important role in the increased mortality associated with NRT in the critically ill. As highlighted previously, nicotine activates α7nAchR and can therefore attenuate the innate immune response, resulting in immune paralysis. As the major causes of death in the NRT group were pneumonia (n = 4) and sepsis (n = 3), this suggests that these patients were more susceptible to infections than were the control group, where two patients died of sepsis and none of other infections. Thus, the absence of increased mortality after NRT in non-critically ill patients in earlier trials may be explained by the fact that these patients were at a much lower risk of acquiring a concomitant infection than intensive care unit patients. Unfortunately, Drs. Lee and Afessa do not mention the prevalence of infections in the NRT and the control groups, nor do they provide data on the amount or concentration of nicotine administered to the patients. This information would certainly help us evaluate the possible role of the cholinergic anti-inflammatory pathway in increased mortality found in these patients.

The authors have not disclosed any potential conflicts of interest.

Matthijs Kox, MSc, Astrid W. Hoedemaekers, MD, PhD, Peter Pickkers, MD, PhD, Johannes G. van der Hoeven, MD, PhD, Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, The Netherlands; Jan C. Pompe, MD, Department of Intensive Care Medicine and Department of Surgery, Section Traumatology, Radboud University Nijmegen Medical Centre, The Netherlands

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The author replies:

We thank Kox and colleagues for their letter regarding our recent article (1). Our study showed that nicotine replacement therapy is associated with increased mortality in the critically ill. However, because of several limitations inherent in our study, more data are needed to confirm our findings. In our article, we speculated that the hemodynamic effects of nicotine, including coronary vasoconstriction and increased heart rate, blood pressure, and myocardial contractility, might explain the increased mortality associated with nicotine replacement therapy in the critically ill. We agree with Kox and colleagues that the cholinergic anti-inflammatory pathway might also play a role. The outcome of several diseases, including some of the critical care syndromes such as sepsis, depends on the delicate balance between proinflammatory and anti-inflammatory pathways. The two extremes of excessive inflammation and immune paralysis (from excessive anti-inflammation) increase morbidity and mortality. The vagus nerve can inhibit the release of macrophage tumor necrosis factor and thus attenuate systemic inflammatory responses. This cholinergic anti-inflammatory response is mediated by the nicotine acetylcholine receptor α7 subunit (2). In addition to its effect on macrophages, cholinergic stimulation also blocks endothelial cell activation and leukocyte recruitment during inflammation (3). Although nicotine plays an anti-inflammatory role by activating the acetylcholine receptor α7 subunit, the impact of this role on outcome in sepsis is not clearly established. In a mice model of sepsis, van Westerloo et al. (4) found that nicotine pretreatment decreased neutrophil influx and proinflammatory cytokine levels but impaired bacterial clearance and worsened survival. However, these findings were not replicated by Wang et al. (5). High mobility group box 1 protein is a mediator of lethal systemic inflammation in sepsis. Wang et al. found that treatment with nicotine attenuates serum high mobility group box 1 levels and improves survival in experimental model of sepsis (5). These conflicting data suggest that more studies are needed to define the impact of nicotine on clinical outcome and its mechanisms of action in sepsis. Animal studies show that nicotine has anti-inflammatory properties. However, we do not know if nicotine causes similar action in humans at doses used for replacement therapy. Because of the design and the small number of events such as sepsis, our study was not adequately powered to address these issues.

The author has not disclosed any potential conflicts of interest.

Bekele Afessa, MD, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN

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Continuous cardiac output monitoring: Really continuous?

To the Editor:

I read with interest the article by Drs. Cooper and Muir (1) in a recent issue of *Critical Care Medicine* and the related editorial by Dr. Michard (2). They agree that continuous cardiac output measurement is not able to correctly predict major cardiac output changes during alterations of hemodynamic status. One of the reasons for such inaccurate measurements might be a low-quality arterial pressure signal, which can be over- or underdamped, as underlined by the authors. However, there is another cause that will occur in the presence of a good-quality pressure waveform: Any change in afterload conditions can be responsible for inaccurate stroke volume value prediction in the absence of a new cardiac output calibration. The continuous car-

diac output measurement is based on the assumption that stroke volume is proportional to the area under the systolic part of the arterial pressure waveform divided by aortic impedance, which represents left ventricular afterload. Considering that aortic impedance is constant, any change in the area of the systolic part of aortic pressure waveform would be due to a change in stroke volume. However, it is well established that during acute hemodynamic alterations, aortic impedance is modified by the baroreflex intervention, in order to keep arterial pressure in a normal range value, but also at times by vasodilating or vasoconstricting mediators. Therefore, considering aortic impedance constant when it has, in fact, increased significantly (as in hypovolemia) can lead to an overestimation of stroke volume and cardiac output, as was the case in this study (1). This confirms, unfortunately, that these systems must be recalibrated every time that left ventricular afterload changes.

The author has not disclosed any potential conflicts of interest.

Bernard Lambermont, MD, PhD, University Hospital of Liege—Medical Intensive Care Unit, Department of Medicine, Hemodynamics Research Center, Liege, Belgium

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The authors reply:

We thank Dr. Lambermont for his interest in our study (1) and his insightful commentary. His comments regarding the role of increases in aortic impedance secondary to compensatory vasoconstriction offer an additional explanation as to the apparent overestimation of cardiac output during severe hypotension as by pressure waveform analysis by the PulseCO system (LiDCO Ltd, London, U.K.). While we did allude to the potential role that changes in arterial compliance would have on the arterial waveform, we did not specifically address changes in arterial impedance in our discussion in the detail that Dr. Lambermont does in his letter. We agree with his opinion that aortic impedance plays an important role in the determination of the arterial pressure waveform and cannot be considered constant after major hemodynamic change. We also agree that the algorithm used to determine cardiac output in this system (which does not take into account changes in impedance) will attribute any change in the arterial waveform to alteration in stroke volume. This could certainly have contributed to the overestimation of cardiac output reported in our study.

The authors have not disclosed any potential conflicts of interest.

Edward S. Cooper, VMD, MS, William W. Muir, DVM, PhD, DACVA, DACVECC, The Ohio State University, Veterinary Clinical Sciences, Columbus, OH

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Continuous cuff pressure control and the prevention of ventilator-associated pneumonia

To the Editor:

We commend Dr. Valencia and coworkers (1) for a well-conducted and important study examining the effect of continuous cuff pressure control on the prevention of ventilator-associated pneumonia. It is not surprising that a difference was not demonstrated by a study of this size, as cuff pressure control can at best reduce, but not eliminate, the rate of leakage of upper airway and gastric secretions. A high-volume/low-pressure (HVLP) cuff, when managed correctly, is an excellent tool for limiting tracheal wall pressure injury when compared with the historical alternative of low-volume/high-pressure cuffed tubes. To perform correctly, the HVLP cuff must have a resting diameter greater than that of the trachea in which it is placed. This means that on inflation within the trachea, there is slack in the cuff material with no circumferential tension in the cuff wall. All the intracuff pressure is therefore transmitted to the tracheal wall, and this provides a convenient means of regulating tracheal wall pressure with the cuff *in situ* (intracuff pressure = tracheal wall pressure). The benefit of tracheal wall pressure control is achieved with a concomitant disadvantage of increased risk for pulmonary aspiration. The slack material in the HVLP cuff wall is in fact an inherent design defect that allows leakage of fluid into the tracheobronchial tree. Within the folds in the cuff material, channels form that allow leakage of fluid to the tracheobronchial tree. The folds are deep within the cuff itself and so are not dependent on the cuff-trachea interface. This leakage is easily and unequivocally demonstrated (with a correctly inflated cuff) in a bench top model and in the pig trachea (2) and has been confirmed in anesthetized patients using direct bronchoscopic visualization of the folds (3) and in the critically ill (2). The effect of this ubiquitous aspiration in the critically ill patient is reflected by the 89% incidence of gastric to pulmonary transfer of material in critically ill patients with HVLP cuffed tubes (4).

Newer cuff technologies have focused on reducing the caliber of the folds by using thinner cuff material. This reduces but does not eliminate the leakage in all tracheal diameters (5). The low-volume/low-pressure cuff (Lotrach, Venner Capital, Singapore, www.lotrach.com) has been developed and shown clinically to eliminate transcuff leakage and pulmonary aspiration when correctly inflated within the trachea using a continuous cuff pressure controller (2).

The pathogenesis of ventilator-associated pneumonia is iatrogenic and multifactorial, and it is vital to use this knowledge to affect the multiple known risk factors. As the incidence of ventilator-associated pneumonia falls with the progressive introduction of preventive measures, there will be a requirement for increasingly large (and probably multicenter) studies to prove the efficacy of individual preventive measures, and possibly combinations of these measures.

New translaryngeal and tracheostomy tube technologies should be developed to provide continuous and safe cuff pressure control, an adequate securing mechanism to reduce unplanned extubation, luminal biofilm reduction, protection against pulmonary aspiration, and convenient subglottic secretion drainage and cleansing—this is the challenge!

Peter J. Young, MD, Queen Elizabeth Hospital, Critical Care Unit, London, United Kingdom; Duncan L. Wyncoll,