Clinical Approach to Advanced Renal Function Testing in Dogs and Cats

Barrak M. Pressler, DVM, PhD

KEYWORDS

• Biomarkers • Fractional excretion • Glomerular filtration rate
• γ-Glutamyl transpeptidase • Microalbuminuria • Urine

KEY POINTS

- Advanced renal function tests may allow earlier detection of reduced renal functional mass and localization of damage to a particular nephron segment, and are required for diagnosis or exclusion of some causes of kidney injury.
- Measurement of glomerular filtration rate (GFR) allows for precise quantitative assessment of remaining filtration and excretion ability by the kidneys.
- Spot samples of simultaneously collected urine and plasma provide clinically reasonable approximations of total daily urine electrolyte excretion.
- The majority of plasma albumin is size and charge excluded from the ultrafiltrate; glomerular damage results in increased filtration of albumin and excretion into the urine. Microalbuminuria may be detected prior to positive reactions on standard urine protein dipstick pads, and before the urine protein:creatinine (UPC) ratio increases above reference range.
- Urinary *N*-acetyl-β-D-glucosaminidase (NAG):creatinine ratio is increased in dogs with chronic kidney disease, pyelonephritis, uncontrolled diabetes mellitus, pyometra, or X-linked hereditary nephropathy but does not differ before versus after control of hyperadrenocorticism with trilostane or transphenoidal hypophysectomy.

Serum biochemical analysis and urinalysis are the mainstay diagnostic tests for initial detection and estimation of severity of kidney disease in dogs and cats. Increased serum creatinine concentration and impaired urine concentrating ability, however, are relatively insensitive for detecting early kidney injury and do not assist in differentiation between glomerular versus proximal or distal tubular damage. Advanced renal

This article originally appeared in Veterinary Clinics of North America: Small Animal Practice, Volume 43, Issue 6, November 2013.
Funding Sources: Morris Animal Foundation, International Renal Interest Society, and The Ohio State University College of Veterinary Medicine.
Conflict of Interest: Previous funding from FAST Diagnostics.
Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, 601 Vernon Tharp Street, Columbus, OH 43210, USA
E-mail address: pressler.21@osu.edu

Clin Lab Med 35 (2015) 487–502
http://dx.doi.org/10.1016/j.cll.2015.05.001 **labmed.theclinics.com**
0272-2712/15/$ – see front matter

function tests, including GFR testing, determining fractional excretion (FE) of electrolytes, and assay of urine biomarkers, may allow earlier detection of reduced renal functional mass and differentiation of various renal and nonrenal differential diagnoses and assist with localization of damage. This article reviews the principles, indications, and limitations of these tests and describes their use in sample clinical scenarios.

GLOMERULAR FILTRATION RATE

Serum creatinine concentration is insensitive for detecting kidney injury. Increases in serum creatinine concentration are mild and often remain within reference range, until approximately 60% to 75% of all nephrons are no longer functional. In contrast, measurement of GFR allows for precise quantitative assessment of remaining filtration and excretion ability by the kidneys. Example situations when GFR measurement may provide critical information regarding remaining kidney function beyond serum creatinine concentration alone include diagnostic evaluation of dogs and cats with unexplained polyuria and polydipsia, to avoid overdosing of medications that are excreted by the kidneys or that have potential nephrotoxic effects, and to predict risk of overt renal failure after nephrectomy in dogs or cats with unilateral kidney disease, such as tumors or pyonephrosis.

Several methods for determination of GFR have been validated in dogs and cats, all of which report the volume of plasma, which has been cleared over a given interval of time, per kilogram of patient body weight. After injecting a substance (the marker) that is eliminated solely via filtration through the glomeruli and which then passes into the urine without being reabsorbed or further secreted by the tubules, the rate at which the concentration of marker decreases in successive blood samples allows calculation of the plasma clearance and GFR.[1] Assays that measure the rate of marker appearance in urine are more accurate than those that assay marker disappearance in plasma (because few markers are solely excreted via glomerular filtration without any tubular reuptake or secretion); however, urine assays that allow calculation of renal clearance (vs plasma clearance) are more cumbersome to perform because they require collection of all urine produced in a 24-hour period. Fortunately, plasma clearance assays using blood sampling techniques are sufficiently close to renal clearance, such that in the clinical setting urine collection is not required.[1–4]

Several markers have been validated for measurement of GFR in dogs and cats, including creatinine, cystatin C (CysC), iohexol, and radiolabeled molecules. In people, GFR is most commonly estimated (rather than measured) using serum creatinine concentration, body weight, and correction factors based on a patient's gender and race. Unfortunately, formulae for estimating GFR from serum creatinine have not proved accurate in dogs and cats due to greater individual, gender, and breed variation than occurs in people.[5,6] Intravenous administration of a sterile creatinine bolus is safe and cost effective; however, comparison of various markers suggests that exogenous creatinine GFR assays underestimate true GFR, likely due to some excretion into the gastrointestinal tract and perhaps tubular reuptake.[2,7,8] CysC is an endogenous protein produced by all nucleated cells at a constant rate that undergoes glomerular filtration without tubular secretion; however, commercial assays are limited, and comparative studies in dogs have suggested lower specificity for detection of reduced kidney function than exogenous creatinine GFR.[9–11]

Iohexol GFR measurement uses a marker that can be easily obtained by veterinarians and has been well validated for use in dogs and cats, and a commercial assay is available at a reasonable cost to owners. After intravenous bolus injection of the same iodinated contrast agent used in diagnostic imaging studies, plasma samples are