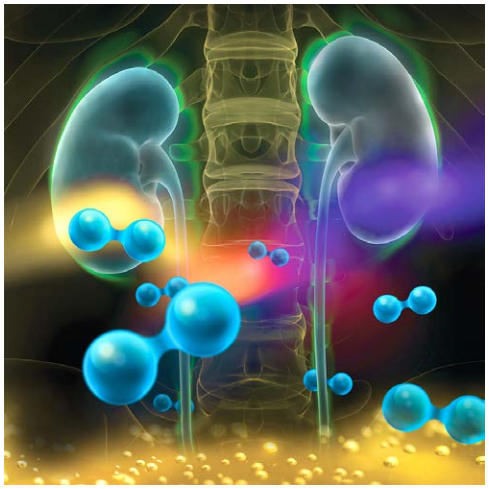
Could Trended Oxygen Partial Pressure in the Urine Be the "ST Segment" Kidney Monitor We've Been Looking For?

Mark Stafford-Smith, M.D., C.M., F.R.C.P.C., M.B.A.

Undiagnosed perioperative ischemia is a serious concern for the practicing anesthesiologist. In this regard, timely sensitive reliable monitors are a key tool to alert, guide, and inform the clinician. Systemic monitors such as pulse oximetry and cardiac output determinations can identify inadequate oxygen delivery to the whole body. However, most pertinent to the current discussion are tools that target organ-specific well-being. A good example is myocardial monitors such as the electrocardiogram (*i.e.*, ST segment) and the development of left ventricular wall motion abnormalities by transesophageal echocardiography (TEE). Paired with effective interventions, the value of all such monitors is their major impact on clinical management and improved surgical outcomes. No anesthesiologist would disagree that, should a patient at any point during the perioperative period unexpectedly develop myocardial ischemia, clinical management would be radically altered from that moment onward with a likelihood that a major adverse outcome might have been averted.



"[There is] a reasonable rationale that oxygen partial pressure in the urine monitoring is ready for more widespread evaluation as a clinical tool…"

Unfortunately for the kidney, current renal monitors do not resemble this paradigm, despite the significant need; acute kidney injury (AKI) is disturbingly common and highly associated with serious adverse outcomes after several major surgical procedures. Of particular interest, then, in this month's issue of Anesthesiology, is the article by Silverton *et al.*[1] outlining their work with a prototype monitor that measures oxygen partial pressure in the urine at the exit from the urinary catheter. In their pilot data from 86 cardiac surgery patients, these authors found that, for individuals with valid urine flow (greater than 0.5 ml/h per kg body weight), lower mean oxygen partial pressure in the urine after cardiopulmonary bypass was independently associated with subsequent AKI.

As a candidate perioperative AKI biomarker, oxygen partial pressure in the urine measurement contrasts favorably with currently available tools. Intraoperative urine output monitoring is tricky to accurately achieve minute to minute and notoriously uninformative, and the role of renal resistive index by TEE is yet to be fully characterized. Elevated renal resistive index (*i.e.*, renal arterial pulsatility), measured intraoperatively by rotating a TEE probe in the stomach posteriorly toward the left kidney, likely reflects insult-related edema and diminished vascular compliance. After cardiopulmonary bypass, intra- and postoperative renal resistive index elevation (peak systolic *vs.* trough diastolic renal Doppler velocities) independently predict subsequent AKI.[2] Other currently available "early" serum and urine AKI biomarkers generally involve obligate delays to obtain signal, requiring at least several hours after surgery to meet criteria that predict subsequent AKI. Of course, while evidence of serum creatinine accumulation remains the accepted standard used in prevalent perioperative AKI diagnostic criteria (*e.g.*, Kidney Disease: Improving Global Outcomes), renal insult defined in such terms permits up to 7 days for serum creatinine rise to confirm AKI postoperatively.

The evidence to support oxygen partial pressure in the urine as a potential monitor of real-time kidney well-being and ischemia rests on a bedrock of basic science accumulated over decades, including (1) recognition that very low oxygen partial pressures deep in the renal medulla are normal at rest, even in healthy individuals (due to vasa recta oxygen countercurrent exchange, a presumed substrate for kidney vulnerability); (2) the physiology of cardiopulmonary

Image: A. Johnson, Vivo Visuals.

This editorial accompanies the article on p. 406. This article has a related Infographic on p. A17.

Accepted for publication May 25, 2021. From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

 Anesthesiology 2021; 135:380–1. DOI: 10.1097/ALN.0000000000003869

<zdoi;. DOI: 10.1097/ALN.0000000000003869>

bypass is typically associated with an exaggerated decline in medullary oxygen partial pressure; and (3) oxygen partial pressure in the urine is a good and almost instantaneous surrogate for renal medullary oxygen partial pressure, in the absence of other confounders.[3,4] Furthermore, numerous studies demonstrate associations between low oxygen partial pressure in the urine during cardiac surgery and subsequent AKI. In fact, whether low oxygen partial pressure in the urine occurs during or after cardiopulmonary bypass, or at other times in the procedure, particularly to greater degrees or for longer periods, it has been associated with subsequent development of AKI.[5] The findings of Silverton *et al*. are wholly consistent with such past studies, supporting the value of low oxygen partial pressure in the urine, reflected in this pilot study using a prototype technology, as a relevant biomarker for subsequent post–cardiac surgery AKI. Notably, while oxygen partial pressure in the urine monitoring has also been studied for noncardiac surgeries, including some that link low oxygen partial pressure in the urine with poorer renal outcome, this topic is considerably less explored.[5]

Combining the evidence provides a reasonable rationale that oxygen partial pressure in the urine monitoring is ready for more widespread evaluation as a clinical tool, particularly during cardiac surgery. However, the proof of concept that oxygen partial pressure in the urine monitoring could guide potential reno-protective interventions to reduce AKI (*e.g.*, enhancing perfusion through the addition of inotropic support to "improve" oxygen partial pressure in the urine) has not been tested clinically. Importantly, there are also caveats in the interpretation of oxygen partial pressure in the urine. Pharmacologic interventions that directly reduce oxygen consumption in the loop of Henle (*i.e.*, loop diuretics) can cause oxygen partial pressure in the urine to rise, and be confused with improved renal physiology, whereas these agents are actually suspect nephrotoxins and ill-advised in the treatment of patients at risk for AKI. Additionally, Silverton *et al*. excluded patients with oliguria, possibly because the authors had concerns that oxygen partial pressure in the urine is less useful in this setting, although there is little evidence to base this assumption on.

Another obstacle to introducing oxygen partial pressure in the urine monitoring into routine practice is lack of rationale for its use, when almost no proven reno-protective interventions exist. Unfortunately, this dispute resembles the chicken and the egg argument. In the search for renoprotective agents, until valid tools that reflect *real-time* well-being of the kidney are available to provide prompt guidance (*e.g.*, oxygen partial pressure in the urine), even interventions that have the potential to benefit the ailing kidney are being used blindly. Such dilemmas can only be reconciled for oxygen partial pressure in the urine monitoring through more research. Future studies are required to further validate the novel oxygen partial pressure in the urine monitoring technology reported by Silverton *et al*. in a multicenter setting. Furthermore, interventional studies are needed that seek to demonstrate a clinical value to oxygen partial pressure in the urine monitoring, as the putative renal "ST-segment" monitor, to alert clinicians to the need for and/or to guide the use of reno-protective therapies that demonstrably improve renal and overall outcome.

There is no question that, while much is already known about oxygen partial pressure in the urine, there is much still to know. However, an undeniable need exists for a *real-time* monitor of renal well-being, and the rationale for oxygen partial pressure in the urine as a candidate is robust. However, no matter how intuitive the logic to support such innovation, if urine oxygen monitoring is to progress to the next stage and become that tool for organ-specific ischemia monitoring, it will also need to leap a mighty but fickle hurdle, that of capturing the imagination of clinicians and researchers alike, to garner the support required to explore the value of this concept in the clinical environment.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Corresponence

Address correspondence to Dr. Stafford-Smith: staff002@mc.duke.edu

References

1. Silverton NA, Lofgren LR, Hall IE, Stoddard GJ, Melendez NP, Van Tienderen M, Shumway S, Stringer BJ, Kang W-s, Lybbert C, Kuck K: Noninvasive urine oxygen monitoring and the risk of acute kidney injury in cardiac surgery. Anesthesiology 2021; 135:406–18
2. Cherry AD, Hauck JN, Andrew BY, Li YJ, Privratsky JR, Kartha LD, Nicoara A, Thompson A, Mathew JP, Stafford-Smith M: Intraoperative renal resistive index threshold as an acute kidney injury biomarker. J Clin Anesth 2020; 61:109626
3. Leonhardt KO, Landes RR, McCauley RT: Anatomy and physiology of intrarenal oxygen tension: Preliminary study of the effects of anesthetics. Anesthesiology 1965; 26:648–58
4. Stafford-Smith M, Grocott HP: Renal medullary hypoxia during experimental cardiopulmonary bypass: A pilot study. Perfusion 2005; 20:53–8
5. Evans RG, Iguchi N, Cochrane AD, Marino B, Hood SG, Bellomo R, McCall PR, May CN, Lankadeva YR: Renal hemodynamics and oxygenation during experimental cardiopulmonary bypass in sheep under total intravenous anesthesia. Am J Physiol Regul Integr Comp Physiol 2020; 318:R206–13