MEASUREMENT OF RENAL FUNCTION.

OBJECTIVE 1: TO UNDERSTAND THE GENERAL PRINCIPLE AND THE METHODS USED TO MEASURE RENAL FUNCTION.

A. Measurement of the varied functions of the kidney depends almost entirely on the application of the principle of conservation. For substances that are not synthesized or metabolized by renal tissue, the amount entering the kidney via the renal artery equals the amount leaving in the renal vein and ureter. Similarly, the amount entering the nephrons by filtration and/or secretion equals the amount leaving by reabsorption and/or excretion. The use of this principle provides the means for indirectly measuring renal blood flow, glomerular filtration rate, and the rates of tubular reabsorption and secretion of various substances.

B. Renal plasma flow can be determined by the principle of conservation and the use of a substance that is not synthesized or metabolized by the kidney. The amount of such a substance entering the kidney per unit time via the renal artery equals the amount leaving via the ureter and the renal vein. The difficulty of obtaining renal venous plasma samples limits the usefulness of this approach to measuring RPF. However, it has been found that the tubular secretory system for para-aminohippurate (PAH) is so efficient that at low plasma concentrations it removes 90% or more of the PAH from the plasma as it flows through the kidney. Thus for practical reasons, the 10% that remains in the renal vein is ignored and it is assumed that the amount entering via the kidneys, renal plasma flow (RPF) x arterial concentration (PPAH), equals the amount leaving via the ureters, urine concentration (UPAH) x urine flow rate (V, ml/min). That is,

\[ RPF \times PPAH = UPAH \times V \]
\[ RPF = \frac{UPAH \times V}{PPAH} \] (Eq. 1)

For the reason indicated above this is an approximation; it is a very useful approximation for physiological measurements, but its use in disease is limited for obvious reasons.

C. Renal blood flow (RBF) equals the flow of plasma (RPF) plus the flow of red cells (RCF). It may be calculated from measurement of the RPF and the hematocrit (Hct), the fraction of blood volume that is composed of cells:

\[ RBF = RPF + RCF \]
\[ RCF = (RBF \times Hct) \]
\[ RBF = RPF + (RBF \times Hct) \]
\[ RBF = \frac{RPF}{1-Hct} \] (Eq. 2)

Units for both RPF and RBF are ml/min.

D. The total plasma volume filtered by the glomeruli per unit time (GFR) can be measured by the use of the conservation principle and a substance that is freely filtered but is not reabsorbed or secreted, so that the amount excreted equals the amount filtered.

One such substance is inulin, a fructose polysaccharide with a molecular weight of approximately 5000. The amount of inulin filtered per unit time by the glomeruli equals the volume of plasma filtered/time (GFR) times the plasma concentration (Pin) (Fig. 4-1). The amount exiting from the ureter per unit time equals the urine flow rate.
(V) times the urine concentration (Uin). Since the tubular cells do not add or remove inulin from the filtrate, the amount entering the nephrons equals the amount exiting and Eq. 3 applies (fig. 4-1). Plasma and urine concentrations and the urine flow rate can be measured so that GFR can be calculated using Eq. 4.

![Fig. 4-1. Measurement of filtration rate.](image)

E. With the use of a measurement of GFR and the conservation principle, the rate of tubular reabsorption of substances from the filtrate or the rate of tubular secretion of substances into the tubular fluid can be measured.

![Fig. 4-2. Measurement of solute reabsorption rate.](image)

1. Most substances handled by the kidney are freely filterable, so the amount filtered per unit time equals the GFR times the plasma concentration of the substance (Ps).
2. The rate of reabsorption (T, for tubular transport) of a solute by the tubules can be determined by calculating the difference between the rate at which it is filtered and the rate it is excreted (Eq. 6, Fig. 4-2).
3. The rate of secretion (T) of a solute can be determined by calculating the difference between the rate of its excretion and the rate it is filtered (Eq. 8, Fig. 4-3).
4. The measurement of the maximum rate of transport (Tm) for a substance is sometimes useful in clinical experiments to determine the amount of functional tubular tissue. The criteria for accurate measurement of Tm are as follows: (1) Plasma levels must be high enough to saturate the transport system. (2) Two consecutive clearance determinations must be made in which the plasma concentration rises, but the calculated rate of transport of the substance does not. This ensures that the tubular maximum has been reached.

**OBJECTIVE 2: TO UNDERSTAND THE CONCEPT OF CLEARANCE.**

A. Clearance is a term used to describe the rate at which the blood is cleared of a substance. It is often used to measure the efficiency of the kidney in removing a substance from the blood. As an example (fig. 4-1): To excrete a substance such as inulin, the kidney filters a large volume of plasma containing inulin, then the tubular cells reabsorb almost all of this fluid, returning it to the circulation without inulin, which remains behind and is excreted in the urine. By this process, the kidney has "cleared" a volume of plasma of the inulin contained within it. Thus the volume of plasma cleared of inulin per unit time (Cin) equals the rate of inulin excretion divided by the concentration of inulin in the plasma from which it was removed:

\[
Cin = \frac{U_{in}V}{P_{in}} \text{ (ml/min)} \quad (Eq. 9)
\]

For inulin the clearance rate is equivalent to the GFR. For PAH the clearance rate is equivalent to the RPF. The clearance volume is a virtual volume, the smallest volume of plasma sufficient to account for the amount of the substance excreted per unit time.

1. For reabsorbed substances, the apparent volume of plasma cleared of the substance/time is smaller than the filtered volume since some of the substance is returned to the plasma from the filtrate by the tubular cells (Fig. 4-2). Nevertheless, the amount excreted/time (UsV) can be considered to have been contained in a virtual volume of plasma (Cs) at the plasma concentration:

\[
Cs = \frac{UsV}{Ps} \text{ (ml/min)}
\]

The volume of plasma from which that substance is removed is less than the GFR or Cin.
2. For substances that are filtered and secreted but not reabsorbed to a significant extent, the amount excreted/time exceeds the amount filtered/time. The volume of plasma cleared of the substance/time is larger than the GFR or Cin because the tubular cells are also removing the substance from plasma in the peritubular capillaries (Fig. 4-3). Still, the amount of the substance excreted/time was contained initially in a certain volume of plasma at the plasma concentration. The standard clearance equation given above may be used to calculate the apparent volume of plasma that was cleared by both filtration and secretion.

B. To summarize, clearance may be defined as the virtual volume of the plasma from which the kidney has removed or 'cleared' a substance per unit time or, to state it another way, clearance is the virtual volume of plasma that contained the mass of a substance that the kidney excreted in a unit of time. For a substance that is neither reabsorbed nor secreted and meets the other criteria given, the clearance rate equals the GFR. From here on the terms GFR and Cin will be used interchangeably. For a substance that is filtered and reabsorbed, Cs<Cin and for a substance that is filtered and secreted, Cs>Cin. These facts are used experimentally to determine how substances are handled by the kidney.

C. The effect of a rise in the plasma concentration of a substance on its clearance rate depends on how the kidney handles that particular substance.

1. For substances that are filtered only, the rate that it is filtered and excreted will increase as the plasma concentration rises, but the volume of fluid that is filtered will not change; thus the volume of fluid that is cleared will not change (A in Fig. 4-4).

2. The transport processes for substances that are reabsorbed and secreted usually can handle only limited amounts and this affects the clearance rates. As the plasma concentration of a reabsorbed substance rises and the amount filtered increases, the transport process becomes saturated and a greater
fraction of the filtered amount escapes reabsorption and is excreted. Because of this, a larger fraction of the filtered fluid is returned to the circulation cleared of the substance, in other words the clearance rate increases (B in Fig. 4-4).

As the plasma concentration of a secreted substance increases and the transport process becomes saturated, a smaller fraction of the total amount in the blood, flowing past the tubular cells, is secreted into the tubules and the volume of plasma cleared of the substance by this process falls (C in Fig. 4-4).

3. An example of the changes that occur when the plasma concentration of a reabsorbed substance such as glucose is increased is illustrated in Fig. 4-5. At the normal plasma level (80 to 100 mg/dl), all filtered glucose is reabsorbed (Fig. 4-5A) and Cg = 0 (Fig. 4-5B). As the plasma concentration rises (100 to 200 mg/dl), the amount filtered/min, and thus the amount presented for reabsorption, increases. The rate of reabsorption increases initially, no glucose is excreted and Cg still equals zero. If the plasma concentration continues to increase (>300 mg/dl), the maximum transport rate (Tmg) is reached. As the amount filtered/min continues to rise above that point, there is no further increase in reabsorption, the excess is excreted at an increasing rate, and the volume of plasma cleared of glucose/min increases and approaches the volume filtered.

Fig. 4-5. The effect of changes in P_g on its rates of filtration, reabsorption, excretion and clearance.

OBJECTIVE 3: TO UNDERSTAND THE MEANS USED TO MEASURE RENAL FUNCTION IN THE CLINICAL SETTING.

A. The clearance of inulin is the most accurate measure of GFR available. However, several factors limit the use of inulin clearance in the common clinical situation. An intravenous injection followed by a constant infusion is required. Complete emptying of the bladder is necessary before the beginning of the clearance period, in order to remove all urine not containing inulin, and again at the end of the period, in order to obtain all urine produced during the period. The urine flow must be high so that enough urine may be obtained in a short period of time to permit analysis and to reduce possible errors introduced by urine remaining in the bladder at the
beginning and end of the clearance period. These requirements often cannot be met in a patient with compromised renal function.

Fig. 4-6. Changes in plasma creatinine concentration and $1/P_{cr}$ as a function of changes in GFR.

Fig. 4-7. Illustration of the utility of measuring $P_{cr}$ in a patient with chronic renal disease.

B. The use of creatinine clearance as a measure of GFR overcomes many of these practical problems, but introduces others. Creatinine (molecular weight = 113) is an end product of protein metabolism. It is always present in the blood, and its concentration (0.5 to 1.2 mg/dl) remains relatively constant over a 24-hour period. This eliminates the need for an intravenous infusion, and therefore a clearance period can extend over a long period of time, usually 24 hours, so that adequate amounts of urine can be obtained and the problem of bladder emptying minimized. Only one blood sample is needed, and it can be taken at any point during the collection period.
1. Creatinine is freely filtered, but it is also secreted into the urine by the proximal tubular epithelium. If creatinine is infused into an individual to raise the plasma concentration, its clearance exceeds the inulin clearance by 10 to 40%. There is some doubt as to whether creatinine is secreted in more than negligible amounts at normal plasma levels, but the preponderance of the evidence indicates that it is. This problem is complicated by the fact that, in the methods commonly used to measure creatinine, other substances in plasma react with the reagents. The nature of these so-called "noncreatinine chromogens" is not known, but evidently their clearance is low and their concentration in urine is nil. Thus in the clearance equation, Ccr = UcrV/Pcr, the value of the denominator is raised by the presence of these chromogens, and the value of the numerator is presumably raised by tubular secretion of true creatinine. These two factors partially cancel each other and the net result is that the clearance approximates the GFR when the kidneys are normal. In using creatinine clearance to measure GFR, the fact that creatinine is secreted should be kept in mind. It is possible that falsely high GFR values may be obtained in patients with poor glomerular function but with good blood flow and tubular function. Conversely, certain drugs (organic cations such as cimetidine and trimethoprim) inhibit tubular secretion of creatinine causing the creatinine clearance, but not the actual GFR, to decrease.

2. The measurement of the plasma creatinine concentration alone can be utilized to follow changes in GFR in a patient with chronic renal disease. The rate of production of creatinine by the body does not vary to an appreciable extent in an individual over a period of time and thus the rate of excretion also varies very little. Since creatinine is excreted primarily by filtration, GFR x Pcr = UcrV. When GFR is reduced the rate of excretion drops momentarily until Pcr rises and the rise in Pcr raises the product GFR x Pcr back to its previous level. In the long run the rate of excretion, UcrV, remains the same. Thus GFR is proportionate to 1/Pcr. In a patient in which renal disease gradually reduces GFR, the initial reductions in GFR produce only small increases in Pcr (100% to 80% of normal GFR in Fig. 4.6A) and it is difficult to discern the change in GFR from the measurement of Pcr alone. As GFR is reduced further, the change in Pcr becomes much greater (80 to 40% in Fig. 4-6A). However the reciprocal of Pcr (1/Pcr) is a straight-line function of the change in GFR (Fig4-6B); comparable changes in 1/Pcr are the result of comparable changes in GFR. Thus the use of the reciprocal makes small changes in GFR more apparent.

Measurement of Pcr and calculation of the reciprocal in a patient with chronic renal disease over a period of time allows one to plot the reciprocal versus time and the plot assists in determining the status of the disease (fig 4-7). If the disease process is accelerated, the reciprocal will fall at an increased rate; if treatment halts the progression of the disease, the reciprocal will stabilize. A word of caution: This tool is useful in following the progress of renal disease in a single individual. However, variations in creatinine production rates and other factors prevent its use in making comparisons among patients.
C. All the difficulties involved in measuring inulin clearance in patients are also encountered in measuring PAH clearance. In addition, a compromised or diseased kidney may not be extracting 90% of the PAH from the plasma flowing through it, so renal venous blood samples must be obtained in order to measure RPF accurately. Consequently, other means of assessing RPF in patients have been developed. In general, these methods are only semi-quantitative, but are much more easily applied to patients. In one of these methods, a substance secreted by tubular cells is labeled with a radioactive isotope (commonly 131I) and given as a single intravenous injection. An isotope counter is placed over the kidney and the amount of isotope appearing in that region of the body is measured. Following the injection, the isotope rapidly accumulates in the normal kidney as the tubules remove the substance from the plasma. After reaching a peak, the amount of isotope present falls at a slower rate as it is excreted in the urine. In other methods, the rate of disappearance of the same type of substance from the circulating plasma is measured after a single injection. This can be done by sequentially removing aliquots of blood and measuring the radioactivity present or by placing a counter over the head and measuring the radioactivity circulating through the head. The rate at which this substance disappears from the blood is largely determined by the rate at which the kidney clears it from the circulating plasma.

D. Clinicians often assess tubular function by measuring the fraction of the filtered amount that the tubules excrete, that is, fractional excretion. The smaller the fraction, the more efficient are the tubules in retaining filtered substances.

1. The fractional excretion of water, FEH2O, is simply the urine flow rate, V, divided by the filtration rate, GFR (Fig. 4-8). The actual measurement is made even simpler by assuming that Ccr equals GFR, as the following equation indicates:

\[
FEH2O = \frac{V}{GFR} = \frac{V}{Ccr} = \frac{V}{(UcrV/Pcr)} = \frac{1}{(Ucr/Pcr)} = \frac{Pcr}{Ucr}
\]

The utility of the ratio, Pcr/Ucr, is that timed, complete, collection of the urine is not required for this measurement. All that is required are samples of the blood and the urine. The fractional reabsorption rate, FRH2O = 1 - FEH2O. The values for FE and FR are usually multiplied by 100 to give the percent of the filtered water that is either reabsorbed or excreted.

![Fig. 4-8. Calculation of fractional water excretion.](image)
2. The same approach can be used to calculate the fractional excretion of a solute, FEs. What is determined is the fraction of the filtered load of solute that is excreted:

\[
FEs = \frac{\text{Exc. Rate}}{\text{Filt. Rate}} = \frac{(UsV)}{(PsGFR)} = \frac{(UsV)}{(PsCcr)} = \frac{[(UsV)/Ps]/(UcrV/Pcr)}{Us/Ps}/(Ucr/Pcr)
\]

![Diagram](https://via.placeholder.com/150)

**Fig. 4-9. Calculation of the fractional excretion of a solute, FE_s.**

(The mnemonic that results, you pee/you pee, is one that any student should be able to remember in association with the kidney.) All that is required to measure the fractional excretion of a solute is a sample of the blood and a sample of the urine and measurements of the solute concentration and creatinine concentration in the two samples. The fractional reabsorption rate, FRs is equal to 1 - FEs. FEs and FRs are usually multiplied by 100 to give the percent of the filtered amount of the substance that is either reabsorbed or excreted. This measurement is most used to express the fractional excretion of Na:

\[
FENa = \frac{(U/P)Na}{(U/P)cr}
\]

The measurement of FE can be used with any solute that the kidney excretes. It is used most often in connection with Na (You pee Na/You pee creatinine). Na is one of the most plentiful solutes in the filtrate and it is reabsorbed by active tubular transport that requires substantial energy consumption. Thus, FENa is an index of the activity and health of the tubules. Normally FENa is usually less than 1%, physiologically it seldom goes above 3%. Thus, in the absence of drugs that inhibit salt reabsorption, values above 3% usually indicate significant impairment of tubular function.

E. Clinicians evaluating renal function may often have different objectives in mind and the type of measurement to perform depends on the objective. In a patient suspected or known to have renal disease, it may be important to evaluate glomerular or tubular function. Then the various uses of creatinine described above can be used to measure glomerular function and the concentration ratios can be used to evaluate tubular function. In other instances, e.g., a bedridden patient receiving a significant volume of intravenous fluids, the physician may be interested in determining if the kidney is maintaining or altering body fluid balance or solute balance. In this situation
measurement of the rate of excretion (V or UsV) is important and permits comparison to the rate of intake.

**Summary of Terms and Equations for Renal Physiology**

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<th>UNITS</th>
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