to the axillary artery. At the level of terminal branches, the median, ulnar, and radial nerves are ensheathed together, with the musculocutaneous nerve following a different anatomic course by piercing the coracobrachialis muscle. There are cases, however, where the musculocutaneous nerve is fused with the median nerve. Anatomic variations of the axillary artery and of the position of terminal branches around the aberrant axillary artery have also been described.

Shoulder and humeral trauma

The main types of shoulder girdle injuries can be categorized as follows: 1) fractures mainly involving the clavicle, the proximal humerus and the scapula; 2) dislocations of the acromioclavicular, sternoclavicular and glenohumeral joints; 3) tears of the rotator cuff and capsular-labral tears.

Clavicular fractures

A clavicular fracture is mainly induced by a fall onto the shoulder, or onto an outstretched arm, or after a direct blow to the clavicle. Branches of cervical (supracleavicular) and brachial (subclavian, suprascapular, and long thoracic) nerve plexuses are combined, and altogether may contribute to the pain transmission after clavicular trauma.

In clinical practice, both cervical and brachial plexus peripheral nerve blocks should be employed to anesthetize the clavicle. Interscalene brachial plexus nerve block with high volume of local anesthetic (LA) can also indirectly anesthetize the cervical plexus. On the contrary, ultrasound-guided intermediate cervical plexus nerve block exactly at the C-6 level can lead to LA diffusion in the interscalene groove and subsequently to brachial plexus components.

From a clinical standpoint, an ultrasound-guided intermediate cervical nerve block at the C4 level (Supplementary Digital Material 1: Supplementary Video 1, 3 seconds, 631 kB) and an ultrasound-guided interscalene brachial plexus nerve block with low dose/volume of LA at the level of C-5 nerve root can be a remedy for pain control in patients with clavicular fractures.

Scapular fractures

A scapular fracture is a fracture of the shoulder blade. High-speed vehicle accidents and motor vehicle collision or falling from a significant height are the main etiology. Scapular fractures are very commonly accompanied by thoracic wall injuries.

The scapular bone is innervated by the brachial plexus (suprascapular nerve, C5, C6 [posteriorly] and the subscapular, C5, C6 [anteriorly] nerves). Additionally, seventeen periscapular muscles carefully hold the scapula in place to coordinate different movements of the upper limb. The innervation of these muscles shows high complexity. The brachial and to some extent the cervical plexus (dorsal scapular nerve innervates the rhomvoid and levator scapulae muscles), as well as the spinal accessory nerve (innervates the trapezious muscle) contribute to the innervation of the periscapular region. Consequently, combined ultrasound-guided cervical and interscalene brachial plexus nerve blocks (Figure 1A) may be employed for the pain management of scapular bone fractures.
Shoulder dislocations

Dislocation of Glenohumeral, Acromioclavicular and Sternoclavicular joint is the result of various types of trauma. The anterior side of the joint (Glenohumeral/Acromioclavicular joint) is supplied from the axillary, subscapular and musculocutaneous nerves, while its posterior side from the suprascapular and axillary nerve. Contribution of the lateral pectoral nerve (sternoclavicular joint) has been described.\(^{15, 20}\)

Interscalene brachial plexus nerve block seems to be the best choice for a regional anesthesia technique in shoulder trauma.\(^{15, 21}\) However, attention should be exercised to the fact that the interscalene nerve block may induce phrenic nerve paralysis.\(^{15}\) In the literature, four possible diaphragm-sparing strategies have been investigated through randomized control trials (combined axillary-suprascapular nerve block, C7 nerve root block, suprascapular nerve block with low (20 mL) volume of LA and LA injection posterolateral to the brachial plexus); however, while significant analgesia was attained for shoulder surgery, none of these diaphragm-sparing strategies has been shown to provide effective surgical anesthesia.\(^{21, 22}\)

Elbow and forearm trauma

The elbow is a hinge joint comprised of three bones: distal humerus, radial head and olecranon-proximal ulna. Any fracture to these bones, known as an elbow fracture, may be associated with a dislocation of the elbow joint. These injuries result from a fall onto an outstretched hand, a direct or indirect blow onto the elbow, or a twisting injury to the arm.\(^{23-25}\)

Proximal and mid-diaphyseal humeral fractures

The most common mechanism for proximal and mid-humeral fractures is a fall on the outstretched arm from a standing height, or a forceful collision against the shoulder and the humerus.\(^{16, 17}\)

The innervation of the proximal humerus stems from the axillary (C5, C6), suprascapular (C5, C6) nerves and the C5 and C6 components of the radial nerve.\(^{9, 18}\) From an anatomic point of view, the supracleavicular nerve leaves very early the brachial plexus (at the level of C5 nerve root or superior trunk). It typically crosses deep to the omohyoid muscle in the supracleavicular region, away from the brachial plexus, before it runs toward the suprascapular notch.\(^{19, 20}\) Although there have been no studies comparing interscalene with supracleavicular block for proximal humeral surgery, the failure of the supracleavicular nerve block to consistently anesthetize the suprascapular nerve, suggests that the interscalene nerve block is more suitable for humeral surgery in the proximal region provided that the phrenic nerve is not concurrently blocked.\(^{21}\)

The mid-humeral anatomy is less complex than that of the proximal region of the humerus. The musculocutaneous nerve predominates in the innervation of the mid-humerus. Minor contribution of the radial nerve is also described.\(^{9, 18}\) Thus far, there are not any studies examining the most suitable nerve block for mid-humeral fractures; however, based on the sensory innervation of this region, one can surmise that the supracleavicular and infraclavicular nerve blocks are the best options.
The innervation of the elbow is complex with almost all the terminal branches of the brachial plexus (musculocutaneous, radial, median and ulnar nerve) participating in its innervation. Components from C5 to C8 nerve roots through the terminal branches of the brachial plexus are distributed in the elbow region making the sensory block of it very challenging at times.9, 10, 18

Forearm fractures account for most upper limb fractures. Wrist, ulnar and radial fractures are secondary to a fall, a road traffic accident or a sporting injury, frequently accompanied by tendon and nerve injuries.26

The ulnar and radial bones receive innervation from the radial (posteriorly) and the median (anteriorly) nerves respectively.9, 10, 18 The ultrasound-guided supraclavicular nerve block with injection of LA in the corner pocket (in close vicinity to the divisions arising from the C8, T1 brachial plexus nerve roots)27 (Figure 1B), the infraclavicular (Figure 2A) and axillary nerve block (Figure 2B) are the most suitable peripheral nerve blocks for elbow and forearm surgery and for postoperative analgesia.28, 29

The major failure of the interscalene block to anesthetize the posterior components of the brachial plexus,30 as well as the high incidence of the diaphragmatic paralysis,22 make it the least appropriate block for surgery for injuries at and below the elbow.

Lower limb trauma

Regional anesthesia of the lower limb can be achieved by blocking branches of the lumbar plexus and/or the sacral plexus.31, 32 Although the anatomic variations of the two nerve structures are less than those of brachial plexus, the knowledge of them is important in clinical practice.

Anatomic variations of the femoral and sciatic nerves

Anatomic variations of the femoral nerve include abnormally long l2 root, early division of the femoral nerve, origin of lateral cutaneous nerve of the thigh from the femoral nerve and splitting of the femoral nerve into two slips by psoas major or accessory slips of iliacus muscle.33

Normally, the sciatic nerve consists of the tibial and the common peroneal nerve components (L4 to S3 spinal nerves).34, 35 In some cases, the common peroneal and the tibial nerves can arise separately below the piriformis and rejoin posterior to quadratus femoris muscle.34, 35 In other cases, the common peroneal nerve emerges above the piriformis and tibial component, runs below the piriformis and descends separately along their course in the posterior thigh. In the popliteal fossa, trifurcation of the sciatic nerve (Figure 3) has been identified as well.34, 35

Hip and proximal femur fractures

Hip and proximal femur fractures are very frequent injuries and are associated with high morbidity and mortality. In fact, the importance of non-opioid analgesia, especially RA techniques, in patients with proximal femoral fractures is emphasized in the guidelines from the Association of Anesthetists of Great Britain and Ireland.31, 32

The hip joint innervation comprises three nerve structures: 1) the femoral nerve; 2) the sciatic nerve; and 3) the obturator nerve. The branch or branches of the femoral nerve arise...
either directly from the femoral nerve, or from its muscular branches (nerves to rectus femoris and pectineus muscles). The articular branch of the obturator nerve supplies the medial portion of the capsule before the nerve exits the obturator foramen. When the accessory obturator nerve is present, it supplies the area usually reached by the branch of the femoral nerve to the pectineus muscles. The sciatic nerve branches (superior gluteal nerve and the quadratus femoris nerve) supply the hip joint posteriorly. Cutaneous innervation of the lateral aspect of the thigh is also predominantly supplied by the lateral cutaneous nerve of thigh, with contribution, proximally, from the sub-costal nerve (T12).36

Ultrasound-guided femoral and fascia iliaca blocks can be easily implemented in patients with hip fractures (Figure 4A, B). The objective of the fascia iliaca block is to anesthetize the femoral and lateral femoral cutaneous nerve and possibly the obturator nerve with a high-volume injection of LA.31, 32 It has been suggested, however, that lumbar plexus block (Figure 5A, B) may be a better option than the femoral/fascia iliaca nerve block in that it anesthetizes simultaneously the femoral, obturator, and lateral femoral cutaneous nerves.37, 38 Nevertheless, for the lumbar plexus nerve block to be carried out, it requires patients’ lateral position and presents high likelihood of perineural bleeding (deep muscular block in close vicinity to the epidural space), especially in patients receiving modern anticoagulants.39 For the latter, there is not compelling evidence to quantify the risk of bleeding, when the lumbar plexus block is implemented by means of either ultrasound guidance or blind methods.

Trauma of the knee joint

The knee joint is innervated by an anterior and a posterior group of sensory nerves. The anterolateral group consists of the lateral femoral cutaneous nerve, the common peroneal nerve, and the femoral nerve branch to the lateral/intermedius vastus muscle. Anteromedially the knee joint receives innervation from the saphenous, the me-

Figure 3.—Trifurcation of the sciatic nerve in the popliteal fossa. The common peroneal nerve, bifurcating in two branches (CP), and the tibial nerve (T) are visualized.

Figure 4.—A) The needle tip is located between fascia iliaca (FIL) and iliopsoas (IL.P) muscle. B) Injection of the local anesthetic (LA) laterally to the femoral nerve (FN) (between fascia iliaca and iliopsoas muscle) leads to an extensive spread of it from lateral to medial.
Ankle and foot fractures

The ankle comprises two joints: the ankle joint: tibia + fibula + talus and the subtalar joint: talus + calcaneus. In ankle fractures, one or more of the bones (distal tibia, distal fibula, and talus) that constitute the ankle joint are fractured. Twisting or rolling the ankle or falling onto the ankle can lead to severe and complex injuries.

Ankle and foot fractures

Femoral and adductor canal nerve blocks in conjunction with or without sciatic nerve block have been suggested for pain control after trauma or interventions in the knee joint. Infiltration anesthesia of the knee capsule constitutes an alternative method. Blockade of the posterior branch of the obturator nerve has also been proposed. The posterior obturator nerve branches can be blocked concomitantly with the anterior obturator branch through an ultrasound-guided subpectineal approach between the pectineus and external obturator muscles. The posterior branch of the obturator nerve can also be blocked selectively in the subinguinal region between the adductor brevis and magnus muscles.

Tibial and peroneal bone fractures

The tibia and fibula fractures belong to lower leg injuries. Fractures of the tibia are generally associated with fibula fractures as well; the mechanism considered is that the force from the tibial bone is transmitted along the interosseous membrane to the fibula.

Both fibula and tibial bone mainly receive innervation from the tibial nerve. Certain, limited, anatomic areas of the two bones are innervated by the common fibular nerve (fibular head) and the saphenous nerve (upper part of the tibia that involves the joint). Therefore, sciatic/tibial nerve block (Figure 6) is sufficient for anesthesia/analgesia of tibial and/or fibular shaft fractures. Anesthesia/analgesia of the fibular head and the tibial plateau fractures requires sciatic/common fibular and saphenous nerve blocks.

Figure 5.—A) Visualization of psoas muscle (PS) between kidney (K) and L3 vertebrae. B) After the localization of the lumbar plexus with neurostimulation technique, an echogenic perineural catheter (CATH) has been placed at the lower third of the muscle exactly above the vertebral body (VRT.B) (shamrock approach). TR: transverse process; SP: spinous process; Q.L: quadratus lumborum muscle.

*Local anesthetic.

Figure 6.—Subgluteal sciatic nerve (arrow) block. The sciatic nerve, hyperechoic structure, is located underneath biceps femoris muscle (B.F) and surrounded by local anesthetic (*).
Peripheral nerve blocks in acute pain management of trauma patients have been confronted in clinical practice. Acute compartment syndrome (ACS), peripheral nerve injuries, regional anesthesia in awake or anesthetized patients, continuous peripheral nerve blocks (CPN Bs), positioning limitations and ultrasound imaging versus neurostimulation techniques are concerns that should be taken into consideration when managing injured patients.

Acute compartment syndrome

ACS occurs when an abrupt increase in the pressure within a closed muscular compartment exceeds the capillary perfusion pressure. ACS is predominantly associated with tibial fracture (mostly the proximal and middle thirds of the diaphysis), but fractures of the forearm can also frequently lead to it. In clinical practice, therefore, pain management of an injured limb should be established by using...
CPNB techniques with LA of low dose/concentration (e.g. ropivacaine<0.2%) and patient-controlled function. Also, if possible, heavy sedation should not be used in awakened patients in the ICU. By such means, any new onset of pain can be recognizable to the attending physician and an alarming sign to possible complications.\textsuperscript{55}

Acute peripheral nerve injuries

Acute peripheral nerve injury is one of the most severe complications of trauma that affects both limbs.\textsuperscript{56, 57} As far as the exacerbation of a nerve deficit is concerned as an additional risk after the implementation of regional anesthesia techniques (nerve trauma from the needle or from LA itself), a subsequent sympathetic nerve block may remarkably improve any neurovascular dysfunction in the injured limb.\textsuperscript{48}

The administration of LAs of low dose/concentration, without vasoconstrictors and the use of atraumatic regional anesthesia needles, can minimize risks of new neurological complications. A thorough neurological examination and meticulous documentation of neurological deficits prior to regional anesthesia and surgery are imperative.\textsuperscript{58} According to our clinical practice, (before patient’s awakening in the operating room or in the ICU), a CPNB (placement of a perineural catheter) is installed without injecting LA. After patient’s arousal and before the catheter is used to deliver LA for analgesia purposes, a detailed neurological examination should be carried out and any new neurological deficit must be recorded.

Regional anesthesia in awake or anesthetized patients

There are no randomized studies available showing that regional anesthesia is better tolerated whenever patients are awake or anesthetized.\textsuperscript{58} Thus far, it has been advocated that in awake patients paresthesia during nerve block procedures can be a warning symptom of intraneural injection. Low pressures (<12 psi) during local anesthetic injections are also a prerequisite to avoid neurological complications.\textsuperscript{58, 59} Moreover, studies have shown that transient or irreversible nerve injury may also occur in awake patients who did not notice any pain during block procedure. Moreover, the use of a peripheral nerve stimulator does not ensure complete safety nor does it exclude intraneural injection of LA.\textsuperscript{58, 59}

Visual inspection, through ultrasound imaging, both of needle tip and local anesthetic spread, can be very useful in identifying intraneural injections.\textsuperscript{60, 61} In a recent review,\textsuperscript{62} it has been contended that patients are no longer needed to be “live monitors” when this technology is applied in clinical practice. Therefore, considering that trauma patients may require excessive sedation in emergencies (as they are frequently restless and flustered), or that they are already sedated/anesthetized either in the ICU or in the operating room, peripheral blocks under general anesthesia or heavy sedation can be cautiously performed under ultrasound guidance in skilled hands.\textsuperscript{62}

Continuous peripheral nerve blocks

CPNB involves percutaneous catheter insertion in the proximity of a peripheral nerve that continuously delivers local anesthetic in the targeted nerve. Perineural catheters can be plain plastic (non-echogenic, non-stimulating), echogenic, stimulating or echogenic and stimulating.\textsuperscript{63-66} Recently, in clinical practice, echogenic catheters have gained popularity since they can be precisely placed close to the targeted nerves in real time (Supplementary Digital Material 3: Supplementary Video 3, 4 seconds, 474 kB).\textsuperscript{66}

In trauma, CPNB can contribute to pain management throughout the perioperative period. They facilitate patient transport, surgical anesthesia, postoperative analgesia, chronic pain prevention and sympathetic block (e.g. tissue flaps). Patients with complex injuries that require repeated surgical interventions, debridement and/or skin grafting frequently benefit the most from CPNBs.\textsuperscript{63-66}

Minor complications of CPNBs comprise dislodgement and occlusion of the catheter, leakage, and infusion pump malfunction. Serious but rare complications are local anesthetic systemic toxicity (LAST), catheter knotting and shearing as well as catheter infection, especially under conditions of limited sterilization (e.g. in emergency room and/or ICU). In fact, indwelling catheter infection is also a great concern in trauma patients, especially in those suffering from diabetes.\textsuperscript{67, 68} The probability of catheter...
infection increases with each additional day of catheter use. Specifically, for peripheral nerve block catheters, the odds of infection are 99% at day 4, 96% at day 7, and 73% at day 15 after their placement.67

Positioning restrictions

The positioning of trauma patients is challenging when a peripheral nerve block is to be performed with a posterior approach. Difficulties are mainly confronted as patients with lower limb fractures must turn from supine to lateral or even worse, to prone position for a lumbar plexus and/or for a posterior sciatic nerve block. The lateral or the anterior (Supplementary Digital Material 4: Supplementary Video 4, 5 seconds, 2 MB) approach can also replace the posterior approach of the sciatic nerve blocks.69, 70 A significant alternative to the lumbar plexus nerve block can be the femoral, fascia iliaca nerve block and the most recently described, fascia transversalis nerve block (Supplementary Digital Material 5: Supplementary Video 5, 5 seconds, 6 MB)31, 32, 71 Finally, cervical collar is a limitation on the access to the supraclavicular region so that the interscalene and supraclavicular brachial plexus nerve blocks cannot be performed.

Ultrasound imaging and neurostimulation technique

With the recent resurgence of ultrasound imaging techniques in RA, there has been much debate on the relative benefits of ultrasound technology in comparison with the neurostimulation technique. Although muscle relaxants are not frequently being used in ICU or emergency room, their administration prevents the use of neurostimulation technique (muscle contractions cannot be elicited).

From a safety point of view, there is no concrete evidence to demonstrate reduction in the frequency of serious complications.72 The chief reason is that severe complications are very rare with both techniques. However, it is common sense that with peripheral nerve blocks (e.g. supraclavicular and PVB) performed very close to structures, whose puncture would result in severe complications (pleura/vessels), their ultrasound visualization can confer higher safety margins.

In conclusion, the appropriate education of anatomy, the application of innovative techniques, such as ultrasound-guided peripheral nerve blocks and the cautious clinical examination can constitute significant pillars of appropriate pain management in trauma patients.

Key messages

• Thorough knowledge of anatomy and particularly of osteotomes results in the very accurate implementation of peripheral nerve blocks in trauma patients.
• Ultrasound regional anesthesia techniques have been shown to provide quality pain relief with an excellent safety profile.
• Acute compartment syndrome, acute peripheral nerve injuries, regional anesthesia in awake or anesthetized patients, continuous or single shot peripheral nerve blocks and positioning limitations are major concerns that should be considered when performing peripheral nerve blocks in injured patients.

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.

Authors' contributions.—Theodossis Saranteas was responsible for review design and writing of the paper. Rizos Souvatzoglou was responsible for the literature search on upper limb. Ioannis Koliantzaki was responsible for the literature search on anatomic variations. Marina Tsouma was responsible for the literature search on rib fracture and for the special considerations. Georgia Eustathiou was responsible for figure and video selection. Vasileios Kontogeorgakos was responsible for the literature search on anatomic variations. Olga Savvidou was responsible for review design and editing.


Death by neurologic criteria: pathophysiology, definition, diagnostic criteria and tests

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Abstract

Death by neurologic criteria is an irreversible sequence of events culminating in permanent cessation of cerebral functions. In this context, there are no responses arising from the brain, no cranial nerve reflexes nor motor responses to pain stimuli, and no respiratory drive. The diagnosis of death by neurologic criteria implies that there is clinical evidence of the complete and irreversible cessation of brainstem and cerebral functions. The diagnosis, confirmation, and certification of death are core skills for medical practitioners. The aim of this review is to discuss the pathophysiology and definition of death by neurological criteria, describing the clinical assessment, and the use of ancillary tests for the diagnosis of brainstem death.

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Key Words: Brain death; Critical care; Neurologic examination; Reflex, pupillary.

The concept of death by neurologic criteria (DNC) was first proposed as “coma depassé” in 1959,1 and subsequently described, fifty years ago, as “brain death” with the first published clinical definition, i.e. the Harvard Brain Death Criteria.2,3 Even if the terminology “brain death” has been traditionally adopted, DNC describes more accurately the modality of determination of death after a devastating brain damage.

Over the last years, many controversies have surrounded the determination of DNC and the difference with brain death, especially among bioethicists and different religious communities. Moreover, there is a fundamental ongoing debate regarding the philosophical definition of death, including the concept of cessation or “organized” function, and death of the person vs. brain death. Furthermore, DNC can be legally defined in different countries in two different ways: “whole” brain death and “brainstem” criteria.

If we assume that the patients’ death coincides with the death of the brain, debate continues over the way to demonstrate the ceasing of brain functions accordingly to the definition of DNC.

For example, alterations in the pituitary functions are common after brain death; however, some authors demonstrated residual pituitary function in brain death patients, due to internal carotids supply.4 We therefore chose the “death by neurologic criteria” since we find it to be more adherent to the clinical aspects of the diagnosis.

Since then, many guidelines and protocols have been published, adopted, and revised worldwide with general acceptance of the concept of DNC among medical, religious, and institutional...
A traumatic, vascular, hypoxic neurological event is the starting point of this process. If therapeutic endeavors fail, the devastating brain injury, i.e., a neurologic injury resulting in an immediate threat to life from a neurological cause, might evolve into DNC.

The key characteristic of the DNC is the complete and irreversible cessation of brainstem and cerebral functions, including breathing and vegetative activities.

In most DNC cases, a progressive increase of intracranial pressure (ICP) produces cerebral venous engorgement, brain swelling, and downward intracranial displacements that compress the brainstem (BS), causing BS ischemia and infarction, until intracranial circulation ceases.

The ischemia spreads in a predictable rostro-caudal pattern, allowing the observer to monitor its development by following its effects on the central nervous system (CNS, Figure 1). First, the pontine ischemia leads to a mixed vagal and sympathetic stimulation. This results in a typical clinical presentation (the so-called “Cushing response”) including bradycardia, hypertension, and an irregular breathing pattern, followed by apnea. In the meantime, spreading of the cerebral ischemia leads to failure of the pituitary and hypothalamic regulatory systems. Also, involvement of the medulla oblongata results in the loss of the vagal and vasomotor nuclei: unopposed sympathetic stimulation, loss of spinal sympathetic pathways, and total sympathetic denervation follows. Sequential systemic physiologic changes occur as different areas of the BS become ischemic (Table I).

The extreme sympathetic discharge associated with brainstem death leads to an extensive rise in circulating catecholamine levels (800% circulating dopamine, 700% epinephrine, and 100%, norepinephrine concentrations). The so-called “sympathetic storm” (Figure 2) produces severe vasoconstriction leading to hypertension, tachycardia, and a secondary increase in myocardial oxygen demand, producing sub-endocardial ischemia. Cardiac injury and electrocardiographic abnormalities (including ST segment and T wave

**Table I.** —Physiologic changes in brain death and their incidence. Modified from McKeown et al.

<table>
<thead>
<tr>
<th>Derangement</th>
<th>Causes</th>
<th>Incidence (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>“Sympathetic storm;” reduced coronary flow;</td>
<td>25-32%</td>
</tr>
<tr>
<td></td>
<td>myocardial damage</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Capillary leaks; acute blood volume re-distribution</td>
<td>13-18%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Vasoplegia, hypovolemia, myocardial abnormalities</td>
<td>81-97%</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Pituitary damage</td>
<td>46-78%</td>
</tr>
<tr>
<td>Disseminated intravascular coagulopathy</td>
<td>Coagulopathy; tissue factor release</td>
<td>29-55%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Reduced metabolic rate; hypothalamic damage;</td>
<td>100% if not prevented</td>
</tr>
<tr>
<td></td>
<td>vasodilation and heat dispersion</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.—Pathophysiology of brain herniation and progressive rostro-caudal ischemia of mesencephalon, pons and medulla oblongata.
Adrenal insufficiency, as well as thyroid abnormalities (including the “sick euthyroid syndrome”), are also common following brain death. Hypothermia occurs very quickly due to the absence of any spontaneous muscle movement and loss of core temperature control. Temperature regulation in humans is controlled by the hypothalamus; after death it ceases to function, and the patient becomes poikilotherm. A core element of organ preservation in organ donor patients is to achieve and maintain normothermia. However, it should be noted that not all not all DNC patients are hypothermic.

At a peripheral organ level, there is the depletion of hepatic glycogen with reduction of hepatic sinusoidal perfusion, systemic activation of coagulation (due to the release of thromboplastin from the ischemic brain), and a general up-regulation of pro-inflammatory mediators.  

Diagnostic criteria

The diagnosis of DNC is clinical. As summarized by Wijdicks, it can be declared when “brainstem reflexes, motor responses, and respiratory drive are absent in a normothermic, non-drugged comatose patient with a known, irreversible, widespread brain lesion, and no contributing metabolic derangements.”

Despite the general consensus about its definition, there are differences between countries regarding the diagnostic criteria and the legal standards that should be satisfied. Differences are recorded in:

- qualification and number of examiners involved;
- the frequency and duration of observations;
- in the need and nature of additional tests to confirm the clinical diagnosis.

In 2014, trying to define a universal consensus, an expert panel divided the process of defining DNC into three steps (which should be carefully approached by the examiner) and defined the minimum clinical standards for each one. 

Whereas is preferable to have a clinician with expertise in Neurointensive care to conduct the clinical examination, a thoroughly conducted clinical evaluation will allow any appointed examiner to make a correct diagnosis and avoid

Figure 2.—Graphical representation of the sympathetic storm consequent to the dramatic increase of intracranial pressure.
mistakes. The main sources of error are the presence of confounding factors or poorly set confirmatory tests.

First, check for the clinical prerequisites and eliminate any confounding factors (Table II).

Once assessed for the presence of coma, the clinician should establish its cause, through an accurate clinical history, laboratory results, and the available neuroimaging. Pharmacologic causes of coma, such as the presence of CNS-depressant drugs or a neuromuscular blocking agent, should be excluded by asking for a drug screen panel, or by computing the known drug’s clearance using five times the drug’s half-life (assuming normal hepatic and renal function), and, if a muscle relaxant has been used, through the recording of a train-of-four stimulation. Severe electrolyte, acid-base, or endocrine disturbances should be ruled out. Hypothermia should be avoided, and normal core temperature should be maintained (>35 °C). Marked hypothermia may confound the neurologic examination directly (the pupils dilate, and the brainstem reflexes become difficult to elicit) and/or by delaying drug metabolism. Also, a normal systolic blood pressure (BPS) with a BPS target ≥100 mmHg should be achieved, often by start of fluids and vasopressors. Moreover, according to recent randomized control trial, thyroid hormone replacement could be taken in consideration in hemodynamically unstable donors.

The observation period is set case-by-case and depends on the underlying condition. If the patient has suffered from an anoxic brain injury after a resuscitated cardiac arrest, then the minimum acceptable time is 24 h.

Then, a clinical evaluation should be performed (Table III):

- coma: clinical examination should demonstrate the absence of movements and motor response to pain. Patients must lack all evidence of responsiveness, meaning that the painful stimuli should not elicit any response other than spinally mediated reflexes. Eye opening or movement in response to pain are absent. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise, since movements originating from the spinal cord or peripheral nerve may occur quite frequently in brain death; absence of brainstem activity: pupillary reflex, oculocephalic and oculovestibular, corneal reflex, facial muscle activity to pain, pharyngeal and tracheal reflex. The integrity of the afferent and efferent pathways of the brainstem reflexes provide the clinical tool to assess the integrity or damage of the cranial nerve nuclei, of the pathways connecting them, and of the suprasegmental structures (Table III);

- absence of breathing drive: the apnea test (AT) is based on the assumption that the rise of arterial partial pressure carbon dioxide (PaCO₂) in a patient will result in respiratory and cerebrospinal fluid acidosis that will activate the respiratory center (Table III). The AT should be performed at the end of the examination, after all other criteria for brain death have been met. In cases of high cervical spinal cord lesions or neuromuscular paralysis, or in patients with severe chronic obstructive pulmonary disease (COPD) with hypercapnia, the test is not considered valid. Other prerequisites for performing the apnea test are normocapnia (PaCO₂ of 35 to 45 mmHg), absence of hypoxia, euvoolemia, and hemodynamic stability. The test can be challenging, especially in particular conditions such as patients receiving extracorporeal membrane oxygenation, but it has been proved to be reliable.

Monitoring the arterial PaCO₂ rise is

<table>
<thead>
<tr>
<th>Clinical prerequisites</th>
<th>To do</th>
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<tbody>
<tr>
<td>Asses the presence of a coma</td>
<td>Assess GCS</td>
</tr>
<tr>
<td>Define irreversible and proximate cause of</td>
<td>Check for pharmacologic causes (e.g. CNS depressants and/or neuromuscular blocking drugs); rule out a high cervical spine injury and an electrolyte, acid-base or endocrine disturbances</td>
</tr>
<tr>
<td>coma</td>
<td>Register starting T and use a warming blanket if needed</td>
</tr>
<tr>
<td>Achieve a core body temperature (T) of 35 °C</td>
<td>Register starting BP and correct eventual loss of peripheral vascular tone and/or hypovolemia; start vasopressors or vasopressin/terlipressin if needed</td>
</tr>
<tr>
<td>Achieve a mean blood pressure ≥100 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

GCS: Glasgow Coma Scale; CNS: central nervous system; T: temperature; BP: blood pressure.
TABLE III.—Steps in brain death clinical evaluation.

<table>
<thead>
<tr>
<th>State of coma</th>
<th>Irreversible lack of responsiveness to noxious stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of brainstem activity</td>
<td>Evaluate: pupillary, oculocephalic, oculovestibular and corneal reflexes; facial muscle activity to pain; pharyngeal and tracheal reflexes.</td>
</tr>
<tr>
<td>Pupillary reflex</td>
<td>The starting diameter of the pupils should be 4-9 mm and each eye should be first tested separately, then the presence of a consensual response should be evaluated. Initially, the operator checks that the pupils of the patient are the same size. Then the operator shines a light on each pupil and checks to see that both pupils have constricted to the same size. Finally, the operator moves the penlight rapidly from the left pupil to the right several times to be sure there is no consistent changes of the pupils. When in doubt, use tools such as a magnifying glass or a pupilometer.</td>
</tr>
<tr>
<td>Oculovestibular reflexes</td>
<td>Even though it can be tested in different ways, in the unconscious patient we usually test the horizontal OVR through the caloric response to cold water, resulting in sustained deviation of both eyes toward the ear being stimulated. To test this reflex, the patient’s head is elevated at 30 degrees above horizontal. After inspecting the ears for obstruction or perforation, the operator injects at least 50 mL of ice water into the external ear canal using a syringe. If the brainstem is intact the slow phase of the nystagmus is directed towards the irrigated area.</td>
</tr>
<tr>
<td>Facial sensation and facial motor response</td>
<td>For the corneal reflex the arch begins from the small unmyelinated pain fibers in the cornea and ends in the dorsal parts of facial nuclei in the pons, causing blinking by contraction of the orbicularis oculi muscles when either cornea is touched. The test is performed by gently touching the edge of the cornea with a cotton or tissue swab while checking for the absence of a reactive bilateral blink. The facial response to pain, or grimacing, is evoked through deep pressure on nail bed, supraorbital ridge, or temporomandibular joint.</td>
</tr>
<tr>
<td>Pharyngeal and tracheal reflexes</td>
<td>The function of the arch composed by the afferent glossopharyngeal (IX CN) and efferent vagus (X CN) cranial nerves is assessed by the presence or absence of the gag reflex to the gentle touch of a sterile tongue depressor (or analog instrument) on each palatal arch separately (stimulation of the posterior pharynx) and by the ability of the patient to cough in response to tracheobronchial suctioning.</td>
</tr>
<tr>
<td>Absence of breathing drive</td>
<td>Perform an apnea test</td>
</tr>
</tbody>
</table>

necessary. Blood gas determination can be done at the bedside, and current handheld devices take about two minutes to give reliable readings.\textsuperscript{20} The patient should be preoxygenated with a fraction of inspired oxygen (FiO\textsubscript{2}) up to 100\% for ten minutes, with a maximum oxygen partial pressure (PaO\textsubscript{2}) limit of 200 mmHg. After an arterial blood gas analysis (ABG) is obtained and the values of PaCO\textsubscript{2} are checked, the patient is disconnected from the ventilator. During the test the patient should be administered through an AMBU bag with PEEP, in order to avoid profound hypoxemia and hemodynamic instability. Visual observation of respiratory movements is recommended for eight to ten minutes. PaCO\textsubscript{2} is then measured just prior to reconnection to the ventilator to confirm that the target is achieved. The test could also be done with the patient connected to the mechanical ventilator set in CPAP with PEEP, with no pressure support and no backup ventilation. This method reduces the risk of lung de-recruitment and help to preserve lung function in case of organ donor. However, attention must be payed to the setting of the ven-
tilator, avoiding the risk of ventilator-triggered breaths.\textsuperscript{30, 43} If the test is positive, no respiratory response is detected, and therefore, the PaCO\textsubscript{2} increases to absolute values above 60 mmHg or >20 mmHg greater than baseline values. The process should be interrupted if oxygen desaturation occurs, cardiac arrhythmias intervene, or blood pressure (BP) decreases.\textsuperscript{44}

Ancillary tests

The ancillary tests (Table IV) are by definition additional tools at our disposal, not substitutes to the clinical process. If the examination cannot be performed entirely or the confounding factors cannot be eliminated, or if there is still some uncertainty regarding the results of the conducted tests, ancillary tests can be integrated into the
failure, coma, absence of brainstem reflexes, and apnea. Repetition of evaluation and description of a trend over time (progressive loss of neurological activities) make the diagnosis certain.

The determination of DNC is a process and its declaration, preceded by the assessment of potential confounding and neurological criteria, has to be considered solid regardless the characteristics of the patient, the medical or legal system, or the religious and cultural background of each country.

**Key messages**

- DNC is a process made of steps that can be followed through reliable testing.
- The DNC patients have lost those neurological function that according to the definition would identify them as alive, regardless of the setting of this diagnosis in terms of legislation in force or cultural background.
- Wrongful diagnosis can be avoided by rigorous appliance of the clinical flowchart, paying attention to potential confounders and known sources of error.
- Ancillary test in the determination of DNC are multiple and should be chosen case by case.

**Conclusions**

Definition and diagnosis of DNC is challenging. However, common core elements apply worldwide and make the diagnosis sound: the presence of a catastrophic brain injury followed by therapeutic diagnostic process and repeated after the observation period if needed. Despite from a theoretical point of view ancillary tests are not necessary, these can be anyway beneficial in order to minimize mistakes and contradictions, especially in the context of huge variability in criteria for determining DNC. The choice of the ancillary test varies according to protocols and legal requirements in each country, but nuclear studies, trans-cranial doppler (TCD), and the four vessels cerebral angiography are the most commonly used, according to the guidelines. Other tests such as electroencephalography (EEG), evoked potentials (SSEP), and computed tomography angiography (CTA) or magnetic resonance imaging (MRI) are part of clinical practice, even though not validated. Every kind of tests presents advantages and disadvantages, and needs to be adequate for the purpose it is being used. Due to its early reliability, the reference standard testing is traditionally a conventional four vessel cerebral angiography, while the use of EEG and SSEP should be targeted for specific populations (for instance if the primary pathology is in the brainstem, then an EEG is useful to make sure that there is significant cortical destruction). Moreover, TCD is not always achievable as some patients do not present an appropriate temporal window.

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EXPERTS’ OPINION

Perioperative hemostatic management in the cirrhotic patient: a position paper on behalf of the Liver Intensive Care Group of Europe (LICAGE)

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ABSTRACT

Recent data demonstrated that amongst patients undergoing elective surgery the prevalence of cirrhosis is 0.8% equating to approximately 25 million cirrhotic patients undergoing surgery each year worldwide. Overall, the presence of cirrhosis is independently associated with 47% increased risk of postoperative complications and over two and a half increased risk of in-hospital mortality in patients undergoing elective surgery. In particular, perioperative patients with chronic liver disease have long been assumed to have a major bleeding risk on the basis of abnormal results for standard tests of hemostasis. However, recent evidence outlined significant changes to traditional knowledge and beliefs and, nowadays, with more sophisticated laboratory tests, it has been shown that patients with chronic liver disease may be in hemostatic balance as a result of concomitant changes in both pro- and antihemostatic pathways. The aim of this paper endorsed by the Liver Intensive Care Group of Europe was to provide an up-to-date overview of coagulation management in perioperative patients with chronic liver disease focusing on patient blood management, monitoring of hemostasis, and current role of hemostatic agents.


KEY WORDS: Liver cirrhosis; Hemostasis; Blood coagulation disorders; Perioperative care.
Patient blood management in perioperative cirrhotic patients

Patient blood management (PBM) is a multidisciplinary, multimodal patient-centered strategy aimed at minimizing the utilization of blood products and improving patients’ outcome. One of the most important fields of application of PBM is the perioperative setting. Indeed, both anemia and transfusion have been associated with increased morbidity and mortality in surgical patients and the systematic application of a PBM program in the perioperative period has been consistently found to positively improve patients’ clinical outcomes following surgery. The concomitant presence, however, of medical illnesses may further complicate the implementation of PBM strategies in the surgical setting and in this context an excellent example is provided by advanced liver disorders. Anemia is a frequent finding in patients with cirrhosis, having a reported prevalence of approximately 60% of cases with a multifactorial etiology including deficiencies in iron/vitamin B12/folate, hypersplenism, malnutrition and complications related to the underlying cause such as alcohol-induced marrow aplasia or anemia related directly to viral liver disease or its treatment. Thus, in the frame of a PBM program, potentially reversible causes of anemia should be diagnostically explored and corrected in such patients in the perioperative period, in order to reduce unnecessary transfusions. This consideration is particularly valid for patients undergoing liver transplantation, being blood transfusion considered a strong predictor of overall survival also after liver transplant (LT). Another critical issue of a PBM program in surgical patients with liver cirrhosis is, however, the appropriate transfusion strategy. A number of randomized trials and meta-analyses have consistently documented the superiority of restrictive (hemoglobin thresholds of less than 7 g/dL, less than 8 g/dL with coexisting cardiovascular disease) compared with liberal red blood cell (RBC) transfusion strategies (hemoglobin thresholds less than 9 g/dL to 10 g/dL) in surgical stable patients in terms of morbidity and mortality. However, in spite of such a transfusion approach endorsed by the majority of the nation-
al and international scientific societies and health authorities, the real-life pertaining patients with liver cirrhosis is quite different. In a large, retrospective nationwide study conducted in the United Kingdom on transfusion practice for patients with cirrhosis, RBCs were transfused in over half of the cases with a presenting hemoglobin higher than 7 g/dL. In addition, about one third of patients who were transfused with blood components for prophylaxis received fresh frozen plasma (FFP), whose clinical prophylactic effectiveness in patients with liver disorders was recently questioned by a large meta-analysis. Viscoelastic test-guided management could help to reduce the use of FFP and guide the use of coagulation factor concentrates such prothrombin complex and fibrinogen concentrate, but more research is needed in this field. The European Society of Anaesthesiology (ESA) guidelines recommend viscoelastic tests in the management of severe bleeding in LT (Grade 1C). Finally, thrombocytopenia in cirrhosis, which has a multifactorial etiology (decreased thrombopoietin synthesis, sequestration in the spleen and increased turnover), may increase the surgical-related bleeding risk. Although many experts recommend prophylactic platelet transfusion before surgery if platelet count is less than 50,000/mm³, there is a substantial lack of evidence from literature to support this practice. Notably, it has been well established that LT can be performed in patients with platelet counts below 50,000/mm³ without the requirement for any perioperative blood transfusions.

LICAGE expert panel conclusions and recommendations are the following:

- Preoperative anemia in cirrhotic patients should be identified and, whenever possible, corrected in order to minimize the risk of exposure to allogeneic RBCs transfusions (1B);
- FFP should be administered in the setting of coagulopathy-associated clinical significant bleeding, while prophylactic use of FFP is not recommended (2C);
- Platelet concentrate should be administered in the setting of clinical significant bleeding. Target platelet levels of 50,000/mm³ are recommended (2C).

Future directions and studies

Despite the complexity and the clinical relevance of the issue, there is a lack of studies on the perioperative care of patients with liver cirrhosis. Adequately powered randomized controlled trials are needed to optimize the PBM approach in surgical patients with advanced liver disease.

How to monitor hemostasis in patients with chronic liver diseases

Patients with advancing liver disease acquire abnormalities in all components that contribute to hemostasis, with consequent alterations in laboratory tests of hemostasis. This section will describe clinically available and preclinical hemostatic tests with a description the caveats of each test, particularly for the patient with cirrhosis.

Platelet function tests

Thrombocytopenia is common in cirrhosis. However, in-vitro studies have suggested that thrombocytopenia is compensated for by highly elevated levels of the platelet adhesive protein von Willebrand factor (VWF). There is ongoing debate on the functionality of platelets in patients with cirrhosis. The ideal platelet function test would assess platelet adhesion, platelet activation, platelet aggregation, and platelet procoagulant activity. Unfortunately, all clinically available platelet function tests only assess one or two of these functions, and different platelet function tests may give very different information. For these reasons, platelet function testing in patients with cirrhosis may not be particularly useful.

The gold standard of platelet function, suspension aggregometry, frequently suggests platelet dysfunction in patients with cirrhosis. However, decreased aggregation may also be explained by thrombocytopenia. Many platelet function tests are in essence unsuitable for thrombocytopenic samples as the thrombocytopenia per se already affects the outcome of the test, and alternatives such as flow-cytometric approaches may be more appropriate. Most platelet function tests are insensitive for VWF levels, which makes them unsuitable to assess platelet function in cirrhotic pa-
tients who commonly have highly elevated VWF levels. The platelet function analyzer (PFA100) is the only clinically used platelet function test that tests platelet reactivity under conditions of flow, and therefore is sensitive for VWF levels. However, the PFA100 is also sensitive for thrombocytopenia and anemia, which obscures test results in cirrhosis. Finally, thrombin generation tests in platelet rich plasma have been interpreted as a platelet function test. Although platelet procoagulant activity is an important contributor to hemostasis, the thrombin generation test is likely not ideal to assess procoagulant activity, for example because in the assay the platelets are only activated by thrombin which is known to elicit only a modest procoagulant response.

Clinically, it is unclear whether a minimal platelet count in the patient with cirrhosis is required for optimal hemostasis. Some studies have suggested thrombocytopenia to increase bleeding risk, but it has not been established with this relation is causal, and whether platelet transfusion would decrease bleeding risk in such patients. Although it has been argued that a minimum of 50-60,000 platelets/mm³ are required, this number is extrapolated from thrombin generation studies, which gives a misleading representation of platelet function. Clearly, clinical studies are required to assess which platelet function tests correlate with clinical bleeding risk (spontaneous and procedure-related), and whether platelet transfusion decreases bleeding risk.

Coagulation tests

The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are frequently prolonged in patients with cirrhosis. However, these tests are only sensitive for plasma levels of procoagulants, as patients with cirrhosis have alterations in both pro- and anticoagulant proteins, they give an inaccurate representation of coagulation potential. The PT and aPTT are therefore unrelated to bleeding risk, and should not be used to guide blood product transfusion in patients with cirrhosis.

A test that much better represents coagulation balance is thrombomodulin-modified thrombin generation, which is sensitive for plasma levels of all pro- and anticoagulant proteins. However, this test is not widely available and in its current form unsuitable for clinical use. A whole blood thrombin generation point-of-care test is in development. Thrombin generation in the absence of thrombomodulin gives misleading information as this test is insensitive for the anticoagulant protein C pathway, which is frequently affected in cirrhosis.

Fibrinogen levels are considered critical in the bleeding risk. As thrombin generation capacity appears preserved even in the sickest patients with cirrhosis, prohemostatic therapy with fibrinogen concentrate may be more relevant than FFP transfusion both in prevention and in treatment of bleeding. However, clinical studies on efficacy of fibrinogen supplementation on prevention or treatment of bleeding are required to firmly establish the role of this intervention and plausible transfusion triggers.

Fibrinolytic tests

There is ongoing debate on whether hyperfibrinolysis is common in patients with advanced cirrhosis, which is at least in part driven by the lack of a validated global fibrinolytic test. It is therefore unknown what really defines a hyperfibrinolytic status in a patient with cirrhosis, although in some situations (e.g., during liver transplantation) the combination of clinical bleeding and fibrinolysis testing (by viscoelastic testing, for example) convincingly demonstrates hyperfibrinolysis. Given the efficacy and safety of antifibrinolytic drugs in decreasing blood loss during liver transplantation, it may be that antifibrinolytic drugs are underused in prevention or treatment of bleeding in other settings.

Whole blood hemostasis tests

Conceptually, rapid, point-of-care whole blood tests are ideally suited to monitor hemostasis in patients with cirrhosis. For this reason, clinicians are increasingly considering TEG or ROTEM as the gold standard, and ignore important limitations of these tests. Besides the lack of endothelial cells and appreciable flow rates, viscoelastic tests are insensitive for VWF and the protein C system, which are both considered important modulators of the hemostatic system in cirrhosis. Therefore, although thromboelastography points to a normal
hemostatic status in patients with cirrhosis, it likely still underestimates hemostatic potential. Nevertheless, viscoelastic tests may be useful to guide transfusion, particularly in the actively bleeding patient, but it is important to realize that cut-off values have not been definitively established.

LICAGE panel conclusions and recommendations are the following:

• PT and APTT are unrelated to bleeding risk. They should not be used to guide blood product transfusion in non-bleeding patients with CLD (1B);
• visco-elastic test reflects better bleeding risk than standard-laboratory tests, but have limitations (1C);
• flow cytometry appears to best capture the capacity of platelets to get activated, but clinical validation in patients with cirrhosis is required (1B).

Future directions and studies

Clinical cut-offs for VET should be determined in the future, particular for preproceural procedure. Thrombomodulin-modified thrombin generation seem to adequately depict the hemostatic rebalanced status in patients with CLD in vitro but clinical studies are needed to confirm this finding.

Current role of hemostatic agents

Evidence for the use of hemostatic drugs

The evidence for the safety, effectivity and indication of blood products like FFP, fibrinogen, prothrombin complex concentrates (PCCs), fibrinolysis inhibitors, desmopressin (DDAVP) and recombinant factor VII activated (rFVIIa) is rather limited in different settings. Sufficient coagulation management should be done with coagulation factors, guided by viscoelastic tests (VET) (e.g. ROTEM or TEG). One major advantage in using VET is the tremendous shorter turnaround time. Prophylaxis and therapeutic use of FFP

At the first attempts for liver transplantation, mass transfusion occurred very often. The common practice was a blind prophylactic transfusion of RBC, FFP and platelet concentrates on a 1:1:1. However, hence surgical expertise and hemostasis knowledge improved, this approach was left.

Fresh frozen plasma contains all coagulation factors, anticoagulant and fibrinolytic proteins as well. The activity of factors corresponds to physiological concentrations but decreases during freezing and thawing. To increase plasma activity of factors, large volumes (10 mL/kg to 30 mL/kg) are required. It is assumed that one unit of FFP increases coagulation factors by only 2-3%. The required volume of FFP may trigger a transfusion associated circulatory overload.

Another shortcoming of FFPs is the risk of pathogen transmission, because FFPs do not undergo pathogen inactivation at most hospitals. Moreover, thawing large volumes is time consuming, which could be harmful in term of a severe bleeding.

Fibrinogen concentrate

Fibrinogen decrease at first to critical levels in the case of bleeding and during liver transplantation. Fibrinogen serum levels, as the last factor in the coagulation cascade, determines together with platelets the clot firmness. Fibrinogen concentrate (FC) as a lyophilized product can easily be reconstituted within few minutes at a high concentration (1 g/ 100 mL) and replacement can be done without a risk of hypervolemia. Disease transmission is abandoned due to pathogen inactivation. In-vitro addition of FC in plasma samples from cirrhotic patients improves clot firmness. A recent review comparing FFPs and FC indicates a beneficial effects in trauma patients in favor of FC.

Prothrombin complex concentrates

PCC can be stratified in four and three factors containing PCC. The infectious risk is very low due to virus elimination. PCCs are approved for vitamin K reversal, but perioperative application is common practice. Although data about PCC in LT is limited, a recent study indicated the efficacy in liver transplantation.
Coagulation management in patients with ESLD was not associated with thrombosis.\textsuperscript{55} A meta-analysis comparing FFPs and PCC for vitamin K reversal showed higher thrombotic risk for FFPs.\textsuperscript{56} The proton trial, a prospective, randomized trial evaluated the prophylactic use of PCC on transfusion rate in liver transplantation.\textsuperscript{57} However, no data are available yet.

**Antifibrinolytics**

Antifibrinolytics, like tranexamic acid (TXA) are used for both, prophylaxis and treatment of hyperfibrinolysis as well. Hyperfibrinolysis is common in liver transplantation and may be associated with bleeding.\textsuperscript{72} In many cases hyperfibrinolysis occurs during anhepatic phase and after reperfusion. There are conflicting results about risks and benefits of antifibrinolytics. A recent Cochrane analysis of three trials with 1913 patients concluded no differences in term of mortality, rate of re-transplantation, and thromboembolic events.\textsuperscript{70} However, the authors did not make a final recommendation in order that the studies were underpowered for assessment of thromboembolic events. There are numerous case reports on thromboembolic events with the use of antifibrinolytics which raise concern for prophylactic use.\textsuperscript{73} Importantly, the incidence of intracardiac thrombosis (IC) (0.7-6.3\%) and pulmonary embolism (0.4-4\%) is high during liver transplantation procedures and mortality was found to reach up to 80\%. The use of antifibrinolytics is guided by VETs at some transplantation centers, as hyperfibrinolysis can be detected by these devices.

**Desmopressin**

Desmopressin is an analog of vasopressin with reduced vasopressor activity. The agent stimulates the release of factor VIII:C and von Willebrand factor from the endothelium. Nasal desmopressin was found to reduce bleeding in dental extraction procedures in patients with liver cirrhosis.\textsuperscript{74} In contrast desmopressin did not improve primary hemostasis in patients with liver cirrhosis.\textsuperscript{75} However, it is important to note, that platelet activation is common due to the presence of highly active von Willebrand multimers, which are not degraded as ADAMTS13 levels are lowered in these patients.

**Potential indications for antithrombotic therapy**

Recognizing, that thromboembolic events, portopulmonary hypertension, hepatopulmonary syndrome as well as the sinusoidal obstruction syndrome are potential risks of hypercoagulability in liver transplantation, it might be worth to...
consider the potential beneficial effect of antithrombin. It is well recognized that antithrombin is often reduced in liver transplantation, that decreased antithrombin levels favor thromboembolic events and heparin refractoriness. In pediatric liver transplantation, 70% of patients had reduced antithrombin activities. In a pilot study Kaneko et al. hypothesized that substitution of antithrombin reduces both fibrinolysis and the decrease of platelets after transplantation. It is important to state, that decreases in antithrombin are especially important in patients treated with coagulation factor-based coagulation management, while antithrombin is (partially) substituted with fresh frozen plasma. The fact, that there are no recommendations about indication, timing, dosing, and risks of antithrombin suggest an important avenue for future research. Conventional antithrombotic treatment is discussed below.

LICAGE panel conclusion and recommendations are the following:
- prophylactic FFP transfusion should be avoided (1C);
- in bleeding patients, once fibrinogen and platelets are replaced and fibrinolysis is excluded, the administration of PCCs may be considered (1C);
- there is no indication for rFVIIa (1A);
- good evidence of beneficial effect of antifibrinolytics (2C).

Future directions and studies
More evidence, hopefully from RCTs, is needed addressing the efficacy and safety of using coagulation factors (namely PCCs) in LT

Multidisciplinary approach to avoid periprocedural bleeding of the cirrhotic patient
Periprocedural bleeding in cirrhotic patients is influenced by multiple factors, like preoperative condition of the patient, anesthesiological care and surgical techniques. A multidisciplinary approach with close collaboration between all concerned disciplines is therefore fundamental.

Preoperative condition
Avoiding periprocedural bleeding already starts preoperatively. Risk factors for periprocedural bleeding should be minimized whenever possible; marginal nutritional state should be avoided, portal hypertension treated, and renal function optimized prior to surgery.

As supported by the NICE guidelines, most centers routinely perform preoperative hemostasis tests. In cirrhotic patients though, prophylactic transfusion based on preoperative hemostasis tests should be avoided. The efficacy of prophylactic transfusion in cirrhotic patients has never been proven and in fact may be counterproductive. Despite improvement of platelet count or PT after transfusions, the volume of transfusions cause increase in portal and central venous pressure and subsequent periprocedural bleeding risk. Besides that, blood transfusion during liver transplantation is associated with increased mortality, brings considerable costs and a risk of devastating transfusion reactions. Therefore, a wait-and-see policy is preferred, in which preoperative prolonged coagulation tests should be accepted, and blood components only be transfused when active, non-surgical bleeding occurs. This policy is supported by the increasing evidence of a ‘rebalanced’ hemostatic profile in cirrhotic patients, with adequate thrombin generation capacity despite prolonged conventional coagulation test.

Anesthesiological care
Anesthesiological strategy to minimize periprocedural blood loss should focus on restrictive fluid infusion policy, to maintain a low central venous pressure (CVP). The CVP, which is already elevated in cirrhotic patients, is directly related to the hepatic vein pressure and is almost linear correlated with the amount of blood loss. Maintenance of a low CVP (<5 cmH₂O) and preoperative CVP reduction by phlebotomy, appeared a beneficial strategy to reduce blood loss during hepatectomy or liver transplantation. Although these studies present some interesting results, there are concerns which should be considered. The study was performed 20 years ago and, since then, many surgical and anesthetic improvements occurred making it difficult to
extrapolate this study’s results to present. In a more recent study Massicotte et al. demonstrated that cirrhotic patients benefit from restrictive fluid management and that the benefit was due to a reduced portal vein pressure, resulting from phlebotomy, rather than from a reduced CVP. Another important anesthetic focus for surgery in cirrhotic patients is monitoring of coagulation abnormalities and its correction, mainly by administration of blood components like fresh frozen plasma (FFP), fibrinogen or platelet concentrates. As mentioned above, also hemostatic drugs can be administered. Routine correction of abnormal coagulation tests with FFPs is not effective in reducing periprocedural blood loss. At present, in a variety of surgical settings cell salvage has been adopted in order to reduce allogenic blood transfusion rates. Its efficacy in reducing blood transfusion in liver transplantation patients was demonstrated. Besides that, in liver transplantation the cell saver could also be used to transfuse the previous obtained blood during phlebotomy. Lastly, hypothermia and metabolic acidosis should be avoided because they may aggravate coagulation abnormalities.

Surgical techniques

To reduce blood loss during liver transplantation, several surgical techniques were modified over time. In the 1980s the veno-venous bypass was introduced. Due to the decompression of splanchnic and retroperitoneal circulation, less hemodynamic changes occurred during anhepatic phase, leading to a reduction of blood loss. A second important step was cava sparing liver transplantation, the so-called piggyback technique, in which the recipients inferior vena cava (IVC) is retained and the donor IVC is anastomosed to it. This enables partial clamping and avoids interruption of blood flow through the IVC, subsequently the venous return to the heart can be maintained. This facilitated better intraoperative hemodynamic stability with a low CVP. Secondly, the piggyback technique eliminated the need for dissection of the retroperitoneum in a patient with portal hypertension and multiple venous collaterals. This technique resulted in liver transplantation with less blood transfusion and shorter warm ischemia times. A next step, to decrease portal venous stasis during hepatectomy, the piggyback technique was combined with temporary portocaval shunts by using end to side portocaval anastomosis or extracorporeal catheters. By reduction of the portal venous pressure, hemodynamic stability improved and blood loss was reduced. This simple and effective combined technique reduced the amount of blood transfusions and hepatic injury, without prolonging operation time. Nonetheless, this method must be further explored in a prospective RCT.

LICAGE panel conclusion and recommendations are the following:

- periprocedural bleeding in cirrhotic patients is influenced by multiple factors including preoperative condition of the patient, anesthesiological care and surgical techniques, which makes a multidisciplinary approach fundamental (1B).
- in cirrhotic patients with preoperative prolonged coagulation tests, a wait-and-see policy is preferred over prophylactic transfusions; blood components should only be transfused when active non-surgical bleeding occurs (1C).
- periprocedural maintenance of a low CVP is a beneficial strategy to reduce blood loss during surgery in cirrhotic patients and can be realized by restrictive fluid infusion policy (2B).

The piggyback technique (2A) and the adoption of intraoperative portocaval shunts (2B) are effective surgical techniques to reduce periprocedural bleeding in liver transplantation.

Future directions and studies

The transplant community should work on better volume assessment tools and better preoperative assessment of bleeding risk factors.

Perioperative thrombotic risk

Thrombotic complications in patients with cirrhosis occur with a greater frequency than in the general population. Risk factors for thrombosis include inherited and acquired deficiency of factors involved in anticoagulation mechanisms, venous stasis and possibly local factors related to the endothelium. The following section briefly discuss the management of perioperative thrombotic events in patients with cirrhosis, being PVT the most frequent.
Portal vein thrombosis

Portal vein thrombosis (PVT) represents the most common thrombotic complication occurring in cirrhosis, with 1-year incidence ranging from 7.4% to 11% up to 24% in cirrhotic patients with HCC. Pathogenesis of PVT is likely to be multifactorial and both local and systemic factors can be involved. The risk of PVT has been shown to be independently associated with the severity of liver disease and severity of portal hypertension. PVT in cirrhotic patients is often asymptomatic or diagnosed in coincidence with variceal bleeding or abdominal pain. After the development of PVT, progression of thrombosis has been reported in 50% of cases in average at two-year follow-up. Portal thrombosis by itself increases the risk of variceal bleeding and related mortality. Correct staging with CT scan and classification according to Yerdel is recommended. In the LT setting, when PVT is complete (or grade III according to Yerdel’s classification), post-transplant survival rates are compromised with an HR of 5.65 (95% CI: 2.15-19.96), P=0.001 and HR 2.48 (95% CI: 0.99-6.17) for 30 day and one year post-LT mortality, respectively. Non-anatomic solutions, particularly porto-caval hemi-transposition (PCHT), do not solve portal hypertension and 1-year mortality has been reported to be 40%. The aim of anticoagulation therapy should be the repermeation of the vessel or reduction of thrombosis extension in order to ensure anatomical reconstruction. To date, data on the efficacy and safety of medical anticoagulation to treat PVT come from seven cohort studies which included 258 patients, most with partial PVT. Globally, the re-permeation rate ranged from 56% to 76%. When anticoagulation is withdrawn, recurrence of thrombosis is frequent. The anticoagulant treatment was not associated with a significant risk of bleeding. Overall, possibly related bleeding complications were seen in only 19/230 (8.2%) patients and not correlated with portal hypertension. In cirrhotic patients, TIPS can be considered to treat PVT in case of thrombus progression despite adequate anticoagulant treatment, in case there is an absolute contraindication to anticoagulation or in case of no response after a maximum of six months of antiocoagulation treatment. Recanalization of the PV is feasible in about 50% to 80% of patients. In presence of extensive thrombosis recanalization of the portal vein by percutaneous approach with TIPS placement is feasible in expert centers with acceptable complication rate.

LICAGE panel conclusion and recommendations are the following:
- in patients with cirrhosis a Doppler ultrasound at 6-month intervals should be used as a screening for the detection of Pvt (C1);
- CT scan/MRI are recommended to evaluate extension of PVT, adopting the Yerdel’s classification (B1);
- anticoagulation is recommended for a period of at least six months (B1);
- in extensive thrombosis or in those patients not responding to anticoagulation transjugular intrahepatic portosystemic shunt could be considered (B2).

Deep vein thrombosis and pulmonary embolism

The association between cirrhosis and risk of pulmonary thromboembolism (PE) or deep vein thrombosis (DVT) amongst hospitalized patients with cirrhosis has been evaluated in retrospective case control studies in which 0.8-7% of cirrhotic patients presented with thrombosis in these sites. Cirrhosis carries a 1.7-fold increased relative risk of venous thrombosis compared to the general population. Interestingly, traditional markers of coagulation impairment in liver disease were not correlated with VTE, but low serum albumin is independently predictive in two studies. Current guidelines do not recognize the thromboembolic risk associated with chronic liver disease. The Padua Prediction Score may be used to decide if patients should be treated with primary prophylaxis or not, although further clinical validation of this score in patients with cirrhosis is required. The reported use of prophylactic anticoagulation for VTE in patients with chronic liver disease remains significantly lower than in other in-patients. The interim suggestion is that VTE pro-
DVT
After liver transplantation, incidence ranges from 3.5% to 8.6%.\textsuperscript{124, 128} Thromboprophylaxis is indicated. In specific conditions: thrombophilia, prolonged immobilization and large blood product transfusion, therapeutic doses of anticoagulation may be indicated.\textsuperscript{124, 129, 130} Treatment is recommended with LMWH\textsuperscript{131} followed by oral anticoagulants. Unfractioned heparin (UFH) cannot be monitored.\textsuperscript{132} Vena cava filter insertion is indicated when anticoagulation is not possible.\textsuperscript{133}

Hepatic artery thrombosis
The incidence ranges from 2.5% to 6%.\textsuperscript{134} Early hepatic artery thrombosis (HAT) leads to acute graft dysfunction; late HAT leads to ischemic cholangiopathy.\textsuperscript{135} Anatomic/mechanical factors are mostly involved, but etiology of cirrhosis (familial amyloidotic polyneuropathy, autoimmune, cholestasis and hepatocarcinoma), thrombophilia donor/recipient, high perioperative transfusion;\textsuperscript{128, 136, 137} PVT and reduced postanastomotic hepatic artery flow were associated with increased risk of HAT.\textsuperscript{139} Early HAT needs immediate graft repermeabilization by endovascular mechanical/pharmacologic thrombolysis, or surgical reconstruction.\textsuperscript{140} Failure of the previous approaches requires urgent re-transplantation.\textsuperscript{141}

Thromboprophylaxis is recommended in small or “non-anatomical” anastomosis, living donor LT, split, poor arterial flow and pretransplant PVT.\textsuperscript{80, 139} Aspirin was associated with significantly lower incidence of early and late HAT.\textsuperscript{139} UFH or LMWH plus aspirin have been proposed in individuals at higher risk.\textsuperscript{145}

PVT after LT
PVT after LT is relatively rare at 0.5-2%. However, early rethrombosis in recipients with PVT prior to LT ranged from 5% to 21%.\textsuperscript{103, 146} Intraoperative thrombectomy and sever portal hypertension have been identified as risk factors.\textsuperscript{147, 148} Early PVT can necessitate urgent retransplantation. Reoperation is the most successful option but percutaneous mechanical/pharmacologic thrombolysis, transjugular approach and systemic heparinization have been attempted.\textsuperscript{124, 130, 149}
Prophylactic anticoagulation is recommended in those patients with previous complete PVT or undergoing “non-anatomical” anastomosis for at least three months. LICAGE panel conclusion and recommendations are the following:

- when intra-cardiac or pulmonary thrombi are suspected during LT, confirmation by intra-operative TEE is recommended (C1);
- systematic early abdominal US is recommended to confirm vascular graft patency (B2);
- anticoagulation in LT is recommended in complicated vascular anastomosis, overtransfusion, pretransplant PVT (especially when intra-operative thrombectomy), and additional thrombophilic conditions (B2);
- aspirin is recommended to prevent both early and late HAT in case of small vessels (living donor LT, split), complicated anastomosis, poor hepatic arterial flow and pretransplant PVT (B1).

Future directions

Future studies should prove efficacy and safety of the different antithrombotic agents in cirrhotic patients, which includes to work out an appropriate monitoring for these drugs.

Antithrombotic treatment management in patients with cirrhosis

The current literature show that anticoagulant therapy in cirrhotic patients is safe as bleeding events do not occur at higher rates than in untreated patients. Anticoagulant therapies include unfractioned heparin, low molecular weight heparins and fondaparinux for acute treatment, and low molecular weight heparins and vitamin K antagonists for long-term treatment. No robust data currently support the use of direct oral anticoagulants (DOACs) in patients with cirrhosis and PVT and the safety and efficacy of DOACs in this setting is still unclear. However, some patients with cirrhosis can receive DOACs for other indications. Patients with cirrhosis can also receive antiplatelet agents because of coronary artery disease. There are no specific recommendations for patients with liver disease on antithrombotic treatment. General recommendations may be used as a guide taking into account the abnormal glomerular filtrate and the thrombocytopenia frequently see in this population (Table I).

There are no specific LICAGE recommendations for patients with liver disease on anticoagulation/antiplatelet agents management. General recommendations may be considered when surgery or other invasive procedures are required in patients under antithrombotic treatment (C2).

### Key messages

- Preoperative anemia in cirrhotic patients should be identified and, whenever possible, corrected in order to minimize the risk of exposure to allogeneic RBCs transfusions. FFP should be administered in the setting of coagulopathy-associated clinical significant bleeding, while prophylactic use of FFP is not recommended. Platelet concentrate should be administered in the setting of clinical significant bleeding. Target platelet levels of 50,000/mm³ are recommended.
- PT and APTT are unrelated to bleeding risk. They should not be used to guide blood product transfusion in non-bleeding patients with CLD. Visco-elastic test reflects better bleeding risk than standard-laboratory tests, but have limitations.
• Prophylactic FFP transfusion should be avoided. In bleeding patients, once fibrinogen and platelets are replaced and fibrinolysis is excluded, the administration of PCCs may be considered. There is no indication for rFVIIa with good evidence of beneficial effect of antifibrinolytics.

• Periprocedural bleeding in cirrhotic patients is influenced by multiple factors such as the preoperative condition of the patient, anesthesiological care and surgical techniques, which makes a multidisciplinary approach fundamental. In cirrhotic patients with preoperative prolonged coagulation tests, a wait-and-see policy is preferred over prophylactic transfusions; blood components should only be transfused when active non-surgical bleeding occurs. Periprocedural maintenance of a low CVP is a beneficial strategy to reduce blood loss during surgery in cirrhotic patients and can be realized by restrictive fluid infusion policy.

• In patients with cirrhosis a Doppler ultrasound at 6-month intervals should be used as a screening for the detection of PVT. CT scan/MRI are recommended to evaluate extension of PVT, adopting the Yerdel’s classification. Anticoagulation is recommended for a period of at least six months. In extensive thrombosis or in those patients not responding to anticoagulation transjugular intrahepatic portosystemic shunt could be considered.

• Patients with cirrhosis are not protected against VTE and should receive antithrombotic prophylaxis in conditions with increased risk for VTE according to standard criteria. When low molecular weight heparins (LMWH) are used laboratory monitoring should not be used.

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For supplementary materials, please see the HTML version of this article at www.minervamedica.it
LETTERS TO THE EDITOR

Fasting guidelines concerning intake of solids of the American Society of Anesthesiologists are not in concert with those of the European Society of Anaesthesiologists

I read with interest the paper of Presta et al. on fasting guidelines before elective surgery.

The authors stated that the recently published American Society of Anesthesiologists (ASA) guidelines are in concert with the 2011 guidelines of the European Society of Anaesthesiologists (ESA). This is inaccurate concerning fasting after intake of solids. According to the ESA guidelines, fasting of six hours is enough, irrespective of the type of food. In contrast, the ASA guidelines require an eight hour (or more) fasting period after the intake of fried foods, fatty foods, or meat. Only after a “light meal” (whatever the definition), is a six-hour fasting period sufficient.

I am not aware of any reports on increased aspiration incidences in Europe since the publication of the ESA guidelines. The “2-6 rule” (intake of water two hours prior to induction of anesthesia and six hours of fasting period for solids) recommended by The Association of Anaesthetists of Great Britain and Ireland is simple and easy to follow for patients, anaesthetists and surgeons. It seems that a change in the ASA fasting guidelines might be warranted.

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Response to ASA and ESA fasting guidelines are not in concert

We wish to thank Dr. Avidan\textsuperscript{1} for his interest and feedback in regards to our recently published manuscript\textsuperscript{2} on the controversies surrounding fasting guidelines before elective surgery. We agree with Dr. Avidan that when we compared the latest NPO guidelines from the American Society of Anesthesiologists (ASA)\textsuperscript{3} to that of the European Society of Anesthesiologists (ESA),\textsuperscript{4} we described them as being in concert with one another, which could be misunderstood by some as being identical which they are not. What we actually meant is that they were for the most part in agreement with one another.

Both guidelines agree on many broad concepts and recommendations. For example, the importance of fasting before surgery, breast milk and non-human milk fasting in infants and certain aspects of fluid fasting prior to surgery. However, as Dr. Avidan has correctly pointed out, the ESA guidelines recommended six hours of fasting from solid food regardless of caloric or fat composition compared to the longer eight hour fast recommended by the ASA guidelines which consider both the amount and type of foods ingested when determining an appropriate fasting period (allowing the six hours fast only for light meals).

With that said, we respectfully disagree with Dr. Avidan that a change of the ASA guidelines to match the ESA recommendation when it comes to fasting from solid food is warranted. It seems like the six hour period recommended by the ESA was arbitrarily decided on, as the only cited evidence to support it is a study from 1983 that included only 45 patients, with many methodologic limitations as highlighted by the guidelines authors, as well as the study authors themselves.\textsuperscript{5} Moreover, many studies have demonstrated that emptying times are quite variable and depend on the volume and nutrient content of the meal. Variability in gastric emptying is seen with increased food weight, caloric density, and the addition of fat.\textsuperscript{6-8} On the whole, the six hours one-size-fits-all approach may not necessarily work here. Hence a longer fasting period of eight hours may be better suited and cover more patients while still having the option for a shorter period of six hours for lighter meals. Additionally, the latest NPO guidelines from the Canadian Anesthesiologists’ Society in 2019,\textsuperscript{9} mirror the ASA recommendations and support a fasting duration of eight hours when meat, fried, or fatty foods are consumed prior to elective surgery.

While we hope that Dr. Avidan is correct that there were no increased incidence of aspiration resulting from following the six-hour recommendation of the ESA guidelines, and no patient was harmed, we caution that the lack of reports may not mean it is not happening. Regrettably, there is a reluctance in reporting poor outcomes. Due to the paucity of concrete evidence to support one recommendation versus another, we are often put into this situation where we depend on consensus and expert opinions to produce the most logical recommendations based on inferences from related research and extensive personal experiences.

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Letters to the Editor

Ultrasound guided erector spinae plane block: an alternative technique for providing analgesia after total hip arthroplasty surgery?

We describe the use of ultrasound guided erector spinae plane (ESP) block for postoperative analgesia in an 85-year-old female, weight 47 kg, height 1.58 cm, American Society of Anesthesiologists physical status (ASA) of IV, who required total hip arthroplasty surgery for pertrochanteric fracture and necrosis of the femoral head.

ESP block is a technique in which local anesthetic is injected between the erector spinae muscle and transverse process, blocking the dorsal and ventral rami of the thoracic and abdominal spinal nerves.1,2

This manuscript was submitted after obtaining the patient’s consent.

In the operating room, the patient received standard heart rate, noninvasive blood pressure and oxygen saturation monitoring and was placed in the lateral position with the site of surgical interest uppermost.

A midline lumbar puncture was performed using a 27-gauge Whitacre spinal needle (PIC, Artsana SpA, Grandate, Como, Italy) at L3-L4 level and 0.5% isobaric bupivacaine 1.6 mL plus Sufentanil 3 mcg was slowly injected.

The surgical procedure was completed in 60 minutes and during surgery the patient did not complain of pain, did not experience respiratory depression or a reduction in heart rate or blood pressure.

At the end of surgery, with the patient placed in the lateral position, an ultrasound guided (SonoSite M-Turbo, SonoSite Inc., Bothell, WA, USA) ESP block at L4 level was performed, in order to control postoperative pain, with a 10-5 MHz linear probe.

The puncture was performed with a 22-G x 50-mm needle (Echoplex+, Vygon, Ecouen-France), using the “out-of-plane” technique and needle tip progression was controlled using ultrasound visualization and hydrolocalization with sterile saline solution 0.9% (0.5 mL). When the needle came into contact with the transverse process. We administered Ropivacaine 0.5% 10 mL plus Dexametasone 2 mg (1 mL) at L4 level (Figure 1).

Three hours after the end of surgery, the degree of the patient’s motor and sensory block was evaluated. The patient was able to move her feet and legs freely, while sensory blockage, assessed by cold sensation with an alcohol-soaked sponge and pin prick testing, showed the diffusion of local anesthetic from T12 level up to L5 level.

Acetaminophen 1 gr intravenously was administered before the end of surgery, and then every eight hours for 36 hours.

Pain never exceeded 3 on the Visual Analogue Scale (VAS) for 36 hours after surgery, no postoperative nausea and vomiting was reported and at 10 hours from the end of the surgery the patient was painlessly mobilized to begin physiotherapy procedures.
ESP block has previously been used for total hip arthroplasty surgery associated with general anesthesia, however its use has never been reported with spinal anesthesia. Consequently, the most commonly used techniques for pain management after total hip arthroplasty are epidural analgesia, psoas compartment block, fascia iliaca block, lumbar plexus block, femoral nerve block.

Our experience cannot be construed as effective based on the outcome of a single case, however, this case suggests that ultrasound guided ESP block could be an effective alternative to other locoregional techniques most commonly used for postoperative pain control after total hip arthroplasty surgery.

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LMA Gastro Airway® Cuff Pilot for endoscopic retrograde cholangiopancreatography: a preliminary experience

Upper gastrointestinal endoscopic procedures are commonly performed under sedation in the ambulatory setting. Sedation with propofol reduces patient discomfort and facilitates endoscopy due to better patient tolerance. However, significant unplanned events including airway obstruction and hypoxia occur in 23% of cases. Hypoventilation due to depression of the respiratory drive and airway obstruction by sedation and analgesic medications are the most common mechanisms of hypoxemia. In addition, the process of esophageal intubation causes voluntary transient apnea or some degree of ventilation-perfusion mismatch. Furthermore, patients with obesity and/or obstructive sleep apnea are at higher risk for airway obstruction during deep sedation. The LMA® Gastro Airway Cuff Pilot (Teleflex Medical, Athlone, Ireland) is a new second-generation supraglottic airway device specifically developed for upper gastrointestinal endoscopy. The device contains a large bore endoscope channel (16 mm internal diameter) which performs proximally and runs parallel along the airway tube. The endoscope channel ends at the cuff distal tip which communicates distally with the upper esophageal sphincter. A well lubricated endoscope may be passed through the endoscope port for upper gastrointestinal endoscopy procedures. We report our preliminary assessment of the effectiveness of device for airway management in adult patients undergoing general anesthesia for ERCP. Data for this retrospective analysis was derived from the difficult airway database collected prospectively from June 2018 to September 2018 at a general community hospital.
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MINERVA ANESTESIOLOGICA

Letters to the Editor

Movement and auscultation, absence of gastric insufflations and by the presence of normal capnogram. The breathing circuit was connected to the airway channel allowing the patient to breathe spontaneously. The ERCP was performed with a 11-mm duodenoscope (Pentax ED-3480 Tokyo, Japan). The study outcomes included insertion success, first attempt success, airway compromise, laryngospasm, bloodstained device, and sore throat. The insertion success rate was 100% with a first attempt success rate of 100%. No airway compromise or laryngospasm or bloodstains on the device were observed. Only one patient experienced a transient sore throat. The endoscopy was performed successfully in all patients. Gastrointestinal endoscopy cases form the largest portion of out of operating room malpractice claims involving anesthesiologists with ERCPs representing most of the total amount paid to patients. During ERCPs general anesthesia may have a higher safety profile ensuring airway control, but so far, few alternative options to the tracheal tube were available. In our experience the LMA® Gastro Airway® Cuff Pilot appears safe and effective for clinical use in upper gastrointestinal endoscopy, also in high risk procedures, of course this study is hypothesis-generating for future research.

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References

Ceftazidime-avibactam salvage therapy in newborn with KPC-producing Klebsiella pneumoniae invasive infections

Ceftazidime-avibactam (CAZ-AVI) is approved for the treatment of complicated MDR Gram-negative, especially Klebsiella pneumoniae KPC (KPC-Kp) infections, with limited treatment options, but clinical trials with CAZ-AVI in pediatric population are lacking.

In Santobono-Pausilipon Hospital, we had successfully treated, after the failure of conventional antibiotic therapy, a new-born with CAZ-AVI for KCP-Kp sepsis. The patient weighed 860 g at birth, was admitted to the neonatal intensive care unit at the twentieth day of life for hypertensive post-hemorrhagic hydrocephalus. After 10 days, he developed a catheter-related blood stream infection (BSI-CR) and meningitis due to KPC-Kp without colonization.

The antibiotic susceptibility tests indicated that KPC-Kp was susceptible to colistin (MIC=2 µg/mL), phosphomycin (MIC≤16 µg/mL) and tigecycline (MIC<0.5 µg/mL), and resistant to meropenem (MIC=16 µg/mL).

In accordance with the body weight (1300 g), colistin (28,000 IU t.i.d. IV), rifampicin (4.5 mg/kg b.i.d. IV) and gentamicin (3.5 mg/kg daily IV) were administered. After one week of antibiotic therapy, due to the persistence of positive CSF culture for KPC-Kp, phosphomycin (45 mg/kg t.i.d. IV) and meropenem (40 mg/kg t.i.d. IV) have been added to the therapy. Furthermore, after two more days, due to the poor clinical improvement, CAZ-AVI was started (75/20 mg/kg t.i.d. IV), discontinuing colistin, rifampicin and gentamicin. After eight days of therapy, due to moderate thrombocytopenia, the dosage of this drug was decreased to 25/6.5 mg t.i.d. IV. Subsequently, after 25 days of CAZ-AVI combination therapy with negative cultures and normal inflammatory biomarkers, the antibiotic therapy was discontinued, although persisted lung and gut colonization. Two days after the antibiotic discontinuation, patient developed clinical condition of sepsis and laboratory diagnosis of KPC-Kp BSI. In accordance to current patient’s body weight (2500 gr at the 34th day of life) antibiotic therapy with phosphomycin (45 mg/kg t.i.d. IV), meropenem (40 mg/kg t.i.d. IV) and CAZ-AVI (25/6.5 mg t.i.d. IV) was started again and prolonged for 22 days. At 30 days’ follow-up, clinical condition was good, without relapse of KPC-KP infections and colonization. Antibiotic drugs duration and time course of C-reactive protein and procalcitonin is reported in Figure 1.

Premature infants, who prolong their stay in hospital and need invasive procedures, are more exposed to hospital-acquired infections and neonatal sepsis. Carbenapenem-resistant Enterobacteriaceae infections are a frequent cause of nosocomial infections and, especially when bacteremia is present, they are associated to high morbidity and mortality. Unfortunately, the genotyping of the KPC-Kp strain is not available. This data could allow us to distinguish between a new infection and a release of the first infection: in a patient who developed rectal and tracheal colonization, we are not being able to exclude a colonization acquired by other patients, admitted to the same ward.

In pediatric patients, ceftazidime monotherapy established a safety profile, promising data for CAZ-AVI are available for complicated urinary tract infection and complicated intra-abdominal infection but, so far, no data are still available for neonatal KCP-Kp BSI infection.
tion. In adults with KPC-Kp BSI, CAZ-AVI, compared to other second line-antimicrobial regimens, reveals a significantly lower 30-day mortality rate. CAZ-AVI in combination might be able to de-colonize from the gut KPC-KP, as demonstrated in adults.

CAZ-AVI might be safe and useful in pediatric population, therefore, prospective clinical trials are recommended.

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References


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