

# Targeting Hypoxia-induced Inflammation

**I**N the current issue of *ANESTHESIOLOGY*, an article by Kim *et al.*<sup>1</sup> from the research laboratory of H. Thomas Lee, M.D., Ph.D., investigates strategies to dampen ischemia-driven inflammation of the kidneys and subsequent multiorgan failure using experimental models of acute kidney injury (AKI). In fact, one of the leading causes of morbidity and mortality in surgical patients is perioperative organ failure, such as failure that occurs in the context of AKI, liver failure, intestinal or myocardial ischemia, stroke, or acute lung injury. A common feature of these perioperative diseases is the presence of hypoxia-induced inflammation.<sup>2,3</sup> The relationship between hypoxia and inflammation under these conditions is interdependent. For example, exposure to ambient hypoxia, as seen during high-altitude mountaineering, is associated with edema of the lungs or brain and systemic inflammatory responses in humans.<sup>4,5</sup> Similarly, short-term exposure of mice to ambient hypoxia (*e.g.*, 8% oxygen over 4–8 h) leads to increased inflammatory cytokine concentrations and pulmonary edema.<sup>6</sup> Moreover, prolonged donor organ exposure to ischemia during organ transplantation is known to enhance graft inflammation and early graft failure.<sup>7,8</sup> For example, the endotoxin receptor toll-like receptor 4 (TLR4) is expressed in the donor kidney during kidney transplantation, and TLR4 expression concentrations increase with prolonged ischemia time. Donor kidneys with a loss-of-function mutation of the TLR4 receptor show attenuated kidney inflammation and an increased rate of immediate graft function.<sup>7</sup> Together, these studies indicate that hypoxia represents an inflammatory stimulus (fig. 1) and suggest that targeting hypoxia-elicited inflammation could represent an important therapeutic approach in perioperative medicine.

Although hypoxia can trigger inflammatory responses, inflammation itself is a cause for tissue hypoxia. During active inflammatory disease, metabolic shifts toward hypoxia are severe.<sup>2</sup> An example for an inflammatory disease characterized by severe tissue hypoxia is acute lung injury. Several factors contribute to pulmonary hypoxia in this context, including attenuated oxygen supply due to airway atelectasis and diminished blood flow to ventilated areas within the lungs. Moreover, the increased metabolic demand by resident cells or recruited inflammatory cells results in profound shifts in the supply/demand ratio of metabolites and oxygen (fig. 1), and hypoxia-driven signaling pathways are activated.<sup>9,10</sup> Tissue hypoxia during inflammation is more than simply a bystander effect; it can greatly affect the develop-

ment or attenuation of inflammation through the regulation of oxygen-dependent gene expression.<sup>11</sup> In fact, studies that target transcriptionally regulated tissue adaptation to hypoxia are an area of intense investigation to prevent hypoxia-induced inflammation and organ failure. For instance, experimental strategies that target hypoxia-driven inflammation have been proposed in the treatment of intestinal, myocardial, or hepatic ischemia; acute lung injury; or AKI.<sup>12</sup>

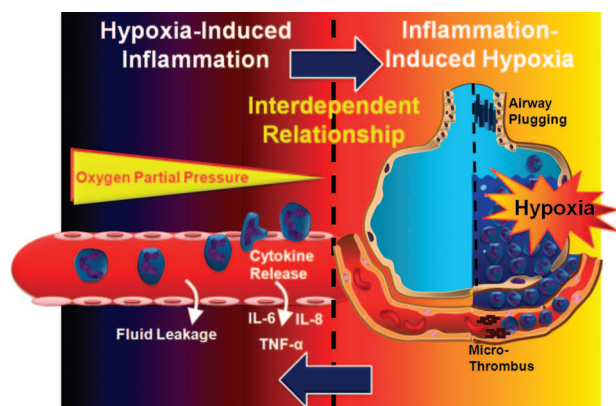
An area in which hypoxia-driven inflammation greatly affects perioperative outcomes is AKI.<sup>13</sup> AKI is characterized by a decrease in the glomerular filtration rate, occurring over minutes to days.<sup>14</sup> In hospitalized patients, more than 50% of AKI cases are related to conditions of renal ischemia or more than 80% are related to the critical care setting.<sup>14,15</sup> A recent study<sup>14</sup> of hospitalized patients revealed that only a mild increase in the serum creatinine concentration (0.3–0.4 mg/dl) is associated with a 70% greater risk of death than in persons without any increase. Moreover, surgical procedures requiring cross clamping of the aorta and renal vessels are associated with renal failure rates of up to 30%. Similarly, AKI after cardiac surgery occurs in more than 10% of patients under normal circumstances and is associated with dramatic increases in mortality. In addition, AKI and chronic kidney disease are common complications after liver transplantation.<sup>16</sup> For example, the incidence of AKI after liver transplantation is at least 50%, and 8–17% of patients require renal replacement therapy.<sup>17</sup> Delayed graft function during kidney transplantation is frequently related to ischemia-associated AKI.<sup>18</sup> In addition, AKI occurs in approximately 20% of patients diagnosed as having sepsis.<sup>15,19</sup>

As shown in the current study by Kim *et al.*,<sup>1</sup> ischemia-induced AKI triggers a downward spiral, leading to subsequent multiorgan failure. The authors elegantly demonstrate that exposure to renal ischemia with concomitant inflammatory activation of the kidneys will result in subsequent gut injury, including breakdown of the intestinal epithelial barrier and massive intestinal inflammation. The intestinal injury will eventually spill over to the liver and cause severe hepatic disease.<sup>1</sup> It is amazing that this downward spiral is initiated by a local injury to the kidneys (fig. 2). As such, it will be of critical importance to understanding the mechanistic aspects of the cross-talk pathway that connects the kidneys and the intestine during hypoxia-driven renal inflammation and to determining how gut inflammation triggers subsequent hepatic injury and multiorgan failure. The current studies demonstrate that volatile anesthetics dampen

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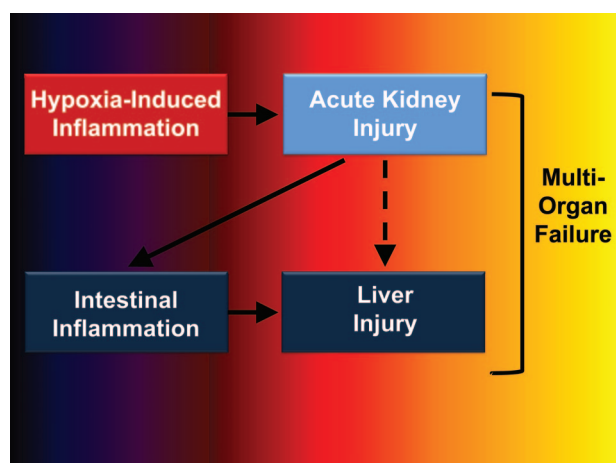
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◆ This Editorial View accompanies the following article: Kim M, Park SW, Kim M, D'Agati VD, Lee HT: Isoflurane activates intestinal sphingosine kinase to protect against renal ischemia-reperfusion induced liver and intestine injury. *Anesthesiology* 2011; 114:363–73.



**Fig. 1.** Interdependent relationship between hypoxia and inflammation. Exposure to ambient hypoxia triggers an acute inflammatory response in different organs, including the kidney, the intestine, the heart, or the lungs. Hypoxia-induced inflammation can manifest itself as increased vascular leakage, accumulation of inflammatory cells in hypoxic organs, or release of inflammatory mediators (e.g., tumor necrosis factor [TNF]- $\alpha$ , interleukin [IL]-6, or IL-8). At the same time (and as shown herein for acute lung injury), inflammation is associated with tissue hypoxia caused by dramatic increases in the demand for metabolites and oxygen by resident cells (e.g., pulmonary and vascular endothelia) and recruited inflammatory cells (e.g., neutrophils). In addition, oxygen supply is attenuated due to pulmonary edema, airway plugging, or microthrombi.

kidney inflammation and multiorgan failure initiated by AKI.<sup>1</sup> In fact, Kim *et al.* found that isoflurane protected against AKI and reduced hepatic and intestinal injury *via* induction of sphingosine kinase 1 in the gut. By combining pharmacological studies with sphingosine kinase inhibitors, and genetic approaches using knockout mice for sphingosine kinase, they elegantly demonstrated a functional role of this pathway in kidney protection. This is consistent with their previous studies<sup>20–22</sup> showing kidney protection *via* sphingosine kinase and sphingosine-1-phosphate-dependent pathways. Interestingly, other experimental studies from



**Fig. 2.** Proposed cross-talk pathways involved in multiorgan failure elicited by acute kidney injury (see Kim *et al.*<sup>1</sup>).

Lee’s laboratory indicate that infusion of local anesthetics (e.g., lidocaine, bupivacaine, or tetracaine) has an opposite effect by potentiating renal dysfunction and kidney inflammation after ischemia–reperfusion injury.<sup>23</sup>

The current studies are consistent with previous research from Lee’s group demonstrating a protective role of extracellular adenosine signaling during AKI. In the extracellular compartment, adenosine stems from phosphohydrolysis of precursor nucleotides, such as adenosine triphosphate and adenosine monophosphate. In fact, conditions of hypoxia (e.g., those that occur during AKI) significantly enhance the production of extracellular adenosine.<sup>24–26</sup> Extracellular adenosine generation and signaling have been strongly implicated in the attenuation of hypoxia-driven inflammation.<sup>12</sup> As such, genetically altered mice that have defects in the enzymatic generation of extracellular adenosine are more prone to develop kidney inflammation and organ dysfunction when exposed to renal ischemia.<sup>27,28</sup> Extracellular adenosine can signal through four individual adenosine receptors (ARs): A1AR, A2AAR, A2BAR, and A3AR. In this context, several studies from Lee’s research team have demonstrated an important role for A1AR in attenuating renal inflammation and preserving organ function during ischemia. For instance, mice with genetic deletion of A1AR exhibit increased renal injury after ischemia and reperfusion injury.<sup>29</sup> Moreover, *A1AR*<sup>−/−</sup> mice show increased mortality, renal dysfunction, and hepatic injury when exposed to murine septic peritonitis.<sup>30</sup> In addition, an elegant proof-of-principle study<sup>31</sup> using a viral overexpression technique revealed that kidney-specific reconstitution of A1AR in *A1AR*<sup>−/−</sup> mice reduces renal ischemia–reperfusion injury. Consistent with the current studies demonstrating a cross-talk pathway between the kidneys, the intestine, and the liver,<sup>1</sup> Lee’s research team was able to demonstrate that protection against AKI *via* A1AR-mediated Akt activation reduces liver injury.<sup>32</sup> Other studies<sup>33</sup> have implicated hypoxia-inducible A2BAR in kidney protection from ischemia. Taken together, these studies highlight that endogenous antiinflammatory pathways that are activated by hypoxia-dependent signaling pathways can be targeted to treat renal inflammation induced by ischemia.

Although many experimental studies, including the exciting contributions of Lee’s research team, have provided new insight into preventing or treating hypoxia-induced inflammation of the kidney, it remains a challenge to implement those approaches into a clinical setting. In fact, treatment approaches to prevent or treat AKI in the perioperative setting are extremely limited. For instance, several clinical trials involving numerous drugs have shown little or no protective effects. Studies investigating the role of dopamine in the prevention of AKI in a perioperative setting have shown no reduction in mortality or renal outcome. Moreover, studies<sup>34</sup> investigating loop diuretics (e.g., furosemide) as a means of kidney protection from AKI observed no reduction in overall mortality. Similarly, studies<sup>35</sup> on the protective effects of the

selective D1-dopamine receptor agonist fenoldopam failed to justify its routine clinical use for perioperative kidney protection. Therefore, future challenges will include systematic approaches to help translate novel experimental approaches of kidney protection from bench to bedside and from mice to human. Moreover, additional mechanistic insights into transcriptionally regulated pathways that dampen hypoxia-elicited kidney inflammation hold the promise for effectively treating hypoxia-driven inflammation. By tapping into endogenous mechanisms of hypoxia-elicited tissue adaptation, such studies could address hypoxia-dependent changes in renal gene expression regulated by micro-RNAs or the direct role of hypoxia sensing and signaling mechanisms in kidney diseases. In fact, I hope that such studies will allow us to further develop therapeutic strategies to dampen inflammation caused by hypoxia while simultaneously increasing ischemia resistance. These therapeutic approaches could be applicable in many perioperative scenarios that involve hypoxia-elicited organ dysfunction, including acute lung injury, organ ischemia, or solid organ transplantation.

**Holger K. Eltzschig, M.D., Ph.D.,** Mucosal Inflammation Program, Department of Anesthesiology, University of Colorado Denver, Aurora, Colorado. holger.eltzschig@ucdenver.edu

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## ANESTHESIOLOGY REFLECTIONS

### Liebig on the 100 Reichsmark Banknote



**Justus von Liebig  
(1803-1873)**

Naturalist Alexander von Humboldt steered Justus Liebig (1803–1873) from Gay-Lussac's private Parisian laboratory (1822–1824) to a chemistry professorship at Giessen in central Germany (1824–1852). There Liebig founded the world's first university-based research laboratory, unveiled chemical isomers, invented his "kali apparatus" (for combustion-based carbon analysis), theorized about chemical radicals, and edited the leading chemical journal. After pioneering nitrogen-based agricultural fertilizers in the late 1830s, Liebig published tomes on agricultural and physiological chemistry. As "*Freiherr* [Baron] von Liebig" by 1845 and "Munich Professor von Liebig" (1852–1873), he presided over the Bavarian Academy of Sciences and then mass produced nutritional meat extracts until his death. From 1935–1945, Liebig's portrait (*above left*) graced the obverse of the 100 Reichsmark banknote. The academic forefather of nearly all of today's professors of organic chemistry, Liebig is hailed by anesthesiologists as the third man to independently discover chloroform. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. [UJYC@aol.com](mailto:UJYC@aol.com).