Measurement of Renal Function with Radionuclides

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For the nuclear physician who wants to measure renal function, the biggest problem may be having to choose among the dozens of methods that have been proposed. An overview will be presented here. The final selection must depend upon the needs of each clinic as well as its technical and financial resources. Except at very low levels of renal function, almost any of these methods can be more reliable than creatinine clearance.

Renal function has classically been measured as clearance of inulin or para-aminohippurate (PAH), using continuous intravenous infusion. These methods are quite demanding on both patient and physician. While they represent by definition the ultimate in accuracy, the precision (reproducibility) of a single measurement is not great. Homer Smith reported a relative s.d. of 8.9% for glomerular filtration rate (GFR) under ideal circumstances—catheterized normal volunteers in the hands of an expert (*1*). This corresponds to 5.1% relative s.d. for the mean of three measurements, or 95% confidence limits of ±10%. Other methods, though less accurate, may be capable of greater precision, and thus be better for documenting serial changes in an individual patient. The classic procedure has been simplified in many ways. Single-injection methods have been used in place of continuous infusion.

Chemical analysis can be avoided by using radioactive drugs. If the radiopharmaceutical is excreted solely by the kidneys and if its plasma clearance curve can be extrapolated to infinite time (i.e., renal function not too low and patient not edematous), then the collection of urine samples can be omitted. Plasma clearance can be estimated from one or two plasma samples, rather than from the complete clearance curve, with enough accuracy for many purposes. An external radiation detector can be used so that not even plasma samples are needed. While there is a price to pay (in terms of accuracy) for each such simplification, the final result, combining

them all, is no worse than the usual clinical alternative, creatinine clearance (except at very low levels of renal function, where direct or indirect measurement of urine activity is needed) (*2*). Gamma camera methods are faster than creatinine clearance, do not require urine collection, and can be combined with renal imaging to determine the function of each kidney separately (split function).

The nuclear medicine techniques used to measure renal function can be classified in various ways. One is to divide them into methods that require a gamma camera but no blood or urine samples, those that require blood and urine samples but no gamma camera, and those that require both the gamma camera and blood and/or urine samples. Our choice for routine clinical monitoring of renal function is to measure effective renal plasma flow (ERPF) from a single-plasma sample 44 min after injection of iodine-131 (^{131}I) hippuran. This is more accurate than methods based on the gamma camera, and much faster than glomerular filtration rate measurement from technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc] DTPA) plasma clearance. However, it is not for everybody. It requires quantitative wet laboratory skills. In an academic department that does a variety of laboratory work, one can find people with the requisite skills. In a clinic that does only imaging, these skills may be hard to find and not worth developing for the sake of a single test. Even where the technical skills are available, current pressures for cost containment oppose the use of time-consuming skilled manual procedures. For these reasons, simple methods based on the camera alone with no laboratory work are of great interest. A number of groups have reported methods for measuring

renal function using the gamma camera with or without additional blood or urine samples. Of these, the most attractive use only the gamma camera, since if blood or urine samples are required, there is little advantage over the well-tested 44-min ERPF or 3-hr GFR methods that use blood samples alone.

Although the camera methods have generally been found to be less accurate than those based on plasma clearance, they compare favorably with creatinine clearance. Satisfactory results require attention to technique. One must insure that deadtime losses are not significant in imaging either the patient or the standard. Empirical equations may be affected by the choice of camera, collimator, and window setting. It is much safer for a clinic to run its own calibration curve using patients of known renal function than to rely on measurements done elsewhere. However, this may not be technically or economically feasible. It is suggested that, in the absence of a proper calibration curve, the user at least examine a substantial series of patients for reasonableness of the results before clinical use.

Changes in renal function can be monitored by following either GFR or ERPF. While GFR is the conventional parameter, ERPF has gained acceptance at our hospital and is our routine measurement. The procedures are essentially the same for either measurement, the main difference being the choice of radiopharmaceutical. GFR is measured with agents that are excreted solely by glomerular filtration, while ERPF is measured with agents that, like the classic agent PAH, are so avidly excreted by the tubules that their excretion is roughly proportional to renal blood flow. Since the normal filtration fraction is 20%, ERPF agents clear from the body about five times as fast as GFR agents. It thus takes much longer to measure GFR than to measure ERPF by plasma clearance (e.g., 3 hr for a single-sample GFR versus 45 min for a single-sample ERPF). The faster method, ERPF, is advantageous for clinics with a heavy caseload. The physiologic regulation of GFR may be closer than that of ERPF, so that diurnal and physiologic variations may be smaller for GFR. Many physicians may prefer GFR on the grounds of familarity. We believe that either parameter is satisfactory for clinical use, and that both of them are preferable to creatinine clearance. Images are poor with OIH, but adequate to distinguish obstruction from parenchymal retention, which is the main consideration in evaluating renal function; anatomic detail is best studied by other imaging modalities. Both ERPF and GFR may be measured simultaneously, so that it is now fairly easy to measure filtration fraction in the clinic.

RADIOPHARMACEUTICALS

Two available agents are secreted by the renal tubules and can be used as PAH analogs for estimation of ERPF: orthoiodohippurate, hippuran (OIH), labeled with either ^{131}I or iodine-123 (^{123}I), and an investigational new drug, [^{99m}Tc]mertiatide (MAG₃). The clearance of OIH is slightly less than that of PAH, yet single injection OIH clearance closely approximates continuous-infusion PAH clearance (3). We suspect this is due to a fortuitous cancellation of errors between the lower clearance of OIH and the failure of the single-injection method (as usually employed) to deal accurately with the first few minutes of the plasma time-activity curve. The clearance of [^{99m}Tc]MAG₃ is little over half that of OIH, but [^{99m}Tc]MAG₃ clearance was closely correlated with OIH clearance in a series of 50 patients (4). It thus appears usable, with a correction factor, as an estimator of ERPF. ERPF can be used like GFR as a routine measure of renal function, and is heavily used in our clinic for that purpose, but some time and education may be required before the referring clinicians gain confidence in this measurement.

Of the numerous agents cleared by gomerular filtration, we shall consider only three. Chromium-51 ethyldiaminetetraacetic acid (EDTA) is probably the most reliable agent when imaging is not required, but no commercial supplier has found it profitable to offer that agent to the United States in a form suitable for human use. Iodine-125 iothalamate is available in this country, but it cannot be used for imaging so that split function measurement with the gamma camera is impossible. It has been well tested using methods that require urine collection (for which extrarenal excretion causes no error), but experience with methods based on plasma clearance alone is limited (5). The agreement of [^{125}I] iothalamate clearance with inulin clearance appears to be the result of a fortuitous cancellation of errors between tubular excretion and protein binding (3,6).

Technetium-99m DTPA is readily available, can be used for imaging and split function measurement, and its clearance agrees closely with that of inulin (7). However, commercial preparations sometimes contain impurities that bind to plasma protein, causing errors in GFR measurement (8–13). They can be removed by ultrafiltration of the plasma prior to counting. They remain in circulation while the technetium-99m DTPA is cleared from the blood and represent an increasing fraction of circulating activity as time passes. The error is greater in normal patients than in those with impaired renal function since the true [^{99m}Tc]DTPA is cleared more rapidly in normals. The amount of impurity depends upon the supplier of the radiopharmaceutical; whether it also varies from lot to lot for the same manufacturer has not been well studied. The amount of impurity also depends on the time interval between kit preparation and injection. Although package inserts sometimes advocate prompt use, the impurities have been reported to decrease with time for a few hours after preparation (9,13). Aging the preparation for one-

half hour before use appears to improve the purity. Purity can be monitored by laboratory tests (9) or by direct comparison of filtered with unfiltered patient plasma. However, it can change with any change in the source or handling of the radiopharmaceutical or with any change in the time interval between kit preparation and usage. Instead of trying to eliminate impurities from the injected dose, which—as seen—can depend on a variety of factors, one can eliminate impurities by ultrafiltering the plasma before counting (10,11).

RECENT GAMMA CAMERA METHODS

Many methods have been proposed for measuring renal function with the gamma camera. These can be classified according to the type of radiopharmaceutical administered and the portion of the camera time-activity curve analyzed. The radiopharmaceuticals can be divided into (a) tubular and (b) glomerular agents. The algorithms can be divided into those based on (a) the vascular transit phase (within the first minute after injection), (b) the nephron transit phase (the first five minutes), or (c) the body transit (or bladder uptake) phase (the first 10 to 30 min). When a tubular transit or body transit method is used with a glomerular agent, it yields an estimate of GFR. When a tubular transit or body transit algorithm is used with a tubular agent, it yields ERPF. When a vascular transit algorithm is used with either agent, it yields renal blood flow (RBF). Grouping the methods into these six categories (two agents × three algorithms) reduces their number to manageable proportions. Methods described prior to 1982 we have reviewed elsewhere (14). Since then, promising new tubular transit methods have been published by Shore (15), Fleming (16), and Rehling (17). Rutland's indices of blood flow (18), while not validated by any independent quantitative measurement, have furnished seminal ideas to subsequent investigators. By exploiting the proximity of bladder to kidney in transplant patients, Oei (19) introduced a body transit method that did not require a bladder probe. Lee (20) used a similar method for two-kidney patients with repositioning for the bladder view. Peters (21), Carlsen (22), and Lear (23) introduced new methods for vascular transit based on the Sapirstein principle. Conrad (24) suggested a simple model for vascular transit that could be adapted for quantitation. Comparisons of these methods with each other, with reference methods, and (for reproducibility) with themselves have been few and incomplete. Fawdry (25), Fleming (16), and Fine (26) have published comparisons, as have we (2,27–29).

The methods available in commercially available nuclear medicine computer systems in the United States are those of Gates (30) (for GFR, using [^{99m}Tc]DTPA) or Schlegel (31) (for ERPF, using [^{131}I]OIH). Schlegel was the first to attempt blood-free methods for measuring renal function with the gamma camera, using a variety of methods in the 1970s and early 1980s. His original method for estimating ERPF employed an improper correction for tissue attenuation, but can still be found in some commercially available software packages, one of which was evaluated by Fine (26) and found unsatisfactory. Corrected implementations of the Schlegel approach were introduced by Bratt (32) in 1981 and by Gates (30) in 1982, in the context of GFR measurement using [^{99m}Tc]DTPA. Both investigators used a similar approach, called the Gates method in the United States. This method is incorporated into several commercially available nuclear medicine computing systems. Bratt and most subsequent investigators have found the method less accurate than claimed by Gates, but still clinically useful (2,25,27,28,32,33). Attempts to use manufacturer-supplied calibration curves with this method have sometimes led to absurd results. The technical environment (camera, collimator, window, ROI) may vary enough from one center to another to prohibit use of a factory-installed calibration curve. The alternative—determining a calibration curve from a series of patients with known creatinine clearance—is unattractive to most nonacademic users. With attention to technical detail and proper calibration, the Bratt-Gates method can give clinically useful results, but care is needed.

The methods of Rehling (17) and Fleming (16) are noteworthy for the high accuracy claimed, better than most workers have reported with the Bratt-Gates method. Independent evaluation of these methods would be desirable, but both are cumbersome to program. Pediatric methods have been developed by Piepsz (2) and by Shore (15). Tissue attenuation is less of a problem in pediatric patients, so that the gamma camera methods may work better in children than in adults.

The methods of Oei (19) and of Lee (20) are based on uptake in the bladder as well as in the kidney. Because of the high target/background ratio for the bladder, this diminishes the error introduced by background corrections. The initial reports have been promising. While straightforward enough in transplants, optimal use in two-kidney patients may require imaging the patient erect or using a separate detector over the bladder. Otherwise, any activity that drains from renal pelvis to bladder when the patient is repositioned will be counted twice.

For some years, various groups have analyzed the bolus transit phase of the renogram to obtain various indices of blood flow, or even quantitative estimates of blood flow, without validating these techniques against any independent quantitative measurements. Only recently have Peters (21) and Carlsen (22) presented data from which it is possible to estimate the accuracy of these techniques. They appear to be clinically useful.

These methods do not yield absolute renal blood flow, but rather its ratio to cardiac output.

Jackson (34) has described a GFR method based on combining camera data with a single 30-min blood and single urine sample. It is faster than GFR methods based on a 3-hr blood sample, and should be especially useful at very low values of GFR where methods based on urine counts are inherently superior. However, a 44-min ERPF is simpler (no urine collection), nearly as fast, and, except at very low GFR, probably of comparable clinical value. Furthermore, a reliable blood sample is obtainable more often than a reliable urine sample.

PLASMA CLEARANCE METHODS

Methods based on plasma clearance are more accurate than ones based on the gamma camera, but require laboratory skills that are not always available. In adults, ERPF can be well estimated by a single-plasma sample drawn 45 min after administration of radioiodinated OIH or [^{99m}Tc]MAG$_3$ and GFR by a single-plasma sample drawn 3 hr after the administration of [^{99m}Tc] DTPA or [^{51}Cr]EDTA (11,14,35–43). Without quibbling over detail, most of these methods seem to give satisfactory results except at very low levels of renal function. Preliminary data suggest that [^{99m}Tc]MAG$_3$ can similarly be used for a single sample ERPF measurement (44).

Two-sample methods are capable of greater accuracy than one-sample methods, but the extra accuracy is probably not required for routine clinical work (11,45). One misconception about two-sample methods should be clarified. When two points are used without urine collection to determine a one-compartment model, the model is inaccurate. By ignoring additional exponential terms in the plasma curve, one omits positive terms in the denominator of the clearance equation and thus overestimates the clearance. The nature of the error and a method of correcting for it was described in detail by Brøchner-Mortensen (46), but his work seems to be little known outside of Europe. One still finds research papers that employ the naive one-compartment model in apparent ignorance of the associated error. If you use a two-sample method for adult patients, be sure to use one that is appropriately corrected (11,41,45,46).

In adults, the one- and two-sample plasma clearance methods have been developed empirically from multi-sample clearance curves. Similar methods can be developed for children, when plasma clearance data become available. Groth and Aasted (47) have presented such a method, but did not describe their data base in much detail. More useful to other investigators are the detailed reports by Tauxe for OIH and diatrizoate clearance in children over 37 lb, with curve parameters and demographic data for each patient (48,49). Similar data

(but including infants) are needed for [^{99m}Tc]DTPA, [^{99m}Tc]MAG$_3$, and [^{51}Cr]EDTA. Multiple sampling is not risky and has long been used for such routine pediatric studies as glucose tolerance. With a heparin lock, there is little discomfort. The problems of parental and institutional consent remain, but are worth overcoming to develop pediatric methods that are both simple and accurate.

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