CONTENTS

1023
EDITORIALS
ECMO management guided by echo: is it feasible?
Tritapepe L.

1026
Microvascular fluid cup: sturdy in the healthy, but bottomless in septic shock
Benes J., Monnet X.

1029
When the nerve block is blocked by local resistance
Qu J. Z., Alston T. A.

1032
Basics to perform and present statistical analyses in scientific biomedical reports. Part 3
Cesana B. M., Cavaliere F.

1036
The high nasal flow therapy for pre-oxygenation: a new strategy for conventional procedures in intensive care settings?
Terragni P., Cossu A. P.

1039
Colloidophobia
Ripollès Melchor J., Fries D., Chappell D.

1043
ORIGINAL ARTICLES
Right ventricle dilation as a prognostic factor in refractory acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation
Lazzeri C., Cianchi G., Bonizzoli M., Baracchi S., Terenzi P., Bernardo P., Valente S., Gensini G. F., Peris A.

1050
Comparison of three videolaryngoscopes for double-lumen tubes intubation in simulated easy and difficult airways: a randomized trial
El-Tahan M. R., Al’ghamdi A. A., Khidr A. M., Gaarour I. S.

1059
Effects of passive leg raising on microvascular venous compartment in critically ill patients
De Blasi R. A., Arcioni R., Brancadoro D., Rocco M.
1069
The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial
Bornemann-Cimenti H., Wejborz M., Michaeli K., Edler A., Sandner-Kiesling A.

1077
Point-of-care-based protocol with first-line therapy with coagulation factor concentrates is associated with decrease allogenic blood transfusion and costs in cardiovascular surgery: an Italian single-center experience
Trevisan D., Zavatti L., Gabbieri D., Pedulli M., Giordano G., Meli M.

1089
Whole-exome sequencing of a family with local anesthetic resistance
Clendenen N., Cannon A. D., Porter S., Robards C. B., Parker A. S., Clendenen S. R.

1098
EXPERTS’ OPINIONS
Hazards of intubation in the ICU: role of nasal high flow oxygen therapy for preoxygenation and apneic oxygenation to prevent desaturation
Ricard J. D.

1107
The risk of infusing gelatin? Die-hard misconceptions and forgotten (or ignored) truths
Pisano A., Landoni G., Bellomo R.

1115
A dynamic view of dynamic indices
Fischer M. O., Guinot P. G., Bias M., Mahjoub Y., Mallat J., Lorne E.

1122
LETTERS TO THE EDITOR
Near-zero difficult tracheal intubation and tracheal intubation failure: too good to be true
Corso R. M., Di Giacinto L., Sorbello M., Piraccini E., Pettrini F.

1123
Besta Airway Algorithm in morbidly obese patients: expertise and safety
Cagnazzi E., Latronico N., Pe F., Mosca A.

1124
Delayed CO₂ embolism: importance of early postoperative surveillance
Leoni A., Antonelli A., Pocar M.

1125
Cervical emphysema and pneumomediastinum due to isolated pharyngeal perforation after blunt trauma
Vissani M., Lentischio L., Nicoletta G., Pugliese F., Fedeli C., Zava R.

1127
TOP 50 MINERVA ANESTESIOLOGICA REVIEWERS

About the cover: The cover shows a genetic variant associated with local anesthetics resistance in the gene encoding for Nav1.5. Immunohistochemical staining shows strong Nav1.5 immunoreactivity in peripheral nerves (C), dorsal root ganglia (D), and the brain (E). Cardiac tissue was stained with Nav1.5 antibody in the absence (A) or presence (B) of a blocking peptide to denote positive and negative controls, respectively. For more information, see article by Clendenen N. et al. on page 1089.
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ECMO management guided by echo: is it feasible?

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In this issue of *Minerva Anestesiologica*, the manuscript by Lazzeri C *et al.* focuses on echocardiographic assessment of the right ventricle in ECMO patients suffering from acute respiratory distress syndrome (ARDS), trying to highlight the predictors of mortality.

Why does echocardiography play an important role in risk stratification of patients undergoing extracorporeal membrane oxygenation for severe respiratory failure? In case of ARDS, after an initial aggressive treatment, the patient can have a worsening of their respiratory insufficiency.

Simultaneously he presents high values of central venous pressure and dilation of inferior vena cava (IVC) with fluid retention both in pleural and in abdomen cavities. Why does that happen?

If we perform an echocardiography evaluation, we can show a dilation of the right ventricle with associated pulmonary hypertension. This picture is well described in literature and is called Acute Cor Pulmonale (ACP). When this situation is present, the therapeutic strategy changes rapidly and it is mandatory to achieve a compromise between the best ventilatory positive end-expiratory pressure (PEEP) and circulatory stability. The therapeutic goal is to use protective ventilation finalized at reducing the right ventricular failure related to an increased afterload of the right chambers. The first step in the treatment of ACP in ARDS patients is the reduction of pulmonary artery hypertension, to reduce the incidence of the right ventricular dysfunction. This has been dramatically reduced by the implementation of protective lung ventilation, but still remains as high as 25%. In case of failure of this treatment, we have to choose other measure of support to protect both the lung and the right ventricle, *i.e.* the VV-ECMO.

The institution of VV-ECMO leads to the resolution of hypoxemia and hypercapnia, and to a reduction of airway pressures, which results in decreased pulmonary vascular resistance. This may reverse the hemodynamic instability associated with the right ventricular dysfunction, as described by Lazzeri C *et al.*

It is very important to assess the right ventricular function day by day with the echocardiography evaluation. Because of the high acoustic impedance caused by high PEEP values, the transthoracic echocardiography (TTE) may not be feasible. Transthesophageal echocardiography (TEE) is preferred because it is easy to perform in the ARDS patients, who are often intubated and sedated.

A recently published position paper on the management of the ECMO recommends that an echocardiography-trained physician should be part of the team caring for patients on ECMO.
However, the role of echocardiography in ECMO is not widely accepted and is still poorly described in the literature.

Echocardiographic examination of the right ventricle requires a long-axis and a short-axis views to evaluate the size of the cavity, the left ventricle relationship and septal kinetics. The assessment can be completed by the Doppler examination of the right ventricular ejection flow and of tricuspid regurgitation when it is present, to measure the systolic pulmonary artery pressure. Measure of TAPSE (tricuspid annular plane systolic excursion) is simple and useful from the point of view of prognosis, and avoids the need to measure the right ventricular FAC (fractional area change), more difficult to assess. In addition, TDI (Tissue Doppler Imaging) of the right ventricle is very useful for measuring the diastolic and systolic function in only few minutes. In literature, authors defined moderate right ventricular dilatation as a ratio greater than 0.6 and major right ventricular dilatation as a ratio greater than or equal to 1. When the right ventricular dilatation is associated with paradoxical septal motion at end-systole, it reflects the systolic overload of the right ventricle, and the systolic eccentricity index has been proposed to “quantify” the systolic overload of the right ventricle.

Pulmonary hypertension is usually associated with tricuspid regurgitation, but it also depends on right ventricular systolic function, and its value can be surprisingly low when associated with low cardiac output. Another sign of right ventricular remodeling in ARDS is the thickness of free wall, related to an increase in afterload in mechanically ventilated patients. Most important is also the detection of a patent foramen ovale (PFO) that can complicate the oxygenation of ARDS patients. The displacement of septum due to the right ventricular dilatation causes the left ventricular hypo-diastolic status, with a consequent low cardiac output syndrome related to the difficult preload of the left ventricle. This is considered an echo-evaluation of right ventricular function in pre-ECMO stage. When the physicians think to institute a VV-ECMO, they need to insert two cannulas, typically in the femoral vein, advanced into the IVC, and in the internal jugular vein, advanced into the superior vena cava (SVC). Alternatively, we have to cannulate both femoral veins choosing to re-inject blood in the cannula positioned in the right atrium. Another possible solution is the use of a double-lumen cannula inserted through the right internal jugular vein until the SVC. In this stage, TEE is of paramount importance to avoid any complication during cannula insertion. An Echo Guided insertion of the cannulas is mandatory and visualization of guidewire through a mid-esophageal bicaval view allows the contemporary view of the IVC, SVC, tricuspid valve, right atrium and atrial septum. It is very important to check the guidewire in both Cavae to avoid any complicated position, i.e. through tricuspid valve into the right ventricle or into the coronary sinus or even worse in the pericardial space.

The echocardiographic control of the tip of the venous cannula is of paramount importance to avoid keeping it too close to the atrial wall or to the other venous cannula and to reduce drainage and produce recirculation with the increase of shunt and subsequent hypoxia. With the echo TEE control, we can achieve an optimal drainage and avoid recirculation. Finally the echo view provides important information to prevent the exclusion of hepatic venous return due to a malposition of inferior cannula. The study of Doppler hepatic vein flow is highly informative in this sense. In addition, the echo control allows us to change the position of the cannula and evaluate how the degree of the patient’s blood volume could affect the performance of the ECMO.

Echocardiography plays a crucial role during every step of ECMO support. It helps the correct positioning of the cannula, and allows a continuous control of the efficacy of the drainage and of the oxygenation. It is evident that echocardiography support cannot lead to an increase of survival in ECMO patient but, as shown by Lazzeri C et al., allows us to stratify the risk of patients with ARDS and to avoid major complications.
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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


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Fluid management in critically ill patients may be extremely difficult. It has been repeatedly demonstrated, that both under-resuscitated and over-resuscitated patients have worse outcomes than those with adequate volume management. Especially in first phases of critical illness it may be of extreme importance to individually tailor the intravenous volume management. It has been proposed by many experts, that dynamic indices should be used to predict cardiovascular system’s reaction to fluid. These methods of preload reserve testing, or fluid responsiveness, have gained large popularity among treating physicians and even the most recent SSC guidelines which has been modified in light of recent evidence recommend the repeated fluid responsiveness assessment. Passive leg raising (PLR) is a very practical and easy to perform tool to test the preload reserve. When performed in a rational way as described in a recent editorial, it enables the assessment of fluid responsiveness of critically ill patients with high sensitivity and specificity. Unlike other methods for the prediction of fluid responsiveness, the PLR test is free of many limitations including spontaneous breathing activity or cardiac arrhythmias. In a recently published intervention study in septic patients the PLR guided fluid management was associated with a significant trend towards better outcomes. But still there is much to learn about the fluid management in critically ill patients. One of the unanswered questions is the behavior of microvascular bed after volume loading and its potential limitation.

In this issue of Minerva Anestesiologica, an experimental study by De Blasi et al. has been published. Using an innovative methodology combining the graduated venular occlusion and near infrared spectroscopy the authors managed to obtain important data regarding the behavior of the microvascular bed in the forearm of critically ill patients and control subjects under PLR testing. This complex (but well described) methodology enabled the authors to estimate not only the stressed and unstressed volumes, but also pressure within the vasculature and microvessel wall tone and flow. A direct comparison between macrohemodynamic indices and microvascular parameters at the bedside was performed. Expectedly, the authors found differences between the microvascular bed parameters of healthy controls and those with critical illness. In healthy controls, the PLR-induced volume shift led to positive response in macrohemodynamic indices (cardiac output, stroke volume).
in a majority of participants. On the contrary, no important changes were observed in the behavior of the microvascular bed, the stressed and unstressed volumes as well as pressures in the vasculature and its compliance remained stable after PLR maneuver.

In the critically ill patients, different behavior of macro- and microvasculature was described, but the most important differences were in those having septic shock. In these patients, volume shifts induced a significant increase of the microvascular bed volume, mostly of the unstressed volume, accompanied by an increase of pressures within and a loss of compliance. In combination with the absence of changes in macrohemodynamic parameters, this suggests derangement of vasomotor tone. In patients with sepsis without shock or with other critical illness, the changes were not that marked and volume changes were directed mostly to the stressed volume compartment. A higher proportion of volume responders and lower incidence of norepinephrine support was observed among these patients.

There are several limitations to this study. First of all, the very small number of subjects and their heterogeneity preclude the authors to draw any strong conclusions. Unlike the control group which has been almost entirely fluid responsive, the number of critically ill patients with preload reserve was rather low, making the extrapolations even more difficult. Besides the cardiovascular system of about a half of the critically ill patients (and all those in septic shock) was supported by norepinephrine, what may mitigate the natural behavior of diseased microvascular bed. The methodology of the study is complex and difficult to reapply by others. Some of the results obtained were quite difficult to explain: For instance, the fact that in healthy subjects PLR increased cardiac output without concomitantly changing stressed volume, pressures and even flow within the vasculature. Last but not least, the forearm skeletal muscle is on the one hand accessible, but may behave in a quite different way from other (and more important) microvascular beds within the body.

Beyond its numerous limitations, from a clinical perspective, this study brings some information that supports our contemporary view on the disease of microcirculation in critically ill patients. It has been proved by many and nicely reviewed by the panel of ADQI Workgroup that vascular content is merely one of the players in the playground of acute hemodynamic instability. Especially in patients with systemic inflammation, derangements in vascular and even more importantly venular tone may play an important role. Besides, vascular barrier breakdown with increased leakage of the circulating fluid volume into the interstitium generously contributes to the final picture. Hence, increasing circulating volume in order to promote venous return and cardiac output may depend not only on the mechanical activity of the pump and Frank-Starling forces, but also on the ability of the vasculature to deal with the fluids infused. According to data presented by De Blasi et al., the PLR-induced increase in unstressed volume and pressures within the vasculature of septic shock patients nicely demonstrate the risks of increasing fluid loading. In some instances, the PLR was neither associated with increased venous flow (and hence venous return) nor with improvement of cardiac output, but was associated with increased postcapillary pressures potentially leading to higher extravasation and edema formation. However, it still remains debatable whether other interventions may have better effect. Norepinephrine, a possible and reasonable alternative to overcome in part the hemodynamic instability by either increasing the vasomotor tone and preload, was administered in patients with septic shock in this study. Decreased microvascular compliance and increase in intravascular pressures were observed among these patients supporting previous clinical observations, but because norepinephrine was not part of the study intervention these observations are only hypothetically linked. In addition, this effect on compliance and pressures is associated with risk of promoting hydrostatic forces driven extravasation. Other interventions (other catecholamines, inodilators) may hypothetically
help to improve the microvasculature in critically ill patients; however, they are not able to reverse shock state when administered alone. In order to do this, fluid infusion and catecholamines are still the mainstay even though it may be difficult to find the balance between them. In the future, studies like the one by De Blasi et al. may help us gain a better understanding of the effect of fluids and vasoactive substances on the microvascular bed.

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EDITORIAL

When the nerve block is blocked by local resistance

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Local anesthetics primarily work by inhibiting voltage-gated sodium channels (VGSCs). The drug molecules are often applied to nerves in pharmacologically massive concentrations. For instance, 1.5% mepivacaine corresponds to 61 mmol/L. Even so, resistance to local anesthetics is sometimes seen, and Clendenen et al. examined a dramatic case in this issue of Minerva Anestesiologica. The patient and two similarly resistant relatives proved to have a point mutation in a specific protein.

There are nine VGSCs present on the surfaces of excitable cells. The channels are numbered Na_v 1.1 through Na_v 1.9. There are regulatory beta subunits, but each channel is comprised mostly by a long protein called the alpha subunit. This loops back and forth across the cell membrane and forms a voltage-sensitive ion pore. Such pores enable axons to conduct electrochemical waves along their lengths.

In the three patients, the amino acid alanine is replaced by aspartate in position 572 of the alpha subunit of the VGSC known as Na_v 1.5. The protein is a chain of 2016 amino acids. The gene encoding that protein is called SCN5A and is located on chromosome 3. Alanine and aspartate are known as A and D, so the substitution is called A572D. Mutation is probably not the most apt word for the widely circulating variant or polymorphism. There are demographic differences, but the A572D form of gene SCN5A is carried and expressed in roughly 0.5% of people. Of course, most carriers have one copy of the ordinary allele and one copy of the A572D allele.

Expression of SCN5A as Na_v 1.5 is prominent in the heart, and variations of that gene can predispose to cardiac arrhythmia. However, it is not clear that the A572D variant is arrhythmogenic. In our institution, local anesthesia resistance is vanishingly rare among patients presenting for electrophysiology procedures. In our informal survey, no resistance cases were identified.

Genetic variation of VGSCs has been linked to congenital pain disorders. Isoforms 1.7, 1.8, and 1.9 are the prominent ones expressed in the peripheral nervous system. Clendenen et al. find that SCN5A is also expressed in peripheral nerves, and they further find that its A572D variant allele coincides with resistance to local anesthesia in three family members. It is interesting that the patients did not have cardiac conduction issues (such as long QT syndrome) even though the affected sodium channel (Na_v 1.5) is expressed more robustly in the heart than in peripheral nerves.

Since Clendenen et al. find that Na_v 1.5 is expressed in peripheral nerves, that channel plausibly participates in pain initiation and propagation. Elsewhere, a patient is reported to concomitantly suffer both a complex regional pain syndrome and resistance to local anesthesia.
The Clendenen finding raises many questions. Perhaps the most important one is whether the A572D variant of Na\textsubscript{v}1.5 is sufficient to cause clinical resistance to local anesthesia. If not, is another factor also required? Overall, what percentage of cases of resistance is caused by the A572D variation or by other variations in Na\textsubscript{v}1.5? Of note, variation F1737A in Na\textsubscript{v}1.7 is associated with local anesthesia resistance. How often is resistance caused by variations in other VGSCs? Are there genetic mechanisms of resistance that do not involve VGSCs? What happens to homozygous patients who have two copies of the A572D allele and no copies of the common allele?

It will be important to show whether or not the A572D substitution actually confers drug resistance on Na\textsubscript{v}1.5. This is a delicate assay that is perhaps best done with the isolated protein. The authors plausibly propose that “the A572D Na\textsubscript{v}1.5 mutation results in increased probability of membrane depolarization in peripheral nerves despite exposure to local anesthetics”.

It is easy to imagine how a variation of a predominant VGSC could engender local anesthetic resistance. It is puzzling that a variation of Na\textsubscript{v}1.5 would completely block local anesthetic function if that isoform comprises only a minor component of the VGSC array of peripheral nerves. Perhaps the A572D variation of Na\textsubscript{v}1.5 perturbs the regulation of the relative expressions of the various types of sodium channels in different tissues. The composition of VGSCs in a particular subset of the fibers in a nerve sheath may determine clinical drug resistance. For instance, so-called C-fibers especially contribute to dull-quality pain, and these are 2-4 times less sensitive than A-fibers to anesthetics.

It is challenging to evaluate a patient’s history of apparent local anesthesia resistance. Skin testing for anesthetic efficacy is possible, but there is no standardized clinical method for doing so. The Clendenen finding points to the possibility of clinically useful genomic assays for both preemptive and post facto diagnosis of this clinical problem.

Identification of genetic mechanisms of local anesthetic resistance may help to devise strategies to overcome the problem. For instance, some anesthetics may be less prone than others to be thwarted by a given genetic variation. Perhaps some variant genes call for relatively high concentrations of an anesthetic. Genetic resistance is potentially pH-dependent, and alkalization with NaHCO\textsubscript{3} may be helpful in some cases. Theoretically, a modified local anesthesia molecule might overcome resistance, but the authors point out that traditional local anesthetics are promiscuous in binding to sodium channels.

Locals interact with a spectrum of receptors, including K\textsuperscript{+} and Ca\textsuperscript{2+} channels as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. It is noteworthy that Clendenen et al. also discovered a variant form of the KCNE2 gene encoding a K\textsuperscript{+} channel in the three related patients. Further research may implicate channels other than VGSCs in local anesthetic resistance.

In the laboratory, an inside-the-pore receptor site for local anesthetics was inferred in part through the artificial creation of mutant channels, including drug resistant ones. It is interesting that some artificial insecticides function as sodium channel blockers, and the targeted insects have been changing their sodium channels accordingly. Sodium channel blockers also occur in nature. An example is tetrodotoxin. As expected, some predators have evolved altered channels in response to tetrodotoxin-wielding prey. It is intriguing to wonder if there are any selective pressures favoring variant sodium channels in humans.

For selective pain therapy, inhibitors of Na\textsubscript{v}1.7 are the main focus of present research. They include small molecules and also peptides based on a tarantula venom protein. However, the Clendenen findings suggest that it is important to block Na\textsubscript{v}1.5 in acute pain.

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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Basics to perform and present statistical analyses in scientific biomedical reports
Part 3

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Reporting studies

The Equator Web site offers links to all major guidelines issued for publication of various types of studies.

Controlled clinical trials

The CONSORT (Consolidated Standards of Reporting Trials) statement deals with CCTs. In addition to the points considered in the “checklist” and its extension, authors should explicitly declare whether they analyzed the intention-to-treat (ITT) or per-protocol (PP) population.

A Consort flow diagram and a table reporting baseline demographic and clinical characteristics in each group should be included in all manuscripts. In the table, many authors show the P-values about the comparison between baseline characteristics. However, this approach lacks of any statistical and scientific rationale and should be avoided. If found, statistically significant differences should not lead to the wrong conclusion that the groups belong to different populations, which is clearly illogical. Indeed, such differences are explained with the probability of a type I error.

Observational studies

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement deals with performing and reporting observational studies. Accordingly, authors should include a flow diagram and a table that reports baseline demographic and clinical characteristics within each group. In observational studies, baseline characteristics should be compared between groups in order to highlight unplanned differences. Unfortunately, the absence of statistically significant differences does not rule out the presence of confounders, nor supports the validity of univariate tests. In fact, comparisons between baseline values are often underpowered for demonstrating small imbalances that can invalidate the results of univariate statistical analysis. Consequently, in observational studies with more than one group, comparisons of the outcomes should be preferably performed by multivariable models in order to adjust for the presence of potentially confounding factors.

Observational studies include cohort, case-control, and cross-sectional studies. Cohort studies are typically prospective, but can be
also retrospective; in both cases, two, usually, cohorts of subjects (studies without a control group are rather case series studies) are followed during a lapse of time to search for a medical event or an outcome that occurs meanwhile. Consequently, this type of observational study often allows to formulate reliable causality relationships by means of the relative risk (RR).

Case-control studies start from a group of patients who presented a disease. A control group is successively formed with subjects, matched for the main factors possibly related to the disease. Their purpose is to assess retrospectively the association between putative risk factors and the outcome by means of the odds ratio (OR), as it is obtained by the logistic regression analysis. Finally, cross-sectional studies assess the prevalence of a condition, mostly a disease, and the potential association with some considered factors. Evidence for a relationship with the outcomes are much weaker than those assessed by case-control studies and especially, by cohort studies.

OR and RR are relative measures of association with a dichotomous outcome (improvement or not, success or not). The “odds” is the ratio between the probability of an outcome and the probability of its opposite; the risk of an outcome is the ratio between the number of subjects with the outcome and the number of the observed subjects. Let’s say that if 80 stroke are registered in 1000 smokers and 40 in 1000 nonsmokers, the odds of having a stroke is, therefore, 0.08696 (80/920) in smokers and 0.041 (40/960) in nonsmokers, whereas the risk of having a stroke is 0.080 (80/1000) in smokers and 0.040 (40/1000) in nonsmokers. Hence, the OR of having a stroke in smokers vs. nonsmokers is 2.0869 (0.08696/0.041), while the RR is 2 (0.080/0.040), very similar to the OR, as it is expected in the case of rare events. Interestingly, OR possesses an invariance property for which it is preferable to RR; indeed, the OR of not having stroke for nonsmokers vs. smokers is 0.4791 (0.041/0.08696), the reciprocal of 2.0869. Otherwise the RR, becomes 0.9583 (from 920/1000 divided by 960/1000), a not relevant value near to the no association value of 1.

Meta-analyses

Meta-analyses are usually aimed at new evidence from negative studies (without statistical significant results) and/or to more precise estimates of effects (i.e. to narrower 95% CIs). On the other hand, contrarily to primary studies, systematic reviews and meta-analysis can hardly add relevant pieces of knowledge to a previous one published on the same subject shortly before. Hence, repeated meta-analyses adding only few trials without obtaining definite results, should be regarded as unnecessary and unworthy of publication.

It is difficult to add any suggestion to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, which consists of a 27-item checklist to which authors are referred. Of particular importance is the inclusion of a PRISMA diagram, of a table that resumes data for each intervention group, and of forest plots to show effect estimates and confidence intervals. The use of $I^2$ as a measure of consistency is recommended. In order to facilitate the reader, authors are encouraged to provide some data as electronic supplements. For instance, criteria and data about possible biases within each study and across studies, as well as the characteristics of the studies included if their number is high (more than 20).

Table I.—Reporting sample size calculation (power analysis).

<table>
<thead>
<tr>
<th>Software</th>
<th>Type</th>
<th>Statistical Significance</th>
<th>Power</th>
<th>Effect size</th>
<th>Target difference</th>
<th>Standard deviation</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>“A priori”</td>
<td>Usually, $\alpha=0.05$, Two-tailed</td>
<td>Usually, 1-$\beta=0.80$</td>
<td>For means, indicatively:</td>
<td>Please justify the choice</td>
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<td>$-0.20$ considered small</td>
<td>$-0.50$ considered medium</td>
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<td>$-0.80$ considered large</td>
<td>Usually, the variability value has to be reported</td>
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</tbody>
</table>
Sample size calculation (power analysis)

It is not ethically and scientifically acceptable that patients, animals and resources (time, money) are employed without an adequate probability of obtaining an evidence-based knowledge.\textsuperscript{13-17} Therefore, a priori sample size calculations should be provided for all studies. In addition to the significance value alpha (usually $\alpha=0.05$, two-tailed) and to the power (1-$\beta$, usually 0.80), authors should report the “effect size”\textsuperscript{18} they aimed at, together with the considered variability value. The effect size is the ratio between the minimum difference that authors deem clinically or biologically relevant in superiority trials (or the maximum difference not clinically or biologically relevant in non-inferiority trials)\textsuperscript{19, 20} and the phenomenon variability. The latter, in the case of a statistical test on the difference between before and after a treatment corresponds to the standard deviation of the population of these differences. The statistical test for which the analysis was set and the software utilized should also be reported (Tables I, II).

In the case of only one group, the sample size is calculated for a test “against an expected value” or for a required precision (95% CI width) of the main outcome estimate, even if the latter approach is not recommended.\textsuperscript{13-17} In order to be clinically sensible and plausible, the expected values or the required precision should be based on the literature available. In case of retrospective observational studies in which the sample size is predetermined, authors should report the differences between proportions (means) that can be demonstrated at a satisfactory power and significance level. Alternatively, correlation and multivariate analysis can be used for sample size justification.\textsuperscript{23, 24} Finally, “a posteriori” power calculations on already collected data is not statistically correct and, consequently, should be avoided.\textsuperscript{25}

Sample size calculation is more difficult (even too much) and may require the involvement of a professional statistician in the case of repeated measurements on the same subject, multifactorial experimental designs (facto-

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**Table II.—Check list for statistical analysis.**

1. Subsection on Statistics in Methods section\textsuperscript{*}
   a. Type of study (examples: prospective cohort study, case-control study, randomized clinical trial – RCT –)
   b. Adherence to recognized guidelines for that type of study
   c. List of all descriptive and inferential procedures
   d. Variable transformations
   e. Power analysis
   f. Missing data
   g. Significance level
   h. Statistical software (included the version)

2. Results section
   a. Suggested decimal places\textsuperscript{*}
   b. Descriptive statistics\textsuperscript{*}
      i. Means (SD) or
      ii. Medians (1\textsuperscript{st} and 3\textsuperscript{rd} quartiles; range)
   c. Correlation analysis\textsuperscript{*}
      i. Coefficient of determination, $R^2$
   d. Regression analysis\textsuperscript{*}
      i. Intercept and regression coefficient with 95% confidence intervals
      ii. Coefficient of determination, $R^2$
      iii. Statistical significance
   e. Multiple regression analysis\textsuperscript{*}
      i. All the variables included in the analysis reported in Method section
      ii. Table with variables in the last multivariable model
      iii. Table with variables significant at the univariate analysis (if more than four)
   f. Univariate survival analysis\textsuperscript{*}
      i. Kaplan-Meier product-limit method
      ii. Graph of the survival function
      iii. Estimated hazard rate
      iv. Number of patients at risk at selected times
   g. Agreement analysis\textsuperscript{*}
      i. Bland Altman plot
      ii. Mean difference between the two methods and upper and lower limits of agreement
      iii. Regression analysis between means and differences
   h. Controlled clinical trials\textsuperscript{*}
      i. Intention-to-treat (ITT) or per-protocol (PP) population
      ii. Table reporting baseline values (no statistical comparison)
      iii. Observational studies\textsuperscript{*}
      iv. Flow diagram
      v. Table reporting baseline values (with statistical comparison)
      vi. Meta analysis\textsuperscript{*}
      vii. PRISMA diagram
      viii. Table resuming data for each intervention group
      ix. Forest plot
   i. Power analysis\textsuperscript{*}

3. References
   a. References for non-standard statistical methods

\textsuperscript{*}Information contained in Cesana BM et al\textsuperscript{21}; \textsuperscript{*}Information contained in Cesana BM et al\textsuperscript{22}; \textsuperscript{*}Information contained in this editorial.
rial ANOVA or ANCOVA models), and multivariable models (multiple linear regression, logistic regression, Cox’s proportional hazard regression, etc.).

References

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12. Equator Network. Enhancing the QAuality and Transpar-

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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The high nasal flow therapy for pre-oxygenation: a new strategy for conventional procedures in intensive care settings?

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Endotracheal intubation is one of the most routinely performed invasive procedures, but also frequently associated with morbidity and mortality.

Severe complications can occur and hypoxemia is most often reported in case of difficult airway access, especially in high-risk oxygen desaturation, as well as obese, critically ill and pregnant patients or in ICU where preoxygenation is much less efficient mainly due to patients’ unstable cardiovascular or respiratory status.

In healthy subjects and in the anesthesia setting, preoxygenation allows the increase of apnea timing without appreciable arterial desaturation. Nevertheless, it is known that preoxygenation promotes atelectasis, which is one of the mechanisms involved in the onset of hypoxemia during intubation.1

Efforts to improve preoxygenation through optimized conventional facemask oxygenation and use of NIV appear only marginally effective to prevent desaturation. NIV presents some limitations, like the compliance of the patient and the need of positive pressure removal to allow for laryngoscopy, thus avoiding any oxygen delivery during attempts.

In the last decades, the interest for High-Flow Nasal Cannula (HFNC) oxygen administration as an alternative technique for NIV or oxygenation has increased.2

The HFNC delivers oxygen flow rates from 40 to 60 liters per minute, improving gas exchange through different mechanisms: by increasing CO2 wash-out from the anatomical nasopharyngeal dead space (high FiO2 delivered due to the absence of oxygen dilution), generating a low level of positive airway pressure (highly dependent of mouth-closing) ensuring the alveolar recruitment and increasing functional residual capacity.3

Moreover HFNC demonstrated an important feature of potential advantage over NIV with possibility to bear oxygenation during laryngoscopy with a sort of “apneic oxygenation”.

HFNC could also be able to contrast desaturation related to O2 diffusion from the alveoli to the capillaries (that decreases alveolar pressure) by generating a flow from the pharynx to distal airways.

In this scenario, the review of Ricard JD published in this issue of Minerva Anestesiologica focuses on the strategies to prevent oxygen desaturation during endotracheal intubation of critically ill patients.4

Comment on p. 1098.
The author describes how several factors can contribute to increase the risks of life-treating hypoxemia during intubation maneuvers in emergency situations.

Conventional preoxygenation has a limited efficacy in ICU patients for several reasons such as hemodynamic instability, ventilation/perfusion mismatch, obesity etc.5

Author suggests an algorithm where high flow nasal oxygen should be taken into account in case of moderate or severe hypoxemia and added to NIV during laryngoscopy for very severe hypoxemic patients.

During orotracheal intubation the decrease of alveolar pressure, due to oxygen absorption in the apnea phase, generates a pressure gradient between alveolar space and pharynx promoting a gas flow from upper to distal airways in absence of respiratory movement.

In this case, the efficacy of HFNC could be related to the optimal conditioning of inspired gases with high FIO₂ delivered (due to the absence of oxygen dilution) coupled to the pharyngeal dead-space washout, rather than the amount of positive pressure generated during apneic oxygenation (presenting, during intubation maneuver, a neurological impairment of the patient).

As reported by Frizzola et al. in an experimental model on the effects of HFNC, with respect to gas exchange, the impact of increasing flow on ventilation and oxygenation occurs regardless of the only tracheal pressure generation.6 In the injured lung model, by increasing CPAP pressure, neither PaCO₂ nor PaO₂ demonstrated progressive changes; however, with HFNC under leak conditions (somewhat as if it was comparable to the open mouth during laryngoscopy) PaCO₂ and PaO₂ improved in a flow dependent response, so that saturation relationships where consistent, in the experimental model, with nasopharyngeal dead space washout as demonstrated in several clinical conditions.

However the benefits of HFNC in patients undergoing endotracheal intubation could be not constant between those with healthy or injured lungs.

In experimental conditions, Engström et al. showed that pharyngeal oxygen administration during apnea, in simulated endotracheal intubation, increased the time until patients became severely hypoxic but did so only when the shunt fraction was below about 25% on a PEEP of 5 cm H₂O.7

On this topic some authors, using HFNC in 20 infants undergoing endotracheal intubation, found that the benefit remarkably differed between those with healthy or injured lungs: during the trial, if desaturation episodes developed, the mouth was gently closed to increase pharyngeal pressure.8

HFNC technique represents a real attractive topic and its application for preventing hypoxemia during intubation in critically ill patients is acquiring interest, as demonstrated by the growing number of clinical trials on this argument.9, 10

As reported by the review of Ricard JD,4 a growing body of evidence suggests that HFNC oxygen therapy is an innovative and effective technique to improve oxygenation and prevent desaturation with different underlying diseases.

However, there is no therapy that is efficient in every patient and in every type of respiratory failure.

Despite promising preliminary data, evidence underscore the need for RCTs to test the effects of HFNC before and during endotracheal intubation in patients stratified according to lung disease.

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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One of the anaesthesiological hot topics of the past years has been the colloid vs. crystalloid controversy. This meanwhile emotional and irrational debate has moved from the scientific arena to the yellow press journalism. The colloid objectors are leading a crusade against these products trying to convert all non-believers, thereby ignoring physiological principles and twisting evidence and facts.

In this issue of Minerva Anestesiologica, Pisanò et al. demonstrate this one-sided view quite nicely.1 Crystallloids are made out to be the one-size-fits-all drug, being ideal to replace any kind of fluid losses including acute bleeding or in acute shock. Crystallloids consist of water and electrolytes and are evenly distributed over the entire extracellular space (divided into 80% interstitial and 20% intravascular space). Whereas losses from this compartment, e.g. urine output and insensible perspiration, are ideally treated with crystallloids, replacing losses from the intravascular compartment, e.g. blood losses, does not make sense. How can a drug be ideal when only 20% remain in the target compartment and 80% is shifted into tissue where it is ineffective and not needed? Moreover, this fluid overload presents as interstitial oedema, impairs microcirculation, organ perfusion and causes subsequent complications such as pulmonary and gut oedema, pneumonia, prolonged ventilation, prolonged gut recovery, abdominal compartment syndrome, impaired wound healing, and increased mortality.2, 3 Colloids in contrast are retained at the functioning barrier and remain intravascularly. This different behaviour means they are not indicated for fluid losses but might be advantageous for intravascular losses. Many trials exist showing that the perioperative use of colloids improves fluid balance and reduces edema formation.4, 5 Moreover, using a goal-directed approach during surgery in hypovolemic patients iso-oncotic hydroxyethyl starch (HES) has shown to achieve a faster and longer-lasting haemodynamic stabilisation, less complication rates, improved lung function, faster gut recovery, shorter hospital stay and shorter duration of ventilation.6, 7 Using dynamic preload parameters several trials have also shown that this colloid significantly increased stroke volume, cardiac output, corrected flow time as well as an improved microcirculatory blood flow and oxygen delivery to organs in comparison to crystallloids.4, 8, 9 Some argue that better hemodynamics and fluid balances are not clinically relevant as despite those improvements some trials show no outcome differences. However, a closer look at the study protocols can be useful. Two recent perioperative double-blind RCTs comparing HES with crystallloids had to switch to “rescue colloids” when the study drug dose limitation of 50 mL/kg was achieved. As a consequence, the patients in the crystallloid group received considerable amounts of colloids (either 1.5 l plasma 4 or 700 mL gelatin 10). Does that show that colloids and crystallloids have similar
effects and that only giving crystalloids is equally effective? Or rather that crystalloids alone are not able to achieve sufficient haemodynamic stabilisation? The only perioperative trial mentioned by Pisano et al.\textsuperscript{1} (all above mentioned aspects and trials were ignored) was the trial from Bayer et al. comparing HES, gelatine and crystalloids in cardiac surgery.\textsuperscript{11} Their HES group experienced a better haemodynamic stability, less fluid overload, better organ function and shorter length of mechanical ventilation — the authors erroneously interpreted the findings as showing HES to be “not more effective” than crystalloids. Their gelatine group actually received no gelatine in the first 3 days. On the other hand the “only crystalloid” group received 1,000 ml of HES as priming solution and during the trial 126 mL/kg “non-crystalloids” (e.g. an 80 kg patient received 10.080 ml non-crystalloids), unfortunately it remains unclear what these fluids were. The same group stated to see no difference in resuscitating patients in septic shock when administering HES or “only crystalloids”.\textsuperscript{12} Only crystalloids meant infusing 1,500 (interquartile range [IQR] 1.000-2.000) mL fresh frozen plasma and 560 (320-1120) mL 20% human albumin, which corresponds to 2.240 (1.280-4.480) mL of iso-oncotic 5% albumin. If a sole crystalloid therapy is so effective why do the authors always use colloids too? But more importantly why ignore this fact and not lead an open and critical discussion?

Pisano et al. main criticism on HES is based on 3 trials — those that caused the official authorities to get involved in 2013. Two of these trials included patients in septic shock.\textsuperscript{13, 14} This patient population completely differs from the perioperative one in that those patients suffer from an impaired permeability barrier with subsequent capillary leak.\textsuperscript{3} The main causes of this barrier impairment are disruptions of glycocalyx and endothelial cell junctions. Glycocalyx degradation is known to be caused by, \textit{e.g.}, sepsis, trauma, ischemia, cytokines and iatrogenic hypervolaemia.\textsuperscript{15} In septic shock this disruption causes colloids to be shifted to a large part into tissue, losing their advantage of high volume effects and increasing the risk of side effects. This could explain why, in the critically ill with either chronic alteration of the glycocalyx and/or de novo disruption, the effects of all colloids and crystalloids result in very similar effects on morbidity and mortality.\textsuperscript{16} As with every drug, side-effects are dependent on the dose, the context, the indication and the product. Old starch preparations with high molecular weight have been frequently associated with kidney dysfunctions and coagulation disorders. Two meta-analyses in surgical patients\textsuperscript{17, 18} have not shown these effects with 6% HES 130, the only HES solution that should be used today. Additionally, the recently published German guidelines on intravascular volume therapy (approved by 14 National Societies) stated that there is “no indication of renal insufficiency associated with the peri-interventional use of HES 130, gelatine or albumin”. Both above-mentioned sepsis trials have been criticised for their methodology and interpretation.\textsuperscript{20} The VISEP study compared a hyperoncotic 10% HES 200 solution (with 40% of patients receiving more than the maximally allowed amount) with a balanced crystalloids solution.\textsuperscript{13} In the 65 study, large amounts of iso-oncotic HES 130 were administered during several days following successful hemodynamic stabilisation\textsuperscript{14} according to the criteria of the Surviving Sepsis Campaign. In both trials, colloids were part of the initially administered intravascular fluids in both study groups. At the time of randomization 12-24 hours after diagnosis of sepsis, most patients were hemodynamically stabilized. Thus, the continued administration of HES in the HES group was highly questionable.\textsuperscript{16, 20} At the end of the trials over 90% of their respective crystalloid group had received colloids during their hospital stay. Again — if pure crystalloids are so successful why use colloids in the vast majority of patients? And why not discuss this aspect objectively and critically? If there are signs of adverse drug effect, it can be because of the drug itself or misuse of it. The recent guidelines took up and confirmed these criticisms: “these studies offer contradictory results and exhibit methodological deficiencies”.\textsuperscript{19} The third critical care trial is the currently under-fire CHEST Trial.\textsuperscript{21} Their HES group had a better kidney function according to the RIFLE score, but also a 1% increased rate of renal replacement therapy (RRT) in the unadjusted analysis. This
Pisano et al. draw their negative conclusions on gelatine without presenting any confirming data. Gelatins have been successfully used for over 100 years providing a large amount of clinical experience with its safety profile. Over time the formulation has been improved several times from oxypolygelatine (1951) to urea-cross linked gelatine (1958), succinylated gelatine (1962) and succinylated gelatine dissolved in balanced solutions (2013). The gelatin molecule is broken down into smaller fragments and eliminated by renal enzyme systems as soon as falling below the renal threshold. According to current knowledge gelatine and its derivatives are not stored in any tissue or organ. Despite that only few trials on the use of gelatine exist, no organ complications due to tissue storage or accumulation have been reported. A meta-analysis including 30 randomized controlled trials (2709 patients) did not detect any differences with regards to renal failure, blood loss or mortality comparing gelatine to crystalloids.27 Above that, there seems to be no clinical relevant interaction and impairment of the coagulation system so that gelatine promises to be a good option in critically ill patients. This is also part of the German guidelines on volume therapy, which state that albumin, gelatine and HES 130 are equivalent and recommend the use of gelatine in acute hypovolaemia in ICU patients if crystalloids alone are inadequate,19 which is exactly what the above-mentioned trials have shown. Pisano and colleagues recommend not to use gelatins and blame them of being old. This undifferentiated statement ignores decades of clinical experience, facts on different gelatines over time and recommendations from high quality guidelines.28

James Hogan wrote in JAMA in 1915 “Resuscitation with colloid is more effective than saline for hypovolemic shock, but insufficient to treat toxemic shock, despite the initial effects of colloid resuscitation on blood pressure.”29 Over 100 years later authors trying to prove him wrong are failing. Sometimes old things can be quite useful. In order to solve the colloid vs. crystalloid debate an open, objective, reasonable and unbiased discussion on a scientific basis is required. But sometimes ignorance is simply bliss.


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Right ventricle dilation as a prognostic factor in refractory acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation

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ABSTRACT

BACKGROUND: The aim of this study was to assess the incidence and prognostic role of echocardiographic abnormalities in consecutive patients with refractory acute respiratory distress syndrome (ARDS) before veno-venous extracorporeal membrane oxygenation (VV-ECMO).

METHODS: In this study 74 consecutive patients with refractory ARDS underwent echocardiography (transthoracic, transesophageal or both, according to the best acoustic window). Baseline characteristics were collected for all patients and the simplified acute physiology score was calculated. At echocardiography the following parameters were considered: left ventricle (LV) ejection fraction, right ventricle (RV) size and function (by means of tricuspid annular plane excursion [TAPSE]) and systolic pulmonary arterial pressure.

RESULTS: At echocardiography, 25 patients showed normal findings (33.8%), 32 patients exhibited isolated pulmonary hypertension (43.2%) and the remaining 17 patients showed RV dilation and pulmonary hypertension (23%). A reduced LVEF (<50%) was observed in 14 patients (18.9%), while RV dysfunction (as indicated by TAPSE<16 mm) was documented in 21 patients (28.4%). The in-Intensive Care Unit [ICU] mortality rate was 41.8%. At stepwise regression analysis the following variables were independent predictor for in-ICU mortality (when adjusted for TAPSE<16 mm): RV end diastolic area/LV end diastolic area (OR 0.21, 95%CI 0.062-0.709, P=0.012), Body Mass Index (BMI) (OR 0.87, 95%CI 0.802-0.958, P=0.004)

CONCLUSIONS: In consecutive patients with refractory ARDS, echocardiographic alterations were common, mainly represented by systolic pulmonary hypertension associated or not with RV dilatation. Moreover, RV dilatation and BMI were independent predictors of in-ICU mortality. On clinical grounds, our findings strongly suggest that echocardiography helps to risk stratifying patients with refractory ARDS requiring VV-ECMO.


Key words: Echocardiography - Respiratory distress syndrome, adult - Heart ventricles.

Since the first report in 1985 by Jardin et al. 1 describing the right (RV) and left ventricle (LV) functions with echocardiography in a small subset of patients with acute respiratory failure, an increasing number of papers have been published on this topic, but the available...
evidence mainly concerns the prevalence and the prognostic impact of acute cor pulmonale (ACP) in acute respiratory distress syndrome (ARDS).2-5

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a well-established therapy in patients with ARDS unresponsive to conventional therapy.6-8 However, to date, there is a paucity of data on cardiac function assessed by echocardiography in these patients, since this technique is mainly used in combination with other data for selecting the type of ECMO, as a visual guide and monitor the cannulation and in the early detection of complications during the procedure of ECMO implantation.9

The present investigation was aimed at assessing the incidence and prognostic role of echocardiographic abnormalities in 74 consecutive patients with refractory ARDS before VV-ECMO.

Materials and methods

From Oct 10 2009 to December 31 2013, seventy four patients with refractory ARDS requiring VV-ECMO were consecutively admitted to our Intensive Care Unit, which is an ECMO referral center. According to our protocol,9, 11, 12 an echocardiographic exam is performed just before ECMO implantation (Echo ECMO Florence Registry). Data were prospective recorded and retrospective analyzed.

Baseline characteristics were collected for all patients and the Simplified Acute Physiology Score (SAPS II) Score was calculated.13 All patients were mechanically ventilated. The ratio PaO2/FiO2 was considered a criterion for ARDS severity.

Echocardiography is performed routinely before ECMO implantation at our Intensive Care Unit (ICU) by the cardiologist (CL and PB) who is part of our ECMO team which also includes an intensivist, a cardiac surgeon and a perfusionist, all trained on ECMO technique and management. The cardiologist’s main task is to evaluate cardiac function in the pre-ECMO phase and guides the correct positioning of ECMO cannulas by transesophageal/trans-thoracic ultrasonography.7, 9, 11, 12

According to our protocol,9, 11, 12, 14 the echocardiographic examination is transthoracic (TTE), transesophageal (TEE) or both, according to the best acoustic window (Esaote MyLab™30Gold Cardiovascular, Esaote S.p.A, Genoa, Italy).15 The LV ejection fraction (LVEF) was estimated by eyeball examination on short-axis views.16 LV systolic dysfunction was defined as LV ejection fraction less than 45%.17

The right ventricle (RV) size was assessed by the RV end-diastolic area (EDA) (four-chamber view) and the ratio between EDA of the right and LVs was calculated (RVEDA/LVEDA). This ratio classifies RV function as normal (<0.6), moderately altered (0.6-0.8), severely altered (>0.8).18

Systolic pulmonary artery pressure (sPAP) was obtained using the simplified Bernoulli’s equation: 4 • (Vmax tricuspid regurgitation)2 + central venous pressure (CVP). To reduce the lack of precision of CVP estimation based on the size of the inferior vena cava, CVP was invasively measured through central venous catheters.5, 15

Tricuspid annular plane excursion (TAPSE)5 was also measured, as the difference of displacement during diastole and systole.5, 17 A TAPSE<16 mm is known to indicate RV dysfunction.5, 15, 19

The requirement of ECMO implantation was decided on the basis of the Italian Ministry of Health criteria, as previously described.11, 12

According to echocardiographic findings, the following subgroups of patients were considered:17
a) group 1: Normal RV dimensions and function, normal values of sPAP;
b) group 2: normal RV dimensions and function, values of sPAP>40 mmHg;
c) group 3: RV dilatation and values of sPAP>40 mmHg

Mortality during ICU stay was the outcome. All participants (or their kins) signed a written inform consent for storing their clinical data. The study is a retrospective analysis of data and the study design was approved by our Institutional Board.
Statistical analysis

Statistical analysis has been conducted with SPSS 13.0 for Windows software (SPSS Inc, Chicago, IL, USA). A two-tailed P-value <0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean±standard deviation (SD). For continuous variables, between-groups comparisons have been performed with Student’s t-test or ANOVA (followed by Bonferroni post-tests if overall P was significant) or by means of Kruskal-Wallis H Test. Categorical variables have been compared with χ².

Univariate analysis (χ² or Fisher’s Exact Test for categorical data; Student’s t-test or Mann-Whitney U Test for continuous data) was used to identify candidate variables (age, gender, Body Mass Index [BMI], pO₂, pCO₂, pH, LVEF, RVEDA/LVEDA ratio, TAPSE, sPAP) for multivariate analysis using a significant threshold.

Backward stepwise logistic regression was performed in order to identify predictors of in-ICU mortality. Hosmer-Lemeshow Test assessed the calibration of the logistic model and a c-statistic was used to test its goodness-of-fit. We assessed intraobserver variability with an intraclass correlation test and interobserver variability with a κ test. A κ up than 0.8 was considered as excellent. The intraclass correlation coefficients are used to assess agreement of quantitative measurements in the sense of consistency which can be defined as the agreement of two quantitative measurements in settings where neither one is assumed “correct” and therefore handles questions of intra- as well as interobserver reproducibility of measurement scales.20

Results

Intraobserver variability was quite good with an intraclass correlation of 0.89 (95% confidence interval, 0.85-0.93) and interobserver variability was also excellent with a κ of 0.96 (95% confidence interval, 0.94-0.97).

Our population comprises mainly males (54/74, 72.9%) (Table I) and ARDS was mod-

| Table I.—Clinical characteristics and echocardiographic findings. |
|-------------------|-----------------|-----------------|-----------------|
|                   | All patients    | ICU patients    | Patients transferred from peripheral hospitals |
| Number            | 74              | 42              | 32              |
| Age (yrs)         | 51.5 ±15.1      | 52.7±16.7       | 49.9±12.9       | NS              |
| SAPS II           | 44.1 ±19.2      | 41.7±18.9       | 46.5±15.4       | NS              |
| SOFA              | 10.7±2.        | 10.3±3.2        | 10.2±2.3        | NS              |
| Males/females     | 54/74           | 32/10           | 29±8.8          | NS              |
| BMI               | 27.9 ±8.5       | 14.5±14.4       | 12.2±6.6        | NS              |
| ECMO duration (days) | 19.9±14.3     | 20.0±15.9       | 21.5±13.2       | NS              |
| Mechanical ventilation (days) | 23.9±17.1 | 23.6±19.6       | 22.7±14.7       | NS              |
| ICU LOS (days)    | 23.9±17.1       | 23.6±19.6       | 22.7±14.7       | NS              |
| Vasopressors      | 37              | 20              | 17              |
| Norepinephrine only | 29              | 15              | 14              | NS              |
| Norepinephrine and dobutamine | 6           | 4               | 2               |
| Dobutamine only   | 2               | 1               | 1               |
| Blood gas analysis |                 |                 |                 |
| PaO₂/FiO₂ ratio   |                 |                 |                 |
| <300              | 9               | 4               | 5               | NS              |
| <200              | 21              | 14              | 7               |
| <100              | 44              | 24              | 20              |
| pH                | 7.36±0.12       | 7.35±0.10       | 7.36±0.12       | NS              |
| pCO₂              | 49.8±26.3       | 50.9±23.0       | 46.5±20.3       | NS              |
| pO₂               | 75.2±23.9       | 87.6±40.7       | 82.5±34.4       | NS              |
| Lactate (mg/dL)   | 2.2±1.9         | 3.6±3.9         | 3.2±4.7         | NS              |

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; SAPS II: simplified acute physiology score; BMI: Body Mass Index; LOS: length of stay.
erate-to-severe in most cases (87.8%) and due to H1N1 infection in 23 patients, H3n2 in 2 patients, viral pneumonia in 8 patients and bacterial pneumonia in the remaining 43 patients. Echocardiography was transthoracic in 26 patients (35.1%), transesophageal in 29 patients and both (transthoracic and transesophageal) in the remaining 29 patients (29.2%). According to echocardiography examination (Tables II, III), 25 patients showed normal findings (group 1, 33.8%), 32 patients exhibited isolated pulmonary hypertension (group 2, 43.2%) and the remaining 17 patients showed RV dilatation and pulmonary hypertension (group 3, 23%). A reduced LVEF (<50%) was observed in 14 patients (18.9%), while RV dysfunction (as indicated by TAPSE<16 mm) was documented in 21 patients (28.4%) (Table II). One patient exhibited acute cor pulmonale and was included in group 3. In the overall population, the in-ICU mortality rate was 41.8%. No difference was observed between ICU patients and those who were transferred from peripheral centers.

**Table II.—Echocardiographic findings.**

<table>
<thead>
<tr>
<th>Echocardiographic findings</th>
<th>All patients</th>
<th>ICU patients</th>
<th>Patients transferred from peripheral hospitals</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>25 (33.8%)</td>
<td>18</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Group 2</td>
<td>32 (43.2%)</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>17 (23%)</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>26 (35.1%)</td>
<td>14</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>TTE + TEE</td>
<td>19 (25.7%)</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>TEE</td>
<td>29 (39.2%)</td>
<td>18</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>33.6±3.5</td>
<td>39.8±7.7</td>
<td>43.6±12.9</td>
<td>NS</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>19.8±2.1</td>
<td>17.7±3.7</td>
<td>17.1±3.2</td>
<td></td>
</tr>
<tr>
<td>TAPSE&lt;16</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF&lt;50%</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>RV/LV EDA area &gt;0.6</td>
<td>21</td>
<td>9</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>ICU Mortality</td>
<td>31 (41.8%)</td>
<td>19</td>
<td>12</td>
<td>NS</td>
</tr>
</tbody>
</table>

TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; sPAP: systolic pulmonary arterial pressure; TAPSE: Tricuspid Annular Plane Excursion; LVEF: left ventricular ejection fraction, RV/LV EDA: right ventricle/left ventricle end-diastolic area. Group 1: normal echocardiographic findings; group 2: normal RV dimensions and function, values of sPAP≥40 mmHg; group 3: RV dilatation and values of sPAP≥40 mmHg.

**Table III.—Clinical characteristics according to echocardiographic subgroups.**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>32</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.3±15.3</td>
<td>49.4±15.4</td>
<td>57.4±13.6</td>
<td>NS</td>
</tr>
<tr>
<td>SAPS II</td>
<td>44.1±19.2</td>
<td>41.6±18.9</td>
<td>46.5±15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Males/females</td>
<td>23/2</td>
<td>19/13</td>
<td>12/5</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>28.3±7.7</td>
<td>26.1±6.5</td>
<td>30.8±11.8</td>
<td>NS</td>
</tr>
<tr>
<td>ECMO duration days</td>
<td>13.5±11.1</td>
<td>14.5±14.2</td>
<td>12.1±6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanical ventilation days</td>
<td>19.9±14.4</td>
<td>20.0±15.9</td>
<td>21.5±13.2</td>
<td>NS</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>23.9±17.1</td>
<td>23.6±19.6</td>
<td>23.3±13.3</td>
<td>NS</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>14</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine only</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine + dobutamine</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.38±0.11</td>
<td>7.35±0.10</td>
<td>7.36±0.11</td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>49.8±26.3</td>
<td>50.9±23.2</td>
<td>41.8±12.1</td>
<td>NS</td>
</tr>
<tr>
<td>pO2</td>
<td>75.2±33.9</td>
<td>86.7±40.7</td>
<td>89.1±39.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lactate (mg/dL)</td>
<td>2.3±1.9</td>
<td>3.6±3.9</td>
<td>3.9±4.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; SAPS II: simplified acute physiology score; BMI: Body Mass Index; LOS: length of stay. Group 1: normal echocardiographic findings; group 2: normal RV dimensions and function, values of sPAP≥40 mmHg; group 3: RV dilatation and values of sPAP≥40 mmHg.
As shown in Table IV, the percentage of patients with TAPSE<16 mm was highest in group 3 who showed the lowest values of TAPSE. Similarly the highest percentage of patients with LVEF<50% was observed in group 3 who exhibited the highest mortality rate. A patent forame ovale was detectable in 2 patients (group 2).

At stepwise regression analysis the following variables were independent predictor for in-ICU mortality (when adjusted for TAPSE<16 mm): RVEDA/LVEDA (OR 0.21, 95%CI 0.062-0.709, P=0.012), BMI (OR 0.87, 95%CI 0.802-0.958, P=0.004). Hosmer-Lemeshow χ² 7.3, P=0.50; Nagelkerke pseudo-R² 0.29.

Discussion

The main findings of the present investigation, performed in 74 consecutive patients with refractory ARDS before VV-ECMO implantation, were as follows: 1) echocardiographic alterations were common in these patients, mainly represented by systolic pulmonary hypertension associated or not with RV dilatation; 2) RV dilatation and BMI were independent predictors of in-ICU mortality. In particular BMI was inversely related to mortality.

In our series, normal findings at echocardiographic examination were observed in about one third of patients (33.8%), while abnormalities were detectable in the remaining two third (66.2%). In particular, systolic arterial hypertension was the most common alteration at echocardiography, being detectable in the majority of patients (in particular in the 43.2% not associated with RV dilation and in the 23% associated with RV enlargement). So far, only few reports assessed systolic pulmonary arterial pressure with echocardiography in patients with acute lung injury (ALI) and/or ARDS and the prevalence of sPaP was not specifically addressed even if Boissier et al. reported that pulmonary hypertension or isolated RV dilatation was detectable in 48% of patients.

We documented for the first time that RV dilatation is an independent predictor of mortality in refractory ARDS before VV-ECMO implantation. Cepkova et al. assessed RV size qualitatively, “according to their laboratory protocol” and, among 42 patients with ALI included in their investigation, RV dilation was observed in the 26% (11/42). Differently, RV dilatation was quantitatively assessed and obviously detected in patients with sPAP, indicated as RV end diastolic area alone or as the ratio RV end diastolic area /LV end diastolic area.

In ARDS patients with a patent forame ovale, when compared to those without, Mekontso-Dessap observed significant higher values of RVEDA/LVEDA ratio associated with higher sPAP and, similarly, Legras et al. reported that ARDS with ACP and PFO exhibited the highest RVEDA/LVEDA ratio. Interestingly Boissier et al. observed that moderate RV dilatation (defined as RV/LD end diastolic area ratio >0.6 and <1) was detectable in the 49% of patients without ACP, thus suggesting that RV dilatation may precede ACP development. In agreement with the study by Boissier et al.,

<table>
<thead>
<tr>
<th>Echocardiographic findings</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAPSE (mm)</td>
<td>19.8±2.1</td>
<td>17.5±2.3</td>
<td>13.2±3.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE &lt; 16</td>
<td>4 (4/28, 12.5%)</td>
<td>17/0 (100%)*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>RV/LV EDA ratio</td>
<td>0.43±0.1</td>
<td>0.48±0.11</td>
<td>0.79±0.1*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sPAP</td>
<td>33.6±3.5</td>
<td>42.5±4.9*</td>
<td>51.2±15.1*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>1 (1/24, 4%)</td>
<td>6 (6/26, 23.1%)</td>
<td>7 (7/10, 70%)*</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU Mortality</td>
<td>11 (11/14, 44%)</td>
<td>9 (9/32, 28.1%)</td>
<td>11 (11/17, 64.7%)*</td>
<td>0.04</td>
</tr>
</tbody>
</table>

TEE: transeophageal echocardiography; TTE: transthoracic echocardiography; sPAP: systolic pulmonary arterial pressure; TAPSE: Tricuspid Annular Plane Excursion; LVEDA: left ventricle end diastolic area; RVEDA: right ventricle end diastolic area; Group 1: normal echocardiographic findings; group 2: normal RV dimensions and function, values of sPAP£40 mmHg; group 3: RV dilatation and values of sPAP>40 mmHg.

*= vs. group 1 P<0.001; **P<0.05 vs. group 2.
we observed that RV dilatation can be detected in about one third of patients (28.7%).

According to our data, on a clinical ground, the detection of RV dilatation at echocardiography identifies a subset of patients with refractory ARDS at higher risk of death, despite VV-ECMO support. Further studies are needed to identify the mechanism(s) accounting for the development of RV dilatation and, afterwards, its management.

In our series, the incidence of ACP is quite low in respect to previous papers, performed both before and in the era of protective ventilation.2, 5, 19, 21 It can be hypothesized that in our population ACP had not enough time to develop since the prompt alert of the ECMO team and the VV-ECMO implantation due to the severe (and/or worsening) respiratory conditions of our patients. However, our data need to be confirmed in larger series of refractory ARDS patients.

Furthermore, we documented that BMI is an independent predictor of in ICU death in refractory ARDS treated with VV-ECMO and that, in particular, lower BMI was associated with higher mortality. Our results are in keeping with those reported by Al-Soufi S et al.28 who, in a retrospective analysis of the International Extracorporeal Life Support Organization enrolling 1334 adult patients supported by VV-ECMO, documented that increased BMI was not a risk factor for in-hospital mortality (even if at univariate analysis increased body weight was associated with a reduced risk of death).

Limitations of the study

A limitation of the present study may be represented by the fact that we report only on one echocardiographic examination (just before ECMO implantation). Data on serial echocardiographic exams during ECMO support might provide information potentially useful for intensivists. In our series, LV ejection fraction was calculated by eyeball, a method which can be performed more rapidly and has been shown a good correlation with the Simpson method in critically ill patients.27

Conclusions

In conclusion, our data strongly suggest that, in patients with refractory ARDS requiring VV-ECMO, echocardiography helps to a more accurate risk stratification, since the detection of RV dilatation identifies a subset of patients at higher risk for early death. Our results, obtained from a preliminary single center study, need to be confirmed in a larger cohort of patients.

Key messages

— To date, there is a paucity of data on cardiac function assessed by echocardiography in patients with ARDS unresponsive to conventional therapy submitted to VV-ECMO.

— In our series, echocardiographic alterations were common, mainly represented by systolic sPAP (associated or not with RV dilatation) and RV dilatation (together with BMI) was an independent predictor for in-ICU mortality.

— Our data strongly suggest that, in patients with refractory ARDS requiring VV-ECMO, echocardiography helps to a more accurate risk stratification.

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.

Comparison of three videolaryngoscopes for double-lumen tubes intubation in simulated easy and difficult airways: a randomized trial

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ABSTRACT
BACKGROUND: The King Vision™ (KVL) and Airtraq® videolaryngoscopes may reduce the time to double lumen tube (DLT) intubation compared to the GlideScope® and MacIntosh in simulated easy and difficult airways.

METHODS: Twenty-one staff anesthesiologists with limited prior experience in using videolaryngoscopes for DLT intubation were assigned randomly to insert a DLT using the MacIntosh, GlideScope®, Airtraq® and KVL videolaryngoscopes on easy and difficult airway simulators in a randomized crossover order. Time to DLT intubation, laryngoscopic view, intubation difficulty, optimizing manoeuvres and failure to intubation — defined as an attempt taking longer than 150 s — were recorded.

RESULTS: The three videolaryngoscopes had comparable times to intubation and glottis visualization in both scenarios. Compared with the MacIntosh, the KVL had longer intubation times in the simulated easy airway scenario (mean 9.2 vs. 21.1 s, respectively, P<0.001). In both scenarios, the Airtraq® took a longer intubation time than the MacIntosh (P<0.001 and P=0.019, respectively). The GlideScope® was easier to use than the Airtraq® and KVL in the easy airway scenario (P=0.021 and P=0.001, respectively). The KVL had higher intubation difficulty scores than the GlideScope® and Airtraq® (P=0.002 and P=0.008, respectively) in both scenarios and required more frequent optimizing manoeuvres than the GlideScope® (P=0.012) in the simulated easy airway. Two participants failed to intubate the difficult airway simulator; one with the MacIntosh and the other with the KVL.

CONCLUSIONS: The Airtraq® and non-channeled KVL required more time over the MacIntosh for DLT intubation, as a primary outcome, but the success rates for the 3 videolaryngoscopes were very high.

(Cite this article as: El-Tahan MR, Al’Ghamdi AA, Khidr AM, Gaarour IS. Comparison of three videolaryngoscopes for double-lumen tubes intubation in simulated easy and difficult airways: a randomized trial. Minerva Anestesiologica 2016;82:1050-8)

Key words: Laryngoscopes - Video-assisted surgery - Intratracheal intubation.

Several regional surveys demonstrated that most thoracic anesthesiologists are using the double-lumen tubes (DLT) as the first-choice lung separation technique.1,3 DLT, when compared with single lumen tracheal tube, can be more difficult to insert in patients with difficult airways. The videolaryngoscopes (VL) have the potential to facilitate the placement of the DLTs for lung separation in patients with potential difficult airway.4,5

The GlideScope® (Verathon Inc., Bothell, WA, USA), a VL with an angulated blade, tended to be one of the most extensively studied VL for placement of the DLT.4,6,7 However, the extreme angulation of these designs may complicate advancing the DLT towards the glottis opening, despite they may provide superior laryngeal visualization.

The channeled yellow Airtraq® (Prodol Meditec S.A., Vizcaya, Spain) and standard non-channeled blade of the King Vision™ (Ambu, Ballerup, Copenhagen, Denmark) may offer additional benefits for DLT intubation in patients...
We hypothesized that the use of the Airtraq® and the standard non-channeled blade of King Vision™ would be associated with shorter times to DLT intubation compared with the Macintosh and GlideScope® laryngoscopes. We have considered to assess the efficacy of each device on manikins before considering to evaluate them in patients undergoing thoracic procedures.

Materials and methods

According to the Research Committee, Anesthesiology Department King Fahd Hospital of the University of Dammam, Saudi Arabia on 20th November 2014, we did not require approval from an institutional ethical review committee. This study was retrospectively registered with www.clinicaltrials.gov (Identifier NCT02640196). Following written consent, 21 staff anesthesiologists at the authors’ department

Figure 1.—A) The MacIntosh, reusable GlideScope® GVL, the yellow Airtraq® and standard non-channeled King Vision™ blades; B) the stylet of a 35-Fr left-side double-lumen tube is bent to fit the natural curve of the MacIntosh, reusable GlideScope® GVL, and standard non-channeled King Vision™ blades; whereas the DLT is loaded through the lumen of the Airtraq® after removal of the stylet.
participated in this randomized, controlled, crossover manikin study. They were informed that they could withdraw from the study at any time and the data on the individual performance were not made available to anyone outside the study team. All anesthesiologists involved in this study were familiar with DLT insertion on a regular basis. All participants had previous experience with the 3 tested VLs (Figure 1) for tracheal intubation; however, the vast majority of them had only used the reusable standard GlideScope® GVL and the single-use yellow Airtraq® and standard non-channeled King Vision™ VLs (Figure 1A, B) for DLT insertion around one to 10 times (Table I).

Two high-fidelity simulators (Airway Management Trainer, model AA-3100, Laerdal Medical Ltd., Orpington, England, UK) were prepared to simulate easy and difficult airway situations, as described by Wang et al.13 and Marshall et al.14 The “easy” airway was established with the manikin in a neutral position (Figure 2A). The “difficult” airway setting was obtained by placing an Oasis Elite™ Prone Head Rest, Adult (140 mm in height) (Covidien, Mansfield, MA, USA) under the occiput and securing the head position with adhesive tape, object to replicate cervical-collar use (Figure 2B). Positioning was confirmed after each attempt to ensure consistency.

Before the study, all participants received a standardized demonstration on the study protocol regarding the correct use of each device for placement of DLT on the “easy” airway simulator, conducted by M-RE (>5 years of experience in using the VLs for DLT intubation). Then each participant was then allowed two practice attempts at DLT intubation with each device, one in a simulated “easy” airway and the second in a simulated “difficult” airway, with the supervision of M-RE who gave them a constructive feedback.

Before each DLT intubation attempt, the manikin, laryngoscope blade and DLT were lubricated. Participants were randomly allocated by M-RE into four groups according to the first intubation method to be performed and the order in which to apply the different laryngoscopes within each group into a simulated “easy” airway by drawing sequentially numbered sealed opaque envelopes containing a computer-generated randomization code groups based on circular permutation (Figure 3). The first group attempted DLT intubation using the MacIntosh (blade size4) laryngoscope, the second using the GlideScope®
GVL (blade size 4), the third using the yellow Airtraq®, and the fourth using the standard non-channeled King Vision™ (size 3). The second and the following devices were determined in the same order in every group as shown in Figure 3. Next, in the same random order, they used the 4 devices into the simulated “difficult” airway conditions. After completing the DLT intubation, participants had a 15-minute break before performing intubation using another laryngoscope. All intubations were performed with a 35-Fr left DLT. The participants were not allowed to watch each other to avoid any learning effect through observation.

In the GlideScope® group, the DLT was inserted as described by Hsu et al. The Airtraq® AWDR video system was used to make sure that the view of the glottis could be shared between operator and investigator. We described earlier four necessary steps to insert a DLT using a non-channeled blade of King Vision™.

When the anesthesiologists encountered difficulty in visualising vocal cords or placing the DLT, they were allowed to use any manoeuvre they would normally use to navigate the DLT into the trachea including readjustment of the blade or DLT or to ask the supervising investigator (AMK, ISG) to help solve the problem, and gave suggestions or instructions. An investigator (AMK, ISG) was available to hand them the DLT, remove the stylet after placement, and inflate the tube cuff.

With each device in each scenario, the primary endpoint was the time to achieve successful DLT intubation, defined as the time when the investigated laryngoscope passed the central incisors to when the tip of the bronchial lumen passed through the glottis, as confirmed visually by the operator (in the Macintosh group) or by the investigator, thanks to display screens (in the VLs groups). The success of DLT intubation in the Macintosh group, was accepted upon declaration of one of the investigators (AMK, ISG) with the use of the glide scope®. Secondary outcomes included the best view during laryngoscopy using the classification described by Cormack and Lehane; the difficulty of intubation, first-pass success calculated as number of first-attempt successes/number of intubation attempts, and number of times that the optimization manoeuvres were required. Additionally, at the end of their par-
participation in the trial, the participants stated which device they preferred after having used the 4 of them.

The difficulty of intubation was evaluated using a visual analog scale (VAS) (ranging from 0, meaning extremely easy, to 100, extremely difficult) expressed by the anesthesiologists after the DLT intubation. Additionally, the failure rate for DLT intubation, defined as an attempt taking longer than 150 seconds, was recorded. The cause of failure was also documented.

The previous DLT intubation experience with the VLs was recorded. All data, with the exception of the DLT intubation difficulty score, were determined by an independent investigator. The participants were not informed about the time taken to achieve any intubations.

Statistical analysis

A pilot study showed that the mean time to DLT intubation using the GlideScope® was 57.8 s with a standard deviation of 4.10 s. An a priori power analysis indicated that a sample size of 16 participants was sufficiently large to detect a 10-second difference in the time to DLT intubation, which was assumed to be of clinical importance during the use of the channelled VL, a type I error of 0.008 (0.05/6 possible comparisons) and a power of 90%. We added more operators (20%) for a final sample size of 21 participants to compensate dropping out during the study.

Statistical comparisons were restricted to between laryngoscope analyses within each scenario. Data were tested for normality using Kolmogorov-Smirnov test. Data for the duration of DLT intubation and the intubation difficulty score were analyzed using one way Analysis of Variance (ANOVA) on ranks with post-hoc Student-Newman-Keuls tests. The Kruskal-Wallis one-way ANOVA was performed to compare the non-parametric values of the 4 groups and post hoc pairwise comparisons were performed using the Wilcoxon rank sum t-test. Categorical variables were compared using McNemar’s test. Data are presented as mean (SD) or number (%). A P value of less than 0.05 was considered as statistically significant.

Results

Twenty three participants (23 male, median age 36 [27-59] years) were assessed for eligibility; two declined to participate. All remaining 21 participants intubated the two simulated settings with each device (Figure 3). Participants’ prior experience in using the three VLS in DLT intubations are presented in Table I.

The three VL had comparable times to DLT intubation (Table II, Figure 4), views obtained at laryngoscopy and success rates in both simulated easy and difficult airway scenarios (Table II).

The Airtraq® took a significantly longer time to DLT intubation than the MacIntosh in both scenarios (mean time; easy settings 21.3 s [95% CI: 16.51 to 26.10] vs. 9.2 s [95% CI: 7.20 to 11.32], P<0.001; difficult settings 25.7 s [95% CI: 19.51 to 31.95] vs. 16.8 s [95% CI: 13.80 to 19.73], P=0.019) (Table II, Figure 4).

The participants found the GlideScope® laryngoscope significantly easier to use than the Airtraq® and King Vision™ vl in the easy airway scenario (P=0.021 and P=0.001, respectively) (Table 2). The use of King Vision™ resulted in a higher score of difficult intubation than the GlideScope® and Airtraq® in the simulated difficult airway scenarios (P=0.002 and P=0.008, respectively). There was a statistical significant difference in number of optimization manoeuvres between the King Vision™ and GlideScope® in the easy airway scenario (P=0.012) (Table II).

Two participants failed to intubate the simulated difficult airway manikin; one with the MacIntosh and the other with the King Vision™. Failure was due to the inability to navigate the DLT through the glottis opening. When participants were asked which laryngo-
success rates. This illustrates how the use of the VLs can be useful for DLT intubation particularly in the difficult airway settings. In contrast to others, who have reported a shorter or a comparable time to DLT intubation in humans, in the present manikin study, the Airtraq® took a longer time to DLT intubation than the Macintosh in both scenarios. This may be due to the diversity of prior operator experience compared with these studies. However, the differences of 9s to 12s between the two devices may be not

**Discussion**

The authors showed that, in simulated easy and difficult airway settings, the use of the GlideScope®, Airtraq®, and King Vision™ for insertion of DLT by less experienced anesthesiologists was associated with comparable intubation times, glottis visualization, and first pass success rates. This illustrates how the use of the VLs can be useful for DLT intubation particularly in the difficult airway settings. In contrast to others, who have reported a shorter or a comparable time to DLT intubation in humans, in the present manikin study, the Airtraq® took a longer time to DLT intubation than the Macintosh in both scenarios. This may be due to the diversity of prior operator experience compared with these studies. However, the differences of 9s to 12s between the two devices may be not

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**Table II.**—Outcome data.

<table>
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<tr>
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<tr>
<td>Easy-airway scenario</td>
<td>Time to DLT intubation (s)</td>
<td>9.2 (4.58)</td>
<td>15.2 (5.31)</td>
<td>21.3 (10.56)*</td>
<td>21.1 (9.31)*</td>
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<td>Cormack Lehane score (I/II/III/IV)</td>
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<td>21/0/0/0</td>
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<tr>
<td></td>
<td>Score of difficult intubation</td>
<td>26 (16.3)</td>
<td>20 (8.10)</td>
<td>30 (13.0)†</td>
<td>35 (14.4)†</td>
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<td></td>
<td>First-pass success (%)</td>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
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<tr>
<td></td>
<td>Number of laryngoscopy attempts (1/2/3)</td>
<td>21/0/0</td>
<td>21/0/0</td>
<td>21/0/0</td>
<td>21/0/0</td>
<td></td>
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<tr>
<td></td>
<td>Number of optimization maneuvers</td>
<td>2 [2-4]</td>
<td>2 [2-3]</td>
<td>3 [2-4]†</td>
<td>4 [2-4]†</td>
<td>0.012</td>
</tr>
<tr>
<td>Difficult-airway scenario</td>
<td>Time to DLT intubation (s)</td>
<td>16.8 (6.53)</td>
<td>19.9 (7.70)</td>
<td>25.7 (13.71)*</td>
<td>21.5 (8.71)</td>
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<td>Cormack Lehane score (I/II/III/IV)</td>
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<td>3/16/2/0</td>
<td>3/16/2/0</td>
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<td></td>
<td>Score of difficult intubation</td>
<td>35 (19.7)</td>
<td>23 (13.5)</td>
<td>25 (13.3)</td>
<td>37 (9.6)†</td>
<td>0.002</td>
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<td>First-pass success (%)</td>
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<td>100%</td>
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<td>Number of laryngoscopy attempts (1/2/3)</td>
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</table>

Data are presented as mean (SD), number, proportion, or median [interquartile range].

*P<0.05 vs. the Macintosh, † vs. the GlideScope®, or ‡ vs. the Airtraq®.

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**Figure 4.**—Time to double-lumen tube (DLT) intubation in the simulated easy- and difficult-airway settings. Data are presented as mean (SD).

*P<0.05 vs. the Macintosh group.
clinically relevant. The King Vision™ was associated with a longer time to DLT intubation than the MacIntosh because the non-channeled design of the King Vision™ has potentially increased the difficulty in passage of the DLT through the trachea. Unfortunately, our result cannot be extrapolated to other VL devices like the C-MAC, McGrath® and Airway Scope®. However, this study is not meant to be a comprehensive review of the performance of all VLs, but is representative of those commonly available at the authors’ center.

In our study, the GlideScope® was the easiest to use in both scenarios. This may be explained by the familiarity of the participants with using the angulated blade design for tracheal intubation. Additionally, the more rigid design of DLTs make them relatively harder to insert it through the channeled Airtraq® blades or alongside the non-channeled King Vision™ blade. In contrast, other investigators found the GlideScope® more difficult to use than the MacIntosh laryngoscope for DLT intubation. That study, however, was done on patients with no predictors for difficult laryngoscopy. Other investigators reported comparable difficult intubation scores with the use of the GlideScope® and Airtraq®, when used by experienced laryngoscopists with over 30 times, whereas the vast majority of operators in the present study has limited experience with using the Airtraq® (<10 times).

The GlideScope®, yellow Airtraq® and the non-channeled King Vision™ accommodate a minimum mouth opening of 25mm, 18mm and 13mm, respectively. We demonstrated before the successful use of the standard non-channeled blade of the King Vision™ for placement of a DLT in a morbidly obese patient with predicted difficult airway. In the present study, the difficulty encountered with the King Vision™ may be related to the fact that the operator is closer to the screen and loses the comfort of a more distant and bigger screen as with the GlideScope® and Airtraq®.

The authors reported that all 4 devices display the larynx (12/84, 14%) viewings were Cormack and Lehane III and none was grade IV in the simulated difficult conditions for DLT intubation. Thus, the three VLs devices have advantages when DLT intubation is not straightforward. However, an improved view of the glottis does not always translate into easier DLT intubation. Similarly, previous reports observed comparable glottic visualization during the use of MacIntosh and Airtraq®. The use of King Vision™ required more frequent optimizing manoeuvres than the GlideScope®, despite comparable visualization of glottis. This could be explained by the occasional problems related to the DLT delivery and advancement into the trachea alongside the non-channeled King Vision™ blade. By contrast, the channeled Airtraq® has a channel to guide the DLT; thus, once an adequate view of the glottis has been obtained, the VL is kept steady and the DLT advanced into the glottis.

In similar to others who have reported overall successful intubation rates of 97% to 100% for the GlideScope®, 6, 18 and 94% for the Airtraq®, 6, 18 and 100% for the glidescope® in the present study all intubations were successful in the GlideScope® and Airtraq® groups. However, it is much higher than the 83% success rate reported by Russell et al. (P<0.001 as tested using χ² test). In that study, the failure rate may be partially inflated by the tight definition of DLT intubation failure, including a 120-s intubation time limit. These studies 6, 7, 18 as well as our study, however, were not powered to test this difference. In our small sample, the failure rate of 4.8% at the first attempt using the MacIntosh and King Vision™ was due to the impaction of the bronchial lumen of the DLT on the vocal cords or anterior larynx. In the two failures, we would not identify if the anesthesiologists able to intubate with another tool after the failure.

Our failure to reject the null hypothesis could be explained by the inherent problems in all manikin studies in that the times required to perform intubation are generally quicker than in patients. Although the present results has a limited clinical importance, our results may therefore have greater applicability to the majority of anesthesiologists who are still learning to use the three devices for DLT intubation, and we have shown that the acute-angle GlideScope® was easiest to use in both simulated
easy and difficult intubation conditions. Additionally, although we were unable to detect statistical differences, the success rates for both GlideScope® and Airtraq® devices were very high in the simulated difficult airway conditions. Of note, the learning curve may apply to the use of different VLS as it has been shown for the use of the GlideScope® alone.6, 7 Further studies in humans are required to extend these findings to the clinical settings in a mixed operators and diverse patient population. The authors assumed that a 15-minute washout period would eliminate the potential problem of carryover effects in our crossover design.

Similar to previous studies 6, 7, 12, 15, 18 the primary outcome in this study was the time to DLT intubation, which reflects the period when patients are at risk of hypoxemia. The difference in intubation duration between the studied devices may not be clinically significant for normal healthy patients, but few seconds may worth for patients undergoing thoracic surgery with potential risk for hypoxemia who were not studied in this study.7 The costs per unit blade of reusable GlideScope® and the single-use yellow Airtraq® and standard non-channeled King Vision™ were calculated at the authors’ center to be equivalent to US$ 13,500, US$ 93, and US$ 100, respectively. Compared with the more expensive bigger screen GlideScope®, the little screen single-use Airtraq® and non-channeled KVL potentially eliminate the risk of cross-contamination and have comparable times to intubation, glottis visualization, and success rate at an affordable lower price. However, these costs may vary from one country to another.

Limitations of the study

There are several limitations to this study. First, the simulator used in this study was not a specifically designed difficult airway simulator and the used cervical-spine immobilization position may be not very difficult. However, the “difficult” airway setting was simulated as described earlier,13, 14 where the spine was immobilized. Second, only size 35 DLTs were studied; however, larger tubes would be much more difficult to navigate through the vocal cords particularly with the yellow Airtraq®.20 Third, the bias of choosing the operators among less experienced anesthesiologists must certainly be taken into consideration, such a choice reduced the general validity of the results and does not help the reader to understand the real value of the used devices. This makes our conclusion difficult to extrapolate to the usual thoracic anesthesiologists who nowadays perform VL on a regular basis. However, we believe that our participants may reflect the more common clinical practice where the anesthesiologist has more experience using the old technique, in this study, the Macintosh and GlideScope® laryngoscopes. Fourth, in similar to previous reports 12, 14 we used the subjective VAS to assess the intubation difficulty rather than the validated intubation difficulty scales as the Adnet’s Scale or Likert scale.11, 13

Conclusions

In conclusion, the authors found that, the Airtraq® and non-channeled King Vision™ VLS required more time over the Macintosh for DLT intubation, but the success rates for the three VLS were very high.

Key messages

— The 3 videolaryngoscopes had comparable times to DLT intubation and glottis visualization in both scenarios.
— The Airtraq® and the non-channeled blade of the King Vision™ took longer times to DLT intubation than the MacIntosh in routine airway management.
— The GlideScope® was easier to use than the Airtraq® and King Vision™ in the simulated routine airway.
— The KVL was more difficult to use than the other two videolaryngoscopes in both simulated scenarios
— The limited experience of the operators in using the videolaryngoscopes for DLT intubation may reduce the general validity of our results.
VIDEOLARYNGOSCOPE COMPARISON FOR DOUBLE-LUMEN TUBES INTUBATION

References

Effects of passive leg raising on microvascular venous compartment in critically ill patients

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ABSTRACT

BACKGROUND: Even though fluid loading is thought to improve organ perfusion, the way in which it does so remains unclear. We assessed how the microvascular bed in skeletal muscle reacts to passive leg raising in patients with and without sepsis or septic shock.

METHODS: We studied 40 critically ill patients (group A) and 30 healthy controls (group B). The forearm microvascular bed was assessed using near-infrared spectroscopy before and after passive leg raising. We measured stressed and unstressed volumes, inside pressures, blood flow, microvascular compliance and tone.

RESULTS: In group A, passive leg raising induced a microvascular bed increase from 4.9 (3.2-6.5) mL/100 mL tissue to 5.7 (3.9-8.1) mL/100 mL tissue (P=0.005), leaving inside pressures unchanged, whereas in group B neither volumes nor pressures changed. Patients without sepsis showed an increase in the stressed volume from 0.22 (0.10-0.28) mL/100 mL tissue to 0.34 (0.23-0.66) mL/100 mL tissue (P=0.039) and a decrease in compliance (P=0.004), whereas, in septic shock, the unstressed volume increased from 4.20 (3.01-5.82) mL/100 mL tissue to 5.32 (4.01-11.50) mL/100 mL tissue (P=0.036). In critically ill patients near-infrared spectroscopy showed no difference in microvascular variables between responders and non-responders to passive leg raising, but responders showed a cardiovascular response shorter than healthy subjects.

CONCLUSIONS: Our study provides evidence that macrocirculatory parameters are unreliable to derive measurements of stressed and unstressed volumes. Our results indicate that in septic shock, the enlargement of the unstressed volume associated with passive leg raising induces loss of fluids to the interstitium, thus leaving organ perfusion unchanged or worse.

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Key words: Skeletal muscle - Venules - Blood volume determination - Venous pressure - Near-infrared spectroscopy.

Critically ill patients customarily receive fluid therapy aimed to increase cardiac output (CO) and guarantee blood perfusion to organs and tissues. Even though fluid infusion could increase CO in responder patients no conclusive evidence exists that this hemodynamic change induces a corresponding increase in overall organ perfusion or causes the opposite effect by enlarging the interstitial space thus reducing oxygen diffusion in tissues involved in systemic inflammation. To predict the cardiac output response to fluid loading and avoid a fluid overload, particularly in patients in whom a preload increase leaves CO unchanged, many investigators have proposed passive leg raising (PLR)\textsuperscript{1-4} as a manoeuvre to be used in ventilated or spontaneously breathing patients.
Theoretically, blood volume recruited by PLR or fluid loading enlarges stressed volume increasing cardiac preload through a rise in the mean systemic filling pressure that becomes rapidly apparent and of short duration despite prolonged leg elevation. Despite the belief that unstressed volume ($V_u$) has only a limited involvement in blood volume expansion, particularly in the body part not affected by changes in gravity, only measurements derived from changes in macrocirculation and indirect data support this concept. About 80% of blood volume is contained in veins and three-quarters of that in small veins and venules. Although the vascular response to fluid loading primarily involves the microvascular bed only a small number of studies have investigated the venous compartment of microcirculation in humans and no study has investigated how rapid changes in blood volume influence $V_u$ and stressed volume ($V_s$) and pressure therein.

Equally importantly, no information has yet shown how the venular compartment reacts to PLR in patients admitted to an intensive care unit (ICU) with a systemic inflammatory response syndrome — a condition which is likely to cause microcirculatory dysfunction. Nor do we know whether eventual changes in the microvascular bed correlate with cardiac responses to fluid loading. Answering these questions might help when deciding whether critically ill patients should undergo fluid loading.

In this observational study, we aimed to highlight how PLR-induced blood volume recruitment distributes in the skeletal muscle microvascular bed of critically ill patients, possibly modifying pressures therein. To do so, first we measured PLR-induced changes in the microvascular bed volume (MBV), its partitioning in stressed and unstressed volumes, the inside pressures, tissue blood flow (tBF), elastic compliance of microvascular bed (mvec) and venular tone ($T_v$) using quantitative near-infrared spectroscopy (NIRS). Then, we compared the values of these variables to those of healthy subjects. The microvascular bed we investigated comprised mainly venules, small veins and to a lesser extent, capillaries, since arterial vessels account for only 3% and are poorly distensible. The relationship between the PLR-induced changes in microvascular NIRS measurements and systemic cardiovascular variables was also assessed.

Materials and methods

This observational prospective study was conducted at the Sant’Andrea University Hospital, Rome, Italy, from April 2014 to October 2015 and enrolled 40 critically ill patients (age >18 years) admitted to the general ICU with any of the following criteria: systemic inflammatory response syndrome, at least one organ requiring functional support, a Simplified Acute Physiology Score (SAPS II) $\geq 21$, and an Injury Severity Score (ISS) $\geq 16$ for trauma patients (group A). The exclusion criteria were: cardiopulmonary edema, severe-to-moderate valvular disease, a history of severe arterial hypertension, acute liver failure, hemorrhagic shock, chronic dialysis, brain death, patients supposed to be discharged from the ICU within 24 hours of presentation and those with a high Body Mass Index (>29.9 kg/m$^2$). We enrolled 30 subjects as healthy controls (group B) in whom we monitored hemodynamic variables using non-invasive devices. The study was approved by the institutional research board (Ref.: 7173/2013) and all subjects or their next of kin gave informed consent to the anonymous use of their personal data at hospital admission.

Protocol

All subjects were placed on a reclining bed (TotalCare® P500, Hill-Rom Corp., Batesville, IN, USA) in a semi-recumbent position with the trunk raised to 45° relative to the lower limbs. A pneumatic cuff was placed around the arm and connected to an automatic inflation system (Hokanson Rapid Cuff Inflator and AG101 Air Source, PMS Instruments Ltd, Maidenhead, England, UK) capable of reaching a predefined cuff pressure ($P_{cuff}$) in less than 0.5 seconds. In each subject a NIRS probe was positioned on the upper face of the brachioradial muscle. To avoid differences in hydrostatic pressure requiring a correction fac-
Near-infrared spectroscopy settings and measurements

Skeletal muscle oxyHb/Mb and deoxyHb/Mb concentrations in µM ([HbO₂/MbO₂] and [HHb/Mb]) were measured using a NIMO-4 continuous-wave quantitative photometer (Nirox srl, Brescia, Italy). Data were acquired at a sampling time of 1 second, thus yielding adequate data to analyze changes in tissue Hb concentration. A detailed description of the methods used to calculate microvascular volume variables (MBV, Vu andVs), pressures in the MBV (PV), in the Vu (threshold pressure: Pit, equal to pressure outside vessels) and in the Vs (Ps) is provided in the Online Supplementary Materials, together with the methods used to calculate mvec, Tv and tBF. Basically, to obtain these variables we applied the same method as used for strain-gauge plethysmography adding the Nirs measurements of MBV and its changes during cumulative P cuff increases in steps from 5 mmHg and increasing pressure in 10, 15, 20, 25, 30, 40 and 50 mmHg (Figure 1).

Invasive hemodynamic monitoring

For measuring central venous pressure (CVP), considered a marker of PLR-induced blood volume recruitment, all subjects in group A had a 3-lumen central venous catheter inserted into the internal jugular veins and connected to a disposable pressure transducer. Mean arterial pressure (MAP) and CO were continuously monitored using a thermistor device close to the central venous catheter and a thermistor-tipped arterial catheter inserted into the femoral artery both connected to an EV 1000 clinical platform monitor (Edwards Lifesciences Corp. Irvine, CA 92614, US). After a calibration of the system performed by thermodilution before PLR, we registered changes in CO or SV based on the arterial pulse contour analysis throughout the study (Volume View set).

Finger arterial pressure CO monitoring

In group B non-invasive arterial blood pressure (ABP Ni) and CO (CO Ni) were measured using a photoplethysmograph system based on a volume clamp method (Nexfin technology, BMEYE B.V, Amsterdam, The Netherlands) using an appropriately sized cuff applied to the mid-phalanx of the middle finger on one hand.

Figure 1.—Representative recording of microvascular blood volume (MBV) measured in healthy subjects with Nirs at various cuff occlusion pressures (P cuff). Linear blood volume change in the range of 20-50 mmHg was taken for calculating microvascular compliance. Linear regression for the first two MBV changes extrapolated to 0 yielded intravascular threshold pressure (Pit), the intravascular pressure (Pi) corresponding to extravascular pressure (Pext). The P cuff-induced MBV changes between the first raise and linear increase represent microvascular bed recruitment. Unstressed volume (Vu) was calculated measuring the MBV at Pi whereas stressed volume (Vs) was derived subtracting Vu from the MBV measured before venous occlusion.
pressure to a value that was 10 mmHg lower than the individual patient’s diastolic pressure, thus affecting veins rather than arteries.\(^{17}\)

Because the Mb concentration in tissue remains constant throughout the study, we attributed changes in light absorption after venous occlusion only to \([\text{HbO}_2]\) and \([\text{HHb}]\). \(T_v\) \(^{18}\) was calculated from the PLR-induced changes in MBV after the microvascular bed was fully recruited and, because the higher the MBV change, the lower was the vascular tone, we expressed the opposite values in mL as a measure of tone, whereas the mvec was calculated from the slope of the MBV increase measured at the two higher cuff pressures.\(^{7,19}\)

Hence, these variables reflect the elastic and tone properties of the stressed volume.

**Statistical analysis**

We calculated that a sample size of 40 patients would have 1.0 power to detect a minimum 0.7 units of mean difference, with a standard deviation (SD) of 1.5 for NIRS variables. Kolmogorov-Smirnov’s test was used to assess normal data distribution. We used one-way analysis of variance (ANOVA) to test data if normally distributed, otherwise the Mann-Whitney U test for between-group comparison and the Wilcoxon signed rank test for paired data were used. Correlation between variables was tested using Pearson or Spearman’s test. Categorical variables were compared using the \(\chi^2\) test. Data were expressed as mean ± SD for ANOVA and median with a 25-75% interquartile range (IQR) for the signed rank tests. P values less than 0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA).

**Results**

All subjects completed the study. No difference between the two groups was observed in gender, demographic, and anthropometric data, apart from the hemoglobin concentration in the blood, as expected (Table I). In the group A, 26 subjects had signs of sepsis (65%) and 15 of them were in septic shock (37.5%).\(^9\)

Norepinephrine (NE) was the only vasoactive agent used in the septic shock patients and in two patients without sepsis. Data of macro and microvascular variables in the subgroups of patients in group A are reported online (Supplementary Table I).

**Effects of PLR on systemic cardiovascular variables**

Responses in CO and/or SV increase to PLR differed markedly in the two groups.

All subjects apart from four in group B (87%) showed a significant CO or SV increase, compared to only 15 of the 40 patients in group A (37.5%). In this group, the distribution of subjects who showed PLR-induced cardiovascular changes (responders) varied markedly among the subgroups of patients: the number of responders was greater in patients with the only sepsis (8 out of 11, 73%) than those with septic shock (3 out of 15, 20%; \(P=0.007\)) or in patients without signs of sepsis (4 out of 14, 29%; \(P=0.040\)) (Online Supplementary Materials). In the 15 responders in group A, the increase in CO or SV appeared within 30 seconds and lasted an average of 62 seconds (range 60-105 seconds). In group B, the time for the CO or SV increase to appear approached that in group A but the increase lasted longer than in group A (mean 112 s, range 94-121 s; \(P=0.024\)). Baseline MAP and SV values were lower in group A than in group B but PLR reduced heart rate (HR) and MAP only in group B (Table II). After PLR, CVP increased in 30 of 40 patients (75%), remained constant in 6, and decreased in 4, but the increase lasted an average of 70 seconds (range 60-95 s). No correlation was found between CVP and \(P_d\) or \(P_s\) values, or between the PLR-induced changes in CO and NIRS microvascular variables in both groups.

**Effects of PLR on microvascular volume and pressure variables**

Baseline MBV, \(V_u\) and \(V_s\) values for group A matched those for group B whereas the
PLR-induced changes in volume variables distinctly differed between the two groups. After PLR, MBV and $V_s$ increased overall in group A but remained unchanged in group B (Table II). Tests used to disclose separately the PLR-induced changes in the $V_u$ and $V_s$ showed that the $V_s$ increased from 0.22 (0.10-0.28) mL/100 mL tissue to 0.34 (0.23-0.66) mL/100 mL tissue in patients without sepsis ($P=0.039$), whereas the $V_u$ increased from 4.20 (3.01-5.82) mL/100 mL tissue to 5.32 (4.01-11.50) mL/100 mL tissue ($P=0.036$) in patients with septic shock (Figure 2).

At baseline, NIRS disclosed similar PV, Pit or Ps values in groups A and B. PLR induced no significant changes in microvascular pressure variables in both groups (Table II) or in the subgroups of patients with and without sepsis. Only in patients with septic shock were the PLR-induced changes in microvascular bed volumes combined with changes in the inside pressures ($V_s$ vs. $P_s$: $r=0.80$, $P=0.005$; $V_u$ vs. $P_{it}$: $r=0.70$, $P=0.024$). In septic shock, changes in pressures correlated also with changes in mvec ($P_{it}$ vs. mvec: $r=0.75$, $P=0.013$; $P_{s}$ vs. mvec: $r=0.70$, $P=0.023$).

Microvascular tone, compliance and blood flow

Because of the great variability in the data (variation coefficient: 1.63), tests showed no difference in baseline mvec values between the two groups. After PLR, mvec decreased

---

**Table I.—Demographic, anthropometric and clinical data, diagnosis, severity scores and outcomes of the 40 critically ill patients (group A) and the 30 healthy controls (group B).**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (N=40)</th>
<th>Group B (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F), N.</td>
<td>22/18</td>
<td>14/16</td>
<td>0.941</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>55.3 (17.1)</td>
<td>46.6 (11.5)</td>
<td>0.092</td>
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<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>23.2 (4.5)</td>
<td>22.3 (1.6)</td>
<td>0.552</td>
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<tr>
<td>SAPSII, mean (SD)</td>
<td>47.3 (12.8)</td>
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<td>SOFA, mean (SD)</td>
<td>7.8 (4.5)</td>
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<tr>
<td>Hemoglobin, mean (SD), g/100 mL</td>
<td>9.7 (1.0)</td>
<td>13.7 (0.6)</td>
<td>&lt;0.001</td>
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<td>Lactates, mmol/L</td>
<td>2.9 (2.6)</td>
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<tr>
<td>pH, units</td>
<td>7.34 (0.04)</td>
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<tr>
<td>Arterial pCO₂ mmHg</td>
<td>45.0 (10.1)</td>
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<td>Type of admission</td>
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<td>Trauma, N. (%)</td>
<td>10 (25)</td>
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<td>Medical, N. (%)</td>
<td>16 (40)</td>
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<td>Unscheduled surgery, N. (%)</td>
<td>14 (35)</td>
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<td>Clinical diagnosis</td>
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<tr>
<td>Severe sepsis, N. (%)</td>
<td>11 (27.5)</td>
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<tr>
<td>Septic shock, N. (%)</td>
<td>15 (37.5)</td>
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<tr>
<td>Acute respiratory failure *, N. (%)</td>
<td>24 (60.0)</td>
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<tr>
<td>Intracranial hemorrhage †, N. (%)</td>
<td>5 (12.5)</td>
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<tr>
<td>Brain damage †, N. (%)</td>
<td>9 (22.5)</td>
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<tr>
<td>Acute kidney injury ‡, N. (%)</td>
<td>7 (17.5)</td>
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<td>Causes of sepsis</td>
<td></td>
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<tr>
<td>Pneumonia, N.</td>
<td>24</td>
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<td>Bacteremia, N.</td>
<td>8</td>
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<td>Peritonitis, N.</td>
<td>10</td>
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<td>Urinary tract infection, N.</td>
<td>9</td>
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<td>Clinical sepsis, N.</td>
<td>2</td>
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<tr>
<td>Mechanical ventilation, N. (%)</td>
<td>30 (75.0)</td>
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<tr>
<td>Dose of norepinephrine, median [25-75% IQR], μg/kg/min</td>
<td>0.20 [0.09-0.38]</td>
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<td>ICU outcome N. (%)</td>
<td>11/29 (27.5)</td>
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<td>Hospital outcome (died/discharged), N. (%)</td>
<td>5/24 (17.2)</td>
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</table>

BMI: Body Mass Index (Du Bois formula); SAPS: Simplified Acute Physiology Score; SOFA: sequential organ failure assessment.

*Acute respiratory failure requiring mechanical ventilation; † Glasgow Coma Score ≤9; ‡ acute kidney injury requiring renal replacement therapy.
subgroups of patients in group A separately, mvec decreased only in patients without sepsis (0.23 (0.07-0.23) mL/mmHg/100 mL tissue vs. 0.17 (0.07-0.20) mL/mmHg/100 mL tissue, P=0.006). Although PLR did not induced statistical changes in tBF the values in septic shock were lower than those measured in the other subgroups of patients and in group B.

The PLR-induced changes in MBV were closely correlated with changes in mvec (r=0.90, P<0.001) and T_v (r=-0.72, P<0.001) in group A and only with changes in T_v (r=-0.77, P=0.002) in group B. In both groups, a close correlation was found between the PLR-induced changes in V_u and mvec (group A: r=0.82, P<0.001; group B: r=0.72, P=0.008) or T_v (group A: r=-0.80, P<0.001; group B: r=-0.83, P<0.001). Among critically ill patients, only in those with only sepsis were the PLR-induced changes in tBF inversely correlated overall in group A but remained unchanged in the group B (Table II).

Table II.—Hemodynamic and microvascular variables in the 40 critically ill patients (group A) and the 30 healthy controls (group B). Results are presented as variables values before (baseline) and 90 s after passive leg raising (PLR).

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<thead>
<tr>
<th></th>
<th>Group A</th>
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<th>Group A</th>
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<th>Base vs. baseline B</th>
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<td></td>
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<td>Base</td>
<td>PRL</td>
<td>P value</td>
<td>Base</td>
<td>PRL</td>
<td>P values</td>
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<td></td>
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<td>HR, bpm</td>
<td>95.7 (22.0)</td>
<td>96.5 (21.9)</td>
<td>0.260</td>
<td>71.8 (8.3)</td>
<td>64.4 (7.2)</td>
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<td>MAP, mmHg</td>
<td>78.9 (12.3)</td>
<td>76.4 (14.3)</td>
<td>0.743</td>
<td>95.8 (9.1)</td>
<td>84.9 (8.7)</td>
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<td></td>
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<td>CVP, mmHg</td>
<td>7.4 (4.2)</td>
<td>11.0 (4.8)</td>
<td>0.006*</td>
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<td>CO, L/min</td>
<td>6.5 (1.3)</td>
<td>6.7 (1.9)</td>
<td>0.069</td>
<td>6.8 (2.1)</td>
<td>7.9 (1.9)</td>
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<td>SV, mL</td>
<td>68.2 (20.0)</td>
<td>69.41 (23.2)</td>
<td>0.828</td>
<td>96.9 (18.6)</td>
<td>112.1 (19.3)</td>
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<td>Hemodynamic variables</td>
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<td>MBV, mL/100 mL tissue</td>
<td></td>
<td>4.9 [3.2-6.5]</td>
<td>5.7 [3.9-8.1]</td>
<td>0.005*</td>
<td>7.5 (5.3)</td>
<td>7.1 (5.9)</td>
<td>0.330</td>
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<tr>
<td>Vu, mL/100 mL tissue</td>
<td></td>
<td>4.8 [3.1-6.2]</td>
<td>5.2 [3.1-7.7]</td>
<td>0.064</td>
<td>7.2 (5.1)</td>
<td>6.5 (5.8)</td>
<td>0.107</td>
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<tr>
<td>Vv, mL/100 mL tissue</td>
<td></td>
<td>0.2 [0.1-0.3]</td>
<td>0.3 [0.2-0.5]</td>
<td>0.001*</td>
<td>0.3 [0.1-0.5]</td>
<td>0.2 [0.1-0.8]</td>
<td>0.273</td>
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<tr>
<td>Pressure variables</td>
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<td>P_v, mmHg</td>
<td></td>
<td>4.9 [4.8-9.7]</td>
<td>7.6 (4.9)</td>
<td>0.151</td>
<td>4.9 [4.8-9.7]</td>
<td>6.9 [4.8-9.6]</td>
<td>0.424</td>
</tr>
<tr>
<td>P_u, mmHg</td>
<td></td>
<td>3.0 [4.5]</td>
<td>4.6 [6.3]</td>
<td>0.177</td>
<td>3.8 [2.8]</td>
<td>5.5 [2.9]</td>
<td>0.120</td>
</tr>
<tr>
<td>P_s, mmHg</td>
<td></td>
<td>4.4 (3.5)</td>
<td>4.1 (3.5)</td>
<td>0.748</td>
<td>2.7 (2.0)</td>
<td>1.9 (1.3)</td>
<td>0.291</td>
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<tr>
<td>Microvascular blood flow</td>
<td></td>
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<tr>
<td>mBF, mL/min/100 mL tissue</td>
<td></td>
<td>27.4 [42.7]</td>
<td>35.1 [57.5]</td>
<td>0.685</td>
<td>25.6 [22.5]</td>
<td>22.3 [25.0]</td>
<td>0.716</td>
</tr>
<tr>
<td>Compliance and tone</td>
<td></td>
<td>0.11 [0.08-0.28]</td>
<td>0.09 [0.06-0.24]</td>
<td>0.004*</td>
<td>0.21 [0.06-0.33]</td>
<td>0.20 [0.06-0.05]</td>
<td>0.840</td>
</tr>
<tr>
<td>mvec, mL/mmHg/100 mL tissue</td>
<td></td>
<td>–</td>
<td>4.2 [-3.5-9.7]</td>
<td>–</td>
<td>2.3 [-1.0-8.6]</td>
<td>–</td>
<td>0.452</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD) or median [25-75% IQR].
HR: heart rate; MAP: mean arterial pressure; CVP: central venous pressure; CO: cardiac output; Sv: stroke volume; MBV: microvascular blood volume; Vu: unstressed volume; Vv: stressed volume; Pu: venular pressure; Ps: intravascular threshold pressure; P_s: stressed pressure; mBF: microvascular blood flow; mvec: microvascular elastic compliance; T_v: venular tone.

*P<0.05.

Figure 2.—Unstressed (black bar) and stressed (white bar) volumes at baseline and after passive leg raising in critically ill patients with and without sepsis and septic shock.
† Stressed volume vs. baseline, P=0.039; † unstressed volume vs. baseline, P=0.036.
with changes in $V_u$ ($r=-0.81$; $P=0.003$) but directly with changes in $V_s$ ($r=0.99$; $P<0.001$).

**Differences in the NIRS variables between responders and non-responders**

Tests comparing the NIRS microvascular variables of responders ($N.=15$) with those of non-responders ($N.=25$) in group A showed no difference between the values measured before and after PLR. Comparing the responders of the two groups, the PLR-induced changes in the $V_u$ showed higher values in group A than in group B (group A, $\Delta V_u 1.5\pm2.2$ mL/100 mL tissue vs. group B, $-0.7\pm1.4$ mL/100 mL tissue, $P=0.009$). Finally, as expected, non-responders in group A showed a higher increase in overall MBV after PLR than responders in group B (group A, $\Delta$MBV 0.4 (-0.1 to 1.8) mL/100 mL tissue vs. group B, -0.3 (-0.8 to 0.0) mL/100 mL tissue, $P=0.015$).

**Discussion**

The first new finding in this study is that PLR-induced blood volume recruitment enlarges the microvascular venous compartment of skeletal muscle, leaving pressures unchanged, in the critically ill patients but not in healthy subjects. In addition, changes in the microvascular bed volumes entail concurrent variations in the elastic compliance and tone of venular vessels. A second finding is that, among critically ill patients, those with septic shock respond to PLR enlarging the unstressed volume and increasing pressures within it (hemodynamically inactive) whereas patients without sepsis enlarge the stressed volume (hemodynamically active).20 Another relevant finding of our study comes from the relationships between the unstressed or stressed volumes and tissue blood flow shown in patients with sepsis and to a lesser extent in healthy subjects, which gives the changes in these venous compartments a role in the control of tissue perfusion. Finally, as we supposed, changes in microvascular variables such as blood flow and vascular pressures cannot be predicted by changes in macrocirculatory cardiovascular variables.

Although PLR caused a CO or SV increase in 37.5% of our critically ill patients, the increase in the CVP values proves that this maneuver recruited blood volume from the lower limbs that was sufficient to cause hemodynamic changes. The PLR-induced effect on systemic perfusion, CO, or SV changes in our patients matched values reported by others 21, 22 in the percentage of responsiveness and the time frame.

Finding that changes in the stressed volume in healthy subjects and most of critically ill patients are not connected with changes in the inside pressure inside contradicts a paradigm of physiology applied to macrocirculation: that systemic vascular compliance, hence stressed volume compliance, remains constant after fluid loading. Based on this assumption, Anderson 23 proposed a derived estimation of $V_s$ in the upper arm by the blood stop flow procedure and, recently, Maas et al. 24 applied this method to patients undergoing cardiovascular surgery for measuring alterations in $V_s$ and $V_u$ following changes in blood volume. Our study showing that, basically, in skeletal muscle, changes in blood volume entail changes in microvascular bed volume without concomitant changes in pressure therein highlights that many factors are involved in microcirculation, making the relationship between volumes and pressures variable and unpredictable. These factors include the recruitment of the microvascular bed, 25 changes in the elastic compliance and tone of the vessels, a close interaction between the microvascular bed and the tissue blood flow, 26 and, in septic shock patients, a leakage of fluids out of the vascular space. These mechanisms require direct investigation of the microvascular bed and render the use of macrocirculatory variables to derive measurements of stressed and unstressed volumes questionable.

Although our study did not intend to describe the venous compartment of microcirculation as the only cause of the cardiovascular response to fluid loading, our results could add knowledge on the factors contributing to venous return. Our findings show that, in critically ill patients, some of the fluids following volume expansion fill the microvascular bed...
differently from those in healthy subjects in whom neurogenic control possibly makes fluids to be more available for systemic circulation. Inflammation affecting the neurogenic control of the microvascular bed could cause a reduction in the elastic compliance as a result of the recruitment of vessels and vasodilation. The possibility that the microvascular bed could be recruited has been amply documented in skeletal muscle and recently confirmed in a previous in-vivo study on healthy subjects as a consequence of a pressure increase in the outflow. In addition, the decoupling between the microvascular volumes and pressures has clinical relevance because it entails a lack of increase in the post-capillary pressure following stressed volume enlargement that prevents this blood volume from contributing to venous return. This could be ascribed as a causal factor for the large number of non-responders among critically ill patients. The finding that enlargement of the microvascular bed occurs also in patients who respond to fluid loading could possibly be explained by the shorter cardiovascular response that these patients show (62 s) compared with healthy subjects (112 s). Hence, the microvascular bed changes that we detected 90 s after PLR could exceed the short-lasting effects of fluid loading on macrocirculation.

The different behaviors between patients with sepsis and septic shock concerning the microvascular bed partitioning and capacitance after fluid loading derives from factors linked to the inflammatory mediators, the severity of sepsis disease, and the use of the vasoactive drugs. In sepsis, the close correlation between changes in the MBVs and in elastic compliance is probably due to the additive effects of circulating mediators, NO, and neurogenic control. We hypothesize that, in sepsis, the increase in elastic compliance could be opposed by the concomitant increase in venular tone likely due to the stretching of vessels resulting in a lack of evident changes in the stressed or unstressed volumes. Because of the close interaction between the tissue blood flow and the stressed or unstressed volume, we first found that in only sepsis fluid loading does not involve changes in the time constant of the vascular bed, hence the tissue perfusion. The different behavior in microvascular regulation between sepsis and the other diseases could somehow explain the higher number of responders in patients with sepsis compared with patients without sepsis or septic shock. However, due to the small number of patients we cannot exclude that a large number of patients could display changes in MBV partitioning.

In septic shock, differently from other clinical conditions, fluid loading leads to an increase in the unstressed volume as a consequence of the increase in vessel capacitance resulting from active dilation of small veins/venules. Our finding in humans agrees with the results of experimental studies in animal models of canine and porcine endotoxemia. The pressure increase in the unstressed volume after fluid loading reflects also an increase in the pressure outside the microvascular bed due to loss of fluids to the interstitium. This phenomenon could also affect tBF and partially explain the deep blood flow reduction observed in septic shock patients. This fluid leakage could reduce the volume to the vascular bed, hence to venous return, and also be an obstacle to oxygen diffusion from capillaries to cells. Because we used norepinephrine almost exclusively in patients with septic shock, the role of this vasoactive drug in the microvascular bed response to fluid loading remains unclear, since its effects overlap the effects due to septic shock. The use of NE could have increased the small vein/venule stiffness, thus justifying the close relationship between changes in the microvascular volumes and pressures. Equally, NE could be also involved in the tBF reduction and in the absence of a relationship between changes in tBF and the stressed or unstressed volumes impeding to maintain constant the tissue perfusion. However, our study might add valuable information to what others have observed about the effects of norepinephrine on preload and CO.

Even though our results disclose changes in MAP and HR only in healthy subjects, we cannot exclude the possibility that PLR could act in both groups by differentially activating microvascular tone through the baroreflex or low-pressure baroreceptors.
The relationship between systemic hemodynamics and microcirculation changes is controversial. Although a significant correlation between systemic hemodynamic parameters and some microcirculatory indices was shown in the early phase of septic shock in patients at the emergency department, it disappeared in the ICU patients.

The deep reduction in the tissue blood flow that we found in septic shock patients results from factors that had occurred over time, thus making microcirculation insensitive to changes in macrocirculation.

**Limitations of the study**

Our study has limitations. One is that the microvascular bed of skeletal muscle contributes about 20% to the overall blood volume. This relatively small contribution could make the observed change less meaningful. Despite this drawback, the changes and correlations that we observed imply that the microvascular changes we noticed in response to PLR-induced preload changes could be extended to the microcirculation in other body areas, as other authors support. Another limitation is the possible inaccuracy of the Mb concentration in tissue; notwithstanding, although the absolute Mb value might be inaccurate, we consider the microvascular bed changes due to PLR manoeuvre in the same subject reliable. A final limitation is the small number of patients in the subgroups studied even though our study yields useful data for clinical purposes.

**Conclusions**

In summary, our study evidenced that the use of macrocirculatory parameters to derive measurements of the stressed and unstressed volumes is questionable. From our data on patients with septic shock, the PLR-induced enlargement of the unstressed volume induces also loss of fluids to the interstitium, hence clinicians should be aware that fluid loading in these patients could leave organ perfusion unchanged or cause it to worsen. Apart from enrolling a larger study sample, future research should seek greater insight into the difference in microvascular partitioning among patients with and without sepsis or septic shock, and assess the role of vasoactive drugs in the relationship between the venous compartment of microcirculation and venous return.

**Key messages**

— In skeletal muscle changes in microvascular bed, stressed and unstressed volume, are uncoupled with changes in the pressures inside. This finding makes questionable use of macrocirculation to derive data on stressed or unstressed volumes.

— PLR and possibly fluid loading lead to an enlargement of the microvascular bed in critically ill patients unlike healthy subjects. This different behavior in microvascular response implies that fluid loading in subjects with a diffuse inflammation with or without sepsis entails transferring part of the blood volume in microcirculation thus affecting the venous return and the cardiovascular response to volume expansion.

— A sudden increase in the blood volume enhances the stressed volume in patients without sepsis and the unstressed volume in patients with septic shock. In septic shock fluid loading induces also a loss of fluids to the interstitium thus hindering the oxygen diffusion from capillaries to cells.

— In critically ill patients the responders to fluid loading do not differ from non-responders in the macrovascular bed changes. In these patients the cardiovascular response to fluid loading is shorter than in healthy subjects.

**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.


For supplemental materials, please see the online version of this article.
The effects of minimal-dose *versus* low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial

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**ABSTRACT**

**BACKGROUND:** Evidence confirms that perioperative ketamine administration decreases opioid usage. To reduce the risk for potential psychodysleptic side effects, however, ketamine dosing tends to be limited to low-dose regimens. We hypothesized that even lower doses of ketamine would be sufficient, with minimal side effects, when used as a component of multimodal perioperative pain management.

**METHODS:** In this triple-blinded, randomized, active- and placebo-controlled clinical trial, patients undergoing elective major abdominal surgery were randomized to one of three treatment groups: low-dose S-ketamine (a 0.25 mg/kg bolus and 0.125 mg/kg/h infusion for 48 hours), minimal-dose S-ketamine (a 0.015 mg/kg/h infusion following a saline bolus), and placebo (saline bolus and infusion). Opioid consumption, pain levels, hyperalgesia at the incision site, and delirium scores were assessed 48 h postoperatively.

**RESULTS:** Patients in the placebo group had the highest cumulative piritramide consumption and the largest normalized areas of hyperalgesia at the incisional site, while those in the low-dose group had the highest delirium scores. Postoperative pain levels did not differ significantly between the treatment groups.

**CONCLUSIONS:** Our data demonstrate that minimal-dose S-ketamine was comparable to the conventional low-dose regimen in reducing postoperative opioid consumption and hyperalgesia. Postoperative delirium, however, was less frequent with the minimal-dose regimen. We therefore suggest that minimal-dose S-ketamine may be a useful low-risk component of balanced perioperative analgesia.

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**Key words:** Ketamine - Hyperalgesia - Delirium - Perioperative period - Postoperative pain.

Ketamine, which was first introduced to anesthesia in the 1970s, has regained broad interest in perioperative medicine within the last few years. With increasing understanding of its multiple modes of action and effects on pain modulation and central sensitization, ketamine has become a rational option for improving perioperative pain management.
Indeed, a broad evidence base now confirms that the perioperative administration of ketamine may decrease opioid consumption.\textsuperscript{2-5} To reduce the risk for potential psychodysleptic side effects, however, the administered doses of ketamine have been limited to a maximum infusion rate of 1.2 mg/kg/h or an intraoperative bolus of 1 mg/kg, which are considered low-dose regimens.\textsuperscript{6}

A recent meta-analysis of different low-dose ketamine regimens showed considerable variation in the modes of application and doses used.\textsuperscript{6} This was also observed in a recent French survey.\textsuperscript{7} In the current literature, some studies have used a single preoperative bolus, some have administered ketamine by continuous infusion, and some have applied a combination of a bolus injection with continuous infusion. Moreover, dosages have varied considerably in this research. Despite these limitations, continuous low-dose ketamine administration for 24-48 hours has been associated with superior effects on residual pain when compared with a single bolus administration, but without major complications.\textsuperscript{6} No clear dose-effect relationship has been detected to date.

We hypothesize that when used as part of the multimodal treatment of perioperative pain, not only would good relief be achieved by lower doses of ketamine than are currently used in low-dose regimens, but that this approach would also be associated with a lower risk for psychodysleptic and other side effects.\textsuperscript{6} Thus, we compared the effects of minimal- and low-dose ketamine regimens on opioid consumption, hyperalgesia at the incisional site, and postoperative delirium.

### Materials and methods

#### Study design

This study was conducted as a triple-blinded, randomized, active- and placebo-controlled clinical trial at the Medical University of Graz, Austria (ClinicalTrials.gov Identifier: NCT01022840). After receiving ethics committee approval, eligible patients were contacted and informed about the study.

#### Inclusion and exclusion criteria

Inclusion criteria were elective major open abdominal surgery (colorectal and hepatic surgery), age >18 years, weight between 40 and 120 kg, and American Society of Anesthesiologists (ASA) physical status class I-III. Exclusion criteria were any acute or chronic pain state treated with opioid therapy, severe liver or kidney dysfunction, severe coronary disease, pregnancy, addiction to alcohol or opioids, present or past psychotic disorders, and poor compliance.

#### Study groups

After receiving written consent, patients were equally randomized to one of three treatment regimens, as follows:

- **Low-dose group**: a 0.25 mg/kg intravenous (i.v.) bolus of S-ketamine after induction of anesthesia followed by a 0.125 mg/kg/h continuous i.v. infusion of S-ketamine for 48 hours;
- **Minimal-dose group**: a 0.9% i.v. saline bolus after induction of anesthesia followed by a 0.015 mg/kg/h continuous i.v. infusion of S-ketamine for 48 hours;
- **Placebo group**: a 0.9% i.v. saline bolus after induction of anesthesia followed by a 0.9% i.v. saline infusion for 48 hours.

The low-dose regimen was administrated following the protocol published by De Kock et al.\textsuperscript{8} S-ketamine was purchased from Pfizer (Ketanest S; Pfizer Cooperation Austria GmbH, Vienna, Austria).

#### Randomization and blinding

The study medication was prepared preoperatively, using a computer-generated randomization list, by an anesthetist who was excluded from any further involvement in the treatment or evaluation of patients. The two syringes for the bolus injection and the continuous infusion were labeled with “Study Medication” and the randomization number of the patient. All involved patients, nurses, and physicians were strictly blinded to group allocation. Likewise, the statistician remained blinded until the end of the analysis.
**Study protocol**

Patients were introduced preoperatively to an 11-point numerical rating scale (NRS) for pain assessment and to a patient controlled analgesia (PCA) device. Anesthesia was induced and maintained following our institutional standards: premedication with 7.5 mg oral midazolam; induction with 2 µg/kg fentanyl, 2-3 mg/kg propofol, and 0.6 mg/kg rocuronium; balanced anesthesia with 0.7-1.0 MAC (minimum alveolar concentration) sevoflurane and 0.1-0.3 µg/kg/min remifentanil; and, for postoperative analgesia, 0.2 mg/kg piritramide and 75 mg i.v. diclofenac, given approximately 30 minutes before the end of surgery. No local or regional anesthesia was applied. After recovery, PCA was provided with i.v. piritramide (CADD®-Solis; Smith Medical ASD Inc., St. Paul, MN, USA) set to a bolus size of 0.02 mg/kg, a lock-out time of 10 minutes, and a maximum of five boluses per hour. In addition, 75 mg diclofenac was administered twice daily by infusion.

Hyperalgesia was evaluated 48 h postoperatively, immediately after the end of the continuous infusion, using a method previously described by our group. Briefly, a 180-mN von-Frey filament (Semmes–Weinstein Monofilament; Touch-Test™ Sensory Evaluators, North Coast Medical Inc., Morgan Hill, CA, USA) was used to test areas around the wound from outside to the center of the incision along four radial lines in 5-mm steps. The first spot on the skin where the patient experienced a “sharp,” “sore,” or “pinpoint” sensation was marked and the distance to the incision recorded. The data were normalized to exclude the effect of incisional length on the area of hyperalgesia. Pain levels were assessed at rest and during movement using the 11-point NRS every 4 hours. In addition, piritramide use was documented 48 h postoperatively.

Postoperative delirium was assessed using the Intensive Care Delirium Screening Checklist (ICDSC) 48 hours postoperatively, immediately after the evaluation of hyperalgesia. This psychometric tool gave a maximum score of eight points from eight different dimensions (level of consciousness, inattention, disorientation, hallucination–delusion–psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance, and symptom fluctuation). A score of more than three was taken to indicate delirium. The German version has previously been validated in a postoperative population.

**Sample size calculation**

When designing the study, no data were available to estimate the effect of minimal-dose S-ketamine on hyperalgesia or postoperative opioid consumption. We therefore calculated the a priori sample size assuming the differences between the dose groups and the standard deviation of 50% each. Setting alpha to 0.05 and beta to 20%, we calculated that an appropriate group size would require 16 patients. We planned to include 20 patients per group (N.=60) to allow for potential dropouts or protocol violations.

**Statistical analysis**

Unless otherwise specified, data are expressed as means ± standard deviations or as medians (95% confidence intervals). Data were tested for normality by using the Shapiro-Wilk’s W test. Differences between groups were calculated by analysis of variance or the Kruskal-Wallis test, as appropriate. The low- and minimal-dose groups were further compared by Student’s t-tests or Mann–Whitney U tests, as appropriate. As this procedure could be interpreted as a multiple comparison, the Bonferroni correction was applied. Statistical analysis was performed using NCSS 10 statistical software (NCSS, LLC., Kaysville, UT, USA).

This manuscript was prepared according to the Consolidated Standards of Reporting Trials (CONSORT) statement.
Results

We included 60 patients over a 42-month period, but 4 patients were excluded, leaving 56 for the final analysis. Reasons for exclusion were postoperative intubation (N.=2), withdrawal of consent (N.=1), and reoperation during the study period (N.=1). The patient flow chart is presented in Figure 1, and the patients’ characteristics are presented in Table I.
Because all patients were treated as defined in the protocol, we did not perform an intention-to-treat analysis.

There were no significant differences in age, weight, height, or ASA classification between the groups. Likewise, no significant differences were found in the length of surgery (skin incision to closure) or in the intraoperative remifentanil dose between the groups. Although the cumulative piritramide dose was significantly lower in the low- and minimal-dose groups compared with the placebo group (low: 42.7±13.4; minimal: 40.2±13.5; placebo: 72.7±15.3; P<0.0001), it did not differ between the two treatment groups (P=0.5850).

The details of piritramide use and pain levels (at rest and during movement) over time are presented in Figures 2 and 3, respectively. No significant differences were observed between the pain scores during rest or movement at any point. However, the ICDSC score was significantly increased in the low-dose group.
Relative consumption at 48 hours being 40% lower in both treatment groups compared with the placebo group. These data are consistent with those of previous reports, and show comparability between conventional low-dose treatment and minimal-dose treatment. Significantly, however, postoperative delirium was less frequent with the minimal-dose regimen.

In recent years, multiple modes of action have been suggested to explain the analgesic properties of ketamine. Although some research has shown the effects of ketamine to be dose dependent, others have indicated that this was not the case, which is consistent with clinical experience in chronic pain management. Of specific interest to this research, oral ketamine has been shown to enhance analgesic treatment in various diseases with oral doses of 1-2 mg/kg/24h. Considering that the oral bioavailability of ketamine is about 20%, these doses are surprisingly low compared with those currently used.

Discussion

Our data showed that minimal-dose S-ketamine was comparably effective to conventional low-dose S-ketamine in reducing postoperative hyperalgesia and opioid consumption. Moreover, pain scores did not differ significantly between the three groups at any observed time point. This may reflect proper usage of PCA, because all patients were instructed to aim for satisfactory pain control. Piritramide use varied significantly at every observed time point, with the cumulative consumption at 48 hours being 40% lower in both treatment groups compared with the placebo group. These data are consistent with those of previous reports, and show comparability between conventional low-dose treatment and minimal-dose treatment. Significantly, however, postoperative delirium was less frequent with the minimal-dose regimen.

Figure 3.—Postoperative pain levels over time. Pain levels in rest and movement during the 48 h postoperatively separated by treatment group (low-dose group: 0.25 mg/kg S-ketamine bolus plus a 0.125 mg/kg/h continuous infusion of S-ketamine for 48 h; minimal-dose group: 0.015 mg/kg/h i.v. infusion of S-ketamine for 48 h; and placebo group: 0.9% i.v. saline infusion for 48 h).

Data are reported as mean ± standard error. No significant differences were found at any time point.
perioperatively, and are comparable to those used in our minimal-dose regimen. Over the history of perioperative care, we have seen ketamine doses decrease from anesthetic to analgesic doses, and further decrease to the adoption of low-dose regimens comparable to that used in this trial. Our data indicated that even lower doses may be sufficient for optimizing pain management among patients after surgery.

Decreasing doses can potentially minimize side effects. Postoperative delirium is a major concern in perioperative medicine, and ketamine has been associated with a prolonged time to resumption of mental orientation. Psychodysleptic symptoms are a well-described side effect of ketamine, with a recent meta-analysis confirming neuropsychiatric side effects to be significantly associated with perioperative ketamine use. Indeed, these effects have been shown to occur with plasma concentrations as low as 50 ng/mL, which roughly equates to a 0.1 mg/kg i.v. dose. Even though the risk is generally regarded as small, the conscious patient should be inform ed and monitored carefully. By contrast, it is also posited that ketamine could decrease postoperative delirium by reducing opioid side effects. In our population, the risk for postoperative delirium was highest in the low-dose group, whereas there were no significant differences between the minimal-dose and placebo groups. This is in accordance with the current literature indicating that psychomimetic effects are dose dependent.

Hyperalgesia is generally regarded as a consequence of central sensitization and plasticity, and has repeatedly been linked to the development of chronic persistent pain. Consequently, its use as a primary parameter is increasingly recommended in studies of incisional pain. Our findings show that there was no significant difference between the low- and minimal-dose ketamine regimens in the reduction of hyperalgesia at the wound site. Compared with placebo, the normalized area of hyperalgesia was less than half the size of that in both ketamine treatment groups.

**Limitations of the study**

The major limitation of our study is that we did not provide longer-term data on the development of persistent postoperative pain. Although this is doubtlessly a pivotal outcome parameter, we only aimed to demonstrate the clinical effectiveness of a minimal-dose regime in the perioperative period. A long-term follow-up study would represent an interesting topic for further research. High doses of intraoperative opioids, particularly remifentanil, have been shown to increase postoperative hyperalgesia. In our population, however, no significant differences were found in intraoperative remifentanil consumption between groups. Therefore, we conclude that opioid-induced hyperalgesia did not skew our observations.

**Conclusions**

In conclusion, a minimal-dose S-ketamine regimen is effective in reducing postoperative opioid consumption and hyperalgesia following abdominal surgery and can reduce the risk of postoperative delirium when compared with a standard low-dose regimen. We therefore suggest that minimal-dose S-ketamine be used as a low-risk component of balanced perioperative analgesia.

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**Key messages**

— This study compared placebo with the effects of two perioperative S-ketamine dosing strategies on postoperative pain, hyperalgesia, opioid consumption, and delirium.

— Minimal-dose S-ketamine (no start bolus plus 0.015 mg/kg/h for 48 hours) was as effective as conventional low-dose S-ketamine (0.25 mg/kg start bolus plus 0.125 mg/kg/h for 48 hours) in reducing postoperative opioid consumption and hyperalgesia, while showing comparable pain control.

— Importantly, delirium was found to occur more often in the low-dose group than in either the minimal-dose group or the placebo group.

— We therefore suggest that minimal-dose S-ketamine infusion may be a useful low-risk supplement for balanced perioperative analgesia.


References

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

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Point-of-care-based protocol with first-line therapy with coagulation factor concentrates is associated with decrease allogenic blood transfusion and costs in cardiovascular surgery: an Italian single-center experience

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ABSTRACT

BACKGROUND: Transfusion in patients having cardiac surgery has been associated with increased morbidity, mortality, and costs. This analysis assessed the impact of a rotational thromboelastometry (ROTEM®)- and functional platelet assessment (Multiplate®)-based protocol for bleeding management on perioperative outcomes and costs in patients undergoing cardiac surgery.

METHODS: This retrospective analysis of the records of all patients who underwent cardiac surgery at the Hesperia Hospital, Modena, Italy, from December 2012 to December 2013 compared outcomes and costs of bleeding management for the two 6-month periods before/after introduction of the ROTEM- and Multiplate-based protocol. Descriptive and correlation analysis were performed as appropriate. Propensity score matching and its correlation analysis were performed.

RESULTS: Data from 768 consecutive patients (mean age ~69 years, ~66% male) were included; 50.7% and 49.3% of patients had surgery before and after protocol introduction, respectively. Significantly fewer patients required transfusions of packed red blood cells after the protocol introduction over the 24 hours postsurgery (100 vs. 197 patients; P<0.001) and during ICU stay (134 vs. 221 patients; P<0.001). A significantly greater proportion of patients treated after protocol introduction received prothrombin complex concentrate (31 vs. 16; P<0.001) and fibrinogen concentrate (36 vs. 13; P<0.001). A significantly greater proportion of patients treated after protocol introduction had an ICU stay duration <48 hours (81.5% vs. 71.5%; P<0.001). ROTEM-based bleeding management was associated with a saving of €128,676.23 for the 379 patients undergoing surgery post-protocol introduction (€339.52 per patient).

CONCLUSIONS: ROTEM-guided bleeding management in patients undergoing cardiac surgery was cost-effective and associated with an increase of administration of coagulation factor concentrates and a decrease of ICU length of stay.

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Key words: Thromboelastography - Blood transfusion - Cardiac surgical procedures.

Perioperative bleeding is common in cardiac surgery and is associated with increases in morbidity and mortality.1, 2 The transfusion of blood products (packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets) remains a preferred treatment: it is estimated that more
than 50% of cardiac surgery patients receive a blood transfusion.\textsuperscript{3, 4} However, transfusion in patients having cardiac surgery has been associated with increased morbidity (increased incidence of acute renal failure, thrombotic/thromboembolic events, transfusion-related immunomodulation with subsequent nosocomial infections and sepsis, transfusion-related acute lung injury, and transfusion-related circulatory overload), mortality, and costs.\textsuperscript{1, 5-9}

Several interventions have been proposed over the years to diagnose and manage hemorrhage during cardiac surgery. Point-of-care (POC) tests, including rotational thromboelastometry (ROTEM), have emerged as a feasible and valid approach for the management of bleeding.\textsuperscript{1, 10} A number of ROTEM-based algorithms for hemostatic management during surgery have been developed.\textsuperscript{1} Evidence suggests that the use of these algorithms reduces the consumption of blood products and has a positive impact on costs.\textsuperscript{11-15} However, studies on ROTEM effectiveness are limited and several aspects related to this methodology are not fully understood. The use of ROTEM in Italy is not widespread; it is mostly used in university hospitals, in liver transplant, trauma surgery and heart surgery units. In our center, ROTEM was used for 8 years without an established protocol for bleeding management. Subsequently, when coagulation factor concentrates (fibrinogen, prothrombin complex) became available, they were used without a protocol and not as first choice.

As our institution refers to the Transfusional Service of a nearby University Hospital, we have to consider a 30-minute transportation time to add to the blood product preparation. For this reason, before introduction of the algorithm, coagulation factor concentrates (Hæmocomplettan P, CLS Behring; Confidex 500, CLS Behring; Uman Complex 500, Kedrion) were considered as buffering therapy in emergent bleeding waiting for the blood product. Blood products were ordered in advance in every intervention at risk of severe acquired coagulopathy (long CPB, clinical condition). Cryoprecipitate is not available according to Transfusional Service policy.

In order to improve our standard of care, in 2013 we developed and instituted a new protocol for hemostatic management during cardiac surgery at the Hesperia Hospital, utilizing coagulation factor concentrates as first choice therapy when suggested by ROTEM results. The algorithm was developed based on similar protocols and studies in the literature.\textsuperscript{11-18} To assess the impact of the new strategy on perioperative outcomes and costs, we conducted a retrospective analysis comparing the data of patients who had cardiac surgery before the institution of the algorithm versus those who had cardiac surgery with ROTEM-guided hemostatic management according to the new protocol.

Moreover, prevention of bleeding was considered in the new protocol by screening patients at risk of acquired thrombocytopathy (Figure 1) with preoperative platelet function assessment. Bedside platelet function testing was suggested as an option to guide treatment interruption rather than arbitrary use of a specified period of delay. Platelet inhibitory response to clopidogrel determines CABG-related bleeding, and a strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients led to $\approx50\%$ shorter waiting time than recommended in the current guidelines.\textsuperscript{19} For these reasons, the 2012 Update of the Society of Thoracic Surgeons Guideline suggested that a delay of even a day or two is reasonable to decrease bleeding and thrombotic risk in ACS patients.\textsuperscript{20} Bedside platelet function testing has been evaluated during clopidogrel exposure but might also be useful in prasugrel- or ticagrelor-treated patients, as recently shown for prasugrel.\textsuperscript{21} At our institution, platelet function assessment has been done with a Multiplate device (Verum Diagnostica GmbH, Munich, Germany).

**Materials and methods**

**Study design and patients**

The study design was a retrospective analysis of the records of all patients who underwent...
Figure 1.—ROTEM-guided protocol for hemostatic management during cardiac surgery. A10: amplitude of clot firmness 10 minutes after clotting time; ADP: adenosine diphosphate aggregometry test; CPB: cardiopulmonary bypass; CRF: chronic renal failure; CT: clotting time; DDAVP: desmopressin; EX: EXTTEM Test; FIB: FIBTEM test; HEP: HEPTEM test; Ht: hematocrit; HMs: hemostasis management system; ICU: intensive care unit; IN: INTEM test; PLT: platelets (units); ROTEM: rotational thromboelastometry; Tc: core temperature; TRAP: thrombin receptor-activated peptide aggregometry test.

Before surgery:
- Thrombocytopenia (<100,000)
- Clopidogrel <5 days
- Acquired thrombocytopenias (sepsis, aortic stenosis, CRF, leukemia, cirrhosis, vascular diseases)

- ADP<31 → Delay surgery by 24 hours and repeat aggregometry
- ADP<31 and surgery that cannot be postponed or TRAP<50 → DDAVP 0.3 mg/kg in 20’ at surgery start, repeatable at CPB discontinuation
  - Order 10 U of PLT for CPB exit
- ADP<50 → DDAVP 0.3 mg/kg in 20’ at surgery start, repeatable at CPB discontinuation

During and after surgery: ROTEM
- Preconditioning checks:
  - pH >7.20
  - Ca++ >1.00 mM
  - Tc >36°C
  - Ht >24%
- High risk patient
- Combined and redo procedures
- Emergency procedures
- Circulatory arrest
- CPB >150
- Bleeding
- Markedly abnormal results during CPB are predictive of a high bleeding risk
- An examination before surgery is not recommended (even if altered, it is highly unlikely that it leads to therapeutic interventions)
- It may be indicated if positive medical history for unexplained bleedings, inherited or acquired coagulopathies

A10EX <30mm and A10me <5mm → FIBRINOGEN 15-50 mg/kg
A10me <30mm and A10me >5mm → DDAVP

If:
- CTme / CTEx <0.8
- A10me <45mm and A10me <15mm
- A10me >45mm and A10me >15mm
  1) Protamine (HMS)
  2) FIBRINOGEN 15-50
  3) CONFIDE

Repeat ROTEM test after every intervention!

Surgical revision

Vol. 82 - No. 10
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cardiac surgery at the study center (Hesperia Hospital, Modena, Italy) from December 2012 to December 2013. In May 2013, an algorithm was developed (Figure 1) for the prevention and management of bleeding during cardiac surgery undertaken at the study center. The analysis compared outcomes (transfusion requirement and length of intensive care unit [ICU] stay) and costs of bleeding management before (from December 2012 to May 2013, 5 months) and after (from June 2013 to December 2013, 6 months) the introduction of the algorithm. The study was approved by the institutional ethics committee (registration number 29/16).

Anesthesia, surgery, and postoperative care

All surgical interventions, between December 2012 and December 2013 were performed by the same team, which consisted of four surgeons and five assistants; the individuals in the team did not change during the above-mentioned period. Premedication of patients was performed with midazolam 0.005-0.01 mg/kg and morphine 0.005-0.01 mg/kg. Fentanyl 1-4 µg/kg and propofol 1-3 mg/kg were administered as induction anesthesia. Maintenance was performed with fentanyl 3-5 µg/kg·h and propofol 3-5 mg/kg·h tailored to clinical response and Bispectral Index. Tranexamic acid 15 mg/kg was administered at the time of induction and after discontinuation of cardiopulmonary bypass (CPB). Heparin and protamine dose were administered according to the HMS Plus hemostasis management system (Medtronic, Minneapolis, US) activated clotting time (ACT) test. Recombinant antithrombin was administered preoperatively to those patients with activity <70%.

Point-of-care tests

At our institution, we routinely use ROTEM and Multiplate for perioperative bleeding management.

ROTEM analyzes viscoelastic changes occurring in blood samples during clot formation.¹ ²² By utilizing a variety of activators, this method provides a detailed analysis of specific aspects of the coagulation cascade and can identify specific cascade abnormalities (unlike conventional coagulation tests).²³ ²⁴ By providing graphic and numeric data on clot formation, ROTEM can detect isolated deficits of fibrinogen (FIBTEM test) and general coagulation factors deficiencies (INTEM and EXTEM tests). Matching these results with special tests (APTEM and HEPTEM), ROTEM analysis provides information on hyperfibrinolysis and the presence of heparin in patient blood.²⁵ ²⁶

A Multiplate device was used to screen platelet function in selected patients (Figure 1). By adding different activators to a patient’s whole blood sample, this device provides information on the grade of inhibition of several pathways of platelet aggregation activation. The ASPI-test examines the arachidonic acid pathway and is therefore sensitive to aspirin administration; the ADP-test examines the ADP-receptor pathway and detects thienopyridines platelet inhibition; the TRAP-test examines the thrombin-receptor pathway and is affected both by GPIIb/IIIa inhibitors and congenital or acquired thrombocytopeny (e.g. uremia). Based on the experience of Ranucci et al., we decided to administer desmopressin (DDAVP) in a dose of 0.3 mg/kg in 20 minutes at skin incision in patients with an ADP-test between 30 and 50, repeatable at CPB discontinuation.²¹ ²⁷ In patients with a history of recent thienopyridines administration and ADP<30 we recommended to postpone the intervention and repeat the platelet aggregometry test 24 hours later, if no urgent surgical indications were present. In every patient with a TRAP-test <50, indicating poor platelets viability, we recommended the administration of DDAVP and platelets transfusion.

Bleeding management

Before introduction of the algorithm, bleeding was managed by administering coagulation factor concentrates and blood products based
on individual clinical judgment and experience without a protocol, in order to correct ROTEM analysis alteration.

After introduction of the algorithm, ROTEM measurements were performed at the following time points: in all high risk patients (those with liver or renal disease, or those with a body mass index >30 kg/m$^2$) and high risk procedures (long predicted CPB times, redo operation) ROTEM analysis was performed before, during and after CPB; in patients who had an unexpected CPB time of >120 minutes, ROTEM analysis was done during and after CPB; ROTEM analysis was done after CPB in patients who had an absence of obvious bleeding causes for whom surgical hemostasis was insufficient after more than 20 minutes. In intensive care, severe bleeding was defined as >1.5 mL/kg/h for 3 consecutive hours on the basis that the ICU team felt this was the threshold above which they would feel compelled to intervene.

PRBC transfusion triggers are indicated in an institutional protocol which did not change over the study period. Pre-CPB transfusion was indicated in order to achieve a predicted in-pump hematocrit (Ht) over 22%. Intra-CPB transfusion were indicated in case of Ht<22%. Post-CPB and ICU transfusion were mandatory with Ht<21%, indicated with Ht<27% (based on clinical, tissue perfusion and hemodynamic evaluation), not indicated with Ht>27% in a normovolemic patient.

**Variables analyzed**

The following data were extracted from patient records: demographic characteristics; baseline cardiac status; preoperative use of antiplatelets and anticoagulant drugs; surgery characteristics; transfusion requirement (PRBC, FFP, platelets, coagulation factor concentrates) perioperatively and during the stay in the ICU; length of ventilation; length of stay in the ICU; need for re-operation for bleeding or tamponade; and mortality. We did not collect data on the use of vasoactive drugs and ROTEM results were not included in the analysis.

**Cost analysis**

Cost analysis considered the resources used for bleeding management, namely: blood products (PRBC, FFP, platelets); coagulation factors (Uman Complex [prothrombin complex concentrate], Confidex [human prothrombin complex concentrate], Haemocomplettan [fibrinogen], Emosint [desmopressin]); ICU admission; re-operation; materials for performing the ROTEM assays. These resources were valued in 2014 Euros and costs were estimated according to records kept in the center’s purchasing department, where all spending related to the cardiac surgeries, including the purchase of blood products from an outside transfusion service, was documented. Mean total direct costs per patient before and after introduction of the ROTEM-guided algorithm for hemostatic management were compared.

**Statistical analysis**

All statistical analyses were performed using the SPSS statistical package (version 20.0) and R software version 2.12. The R package of MatchIt was used for the propensity score (PS) analysis.

Data before and after introduction of the ROTEM-guided algorithm were analyzed descriptively (percentages or mean±standard deviation [SD] for normal distributed variables; median±1st and 3rd quartile for non-normal distributed variables) and using the chi-square test, analysis of variance (ANOVA) and Kruskall-Wallis Test, as appropriate. Significance was assumed if the P value was <0.05. PS matching, binary logistic regression models, and Kaplan Meier analyses were also performed. Propensity matched statistics have been proposed to correlate similar samples of patients before and after the introduction of protocols. We performed caliper matching on the PS (nearest available matching). Pairs (normalized and non-normalized groups) on the PS logit were matched to within a range of 0.2 multiplied by the standard deviation. Covariates included in the model were age, gender, weight, height,
Body Mass Index (BMI), smoking status, European System for Cardiac Operative Risk Evaluation (EuroSCORE), Canadian Cardiovascular Society angina grading scale (CCS), New York Heart Association (NYHA) Functional Classification, left ventricular ejection fraction (LVEF), extracorporeal circulation (ECC) time, clamp time and presence of comorbidity. Data on antplatelet therapy were not included in the model as the use of Multiplate changed the management of these patients. The P.S. matching algorithm selected 660 matched patients (330 in each group).

Results

Data from 768 consecutive patients undergoing cardiac surgery were included in the study. Of these, 389 (50.7%) patients had surgery before the institution of the new protocol for bleeding management and 379 (49.3%) patients had surgery after institution of the new protocol. A total of 29 interventions were postponed in patients showing adenosine diphosphatase (ADP) aggregometry less than 30. Patient demographic and clinical characteristics are shown in Table I. Overall, demographic

<p>| Table I.—Patient demographic characteristics and cardiac status before surgery (all population and Propensity Score population). |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-ROTEM-based protocol (N.=389)</th>
<th>Post-ROTEM-based protocol (N.=379)</th>
<th>Propensity Score Pre-ROTEM-based protocol (N.=330)</th>
<th>Post-ROTEM-based protocol (N.=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.0±11.8</td>
<td>69.2±11.6</td>
<td>69.1±11.39</td>
<td>69.3±11.71</td>
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<tr>
<td>Gender, N. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>131 (33.7)</td>
<td>134 (35.4)</td>
<td>110 (33.3)</td>
<td>115 (34.8)</td>
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<td>Male</td>
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<td>245 (64.6)</td>
<td>220 (66.7)</td>
<td>215 (65.2)</td>
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<td>Weight, kg</td>
<td>77.0±14.9</td>
<td>75.8±15.6</td>
<td>77.0±15.0</td>
<td>76.4±14.66</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.0±9.6</td>
<td>167.3±11.7</td>
<td>167.9±9.57</td>
<td>167.9±8.69</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2±4.7</td>
<td>28.7±28.7</td>
<td>27.2±4.76</td>
<td>27.0±4.32</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>6.0±2.8</td>
<td>6.2±3.0</td>
<td>6.0±2.77</td>
<td>6.0±2.90</td>
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<tr>
<td>CCS, N. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>238 (61.2)</td>
<td>213 (56.2)</td>
<td>197 (59.7)</td>
<td>182 (55.2)</td>
</tr>
<tr>
<td>I</td>
<td>9 (2.3)</td>
<td>8 (2.1)</td>
<td>7 (2.1)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>II</td>
<td>111 (28.5)</td>
<td>127 (33.5)</td>
<td>99 (30.0)</td>
<td>112 (33.9)</td>
</tr>
<tr>
<td>III</td>
<td>31 (8.0)</td>
<td>31 (8.2)</td>
<td>27 (8.2)</td>
<td>29 (8.8)</td>
</tr>
<tr>
<td>NYHA, N. (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>I</td>
<td>104 (26.7)</td>
<td>123 (32.5)*</td>
<td>101 (30.6)</td>
<td>111 (33.6)</td>
</tr>
<tr>
<td>II</td>
<td>193 (49.6)</td>
<td>138 (36.4)*</td>
<td>143 (43.3)</td>
<td>122 (37.0)</td>
</tr>
<tr>
<td>III</td>
<td>87 (22.4)</td>
<td>116 (30.6)*</td>
<td>83 (25.2)</td>
<td>95 (28.8)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (1.3)</td>
<td>2 (0.5)*</td>
<td>3 (0.9)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>LVEF, N. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>270 (69.4)</td>
<td>255 (67.3)</td>
<td>228 (69.1)</td>
<td>223 (67.6)</td>
</tr>
<tr>
<td>30-49%</td>
<td>116 (29.8)</td>
<td>123 (32.5)</td>
<td>101 (30.6)</td>
<td>106 (32.1)</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Comorbidities, N. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>382 (98.2)</td>
<td>355 (93.7)*</td>
<td>323 (97.9)</td>
<td>324 (98.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>84 (21.6)</td>
<td>100 (26.4)</td>
<td>67 (20.3)**</td>
<td>89 (27.0)**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>214 (55.0)</td>
<td>221 (58.3)</td>
<td>178 (53.9)***</td>
<td>199 (60.3)***</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (0.5)</td>
<td>10 (2.6)**</td>
<td>2 (0.6)****</td>
<td>9 (2.7)****</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>19 (4.9)</td>
<td>23 (6.1)</td>
<td>15 (4.5)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>11 (2.8)</td>
<td>9 (2.4)</td>
<td>9 (2.7)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>CHF</td>
<td>2 (0.5)</td>
<td>0</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>16 (4.1)</td>
<td>27 (7.1)</td>
<td>14 (4.2)</td>
<td>22 (6.7)</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation unless otherwise stated.

*P<0.001 pre- vs. post-ROTEM protocol; **P<0.02 pre- vs. post-ROTEM protocol; ***P<0.05 pre- vs. post-ROTEM protocol; ****P<0.01 pre- vs. post-ROTEM protocol; *****P=0.03 pre- vs. post-ROTEM protocol.

BMI: Body Mass Index; CCS: Canadian Cardiovascular Society Angina Grading Scale; CHF: congestive heart failure; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association functional classification; ROTEM: rotational thromboelastometry.
and baseline heart disease characteristics of the two groups were similar, although there were some differences in New York Heart Association classifications and incidence of comorbidities. Surgical characteristics of the two groups were also comparable (Table II). The majority of patients before and after protocol introduction underwent elective surgery (92.5% and 92.9%) and the most frequent intervention was valve surgery (42.4% and 40.1%) followed by coronary artery bypass grafting (CABG, 24.2% and 31.4%). We excluded from analysis off-pump CABG (7 and 5 cases before and after protocol introduction). Antiplatelets drugs administered preoperatively are summarized in Table II.

Data related to the use of blood products and coagulation factors concentrates are summarized in Table III. Overall, 221/389 patients (56.8%) treated before protocol introduction and 182/379 (48.1%) treated after protocol introduction were transfused (P<0.01). Nine patients in each group (2.3% vs. 2.4%, respectively) died within 30 days of surgery.

Patients undergoing cardiac surgery after introduction of the new protocol for hemostatic management had a shorter duration of ventilation and stay in the ICU than patients having surgery before the protocol introduction, and fewer patients in this group required reoperation compared with patients who underwent surgery before protocol institution (Table IV); however, these differences between groups were not statistically significant. A significantly greater proportion of patients treated after protocol introduction than before had an ICU stay duration shorter than 48 hours (81.5% vs. 71.5%; P<0.001) and a smaller proportion had

### Table II.—Surgery characteristics, preoperative coagulation testing and antiplatelet drug exposure (all population and Propensity Score population).

<table>
<thead>
<tr>
<th>Procedure type, N. (%)</th>
<th>Pre-ROTEM-based protocol (N.=389)</th>
<th>Post-ROTEM-based protocol (N.=379)</th>
<th>Pre-ROTEM-based protocol (N.=330)</th>
<th>Post-ROTEM-based protocol (N.=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECC, minutes</td>
<td>99.3±41.5</td>
<td>98.8±50.1</td>
<td>98.2±41.4</td>
<td>97.9±48.20</td>
</tr>
<tr>
<td>Cross-clamp, minutes</td>
<td>67.5±30.2</td>
<td>65.5±31.0</td>
<td>66.1±28.39</td>
<td>65.6±31.24</td>
</tr>
<tr>
<td>Procedure type, N. (%)</td>
<td>Elective</td>
<td>360 (92.5)</td>
<td>352 (92.9)</td>
<td>306 (92.7)</td>
</tr>
<tr>
<td></td>
<td>Urgent</td>
<td>4 (1.0)</td>
<td>3 (0.8)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Emergency</td>
<td>25 (6.4)</td>
<td>24 (6.3)</td>
<td>20 (6.1)</td>
</tr>
<tr>
<td></td>
<td>Redo surgery</td>
<td>15 (3.9)</td>
<td>26 (6.9)</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Surgery type, N. (%)</td>
<td>CAVBG</td>
<td>94 (24.2)</td>
<td>119 (31.4)</td>
<td>84 (25.5)</td>
</tr>
<tr>
<td></td>
<td>Valvular</td>
<td>165 (42.4)</td>
<td>152 (40.1)</td>
<td>141 (42.7)</td>
</tr>
<tr>
<td></td>
<td>Dissection</td>
<td>8 (2.1)</td>
<td>7 (1.8)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Aortic arch surgery</td>
<td>5 (1.3)</td>
<td>3 (0.8)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Aortic root surgery</td>
<td>38 (9.8)</td>
<td>40 (10.6)</td>
<td>30 (9.1)</td>
</tr>
<tr>
<td></td>
<td>CABG + valvular</td>
<td>49 (12.6)</td>
<td>37 (9.8)</td>
<td>40 (12.1)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>30 (7.7)</td>
<td>21 (5.5)</td>
<td>25 (7.6)</td>
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<td></td>
<td>Refusing transfusions, N. (%)</td>
<td>5 (1.3)</td>
<td>6 (1.6)</td>
<td>3 (0.9)</td>
</tr>
</tbody>
</table>

Table II.—Surgery characteristics, preoperative coagulation testing and antiplatelet drug exposure (all population and Propensity Score population).

Values are mean±standard deviation unless otherwise stated. Urgent surgery was defined as surgery that may be delayed up to 24 hours. Emergency surgery was defined as surgery that should be performed as soon as possible. ADP: adenosine diphosphate aggregometry test; ASP: aspirin aggregometry test; CAVBG: coronary artery bypass graft; ECC, extracorporeal circulation; ROTEM: rotational thromboelastometry; TRAP: thrombin-receptor activated peptide aggregometry test.

**Vol. 82 - No. 10**

**MINERVA ANESTESIOLOGICA**

1083
The mean hemoglobin level before surgery and at ICU discharge was similar in the two groups (respectively 12.4±1.6 and 9.1±0.9 mg/dL preprotocol versus 12.7±1.8 and 8.9±1.0 mg/dL postprotocol introduction). Stroke was diagnosed in one patient in each group. No postoperative myocardial infarction due to acute graft obstruction was registered in the two groups.

Propensity score matching results are also reported in Table I, II, III and IV. Kaplan-Meier analysis on the PS population showed a significantly higher pre-ROTEM estimated time of ventilation (31 hours vs. 28 hours, P<0.001) and a significantly lower post-ROTEM length of stay in ICU (65 hours vs. 61 hours, P=0.047).

The results of the cost estimates of the resources used for bleeding management before and after institution of the new protocol are summarized in Table V. Bleeding management using the ROTEM-guided protocol was associated with a saving of €128,676.23 for the 379 patients undergoing surgery postprotocol introduction (€339.52 per patient). This was mainly triggered by a decreased use of PRBC, shorter duration of ICU stay, and reduction in the number of reoperations.

**Discussion**

This manuscript describes the results of a retrospective analysis aiming to determine the

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**Table III.—Use of blood products and coagulation factor concentrates (all population and Propensity Score population).**

<table>
<thead>
<tr>
<th></th>
<th>Pre-ROTEM-based protocol (N.=389)</th>
<th>Post-ROTEM-based protocol (N.=379)</th>
<th>Propensity Score</th>
<th>Pre-ROTEM-based protocol (N.=330)</th>
<th>Post-ROTEM-based protocol (N.=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Erythrocytes Units</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (N., %)</td>
<td>221 (56.8)</td>
<td>182 (48.1)*</td>
<td>186 (56.4)</td>
<td>159 (48.3)**</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>1 (0-95)</td>
<td>0 (0-30)</td>
<td>1 (0-21)</td>
<td>0 (0-30)</td>
<td></td>
</tr>
<tr>
<td>1st-3rd quartiles</td>
<td>0-3</td>
<td>0-2</td>
<td>0-3</td>
<td>0-2</td>
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<tr>
<td><strong>24h Erythrocytes Units</strong></td>
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<tr>
<td>Patients (N., %)</td>
<td>197 (50.6)</td>
<td>100 (26.4)**</td>
<td>164 (49.7)</td>
<td>88 (26.7)**</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>1 (0-17)</td>
<td>0 (0-12)**</td>
<td>0 (0-15)</td>
<td>0 (0-10)**</td>
<td></td>
</tr>
<tr>
<td>1st-3rd quartiles</td>
<td>0-2</td>
<td>0-1</td>
<td>0-2</td>
<td>0-1</td>
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<tr>
<td><strong>ICU Erythrocytes Units</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients (N., %)</td>
<td>221 (56.8)</td>
<td>134 (35.4)**</td>
<td>186 (56.4)</td>
<td>119 (36.1)**</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>1 (0-83)</td>
<td>0 (0-29)**</td>
<td>1 (0-21)</td>
<td>0 (0-29)**</td>
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<tr>
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<tr>
<td><strong>Fresh Frozen Plasma Units</strong></td>
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<tr>
<td>Patients (N., %)</td>
<td>33 (8.5)</td>
<td>21 (5.6)</td>
<td>26 (7.9)</td>
<td>17 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>0 (0-37)</td>
<td>0 (0-42)</td>
<td>0 (0-6)</td>
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<tr>
<td>1st-3rd quartiles</td>
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<tr>
<td><strong>Platelets Units</strong></td>
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</tr>
<tr>
<td>Patients (N., %)</td>
<td>23 (5.9)</td>
<td>28 (7.4)</td>
<td>17 (5.2)</td>
<td>23 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>0 (0-18)</td>
<td>0 (0-5)</td>
<td>0 (0-4)</td>
<td>0 (0-5)</td>
<td></td>
</tr>
<tr>
<td>1st-3rd quartiles</td>
<td>0-0</td>
<td>0-0</td>
<td>0-0</td>
<td>0-0</td>
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</tr>
<tr>
<td><strong>Human Complex units</strong></td>
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</tr>
<tr>
<td>Patients, N. (%)</td>
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<td>0</td>
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</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>4.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Conifider units</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, N. (%)</td>
<td>16</td>
<td>31***</td>
<td>11</td>
<td>26***</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>1.9 ± 0.7 (1-3)</td>
<td>2.1 ± 1.1 (1-4)</td>
<td>1.6 ± 0.6 (1-3)</td>
<td>2.2 ± 1.0 (1-4)</td>
<td></td>
</tr>
<tr>
<td><strong>Haemocomplettan units</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, N. (%)</td>
<td>13</td>
<td>36**</td>
<td>9</td>
<td>29**</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>1.8 ± 0.6 (1-3)</td>
<td>2.4 ± 1.0 (1-6)</td>
<td>1.9 ± 0.6 (1-3)</td>
<td>2.6 ± 1.0 (1-6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±standard deviation (range) unless otherwise stated.

*P<0.02 pre- vs. post-ROTEM protocol; **P<0.001 pre- vs. post-ROTEM protocol; ***P<0.05 pre- vs. post-ROTEM protocol.

ICU: intensive care unit; ROTEM: rotational thromboelastometry.
The analysis showed that introduction of the protocol led to a reduction in the number of units of PRBC administered over 24 hours and costs. The impact of a ROTEM-based protocol for the management and prevention of surgery-associated bleeding on perioperative outcomes and

### Table IV. Duration of mechanical ventilation, length of stay in the intensive care unit, and need for revision surgery (all population and Propensity Score population).

<table>
<thead>
<tr>
<th></th>
<th>Pre-ROTEM-based protocol (N=389)</th>
<th>Post-ROTEM-based protocol (N=379)</th>
<th>Propensity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of ventilation, hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>10 (2-2520)</td>
<td>8 (2-2880)*</td>
<td>10 (2-2880)*</td>
</tr>
<tr>
<td>1st-3rd quartiles</td>
<td>(6-10)</td>
<td>(7-10)</td>
<td>(7-10)</td>
</tr>
<tr>
<td><strong>Length of ICU stay, hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>19 (3-4680)</td>
<td>18 (2-2400)**</td>
<td>20 (3-1472)</td>
</tr>
<tr>
<td>1st-3rd quartiles</td>
<td>(16-66)</td>
<td>(16-40)</td>
<td>(18-66)</td>
</tr>
<tr>
<td><strong>Patients needing revision surgery, N. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;48 hours, N. (%)</td>
<td>278 (71.5)</td>
<td>309 (81.5)*</td>
<td>239 (72.4)</td>
</tr>
<tr>
<td>48 hours – 7 days, N. (%)</td>
<td>90 (23.1)</td>
<td>43 (11.3)*</td>
<td>75 (22.7)</td>
</tr>
<tr>
<td>&gt;7 days, N. (%)</td>
<td>21 (5.4)</td>
<td>27 (7.1)</td>
<td>16 (4.8)</td>
</tr>
</tbody>
</table>

*P<0.001 **P=0.002 ***P<0.05 vs. post-ROTEM-based protocol.

ICU: intensive care unit; ROTEM: rotational thromboelastometry.

### Table V. Cost estimates before and after introduction of a ROTEM-guided protocol.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unit cost (£)</th>
<th>Units pre-ROTEM-based protocol (N.)</th>
<th>Cost pre-ROTEM-based protocol (£)</th>
<th>Units post-ROTEM-based protocol (N.)</th>
<th>Cost post-ROTEM-based protocol (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC</td>
<td>188.65</td>
<td>891</td>
<td>168087.15</td>
<td>701</td>
<td>132243.65</td>
</tr>
<tr>
<td>FFP</td>
<td>161.00</td>
<td>132</td>
<td>21252.00</td>
<td>121</td>
<td>19481.00</td>
</tr>
<tr>
<td>Platelets</td>
<td>203.00</td>
<td>54</td>
<td>10962.00</td>
<td>45</td>
<td>9135.00</td>
</tr>
<tr>
<td>ICU stay</td>
<td>104.16b</td>
<td>9.96 x 389</td>
<td>403662.97</td>
<td>7.69 x 379</td>
<td>305375.36</td>
</tr>
<tr>
<td>Re-intervention for bleeding</td>
<td>2775.00c</td>
<td>20</td>
<td>55500.00</td>
<td>11</td>
<td>30525.00</td>
</tr>
<tr>
<td>Coagulation factor concentrate</td>
<td>120.00</td>
<td>4</td>
<td>480.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>CONFIDEX</td>
<td>139.00</td>
<td>30</td>
<td>4170.00</td>
<td>65</td>
<td>9035.00</td>
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<tr>
<td>HAEMOCOMPLETTAN</td>
<td>400.00</td>
<td>23</td>
<td>9200.00</td>
<td>85</td>
<td>34,000.00</td>
</tr>
<tr>
<td>Other protocol drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMOSINT</td>
<td>1.83</td>
<td>430</td>
<td>786.90</td>
<td>622</td>
<td>1138.26</td>
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<tr>
<td>Consumable materials for ROTEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cuvette</td>
<td>1483.20</td>
<td>5</td>
<td>7416.00</td>
<td>3</td>
<td>4449.60</td>
</tr>
<tr>
<td>EXTEM</td>
<td>432.00</td>
<td>5</td>
<td>2160.00</td>
<td>2</td>
<td>864.00</td>
</tr>
<tr>
<td>EXTEM S</td>
<td>193.92</td>
<td>0</td>
<td>0.00</td>
<td>14</td>
<td>2714.88</td>
</tr>
<tr>
<td>FIBTEM</td>
<td>320.00</td>
<td>0</td>
<td>2240.00</td>
<td>2</td>
<td>640.00</td>
</tr>
<tr>
<td>FIBTEM S</td>
<td>304.80</td>
<td>0</td>
<td>0.00</td>
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<td>4267.20</td>
</tr>
<tr>
<td>HEPTEM</td>
<td>480.00</td>
<td>2</td>
<td>960.00</td>
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<tr>
<td>HEPTEM S</td>
<td>319.20</td>
<td>0</td>
<td>0.00</td>
<td>11</td>
<td>3511.20</td>
</tr>
<tr>
<td>INTEM</td>
<td>432.00</td>
<td>6</td>
<td>2592.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>INTEM S</td>
<td>193.92</td>
<td>0</td>
<td>0.00</td>
<td>14</td>
<td>2714.88</td>
</tr>
<tr>
<td>STARTEM</td>
<td>162.00</td>
<td>7</td>
<td>1134.00</td>
<td>3</td>
<td>486.00</td>
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<tr>
<td><strong>Total consumable costs</strong></td>
<td>16,502.00</td>
<td></td>
<td>19,647.76</td>
<td></td>
<td></td>
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<tr>
<td><strong>TOTAL COST</strong></td>
<td>707,105.02</td>
<td></td>
<td>578,428.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL COST DIFFERENCE</strong></td>
<td>-128,676.23</td>
<td></td>
<td>-128,676.23</td>
<td></td>
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</tr>
<tr>
<td><strong>COST DIFFERENCE PER PATIENT</strong></td>
<td>-339.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Calculated based on an 8-hour nurse shift multiplied by the number of patients, and divided by 2 (2 beds covered per nurse).

*b* Per 8-hour nurse shift

*c* Per intervention

FFP: fresh frozen plasma; ICU: intensive care unit; PRBC: packed red blood cells; ROTEM: rotational thromboelastometry.
during the ICU and hospital stay, and a significant increase in the number of patients leaving the ICU within 48 hours postsurgery. Use of the protocol led to a decrease in costs of approximately €339 per patient.

When comparing the number of units of FFP and platelets transfused, there was no statistically significant difference before and after the ROTEM protocol introduction. That the change in these endpoints is not more marked is likely due to the fact that a ROTEM-based strategy utilizing aggregometry and coagulation factor concentrates was already in place at the center, albeit one that was used in a far less organized manner. Moreover, the number of interventions postponed because of ADP aggregometry less than 30 (29 patients) could be the reason for the slight increase of platelets transfused. The introduction of a more regulated protocol resulted in the increased use of coagulation factor concentrates rather than a change in use of FFP and platelets.

Notably, better coagulation control post-protocol resulted in a reduction in the number of patients transfused during the perioperative 24 hours, ICU stay and hospital stay, and a greater proportion of patients staying in the ICU for less than 48 hours. Transfusions are associated with several complications, including transfusion reactions, acute lung injury, circulatory overload, and immunomodulation; the decrease in the number of per-patient transfusions may be the first step in reducing transfusion-related complications.

The protocol implemented was developed based on the clinical experience in the center and published literature on the topic of managing surgical bleeding. Since ROTEM and Multiplate aggregometry were established methods at our center, and coagulation factor concentrates were already in use, implementation of the protocol was relatively simple. The use of the protocol has increased the use of coagulation factor concentrates, and given the center’s staff common objectives, resulting in a greater uniformity of behavior and an improvement in post-surgical outcomes.

The improvements in outcomes seen in this study are similar to those seen in the literature. In one Turkish study, patients undergoing elective CABG either had clinician-directed transfusion, or transfusion guided by a routine thromboelastography algorithm; use of the algorithm resulted in a reduction in blood products (FFP, platelets) versus clinician-directed management. Another group of patients undergoing CPB demonstrated reduced transfusion requirement and 24-hour postoperative bleeding with the use of a thromboelastometry test-guided algorithm. Several studies investigated the use of coagulation management algorithms in settings including aortic arch replacement/aortic dissection, cardiovascular surgery, trauma and transplant surgery; these studies also found that use of an algorithm reduced transfusion requirements, thromboembolic/thrombotic events, and the incidence of massive transfusion. A recently published review article reported on 16 studies (including 8507 cardiac surgical patients overall) dealing with transfusion protocols in cardiovascular surgery comparing POC-based algorithms versus algorithms based on routine laboratory testing and clinician discretion or standard of care. All 16 studies demonstrated a reduction in transfusion requirements in the POC group. The effect size was dependent on study population (simple CABG surgery or complex cardiac/aortic surgery), the average blood loss, the extent of POC diagnostics (viscoelastic tests only or viscoelastic tests plus Multiplate), and the first-line use of coagulation factor concentrates. Seven studies reported a reduction in the incidence of mediastinal re-exploration and a reduction in hospital costs. Our observations are in agreement with these results: the signal of reduction in allogenic blood transfusion and costs provided by the adoption of a POC-based protocol seems to be amplified by the first-line therapy with coagulation factor concentrates.

The present study also demonstrated a reduction in costs, but it should be noted that the actual cost reduction is most likely less than reported here. The calculation of costs assumed that bed saturation in the ICU was
always 100%, while data from the center shows that actual total bed saturation is 65-70%; this means that the cost savings are likely to be proportionally less. However, studies have reported that excessive post-operative bleeding is associated with significant costs, and any intervention resulting in lower bleeding rates is likely to lead to substantial cost savings. In addition, cost reduction has been reported in studies similar to the present analysis, with savings of €2757 per case in one study of a ROTEM-based algorithm and an overall combined saving of 44% in another. Overall, these results suggest that the use of a ROTEM-based algorithm for bleeding management is, nevertheless, still likely to be cost saving.

Limitations of the study

This study has several limitations associated with the retrospective nature of the design, the short follow-up period, and that it took place at a single center.

Conclusions

In conclusion, the introduction of a POC-based protocol with first-line therapy with coagulation factor concentrates for the management of bleeding during cardiac surgery in a single center in Italy was associated with a significant decrease in the use of PRBC and shorter ICU stay.

The protocol also led to a decrease in costs associated with bleeding management during surgery, suggesting that it is an effective and potentially cost-saving option for the management of bleeding in this setting.

Taking into consideration the increasing number of studies reporting positive clinical and economical results linked to POC-based management of bleeding with coagulation factor concentrates in cardiovascular surgery patients, it is our opinion that this strategy should be considered as a standard of care in this setting. However, these results should be confirmed by a multicenter prospective randomized trial.

Key messages

— A POC-guided treatment of perioperative bleeding in cardiac surgery positively affected time of mechanical ventilation and ICU stay.
— A POC-based protocol was associated with a significant reduction of PRBC transfused perioperatively.
— Administration of coagulation factor concentrates according to a POC-based protocol has proven to be cost-effective.

References


Whole-exome sequencing of a family with local anesthetic resistance

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ABSTRACT

BACKGROUND: Local anesthetics (LA) work by blocking sodium conductance through voltage-gated sodium channels. Complete local anesthetic resistance is infrequent, and the cause is unknown. Genetic variation in sodium channels is a potential mechanism for local anesthetic resistance. A patient with a history of inadequate loss of sensation following LA administration underwent an ultrasound-guided brachial plexus nerve block with a complete failure of the block. We hypothesized that LA resistance is due to a variant form of voltage-gated sodium channel.

METHODS: Whole-Exome Sequencing. The patient and her immediate family provided consent for exome sequencing, and they were screened with a questionnaire to identify family members with a history of LA resistance. Exome sequencing results for four individuals were referenced to the 1000 Genomes Project and the NHLBI ESP to identify variants associated with local anesthetic resistance present in less than 1% of the general population and located in functional regions of the genome.

RESULTS: Exome sequencing of the four family members identified one genetic variant in the voltage-gated sodium channel shared by the three individuals with LA resistance but not present in the unaffected family member. Specifically, we noted the A572D mutation in the SCN5A gene encoding for Na1.5.

CONCLUSIONS: We identified a genetic variant that is associated with LA resistance in the gene encoding for Na1.5. We also demonstrate that Na1.5 is present in human peripheral nerves to support the plausibility that an abnormal form of the Na1.5 protein could be responsible for the observed local anesthetic resistance.

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Key words: Exome - Anesthesia, local - Peripheral nerves - NAV1.5 Voltage-Gated Sodium Channel.

Local anesthetics (LAs) are a class of medications that render tissue insensitive to pain by interrupting transmission of stimuli from peripheral nerves to the brain.1 LAs work by blocking sodium conductance through voltage-gated sodium channels, thereby preventing an action potential from relaying information to the brain.2, 3 LA administration is common in clinical practice and is highly effective in preventing pain at the site of tissue injury.

Failure of LAs to produce blockade of nociception is uncommon and usually due to medication not being delivered to the targeted nerve in sufficient quantity, dispersion of LA from the site of action, an acidic environment limiting the concentration of the freebase form, or inability of the LA to access its binding site on the cytoplasmic pore of voltage-gated sodium...
channels. In a prospective study of 2000 cases, failure to attain spinal anesthesia by intrathecal injection of LA occurred in approximately 3% of cases. The most common reason for failure was inadequate sensory level for the surgery; although, 12 cases had complete failure despite confirmation of cerebral spinal fluid flow before and after injection of LA. Complete resistance despite skin infiltration and confirmed drug delivery has been reported in a small number of cases, in patients with Ehlers-Danlos type III syndrome, and in a larger screening study where patients self-reported LA resistance. The cause of such resistance is unknown; however, genetic variation is a proposed mechanism.

We hypothesized that LA resistance could be due to a variant form of voltage-gated sodium channel that is incompletely inhibited by LAs. We tested this hypothesis by clinically confirming complete LA resistance in a patient presenting for elective surgery. We surveyed the patient’s immediate family for similar resistance to LAs and performed whole-exome sequencing to screen for genetic variants in voltage-gated sodium channels. We referenced their exome sequences to publically available genetic databases and screened for pathogenic mutations. We identified a genetic variant in the \( SCN5A \) gene that is shared by these affected family members and may be associated with LA resistance. We also performed immunohistochemistry on cadaveric human peripheral nerves, dorsal root ganglia, spinal cord, and cerebral cortex to compare the distribution of \( Na_1.5 \) and \( Na_1.7 \) sodium channels in human tissue to demonstrate that \( Na_1.5 \) is detectable on peripheral nerves, dorsal root ganglia, and cerebral cortex.

**Materials and methods**

The Mayo Clinic Institutional Review Board approved the study (IRB 12-000139) and all study participants provided written informed consent.

**Identification of a patient with local anesthetic resistance**

A 37-year-old woman with American Society of Anesthesiologist physical status II had a mass on her left anterior elbow with preoperative magnetic resonance imaging indicating a lipoma.

The anesthesia plan consisted of an ultrasound-guided supraclavicular brachial plexus nerve block and intravenous sedation. A Sonosite M-Turbo ultrasound unit (Sonosite Inc, Bothell, WA, USA) with a high-frequency 5 MHz - 12 MHz linear transducer was used to identify the subclavian artery, first rib, and brachial plexus. A supraclavicular brachial plexus injection was performed with an in-plane lateral to medial ultrasound approach using a 22-gauge, 50 mm needle (Stimuplex R; B.Braun, Bethlehem, PA, USA). A total of 30 mL of 1.5% mepivacaine was administered, with the initial 15 mL placed in the corner bordered by the subclavian artery medially and the first rib inferiorly and the remainder was injected superiorly (Figure 1).

The patient was observed for 30 minutes for sensory or motor changes, and complete failure of the block was noted. The lipoma was excised without complication under general anesthesia, and at the end of the procedure the surgeon infiltrated the wound with 12 mL of 0.5% ropivacaine. Ninety minutes after the block was performed, the patient had no sensory or motor block of her left arm, forearm, or hand.

**Participant questionnaire**

The proband’s father, mother, and maternal half-sister completed a questionnaire to gather information about family history and resistance to local anesthetics. In a prospective study of 2000 cases, failure to attain spinal anesthesia by intrathecal injection of LA occurred in approximately 3% of cases.
demographic and medical information. The demographic information included age, gender, height, and weight. The medical questions were designed for “yes” or “no” responses, and, if they answered “yes,” the participants were asked to explain their answer in more detail in a space provided. These questions were included to determine which relatives exhibited LA resistance as well as to reveal any clinical features that may be linked with genes known to be associated with pain perception/analgesia. Specifically, the medical questions asked whether the participants: 1) experienced pain after LA was administered during a dental or other medical procedures; 2) felt that he/she is more sensitive to pain than others; 3) felt that he/she is less sensitive to pain than others; 4) felt that he/she is more sensitive to hot or cold temperatures than others; 5) felt that he/she is less sensitive to hot or cold temperatures than others; or 6) had seizures/epilepsy, schizophrenia, headaches/migraines, chronic pain, heart arrhythmia, or other neurologic conditions.

**Whole-exome sequencing**

Study participants provided DNA samples via an Oragene saliva kit for whole-exome sequencing. The Mayo Clinic Molecular Biology Core Facility performed whole-exome sequencing. Paired-end libraries were prepared using 1.0 μg of genomic DNA following the manufacturer’s protocol (Agilent) using the Agilent Bravo liquid handler. The concentration and size distribution of the completed libraries was determined using an Agilent Bioanalyzer DNA 1000 chip (Santa Clara, CA, USA) and Qubit fluorometry (Invitrogen, Carlsbad, CA, USA). Whole-exon capture was carried out using 750 ng of the prepped library following the protocol for Agilent’s SureSelect Human All Exon v4 + UTRs 71 MB kit. The purified capture products were then amplified using the SureSelect Post-Capture Indexing forward and Index PCR reverse primers (Agilent) for 12 cycles. The concentration and size distribution of the completed captured libraries was determined on Qubit (Invitrogen) and Agilent Bioanalyzer DNA 1000 chip. The proband library was sequenced at an average coverage of ~250X and other family members were sequenced at an average coverage of 60-120X following Illumina’s standard protocol using the Illumina cBot and cBot Paired end cluster kit version 3. The flow cells were sequenced as 101 X 2 paired end reads on an Illumina HiSeq 2000 using TruSeq SBS sequencing kit version 3 and HCS v2.0.12 data collection software. Base-calling was performed using Illumina’s RTA version 1.17.21.3.

**Read alignment and variant calling**

The read QC and alignment, variant calling, and variant/gene annotation were performed using an in-house analytic pipeline GenomeGPS (GGPS). Specifically, read qualities were examined by FastQC. The 100 base paired-end reads were mapped to Human Reference Genome build 37 using NovoAlign (Novocraft Technologies Sdn Bhd, Selangor, Malaysia). The duplicated reads were removed using the SAMtools’s rmdup method. The alignment was then improved using the Genome Analysis ToolKit (GATK) for local realignments and quality score recalibration. Single nucleotide variants (SNVs) and small insertions and deletions (INDELs) were called using GATK’s UnifiedGenotyper. The variants were annotated to provide information including: 1) variant physical positions; 2) calling information (read depths, depth of alternative allele supporting reads, average mapping quality score etc.); 3) impact of variants on genes/proteins using SNPEFF and the variant functional predictions using SIFT and PolyPhen. All variants passed QC were included in the Genetic Variant Analysis. All variants were categorized into three tiers: Tier-I variants, consisting of splice/nonsense/frameshift variants, are the most likely to be pathogenic; Tier-II variants (missense or nonsynonymous variants, as well as SNVs/INDELs located in promoter and other regulatory domains) and Tier-III variants (synonymous mutations,
variants in 5’UTR and 3’UTR regions, and intergenic/intronic variants) are expected to be the most numerous.

**Genetic variant analysis**

Variant analysis was performed using Ingenuity Variant Analysis software (Qiagen, Hilden, Germany). To identify potential causative variants for LA, variants were selected that segregated in affected family members. From these, variants were excluded if not located in coding or functional regions of the genome. Variants were further excluded if the frequency was greater than 1% in the public genome variant databases dbSNP and 1000 genomes. The remaining variants were analyzed in silico for effect on protein function using the SIFT and PolyPhen-2 mutation-prediction programs.

**Immunohistochemistry**

Cadaveric human peripheral nerve tissue, dorsal root ganglion, spinal cord, and brain without evidence of disease was labeled with polyclonal rabbit anti-human Na,1.5 and Na,1.7 at a 1:50 and 1:400 dilution, respectively (Alomone laboratories). Secondary staining with rabbit labelled polymer (DAKO Cytomation) was performed with 3,3’-Diaminobenzidine (DAB +, DAKO Cytomation) followed with a light Gill 1 hematoxylin counterstain. Antibody specificity was confirmed with a targeted blocking peptide specific to each antigen (Alomone laboratories). Normal human myocardium was labeled as a positive control for Na,1.5 and normal peripheral nerve was labeled as a positive control for Na,1.7. Immunohistochemistry on peripheral nerves was repeated in three separate individuals from different sites (left leg amputation, neuroma, and left leg sural nerve).

**Results**

**Identifying the proband and familial screening**

A patient with clinically apparent LA resistance was identified incidentally after presenting for elective surgery involving her upper extremity. The patient reported a history of failed LA nerve blocks placed by her dentist, inadequate loss of sensation with subcutaneous LAs for intravenous access, and failed block to LA placed by a cardiologist prior to cardiac catheterization. An ultrasound-guided supraclavicular brachial plexus block failed despite confirmation of LA spread (Figure 1).

A detailed evaluation of the proband’s medical history revealed a lack of clinical symptoms that are linked with genes known to be associated with pain perception/analgesia. The proband reported a family history of LA resistance in her mother and maternal half-sister (Figure 2). These family members and her reportedly unaffected father were contacted and provided demographic information, medical information, and tissue samples. The mother, age 65, reported LA resistance, high pain tolerance, and sensitivity to hot and cold temperatures. She denied a history of seizures, schizophrenia, headaches, chronic pain, heart arrhythmia, and other neurologic symptoms. The proband’s maternal half-sister, age 43, also reported LA resistance. She described failure of a lower extremity nerve block for ankle surgery and had received multiple LA injections during dental procedures with brief and inadequate loss of sensation. She expressed variable pain tolerance and increased...
doses of analgesic medications to relieve pain. She denied sensitivity to hot and cold temperatures, seizures, schizophrenia, heart arrhythmia, and other neurologic symptoms. The proband’s father, age 68, confirmed appropriate sensation loss with LA. He reported a subjectively high pain tolerance and denied sensitivity to hot and cold temperatures, seizures, schizophrenia, headaches, and other neurologic symptoms. The proband, mother, and maternal half-sister have a positive history of LA resistance, which indicated a possible genetic etiology.

Exome sequencing and genetic analysis

Whole-exome sequencing of the four family members was performed to identify genetic variants shared by the three individuals who had LA resistance but not shared in the unaffected family member. Three hundred and ninety-six genetic variants associated with 225 genes segregated in the affected relatives.

Variants located in candidate genes associated with pain and analgesia are listed in Table I. Only one variant was identified in a voltage-gated sodium channel susceptible to LA inhibition (Na\(_{\text{v}}1.5\)). Specifically, we noted the A572D mutation in the SCN5A gene encoding for Na\(_{\text{v}}1.5\).

Nav1.5 in peripheral nerves and central nervous system

Na\(_{\text{v}}1.5\) has been extensively studied in cardiac but not nervous tissue. To determine whether Na\(_{\text{v}}1.5\) is present in peripheral nerves, we performed immunohistochemistry with highly specific antibodies on healthy human tissue (Figure 3). Staining of peripheral nerve tissue revealed Na\(_{\text{v}}1.5\) immunoreactivity

<table>
<thead>
<tr>
<th>Chr#</th>
<th>Position</th>
<th>Gene Symbol</th>
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<td>Promoter; Intronic</td>
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throughout the cell body, along the peripheral nerve fiber and on dorsal root ganglia. Na\textsubscript{1.7} immunostaining served as a positive control for peripheral nerve and dorsal root ganglia. These results demonstrate that Na\textsubscript{1.5} is expressed in peripheral nerves, suggesting this channel may be involved in pain perception, similar to Na\textsubscript{1.7}.

To investigate whether Na\textsubscript{1.5} is present in the central nervous system, we performed immunohistochemistry on healthy human cerebral cortex and spinal cord. The results were compared to the presence of Na\textsubscript{1.7} by immunohistochemistry. Na\textsubscript{1.5} and Na\textsubscript{1.7} were detected on healthy human cerebral cortex but not spinal cord. Microarray expression data from six healthy human brains demonstrate that Na\textsubscript{1.5} and Na\textsubscript{1.7} transcripts are present in significant quantities, corroborating our immunohistochemical data.20

**Discussion**

Resistance to LA has been documented in humans, and prior exposure to scorpion venom and genetic variance are putative mechanisms.5-7, 10 During routine clinical care, we identified a patient demonstrating a lack of local anesthesia with lidocaine, mepivicaine, and ropivacaine and a lack of motor blockade with mepivacaine and ropivacaine.

To explore whether LA resistance is associated with genetic variation in voltage-gated sodium channels, we performed whole-exome sequencing on a family with three of four individuals reporting LA resistance. Patients with Ehlers-Danlos syndrome type III consistently demonstrate LA resistance as determined by pain threshold to laser stimulation following topical or subcutaneous LA administration.8 This resistance is not due to rapid dispersion of the medication as measured by movement of radiolabelled solution in Ehlers-Danlos syndrome type III following deep dermal injection, suggesting that the LA fails for another reason.9 Genetic variation may account for the variability in sensitivity to different LAs identified in a case series of patients self-reporting LA resistance. Of the 250 patients tested, 53% demonstrated resistance to at least one LA following subcutaneous infiltration, with 36% responding only to mepivicaine and 17% only to lidocaine.10 All available LAs bind to sodium channel subtypes indiscriminately, and differential blockade is not observed clinically. The LA binding site does not differ substantially between sodium channel subtypes, and LAs have multiple points for molecular rotation, which may limit specificity for individual subtypes.21

Our results suggest that a variant form of the SCN5A gene encoding for Na\textsubscript{1.5} is associated with LA resistance in this family. Na\textsubscript{1.5} has been extensively studied for its action in cardiomyocytes, but its role in the nervous system is unknown. We noted that Na\textsubscript{1.5} is detectable by immunohistochemistry in postmortem human samples of peripheral nerves, dorsal root ganglia, and cerebral cortex. Microarray data from the Allen Brain Atlas show that SCN5A (Na\textsubscript{1.5}) and SCN9A (Na\textsubscript{1.7}) are expressed in the human cerebral cortex and subcortical structures.20

The A572D variant in SCN5A is present in 0.5% of the general population and was initially identified in an individual with long QT syndrome.22 Of note, the proband did not meet diagnostic criteria for long QT syndrome because her EKG demonstrated normal sinus rhythm and right ventricular conduction delay with a QT interval of 400 msec and a QTc of 444 msec despite her carrying the A572D variant. Subsequent studies noted an association between the variant and sudden cardiac death and long QT syndrome; however, further study demonstrated that A572D was not causative in either condition.23 This variant results in an amino acid change from alanine to aspartate at position 572 located between the D1-D2 inter-domain linker of the Na\textsubscript{1.5} sodium channel.22 A572D confers a susceptibility to arrhythmia when present in cardiomyocytes by mimicking phosphorylation at the S571 regulatory site on Na\textsubscript{1.5} that is targeted by CAMKII, decreasing the resting membrane potential, increasing the probability of depolarization, and resulting in a shorter recovery time compared to the wild-type sodium chan-
CAMKII also regulates membrane resting potential in neurons. We postulate that the A572D Na<sub>1.5</sub> mutation results in increased probability of membrane depolarization in peripheral nerves despite exposure to LAs.

Furthermore, point mutations in both SCN5A (Na<sub>1.5</sub>) and SCN9A (Na<sub>1.7</sub>) have been shown to decrease the effect of LA on sodium channels. The F1486 deletion in Na<sub>1.5</sub> abolishes binding of lidocaine to the channel in the inactivated state, resulting in resistance to lidocaine’s blockade of the channel. The F1737A mutation in Na<sub>1.7</sub> results in decreased affinity of lidocaine and tetracaine for the resting state of the Na<sub>1.7</sub> channel and decreases use-dependent block of the channel by both LAs.

Both of these mutations are near the pore region, allowing sodium ion conductance. In contrast, the mutation we identified is distant from the pore region and LA binding site on sodium channels and may confer LA resistance by altering resting membrane potential rather than interfering with drug binding. Calcium, calmodulin, and CAMKII have been shown to alter cardiac and neuronal membrane excitability by regulating sodium channel inactivation and manifesting clinically as arrhythmia or autism. Similarly, the A572D mutation on Na<sub>1.5</sub> may interfere with calcium-mediated regulation and manifest as clinically observed LA resistance.

**KCNE2**

The family members demonstrating LA resistance also shared a mutation in KCNE2, which encodes for a potassium ion channel inhibited by LAs (LQT5). Although KCNE2 is widely expressed in adult mouse spinal cord as noted in the Allen Brain Atlas, the Human Protein Atlas does not demonstrate the presence of significant LQT5 in human peripheral nerves. Thus, the observed KCNE2 mutation is not likely to cause LA resistance.

The frequency of local anesthetic resistance is unknown, but approximately 36 million people worldwide carry the A572D mutation and may be affected. Genetic testing is cost prohibitive, with clinical exome sequencing costing less than $6000 per test and clinical single nucleotide polymorphism testing costing approximately $200. A diagnosis of local anesthetic resistance is based on clinical findings, but validation of a genetic cause of local anesthetic resistance would permit confirmatory testing in the future. Whole-exome sequencing of a family with LA resistance revealed that the affected individuals shared an A572D mutation on Na<sub>1.5</sub>. Although Na<sub>1.5</sub> is the predominant sodium channel in cardiomyocytes, it is also detectable on human peripheral nerves, dorsal root ganglia, and cerebral cortex. These results provide evidence for a possible genetic etiology for LA resistance in humans, which warrants further research. Clinically, a failed regional block should prompt a screening test with skin infiltration of multiple local anesthetics followed by sensory assessment. If one or more local anesthetics result in loss of skin sensation the regional block should be repeated with the effective local anesthetic. If none of the local anesthetics are effective, they will require general anesthesia for the scheduled procedure. The patient should be informed about their complete local anesthetic resistance and have the diagnosis documented in their medical record.

**Conclusions**

Resistance to local anesthetics in humans has been documented in the literature, and one postulated mechanism is related to genetic variance. We identified a genetic variant in the gene encoding for Na<sub>1.5</sub> that is associated with LA resistance. We also demonstrate that Na<sub>1.5</sub> is present in human peripheral nerves to support the plausibility that an abnormal form of the Na<sub>1.5</sub> protein could be responsible for the observed LA resistance. Limitations of this study are that only one family with local anesthetic resistance was studied and the mutation identified may be correlated with local anesthetic resistance without being causative. Future work is needed to test for genetic variants in more
patients with local anesthetic resistance and the variant sodium channels will need to be tested in vitro to confirm the local anesthetic resistance.

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**Key messages**

— Complete local anesthetic resistance is uncommon but may be diagnosed by confirming medication delivery around a nerve and testing for loss of sensation or motor function.

— The Na,1.5 sodium channel is present on both cardiomyocytes and peripheral nerves.

— A family with local anesthetic resistance shared the A572D mutation in the SCN5A gene which may indicate a genetic etiology for local anesthetic resistance.

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23. Milan DJ, Melman YF, Ellinor PT. Rare ion channel polymorphisms: separating signal from noise. Heart Rhythm 2010;7:920-1.

Conflicts of interest.—Steven Clendenen receives speaker’s fees from the Institute for Advanced Medical Education and Mallinckrodt Pharmaceuticals.


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Acute respiratory failure is one of the leading causes of ICU admission. For patients with de novo (i.e., hypoxemic) acute respiratory failure, respiratory support included until recently, conventional oxygenation, in some instances noninvasive ventilation (NIV) and ultimately invasive mechanical ventilation. During these last years, introduction of high flow oxygen in the adult ICU has brought another option in the armamentarium of respiratory failure management. Until very recently, the exact place of this technique was not clearly defined, but thought somewhere between conventional oxygenation and NIV, without challenging the preexisting order in the ventilatory management of acute respiratory failure. Changes in the management of patients with acute hypoxemic respiratory
failure are however bound to occur following the resounding demonstration of high flow nasal cannula oxygen’s efficacy in these patients. This study unambiguously showed that these patients had a lower mortality when treated with high flow nasal oxygen compared to those treated either with conventional oxygen or in combination with NIV. In addition, use of high flow nasal oxygen avoided intubation in the sub-group of patients exhibiting a low PaO$_2$/FiO$_2$ ratio (<200). These cogent results confirm those of a number of observational studies performed earlier that had showed that respiratory status of patients with acute respiratory failure was significantly improved with high flow nasal oxygen. Although they did suggest that intubation may have been avoided in some patients, design of these studies precluded any formal demonstration. Nonetheless, and despite these changes, need for intubation remains important when respiratory condition deteriorates and places these severely hypoxemic patients at higher risks of desaturation than patients without respiratory failure.

This review will focus on the potential high flow nasal oxygen bears to improve pre-oxygenation for intubation in the ICU setting. Other aspects surrounding improvement of intubation will not be detailed and have been reviewed elsewhere.

Hazards of intubation in the ICU

It has been long shown that intubation of critically ill patients in the ICU is hazardous. This results from the combination of a multitude of factors (related to the patient, the environment and the situation) that all contribute to intubation’s dangerousness: unstable patients, rapidly deteriorating, with decreased physiologic reserve, full stomach and biological abnormalities that may worsen laryngoscopy feasibility because of increased risk of bleeding (coagulopathy, low platelet count, ongoing anticoagulants); physicians in charge with variable levels of expertise in airway management; and sometimes unanticipated extreme emergency. Although incidence of difficult intubation is higher in the ICU than in the operating room (OR), it is generally agreed upon that the major problem posed in the ICU is oxygenation rather than intubation per se, as in the OR. One of the most common features of critically ill patients’ intubation is occurrence of profound desaturation (defined as SpO$_2$ below 80%). This has been observed in all the studies on the subject with a striking consistency in the proportion of patients experiencing such desaturation, between 20 and 25%. One can intuitively suspect that the profounder the patient’s baseline hypoxemia, the greater the risk of desaturation during laryngoscopy. In addition, there is a direct relationship between the number of attempts and the incidence of desaturation, an intubation requiring more than two attempts increases by more than 10-fold the risk of severe hypoxemia. In turn, the greater the desaturation, the greater the risk for cardiac arrest. Hence, ensuring adequate oxygenation throughout the procedure is of utmost importance.

Although it is beyond the scope of this review to discuss in detail this aspect, one must bear in mind that optimal timing of intubation is a crucial and key determinant in the risk of desaturation. Indeed, one of the most challenging decisions in the management of patients with hypoxemic acute respiratory failure is to decide when to move from spontaneous breathing to invasive mechanical ventilation. Since it has been shown in the past that delaying intubation and invasive mechanical ventilation may worsen patient outcome, use of strict, simple, predefined criteria to initiate intubation are necessary to avoid detrimental delays. For example, the Florali study used the following criteria: 1) signs of persisting or worsening respiratory failure, defined by at least two of the following criteria: a respiratory rate above 40 breaths/min, lack of improvement of signs of high respiratory-muscle workload, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO$_2$ below 90% for more than 5 min without technical dysfunction, or intolerance to oxygenation techniques; or 2) hemodynamic instability (defined by a systolic blood pressure below 90 mmHg, a mean blood pressure below 65 mmHg or requirement for
vasopressor); or 3) deterioration of neurologic status (Glasgow coma scale below 12 points).

Although high flow nasal oxygen may avoid further need for mechanical ventilation in some patients with acute respiratory failure,\textsuperscript{2,8} it may unduly delay initiation of mechanical ventilation in others and worsen their outcome,\textsuperscript{19} as already evidenced for NIV.\textsuperscript{21-25} Hence timely intubation is important to avoid morbidity and mortality associated with prolonged use of high flow oxygen. In that respect, it is interesting to note that in studies where high flow oxygen failure was not associated with increased mortality, duration of high flow was shorter in patients that failed high flow than in those who succeeded,\textsuperscript{6} whereas in studies in which high flow oxygen failure was associated with increased mortality, duration of high flow oxygen was significantly longer in case of failure,\textsuperscript{26} highlighting the importance of judicious timing of intubation.\textsuperscript{27}

Because high flow nasal oxygen has been used in severely hypoxic patients, a number of them have naturally required invasive mechanical ventilation given the high intubation rates in these patients. Hence, in our daily practice we started keeping the high flow device in place while instituting the intubation procedure (rather than downgrading the oxygen support to a facemask) and noticed remarkable intubation conditions.\textsuperscript{6} This prompted us, as well as others, to investigate the use of high flow oxygen to prevent desaturation during tracheal intubation of critically ill patients. There are several means by which high flow nasal oxygen may improve oxygenation during tracheal intubation and two distinct but contiguous phases of tracheal intubation, preoxygenation and perlaryngoscopy oxygenation need to be discussed. The former has received considerable attention (obviously in the OR but also too in the ICU); which is less the case for the latter.

Means to improve preoxygenation

Preoxygenation, also termed denitrogenation, aims at bringing nitrogen level in the alveolus to null with complete replacement by oxygen. In stable patients undergoing elective surgery, this phase enables to ensure several minutes of apnea without desaturation. In the ICU however, the instrumental studies by Thomas Mort have shown that, contrary to the OR, conventional preoxygenation is of limited efficacy in critically ill patients. In one study, a total of 36% of patients had minimal changes (±5%) in their baseline PaO\textsubscript{2}, and only 19% increased their baseline Pao\textsubscript{2} by at least 50 mmHg after properly conducted preoxygenation.\textsuperscript{28} In a subsequent study, he showed that prolonging preoxygenation from 4 to 8 minutes provided little benefit in terms of oxygenation since Pao\textsubscript{2} rose from to 83 to 92 mmHg.\textsuperscript{29} Numerous reasons concur to limit efficiency of preoxygenation in ICU patients: cardiopulmonary underlying disease, anemia, low cardiac output, hypermetabolic states, ventilation/perfusion mismatch, obesity, pain, etc.

NIV has been to date, the most efficient means to improve preoxygenation. In the pivotal study by Baillard \textit{et al.},\textsuperscript{30} hypoxic patients were randomized to receive either bagvalve preoxygenation or NIV for 4 min. in patients that received niv, spo\textsubscript{2} was significantly higher than the control group at the end of the preoxygenation period. This benefit was maintained during laryngoscopy in most, but not all patients. importantly, several patients experienced profound desaturation (spo\textsubscript{2}<80%) during laryngoscopy despite the transient improvement obtained by NIV during the preoxygenation period. This phenomenon clearly underlines the necessity to ensure some form of oxygen supply during laryngoscopy, however short this act may be. By essence, this may not be accomplished by NIV. In addition, a significant number of patients may not benefit from this technique because of contraindications (all the contraindications to NIV, including neurological impairment, agitation, etc). Moreover, it has been shown that use of NIV for preoxygenation can induce gastric distension.\textsuperscript{31} Although this is probably inconsequential for patients in the OR, it could be more problematic in higher-risk patients such as those in the ICU with a full stomach. Finally, the technique might be a little cumbersome to be applied systemically to
all patients requiring tracheal intubation in the ICU, as suggested by a follow-up study that showed that NIV was “spontaneously” used in less than half the patients requiring urgent intubation.32

Improvement of preoxygenation with high flow nasal cannula oxygen

High flow oxygen has clearly shown its superiority over conventional facemask during acute respiratory failure to improve oxygenation. Contributors to this improvement (high FiO₂ along with high flow that enhances pharyngeal deadspace washout and also induces a modest PEEP effect that has been shown to increase end expiratory lung volume) could therefore also contribute to improve preoxygenation. In a quasi-experimental study, comparing preoxygenation performed “conventionally” with a nonrebreathing facemask (with the addition of 6 L/min oxygen flow administered through a nasopharyngeal catheter during the apnea period as routinely done in our ICU) to preoxygenation with high flow nasal oxygen (60 L/min, FiO₂:1), we were able to show that in patients with mild-to-moderate respiratory failure, oxygen saturation at the end of the preoxygenation period was significantly greater in patients that preoxygenated with high flow oxygen.33 This beneficial result with high flow was not found in another study using the same comparators and endpoints.34 In their study, Vourc’h et al.34 observed similar saturation levels at the end of the preoxygenation period between high flow and conventional oxygen. Of note, the patients included in their study were more severe in terms of hypoxemia. In addition, patients randomized to receive high flow as preoxygenation technique were possibly more severe since a greater proportion of them were already either under high flow or NIV.34

Means to improve perlaryngoscopy oxygenation

As mentioned above, the ultimate goal of preoxygenation is to provide sufficient oxygen reserve at the alveolar level to allow for the laryngoscopy to be performed without desaturation. While this is achieved in the majority of patients undergoing elective surgery, this is not the case in the critically ill.28, 29 Hence, addition of pharyngeal oxygen via a small catheter has been suggested by some but without extensive evaluation in critically ill patients. In ASA status 1 or 2 patients undergoing elective surgery, Teller et al evaluated the benefit of administering a 3-L oxygen flow via a nasal catheter during apnea. When patients received pharyngeal oxygen insufflation, saturation never fell below 97% during the entire 10-min apnea period and mean lowest oxygen saturation was 98%. In the absence of oxygen supplementation, apnea was considerably shortened to 6.8 minutes and lowest mean oxygen saturation was only 91%.35 Similar findings were reported by Taha et al. in ASA 1 or 2 patients, randomized to receive either 5L/min oxygen via a nasopharyngeal catheter or no oxygen. In the latter group, SpO₂ fell to 95% within a mean apnea time of 3.65 minutes, whereas in the supplemental oxygen group, SpO₂ was maintained in all patients at 100% throughout the 6 min of apnea.36 These results were reproduced in obese patients where nasal oxygen supplementation prolonged apnea time without desaturation.37 Of note, these studies were performed in the OR, and their results may not be fully reproducible in the ICU setting.

What is the purpose of administering oxygen at the pharyngeal level in the absence of respiratory movement? The answer lies in the concept of apneic oxygenation described decades ago by Draper et al.38 and named at the time, diffusion respiration. During apnea, the constant circulation in the alveolar capillaries of reduced hemoglobin drives oxygen absorption from the alveolus to the capillary blood at a rate of 250 mL oxygen/minute. This causes a decrease in alveolar pressure, and creates a pressure gradient between the alveolus and the upper airway which generates a flow of air from the pharynx to the distal airway. If this air is enriched in oxygen, apneic oxygenation occurs. This phenomenon first described in dogs38 was confirmed in patients undergo-
ing elective surgery. In a famous study, Frumin et al. showed that patients could sustain a prolonged period of apnea (up to 55 min) without desaturating providing an adequate oxygen supply at the upper airway. Key determinants for effective apnea oxygenation to occur are the following: adequate circulation, adequate and constant supply of fresh oxygen, patent upper airway. Subsequent studies have highlighted some of these key factors. If, for example, oxygen is replaced by room air, then arterial oxygen partial pressure decreases very rapidly.

Table I summarizes the recent studies that aimed at preventing desaturation during laryngoscopy outside the OR, all based on the principle of apneic oxygenation except for the use of NIV in the study by Baillard et al. In our study, oxygen saturation remained stable during the first minutes of the procedure in the high flow oxygen group, which was not the case in the conventional preoxygenation group, suggesting that some form of apneic oxygenation occurred. This was not the case in the Vourc’h study, since there was no difference in the lowest saturation between the two groups (conventional preoxygenation and high flow oxygen).

<table>
<thead>
<tr>
<th>Study first authors, year of publication</th>
<th>Study design, setting, N. of patients</th>
<th>Comparators (number of patients per group)</th>
<th>Main outcome measure</th>
<th>Number of patients with desaturation &lt;80% (or % of pts)</th>
<th>Comments</th>
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<tr>
<td>Baillard, 2005</td>
<td>Open label, randomized trial ICU, 53 patients</td>
<td>– NIV (26) – Bagvalve (27)</td>
<td>Lowest SpO₂: NIV: 93% Bagvalve: 81%</td>
<td>NIV: 2 Bagvalve: 12</td>
<td>All patients with NIV contraindications excluded; no oxygen supply during laryngoscopy</td>
</tr>
<tr>
<td>Miguel-Montanes, 2015</td>
<td>Quasi-experimental sequential study, ICU, 101 patients</td>
<td>– High flow nasal O₂ (51) – High FiO₂ facemask (50)</td>
<td>Lowest SpO₂: High flow: 99% Facemask: 94%</td>
<td>High flow: 1 Facemask: 7</td>
<td>Non randomized, severe hypoxemic patients not included (already preoxygenated with high flow nasal O₂)</td>
</tr>
<tr>
<td>Vourc’h, 2015</td>
<td>RCT ICU, 119 patients</td>
<td>– High flow nasal O₂ (62) – High FiO₂ facemask (57)</td>
<td>Lowest SpO₂: High flow: 91.5 Facemask: 89.5</td>
<td>High flow: 16 Facemask: 13</td>
<td>No evidence of upper airway patency (no mention of jaw thrust)</td>
</tr>
<tr>
<td>Wimalasena, 2015</td>
<td>Retrospective, before after Out-of-hospital, 728 patients</td>
<td>– nasal O₂ (15L/min) (310) – No oxygen (418)</td>
<td>% patients with SpO₂ below 93% (any time): nasal O₂: 16.5 No oxygen: 22.6</td>
<td>Nasal O₂: 12 No O₂: 18</td>
<td>Retrospective, recordings of SpO₂ were reported by clinicians (no direct readings from stored data)</td>
</tr>
<tr>
<td>Semler, 2015</td>
<td>Open label, randomized trial ICU, 150</td>
<td>– Nasal O₂ (15L/min) (77) – No oxygen (73)</td>
<td>Lowest SpO₂ nasal O₂: 92% no O₂: 90%</td>
<td>Nasal O₂: 4% No O₂: 18%</td>
<td>No evidence of upper airway patency (no mention of jaw thrust); not really “high” flow (only 15 L/min)</td>
</tr>
<tr>
<td>Sakles, 2016</td>
<td>Observational before, after study, emergency department, 127</td>
<td>– Nasal O₂ (15L/min) (72) – No oxygen (55)</td>
<td>% patients with SpO₂ below 90% – nasal O₂: 7% – no O₂: 29%</td>
<td>Nasal O₂: 4% No O₂: 18%</td>
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</table>

Table I.—Interventions to prevent desaturation during emergent intubation outside the operating room.
et al., nor in the study by Semler et al. Jaw thrust was not part of their procedure, or at least not mentioned as such. One can therefore hypothesize that a certain degree of pharyngeal obstruction may have occurred, explaining why high flow oxygen was not superior to either low flow, or no oxygen. Second, Semler et al. used only 15 L/min oxygen in their interventional group. This is clearly not “high” flow, in comparison with the 60 L/min that can be achieved with the high flow nasal cannula devices. Again, combined with the absence of jaw thrust, one can easily imagine that apneic oxygenation did not occur. Outside the ICU, two studies recently reported results of the implementation of apneic oxygenation in a rapid sequence induction intubation protocol (Table I). Both studies found that implementing 15 L/min supplemental oxygen via nasal cannula during laryngoscopy significantly reduced incidence of desaturation during intubation of either intracranial haemorrhage patients in the emergency department, or of out-of-hospital patients. These results contradict those of Semler et al. despite the use of the same oxygen flow. Taken together, there does seem to exist a benefit in apneic oxygenation and in the use of high flow oxygen. Further studies are warranted to confirm these beneficial effects. Table II summarizes strengths and limits of NIV and high flow nasal oxygen when used to preoxygenate patients in the ICU.

**Future studies**

As mentioned above, NIV has been shown to improve preoxygenation in patients with acute respiratory failure. Such improvement was also seen in some but not all studies using high flow nasal oxygen in comparison with standard preoxygenation. Given the recent results regarding high flow nasal oxygen and NIV in patients with acute respiratory failure, the question arises as to how high flow oxygen compares with NIV to prevent desaturation during preoxygenation in patients with acute hypoxemic respiratory failure. A large multicenter RCT (Florali2) will randomize patients who require urgent intubation in the ICU either to high flow nasal oxygen or to NIV to ensure preoxygenation (NCT02668458). Another study, comparing use of NIV alone to NIV plus high flow to ensure oxygenation during intubation is currently recruiting patients (NCT02530957).

**Take home message**

A practical approach to preoxygenation is provided in Figure 1, based on patient severity and type of oxygen support present at the time.

**Table II.—Comparison of NIV and high flow nasal oxygen during preoxygenation.**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Limits</th>
<th>Settings</th>
</tr>
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<tbody>
<tr>
<td>Noninvasive ventilation</td>
<td>Positive pressure allowing alveolar recruitment</td>
<td>Several contraindications (coma, agitation, uncooperative patient, contraindications to NIV)</td>
</tr>
<tr>
<td></td>
<td>Strong evidence from one randomized study</td>
<td>Risk of gastric distension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No oxygen during laryngoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results not replicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generalizability?</td>
</tr>
<tr>
<td>High flow nasal oxygen</td>
<td>Simplicity of use</td>
<td>Discrepant results between studies</td>
</tr>
<tr>
<td></td>
<td>Feasibility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allows pursuit of oxygenation during laryngoscopy providing apneic oxygenation</td>
<td>Limited alveolar recruitment</td>
</tr>
<tr>
<td></td>
<td>Same device kept from patient admission to intubation</td>
<td></td>
</tr>
</tbody>
</table>
HAZARDS OF INTUBATION IN THE ICU

Figure 1.—Pragmatic algorithm of intubation in the ICU.

1NIV: noninvasive ventilation; 
2using the MACOCHA Scale.

of the decision to intubate the patient. Although one may argue that patients with acute respiratory failure should no longer be managed with a high FiO2 facemask given the accumulating data showing the superiority of high flow oxygen, we decided to keep the facemask in the algorithm because indication for intubation may be governed by non-respiratory reasons. We also acknowledge the fact that there is discrepant findings regarding high flow oxygen, at least in the more hypoxemic patients, and that to date, no study has compared high flow oxygen to NIV. Hopefully, this algorithm will be simplified when the above-mentioned studies will have been conducted.

Conclusions

Life threatening hypoxemia is the most frequent reported complication of intubation in the ICU. These desaturations occur during apnea and despite properly preoxygenation. Thus improving peraryngoscopy oxygenation is a crucial step to reduce morbidity of urgent tracheal intubation in the ICU. Because high flow oxygen is becoming the first line ventilatory support for acute respiratory failure, it should be initiate right from ICU admission (and perhaps before in the ED) and for practical reasons, can be easily maintained if patient requires intubation. Future studies will provide insight into which will require NIV, and those that might even require both: preoxygenation with NIV and apneic oxygenation with high flow oxygen.

Key messages

— Life-threatening desaturation is a frequent complication of intubation in criti-
cally ill patients in the intensive care unit despite appropriate preoxygenation.

— Alternatives to conventional preoxygenation are warranted to prevent these profound desaturations from occurring and noninvasive ventilation and high flow nasal oxygen may contribute to improve preoxygenation and limit these desaturations.

— High flow nasal oxygen has the additional benefit of providing apneic oxygenation during rapid sequence induction although discrepant results have been reported that highlight the determinants of apneic oxygenation.

— When using high flow nasal oxygen to preoxygenate patients requiring intubation, jaw thrust must be performed to ensure patent airway and high oxygen flow rates should be used.

References


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Fluid therapy has always been considered a cornerstone of perioperative and critical care medicine. Doubtless, hypovolemia and the consequent end-organ hypoperfusion can lead to fatal complications in surgical and/or intensive care unit (ICU) patients and, accordingly, are to be avoided. On the other hand, there is increasing evidence that an excessive administration of fluids may negatively affect survival in critically ill patients. Fluid overload was associated with increased mortality in different ICU settings \(^1\)\(^-\)\(^3\) and, in particular, in patients with acute kidney injury (AKI).\(^4\)\(^-\)\(^10\) Furthermore, the use of some kinds of fluids (particularly synthetic colloids), regardless of the volume, has been shown to increase both mortality \(^11\) and the risk for renal replacement therapy (RRT) need (Table 1).\(^12\)\(^-\)\(^16\) Finally, it has long been known that colloids cause a dose-dependent impairment of coagulation, although to a different extent depending on the different molecules.\(^17\) The type of fluids used in the ICU varies widely among different countries. Until a few years ago, in Europe colloids were used for fluid resuscitation much more than in USA and
New Zealand, where the use of crystalloids is largely predominant. Moreover, hydroxyethyl starches (HES), a family of modified maize- or potato-derived polysaccharides which vary in their molecular weight and mean number of hydroxyethyl residues per glucose unit (the so-called molar substitution), were the most used among colloids in some European countries, including France, Denmark and Italy, and were also widely used, along with gelatins, in other countries such as the United Kingdom and Germany. In the last few years, however, HES solutions were withdrawn from the market and then re-introduced with many restrictions. Fearing that clinicians could replace HES with gelatins for those clinical conditions for which HES solutions are now contraindicated, we want to warn them that the same safety concerns that led to restrict the use of HES are likely to apply also to gelatins, the use of which should be accordingly discouraged.

### Table I.—Main clinical investigations reporting major adverse effects of either hydroxyethyl starches (HES) or gelatins. Crystalloid/colloid ratios are also indicated when available.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Population</th>
<th>N.</th>
<th>Colloid</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunkhorst et al. (VISEP) 13</td>
<td>RCT</td>
<td>Severe sepsis</td>
<td>537</td>
<td>HES 200/0.5</td>
<td>Ringer lactate</td>
</tr>
<tr>
<td>Perner et al. (6S) 11</td>
<td>RCT</td>
<td>Severe sepsis</td>
<td>804</td>
<td>HES 130/0.42</td>
<td>Ringer acetate</td>
</tr>
<tr>
<td>Myburgh et al. (CHEST) 12</td>
<td>RCT</td>
<td>General ICU</td>
<td>7000</td>
<td>HES 130/0.4</td>
<td>0.9% NaCl</td>
</tr>
<tr>
<td>Bayer et al. 15</td>
<td>Sequential observational study</td>
<td>Severe sepsis</td>
<td>1046</td>
<td>4% gelatin</td>
<td>Crystalloids</td>
</tr>
<tr>
<td>Thomas-Rueddel et al. 16</td>
<td>Meta-analysis</td>
<td>Critically ill, trauma, emergency, or elective surgery patients</td>
<td>3275</td>
<td>Gelatins</td>
<td>Crystalloids or albumin</td>
</tr>
<tr>
<td>Bayer et al. 14</td>
<td>Sequential observational study</td>
<td>Cardiac surgery</td>
<td>6478</td>
<td>4% gelatin</td>
<td>Crystalloids</td>
</tr>
</tbody>
</table>

Statistically significant differences are reported in italics. RCT: randomized controlled trials; ICU: intensive care unit; AKI: acute kidney injury; RRT: renal replacement therapy; RBC: red blood cells; FFP: fresh frozen plasma; RR: relative risk; CI: confidence interval; OR: odds ratio. *Multiple logistic regression analysis.
The risk of infusing gelatin

[CI] 1.01-1.36; P=0.03). The CHEST Trial, in which 7000 ICU patients (mostly surgical or septic) were randomized to receive the same volume of either 6% HES 130/0.4 or 0.9% sodium chloride (NaCl) for fluid resuscitation for 90 days after randomization or until ICU discharge or death, is the largest blinded RCT on fluid therapy performed so far. Although it failed to show any difference in mortality (most likely because the amounts of toxic fluids were smaller than in previous studies), its key finding was a significantly increased RRT rate in the HES group as compared with the NaCl group (7 vs. 5.8%, P=0.04). Moreover, post-hoc analyses showed a significant increase in serum creatinine levels during the first week and a significantly reduced overall urine output in the HES group as compared with the NaCl group (P=0.004 and P=0.003, respectively).

After a few months, HES was back in our hospitals, but with many more restrictions than indications. According to the EMA resolution, the use of HES solutions should be now only limited to “the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient”, while it is contraindicated in sepsis, burns, critically ill patients, patients with renal impairment or on RRT, and patients with severe coagulopathy. In the same period, also in USA the Food and Drug Administration (FDA) released a “boxed warning” with similar restrictions.

Several subsequent meta-analyses confirmed an increased risk of AKI, RRT, red blood cell (RBC) transfusions, and mortality with HES administration, confirming that in ICU patients, especially those with sepsis, risks likely outweigh benefits also with “modern” HES solutions.

The use of synthetic colloids for fluid resuscitation...
citation in ICU patients was already progressively decreasing in some countries, such as Australia and New Zealand, primarily due to a decreased use of gelatins and an increased use of buffered crystalloid solutions. However, unlike in USA and Australia, HES was widely used in Europe and, in particular, in Italy, where many physicians believed that synthetic colloids have a much greater volume-expansion effect than crystalloids, and are thus indispensable when volume expansion is urgently needed. According to this rather ingrained belief (which is probably a misconception), and practically deprived of HES, European anesthesiologists and intensivists might be tempted to rely once again on the “old” gelatins. They should not.

Colloids are better: reality or misconception?

Due to their longer persistence in the intravascular compartment, colloids are traditionally believed to be more effective than crystalloids as plasma volume expanders. Accordingly, they theoretically allow clinicians to achieve certain hemodynamic goals with a lower amount of fluids, thus potentially minimize the risk of volume overload and tissue edema. In most RCTs of fluid therapy, however, the total volume of fluids administered in the crystalloid groups was only slightly higher than in the colloid groups, and the colloid:crystalloid ratio was never higher than 1:1.5, 12, 13, 34-36 very far from the 1:4 ratio typically taught in medical schools (see Table I). The total amount of fluids administered was even not different between groups in the “6S” trial. Similar results were found by Bayer et al. in two sequential analysis observational studies involving 6478 patients undergoing cardiac surgery 14 and 1046 patients with severe sepsis, 15 respectively. Both investigations reported a colloid:crystalloid ratio of 1:1.4 for HES and, remarkably, of 1:1.1 for gelatin, suggesting that the supposed advantage of colloids in terms of fluid balance is very modest, and even less prominent for gelatins. Moreover, there was not significant difference in the speed of shock reversal between patients with severe sepsis receiving either colloids or crystalloids.15

Ultimately, if one of the reasons to use synthetic colloids is to minimize the risk of renal impairment (and mortality) which may be associated to fluid overload and interstitial edema, it should be remembered that no large RCT comparing colloids with crystalloids found an increased risk of AKI or mortality with crystalloids. Conversely, as mentioned, most of them showed a higher rate of AKI and/or an increased risk of RRT need in patients receiving HES. After so many years of use, neither the efficacy nor the safety - as discussed in the following sections - of synthetic colloids have been proven, although some authors suggested that this may be due to methodological issues (maybe a clear symptom of how clinicians are fond of these drugs).

Gelatins impair coagulation at least as much as HES

Gelatins are polypeptide molecules deriving from bovine collagen which are available on the market (not in USA) as urea-linked gelatin, succinylated gelatin (modified fluid gelatin, MFG), and oxypolygelatin. In USA, the FDA withdrew the authorization for the clinical use of gelatin solutions as far back as in 1978 due to reduced coagulation and prolonged bleeding time. In fact, in addition to dilutional coagulopathy to which all kind of fluids may contribute, all colloids can specifically affect hemostasis due to an impairment of both coagulation (decreased von Willebrand and VIII factors, reduced thrombus formation, impaired interaction between thrombin and fibrinogen and between factor XIII and fibrin, and reduced clot resistance to fibrinolysis) and platelet function. When compared with HES 130/0.4, gelatins have been found to reduce the strength of the fibrin clot to a lesser extent. However, the final effect is likely similar due to their slightly lower efficacy as volume-expanders. They also cause a more pronounced reduction in von Willebrand and VIII factors.
Moreover, as well as HES solutions, both MFG and urea-linked gelatin solutions seem to inhibit platelet aggregation.

Adverse effects of gelatins on coagulation similar to those of HES solutions are also suggested by the above mentioned sequential studies. Cardiac surgery patients treated with either HES or gelatins received significantly more platelet concentrates than patients treated with crystalloids, although the number of patients who needed RBC transfusions was not different among groups. Most remarkably, septic patients in both synthetic colloid groups (HES and gelatin) received significantly more RBC and fresh frozen plasma transfusions as compared with the crystalloid group. A trend toward an increased exposure to allogeneic transfusion in patients receiving gelatins as compared with patients receiving either crystalloids or albumin was also found in a meta-analysis of 7 RCTs. However, as pointed out by the authors, there was high heterogeneity among the included RCTs, and none of them was adequately powered to assess the rate of relevant outcomes.

Gelatins might be even more nephrotoxic than HES

Synthetic colloids may harm the kidney mainly due to osmotic nephrosis, consisting in cellular vacuolization and swelling in the proximal tubules, probably following pinocytosis, and storage into vacuoles, of filtered colloid molecules. Unfortunately, the potential renal toxicity of gelatins has never been studied in adequate RCTs (probably because it is much less used than “modern” HES solutions among synthetic colloids). However, two animal studies found more severe renal injury with 4% gelatin as compared with 6% HES 130/0.4-0.42 in experimental models of sepsis and shock. In particular, Simon et al. found a significant increase in osmotic nephrosis-like renal lesions with gelatin as compared with HES in a swine model of shock. These findings are consistent with those of a recent small RCT comparing the renal effects of 4% gelatin and 6% HES 130/0.4 in 36 patients undergoing elective living-donor liver transplantation. Postoperative creatinine levels were significantly higher as compared to baseline in the gelatin group but not in the HES group. Moreover, postoperative estimated glomerular filtration rate was significantly lower and postoperative urine albumin:creatinine ratio was significantly higher, as compared to preoperative values, in the gelatin group. Stage 1 AKI occurred in 5 patients in the gelatin group and in 2 patients in the HES group. Of course, no definitive conclusions can be drawn from this study.

Thus, if renal adverse effects of gelatins are not worse than those of HES, they are most probably similar. In the sequential analyses by Bayer et al., AKI rates and RRT needs were significantly higher in both septic and cardiac surgery patients who received 4% gelatin (as well as in those receiving HES) compared with patients receiving crystalloids in the subsequent periods. Maybe, gelatins are less nephrotoxic only when compared to the “older” HES solutions, as suggested by a multicenter RCT, including 129 patients with severe sepsis, which found a lower rate of acute renal failure and oliguria, and a lower peak of serum creatinine, in patients receiving 3% MFG as compared with HES 200/0.6-0.66.

Gelatins: another toxic and ineffective agent?

Bayer and colleagues found significantly increased in-hospital mortality among cardiac surgery patients who received 4% gelatin as compared with those who received crystalloids for perioperative fluid therapy. After adjustment for several prognostic factors such as age, hypertension, diabetes mellitus, cirrhosis, severe sepsis or septic shock, New York Heart Association class IV, Simplified Acute Physiology Score II, prior myocardial infarction, pulmonary hypertension, cardiopulmonary bypass and aortic cross-clamp time, serum creatinine, and administration of specific drugs (noradrenaline, adrenaline, diuretics, angiotensin-converting-enzyme inhibitors,
non-steroidal anti-inflammatory drugs, some antimicrobials, iodinated contrast media), the odds ratios for in-hospital mortality with 4% gelatin vs. crystalloids were 1.72 (95% CI 1.15-2.58, P=0.008) and 1.40 (95% CI 1.07-1.84, P=0.016) on multiple logistic regression and propensity score stratification, respectively.

A trend toward increased mortality in patients receiving gelatins compared with patients receiving either crystalloids or albumin was also found in a meta-analysis of 10 RCTs. Other investigations found similar mortality rates between fluid therapy with either gelatin or crystalloids in both patients with severe sepsis and critically ill patients. In particular, Perel et al. analyzed 11 RCTs (including 506 patients, overall) and found no statistically significant difference in cumulative mortality between patients receiving modified gelatin or crystalloids (risk ratio 0.91, 95% CI 0.49-1.72). In addition to possibly increasing mortality, gelatins are much more expensive than crystalloids. According to this consideration alone, their use appears to be unjustified. Moreover, gelatins probably carry a higher risk of anaphylactic reactions as compared to other colloids. This issue became evident soon after their introduction into clinical practice. There are many reports in literature of perioperative (or periprocedural) severe anaphylactic reactions due to the administration of intravenous gelatins, with fatal events reported also very recently. Another reason (if it is really needed) to avoid them.

Conclusions

In conclusion, the era of artificial colloids is coming to an end. It is likely that history of medicine will reflect in amazement on how doctors decided to give extracts of either corn or potatoes (starches) or extracts of horses’ hooves (gelatins) intravenously to patients, believing that such interventions would be beneficial. Modern evidence-based medicine is clear on this issue: artificial colloids are harmful and cost much more than crystalloids. There is simply no reason to prescribe them.

Key messages

— According to randomized evidence of increased mortality and renal replacement therapy needs, the use of HES solutions has been recently highly restricted by the European Medicines Agency with, in practice, many more contraindications than indications.

— Since synthetic colloids are still believed to be much more effective as volume expanders than crystalloids (but this is probably largely overrated), physicians might be tempted to return to the “old” gelatins in order to replace HES.

— Gelatins impair coagulation at least as much as HES, and may be even more nephrotoxic than HES.

— As compared with crystalloids, gelatins do not improve outcomes of critically ill patients (on the contrary, they might even increase mortality) and are much more expensive. Accordingly, their use should be discouraged.

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A dynamic view of dynamic indices

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ABSTRACT

Dynamic indices (based on cardiopulmonary interactions in mechanically ventilated patients in sinus rhythm) have been developed as simple tools for predicting fluid responsiveness in the absence of cardiac output monitoring. Although the earliest dynamic indices relied on the invasive measurement of pulse pressure variations or stroke volume variations, the most recently developed indices are based on non-invasive photoplethysmography. However, a number of confounding factors have been found which decrease the clinical value of these indices. The present experts’ opinion explains why changes in dynamic indices during hemodynamic maneuvers might be an interesting alternative to using them accurately at bedside.

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Key words: Cardiac output - Hemodynamics - Physiologic monitoring - Plethysmography - Blood pressure - Stroke volume.

Fluid loading remains a major problem in the routine care of critically ill patients and high-risk surgical patients. Most of the approaches currently used are empirical and not evidence-based.1 This is not the case of the mini-fluid challenge,2 the passive leg-raising test (PLR)3 and the end-expiratory occlusion maneuver,4 which are reportedly good predictors of fluid responsiveness when cardiac output monitoring is used, although the last technique is not always available at the bedside.1, 5 Another way of predicting fluid responsiveness involves dynamic indices based on cardiopulmonary interactions in mechanically ventilated patients in sinus rhythm, previously described as the functional hemodynamic monitoring.6 These dynamic indices constitute simple, widely available tools for bedside use with the high-risk surgical patients in the intensive care unit (ICU) or the operating theater. The simplest, most popular tool is pulse pressure variation (PPV) measurement, which was initially described in septic, critically ill patients.7 Thereafter, the stroke volume variation (SVV) has been described as accurately predict fluid responsiveness.8 Recently, some promising
non-invasive approaches (using continuous, non-invasive arterial pressure monitoring\(^9\), \(^{10}\) or the changes in the plethysmographic waveform in mechanically ventilated patients\(^{11}\), \(^{12}\)) have been described. Dynamic indices over static variables are recommended for predicting fluid responsiveness, when applicable.\(^{13}\) However, confounding factors may decrease the clinical value of these dynamic indices.\(^{14}\) A potentially valuable alternative is the dynamic use of dynamic indices, i.e., the use of rapid changes in these indices (PPV, SVV, and changes in the plethysmographic waveform in mechanically ventilated patients) during hemodynamic maneuvers to accurately predict fluid responsiveness without interpretation bias.\(^{15}\)

Hence, the present experts’ opinion seeks to 1) describe the currently available tools and their limitations, 2) develop the “dynamic use of dynamic indices” concept, and 3) explore the perspectives for these techniques.

The currently available dynamic indices

**Invasive PPV**

The PPV was firstly described using the following formula:

\[
\text{PPV} = \frac{(\text{PP}_{\text{max}} - \text{PP}_{\text{min}})}{\frac{1}{2}(\text{PP}_{\text{max}} + \text{PP}_{\text{min}})}
\]

where \(\text{PP}_{\text{max}}\) and \(\text{PP}_{\text{min}}\) represent the maximal and the minimal amplitude of the arterial pulse pressure waveform over one respiratory cycle, respectively.\(^{7}\) The PPV was initially calculated manually over a single respiratory cycle. Using a 60-second moving window, the PPV is now assessed accurately and automatically based on the arterial blood pressure alone, which eliminates the need of simultaneous recording of airway pressure.\(^{16}\)

From a physiological point of view, as the pulse pressure was correlated with stroke volume, PPV could follow the volume changes in arteries. From the free by Aboy,\(^{16}\) several different algorithms of PPV calculation were developed by some manufacturers using different time moving windows and signal interpretation such as extrasystole exclusion.\(^{17}\) Many manufacturers have developed hemodynamic monitors that include PPV in standard bedside monitors (IntelliVue, Phillips Medical Systems, Andover, MA, USA; Carescap, GE Healthcare, WI, USA), and in bedside designed hemodynamic monitors (PulsioFlex and PiCCO\(_2\), both by Pulsion Medical, Munich, Germany; FlocTrac and EV1000, both by Edwards Lifescience, Irvine, CA, USA; LiDCO Rapid/Unity, LiDCO Ltd., Cambridge, England, UK; MostCare, Vytech Health, Laboratoires Pharmaceutiques Vygon, Ecouen, France).

**Non-invasive PPV**

Totally non-invasive measurement systems (based on photoplethysmography) are now offered by some manufacturers (e.g. the ClearSight system by Edwards Lifesciences, the former Nexfin device [BMYe, Amsterdam, the Netherlands], and the CNAP system [CNS Systems Medizintechnik AG, Graz, Austria]). The PPV is averaged over different time moving periods. These automated, plug-and-play devices use a finger sensor connected to a dedicated monitor, which meets the simplified criteria needed at the bedside.\(^{18}\)

**Stroke volume variation**

In addition to PPV, the SVV was introduced as a dynamic preload indicator that is calculated from percentage changes in stroke volume (SV) during ventilatory cycle. Many manufacturers have developed hemodynamic monitors that include SVV (esophageal Doppler monitoring in addition to the devices previously described for PPV). Calculation of SVV is based on the percentage of change between the maximal and minimal SVs divided by the average of the minimum and maximum over a floating period,\(^{8}\) or on the difference between maximal and minimal SVs divided by the average of the minimum and maximum SV over one respiratory cycle.\(^{19}\) SVV was demonstrated to be a good indicator of fluid responsiveness in operating room and ICU.\(^{19, 20}\)
Non-invasive SVV

Totally non-invasive measurement systems (based on photoplethysmography) are now offered by some manufacturers (e.g. the ClearSight system, the former Nexfin device, and the CNAP system).

The delta-POP and the Plethysmographic Variability Index (PVI)

Using usual pulse oximetry sensor, the analysis of changes in the plethysmographic waveform in mechanically ventilated patients has been proposed as a non-invasive alternative to PPV. The delta-POP was firstly described using the following formula:

\[
\text{Delta-POP} = \frac{(\text{POP}_{\text{max}} - \text{POP}_{\text{min}})}{[(\text{POP}_{\text{max}} + \text{POP}_{\text{min}}) \times 0.5]}
\]

where \( \text{POP}_{\text{max}} \) and \( \text{POP}_{\text{min}} \) represent the maximal and the minimal amplitude of the plethysmographic waveform over one respiratory cycle, respectively.\(^\text{11}\) The delta-POP was manually calculated, in contrast with the PVI which is continuously displays for a 2-to-4-minute moving window.\(^\text{12}\) The PVI needs a dedicated monitor (e.g. the Radical 7 by Masimo Corporation, Irvine, CA, USA). A recent meta-analysis showed that delta-POP and PVI are equally effective for predicting fluid responsiveness in mechanically ventilated adult patients in sinus rhythm.\(^\text{21}\)

Limitations of dynamic indices

Limitations that apply to all dynamic indices

Over the last ten years, reports of various limitations have fueled the continuing debate on the clinical value of dynamic indices.\(^\text{22, 23}\)

Firstly, the validity of a dynamic index depends on three mandatory prerequisites: continuous arterial pressure monitoring, a regular sinus rhythm, and mechanical ventilation (i.e. in the absence of spontaneous breathing).\(^\text{7}\) Recent surveys showed that 18% to 42% of critically ill patients met all three criteria.\(^\text{14, 24}\) Secondly, a number of confounding factors may change a dynamic index’s threshold value. Right ventricular dysfunction and intra-abdominal hypertension\(^\text{25}\) may increase the PPV threshold. In contrast, a low tidal volume (<8 mL/kg),\(^\text{26}\) low pulmonary compliance (<30 cm-H\(_2\)O/mL)\(^\text{4}\) and a low heart rate/respiratory rate ratio (<3.6)\(^\text{28}\) may decrease the PPV threshold (Figure 1). Thirdly, changes in the threshold value may explain a wide inconclusive class of response. The proportion of patients in this “gray zone” is reportedly about 25% in the operating theater (with PPV values between 9% and 13%)\(^\text{29}\) and 62% in the ICU (with PPV values between 4 and 17%).\(^\text{30}\) Fourthly, the PPV is difficult to interpret at the bedside. In a recent survey of French anesthesiologists and intensivists (based on clinical vignettes), only 60% of the responders were aware of the three prerequisites for PPV validity, and none was able to interpret the PPV correctly with regard to all the confounding factors.\(^\text{15}\) Lastly, dynamic indices have rarely been evaluated in large, randomized studies, although encouraging results have been reported in studies with a small number of patients and widely differing protocols and optimization targets (mean arterial pressure, Cardiac Index, stroke volume, central venous pressure, central venous oxygen saturation, etc.). In view of this great heterogeneity, the conclusions of a recent meta-analysis may be questionable.\(^\text{31}\)

Although dynamic indices were firstly described as a simple tool for predicting fluid
responsiveness, their application requires a degree of caution. Accordingly, Sondergaard suggested a checklist before using PPV to guide fluid therapy.\textsuperscript{23}

**Specific limitations of non-invasive PPV and SVV measurements**

Few studies have compared non-invasive PPV measurements with the invasive PPV measurements for predicting fluid responsiveness, with controversial results.\textsuperscript{9, 32}

**Specific limitations of delta-POP and PVI**

For example, calculation of the PVI is based on changes in the Perfusion Index (PI; the ratio between the alternating current and the direct current components), as follows:

\[
PVI = \frac{P_{\text{max}} - P_{\text{min}}}{P_{\text{max}}}
\]

where \(P_{\text{max}}\) and \(P_{\text{min}}\) represent the maximal and the minimal amplitude of the plethysmographic waveform over one respiratory cycle, respectively.\textsuperscript{12} This equation explains two limitations: 1) small changes in PI can lead to large changes in PVI, and 2) the PI depends on sympathetic vasomotor tone as well as the stroke volume. Precisely, the pulsatile plethysmographic and photo-plethysmographic amplitude is due to pulsatile changes of the arteriolar blood volume into the tissue under the beam. The blood volume pulsations (\(\Delta V\)) are related to the systemic intravascular pulse pressure (\(\Delta P\)) according to the relationship: 

\[
\Delta V = \Delta P \times D,
\]

where \(D\) is the distensibility that is influenced by intravascular volume status and by sympathetic activity directed to the vessels. As demonstrated by Colombo et al., the indices derived from the pulsatile photo-plethysmography are affected by a stimuli that activate the sympathetic branch of the autonomic nervous system.\textsuperscript{33} In this context, a (relative) hypovolemia represent probably only one stimulus among many others. Indeed, pain, hypothermia and vasopressor use can decrease the PVI’s ability to predict fluid responsiveness.\textsuperscript{34} These explanations could explain why the value of using a non-invasive PVI in the ICU is subject to debate.\textsuperscript{34-37} Interestingly, it was recently reported that a forehead sensor could be more accurate than a finger sensor for predicting fluid responsiveness in critically ill patients with high vasomotor tone.\textsuperscript{38}

The dynamic use of dynamic indices

**Efficacy of fluid challenge**

In contrast to changes in arterial pressure components, changes in an invasively measured PPV were able to detect a fluid-challenge-induced increase in cardiac output of more than 15% with good sensitivity and specificity, and with only a small proportion of patients in the “gray zone”.\textsuperscript{39} In view of the relationship between fluid loading and cardiac output, this approach may enable clinicians to proceed with or stop fluid loading accordingly; fractional fluid loading could be guided by changes in the PPV. Of course, this strategy would need to be evaluated in dedicated studies. Encouraging results have been recently described for the PPV- and PLR-based titration of fluid responsiveness in septic patients; guidance with preload dependence indices was associated with a lower daily fluid intake than a control technique based on central venous pressure guidance, and did not worsen the clinical outcome.\textsuperscript{40}

**Mini-fluid challenge**

Recently, a decrease in PPV or SVV during a mini-fluid challenge (infusion of 100 mL of 4% human serum albumin over 60 seconds) was found to accurately predict fluid responsiveness in septic, mechanically ventilated patients with a low tidal volume.\textsuperscript{41} Whereas the baseline PPV and SVV values were not predictive of fluid responsiveness, the change in PPV or SVV induced by the mini-fluid challenge yielded excellent sensitivity and specificity values. The small proportion of patients (12%) in the “gray zone” further emphasized the clinical applicability of the “dynamic use of dynamic indices”. Interestingly, the changes
in PPV or SVV gave better results than changes in continuous cardiac output monitoring (a calibrated pulse contour analysis using the PicCO device). Hence, a strategy based on changes in PPV or SVV would be less invasive than the assessments of fluid responsiveness described above.

**Passive leg raising test**

Although baseline PVI can detect cardiac output changes following PLR in spontaneously breathing volunteers, there are no data on the ability of changes in dynamic indices during PLR to predict fluid responsiveness.

**Future perspectives for dynamic indices**

**Combinations of dynamic indices**

The combination of dynamic indices might increase the predictive value for fluid responsiveness. In a comparative study of three PVI measurement sites, combining the PI and PVI thresholds increased the specificity and the positive and negative predictive values for predicting fluid responsiveness. Further studies are now required for the development of reclassification methods and progressive models (based on various hemodynamic variables and maneuvers) able of safely predicting fluid responsiveness at the bedside.

**Assessment of dynamic arterial elastance**

Encouraging results have been reported for use of the PPV/SVV ratio as a guide to dynamic arterial elastance (Ea\textsubscript{dyn}) in operating theater or ICU, in mechanically ventilated patients or spontaneously breathing patients. Ea\textsubscript{dyn} may constitute a functional approach to arterial tone assessment in the same way as preload responsiveness indices that are used to predict fluid responsiveness to a change in cardiac preload. Ea\textsubscript{dyn} was able to predict the hemodynamic response in mean arterial pressure (MAP) to fluid administration in hypotensive, preload-dependent patients. In surgical patients, Ea\textsubscript{dyn} was found to successfully discriminate responders and non-responders to vasopressor dose de-escalation with volume expansion. In sepsis patients receiving norepinephrine, the Ea\textsubscript{dyn} predict the decrease in arterial pressure following a norepinephrine dose reduction. Finally, Ea\textsubscript{dyn} might constitute an easy-to-use, functional tool for arterial-tone assessment and thus may help to identify patients likely to benefit from vasopressor treatment.

**Right ventricular dysfunction**

PPV could not accurately predict fluid responsiveness in heart surgery patients and septic, critically ill patients with increased pulmonary artery pressure. Patients with right ventricular dysfunction (defined as a peak systolic velocity of tricuspid annular motion <0.15 m/s, as assessed by tissue Doppler echocardiography) may have a higher PPV threshold; if so, this would explain a large proportion of “false-positive” preload-dependent patients. However, the absence of a decrease or indeed an increase in dynamic indices after fluid loading (when the baseline PPV is high) should be considered as an indicator of right ventricular dysfunction. In this context, changes in dynamic indices could usefully indicate the need for echocardiography.

**Conclusions**

According to recent guidelines, dynamic variables (rather than static variables) should be used to predict fluid responsiveness (when applicable), and fluid resuscitation should be guided by monitoring more than one hemodynamic variable. Caution must be used when dynamic indices are used alone (in view of their many limitations). At the bedside, changes in dynamic indices (rather than absolute values) may be more predictive of fluid responsiveness and may thus avoid the effects from confounding factors (i.e. the “gray zone”). Large-scale validation studies are now mandatory for confirming this hypothesis and defining perspectives for the reliable clinical use of dynamic indices.
Key messages

— Dynamic indices were developed to predict fluid responsiveness in mechanically ventilated and sinus rhythm patients. However, caution must be used when dynamic indices are used alone, because of their many confounding factors that may change their cut-off value.

— At the bedside, changes in dynamic indices (rather than absolute values) may be more predictive of fluid responsiveness or efficacy of fluid challenge, and may thus avoid the effects from confounding factors.

— Large-scale validation studies are now mandatory for confirming this hypothesis and defining perspectives for the reliable clinical use of dynamic indices.

References


Conflicts of interest.—Matthieu Biais has receive honoraria as a lecturer from Edwards Lifescience and Pulsion Medical Systems. All other authors declare that they have no conflict of interest regarding the material discussed in this manuscript.

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Near-zero difficult tracheal intubation and tracheal intubation failure: too good to be true

Dear Editor,

We read with interest the article published by Cagnazzi et al. on the successfully implementation of Besta Airway Algorithm in a morbidly obese population, but we would like to point out some concerns about the final message given to the readers of this study:

1. Authors state that there was mandatory need of expert Glidescope (GVL) users for obese patients, and not simply “standard” GVL users. They someway fix expertise level as >20 GVL uses, whereas paper from Cortellazzi et al. clearly identifies in more than 70 uses the minimum learning curve for GVL. This is probably one of reasons why the first attempt success rate reported by Cagnazzi is 87%, that is lower than results reported by Yedemann et al. in a similar population study. This is, in our opinion, a very important point to clarify before implementation of GVL in routine daily practice.

2. Authors use the IDS and a CL >3 as marker of difficult tracheal intubation (DTI), while we think this is a common misunderstanding, first of all because CL grading was designed for direct laryngoscopy and is not automatically adaptable to indirect (“look around the corner”) laryngoscopy, and second because with videolaryngoscopes it is not so rare to observe the “I can see but I can’t intubate scenario”, meaning that intubation could be challenging if not impossible despite a good laryngeal view. On this point of view, using a specific videolaryngoscopy score as that proposed by Freman-Cortellazzi et al. could be more objective, allowing not overestimate the videolaryngoscopy efficacy and thus resulting safer.

3. The incidence of Difficult Mask Ventilation (DMV) was 8% (17 patients), as reported by literature, with transient desaturation in 7 patients (3.2%). We think that this is the main limitation of the proposed Besta Airway Algorithm, since El Ganzouri Risk Index does not predict reliably the DMV: any videolaryngoscope (VLS) algorithm should clearly exclude difficult to ventilate patients taking account that no VLS will ever allow oxygenation/ventilation, which is a mandatory safety issue in predicted difficult airways and an even more important goal for a safe obese airway management.

In conclusion, this interesting study provides us new data on the endless debate about the role of videolaryngo-
scope in difficult airway management, alerting everyone for the need to standardize perioperative strategies in order to guarantee airway safety management particularly for the obese patient. How can we identify and how can we manage the patients with predicted DMV? How can we define expert an operator? Which back-up device should be used in case of GVL failure? These are just some of the questions to be answered by the forthcoming studies.

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Delivered to The Editor

We thank Dr. Corso et al.1 for their comments, which give us the opportunity to clarify some of the results of our study.2

We agree about the importance of adequate training before implementation of Glidescope videolaryngoscope (GVL) in clinical practice. When our study began, the Cortellazzi’s paper3 had not been published yet: we used the CUSUM curve methodology which attests the expert status of the operator4 objectively. The Yedemann study was not powered to detect differences in first time intubation success. In fact, differences in first time intubation success between GVL and Fasttrach were not statistically significant (92% versus 84%, P=0.22). Therefore, it is highly unlikely that the differences between Yedemann results and ours (87%) be significant.

We agree that the use of C&L alone can be misleading. Conversely, the concurrent documentation of C&L, IDS, the device used, and the alternative solutions adopted, provides the same information, if not more, as the Fremanote score, which, to the best of our knowledge, has been evaluated only preliminarily in non-obese simulation settings. The “I can see but I can’t intubate” scenario typically takes place with a “non-expert/non-routine GVL user”. The Besta Airway Algorithm rescue plan consists in not reiterating the intubation attempts,5 oxygenating and awakening the patient: the habit of declaring failure of intubation early on, irrespective of the glottis view, and of moving early to laryngeal mask ventilation, are the pillars of a safe patient awakening. The fact that the videolaryngoscope (VLS) looks ‘around the corner’ implies a better glottis view and a better chance of awakening. The fact that the videolaryngoscope (VLS) looks ‘around the corner’ implies a better glottis view and a better chance of awakening. The fact that the videolaryngoscope (VLS) looks ‘around the corner’ implies a better glottis view and a different technique for intubation but the anatomical structures to describe remain the same. The C&L score simply aids with the classification of the visible structures.

We agree that a strategy to prevent difficult mask ventilation (DMV) has to be put in place but which is the safest way has yet to be established.6 The available predictors for DMV and IMV7 do not reach sufficient accuracy, and hence it is difficult to establish a threshold value without generating a high number of false positives: to schedule these patients for awake-fiberoptic intubation might not be always a feasible nor an adequate approach. In the Besta Airway Algorithm several modalities of DMV/desaturation prevention are implemented, among which the exclusion of patients with neck abnormalities, the awake-fiberoptic intubation, the measure of not reiterating intubation attempts5 and the prompt institution of laryngeal mask ventilation. It goes without saying that VLS does not oxygenate, however, the high probability of an uneventful GVL intubation makes DMV less likely. Six out of the seven transient desaturations described in our study occurred when an orotracheal tube was already rightly positioned and were therefore rapidly corrected. Our results suggest that the Besta Airway Algorithm can be safely implemented in clinical practice. That said, we agree with Corso et al. that every effort to further reduce the risk of DMV should be made and future studies directed at strengthening the induction strategy (e.g. a pharmacological approach for maintaining spontaneous breathing) should be undertaken.

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Dear Editor,

Carbon dioxide (CO₂) peritoneal insufflation is daily-performed for laparoscopy. Intravascular CO₂ entrapment, and subsequent embolization, is clinically apparent in 0.0014-0.6% of the cases, but fatal in 30%.1 Conversely, 5-30% of perioperative complications, often requiring intensive care, occur in ASA physical status I-2 patients.2 We present a case of delayed CO₂ embolism following laparoscopy, manifesting outside the operative theatre. Consent for scientific purposes was obtained with informed consent for anesthesia.

A 61-year-old woman (height 150 cm, weight 45 kg; ASA Score 2) with malignancy and no cardiovascular risk factor underwent laparoscopic right hemicolectomy. No instability ensued during anesthesia induction (2 mg/kg propofol, 2 µg/kg fentanyl) or maintenance (6% desflurane). Atracurium (induction, 0.5 mg/kg; 10 mg boluses, as needed) provided muscle relaxation. CO₂ insufflation was initiated in the supine patient, attaining a 15-mmHg intraabdominal pressure. A Trendelenburg and left lateral decubitus (Durant’s manoeuvre) was maintained for 120 minutes, reaching 35 °C intraoperative esophageal temperature. Neuromuscular blockade was reversed with atropine and neostigmine, and the patient was transferred awake to the recovery room in a 30° head-up position, with ongoing 50 mL/h fluids after receiving 1500 mL intraoperatively.

After 20 minutes the patient became acutely agitated, tachypneic and hypotensive (60/45 mmHg), developing venous congestion, atrial fibrillation (150 beats/min), ECG repolarization abnormalities (Figure 1), and metabolic acidosis (pH 7.22; PaO₂ 100 mmHg; PaCO₂ 32 mmHg; HCO₃⁻ 18 mEq/L; BE -13 mmol/L). Echocardiography showed right ventricular distension, diffuse hypokinesia, and atrial septal leftward bulging but no shunts. Central venous pressure was 15 mmHg. Resuscitation comprised 100% oxygen and intravenous epinephrine infusion (0.1 µg/kg/min). Conditions progressively resolved and epinephrine was discontinued after 3 hours, with normalized ECG, ventricular function, and arterial and central venous pressures. Angiography ruled out coronary disease. Troponin I was mildly elevated (peak 0.26 ng/L) and the patient was discharged 15 days postoperatively with no sequelae.

High solubility and rapid absorption renders CO₂ the most employed gas to induce pneumoperitoneum for laparoscopy. Volume and timing of CO₂ absorption and elimination capacity determine embolism severity, ultimately manifesting as a “gas lock” in the pulmonary circulation, with acute right ventricular afterload mismatch and circulatory collapse. Positive peritoneal pressure may enhance CO₂ entering the circulation through delayed CO₂ embolism: importance of early postoperative surveillance

![Figure 1.—ECG recorded immediately after circulatory collapse, showing atrial fibrillation, diffuse S-T segment depression, markedly in the anterolateral leads, primarily suggesting diffuse sub-endocardial ischemia in the left coronary territory.](image-url)
an injured vessel, whereas portal system gas entrapment is supposed to account for later onset embolization.\(^3\) Paradoxical embolism from a systemic vein has also been described, typically through a patent foramen ovale, but also across physiological intrapulmonary shunts with no evidence of intracardiac shunts.\(^4\)

We speculated that CO\(_2\) initially entered the bloodstream during removal of the resected colon through the small incision with stretched tissues and a CO\(_2\)-pressurized peritoneal cavity. The steep head-down and left lateral decubitus displaced gas predominantly to the right and caudally, determining temporary intravascular entrapment in the portal circulation or, possibly, right ventricular apex, and subsequent pulmonary migration only after the patient was positioned in a 30\(^\circ\) head-up decubitus, explaining later onset presentation.\(^3\)

In conclusion, life-threatening CO\(_2\) embolism may present with delay during early hours following laparoscopy, which emphasizes the critical importance of postoperative surveillance despite minor comorbidities.

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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.

Cervical emphysema and pneumomediastinum due to isolated pharyngeal perforation after blunt trauma

Dear Editor,

Pharyngeal lesion after blunt trauma is a rare occurrence.\(^3\) Nevertheless, early diagnosis is essential in order to prevent life-threatening complications, like retropharyngeal abscess, mediastinitis and airway compromise. In this paper we report our management of a case of hypopharyngeal perforation after blunt trauma.

After a car accident, a 21-year-old man was transferred to the Emergency Department. He reported hitting his head, neck and chest on the steering wheel and windscreen of the car because he did not wear seat belt and the air bags did not open. In the first examination, his vital signs were stable, but he was found to have neck crepitus and shallow abrasions. However, no evidence of penetrating trauma emerged. He suffered from dyspnea, neck pain, odynophagia and hemoptysis. A computed tomography (CT) was performed and it demonstrated cervical emphysema, massive pneumomediastinum and a lesion of the posterior wall of the hypopharynx extending for 2.5 cm, in correspondence of pharyngo-esophageal junction (Figure 1). No foreign bodies were identified nor were other lesions found in the body. A bronchoscopy revealed a normal larynx and tracheobronchial tree. Because of ingransecive cervical emphysema and dyspnea, the patient required endotracheal intubation and the admission to our Intensive Care Unit (ICU). Antibiotic therapy was started and a nasogastric tube was inserted, under laryngoscopy vision, for enteral feeding. Because of the size of the lesion and the involvement of the upper esophagus, we opted for transorally surgical repair. After two days, a neck and chest radiogram revealed reabsorption of air and the patient was successfully extubated and discharged from our ICU without sequelae.

Injury to the pharynx most commonly occurs after instrumentation, such as difficult intubation or head and neck surgery, or foreign body ingestion. Traumatic pharyngeal lesion can be the consequence of a penetrating or blunt trauma; the latter is a very rare cause of pharyengo-esophageal injury (<1%).\(^2\) In our case, as no signs of penetrating trauma were identified, we can speculate that a sudden pressure increase in the pharynx during blunt trauma of the neck might have caused tearing of the posterior hypopharyngeal wall (barotrauma). Alternatively, the hyperextension and flexion of the neck, after fast deceleration, may have pushed the pharyngo-esophageal junction against the

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surgical repair should be considered for large perforation and for tears that extend into the esophagus.  
Matteo VISSANI 1 *, Liana LENTISCHIO 1, Giammichele NICOLETTA 1, Fabrizio PUGLIESE 2 Costanzo FEDELI 3, Raffaele ZAVA 1

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Figure 1.—CT scan of the neck: white arrow indicates the pharyngeal lesion. Note the surrounding cervical emphysema.

cervical spine, thus entrapping the hypopharyngeal wall between the vertebral bodies as hyperextension changed into flexion. In this case, the immediate intubation of the trachea isolated the pharyngeal lesion and prevented further impairment of the airway and prompt antibiotic therapy together with surgical repair avoided mediastinitis. The prognosis of pharyngeal and cervical esophageal injuries depends on many factors, such as associated injuries, shock on admission, mechanism of injury and timing of operation: in our case prognosis was good because of the early detection and treatment of the lesion and the mechanism of injury (blunt trauma). As regards the treatment, conservative management with antibiotics and fasting can be reserved for small perforation (<2 cm) limited to the pharynx while...
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<table>
<thead>
<tr>
<th>Surname</th>
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<tbody>
<tr>
<td>Savoia</td>
<td>Gennaro</td>
<td>11</td>
</tr>
<tr>
<td>Biasucci</td>
<td>Daniele Guerino</td>
<td>11</td>
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<tr>
<td>Camporesi</td>
<td>Enrico Mario</td>
<td>10</td>
</tr>
<tr>
<td>Agrò</td>
<td>Eugenio Felice</td>
<td>9</td>
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<td>Ezzeldin</td>
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<td>Cattano</td>
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