Clinical evaluation of renal function

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Current clinical practice requires that the physician understand and evaluate renal function. Traditionally, the functions of the kidney have been considered as being either glomerular or tubular; modern concepts of renal physiology would require the inclusion of endocrine and metabolic functions as well. The intent of this discussion is to review current methods of evaluating renal tubular and glomerular function.

Tubular function

Evaluation of renal tubular function cannot be accomplished by any single test. This is because the tubules have such varied and complex functions. Testing of certain tubular functions is of clinical importance because tubular dysfunction may be responsible for certain clinical disorders and among the earliest indicators of renal parenchymal disease. Renal concentrating and diluting ability as well as renal acidification are among the most useful indicators of tubular health.

Tests of concentrating ability

Impaired renal concentrating ability is one of the earliest indicators of many different types of renal parenchymal disease and may be a clue to a renal parenchymal disorder before any abnormality in blood urea nitrogen (BUN) or serum creatinine (Cr) is detected.[1]

To test concentrating ability one must have an adequate stimulus for water conservation (a period of fluid restriction) and a means for measuring the tonicity or concentration of the urine. Measurement of urine osmolality by freezing point depression is one of the most reliable methods of determining urine tonicity. After a 24-hour period of fluid restriction, the urine osmolality will be greater than 900 mOsm in healthy humans.[2] These values will be somewhat less in the aging patient.[2, 3] If urine osmolality determinations are not available, then specific gravity is somewhat more crude but still a useful method.[4] The urine specific gravity is only a rough equivalent to osmolality over a wide range of urine concentrations.[5] Urine concentrating function is usually normal if specific gravity is greater than 1.026 after 24 hours of fluid deprivation.[3]

Tests of concentrating function may be abnormal for a variety of reasons. Abnormal renal concentration occurs early in many renal diseases, and hence becomes a useful early detection test for renal parenchymal disease. Glomerulonephritis, pyelonephritis, nephrosclerosis, hypokalemic and hypercalcemic nephropathy, sickle-cell disease, and analgesic nephritis are only a few of the disorders associated with renal concentrating defects.[6] The mechanisms for the concentrating abnormality vary. In chronic renal failure a relative solute diuresis in surviving nephrons is thought to explain the defect.[6] A decrease in water permeability of the tubule is thought to be present in hypokalemic and hypercalcemic nephropathy.[7, 8] In sickle-cell disease a perturbation of the medullary interstitial gradient occurs.[9]

Even a normal kidney will not be able to concentrate maximally if the kidney is under the influence of a solute diuresis (e.g., glucosuria) or the effects of loop diuretics (e.g., ethacrynic acid, furosemide).[10, 11] Both of these factors interfere with the ability of the kidney to maintain a hypertonic medullary interstitium, which is necessary for normal renal concentrating function. Likewise, urine concentration will be abnormal in a normal kidney if there is decreased solute excretion because of decreased salt (sodium) or protein intake.[12]

Care must be taken in interpreting renal concentrating ability when urine specific gravity methods are used. This is because various substances (intravenous pyelogram, dye, glucose, and large quantities of protein) present in the urine, and certain physical factors such as temperature (refrigeration) will cause the specific gravity to be falsely high.[13] None of these factors influences the osmolality determination.

Renal diluting ability

Normal adults given 1,000 to 1,500 ml of water (20 ml/kg) for a short period will be able to excrete more than 50% in 3 hours and will have a minimum urine specific gravity of 1.003 or urine osmolality of less than 100 mOsm.[13] Disordered diluting ability occurs in congestive heart failure, cirrhosis, adrenal insufficiency, hypothyroidism, the syndrome of inappropriate antidiuretic-hormone secretion, and various renal diseases.[14-17] The causes are varied, but include diminished glomerular filtra-

tion rate, exaggerated proximal tubular reabsorption of sodium and water, increased solute diuresis per nephron, excessive production of antidiuretic hormone, and disordered renal tubular cell function. Even a normal kidney will fail to dilute properly if under the influence of a solute diuresis (mannitol, glucose) or of one of the thiazide or loop diuretics (furosemide or ethacrynic acid). The diuretics impair diluting ability by blocking sodium reabsorption at sites where sodium is reabsorbed without water (so-called diluting sites).[11]

Renal acidification

Although the intricacies of renal acidification mechanisms cannot be discussed in this review, a few comments are pertinent. The adequacy of renal hydrogen ion excretion can be assessed most accurately by the complicated measurement of titratable acid and ammonia excretion following ammonium chloride loading.[18] However, a clue to the adequacy of renal hydrogen excretion can be obtained by urine pH determinations in the presence of systemic acidosis. Normal patients and even most with chronic renal failure will have a urine pH below 6.0 in systemic acidosis or after suitable acid load.[18, 19] The failure to lower the urine pH to less than 6.0 may be a clue to a renal tubular disorder; its further definition will require more sophisticated tests. It should be remembered that urinary infections with various bacteria may also cause an alkaline urine in systemic acidosis. Hence, urine cultures must be evaluated before final interpretation of urine pH data can be made.

Glomerular function

The tests used to estimate glomerular filtration function are often selected on the basis of low cost, clinical availability, ease of performance, and reproducibility. Two such tests, blood urea and serum creatinine, have widespread use. Both urea and creatinine are removed from the blood by glomerular filtration. Their concentration in the blood is an index of glomerular function. Blood creatinine concentration is influenced little by factors other than size and muscle mass of the patient and glomerular filtration.[20, 21] Hence, serum creatinine is a useful and reliable measure of glomerular function. Urea, by contrast, is influenced by body nitrogen balance and extremes of fluid balance.[22] Therefore, it is less reliable as an index of glomerular function.

The normal serum creatinine ranges between 0.6 and 1.1 mg/100 ml in women and between 0.8 and 1.36 mg/100 ml in men.[21, 23] It is important to realize that any limitation of glomerular filtration rate (GFR) causes decreased creatinine excretion until a new and higher serum creatinine steady state is reached. At that new higher serum creatinine, daily creatinine excretion will be identical to normal, but will be accomplished at the expense of an elevated serum creatinine. Therefore, the serum creatinine can only be a valid estimate of GFR when the blood creatinine levels are stable.

The relationship between serum creatinine and GFR is depicted in *Figure 1*. For every 50% reduction in GFR, there is a doubling of serum creatinine. Thus, when the serum

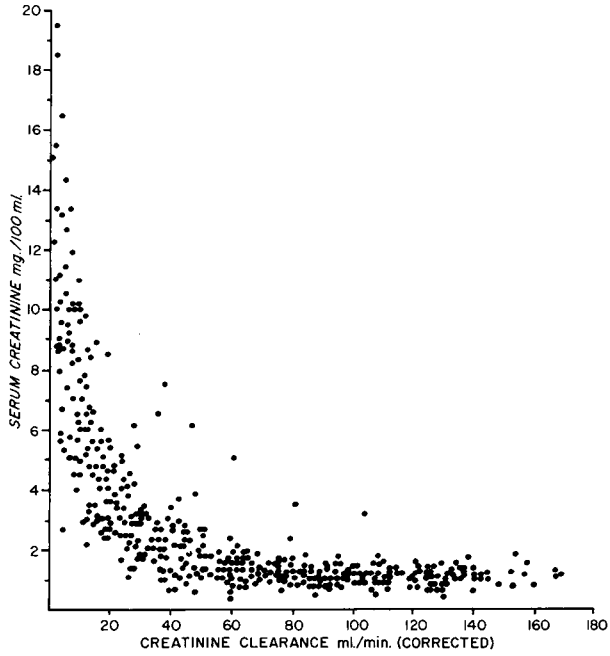

Fig. 1. Relationship between serum creatinine and glomerular filtration rate.

creatinine level rises from 1 to 2 mg/100 ml, the GFR has fallen to 50% of normal; when the creatinine is 4 mg/100 ml, the GFR is 25% of normal; when the creatinine is 8 mg/100 ml, the GFR is 12.5% of normal. Therefore, it should be clear that a change in serum creatinine from 1 to 2 mg/100 ml represents a far more important decrease in GFR (50%), than does a change from 7 to 8 mg/100 ml (2% to 3% change).

On the basis of these relationships, when the serum creatinine is in the range of 4 to 8 mg/100 ml, one can easily estimate the approximate GFR. However, when the serum creatinine is in the range of 1 to 1.5 mg/100 ml, this is more difficult, because the serum creatinine corresponding to a GFR of 100% of normal varies depending on muscle mass and body size. A serum creatinine of 1 mg/100 ml may be abnormal for a small woman, whereas a serum creatinine of 1.5 mg/100 ml may be normal for a large man.

For these reasons, it is helpful to measure GFR to establish baseline values, especially when serum creatinine is in or near the normal range. Endogenous creatinine clearance (Ccr) is the most widely used clinical test to measure GFR. Most commonly, the Ccr is calculated from the concentration of creatinine in a timed urine specimen and the simultaneously measured serum creatinine according to the formula [Ccr = (urine creatinine × urine flow rate)/serum creatinine]. Comparisons between inulin clearance (Cin), considered by many to be the most accurate measure of GFR, and Ccr have been studied by several investigators. It has been found that creatinine clearance is usually higher than inulin clearance and often over-

estimates the GFR by 10% to 15% in the nearly normal range and by 40% to 50% when the GFR is significantly impaired.[24-26] Practically, this is not as important an error as it might seem. In clinical use, it is not usually a critical error if the Ccr is 115 ml/min when the Cin is 100 ml/min (a 15% error); also, it matters little that the creatinine clearance is 12 ml/min while the inulin clearance is 6 to 8 ml/min; both would represent nearly end-stage renal excretory function.

There are other important considerations in using the serum creatinine as an estimate of GFR. One has to do with the chemical method used to measure serum creatinine. The true creatinine and autoanalyzer methods are similar and most accurate. The total creatinine chromagen method measures creatinine and other creatinine-like chromagens. With this latter method serum creatinine is spuriously high and will underestimate glomerular filtration.[21, 23, 24]

Another source of error in creatinine determination has to do with the creatinine production in severe chronic renal failure. It is thought that the decrease in muscle mass in severe renal failure results in less creatinine production. This results in serum creatinine levels lower than would be expected for the degree of impairment of GFR.[25] Probably, this is one of the reasons why endogenous creatinine clearance overestimates GFR as worsening renal failure occurs.

Accurate measures of GFR in clinical medicine are becoming necessary because of drug efficacy studies for the treatment of various glomerular diseases. Inulin clearance requires cumbersome infusion techniques and complicated chemical analyses. Other substances to measure GFR have been sought.

One such substance, ^{125}I iothalamate, has been tested by several groups[26-28] and is used in our laboratory. It has the advantage of requiring no intravenous infusion, and no chemical analyses, of using very small sample volumes of blood and urine (0.5 cc), and of being as accurate as inulin. It has the disadvantage of requiring timed urine collections and of being a radioisotope which requires scintillation counting equipment.

Iothalamate is handled by the kidney in a fashion similar to inulin.[29] Previous studies have demonstrated that the clearance of isotopically labeled iothalamate administered by continuous intravenous infusion or by single subcutaneous injection was nearly identical to simultaneously measured inulin clearances.[26] For convenience, we chose to administer the ^{125}I iothalamate subcutaneously. The details of the method are as described by Israelit et al.[26] In 10 patients, 17 simultaneous inulin and iothalamate clearances were performed (*Fig. 2*). Very good correlation was observed. A

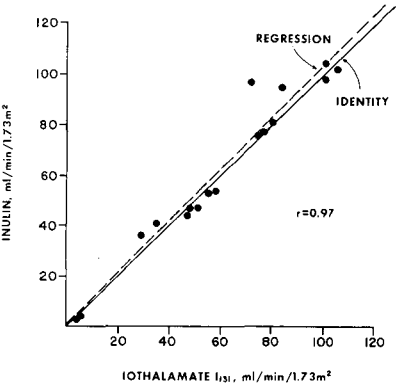

Fig. 2. Relationship between iothalamate ^{125}I and inulin clearances.

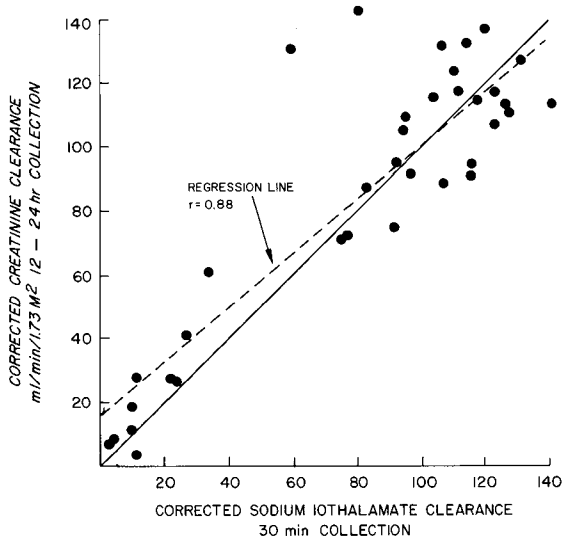

Fig. 3. Relationship between sodium iothalamate ^{125}I and creatinine clearance is depicted. Note that the creatinine clearance significantly overestimates the iothalamate clearance at the lower levels of glomerular filtration rate.

comparison was made between iothalamate clearance and a 12- or 24-hour creatinine clearance obtained the same day (*Fig. 3*). Here there was considerable variation between clearance results. The wide variation between Ccr and iothalamate clearance is most probably due to inaccuracies in urine collections for the 12- or 24-hr Ccr. Longer collection periods have been favored because the chances of urine collection errors would be reduced. However, in our experience with both outpatients and hospitalized patients, extended urine collection periods are likely to be inaccurate more often than not.

Such studies as these suggest that ^{125}I iothalamate clearances may be an accurate and convenient method for the determination of GFR in certain clinical situations. They still require carefully timed urine collections, but do not have the error of Ccr methods.

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