Renal Angina: Right Concept...Wrong Name?

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AKI is the loss of kidney function over a period of hours to days. Although the definition is easily stated, operationalizing it in a form that can be readily applied in clinical practice and in research settings has been a challenge. Markers of glomerular filtration, including serum creatinine and urine output, generally lag behind the actual onset of parenchymal kidney injury and reliance on these functional parameters for early detection of kidney damage may delay diagnosis. Although some might argue that this has minimal clinical consequence given the absence of effective pharmacologic interventions, the inability to rapidly diagnose AKI has been one of the barriers to developing effective pharmacologic therapies to mitigate parenchymal damage in the minutes to hours after an inciting insult (1). AKI is not a homogeneous syndrome, which further complicates the situation. Patients may sustain a reduction in kidney function from fluctuations in renal perfusion or obstruction to urine flow without sustaining significant parenchymal damage. Thus, a major focus in AKI research over the past decade has been the identification and validation of novel biomarkers of kidney damage to facilitate rapid identification of patients with intrinsic AKI (2).

By analogy with cardiology, this quest for biomarkers has been characterized as a search for a “renal troponin” that will allow transformation of the management of AKI from the current paradigm of supportive care, as characterized the management of acute myocardial infarction before the current era of lytic therapy and percutaneous coronary intervention, to a new paradigm of biomarker-guided targeted intervention (3). Although multiple candidate urine and plasma biomarkers have been identified, including kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, IL-18, liver fatty acid binding protein, and several others, to date, none has been demonstrated to have sufficient diagnostic discrimination to transform the management of AKI as cardiac troponin and other biomarkers transformed the management of acute myocardial infarction.

One of the potential reasons for the disappointing performance of these biomarkers has been difficulty in identifying the correct population for their application. Simply stated, unlike acute myocardial infarction, AKI does not hurt. Although cardiac troponin has high sensitivity and specificity for the diagnosis of acute myocardial infarction when assayed in patients with retrosternal chest pain and shortness of breath, it has poor diagnostic discrimination when measured in patients with atypical or absent symptoms.

Prompted by recognition of the need to identify patients at high risk for AKI in order to effectively utilize kidney injury biomarkers in clinical practice, Goldstein and Chawla proposed the concept of “renal angina” in a commentary published in CJASN nearly 4 years ago (4). In their conceptual model, renal angina is defined by a combination of risk factors (e.g., age, diabetes, CKD, sepsis, cirrhosis, postsurgical state, and critical illness) and clinical context. They proposed that among high-risk patients, the development of oliguria, any increase in serum creatinine, or development of fluid overload constitutes a “renal anginal equivalent” and should prompt immediate evaluation for evidence of impaired renal perfusion and should trigger more frequent monitoring of serum creatinine and urine output and assessment of biomarkers to facilitate the diagnosis of AKI.

Over the past 4 years, Goldstein, Chawla, and colleagues have published a series of articles attempting to operationalize this concept of renal angina, including two articles in this issue of CJASN (7,8). Basu and colleagues developed a pediatric renal angina index (RAI), calculated as the product of scores for risk of AKI (very high risk: 5 points; high risk: 3 points; moderate risk: 1 point) and clinical signs of injury (no decrease in estimated creatinine clearance [eCCl] or <5% fluid overload [FO]: 1 point; 0%–25% decrease in eCCl or 5%–10% FO: 2 points; 25%–50% decrease in eCCl or 10%–15% FO: 4 points; ≥50% decrease in eCCl or ≥15% FO: 8 points). They defined a RAI score ≥8 as renal angina and reported that its presence on admission to the intensive care unit predicted the development of severe AKI (defined as a >200% increase in serum creatinine 72 hours after intensive care unit admission), with a C-statistic of 0.74–0.81, a positive predictive value of 18%–40%, and a negative predictive value of 92%–99% (6). In this issue of CJASN, Basu and colleagues report on the combination of the RAI and three candidate biomarkers—neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-8, and neutrophil elastase-2—in a cohort of 214 children with severe sepsis or septic shock (7). Although individually the biomarkers provided less diagnostic discrimination for AKI than the RAI, when they were combined with the RAI, either individually or in pairs, the overall predictive performance for diagnosis of AKI improved, albeit modestly.

Also in this issue of CJASN, Cruz and colleagues report on a different model for operationalizing renal angina in adults (8). Using recognized acute (hypotension, high-risk surgery, nephrotoxin exposure, and sepsis) and major (advanced age, diabetes mellitus,
CKD, and cardiovascular disease) and minor (hypertension, morbid obesity, hyperbilirubinemia, cerebrovascular accident, AIDS, and malignancy) chronic risk factors for the development of AKI, they categorized patients into the following strata: very high risk (septic shock or receiving vasopressors and mechanical ventilation), high risk (one acute and one major chronic risk factor, one acute and two minor chronic risk factors, or two acute risk factors), and moderate risk (one major chronic or one acute risk factor, or multiple chronic risk factors and no acute risk factors). They then defined renal angina based on the daily increase in serum creatinine, using smaller thresholds in higher-risk patients (≥0.1 mg/dl if very high risk, ≥0.3 mg/dl if high risk, and ≥0.4 mg/dl if moderate risk). In a cohort of 506 critically ill patients, application of this renal angina construct predicted the development of severe AKI (defined as a ≥200% increase in serum creatinine or RRT within 7 days) with a sensitivity of 92%, specificity of 62%, positive predictive value of 16%, and negative predictive value of 99%. Notably, >90% of the patients who fell into the very-high-risk category met the definition of renal angina.

Although there is clearly a need for early identification of patients with AKI, there are several aspects of renal angina that are problematic. The first issue is with the terminology itself. It should be recognized that although the original use of the term as a rhetorical device highlighted the parallel with acute coronary syndrome, it was a misuse of the word angina. This term is derived from the Latin word angina, where it refers to an acute throat infection (quinsy), and from the Greek αγγία (ankhône) meaning strangling and refers to spasmodic attacks of intense suffocative pain (9). Although there are many clinical syndromes beyond cardiac angina (angina pectoris) that use the term angina, including Ludwig’s angina, Vincent’s angina, herpetic angina, and mesenteric angina, all of these are characterized by pain. Thus, the term renal angina is incorrect from an etymologic standpoint and should be abandoned.

A second and more important issue derives from the relationship between the criteria used to define renal angina and the consensus definitions for AKI. Unlike the patient presenting with chest pain, in which the manifestations that prompt diagnostic evaluation for myocardial infarction are distinct from the criteria for diagnosis, the manifestations of renal angina—change in serum creatinine (or in the case of the pediatric RAI, change in eCcr) and change in urine output—are the same as those used to diagnose AKI just of a lesser degree. It is not possible to sustain a 200% increase in serum creatinine without first having a 100%, 50%, or even a 0.1 mg/dl increase in serum creatinine. Similarly, in order to have 6, 12, or 24 hours of oliguria, one must first have a shorter duration of diminished urine output. The underlying concept of renal angina is that in high-risk patients, falling short of the diagnostic criteria for AKI does not mean absence of disease and should heighten vigilance in monitoring kidney function. Conceptually, this returns full circle to the initial RIFLE criteria for AKI (10) in which risk (≥50% increase in serum creatinine or oliguria for 6 hours), injury (≥100% increase in serum creatinine or oliguria for 12 hours), and failure (≥200% increase in serum creatinine, oliguria for 24 hours, or anuria for 12 hours) were not stages of AKI, as they were recast in the subsequent Acute Kidney Injury Network (11) and Kidney Disease Improving Global Outcomes (12) criteria, but rather a progressive series of definitions providing increasing specificity at the expense of decreasing sensitivity. The proposed construct of renal angina merely widens the net, moving to a more sensitive set of criteria in patients identified as having greater risk factors.

These concerns regarding both the terminology of renal angina and the linked relationship between the proposed criteria and the definition of AKI do not diminish the need for a readily ascertainable AKI risk index. The ability to identify the appropriate high-risk population for biomarker measurement will be critical to their effective clinical application. The concept proposed by Goldstein and Chawla and the current validation studies have helped move the field forward; however, there is still much more work to be done.

Disclosures
P.M.P. is a Deputy Editor of CJASN and serves as a consultant for Complexa, Inc.

References

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See related articles, “Incorporation of Biomarkers with the Renal Angina Index for Prediction of Severe AKI in Critically Ill Children,” and “Utilization of Small Changes in Serum Creatinine with Clinical Risk Factors to Assess the Risk of AKI in Critically Ill Adults,” on pages 654–662 and pages 663–672 respectively.