associated with neurons (4). Although argon showed a protective effect in neurons in dentate gyrus, whether argon has an effect on the neurons in other areas (e.g., cortex) which contribute to the final indifference in neurofunction should be clarified.

The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

The letter of Shao and Zhang (1) raises some valuable questions: They address the unknown causality of neuroprotection and the alteration of hypoxia-inducible factor (HIF)-1α and heme oxygenase (HO)-1 signaling after argon treatment in an experimental subarachnoid hemorrhage (SAH) model. Furthermore, more specific methods to asses neuronal loss particularly related to functional outcome are suggested. In fact, argon treatment after experimental SAH resulted in reduction of neuronal loss and induction of HIF-1α and HO-1. However, a definite causality is not derived by our data (2). We agree with the authors that further studies are needed to elucidate if alterations in HIF-1α and HO-1 signaling after SAH actually lead to neuroprotection and if this constitutes one aspect of argon's mechanism of action. Notably, concerning argon's mechanism of action, involvement of the HO-1 pathway (3) as well as HIF-1α signaling have been previously shown (4, 5). Considering the therapeutic consequences, one has to bear in mind the global role of the HIF-1α cascade (6). Therefore, more in-depth understanding of argon's mechanism of action and its potential influence on HIF-1α and HO-1 signaling is definitively required.

Concerning the functional outcome, we feel that the diffuse lesion pattern generated by SAH may not necessarily be rated adequately by the common neuroscores and functional tests used assessing neurologic status in rodent models. Thus, for further studies, functional outcome has to be assessed in a more sophisticated manner or other endpoints should be chosen (7).

Altogether, we appreciate the interest and look forward to further studies on innovative therapeutic strategies after SAH.

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Iron Parameters Determine the Prognosis of Critically Ill Patients: Facts and Fiction

To the Editor:

Anemia of inflammation is not uncommon in critically ill patients (1). Recent studies have confirmed a pivotal role for the hepcidin-ferroportin axis in the development of anemia of inflammation and stressed the complex pathogenesis of this disorder (2). Hepcidin has been found to be a sensitive diagnostic tool for identifying iron deficiency (3). The influence of iron metabolism variables, such as serum iron, hepcidin, ferritin, transferrin, and transferrin saturation (TSAT), on survival outcome in critically ill patients has not been understood. In a recent issue of *Critical Care Medicine*, Tacke et al (4) present their data regarding the association of iron metabolism variables in patients upon admission to ICU with short- and long-term mortality. They identified the variables of iron metabolism as the strong outcome predictors in ICU patients. More importantly, TSAT constitutes the only

variables of iron metabolism that can independently predict both short- and long-term mortality of the ICU patients.

When compared with blood samples taken from nondiabetic blood donors, those taken from ICU-admitted patients upon admission displayed significantly decreased serum iron/transferrin/hemoglobin and elevated ferritin/hepcidin. In Kaplan-Meier analysis, lower iron levels (cutoff, 10.5 μmol/L) were associated with better short- and long-term survival. We also noticed (Fig. 2*A*) that patients who died during ICU stay showed significantly higher serum iron compared with those survived. These data indeed confuse us as the value of the relatively higher iron in nonsurvivors was in fact lower than the control group (17.7 μmol/L). Do these data imply that iron deficiency can be a predictor for survival in critically ill patients? Obviously it is a logical error! However, we cannot disregard the statistical significance of the studied relationships. The mechanism of anemia of inflammation has not been understood. There may exist intermediates that can up-regulate lowered iron by certain mechanism in critically ill patients, which then cause worse patient outcome.

The intrinsic links among serum iron, ferritin, transferrin, and TSAT indicate inherent bias underlying the results from univariate Cox regression analyses. Although these variables were found to be predictors for mortality, TSAT was the only variable that independently predicted both short- and long-term mortality in multivariate analyses. In other words, there was no relationship among mortality and serum iron, ferritin, transferrin, and hepcidin, respectively. Furthermore, according to Table 3, TSAT did not correlate with inflammatory markers such as *C*-reactive protein, procalcitonin, and interleukin-6 in ICU patients. This means that TSAT was unrelated to inflammation but correlated with mortality. Such analysis is interesting because there may exist a critical role for TSAT in deterioration of critically ill patients independent of inflammation. However, this may not be true because a prospective study has revealed that *C*-reactive protein concentrations on day 1 inversely correlated with TSAT ($r = –0.49$; $p = 0.0001$) (5).

We believe that the study performed by Tacke et al (4) would be more informative if analyses were guided by clinical relevance instead of statistical significance.

The authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

We appreciate the interest by Jiang et al (1) as well as their critical comments. As demonstrated in our work (2) as well as in previous studies (3), parameters of iron metabolism display profound alterations in critically ill patients, and hypoferremia (i.e., decreased iron serum levels) is one of these changes. In fact, hypoferremia is considered a key host defense mechanism against infectious diseases (4). This fact spurred our analyses, and we were intrigued to see that critically ill patients that were not able to sequester their iron out of the serum in order to induce hypoferremia displayed a worse prognosis. As Jiang et al (1) acknowledged correctly, our data revealed a clear association between iron parameters and mortality in critically ill patients. The fact that transferrin saturation (TSAT) constituted the only independent iron-related predictor of both short- and long-term mortality by multivariate analysis does by no means disregard the value of the other iron parameters. Rather than that, these findings highlight the strong interdependence of the parameters related to iron metabolism.

Regarding the relationship between iron parameters and inflammatory parameters, an unequivocal correlation exists between ferritin and *C*-reactive protein (CRP) (2), whereas, a correlation between TSAT and CRP seems to be less obvious and may depend on the clinical scenario. The potentially relevant variables include the source of CRP elevation that differs between surgical and internal medicine patients, the acuity and stage of the infection, or the proportion of septic versus nonseptic patients (2, 5). The fact that we observed no significant correlation between TSAT and CRP but demonstrated a marked prognostic property of TSAT suggests that the effect of TSAT is likely to be independent on inflammatory reaction.

The above thoughts highlight the complexity of iron metabolism in critically ill patients as well as the fact that further research is urgently needed to substantiate the hypotheses raised by the novel findings of our article. In particular, the ongoing interventional clinical trials will be crucial to dissect the role of iron metabolism in critically ill patients. Nonetheless, we are happy to note that the clear association between routinely used iron parameters and patient's prognosis at the ICU provoked vivid discussions on the pathogenic mechanisms and clinical consequences.

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Iron Availability and Outcomes in Critical Illness

To the Editor:

We read with interest the article in a recent issue of *Critical Care Medicine* by Tacke et al (1), in which they report the measurement of multiple serum iron parameters in a cohort of patients admitted to the ICU. Their principal finding was the positive correlation of transferrin saturation at admission with short- and long-term mortality. The authors suggest that elevated serum iron availability may worsen prognosis in critical illness, possibly through the production of reactive oxygen species and/or the increased supply of iron to invading microorganisms, and they call for prospective trials of iron chelators in critical illness and sepsis.

We would like to make two brief comments on this work. The first is related to the utility of transferrin saturation as an index of iron availability in patients with critical illness. As acknowledged by the authors, serum transferrin typically falls substantially in septic patients, reflecting its nature as a negative acute phase protein. The assumption that calculated transferrin saturation remains proportional to tissue iron availability in the context of low transferrin and hypoferremia may not be correct. Interestingly, a previous ICU study using an index of iron availability (red cell hypochromasia) based on tissue utilization rather than serum iron parameters reported that iron deficiency, rather than increased iron availability, was associated with adverse outcomes (2).

Our second point is related to the use of iron chelators in patients with sepsis and/or critical illness. Although this strategy may theoretically impede microbial growth, the notion of a direct link between iron availability and infection in critical illness has been challenged by recent studies. For example, the use of repeated doses of IV iron in ICU trauma patients was not associated with an increase in the rate or severity of infection, compared with placebo (3). In addition, any potential benefits of iron chelation would need to be weighed against the potential for increases in pulmonary vascular resistance and right ventricular afterload (4). Several observations suggest that this effect would be a significant concern. First, the iron chelator desferrioxamine is known to induce modest pulmonary vasoconstriction in healthy volunteers, possibly by activating the hypoxia-inducible factor transcriptional pathway (5). Second, in patients with chronic pulmonary hypertension at high altitude, depletion of iron stores was observed to increase systolic pulmonary artery pressure (6). Third, in otherwise healthy adults with iron deficiency, the pulmonary hypertensive response to acute hypoxia is markedly enhanced, and can be greatly attenuated by IV iron supplementation (7).

In combination with the recent findings of Tacke et al (1), these observations suggest that the relationship between iron availability and outcome in the ICU is likely to be complex, and bring into focus the difficulty of assessing iron status in patients with critical illness. Ongoing clinical trials of IV iron in the ICU, such as the Intravenous Iron or Placebo for Anaemia in Intensive Care trial, may shed more light on this important issue.

Dr. Frise disclosed he is the recipient of a British Heart Foundation Clinical Research Training Fellowship (FS/14/48/30828). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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The authors reply:

We would like to thank Talbot et al (1) for their excellent comments on our recently published work (2). We intentionally chose transferrin saturation as a robust parameter used in the clinical routine, despite the fact that it cannot completely capture the complex changes in iron metabolism that occur during sepsis. Our data suggest that in a subset of ICU patients, iron cannot be efficiently sequestered in the serum, and that this fact is associated with adverse disease outcome (1). Although we did not directly assess the tissue iron availability in our cohort, the low transferrin levels in our patients and the association of low transferrin with adverse outcome are very well in line with previous reports suggesting that an inadequate iron supply to the tissues may worsen the prognosis of ICU subjects (3).

Similarly to the lack of its precise characterization, the treatment of iron dysregulation that occurs in ICU patients will likely be challenging and will have to take into account the detrimental consequences of both iron overload and iron deficiency. For the latter, the mentioned study demonstrating a stronger response to hypoxia in individuals with iron deficiency represents a clear memento (4). Although iron chelators are widely used in the clinics and are generally considered to be safe, their potential side effects in the very frail group of ICU patients have to be taken very seriously. As a potentially promising alternative to iron chelators, a supplementation of transferrin would both sequester the detrimental labile iron pool and improve the delivery of iron to the tissues.

As highlighted by the vivid discussion in response to our article and the above considerations, iron metabolism remains an incompletely understood and exciting area of research and its better understanding holds a promise to translate into improved therapy of ICU patients.

Dr. Nuraldeen's institution received funding (supported, in part, by the Interdisciplinary Center for Clinical Research [IZKF] within the faculty of Medicine at the RWTH Aachen University and by the Deutsche Forschungsgemeinschaft [DFG] SFB/TRR57 [to Drs. Tacke, Trautwein, and Strnad]). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Do Earplugs Reduce Delirium in the ICU?

To the Editor:

We read the interesting meta-analysis about the efficacy of earplugs as a sleep hygiene strategy for reducing delirium in the ICU published in a recent issue of *Critical Care Medicine* by Litton et al (1). The topic is crucial since up to one third of the ICU patients present delirium, and it could be associated to mortality (2).

We analyzed in detail the article of the meta-analysis and the Supplementary Appendix 1–3.

We have some significant questions to address about the present meta-analysis.

In the article, neither in the text nor in the figures, *p* value for effect was not reported, and the only *p* value reported was the *p* value for heterogeneity. Furthermore, in the article, it is impossible to find the number of events per study and the total number of events. These significant deficiencies do not allow the extent and power of the results to be understood.

In the Introduction and Methods paragraphs, the authors exposed the secondary aim of the study: the assessment of the effect of earplugs on ICU length of stay. Unfortunately, ICU stay analysis is not mentioned in the results.

Finally, when reading results from the largest randomized trial (RT) included in the meta-analysis (3), it states: "The incidence of delirium, however, was not different for both groups." When analyzing the article in detail, the RT (3) found that 20.3% of the patients in the earplugs group (14/69 patients) versus 19.4% of the patients in the control group (13/67 patients) presented delirium (Fig. 2 in the RT). The trial (3) employed the Neelon and Champagne Confusion Scale (4) and it found a lower incidence of mild confusion, according to this scale. Mild confusion and delirium are different entities as reported in the article of the RT (3) and also when it is compared with Confusion Assessment Method for the ICU (4). In conclusion, we cannot understand how the meta-analysis (1) can report that the relative risk for this RT is 0.58 (95% CI, 0.40–0.84), considering the fact that the results of the meta-analysis are strongly influenced and driven by the statistical report of this included trial (3).

The authors have disclosed that they do not have any potential conflicts of interest.

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