Glomerular Filtration Rate in General Small Animal Practice

Eric H. Linnetz, DVM, DACVIM
Chippens Hill Veterinary Hospital
Bristol, Connecticut

Thomas K. Graves, DVM, PhD, DACVIM
University of Illinois at Urbana-Champaign

Abstract: Quantitative evaluation of renal function in small animal general practice has remained essentially unchanged for decades. Glomerular filtration rate (GFR) is considered the gold standard for evaluating functional renal mass in veterinary medicine. For practical and financial reasons, GFR testing was previously available only at referral veterinary hospitals. Newer techniques for estimating GFR now allow the routine performance of this test in any small animal practice.

For decades, quantitative evaluation of renal function in small animal, primary care practice has been limited to the measurement of serum creatinine, serum urea nitrogen, and urine specific gravity. However, these parameters are rather insensitive because they are altered only after 60% to 75% loss of renal function. They are also not specific because they may be influenced by nonrenal variables or diseases. Although abdominal ultrasonography has dramatically enhanced the ability to evaluate the kidneys in animals with renal disease, it provides no quantitative measure of renal function. The quantitative assessment of functional renal mass in general practice has remained essentially unchanged for more than 50 years.

Measures of renal function that are sensitive to mild decreases in renal function exist. Glomerular filtration rate (GFR) has long been considered the best reflection of renal function in human and veterinary medicine because it is directly related to functional renal mass. However, practical and financial considerations have limited the use of this test to veterinary teaching hospitals, large private hospitals, and research settings. As a result, most private veterinary practitioners do not perform GFR studies, and many are unfamiliar with GFR testing techniques.

Principles of Glomerular Filtration Rate Estimation

Renal excretory function may be conceptually divided into glomerular function (filtration) and tubular function (secretion and absorption). Through a combination of these processes, the kidneys perform their principal physiologic role: regulation of the volume and composition of extracellular fluid. Although glomerular and tubular function cannot be directly measured, they can be estimated based on the principle of clearance.

Clearance is defined as the volume of fluid completely cleared of a substance during a given period of time. This is not an actual volume. Rather, it is the conceptual volume that previously contained the amount of substance that has been removed. For example, if clearance is 10 mL/min, then the amount of substance removed each minute will be equal to the amount present in 10 mL of fluid. Note that clearance refers to the rate at which a fluid is cleared of a substance and not to the quantity of substance removed.

Total plasma clearance is equal to the sum of the individual routes of plasma clearance. One potential route, renal clearance, represents the sum of the processes of glomerular filtration, tubular secretion, renal metabolism, and renal retention of the substance. Urinary clearance refers to the volume of plasma cleared of a substance that eventually appears in the urine. Because not all substances cleared by the kidneys necessarily appear in the urine (e.g., if renal retention or metabolism occur), urinary clearance can differ from renal clearance.

If a substance is solely cleared by the kidneys and undergoes no renal retention or metabolism, then plasma clearance, renal clearance, and urinary clearance will be identical. In this instance, the only route of elimination from...
the plasma is through the kidneys, and all of the substance cleared by the kidneys appears in the urine. Furthermore, if the substance is filtered at the glomerulus and does not undergo tubular secretion, then glomerular filtration represents the only route of removal of the substance from plasma, and any of the three clearances (plasma, renal, or urinary) provides an estimate of GFR. Such a substance is called a filtration marker. The ideal filtration marker is one that:

1. is freely filtered at the glomerulus;
2. is not secreted, absorbed, or metabolized by the renal tubules;
3. is not protein bound in the plasma;
4. does not enter erythrocytes;
5. has no other routes of clearance from the plasma; and
6. does not itself alter GFR.

Inulin is the classic ideal filtration marker. Various techniques for estimating GFR in veterinary medicine exist. They differ by filtration marker, sampling technique, speed, cost, mathematical model, and need for specialized facilities or licensing.

The most obvious difference among techniques is the choice of filtration marker. Filtration markers are classified as either possessing or lacking a radionuclide (BOX 1). Because radionuclides require special facilities, licenses, and training, their use is limited in veterinary medicine. Filtration markers lacking a radionuclide are subdivided into iodinated and noniodinated agents. These markers do not require special facilities, licenses, or handling procedures. Iodinated agents are further classified as either ionic or nonionic and as either hypertonic or isotonic.

**Glomerular Filtration Rate Estimation Using Urinary Clearance**

The historical gold standard for estimating GFR in veterinary medicine is urinary clearance of inulin. Inulin, a fructose polymer, is eliminated from plasma exclusively by glomerular filtration, is not reabsorbed or metabolized in the kidneys, and does not itself alter GFR. Thus, inulin closely meets the criteria for the ideal filtration marker.

To measure urinary inulin clearance, a constant-rate infusion of inulin is administered to establish a steady-state plasma concentration. The bladder is evacuated by urinary catheterization, a period of time is allowed to elapse, and catheterization is repeated to collect the urine formed during the interval. Urine flow (volume of urine produced per unit of time), urine concentration of inulin, and plasma concentration of inulin are measured.

These three parameters—urine flow, urine concentration of inulin, and plasma concentration of inulin—are used to calculate urinary clearance of inulin:

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\text{Clearance} = \frac{\text{urine flow} \times \text{concentration of inulin in urine}}{\text{concentration of inulin in plasma}}
\]

Reported values for normal urinary inulin clearance (mean ± standard deviation) are 3.39 ± 0.73 mL/min/kg for dogs and 3.51 ± 0.60 mL/min/kg for cats. Because measurement of urinary clearance requires urine collection, this technique has several important disadvantages. Urine collection, whether performed by urinary catheterization or with a metabolic cage, is cumbersome and prone to sampling error. In addition, urinary catheterization generally necessitates sedation or anesthesia, which not only poses risk to the patient but also can alter GFR. Thus, estimation of GFR by urinary inulin clearance is impractical for routine use in general practice.

**Glomerular Filtration Rate Estimation Using Plasma Clearance**

An ideal filtration marker allows estimation of GFR by urinary, renal, or plasma clearance. Thus, an alternative to measuring urinary clearance is to measure plasma clearance. Plasma clearance is determined by measuring the rate of disappearance of a marker from plasma after bolus injection. The major advantage of this method is that only plasma samples are required, eliminating the need for urine collection.

Mathematically, the calculation of plasma clearance is more complicated than that for urinary clearance. A plasma
disappearance curve is generated by plotting the logarithm of plasma concentration of the marker versus time (FIGURE 1). Using mathematical models, the area under the plasma disappearance curve (AUC) is calculated. Plasma clearance is then calculated by dividing the dose of the marker administered by the AUC.

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\text{Clearance} = \frac{\text{Dose}}{\text{AUC}}
\]

Plasma clearance of iohexol is particularly suitable for private small animal practice. Iohexol is a sterile, nonionic, iodinated contrast agent. It is commercially available (Omnipaque, GE Healthcare, Princeton, NJ), affordable, extremely stable, and allows for analysis of small sample volumes. Because iohexol is neither ionic nor hyperosmolar, adverse events with its administration are rare, even in patients with compromised renal function. Importantly, iohexol sample analysis and clearance calculation are readily available to private practitioners at the Diagnostic Center for Population and Animal Health at the Michigan State University College of Veterinary Medicine (http://www.animalhealth.msu.edu/Bin/Catalog.exe?Action=Test&Id=1578).

Among the various protocols for plasma iohexol clearance, the most appealing require only three plasma samples drawn 2, 3, and 4 hours after injection. Using this limited sampling strategy, reported values of GFR in healthy dogs include 2.9 ± 0.3 mL/min/kg (mean ± SD) and 1.56 to 2.96 mL/min/kg (range; no median reported). Reported values in healthy cats include 3.64 ± 0.13 mL/min/kg (mean ± SD) and 3.22 to 6.23 mL/min/kg (range; median, 3.68). Adverse events were reported in only one study and were limited to transient vomiting in three of nine cats receiving simultaneous bolus injection of iohexol and inulin.

Another plasma clearance technique for estimating GFR is clearance of exogenously administered creatinine. Creatinine meets most of the criteria of an ideal filtration marker. Although intravenous injection of creatinine may seem counterintuitive, creatinine administration is safe and remarkably well tolerated. Although serum creatinine is a component of azotemia, it does not contribute to uremia, and no adverse events have been reported in dogs or cats. The protocol for plasma clearance of exogenous creatinine is similar to that for plasma clearance of iohexol. Various protocols have been explored in dogs and cats. Although these studies provided encouraging results, more work is needed to establish specific protocols and reference ranges. We know of no commercially available formulation of creatinine for injection. Reagent-grade creatinine has been used in research settings but is not recommended for clinical patients.

**Standardization of Glomerular Filtration Rate to Body Size**

The standard unit of clearance is milliliters per minute (mL/min). When estimated GFR is expressed in mL/min, however, its utility is limited because it does not account for patient size. Normal GFR in mL/min for a cat might differ greatly from that for a dog. Even within the same species, a toy-breed dog would have a GFR that differs greatly from that of a giant-breed dog when expressed in mL/min. To compensate for this variation in patient size, GFR in human and veterinary medicine is typically standardized to some measure of body size. Body surface area (human medicine) and body mass (human and veterinary medicine) are
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Key Points

- Glomerular filtration rate (GFR) is the gold standard for evaluating functional renal mass.
- An affordable, practical technique for GFR estimation is now available to the small animal general practitioner.
- GFR estimation can be useful in many situations in general practice.

most often used. In veterinary medicine, GFR is most often expressed as mL/min/kg, allowing comparison of patients of different size.

A third method of standardization to body size in human and veterinary medicine uses extracellular fluid volume (ECFV).13,14,18 One attractive feature of this method is that the primary role of the kidneys is the regulation of the size and composition of the ECFV. Thus, standardizing GFR to ECFV seems physiologically appropriate. There are techniques for estimating the GFR:ECFV ratio that require minimal patient sampling and do not require measurement of the administered dose of the filtration marker. An in-depth discussion of the principles and methods of using ECFV to standardize GFR to body size can be found in the review by Peters13 and elsewhere.7,14

Indications for Glomerular Filtration Rate Estimation

GFR assessment has many uses in general practice. The following are a few examples:

- Detecting renal disease in animals with nonrenal conditions that impair urine-concentrating ability. Diabetes mellitus, hyperadrenocorticism, hypercalcemia, and diuretic therapy for congestive heart failure are all common causes of impaired urine-concentrating ability in small animals. Animals with these disorders frequently have concurrent renal disease. Detecting nonazotemic renal disease in these patients is difficult because most have polyuria and isosthenuria due to their concurrent condition. In addition, dehydration may cause mild prerenal azotemia, and urine-concentrating ability cannot be used to distinguish this condition from mild renal azotemia in these animals. Only GFR estimation can accurately identify renal disease in these patients.

- Screening hyperthyroid cats before sodium iodide I 131 therapy. Treatment of hyperthyroidism in cats results in a decrease in GFR.24 Methimazole therapy may be used before definitive treatment with sodium iodide I 131 to ensure that the patient tolerates euthyroidism. However, some cats do not tolerate methimazole therapy, or their owners are unable to administer medication. In these cases, GFR estimation can be used to quantify the degree of renal dysfunction. Thus, the clinician could better select which patients are likely to do well with sodium iodide I 131 therapy and which patients are better managed with titrated methimazole therapy or other medical therapies.

- Excluding renal disease as a cause of polydipsia and polyuria before water deprivation. Water deprivation (or, in some cases, gradual water restriction) is used to evaluate challenging cases of polydipsia and polyuria such as central diabetes insipidus, primary polydipsia, and some cases of hyperadrenocorticism. However, nonazotemic renal disease can manifest exclusively with polydipsia, polyuria, and isosthenuria as well. In a renal patient, deliberate induction of dehydration can precipitate an azotemic crisis.25 Thus, GFR estimation is essential to excluding renal disease before instituting water deprivation or restriction in an isosthenuric patient.3,25

Interpretation of Estimated Glomerular Filtration Rate Results

GFR can vary significantly between animals, whether healthy or during various clinical stages of renal disease. Similarly, reference ranges vary because different laboratories and investigators use different iohexol doses, sampling protocols, and analytic techniques. Therefore, it is difficult to define specific ranges of GFR that correlate to subclinical renal disease versus mild, moderate, or severe clinical renal disease. As illustrated by the examples in the previous section, the utility of GFR estimation at our current level of understanding is to distinguish normal from abnormal GFR states or to track changes within the same patient over time. Therefore, estimated GFR results should not be interpreted in isolation, but rather within the context of the signalment, history, clinical signs, and laboratory data for a given patient.

Conclusion

Plasma clearance of iohexol is a practical, affordable, and readily available test. The information gained can be invaluable to the safe and accurate diagnosis of a variety of conditions. It arguably represents the most significant advance in the quantitative assessment of renal function in general practice since the routine availability of serum creatinine and urea nitrogen assays.

References


### 1. Which of the following is not a criterion of the ideal filtration marker?
- a. It is not metabolized by the renal tubules.
- b. It is highly protein bound in plasma.
- c. It is freely filtered at the glomerulus.
- d. It has no other routes of clearance from plasma.
- e. It does not enter erythrocytes.

### 2. Which statement regarding GFR is incorrect?
- a. It is considered the best assessment of renal function in veterinary medicine.
- b. It is insensitive to declines in renal function of <60%.
- c. It is directly related to functional renal mass.
- d. The historical gold standard technique for its estimation is urinary inulin clearance.
- e. It may be estimated with clearance studies but not directly measured.

### 3. The concept of clearance
- a. describes the amount of a substance removed from a fluid during a given period of time.
- b. states that clearance depends on the starting concentration of a substance within a fluid.
- c. applies only to substances in plasma that are removed by the kidneys.
- d. describes the volume of fluid cleared of a substance during a given period of time.
- e. describes the time required for half of a volume of fluid to be cleared of a given substance.

### 4. Renal clearance of a substance does not include
- a. tubular secretion.
- b. glomerular filtration.
- c. tubular absorption.
- d. metabolism by the renal tubular epithelium.
- e. retention of the substance within the kidneys.

### 5. Which statement is false regarding the measurement of urinary clearance of inulin?
- a. It requires collection of urine samples.
- b. It requires sophisticated mathematical models for its calculation.
- c. It requires a constant-rate infusion.
- d. It is the historical gold standard for measuring GFR.
- e. It frequently requires sedation or anesthesia.

### 6. Iohexol is particularly suited to use as a filtration marker in private small animal practice because it is
- a. ionic.
- b. hyperosmolar.
- c. readily analyzed at any commercial laboratory.
- d. very stable.
- e. a very safe radionuclide.

### 7. Which statement is false regarding the measurement of plasma clearance of iohexol?
- a. It requires large sample volumes for analysis.
- b. It requires sophisticated mathematical models for its calculation.
- c. It may be performed with limited serum sampling between 2 and 4 hours following injection.
- d. It does not require collection of urine samples.
- e. It can be readily performed in general practice.

### 8. The principal physiologic role of the kidneys can be described as
- a. producing urine with a high urine specific gravity.
- b. maintaining adequate blood pressure by modulating systemic vascular resistance.
- c. preventing excessive loss of protein through the urine.
- d. metabolism and excretion of drugs and toxins.
- e. regulation of the composition and volume of the extracellular fluid.

### 9. Which of the following does not contribute to plasma clearance of a substance?
- a. glomerular filtration.
- b. hepatocellular metabolism.
- c. binding by plasma proteins.
- d. uptake of the substance by muscle.
- e. secretion into the bile.

### 10. The historic gold standard for estimating GFR in veterinary medicine is
- a. plasma clearance of 99mTc-DTPA.
- b. urinary clearance of endogenous creatinine.
- c. renal clearance of endogenous creatinine.
- d. urinary clearance of inulin.
- e. plasma clearance of iohexol.