Prostaglandin-Based Renal Protection Against Contrast-Induced Acute Kidney Injury

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It has been known for >3 decades that the kidneys rely considerably on a group of prostaglandins that are locally produced in both a constitutive and inducible fashion, primarily in the medulla, to regulate renal blood flow and a variety of functions in tubular cells that occupy that region of the kidney. Arachidonic acid released from phospholipids is converted by cyclooxygenase (COX-1 constitutively, COX-2 inducibly) in the kidney to PGI₂, PGE₂, PGF₂α, PGD₂, and thromboxane A₂. PGE₂ and PGF₂α are produced predominantly but not exclusively in the renal medulla, whereas degradative enzymes are present in both the cortex and medulla. Prostaglandins enter the tubular lumen by facilitated transport and are partially reabsorbed from the urine in the distal nephron, with urinary levels reflecting renal synthesis. In response to ischemia, vasoconstriction, norepinephrine, or angiotensin II, the kidney increases prostaglandin synthesis to modulate renal vascular resistance with a predominance of PGI₂ and PGE₂, which are vasodilatory, in contrast to PGF₂α and thromboxane, which are vasoconstricting.¹ These actions may be more pronounced in patients with diabetes mellitus because both the endothelial isofrom of nitric oxide synthase and the COX-1 and COX-2 enzymes lose their normal regulation in the outer medulla of diabetic rats.²,³ In addition to these effects in diabetic patients, prostanoids appear to offset the vasoconstrictive effects of iodinated contrast agents. For example, Agmon and coworkers⁴ examined the effects of vasodilatory prostaglandins on outer medullary blood flow in a rat model of contrast nephropathy and demonstrated that the inhibition of prostanoïd production more than doubled the number of necrotic tubules in the outer medulla. Prasad and colleagues⁵ measured rat medullary blood flow in real time and demonstrated that prostanoids exert more vasodilatory effects than nitric oxide. These findings illustrate the importance of the prostanoïds in maintaining outer medullary blood flow to the kidney. Moreover, these observations provide a physiological basis for the common recommendation that patients discontinue nonsteroidal antiinflammatory agents, which work above and beyond aspirin, before contrast exposure to impair constitutive (COX-1) and inducible (COX-2) production of prostaglandins.

In this issue of Circulation, Spargias and coworkers⁶ present the results of a small but well-executed prospective, randomized, placebo-controlled trial of iloprost, a PGI₂ (prostacyclin) analog, working presumably as a renal vasodilator and cellular protective agent downstream in the prostaglandin cascade (see the Figure), in the prevention of contrast-induced acute kidney injury (CI-AKI). Iodinated contrast is known to affect vascular regulation of blood flow characterized by an initial release of nitric oxide from endothelial cells, triggering a transient vasodilation followed by vascular smooth muscle contraction and more prolonged vasoconstriction.⁷ Because iodinated contrast is water soluble and remains in the vascular space, these effects are transitory during intravascular administration and result in only minor hemodynamic fluctuations and sensations of warmth and discomfort. In the kidneys, however, the water-soluble contrast after glomerular filtration concentrates in the urinary space within the renal tubules, causing tubular cell damage, extravasation into the peritubular space, and constriction of the lattice-like peritubular blood vessels in the outer medulla (the Figure).⁸–¹⁰ Here, sustained vasoconstriction that can last for hours to days occurs, resulting in ischemic injury to the outer medulla, particularly in those with chronic kidney disease and diabetes mellitus.¹¹,¹² When there is considerable damage to enough nephron units in a diseased set of kidneys, a rise in serum creatinine is visible to the clinician, and CI-AKI is noted. Hence, the goal of administering iloprost is to attenuate the peritubular vasoconstriction and potentially to mitigate some of the ischemic injury expected from contrast extravasation. In addition, iloprost may offer cytoprotection to renal tubular cells during the exposure.¹³ A prior trial of PGE₁ (alprostadiol) in the prevention of CI-AKI was promising at an intermediate dose of 20 ng · kg⁻¹ · min⁻¹, presumably achieving a balance between intrarenal vasodilation without systemic hypotension.¹⁴

The present trial used 1 ng · kg⁻¹ · min⁻¹ iloprost (chosen over 2 ng · kg⁻¹ · min⁻¹ to avoid systemic hypotension) 30 to 90 minutes before and 240 minutes after contrast exposure in moderate-risk patients undergoing angiography and coronary intervention. The infusion was generally safe and well tolerated. The CI-AKI end point was observed in 8 of 103 (7.8%) and 23 of 105 (21.9%) (odds ratio, 0.29; P=0.005), meeting the expected 70% relative risk reduction stated in the Methods. Like so many trials in this field, the expected benefit is too great, yielding sample sizes that are too small.
and hence unstable point estimates. If, by chance, 3 more subjects with CI-AKI had landed in the iloprost group from the placebo group, then the P value would have been 0.09, and this trial would be considered neutral. Nonetheless, it is a positive trial and can be considered a useful pilot for larger definitive trials.

Such definitive trials should probably consider an approach to affect the multiple mechanisms involved with CI-AKI, including vasoconstriction, urinary stasis, tubular extravasation, cellular toxicity, oxidative stress, and probably later inflammation. In addition, these trials need to consider more sensitive panel measures of AKI, including injury markers such as neutrophil-gelatinase-associated lipocalin, kidney injury marker-1, interleukin-18, liver fatty acid binding protein, and others. Better indicators of rapidly changing renal filtration function, including serum cystatin C or plasma clearance rates of fluorescent filtration markers in the urine, are needed. Lastly, assiduous measurement of serum creatinine at 48, 96, and 168 hours is required to capture all the cases of CI-AKI according to a creatinine-based definition. Why such a complex array of measures for this problem? What is needed from trials of iloprost or any therapy is internal biological consistency, ie, confidence that markers of pathobiology are consistently demonstrating benefit, neutrality, or harm. Most important, pivotal trials need to position clinically meaningful outcomes that are directly caused by or complicated by CI-AKI as a composite primary end point over ≥90 days, including death, dialysis, persistent kidney injury, myocardial infarction, stroke, heart failure, and rehospitalization for renal, cardiac, and other causes.

In summary, Spargias et al demonstrate that iloprost, an intravenously administered PGI2 analog, is promising as a future prophylactic agent, possibly in combination with other strategies such as intravenous volume expansion and other renal protective agents, in the prevention of CI-AKI.

Disclosures

None.

References


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