Distant organ injury following acute kidney injury

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ACUTE KIDNEY INJURY (AKI) is associated with unacceptably high mortality that can range from 40 to 60% in some cases (14). The incidence of AKI continues to increase (15, 16) and is associated with a changing spectrum of illnesses, significant comorbid and extrarenal complications (12), and unsatisfactory preventive or treatment strategies (5). The etiology of AKI is diverse, and ischemia constitutes the major cause of this condition. Ischemic AKI is a dynamic process that often coexists with multiple organ failure and involves hemodynamic alteration, inflammation, and direct injury to the tubular epithelium (9). Interestingly, renal failure per se usually is not the cause of death in AKI (7), but rather both cardiogenic (2, 10) and noncardiogenic acute lung injury (ALI) (13) account for the high mortality associated with AKI. These comorbid conditions can explain the failed treatment regimens, especially when mortality is used as a clinical trial end point. Currently, the mortality of combined AKI and ALI is extremely high and may approach 80% (11). Therefore, defining the mechanism by which AKI causes ALI is important if we are to be successful in reducing overall mortality associated with AKI. Experimental studies demonstrated increased pulmonary vascular permeability, lung edema, alveolar hemorrhage, and leukocyte trafficking following ischemic AKI (1, 6, 8). The recent work of Hoke et al. (4) has shed new light on the role of the kidney in lung injury. In their study, they sought to determine the effect of an acute cessation of kidney function on lung injury. The absence of clearance was achieved by either bilateral nephrectomies or by bilateral renal pedicle clamps. The latter method using bilateral pedicles clamp for 22 min was associated with effects related to ischemia-reperfusion. AKI induced by ischemia-reperfusion or bilateral nephrectomy was associated with a change in level and pattern of serum cytokines. However, lung injury was similar following renal ischemia-reperfusion or bilateral nephrectomies. These results suggest that the absence of kidneys results in lung injury independent of ischemia-reperfusion. By inference, these results indicate a potentially important role that the kidneys play in maintaining serum cytokine balance and pulmonary homeostasis.

In this issue of the American Journal of Physiology-Renal Physiology, Hassoun and colleagues (3) addressed the functional and genomic response of the lung following acute renal ischemia-reperfusion injury or bilateral nephrectomies. Interestingly in contrast to the results of Hoke et al. (4), these authors found bilateral renal ischemia-reperfusion injury and bilateral nephrectomies produced disparate effects on lung structure and function. They further correlated these changes with differential lung transcriptome using a global gene expression-profiling model. Global gene expression profiling is a robust tool for identification of diagnostic and mechanism-related candidate genes and can also provide insights into mechanisms of gene regulation, evolution, and the etiology of disease. Their data provide clear distinctions of ischemia-related changes compared with bilateral nephrectomy-related changes in the lung genomic profile. Using bioinformatic analysis, they identified several potentially important genes of an early phase of the immunoinflammatory pathway and a later phase of the apoptotic pathway. These data are scientifically and clinically relevant in defining the complex cross talk between the lung and kidney and will provide insight into human AKI.

These new data by Hassoun et al. (3) and Hoke et al. (4) leave unresolved whether organ ischemia-reperfusion injury is necessary to elicit distant lung dysfunction. Different clamp times between the two studies may be responsible for the discrepancy observed in lung injury. Because there was no direct measure of intravascular volume, this factor cannot be excluded as a contributor to acute lung injury. Additional studies will be necessary to carefully address the contribution to lung injury of increased pulmonary capillary pressure. Furthermore, a more detailed analysis of the mechanism of lung injury is necessary including the role of immune cells and other resident cells. Analysis of lung gene profiles in response to kidney injury will be important in identifying novel genes that may contribute to the pathogenesis of distant lung injury. Ultimately, these studies will need to be translated to human AKI with hopes of improving the morbidity and mortality associated with this devastating disorder.

GRANTS

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REFERENCES


