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Kidney and Brain, an Unbroken Chain

The kidney is one of the organs most affected in critical illness. Depending on the primary reason for admission and type of intensive care unit, up to one-half of critically ill patients will experience acute kidney injury (AKI), defined by consensus guidelines as an acute decrease in glomerular filtration rate that manifests as a change in serum creatinine or urine output (1). The strong dose-dependent association between AKI, short- and long-term mortality and morbidity, and worsening chronic kidney and cardiovascular disease is well documented (2–4). The risk of other complications is higher among patients with AKI and, not surprisingly, an episode of AKI significantly increases hospital cost, especially in the setting of sepsis and mechanical ventilation (5, 6). Acute brain dysfunction is another increasingly recognized complication, with lasting consequences among critically ill

patients. Although seemingly intuitive, the association between AKI and delirium and coma has not been well studied. In their elegant study in this issue of the *Journal*, Siew and colleagues (pp. 1597–1607) (7) address this gap by examining the association between AKI and daily mental status in the secondary analysis of data from a prospective cohort study examining the risk factors of long-term cognitive impairment among critically ill patients with acute respiratory failure and/or shock (8).

Out of 521 patients enrolled between 2007 and 2010, the authors used single-center data for 466 patients without preexisting severe kidney disease, and available serum creatinine measurements, to stage AKI using consensus Kidney Disease Improving Global Outcomes criteria. Mental status was assessed twice daily by trained research personnel up to 30 days after enrollment and was defined as normal, coma (Richmond Agitation-Sedation Scale < −4), or delirium (positive Confusion Assessment Method while in the intensive care unit). Using first-order multinomial transition models, the probability of each mental status outcome was estimated as a

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function of the previous day's mental status, most current AKI status, sex, race, nonrenal organ failure, sepsis, and sedative exposure. Out of 5,056 total patient-days included in the study, mental status was normal during 2,672 (52.8%), delirium during 1,655 (32.5%), and comatose during 740 (14.6%). The prevalence of AKI was 65%, and 10% of patients with AKI were administered renal replacement therapy (RRT). Among patients not requiring RRT, moderate and severe AKI were associated with 2.5-fold and 3-fold increases in the odds of delirium and coma, respectively. Among the small proportion of patients receiving RRT, the association between severe AKI and both outcomes was attenuated when compared with non-RRT days. Nonrenal Sequential Organ Failure Assessment score was not associated with either outcome, whereas sepsis demonstrated a substantially weaker association. The most important determinant of each outcome was the previous day mental status that, by the nature of transitional modeling, reflected the combined effect of all covariates that influenced mental status during the period of time before the current observation. As expected, the sedative dose was a significant determinant of delirium and coma. Although the reduced renal clearance contributed to the observed association between AKI and delirium, a subgroup analysis of patients who never received a benzodiazepine demonstrated a preserved association, thus confirming the existence of other mechanisms contributing to this association.

Markedly increased incidence in cerebrovascular disease (ischemic and hemorrhagic stroke) and accelerated cognitive dysfunction (delirium, encephalopathy, and dementia) are well-recognized complications of chronic kidney disease, and the risk for their occurrence is proportional to the decline in glomerular filtration rate. The kidney and brain share the susceptibility for microvascular injuries that may be a consequence of their vascular supply, as they are both low-resistance end organs exposed to high-volume blood flow throughout the cardiac cycle (9). The accelerated atherosclerosis in chronic kidney disease is mediated by both traditional and kidney-specific risk factors (such as oxidative stress, inflammation, low glomerular filtration rate, albuminuria, malnutrition, and hyperhomocysteinemia) and may further accentuate the chronic degenerative changes in both organs (10).

AKI is a hyperinflammatory state, mainly but not exclusively through activation of the innate immune system via toll-like receptors. The augmented local and systemic production of potent inflammatory cytokines, such as tumor necrosis factor and IL-6, contributes to harmful brain-kidney interaction (11, 12). The inflammatory processes during AKI increase oxidative stress and might induce secondary alterations in water and electrolyte balance, leading to an accumulation of uremic toxins, such as guanidine, guanidine-succinic acid, methylguanidine, and creatinine (13). Furthermore, uremia alters the metabolism of neurotransmitters such as dopamine and in animal models leads to learning and memory issues, anxiety, and depression (14). Thus, recurrent episodes of AKI may accelerate not only progressive kidney damage but also brain damage.

Siew and colleagues remind us of the critical role the kidney plays in maintaining the fragile homeostasis in critically ill patients (7). Intensivists should keep in mind that most benzodiazepines and opiates, and their metabolites, are cleared by the kidney, so these drugs should be used with caution or avoided entirely in patients with AKI. Studies of the role of RRT on changing neurologic prognoses in patients with chronic renal failure have not been

conclusive to date (10). This study provocatively resurrects a hypothesis to be tested—whether RRT diminishes neurotoxicity in AKI by clearing sedatives, antibiotics, or other metabolites. Most importantly, with new approaches to detecting early AKI now emerging (15), our ability to prevent or ameliorate the progression of AKI detected in its early stages needs to be tested. If successful, such interventions may prove to attenuate the risk of other organ dysfunctions, including the brain. ■

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Expiratory Diaphragmatic Recruitment in Acute Respiratory Distress Syndrome

A Happy Coincidence or Much More?

End-expiratory lung volume (EELV) is too often incorrectly thought of as a passive phenomenon, whereby elastic recoil of the lung and chest wall reaches a placid equilibrium. The physiology of EELV, however, is more complex than this. After administration of a neuromuscular blocking agent, EELV decreases by 500 ml or more (1). Accordingly, EELV cannot simply be the result of a balance between elastic recoil pressures of the lung and a relaxed chest wall. On the contrary, the decrease in EELV after neuromuscular blockade results from an interplay of several factors, including shifts of intrathoracic blood (2), cranial displacement of the diaphragm (1), and cessation of end-expiratory inspiratory muscle activity (3). The latter is not limited to end exhalation, but accompanies exhalation in its entirety (Figure 1). In asthma, inspiratory muscle activity during exhalation, also known as postinspiratory inspiratory muscle activity (4–6), is sufficient to break expiratory airflow (4). As a result, lung volume does not fall to the level achieved by complete muscle relaxation, even in the absence of expiratory flow limitation (7). The active increase in EELV maintains airway patency (6) and minimizes flow limitation during bronchoconstriction (7).

In this issue of the *Journal*, Pellegrini and colleagues (pp. 1608–1616) expand our understanding of postinspiratory inspiratory muscle activity by investigating a pig model of mild acute respiratory distress syndrome (8). The investigators tested the hypothesis that postinspiratory diaphragmatic activity stabilizes peripheral airways and reduces cyclic expiratory lung collapse. They noted that the decrease in EELV obtained by reducing the ventilator's positive end-expiratory pressure (PEEP) during spontaneous breathing was associated with increases in expiratory electrical activity of the diaphragm—a finding confirming the observations of Allo and colleagues (9) who reported that application of PEEP is associated with a dose–response reduction in expiratory diaphragmatic electrical activity. In addition, using computed tomographic imaging, Pellegrini and colleagues (8) noted, for the first time, that expiratory diaphragmatic activity was associated with delayed and reduced expiratory collapse and increased lung aeration. The investigators conclude that the diaphragm protects against lung collapse during exhalation.

Pellegrini and colleagues (8) recorded the electrical activity of the crural diaphragm using an esophageal catheter equipped with multiple array electrodes. Accordingly, they had to rely on complex data processing to account for the movement of the diaphragm relative to the electrodes to eliminate the influence of the electrocardiogram, motion-induced disturbances, and background noise (10). The soundness of this approach is supported by robust experimental evidence (10, 11), suggesting that diaphragm electrical signals during exhalation were not artifactual, but true biological phenomena.

The study was not designed to elucidate the mechanisms eliciting postinspiratory diaphragmatic activity. Consequently, we can only speculate on this issue. Discharge of intrapulmonary afferents has been implicated with postinspiratory diaphragmatic activity (4, 10). Studies in infants and animals suggest this to be a reflex response induced by lung derecruitment (10). Experimental vagotomy abolishes this reflex (10). Intrapulmonary afferents, however, are not indispensable for reflex responses of inspiratory muscles (12). Indeed, the discharge of diaphragmatic muscle spindles (13) can modulate muscle recruitment even in vagotomized patients (12). This observation raises the possibility that, in the study by Pellegrini and colleagues (8), diaphragmatic shortening by the application of PEEP could have unloaded muscle spindles (13) and, thus, reduced the discharge of type Ia sensory fibers that innervate them. Type Ia sensory fibers are facilitatory on α motoneurons (13). Therefore, a reduction in type Ia afferent discharge, if it occurred, could have participated in the PEEP-associated decrease of postinspiratory diaphragmatic activity (8).

In spite of similar levels of external PEEP, Pellegrini and colleagues (8) noted that lung aeration was better preserved when the diaphragm contracted during exhalation than during controlled mechanical ventilation. They reason that the purpose of expiratory diaphragmatic contraction was to delay and reduce the expiratory collapse and to increase lung aeration. Is this finding a happy coincidence, or can it be interpreted in teleological terms? To answer this question, the investigators should have recorded the electrical activity of the diaphragm after vagotomy (9, 13, 14). If vagotomy reduces or eliminates postinspiratory diaphragmatic activity, it would be more plausible to support a teleological underpinning of their observations (8). This possibility is backed by a previous report of a decrease in the diaphragm's tonic electrical

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