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The Yin and Yang of the Renin–Angiotensin–Aldosterone System in Acute Kidney Injury

Despite intensive research, the pathophysiology of acute kidney injury (AKI) in critical illnesses remains poorly understood, as do the links between AKI and poor outcomes. Post–cardiac surgery AKI is not exempt. Multiple, heterogeneous mechanisms are likely in play. Hemodynamic factors, systemic inflammatory response, and cardiopulmonary bypass–induced hemolysis certainly contribute (1, 2). Other contributing factors remain unrecognized or underexplored, such as the complex role of the renin–angiotensin–aldosterone system (RAAS) (3).

In a fascinating study published in this issue of the *Journal*, Küllmar and colleagues (pp. 1119–1126) report the association between postoperative plasma renin level and the risk of developing AKI after cardiac surgery (4). Plasma renin levels measured 4 hours after cardiopulmonary bypass were strongly associated with AKI, whereas preoperative values were not. Patients with higher postoperative plasma renin levels and higher changes in plasma renin compared with preoperative values (Δ-renin) developed more AKI than patients with lower levels and smaller changes. Patients with AKI had a median (interquartile range) rise in plasma renin of 99.6 μU/ml (6.7, 318.0; $P < 0.001$). This Δ-renin was the strongest predictor of postoperative AKI in the study (area under the curve–receiver operating characteristic, 0.817) and superior to urinary AKI biomarkers DKK3 and [TIMP-2]* [IGFBP7].

The primary hypothesis of the authors is that an angiotensin II deficit occurs after cardiac surgery to explain these findings. In a feedback loop, renin is released in response to decreased activation of the AT1R (angiotensin II type 1 receptor) by angiotensin II (Figure 1, Scenario 1). This can be caused by either impaired generation of angiotensin II or AT1R blockade. Angiotensin II is produced when the endothelial membrane–bound enzyme ACE (angiotensin-converting enzyme) cleaves angiotensin I. Conditions associated with endothelial dysfunction, such as septic shock or cardiopulmonary bypass, can reduce ACE activity, decrease angiotensin II, and increase renin levels (5, 6). Decreased expression of AT1R was also reported in sepsis-associated AKI (7). This hypothesis is supported by several findings in Küllmar and colleagues, including higher and more prolonged vasopressor requirements, high Δ-renin levels, and higher renin over aldosterone ratio in patients with AKI. Of note, although patients treated with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) had higher plasma renin levels and overall higher risk of AKI, no interaction was found between ACEi/ARB therapy and Δ-renin for predicting AKI.

An alternative hypothesis to that of Küllmar and colleagues is that significant activation of the RAAS occurs after cardiac surgery (with consequently high angiotensin II tone), triggering intrarenal vasoconstriction, decrease in renal blood flow, and regional inflammation (Figure 1, Scenario 2). Unfortunately, plasma angiotensin II levels were not available in the study, thus making it impossible to definitively distinguish the two possibilities. The alternate hypothesis is supported by lower blood pressures (a trigger for RAAS activation) in the group with AKI and supranormal plasma levels of both renin and aldosterone after surgery (8). Furthermore, there are many reports of decline in renal blood flow associated with elevated intrarenal vascular resistance and increased angiotensin II levels after cardiac surgery (9, 10). In this line, the use of intrarenal vasodilators has long been proposed to decrease the risk of post–cardiac surgery AKI.

What Are the Implications of This Study?

This study clearly demonstrates that plasma renin elevation after cardiac surgery is associated with AKI risk and strongly implicates the RAAS. The RAAS clearly holds a pivotal pathophysiologic role in cardiovascular and renal diseases, including AKI (11). Elevated plasma renin is associated with poor outcomes both in chronic conditions such as heart failure and acute conditions such as vasodilatory shock. A *post hoc* analysis of the ATHOS-3 trial (angiotensin II versus placebo in catecholamine-resistant vasodilatory shock, defined as a need for norepinephrine >0.2 μg/kg/min) demonstrated that high plasma renin was associated with a risk of death and nonrecovery from AKI (6, 12). Angiotensin II has long been known as a mediator of renal injury in the subacute and chronic settings. Angiotensin II promotes

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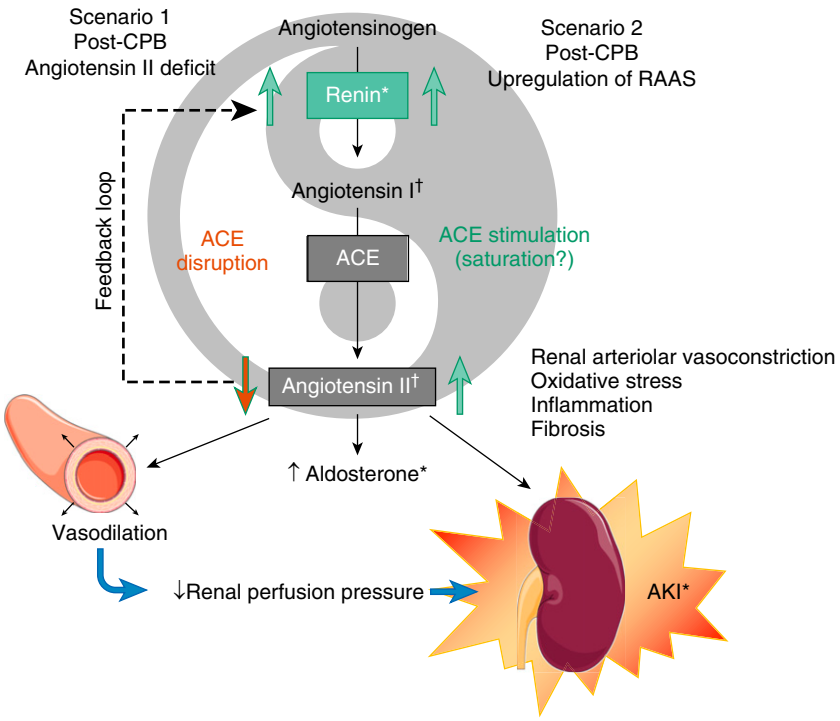

Figure 1. Schematic of possible RAAS perturbations leading to AKI after CPB. ACE = angiotensin-converting enzyme; AKI = acute kidney injury; CPB = cardiopulmonary bypass; RAAS = renin–angiotensin–aldosterone system. *Finding of Küllmar and colleagues. †Indeterminate.

inflammation, oxidative stress, and fibrosis (13). Patients with congestive heart failure, hypertension, and chronic kidney diseases have better outcomes when treated with inhibitors of the RAAS. Data from observational studies yield conflicting results regarding the impact of RAAS blockade during cardiac surgery (8, 14). In a small pilot randomized trial among patients chronically treated with ACEi or ARB, stopping the treatment 48 hours before cardiac surgery was not associated with better outcomes or lower incidence of AKI compared with the group who continued the treatment until surgery (15). RAAS blockade has been suggested to improve post-AKI survival, even though well-designed prospective interventional studies are still lacking (16).

The hypothesis in Küllmar and colleagues would provide ground for a potential use of angiotensin II infusion in post–cardiac surgery distributive shock. Although very appealing, this hypothesis needs to be balanced and refined. Although angiotensin II infusion was associated with better survival only in patients with high plasma renin levels in a *post hoc* analysis of ATHOS-3, the study mostly enrolled patients with sepsis, which might involve different mechanisms (6). Furthermore, administration of angiotensin II was not stratified by plasma renin level. If an angiotensin II deficit exists, it appears somehow relative with increased renin over aldosterone ration in Küllmar and colleagues. To what extent this represents a relative angiotensin deficit in the most severe patients or an activation of the RAAS with saturation of ACE activity is uncertain.

To conclude, the prognostic value and role of the RAAS in AKI is increasingly recognized. The study from Küllmar and colleagues provides important insight in the setting of cardiac surgery. We now must better understand the full profile and timing of RAAS alterations in critical illness and the impact of modulating it, both in the acute and postacute phase. Overall, the impact of short-term infusion of angiotensin II on renal injury and survival in patients with shock remains largely unknown. Although some patients might benefit from RAAS blockade, even during the acute phase of shock, others might benefit from angiotensin II infusion. Still other phenotypes may require both therapies at different times—and many others may do best with no intervention at all. Better phenotyping of patients and more well-designed interventional trials are definitely needed to better the understand the Yin and Yang of the RAAS in AKI and critical illness. ■

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Professor Pangloss and the Pangenome: Does *Staphylococcus aureus* Have the Best of All Possible Worlds?

In Voltaire's 1759 novel *Candide*, the eponymous hero is indoctrinated by his tutor, Professor Pangloss, to believe that "everything is for the best in the best of all possible worlds." In this issue of the *Journal*, Long and colleagues (pp. 1127–1137) present a meticulous and detailed analysis of whole genome sequencing data of 1,382 isolates of *Staphylococcus aureus* from 246 children with cystic fibrosis (CF), attending five U.S. care centers (1). The authors suggest that *S. aureus*, through access to an open pangenome (the collective genetic content of all isolates), develops persistent genotypes, well adapted to the CF lung. For *S. aureus*, this may indeed be "the best of all possible worlds." The authors offer us some intriguing insights into how *S. aureus* achieves this and the implications this may have for the patient with CF.

In the first account of CF, Dorothy Andersen described ". . . plugging of the lumens of most if not all of the bronchi with tenacious, greenish-gray mucopurulent material . . ." (2). We now know that these appearances result from dysfunction of the CF transmembrane conductance regulator, leading to viscid respiratory secretions, failure of the mucociliary escalator, bacterial infection, and bronchiectasis (3). In a subsequent article (4), Andersen described the microbiology of CF as, "Cultures taken early in the course of the disease grow *S. aureus* hemolyticus in nearly every case. . . ." Contemporary registry data support the high prevalence of *S. aureus* early in life, but suggest that the organism is present in over half of individuals with CF well into the fourth decade (5). Long and colleagues describe some of the secrets behind the organism's remarkable longevity in the CF airway.

Almost half of the 246 children studied were infected with multiple, coexisting *S. aureus* lineages, often with different antibiotic susceptibility profiles. The authors show that these infections were more often concurrent than they were sequential. Multiple lineages of *S. aureus* do not primarily arise from hypermutation of resident organisms in the CF airway—mutation rates in this study were comparable to other patient groups. Mutations in the *agrA* and *rsbU* transcriptional regulators, well recognized as important mediators of the acute–chronic transition in *S. aureus*, were common in *S. aureus* isolates in this study and were confirmed to modulate virulence through altered protease production and hemolysis.

But the ability to interrogate relationships between pathogen genotype and patient history in this large cohort adds interesting new detail to the picture of how persistent infection is established. Mutations in *thyA*, which confer resistance to trimethoprim-sulfamethoxazole, were associated with the patient being treated

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