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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 delimited 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 H_2O and 24 cm H_2O 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 interphase) 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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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 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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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 precisions 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 entire 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

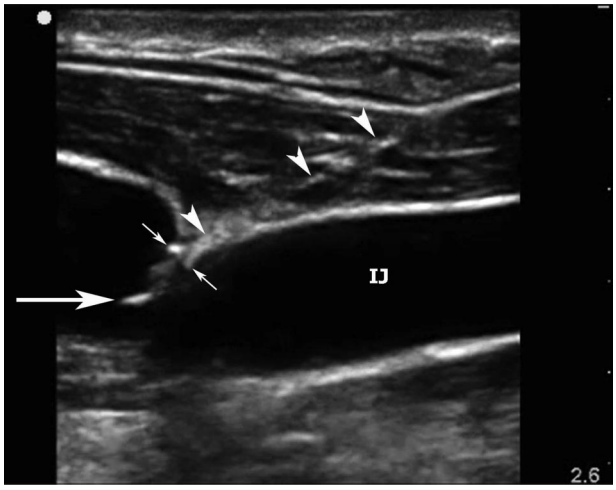

Figure 1. Needle (*arrow heads*) inserted into the internal jugular (IJ) vein. The anterior venous wall collapsed into the lumen and the needle tip just broke through (*large arrow*). The anterior venous wall is still "tenting" significantly into the lumen of the IJ vein, as denoted by the *small arrows*. However, it had been at the needle tip, nearly touching the posterior wall.

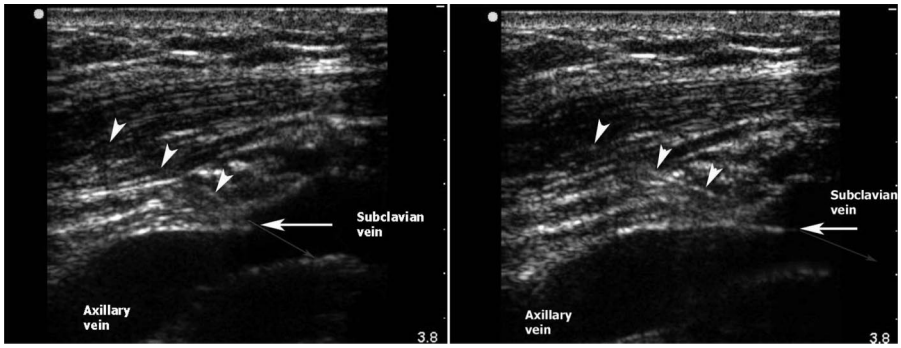

Figure 2. A subclavian catheter inserted in a hypovolemic, septic patient. In the left frame, the needle (*arrow heads*) has not popped into the vessel and the venous wall is tenting around the needle tip (*large arrow*). The expected path (*faint arrow*) will take the needle directly into the posterior 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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(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 nonhomogeneous 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 medium 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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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 ^{18}FDG 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 ^{18}FDG is delivered via the bloodstream, lung regions that are not perfused at all will not take up ^{18}FDG. Whether ^{18}FDG uptake measured by the net uptake rate (Ki) is systematically related to perfusion such that regions with higher perfusion consistently show higher Ki is, however, debatable.

Several investigators have shown, in different settings, that ^{18}FDG uptake is not directly related to regional perfusion (references 38–42 in the paper). In two different models of unilateral lung injury (injurious ventilation) (4) and smoke inhalation (5), it has been shown that ^{18}FDG 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 ^{18}FDG has a low extraction ratio in the lung, its pulmonary uptake tends not to be perfusion-limited. Furthermore, to quantify ^{18}FDG uptake, we used Ki, a measurement of the amount of ^{18}FDG 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 at 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 ($Pa_{O_2}/F_{I_{O_2}}$: 123 ± 23 torr [16.4 ± 4.3 kPa] vs. 180 ± 28 torr [24.0 ± 3.7 kPa], $p = .053$; and Pa_{CO_2}: 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 ^{18}FDG 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 ^{18}FDG occurs by perfusion and in certain conditions both regional perfusion and ^{18}FDG 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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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 control a chaotic system can completely 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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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

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DOI: 10.1097/CCM.0b013e3181c30cbc

The author replies:

We would to like to thank Dr. Finkielman for his correspondence. His point is well taken and we recognize that the population included was predominantly surgical. However, our inclusion criteria allowed enrolling patients who were ventilated for ≥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.

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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 patients 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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