Lactate: An unusually sensitive parameter of ensuing organ failure?

To the Editor:

With interest we read the article on the association among blood lactate levels, Sequential Organ Failure Assessment subscores, and mortality by Jansen et al (1). Their retrospective results indeed suggest blood lactate levels are related to Sequential Organ Failure Assessment scores, particularly during the early phase of an intensive care unit (ICU) stay. Although the findings of Jansen et al are interesting, we would like to raise some concerns.

First, the authors demonstrated differences in outcome based on area under the lactate curve (AUC) between survivors and nonsurvivors. The upper normal lactate limit was defined as 2.0 mmol/L, which was also used to compute the AUC. In survivors (n = 105), the median AUC was 0 for all used lactate values (initial, maximal, total, and mean lactate). In nonsurvivors (n = 29), the median AUC varied between 0 and 0.5, including the AUC of total lactate (AUC, 0.5; interquartile range, 0–2.7). We assume that the units used in this table are days/mmol/L. To understand the real lactate load, we also assumed the median length of stay in the ICU of nonsurvivors equaled the median ICU length of stay of the total population (2.75 days). This means a median total lactate load of only 2.2 mmol/L during 1 day in nonsurvivors. We think it hard to understand these values in relation to the reported differences in clinical outcome. If such a small level above the upper normal limit would mean such a strong difference in outcome, we should consider a large abasement of the normal upper limit. That is unlikely to happen. On the other hand, the AUC might prove to be an extremely sensitive parameter. Indeed, shorter duration of hyperlactemia (“lactime”) (2) and higher lactate clearance (3) are important, but if we overparse lactate as a prognostic parameter, we would neglect the complexity of the origin of lactate both in general and in critically ill patients (4, 5).

Second, Jansen et al described a clinically relevant association in the early phase of ICU stay between failure of the cardiovascular system and lactate-derived parameters. They suggested that hyperlactatemia in critically ill ICU patients illustrates the severity of the initial cardiovascular collapse. This may indicate the presence of hypoperfused organ systems without simultaneous global hypotension (6, 7). However, the Sequential Organ Failure Assessment cardiovascular subscore is not only determined by systolic blood pressure (mm Hg), but also by the use of vasopressors (in μg/kg/min). The difference in use of vasopressors between survivors and nonsurvivors is not obvious from the presented data. This is unfortunate, because others have prospectively shown that patients with higher lactate clearance had favorable outcome but with inconsistent differences in either the use of vasopressors in survivors compared with nonsurvivors or patient assigned to standard therapy or early goal-directed therapy (3, 8). We agree with the authors that prospective studies are needed to improve insight in the causal relationship between hyperlactemia and individual organ dysfunction. The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We would like to thank Dr. Van Beest and colleagues for their comments (1). The parameter Mean LactateAUC−2 provides the best estimate of the mean lactate load per day. It is correct that the median value for this lactate parameter of 0.2 days/mmol/L in nonsurvivors can be interpreted as a lactate load of 2.2 mmol/L per day. However, we believe that conclusions on the appropriateness of the upper normal cutoff level cannot be drawn on the basis of comparing median values (we did not use mean value because LactateAUC−2 was not normally distributed) between survivors and nonsurvivors. The area under the receiver operating characteristic (AUROC) curve of Mean LactateAUC−2 for 28-day mortality was only 0.64 (95% confidence interval, 0.51–0.77). We therefore agree with Dr. Van Beest et al that the prognostic value of lactate should not be overrated and that the complexity of its origin in critically ill patients should not be neglected (2). This is reflected by the stronger relationship between hyperlactatemia and the respiratory and coagulation Sequential Organ Failure Assessment (SOFA) subscores than with the cardiovascular subscore.

Nonsurvivors were more frequently treated with vasoactive medication as 66% (19 of 29) of the nonsurvivors required vasopressors or inotropes at least once during their intensive care unit stay (maximal cardiovascular SOFA subscore of 2 for 28-day mortality was only 0.64 (95% confidence interval, 0.51–0.77). We therefore agree with Dr. Van Beest et al that the prognostic value of lactate should not be overrated and that the complexity of its origin in critically ill patients should not be neglected (2). This is reflected by the stronger relationship between hyperlactatemia and the respiratory and coagulation Sequential Organ Failure Assessment (SOFA) subscores than with the cardiovascular subscore.

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of 2) as opposed to 35% (37 of 105) in survivors ($p = .005$). Forty-five percent (13 of 29) of the nonsurvivors required vasopressors or inotropic agents during the first day (initial cardiovascular SOFA score of 2) as opposed to 30% (32 of 105) in survivors ($p = .18$).

The authors have not disclosed any potential conflicts of interest.

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Corticosteroids and the original vasopressin and septic shock trial subgroups

To the Editor:

The article by Russell et al (1) entitled “Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock” represents a post hoc subgroup analysis of the Vasopressin and Septic Shock Trial, which attempts to clarify the interaction of vasopressin and corticosteroids in septic shock. In the earlier publication of the Vasopressin and Septic Shock Trial results published last year, patients with less severe shock (norepinephrine requirements >5 μg/min but <15 μg/min) treated with vasopressin (up to 0.03 units/min) had significantly lower 28-day and 90-day mortality rates when compared to patients treated with norepinephrine alone (2). By contrast, vasopressin had no effect on mortality in patients with more severe shock (norepinephrine requirements greater than 15 μg/min). Because these less and more severe shock groups were identified a priori and patients in these two groups were randomized independently, the original report appeared to provide high-quality evidence supporting the use of vasopressin in patients with less severe shock (3). In the current article, however, this evidence appears refuted by the post hoc analysis presented. In particular, the results of the current article suggest a benefit of vasopressin only in the subgroup of patients treated with steroids, who were also more likely to be in the more severe shock group. Conversely, the patients who were not treated with steroids, and who were also more likely to be in less severe shock group, had an increased mortality with vasopressin. The present results thus appear to contradict those of the original report. Perhaps, this striking inconsistency would be clarified if the present post hoc analysis also included the a priori subgroup stratification of the original report. Notably, this central paradox is not discussed in either the discussion of the present report or the editorial by Annane (4), who concluded that the data supported the use of corticosteroids and vasopressin only in patients with more severe shock. Clearly, the results of the present report suggest that the interaction of vasopressin and corticosteroids should be examined in a randomized trial, as suggested, and we agree with both the authors and Annane that a randomized trial with multifactorial design is needed to answer this more complex question. We would add, however, based on the previously reported Vasopressin and Septic Shock Trial results, that the factorial design should again include a priori stratification of patients with more severe vs. less severe shock.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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The authors reply:

Thank you to Southard and Boyle, whose main point is that there appears to be an inconsistency between the results of Vasopressin and Septic Shock Trial (1) for use of vasopressin vs. norepinephrine in less and more severe shock subgroups. In the current article, we compared the interaction of vasopressin and corticosteroids (2), because more patients who received corticosteroids were in the more severe shock subgroup. We report the overlap of severity of shock, use of corticosteroids, and 28-day mortality in Vasopressin and Septic Shock Trial (Table 1).

We evaluated the interaction between treatment group (vasopressin vs. norepinephrine) and use or nonuse of corticosteroids on mortality in the less and more severe shock subgroups separately. There was a significant interaction in the severe shock subgroup ($p = .03$), and a trend to a significant interaction in the more severe shock subgroup ($p = .06$).

Therefore, there is no marked inconsistency between these two subgroup results; the only significant difference in mortality was between patients treated with vasopressin compared to norepinephrine in the less severe subgroup who also received corticosteroids. As Southard and Boyle indicate, post hoc analyses must be interpreted cautiously, especially when some subgroups have a small sample size.

Interestingly, vasopressin levels tended to be higher in both less and more severe shock subgroups treated with corticosteroids: less severe shock group had a median of 6 hrs of 56.0 vs. 79.5 pmol/L (no corticosteroids vs. corticosteroids, $p = .10$) and at 24 hrs of 45.5 vs. 95.9 pmol/L ($p = .11$); more severe shock group had a median at 6 hrs of 37.2 vs. 75.7 pmol/L ($p = .04$) and at 24 hrs of 72.6 vs. 100.3 pmol/L ($p = .31$). However, the number of patients in each subgroup is low; therefore, only one result achieved statistical significance.

Other investigators have reported similar findings. Bauer et al (3) found a positive interaction of vasopressin and corticosteroids in a nonrandomized cohort of patients with septic shock, all of whom received vasopressin. Patients who received corticosteroids and vasopressin had lower mortality rates (47.6% vs. 80.9%; $p = .02$) compared with patients who did not receive corticosteroids with vasopressin. Furthermore, a randomized, blinded, placebo-controlled trial (n =
100) of vasopressin plus corticosteroids or placebo in human cardiac arrest found a beneficial interaction of vasopressin and corticosteroids (4). Patients who received vasopressin plus corticosteroids had more frequent return of spontaneous circulation (81% vs. 52%; \( p = .003 \)) and higher survival rates (19% vs. 4%, \( p = .02 \)) than patients who received vasopressin plus placebo.

The mechanisms of the vasopressin/corticosteroid interaction remain unclear (2). Additional recent studies have shown that vasopressin increases levels of adrenal corticotropic hormone and corticosterone (5).

The authors have not disclosed any potential conflicts of interest.

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Point-of-care glucose measurement systems should be used with great caution in critically ill intensive care unit patients

To the Editor:

Meynaar et al assessed the accuracy of the AccuChek point-of-care glucose measurement system in the intensive care unit (ICU) setting (1). The authors conclude that the AccuChek glucose measurement in whole blood with a correction factor has acceptable accuracy for use in ICU patients. We recently demonstrated that the AccuChek (using plasma referenced test strips) failed the International Organization for Standardization (ISO) criteria in our study in >13% of samples (2). The ICU population that was studied by Meynaar et al had lower Acute Physiology and Chronic Health Evaluation II scores on hospital admission compared to our study (17.8 ± 6.7 vs. 21.0 [16–25]) and included a higher number of surgical patients (47% vs. 16%). Because patients with inaccurate glucose values had a higher disease severity score and mortality, the discrepancy between the results found by Meynaar and our study group may be related to the less severely ill study population. This is supported by the fact that in the same study the AccuChek was highly accurate in non-ICU patients (2.5% inaccurate samples according to ISO standards). Because we found different accuracy levels for the same test device between different populations, it is seems likely that the confounding factor is patient related.

The authors suggest that with the use of a correction factor the values obtained with the AccuChek have an acceptable accuracy for use in critically ill patients. Correction results in a better comparability between laboratory and AccuChek measurements but the results still do not meet the ISO criteria. In addition, using the correction factor, the number of AccuChek values higher than the reference values increased from 3.4% to 14.2%. The increased number of falsely elevated glucose values will result in a higher incidence of misinterpretation of high glucose values with subsequent inappropriate insulin administration or masking of true hypoglycemia. Iatrogenic hypoglycemia, which is difficult to detect in patients who are intubated and sedated, is a major risk using tight glycemic control protocols and associated with increased mortality (3). The AccuChek should be used with great caution in critically ill ICU patients, especially when aiming at tight glucose control.

The authors have not disclosed any potential conflicts of interest.

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The authors reply:

We thank Dr. Hoedemaekers and colleagues for their critical appraisal of our study, pointing out that the AccuChek point-of-care glucose measurement system should be used cautiously in critically ill patients. Although the critical care community has put major efforts in
stressing the importance of achieving tight glycemic control over recent years, the accurate measurement of glucose is still an underresearched area.

Dr. Hoedemaekers et al in their study found the AccuChek to be less accurate than we did (1, 2). International Organization for Standardization (ISO) 15197 guidelines require at least 95% of the point-of-care measurements to deviate no more than 20% from the reference if the reference is ≥75 mg/dL or to deviate no more than 15 mg/dL if the reference is <75 mg/dL. In the study by Dr. Hoedemaekers et al, 13.7% of measurements failed to meet ISO criteria, whereas in our study 5.9% of measurements were outside the ISO range if a serum calibration was used and 9.6% if a whole blood calibration was used.

First, let us look at the calibration matter. Point-of-care measurements are done in whole blood whereas the reference is glucose as measured in serum. To have results of the AccuChek reflect more accurately the serum results, the manufacturer decided to use a correction factor of 1.080 to convert whole blood results into “serum-like” results. This was implemented worldwide with the “serum calibrated test strip” only in our unit and after the study was performed. So, to judge the AccuChek, we should study the “serum-like” results, not the whole blood results. The factor of 1.080 as implemented by Roche was almost exactly the same as the 1.086 that we calculated from our results; so, we regarded the corrected results or [(whole blood result) × 1.086] as the serum-like result. Also, our study justifies the correction factor as applied by the manufacturer.

Second, let us look at the calibration matter. Point-of-care measurements are done in whole blood whereas the reference is glucose as measured in serum. To have results of the AccuChek reflect more accurately the serum results, the manufacturer decided to use a correction factor of 1.080 to convert whole blood results into “serum-like” results. This was implemented worldwide with the “serum calibrated test strip” only in our unit and after the study was performed. So, to judge the AccuChek, we should study the “serum-like” results, not the whole blood results. The factor of 1.080 as implemented by Roche was almost exactly the same as the 1.086 that we calculated from our results; so, we regarded the corrected results or [(whole blood result) × 1.086] as the serum-like result. Also, our study justifies the correction factor as applied by the manufacturer.

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Therapeutic effects of erythropoietin in murine models of endotoxin shock

To the Editor:

We read with great interest the article by Aoshiba et al (1) about the therapeutic effects of erythropoietin in murine models of endotoxin shock. The authors indicate that their report is the first to document the beneficial effects of erythropoietin in experimental endotoxin shock, exploring a new avenue of erythropoietin use in the intensive care unit beyond its use for correction of anemia. Their study demonstrates that erythropoietin in endotoxin-exposed BALB/c mice significantly reduces apoptotic cell death, liver enzyme release, and renal and hepatic tissue hypoxia (1). In fact, these results confirm the results of a previous study of our group, demonstrating in endotoxin-exposed C57BL/6J mice that the long-acting erythropoietin analogue darbepoetin-alpha reduces hepatic microvascular perfusion failure, liver enzyme release, and apoptotic as well as necrotic cell death (2). Aoshiba et al further demonstrate that erythropoietin reduces the lipopolysaccharide (LPS)-associated increase of inducible nitric oxide synthase (iNOS) expression, nitric oxide production and peroxynitrite formation (1). They speculate that the increased iNOS after LPS produces large amounts of nitric oxide, which contribute to injury and mortality by causing hypotension, leading to tissue hypoperfusion and hypoxia. They hypothesize that the inhibition of iNOS-mediated nitric oxide production by erythropoietin may have attenuated the LPS-mediated tissue hypoxia (1).

We feel that a further aspect of the pleiotropic erythropoietin actions should be considered for interpreting these results. Beside inhibition of iNOS, erythropoietins are well known to induce expression of endothelial nitric oxide synthase (eNOS) (3). eNOS has been shown to act highly beneficial in pathologic conditions such as ischemia-reperfusion, chronic tissue hypoxia, hemorrhage-induced vasospasm, microvascular thrombus formation, and peri-hematomal inflammation. This protection is attributable to reverse of arterial spasm (4), arteriolar dilation (5), and improvement of capillary perfusion (6), resulting in an increase of tissue oxygenation (6). Because microcirculatory dysfunction and tissue hypoxia in sepsis-associated organ failure is not primarily caused by a generalized hypotension but by a heterogeneous capillary perfusion failure attributable to dysfunction of vasomotor control, recovery of the regulatory mechanisms of the microcirculation by eNOS-mediated nitric oxide may have contributed to the protection achieved by erythropoietin also after LPS exposure. This view is supported by the results of the aforementioned study, demonstrating...
Cytomegalovirus reactivation in the intensive care unit: Not a cause of late-onset ventilator-associated pneumonia

To the Editor:
I read with interest the study by Chiche et al on cytomegalovirus (CMV) reactivation of in ventilated intensive care unit (ICU) patients, and several points merit comment (1).

CMV is a herpes virus characterized by survivability with intact cell-mediated immunity (CMI) and latency until reactivated if CMI wanes. Until reactivated, CMV resides in lymphocytes. CMV polymerase chain reaction and antigen assays detect lymphocyte reactivation. CMV antigenemia in the ICU may be a marker for immunosuppression. Mechanical ventilation is sufficiently stressful to transiently impair CMI and permit CMV reactivation. Importantly, CMV reactivation lymphocytes are not synonymous with clinical infection (2, 3). Primary or reactivation CMV infection usually involves the lung, e.g., pneumonia. Prolonged ventilator day/complications noted in CMV antigen-positive patients in the Chiche study are best regarded as a marker of impaired CMI/comorbidity in ICU patients (1).

CMV, like Herpes simplex virus-1 (HSV-1), may reactivate in ventilated patients. Unlike CMV, HSV-1 reactivation manifests as late-onset ventilator-associated pneumonia (VAP) and “failure to wean.” Patients with HSV-1 late-onset VAP have good cardiopulmonary function and should be easily “wean-able,” but instead remain unexplainably severely hypoxic. Diagnosis of HSV-1 late-onset VAP is best made by cytologic examination of BAL respiratory secretion specimens.Cytopathic effects of HSV-1 or CMV in broncholavage/lung specimens cytopathic effects are patho-pneumonic of active lung infection, i.e., pneumonia (4).

CMV cytopathic effects are readily distinguishable from HSV-1 cytrophic effects. Unlike HSV-1, CMV reactivation with infection is also accompanied by extra-pulmonary organ involvement.

Unlike HSV-1, in immunocompetent hosts, the most common laboratory markers accompanying CMV pneumonia are otherwise unexplained leukopenia, relative lymphopenia, atypical lymphocytes, thrombocytopenia, and mild increases in serum transaminases (5).

Our recent experience with ventilated ICU patients undergoing diagnostic bronchoscopy for late-onset VAP, we found no patient had CMV cytopathic effects alone or together with HSV-1.

These findings also have important therapeutic implications. Patients with HSV-1 late-onset VAP readily respond to acyclovir and rapidly become weanable. However, acyclovir is ineffective against CMV, and ganciclovir treatment is problematic.

In conclusion, in our experience, HSV-1 is a common cause of late-onset VAP in ventilated ICU patients, CMV lymphocyte reactivation in ventilated ICU patients is common because most ICU patients are CMV seropositive. However, CMV reactivation does not appear to manifest as systemic infection, e.g., CMV late-onset VAP in ICU patients with unexplained hypoxemia. At present, the diagnosis of CMV late-onset VAP is best made by demonstrating CMV cytopathic effects in BAL/lung biopsy specimens and by demonstrating signs of systemic infection, i.e., increased serum transaminases, leukopenia, atypical lymphocytes, etc. Because most ventilated ICU patients are CMV seropositive, CMV antigenemia/polymerase chain reaction indicates lymphocyte reactivation, which is not, per se, indicative of clinical CMV systemic infection, particularly late-onset VAP. In ventilated ICU patients, HSV-1 is a common cause of late-onset VAP, but in our experience, CMV is not.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES

The authors reply:
We have read with interest the letter from Dr. Burke Cunha et al pointing out the problem of the causality of cytomegalovirus (CMV) infection on increased morbidity and/mortality observed in previously immunocompetent intensive

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care unit (ICU) patients (1). The authors suggested that, unlike herpes simplex virus serotype 1 (HSV1), CMV is not per se a pathogen causing late-onset ventilator-associated pneumonia. They underlined the distinction between CMV reactivation and CMV infection.

In previous studies, we had analyzed the results of 100 consecutive open-lung biopsies performed after ≥5 days of acute respiratory distress syndrome in ICU patients with negative microbiological cultures (2–4). CMV cytopathic effects were found in 30 patients, whereas HSV was identified in only three patients (4). Thus, CMV definitely causes biopsy-proven late-onset ventilator-associated pneumonia.

The lack of extrapulmonary manifestations of CMV disease (i.e., thrombocytopenia or mild increases in serum transaminases) does not exclude the diagnosis. If useful in a community context, they are unspecific after 2 wks or 3 wks of ICU stay. The absence of “mucosal alert” (which characterizes HSV) in CMV infection could explain, at least in part, the absence of CMV infection reported by Dr. Cunha and colleagues. Apart from lung biopsy, only a systematic and extended screening in blood and/or bronchoalveolar lavage (when there is a suspicion of ventilator-associated pneumonia) during the ICU stay permits one to diagnose CMV reactivation.

Finally, even if CMV infection in our work must not be misinterpreted as proven CMV disease, CMV reactivation is thought to have immunosuppressive and/or profibrotic role by itself, and may favor bacterial and fungal nosocomial infections, which are associated with an increased morbidity. In a prospective study, Cook et al found a high prevalence of both HSV and CMV infection, but only patients experiencing CMV reactivation had a higher morbidity, whereas HSV-positive patients had length of hospital stay, length of ICU stay, and duration of mechanical ventilation comparable with those of patients without viral infections (5).

To conclude, we still have no answer to the question: “Should previously immunocompetent ICU patients be treated with antiviral therapy in case of CMV reactivation?” But we strongly suggest that patients with late-onset ventilator-associated pneumonia and no evidence of bacterial pathogen should be screened for CMV infection, even in the absence of extrapulmonary involvement.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES

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Superiority of levosimendan over dobutamine in right ventricle failure

To the Editor:

We have read the article by Russ et al (1) that was published in Critical Care Medicine recently. The article was about the beneficial effects of levosimendan in acute myocardial infarction complicated by cardiogenic shock. Results showed that levosimendan enhanced right ventricular (RV) cardiac power index and decreased pulmonary vascular resistance without significant change in central venous pressure or mean pulmonary arterial pressure. Authors claimed that impact of levosimendan on RV has not been determined yet. At this point, we want to denote our opinion on this subject and share findings of our recent study (2).

In our study, we investigated whether levosimendan or dobutamine yielded more desirable RV performance in patients with severe biventricular failure. The study protocol included consecutive patients (n = 40), hospitalized with New York Heart Association class III or IV symptoms attributable to chronic systolic heart failure, having left ventricular ejec-
tion fraction of <35%, accompanying moderate-to-severe RV dysfunction. Definition for RV dysfunction was an RV fractional area change of ≤24%, and tricuspid annular plane systolic excursion, as a measure of RV base-to-apex shortening during systole, of ≤15 mm as a cut-off point with prognostic impact (3). Levosimendan was administered for 24 hrs, initially at a rate of 0.1 μg/kg per minute, and up-titration in the infusion rate was suggested if tolerated. Dobutamine was administered at least for 24 hrs; dose was allowed initially to be at a rate of 5 μg/kg per minute. After the infusion, ejection fraction improved and systolic pulmonary artery pressure decreased significantly in both groups (Table 1). Tricuspid annular plane systolic excursion and RV fractional area change were improved significantly in patients with levosimendan compared to patients with dobutamine. As a result, levosimendan seemed to provide more beneficial effects among patients with biventricular systolic heart failure, along with decrease in pul-
monary pressure and increase in RV contrac-
tility, both of which may be acting together on the net effect. The favorable effects of levosimendan on RV systolic dysfunction might have resulted partially from the improvement of left ventricular function. However, only levosimendan improved RV systolic function significantly, despite both drugs improving left ventricu-
lar function almost to same degree.

In conclusion, we suggest that levosi-
mendan has enhancing effects on RV, as in cases of acute-onset heart failure, like Russ et al described, or in cases of acute decompensated long-term heart failure that we subjected in our work. Two studies corre-
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The authors reply:

The favorable effects of levosimendan on right ventricular function described by Dr. Yilmaz et al (1) are in line with our experiences. However, some differences between these two studies should be noted.

**Infarction Related Cardiogenic Shock Versus Decompensated Heart Failure**

Cardiogenic shock is an acute event in patients who usually did not suffer from heart failure before the index event. Furthermore, survivors of cardiogenic shock often have a good long-term prognosis with >80% being in New York Heart Association Class I and II (2). In contrast, patients with congestive heart failure suffer a chronic deteriorating course with multiple episodes of decompensation, finally leading to refractory heart failure and death. A single intervention like the application of levosimendan for 24 hrs that improves biventricular cardiac function is more likely to have an impact on long-term survival in the former scenario, whereas there was no improvement with a single application of levosimendan in a large trial on decompensated heart failure (SURVIVE Trial) (3).

**Invasive Hemodynamic Monitoring Versus Repeated Echocardiographic Imaging**

Both measures have their specific pitfalls. Although positive-pressure ventilation affects the accuracy of pressure measurements, supine positioning, lack of tricuspid regurgitation, high interobserver variability, and difficulties in determining right atrial pressures (which are necessary to estimate peak pulmonary artery pressure) are specific uncertainties of echocardiography. Nevertheless, echocardiography is a powerful tool—charmed by its noninvasiveness—in the management of critical care patients. Further investigations must explore which method is more useful in the specific situation.

Interestingly, although levosimendan decreased pulmonary artery pressure in the study by Dr. Yilmaz et al, we did not notice this effect (1). In our opinion, this difference is mostly due to a different volume management strategy. Dr. Yilmaz et al did not change infusions during levosimendan treatment, which resulted in negative volume balance and reduced right ventricular filling pressures (as represented by higher degrees of inferior caval vein collapse of more than 50% after levosimendan treatment) (4). In contrast, in cardiogenic shock patients, additional volume application was necessary with afterload lowering (Fig. 1). In cardiogenic shock, adequate volume management is an important safety issue when levosimendan is applied.

Like Dr. Yilmaz et al, we found a positive effect on diuresis (Fig. 1); however, we did not note an improvement in renal function (creatinine, creatinine clearance). Again, this could be due to the higher number of acute renal failure events in cardiogenic shock compared with decompensated heart failure. However, it remains an interesting question if levosimendan is actually capable of improving renal function, or, if the increase in diuresis reflects rather hemodynamic improvement without an impact on renal function in terms of creatinine clearance, etc.

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The authors reply:

The favorable effects of levosimendan on right ventricular function described by Dr. Yilmaz et al (1) are in line with our experiences. However, some differences between these two studies should be noted.

**Table 1. Temporal change of parameters (before vs. after) in levosimendan and dobutamine arms**

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>EF, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td>22 ± 6</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td>12.3 ± 1.3</td>
<td>14.2 ± 2.5</td>
</tr>
<tr>
<td>RVFAC, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td>18.7 ± 3.7</td>
<td>23.8 ± 4.6</td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td>54 ± 8</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>Less than 50%</td>
<td>27/27</td>
<td>13/13</td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.35 ± 0.37</td>
<td>1.13 ± 0.39</td>
</tr>
<tr>
<td>(p_{a,b})</td>
<td>0.599</td>
<td></td>
</tr>
<tr>
<td>24-h Urine output, mL/day</td>
<td>922 ± 748</td>
<td>1637 ± 688</td>
</tr>
</tbody>
</table>

L, levosimendan; D, dobutamine; EF, ejection fraction; RVFAC, right ventricular fractional area change; SPAP, systolic pulmonary artery pressure; IVC, inferior vena cava.

\*p for comparison of both groups before infusion; \(p\) for comparison of both groups after infusion; \(p\) for temporal change of parameters.
In conclusion, levosimendan actually seems to be a useful treatment alternative in acute right ventricular failure of different origin.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


DOI: 10.1097/CCM.0b013e3181c30df6

Dynamic alveolar mechanics in acute lung injury

To the Editor:

We read with great interest the article “Alveolar dynamics in acute lung injury: Heterogeneous distension rather than cyclic opening and collapse” by Mertens et al (1). We agree that it is critical to understand the mechanics of the alveolus and alveolar ducts to approach protective mechanical ventilation scientifically. However, we have several questions on the interpretation of the results in this article.

Our first problem with the interpretation of the data in this article is the description of objects seen with intravital microscopy as “alveolar clusters.” It has recently been shown by Mitzner’s group that mouse alveoli range in size from 35 to 45 μm (2). The photomicrographs in Figures 2 and 3 describe the objects as alveolar clusters, but these clusters are only slightly larger than 40 μm in diameter. This suggests by size alone that these are alveoli rather than alveolar clusters. The use of optical coherence tomography to measure the mechanics of alveoli not attached to the pleural surface only measured to a depth of approximately 50 μm, which would barely exceed the size of a single alveolus. Thus, it is possible that the reason why alveolar area measured by optical coherence tomography was one-third less than measured by intravital microscopy because it was measuring the distal portion of a subpleural alveolus.

The use of the “light-refracting structures” to calculate alveolar compliance is not adequately justified in this article. What evidence is there that these structures are related to alveolar compliance, and what is the justification for using the density as a measure of compliance? We also observe these structures using our in vivo microscope (3), along with other investigators (4), and have identified these structures as being the borders of alveolar capillaries (3, 4). An excellent video clearly identifying the “light-refracting structures” as being capillaries with red blood cells flowing through them in single file is shown as a supplementary video in the Jaryszak article (4).

We have demonstrated that at low positive end-expiratory pressure (5 cm H2O), the capillary pressure is greater than alveolar pressure, the capillaries are perfused, and the capillary borders (“light-refracting structures”) can be easily seen (west lung zone III; 3, Fig. 1A). At high positive end-expiratory pressure (15 cm H2O), the alveolar pressure exceeds capillary pressure and the capillaries are compressed, perfusion is blocked, and the “light-refracting structures” disappear (west lung zone I; 3, Fig. 1B). Thus the “light-refracting structures” would better serve as measure of alveolar and capillary pressure rather than compliance.

Stable alveoli after lung injury are not unique to the Merten study. Although most lung injury models that we have tested cause unstable alveoli, we found that endotoxin does not (5). We demonstrated that TWEEN instillation, ventilator-induced lung injury, and intravenous oleic acid all caused unstable alveoli, whereas alveoli were stable after intravenous endotoxin with the identical degree of lung injury indicated by partial pressure of oxygen/inspired partial pressure ratio. It is possible that endotoxin caused alveolar flooding such that the alveoli were stable but fluid-filled. A similar mechanism could explain the alveolar stability after hydrochloric acid instillation in the Merten study.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


DOI: 10.1097/CCM.0b013e3181bfe74f

The authors reply:

We appreciate the comments of Drs. Nieman and Gatto on our recent article in which we report that volume changes in both healthy and acid-injured mouse lungs are caused by alveolar distension rather than cyclic opening and collapse (1).

In their letter, Drs. Nieman and Gatto address a remarkable topic, namely, the identification of individual alveoli by intravital imaging technologies. Alveoli are anatomical structures that form hollow cavities, yet their configuration varies considerably so that any definition of their geometry must be kept in general terms (2). In two-dimensional images from the lung surface as well as in three-dimensional reconstructions, the terminal airspace structures present multiple bulges and pockets that undergo constant dynamic change (1), thus generating a plethora of shapes resembling anything from round circles to emarginated clover leaves. Whereas stereological approaches can resort to the free ends of the alveolar septae for the determination of alveolar numbers (3), the precise definition of what constitutes an individual alveolus in dynamic intravital 2D and 3D imaging becomes virtually impossible. Whereas we agree with Drs. Nieman and Gatto that the airspace units visualized in our study are frequently comparable in size to single alveoli as seen in histostereology, we deliberately refrained from referring to them as “alveoli” for lack of histomorphological verification but termed them “alveolar clusters” defined as individual delaminated aerated structures discernible on the lung surface.

The subsequent question as to the measurement of alveolar compliance in our study apparently results from the impression that the latter was calculated from the reported “light refracting structures” within the alveolar clusters. This was not the case. As stated in the methodologic section, alveolar compliance was calculated as the fold increase in alveolar area between images taken at 0 cm H2O and 24 cm H2O ventilation pressure. The notion that “light refracting structures” represent alveolar capillaries, which collapse with higher inflation pressures, is specifically presented in our discussion.

Finally, Drs. Nieman and Gatto speculate that the lack of cyclic alveolar opening and collapse in acid-injured lungs may be the result of alveolar flooding, causing alveolar stability. We have effectively ruled out this possibility by use of optical coherence tomography, which is ideally suited to discriminate between air- and fluid-filled spaces. Cyclic opening and collapse were similarly absent in uninjured lungs, further consolidating the notion that alveolar stability does not result from alveolar flooding. Importantly, these findings identify alveolar stability as the physiologic state at which lung volume change occurs during mechanical ventilation and refute the previous hypothesis that the normal lung expands primarily by alveolar recruitment (4). Conversely, we have observed occasional alveolar instability in conditions of severe lung edema (unpublished observations), a finding that is in line with the notion that alveolar instability (defined in intravital microscopy as cyclic appearance/disappearance of light reflection by the air-fluid interface) may present cyclic aeration of fluid filled, yet not necessarily collapsed, alveoli (5).

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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An unseen danger: Frequency of posterior vessel wall penetration by needles during attempts to place internal jugular vein central catheters using ultrasound guidance

To the Editor:

We read with interest the article by Blaivas and Adhikari (1), which reported the incidence of posterior wall penetration during ultrasound-guided cannulation of the internal jugular vein. As they noted, this is a frequent occurrence among inexperienced operators, but it also occurs with experienced operators. The authors proposed using the longitudinal view during ultrasound guidance, instead of the transverse view, because the former appears to decrease the frequency posterior wall penetration. However, their article does not mention the orientation of the bevel during insertion, which may also contribute to the frequency of posterior wall penetration.

Traditional teaching is to insert the needle with the bevel facing up (2–4). Online teaching videos also demonstrate this technique (5). The rationale for the bevel-up approach is to allow the sharp point of the needle to penetrate the skin and blood vessel, facilitate more direct flow of blood into the syringe, and promote passage of the guide wire into the lumen of the blood vessel. However, the sharp point of the needle frequently penetrates both the anterior and posterior walls of the blood vessel. This probably occurs because the anterior and posterior walls of the blood vessel are often juxtaposed during central venous cannulation and the sharp point of the needle easily penetrates the interface of the blood vessel walls. This is particularly common
among volume-depleted patients in whom the internal jugular vein has collapsed.

We have found that insertion of the needle with the bevel facing down and parallel to the skin reduces the frequency of posterior wall penetration. Whereas juxtaposition of the anterior and posterior walls still occurs with the bevel-down approach, the interface between the walls of the blood vessels is less likely to be pierced by the needle, leaving the posterior wall intact. Blood flow through the needle does not seem to be compromised with this technique; however, it is not unusual to find that the needle is positioned against the posterior wall, making it difficult to thread the guide wire. Slight retraction of the needle by 1 to 3 mm is sufficient to resolve this issue. During cannulation of the subclavian vein, rotation of the needle by 90° (so that the bevel faces the patient’s feet) may also facilitate passage of the guide wire in the proper direction.

In summary, we agree that visualization of the blood vessel in the longitudinal axis during central venous catheter insertion may reduce the frequency of posterior wall penetration. However, we believe that the bevel-down technique also reduces posterior wall penetration. Regardless of whether longitudinal visualization, bevel-down penetration, or both are used, proper training and experience are necessary to perform central venous catheter insertion correctly.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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The author replies:

I would like to thank the authors for writing. The exchange of ideas, techniques, and tricks of the trade is extremely important. Like many people, we used the “bevel up” approach for the same good reasons that are mentioned. The suggestion made is a great one and I have learned long ago the value of having an arsenal of tricks for deployment in difficult situations. However, it is critical to note that the long axis, dynamic ultrasound guidance approach is actually ideal for the situations described by the authors. In fact, it is probably the ultimate solution due to the precision this method allows. As Desiderius Erasmus of Rotterdam wrote, “In the land of the blind, the one eye man is king” and this saying reflects the effect ultrasound guidance in long axis can have in difficult vascular access cases.

Because the entirety of the needle should be visualized in its length (with the vessel seen in its length as well), the clinician not only guides the needle to the vessel with precision but also precisely guides the needle tip within the lumen of the vessel (1, 2). Figure 1 shows a needle that had been driven deeply into the internal jugular of a septic patient and is now being pulled back. This image is part of a video, which showed the needle just shy of touching the posterior wall when the needle finally popped through the tenting anterior wall. The high precision achieved with long axis ultrasound guidance allowed the user to carefully bring the needle tip close to the posterior wall without penetrating it.

In hypovolemic patients, where the anterior wall may actually collapse and touch the posterior wall as the authors describe, the long axis approach is again of tremendous value (3). As the anterior venous wall starts to collapse, the user notices this in real time and has several options. In the case of the subclavian and jugular approaches, it is possible to synchronize further needle penetration with the patient’s respiratory/ventilatory cycle, waiting for the vessel to dilate and then gently plunge in further. An even more successful maneuver involves manipulation of the angle of attack the needle takes with respect to the vessel. Once the anterior vessel wall is hooked by the bevel up needle, you can actually flatten the needle and syringe, and instead of pushing the needle tip toward the posterior wall, you can push it into the length of the venous lumen (Fig. 2). Eventually, the venous wall will give and you will be through without any danger of penetrating both walls. Finally, if there is trouble passing the guidewire, ultrasound can be incredibly helpful for fine needle and wire manipulation and successful passage of a troublesome wire.
Figure 2. A subclavian catheter inserted in a hypovolemic, septic patient. In the left frame, the needle (arrow heads) has not popped into the vessel and the venous wall is tenting around the needle tip (large arrow). The expected path (faint arrow) will take the needle directly into the posterior wall of the vessel, and it did. The angle of the needle was then changed to a more horizontal approach as seen on the right. The needle tip has still not popped through and the wall is tenting significantly. The expected path of the needle (faint arrow) took the needle tip and tenting wall down the length of the vessel and eventual successful cannulation, without contacting the posterior wall of the vessel.

(4). The beauty is that every bit of this detail can be seen in long axis.

The author has not disclosed any potential conflicts of interest.

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REFERENCES


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(18)-F-fluorodeoxyglucose positron emission tomography/computed tomography study in acute lung injury/acute respiratory distress syndrome

To the Editor:

We read with great interest the work by Bellani et al (1) published in a recent issue of Critical Care Medicine regarding the increase in metabolic activity in the lungs of patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).

In accordance with other investigators (2, 3), the authors have reported an increase in (18)-F-fluorodeoxyglucose (FDG) uptake in the lung parenchyma of a small and heterogeneous group of ALI/ARDS patients using positron emission tomography/computed tomography scan in different phases of the disease. Additionally, the authors found heterogeneity in FDG uptake when regional metabolic activity was correlated with lung aeration compartments (hyperinflated, normally aerated, poorly aerated, and non-aerated regions) based on computed tomography density.

However, we believe that the heterogeneity in metabolic activity in lung compartments reported by Bellani et al relates, at least in part, to the nonhomogenous pattern of distribution of perfusion in ALI/ARDS patients.

Some studies have reported a redistribution of pulmonary blood flow from poorly and non-aerated regions toward better-aerated areas in an experimental model of ALI/ARDS, most probably induced by the pulmonary hypoxic vasoconstriction (4). Additionally, the hyperinflated areas can also be less perfused depending on the balance between the regional alveolar and capillary pressure. Accordingly, if the alveolar pressure exceeds the capillary pressure, the pulmonary blood flow from hyperinflated regions might be redistributed to normally aerated, poorly aerated, and non-aerated regions (5). However, if the pulmonary hypoxic vasoconstriction mechanism is active, the blood will be redistributed again from non-aerated areas toward normal ones. As a result, the normally aerated areas will be more perfused than the others, but if the pulmonary hypoxic vasoconstriction is inactive (for instance, during sepsis), the pulmonary blood flow will increase across the entire spectrum of computed tomography attenuations from hyperinflated to non-aerated regions.

As can be observed in Figure 4 in the work by Bellani et al, there are some lung areas corresponding to hyperinflated regions, where FDG uptake is low. This observation seems to follow an anatomical segmentation (superior lingular segment in patient 7, and lateral segment in the middle lobe of patient 4). Additionally, it is noteworthy that hyperinflated lung areas, presented in Figure 5, correspond to the areas of lower metabolic activity in all but one patient. In seven of these patients (empty symbols), the FDG uptake increased as computed tomography attenuation increased from hyperinflated to non-aerated regions, possibly representing a pattern in which there was no pulmonary hypoxic vasoconstriction compensation. In the other three patients (filled symbols), the metabolic rate was higher in regions of normal lung attenuation where, most likely, more pulmonary blood flow was presented by the redistribution of blood from hyperinflated, poorly aerated, and non-aerated regions toward normally aerated ones.

Based on these aspects we believed that redistribution of pulmonary blood flow is an important aspect to be considered in the analysis of metabolic rate in ALI/ARDS positron emission tomography/computed tomography studies.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


DOI: 10.1097/CCM.0b013e3181be7de

The authors reply:

We thank Dr. Rodrigues et al for their interest in our work (1) and for their interesting comment underlining the importance of regional perfusion in the interpretation of 18FDG uptake (2). As they point out, perfusion in healthy and diseased lungs can be very heterogeneous (3); this was likely the case in our patients. When 18FDG is delivered via the bloodstream, lung regions that are not perfused at all will not take up 18FDG. Because 18FDG has a low permeability for lung tissues (3), it has been shown that 18FDG uptake was always greater in the injured, inflamed lung than in the uninjured lung independent of whether perfusion was higher in the injured or in the control lung. Because 18FDG has a low extraction ratio in the lung, its pulmonary uptake tends not to be perfusion-limited. Furthermore, to quantify 18FDG uptake, we used Ki, a measurement of the amount of 18FDG transferred from blood into tissue. This is a crucial methodologic difference with previous studies which measured regional activity (references 2 and 3 in the letter). Regions with high perfusion will tend to yield high activity measurements irrespective of whether tissue uptake is increased or not.

Figure 5 in our paper shows that, whereas in seven patients (empty symbols) Ki increased with regional density, three patients showed higher Ki in normally and poorly aerated lung than in nonaerated lung (filled symbols). Dr. Rodrigues et al suggested that pulmonary hypoxic vasoconstriction, redistributing blood flow to the regions of normal aeration, could account for the lower metabolic rate in high-density regions in these three patients. If this were the case, these patients would be expected to show better gas exchange than the rest of the population. In contrast, their gas exchange was actually worse (PaO2/FIO2: 123 ± 23 torr [16.4 ± 3.3 kPa] vs. 180 ± 28 torr [24.0 ± 3.7 kPa], p = .053; and PaCO2: 59.9 ± 7.7 torr [8.0 ± 1.0 kPa] vs. 41.0 ± 6.8 torr [5.5 ± 0.9 kPa], p < .05); these data were not included in the manuscript because the small sample size does not allow a definitive conclusion, but they challenge the hypothesis of a stronger pulmonary hypoxic vasoconstriction in the patients corresponding to the filled symbols. On the other hand, the progressive increase in 18FDG uptake with increasing computed tomography density observed in seven patients does not necessarily imply blunted or absent pulmonary hypoxic vasoconstriction as Ki is expected to increase with density because denser regions have more tissue (cells) and less air (4).

In conclusion, although we cannot rely on a direct measurement of regional perfusion (which was not obtainable in our patients), and although it is clear that delivery of 18FDG occurs by perfusion and in certain conditions both regional perfusion and 18FDG uptake could increase, the arguments we presented suggest that heterogeneity in regional perfusion was not a major determinant of the spatial heterogeneity of Ki and, in particular, of the two distinct regional patterns observed in our population.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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Chaotic adaptive mechanisms are operational during low-flow states

To the Editor:

We have read the article by Dr. Wan et al entitled “Preserved cerebral microcirculation during cardiogenic shock” with great interest (1). We believe that the authors’ findings represent evidence for a preprogrammed adaptive response in low-flow states, which aims a survival advantage.

This adaptive response is operational in both cellular and systemic levels. Cellular hibernation observed in septic shock represents another mechanism that is operational in this response. By decreasing mitochondrial metabolism, tolerance of the cells to hypoxia is increased. Furthermore, we believe that changes in microcirculation and induced apoptosis may be other aspects of this adaptation, which kill some portion of the cellular population to increase the oxygen delivery to the remaining cells, by which the whole progeny is saved and can recover after the perfusion is corrected.
Despite enormous evidence on the presence of an adaptive response that aims toward a survival advantage, a safe and reproducible therapy is still lacking. We think that the underlying reasons are our tendency to explore the disease states in a reductionist approach and the limitations of research methods.

The nonlinear interactions of organ systems within themselves and with the therapeutic interventions demonstrate that the disease states we are working on represent complex systems (2). Chaotic and complex systems are dynamic systems, which are highly sensitive to initial conditions. Even a small difference, which is insignificant within the context of currently used reductionist statistical methods, can be augmented by the succeeding steps and result in significant differences in the system behavior. These differences are unpredictable and may cause “emergent behaviors” of the system, which cannot be explained by linear statistical methods even if the properties of components and their relationships with each other are known in detail (3). Additionally, chaotic and complex systems are adaptive and aim to settle to an order. The point at which to intervene to change the result.

That is why we think that disease states encountered in critical care must be evaluated within the context of chaos and complexity theories, which may provide ways to use these adaptive mechanisms as therapeutic tools, rather than fighting with them.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES

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Randomized trial of light versus deep sedation on mental health after critical illness

To the Editor:

I have read with great interest the negative study (1) by the group led by Dr. Treggiari, and their efforts in conducting the study need to be commended.

In my opinion, one of the big problems with the study is the population studied. According to the authors, subjects were eligible to enter the trial if they were adults admitted to the intensive care unit and they were expected to receive mechanical ventilation for at least 12 hrs. Surprisingly, 100 of the 129 patients included in the study were postsurgical patients as shown in Table 1 in their paper. Also, because the mean Ramsay score was 4 at the time of admission to the intensive care unit, were these patients still under the effects of anesthesia? Were these patients still paralyzed? Why were these postsurgical patients admitted to the intensive care unit? How many of these surgeries were planned and how many were emergencies? In addition, 89 patients fell in the cardiovascular diagnostic category. Were most of these patients post coronary artery bypass graft?

These points are not trivial when attempting to study sedation as most of these patients, for example, postcoronary artery bypass graft patients, are awake and extubated before the next morning. Do the authors believe that it is appropriate to conduct a trial of light versus deep sedation in the postsurgical setting?

The author has not disclosed any potential conflicts of interest.

Javier Daniel Finkielman, MD, Intensive Care Unit, Saint Alexius Medical Center, Bismarck, ND

The author replies:

We would like to thank Dr. Finkielman for his correspondence. His point is well taken and we recognize that the population included was predominately surgical. However, our inclusion criteria allowed enrolling patients who were ventilated for \( \geq 12 \) hrs, leading to the inclusion of a number of patients following major surgical procedures. It is important to emphasize that, despite the relatively short duration of mechanical ventilation in this patient population, the study was able to demonstrate a reduction in length of mechanical ventilation and of intensive care unit (ICU) stay. Even though the active intervention was not that prolonged, the study suggests that an even greater effect might occur if it were used in a more prolonged manner. This observation highlights the importance of minimizing sedation via continuous infusion.

Furthermore, previous studies have demonstrated that patients admitted to the ICU after cardiac surgery have heightened risk of posttraumatic stress disorders (1, 2). Other studies have investigated different sedation weaning protocols in ICU patients admitted post cardiac surgery (3). Therefore, investigating the effects of ICU sedation is highly relevant in this patient population.

We acknowledge there are limitations in our study. Nevertheless, this trial greatly contributes to the overall knowledge of mental health effects of ICU sedation by confirming results from previous studies of more limited quality. From a clinician perspective, it is reassuring to know that reducing ICU stay and mechanical ventilation can be achieved without exacting a psychological cost. Our study provides an important piece in the context of a shifting paradigm in the way sedation is provided in the ICU.

Thank you for the opportunity to respond to your comments.

The author has not disclosed any potential conflicts of interest.

Miriam Treggiari, MD, PhD, MPH, Department of Anesthesiology, and Pain Medicine, University of Washington, Seattle, WA

REFERENCES
Acute lung injury in children: Importance of host factors

To the Editor:

We enjoyed reading the review article by Dr. Randolph on acute lung injury (ALI) in children (1). The author states that risk factors and pathophysiology of ALI are similar in adults and children. Conditions, such as pneumonia, sepsis, aspiration, and trauma, may—comparable to adults—trigger ALI in children (2). However, much less is known about host susceptibility for developing ALI when exposed to such triggers. From this point of view, risk factors for ALI in children and adults may differ. For example, in adults, angiotensin-converting enzyme (ACE) polymorphism is known to modulate the severity of ALI (3). However, in a study in 216 children admitted to a tertiary pediatric intensive care unit, the ACE genotype did not seem to influence the prevalence and course of ALI (4). Furthermore, diabetes mellitus is thought to be protective against ALI in adults, but this has not been investigated in children (5). In this context, we would mention children with Down syndrome, whom we found to be very susceptible for developing ALI, independent from the initial trigger (6). A correlation between Down syndrome and ALI has thus far not been described in adults.

Interestingly, despite the high occurrence of ALI in children with Down syndrome, the mortality rate is very low. Likewise, in children in general, the mortality rate of ALI is low compared with adults (1). Recent experimental studies have shown age-dependent lung responses to infection and mechanical ventilation (7). This strongly suggests that the pathophysiology of ALI might also be influenced by age, as are susceptibility and outcome.

Therefore, we would like to emphasize the importance of ongoing research into (age-dependent) host factors associated with ALI. If we are able to improve our knowledge in this field, future trials for new treatment and prevention strategies can be directed toward more specific patient groups, possibly leading to better results than the present clinical trials, as reviewed by Dr. Randolph.

The authors have not disclosed any potential conflicts of interest.

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REFERENCES


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