CHAPTER 9

Glomerular Filtration Rate, Renal Functional Reserve, and Kidney Stress Testing

Claudio Ronco and Lakhmir S. Chawla

OBJECTIVES

This chapter will:
1. Describe the process of glomerular filtration.
2. Characterize the mechanisms involved in glomerular filtration.
3. Summarize the pathophysiologic changes of glomerular filtration rate that occur in acute kidney injury.
4. Discuss the meaning of baseline glomerular filtration rate and the concept of renal functional reserve.
5. Present the importance of the kidney stress testing.

Glomerular filtration rate (GFR) usually is accepted as the best overall index of kidney function in health and disease. Normal GFR (>90 mL/min) varies with age, sex, and body size. It is approximately 120 to 130 mL/min/1.73 m^2 in young adults and declines with age (Fig. 9.1).[1] A decrease in GFR precedes the onset of clinical kidney failure; therefore a persistently reduced GFR is a specific indication of chronic kidney disease (CKD), whereas an abrupt reduction of GFR that is possibly transient in nature may be used to describe acute kidney injury (AKI). With a GFR less than 60 mL/min/1.73 m^2, the prevalence of complications and the risk of cardiovascular disease seem to be higher in CKD and AKI.[2–4]

The physiologic mechanism of glomerular filtration generally is clearly understood. However, a more complex issue is the measurement of GFR in clinical practice and especially the definition of "normal" renal function. In fact, *renal function* cannot be defined solely from GFR, because the convective transport of solutes in Bowman's space is just one of the many functions of the kidney. Furthermore, the measurement of GFR, or its calculation from derived equations, can be complex and faulty. Finally, GFR is not a fixed function, but rather it may display significant variations among individuals or even in different conditions within one individual. All of these aspects have an important impact on the diagnosis and staging of CKD, but they are similarly important in the evaluation of kidney function in patients in intensive care units (ICUs) with or without AKI. In this chapter, we try to elucidate some of the aspects related to GFR in the clinical setting.

MECHANISM OF GLOMERULAR FILTRATION

The process of glomerular filtration[1] is a typical model for transcapillary ultrafiltration. *Ultrafiltration* is a process whereby plasma water, which contains solutes and crystalloids but not cells or colloids, is separated from whole blood by means of a pressure gradient through a semipermeable membrane. The pressures involved in the process are typical Starling forces, that is, hydrostatic and colloid osmotic (oncotic) pressures.

The filtration gradient results from the net balance between the transcapillary hydraulic pressure gradient (ΔP) and the transcapillary colloid osmotic pressure gradient ($\Delta\pi$). Such pressure, multiplied by the hydraulic permeability of the filtration barrier *(K),* determines the rate of fluid movement (ultrafiltration = J_w) across the capillary wall, as follows:

$$J_w = K(\Delta P - \Delta\pi)$$

Obviously, J_w results from the sum of different local fluid movements along the length of the capillary, and thus the equation describes an average phenomenon.

The product of the surface area for filtration *(S)* and average values along the length of the glomerular capillary determines the single-nephron glomerular filtration rate (SNGFR), as follows:

$$\text{SNGFR} = KS(\Delta P - \Delta\pi) = K_f P_{uf}$$

where K_f is the glomerular ultrafiltration coefficient and P_{uf} is the mean net ultrafiltration pressure.

The barrier for ultrafiltration is complex, consisting of the glomerular capillary endothelium with its fenestrations, the glomerular basement membrane, and the filtration slits between the glomerular epithelial cell foot processes. Anatomic alterations in various components of the glomerular filtration barrier play a crucial role in determining glomerular hydraulic conductivity and hence glomerular filtration in disease states.

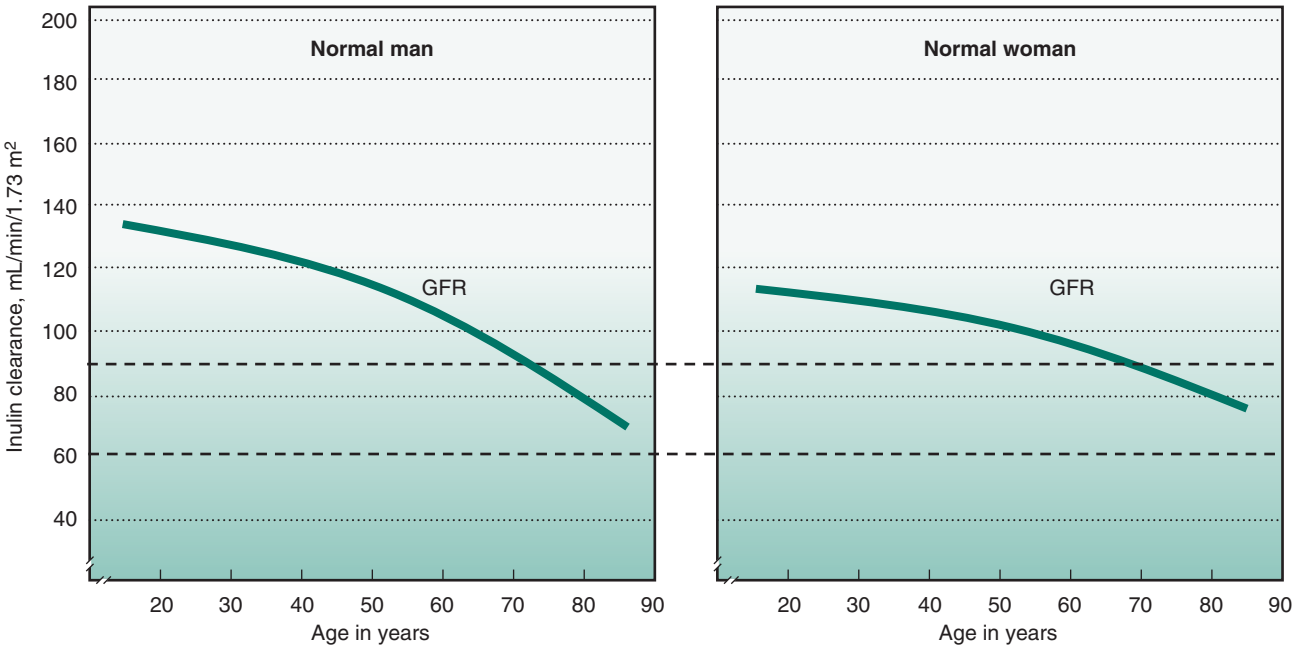

FIGURE 9.1 Glomerular filtration rate in healthy individuals by gender and age.

The surface of a single glomerular loop is difficult to assess because of the variable number of capillaries, the varying proportion of capillaries that are perfused, and the extent of stretching of the capillaries.

For the same reason, the permeability coefficient is difficult to determine, but calculations can be made with specific techniques in selected experimental animals for single nephrons. The glomerular ultrafiltration coefficient is reduced in a variety of kidney diseases. Experimental glomerulonephritis, acute renal failure (ARF), chronic ureteral obstruction, puromycin aminonucleoside–induced nephrosis, and chronic protein malnutrition can affect K_f. At the same time, the permeability to solutes may be altered with the appearance of proteins in the urine because of loss of permselectivity. In addition, the hydraulic permeability of the glomerular basement membrane is related inversely to $\Delta\pi$, suggesting that K_f may be directly affected by $\Delta\pi$. The hydraulic conductivity of the glomerular basement membrane and K_f also are affected by the plasma protein concentration.

The behavior of the pressure in the glomerular capillary is interesting, and it has been considered similar to the behavior that can be experimentally determined in artificial hollow fibers of hemofilters. As blood moves through the capillary, water is removed by ultrafiltration. This results in a progressive decrease of hydraulic pressure in the blood compartment with a parallel increase in the counterpressure generated by the progressive increase in plasma proteins. Different profiles can be postulated for the colloid osmotic pressure (Fig. 9.2), but it has been demonstrated that in fluid-depleted animals, filtration pressure equilibrium (FPE) occurs along the length of the capillary.[1] This means that hydrostatic and colloidoosmotic pressures equalize at a given point and filtration stops before the end of the capillary. Progressive expansion of the extracellular fluid volume (or progressive increase in extracorporeal blood flow in artificial fibers) results in a progressive shift of the FPE points toward the end of the capillary until such equilibrium does not occur any more.

Changes in GFR and *filtration fraction* (the ratio between the GFR and the plasma flow rate) as a function of selective alterations in plasma flow, hydrostatic pressure, or oncotic pressure at the inlet of the capillary can be predicted by a mathematical model consisting of a system of identical capillaries in parallel (homogeneous model). Such an approach obtained relatively good correlation with experimental data in animals.[1] However, the anatomy of the glomerular capillary network is far more complex with capillary loops varying in length. Even when the data suggest that the overall network is at filtration pressure dysequilibrium, FPE may be achieved in some parts of the capillary network. Using a mathematical model based on a capillary network reconstructed from serial sections of the glomerulus (network model), it was found that calculated values of K_f from the homogeneous model were somewhat lower than those obtained from the network model.[1] This discrepancy became greater as FPE was approached. Therefore it is evident that the permeability coefficient of the glomerular membrane can be studied only in conditions in which FPE does not occur. In these conditions, in fact, the entire surface of the capillary is not used for filtration, and the real effective surface used for filtration cannot be determined.

Different points of FPE along the length of the capillary correspond to different levels of filtration fraction and have significant effects on the proximal and distal tubular physiologic response. At the same time, it becomes clear that all conditions altering blood flow to the capillary (i.e., ischemia, sepsis, cardiac dysfunction) can be tolerated only while renal blood flow autoregulation is intact. When autoregulation is lost or the delicate equilibrium between afferent and efferent arteriolar tone is altered, blood flow and filtration fraction are altered, as are the intraglomerular hemodynamics and the process of ultrafiltration. This issue is especially important if we consider that most of the preglomerular pressure drop between the arcuate artery and the glomerulus occurs along the afferent arteriole, whereas approximately 70% of the hydraulic pressure drop between the glomerular capillaries and the renal vein takes

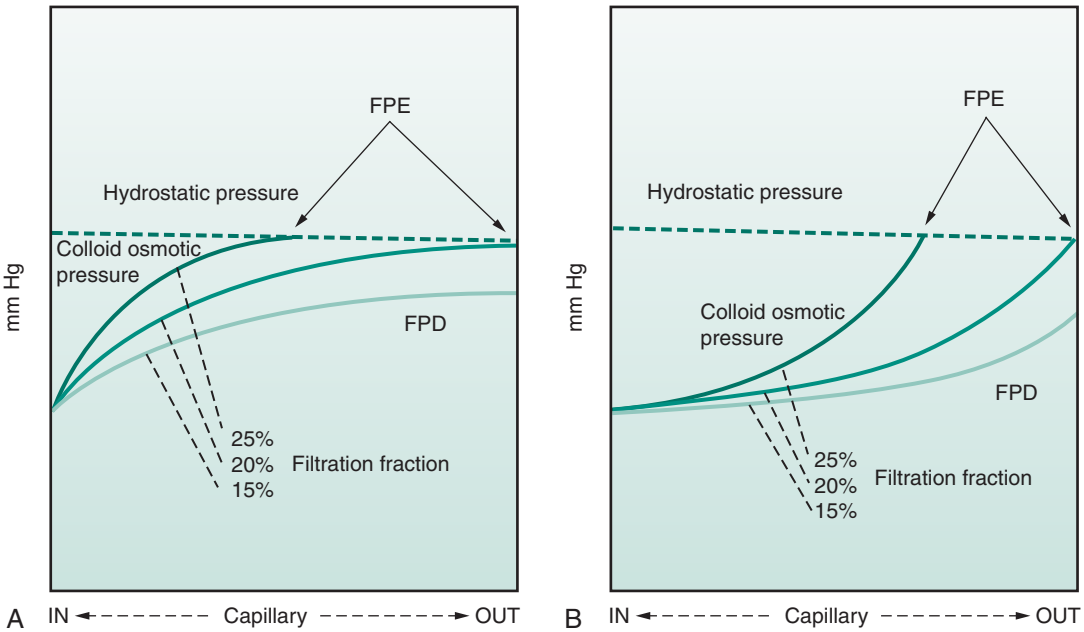

FIGURE 9.2 The concept of filtration pressure equilibrium (FPE) in the glomerular capillary. As blood moves through the capillary, water is removed from blood by ultrafiltration. The resulting progressive increase in protein concentration is paralleled by a rise in colloid osmotic pressure. Two possible profiles of colloid osmotic pressure have been hypothesized, one in which the increase is steep in the proximal part of the capillary, reaching a plateau in the distal part (A), and another in which the increase is slow in the proximal part, becoming exponential in the distal part (B). There is no agreement as to which profile more accurately reflects the real phenomenon. Independent of the profile, colloid osmotic pressure rises until it equals the hydraulic pressure inside the capillary, and filtration ceases. The point of FPE moves along the length of the capillary in response to different blood flows. While FPE is maintained, filtration fraction is fairly constant. When FPE is lost (FP dysequilibrium [FPD]), the filtration fraction changes. These findings relate mostly to the patient's hydration status and to the flow autoregulation mechanism.

place along the efferent arterioles. Thus these two anatomic sites are important determinants of the intraglomerular hemodynamics.

Another important concept is tubular-glomerular feedback. The macula densa region of the nephron is a specialized segment of the nephron lying between the end of the thick ascending limb of the loop of Henle and the early distal convoluted tubule. It runs between the angle formed by the afferent arteriole and the efferent arteriole, adjacent to the glomerulus of the same nephron. This anatomic arrangement, the juxtaglomerular apparatus, is suited ideally for a feedback system in which a stimulus received at the macula densa may be transmitted to the arterioles of the same nephron to alter GFR. Changes in the delivery and composition of the fluid flowing past the macula densa have been shown to elicit rapid changes in glomerular filtration of the same nephron, with increases in the delivery of fluid out of the proximal tubule resulting in reductions in filtration rate of the same nephron. The effect is mediated by a continuous fine regulation of the afferent and efferent arteriolar tone (Fig. 9.3). This process is called *tubular-glomerular feedback*. Agents that interfere with sodium chloride transport in the macula densa cells inhibit the feedback response and consequently alter the physiologic regulation of GFR.

Another important mechanism is the neural regulation of GFR. The renal vasculature—the afferent and efferent arterioles, the macula densa cells of the distal tubule, and the glomerular mesangium—are richly innervated. Innervation is supplied by renal efferent sympathetic adrenergic nerves and renal afferent sensory fibers. Neurologic stimuli may contribute to the alteration of vascular tone and tubular-glomerular feedback as well as vasoconstriction mediated by renin secretion.

A variety of hormonal and vasoactive substances influence glomerular ultrafiltration, modifying the tone in the arcuate arteries, interlobular arteries, and afferent and efferent arterioles. Vasoconstricting or vasodilating substances thereby regulate the tone of preglomerular and postglomerular resistance vessels to control renal blood flow (RBF) as well as glomerular capillary hydraulic pressure and the glomerular transcapillary hydraulic pressure gradient. Glomerular filtration also can be regulated by mesangial cell activity (production of a substance or proliferation and contraction) and by glomerular epithelial cells (podocytes). The renal vasculature and glomerular mesangium respond to a number of endogenous hormones and vasoactive peptides through vasoconstriction and reductions in the glomerular ultrafiltration coefficient. Among these compounds are angiotensin II, norepinephrine, leukotrienes C_4 and D_4, platelet-activating factor (PAF), adenosine triphosphate (ATP), endothelin, vasopressin, serotonin, and epidermal growth factor.

A special mention should be made of norepinephrine, because its use in the critically ill patient with septic shock and AKI often is questioned but necessary. Norepinephrine is a potent vasoconstrictor that promptly increases arterial blood pressure when administered systemically. In the kidney, norepinephrine induces vasoconstriction of the preglomerular vessels and efferent arteriole, theoretically decreasing blood flow. However, a rise in intraglomerular pressure prevents a flow-induced decrease in GFR and frequently preserves diuresis in septic patients.

Among vasodilator substances, nitric oxide influences glomerular filtration. Endothelial cells of arteries and veins release an endothelium-derived relaxing factor (EDRF) that is either nitric oxide or an unstable nitroso compound that yields nitric oxide. EDRF formation in the vascular

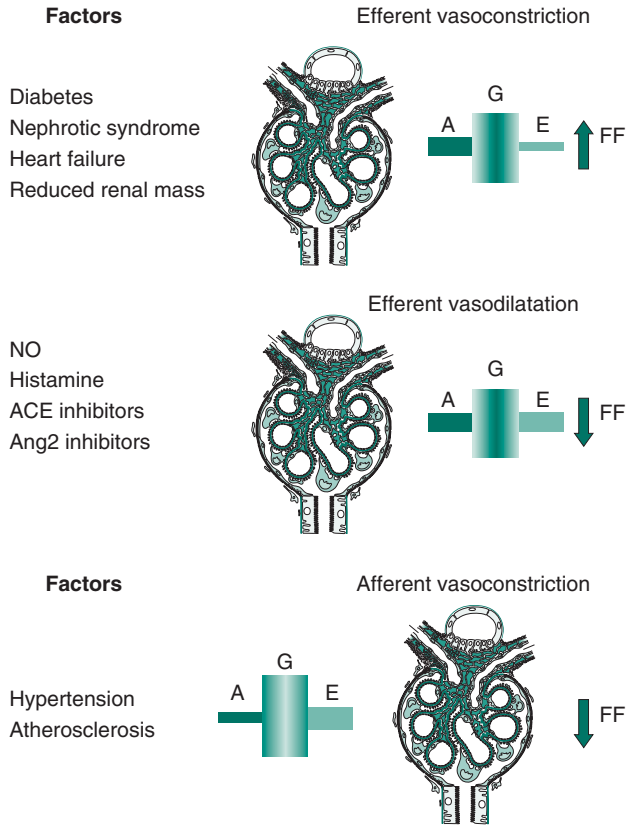

FIGURE 9.3 Physiologic and pathologic conditions that may affect the intrarenal glomerular hemodynamics and relevant action of some pharmacologic agents. FF = filtration fraction, NO = nitric oxide, ACE = aniotensin converting enzyme, ANG2 = angiotensin 2.

endothelium is stimulated by an excess of vasoconstricting agents. EDRF plays a major role in modulating renal hemodynamics and systemic blood pressure, and it also is involved in the mechanism of hyperfiltration in some conditions, such as diabetes. Other vasodilators are prostaglandins. The vasodilator prostaglandins PGE_1 and PGE_2 and prostacyclin generally increase RPF but not necessarily GFR, because they may not affect intraglomerular pressure.

Histamine, a potent vasodilator of the renal circulation, promotes large increases in RPF and RBF mediated by histamine H_2 receptors. This substance activates adenylate cyclase, increasing cellular concentrations of the vasodilator cyclic adenosine monophosphate (cAMP). Despite this, histamine does not substantially alter GFR. Bradykinin, another potent renal vasodilator, produces large increases in renal and glomerular blood flow mediated through the bradykinin B_2 receptor. Much like PGE_2 and prostacyclin, however, bradykinin does not substantially increase GFR. Acetylcholine raises urinary excretion of cyclic guanosine monophosphate (cGMP), and the renal and systemic vasodilation induced by acetylcholine is thought to be mediated to a large extent through the stimulation of EDRF production. Acetylcholine also does not significantly alter GFR. Insulin and glucocorticoids also increase renal blood flow and possibly GFR. The effect seems to be EDRF mediated. Other vasodilating factors are insulin-like growth factor, calcitonin gene-related peptide, and cyclic adenosine monophosphate. Finally, another series of hormones seen to affect GFR are parathyroid hormone (PTH), PTH-related protein, natriuretic peptides, adenosine, and adrenomedullin.

MEASUREMENT OF GLOMERULAR FILTRATION RATE

We use "clearance" as a tool to estimate GFR. Why? Human beings were not created equal. Teleologically speaking, however, human organ function is designed to maintain life parameters as close as possible to normal. Kidneys are not an exception to this rule. They may be bigger or smaller, but they are designed to maintain the internal milieu, as Claude Bernard suggested. A simple measure of solute concentration in blood or of solute excretion or urine output cannot describe the real "function" of the organ. It takes an integration of all these parameters, appropriately combined, to enable a simple computation of "clearance."[5,6] Thus clearance is a tool for comparing renal function among different individuals independently (at least in great part) of urine flow, body size, and solute concentration in blood. Of course, along the nephron, the fluid filtrated by the glomerulus is manipulated, varying its final composition. Therefore, for the computation of clearance as a surrogate of GFR, we need a molecule with ideal features: full filtration by the glomerular membrane (sieving = 1), absence of reabsorption or secretion in the tubular part of the nephron, and ease of measurement; and if we use an exogenous substance, it must be nontoxic for the organism.[7]

In 2006 Stevens et al.[8] reported that measuring GFR with the ideal exogenous marker molecules is expensive and complex and that it leads to a 5% to 20% error in various daily measurements. On the other end, the measurement of clearance with endogenous filtration markers such as creatinine is cheaper but also subject to errors, especially when timed or 24-hour urine collection is involved. In a steady-state condition, the serum level of an endogenous marker is correlated with the reciprocal of the level of GFR, making it possible to estimate GFR without urine collection.[9,10] For creatinine, however, variations in the amounts of tubular secretion, altered extrarenal elimination, and variable generation rates make the use of a single reference range for serum creatinine value inadequate to distinguish between normal and abnormal GFR.[11] Other researchers have proposed cystatin C as a better filtration marker than creatinine, but this suggestion is still controversial, and no definitive statements can be made.[12,13] Certainly it would be useful to have a direct measure of the concentration of the marker molecule in the filtrate. Indeed, this is exactly what can be done in some forms of renal replacement therapy, such as hemofiltration, in which clearance can be quantitated precisely. This measurement, unfortunately, can be used only to compare efficiency of different treatments in a given moment, not as a tool to establish the effect of treatment on the patient. The reason is that extracorporeal clearance cannot be compared with a GFR unless the treatment is continuous, as in continuous venovenous hemofiltration (CVVH) or continuous ambulatory peritoneal dialysis (CAPD). In all other techniques, serum levels are far from being in steady-state conditions, and similar clearances lead to different mass removal rates.

The National Kidney Disease Education Program (NKDEP) of the National Institute of Diabetes and Diseases of the Kidney (NIDDK), the National Kidney Foundation (NKF), and the American Society of Nephrology (ASN) recommend estimation of GFR (eGFR) from serum creatinine using the Modification of Diet in Renal Disease (MDRD) study equation.[2,14–16] This equation uses the serum creatinine value in combination with age, sex, and race to estimate GFR, and thereby avoids several of the limitations to the use of

the serum creatinine value alone.[16] The MDRD study equation, which has been developed and validated rigorously, is more accurate than measured creatinine clearance from 24-hour urine collections.[15,16]

The equation is as follows:

$$\text{GFR} = 186 \times (P_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

where GFR is expressed in mL/min/1.73 m^2, P_{cr} is serum creatinine expressed in mg/dL, and age is expressed in years. The four-variable equation has an R^2 value of 89.2%; 91% and 98% of the estimated values in the MDRD study fell within 30% and 50% of measured values, respectively. Thus GFR can be estimated using different equations that take account of race, gender, age, and body size.

The MDRD study equation, derived from the study carried out in 1999,[15] was reasonably accurate and probably more precise than the previous Cockcroft-Gault equation developed in 1973[10] for patients with CKD. However, both equations have been reported to be less accurate in patients without CKD.[8,17] In several conditions, eGFR from the MDRD study equation can be significantly lower than direct measurements of renal clearance, potentially leading to a false-positive diagnosis of chronic renal disease (eGFR < 60 mL/min/1.73 m^2) with important consequences.[17] This phenomenon has been more evident in Europe than in the United States, and a possible explanation is different calibrations of serum creatinine assays among laboratories.[18]

The MDRD study equation was validated in a group of patients with CKD (mean GFR 40 mL/min/1.73 m^2) who were predominantly white and did not have diabetic kidney disease or kidney transplants.[15] This equation has been validated in diabetic kidney disease, kidney transplant recipients, and African Americans with nondiabetic kidney disease.[19,20] However, it has not been validated in children (age < 18 years), pregnant women, elderly patients (age > 70 years), racial or ethnic subgroups other than white and African American, individuals with normal kidney function who are at increased risk for CKD, or healthy individuals. Furthermore, any of the limitations of the use of serum creatinine, as related to nutritional status or medication use, are not accounted for in the MDRD study equation.[8,15,16] Despite these limitations, GFR estimates using this equation are more accurate than serum creatinine alone. Understanding these limitations should help clinicians interpret GFR estimates. A more accurate estimation of GFR may be obtained with a clearance measurement (e.g., creatinine, iothalamate, iohexol, inulin).

At this time, two important points must be clarified. First, we know from different studies that even minimal reductions in GFR may result in an increased risk of death, cardiovascular disease, and hospitalization.[21,22] The evaluation and management of such complications definitely pertain to the nephrologist, who is well aware of the full spectrum of problems in these circumstances. An early referral to a nephrologist may result in better management of CKD and its complications but also may have a significant impact on the administration of appropriate medications and ultimately on the progression of the nephropathy. For these reasons, monitoring GFR and identifying an early reduction in GFR may become quintessential in the prevention of kidney and cardiovascular disease. The effect on healthcare systems and providers, together with the benefits for the entire population, is clearly evident. Second, on the basis of potential GFR underestimation from inaccurate serum creatinine measurements (or, better, calibrations), we may be facing a "false epidemic" of mild CKD with a tremendous overload of nephrologic centers through a series of referrals made by general practitioners according to nephrologists' suggestions and guidelines. What should we then do? We know that GFR estimates can be inaccurate under some circumstances, such as dietary disorders, altered muscle mass, exercise, and laboratory calibration changes. Such inaccuracies may have a little impact on a subject with overt renal dysfunction but may be crucial in subjects with GFR estimates between 60 and 90 mL/min/1.73 m^2. In these latter cases, exogenous marker clearance may be the solution or at least may represent an important auxiliary tool.[7]

GFR declines with aging. Although the age-related decline in GFR has been considered part of normal aging, decreased GFR in the elderly is an independent predictor of adverse outcomes such as death and cardiovascular disease.[22] In addition, decreased GFR in the elderly requires adjustment in drug dosages, as in other patients with CKD. Generally, drug dosing is based on GFR levels that are not adjusted for body surface area (BSA). In practice, adjusted GFR estimates are adequate except in patients whose body size differs considerably from average. In these patients, unadjusted estimated GFR can be computed by the following formulas:

$$\text{GFR [estimate] (mL/min)} = \text{GFR estimate (mL/min/1.73 m}^2) \times \text{BSA}$$

$$\text{BSA} = W^{0.425} \times H^{0.725} \times 0.007184 / 1.73 \text{ m}^2$$

where W is weight and H is height. All of these issues must be considered once GFR is evaluated in the critically ill patient in whom a preexisting GFR decline could have been present, in whom hormonal and nutritional disorders are present, or who is receiving significant pharmacologic support, with the enormous potential of physiologic interactions.

GFR AND ESTIMATED GFR IN ACUTE KIDNEY INJURY

In patients with AKI, eGFR has not yet been validated; furthermore, it should be stated clearly that eGFR is not an equivalent measure of GFR but only a transformation of the serum creatinine value into a parameter that is static and is not immediately related to the physiology of the glomerular function in a specific moment.[23]

Accurate estimation of GFR from serum creatinine values requires a steady state of creatinine balance; that is, serum creatinine concentration is stable from day to day. This is true whether the serum creatinine value is used alone, in the MDRD study equation, or in other estimating equations such as the Cockcroft-Gault formula. However, the serum creatinine value can provide important information about the level of kidney function even when it is not in a steady state. Estimated GFR overestimates true GFR when serum creatinine levels are rising and underestimates GFR when serum creatinine levels are falling. In general, if the serum creatinine value doubles within 1 day, the GFR is near 0.

On the basis of these concepts, the definition of AKI should include the physiologic concepts of "normality," the presence of residual RFR, and, finally, the dynamic modifications of GFR within hours during the clinical course. Therefore estimated GFR is not a parameter that can be used to define or classify AKI.

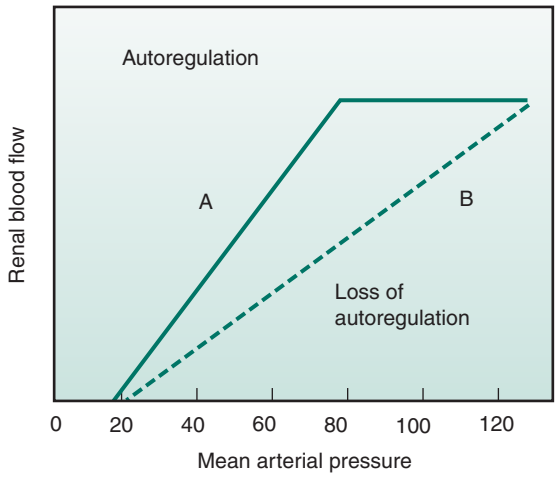

FIGURE 9.4 The concept of renal blood flow autoregulation. Renal blood flow is kept fairly constant in the presence of significant variations of renal perfusion pressure *(line A)*. When a pathologic event occurs, the mechanism is lost, and even small variations in perfusion pressure result in significant variations of renal blood flow *(line B)*.

Regulation and Measurement of GFR in Acute Kidney Injury

In different clinical conditions, renal blood flow is maintained at steady levels through autoregulation (Fig. 9.4). Significant variations in blood pressure are counterbalanced by changes in the renal vascular tone, and the final result is the maintenance of blood flow within normal ranges.[1] The same is true for GFR, which is also kept constant by tubular-glomerular feedback, as already described.[1] In detail, GFR depends on the transcapillary pressure gradient, which is regulated by a fine tuning of the tone of afferent and efferent arteries. This mechanism enables compensation for changes in plasma flow through a variation in filtration fraction. Although this parameter is regulated to keep it around 20%, significant variations in filtration fraction may allow GFR to remain stable in the presence of plasma flow variations. The combined effect of autoregulation and filtration fraction determines the quantity and composition of the urine. In the so-called *syndrome of prerenal dysfunction,* the loss in renal perfusion resulting from arterial underfilling produces a temporary decrease in glomerular filtration and lower sodium content in the tubular lumen, which is counterbalanced rapidly by an increase in reabsorption of sodium and water (leading to a reduced fractional secretion of sodium, high urine osmolality, and oliguria), whereas glomerular hemodynamics are adjusted to increase filtration fraction even though GFR may decrease and the serum creatinine level may rise.

If the patient receives a fluid infusion and extracellular volume expansion therapy, these conditions may be reversible, and the original equilibrium can be restored. In some pathologic conditions, however, or when arterial underfilling remains untreated for longer times, the original alteration, which is functional in nature, may become structural, and parenchymal damage may occur. In such conditions, autoregulation is lost, glomerular hemodynamics and the tubular glomerular feedback are altered, and so is the modulation of filtration fraction. The GFR decreases with a progressive increase in the fractional excretion of sodium and a progressive reduction in urine osmolality.

Subjects with partial or total loss of renal functional reserve (RFR) because of previous damage or loss of nephron mass may be more likely than others to demonstrate a rapid passage from the high-risk condition to the overt clinical phase of AKI. In the absence of previous baseline and test GFR determinations, this possibility may explain the variability of responses observed to ischemic insults, hypovolemia, and fluid infusion.

Urea and blood urea nitrogen (BUN) values are nonspecific indicators of renal function; they are very poor markers of GFR relative to creatinine and thus are not discussed further. However, a serum creatinine value of 1.5 mg/dL (133 μmol/L), in a steady state, corresponds to a GFR of about 36 mL/min in an 80-year-old white woman but to a GFR of about 77 mL/min in a 20-year-old African American man. Similarly, a serum creatinine value of 3.0 mg/dL (265 μmol/L) in a patient in whom renal impairment is suspected would reflect a GFR of 16 mL/min in the elderly woman but 35 mL/min in the young man. In both cases, a doubling of the serum creatinine value corresponds to a decrease in GFR of approximately 50% (exactly a 55% decrease in the preceding example), because there is an inverse relationship between GFR and serum creatinine value. Thus, although every classification of AKI in the literature relies on some threshold value for serum creatinine value, *no single creatinine value corresponds to a given GFR in all patients*.[23] Therefore *the change* in creatinine is useful in determining the presence of AKI, although, as specified in Chapter 11, creatinine change occurs over a certain time frame, and serum creatinine is not sensitive enough to describe rapid variations of GFR. In fact, like creatinine clearance, the serum creatinine value is not an accurate reflection of GFR in the non–steady-state condition of AKI. During the evolution of dysfunction, the serum creatinine will *underestimate* the level of dysfunction. Nonetheless, the extent to which the serum creatinine value changes from baseline (and perhaps the rate of change as well) to some degree reflects the change in GFR. Serum creatinine is measured readily and easily and is reasonably specific for renal function. Thus serum creatinine (or creatinine clearance) is a reasonable approximation of GFR in most patients with normal renal function.[8] Creatinine is formed from nonenzymatic dehydration of creatine in the liver, and 98% of the creatine pool is in muscle. Critically ill patients may have abnormalities in liver function and markedly decreased muscle mass.[4] Additional factors influencing creatinine production are conditions of increased production, such as trauma, fever, and immobilization, and conditions of decreased production, including liver disease, reduced muscle mass, and aging. In addition, tubular reabsorption ("backleak") may occur in conditions associated with low urine flow rate. Finally, the volume of distribution (V_D) for creatinine (total body water) influences the serum creatinine value and may be increased dramatically in critically ill patients. There is currently no information on extrarenal creatinine clearance in ARF, and a non–steady-state condition often exists.[23]

Once glomerular filtration has reached a steady state, it can be quantified by measurement of 24-hour creatinine clearance. Unfortunately, the accuracy of a creatinine clearance (even when collection is complete) is limited because, as GFR falls, creatinine secretion is increased and thus the rise in serum creatinine value is less.[6,10,11] Accordingly, creatinine excretion is much greater than the filtered load, resulting in a potentially large overestimation of the GFR (as much as a twofold difference). Therefore creatinine clearance represents the upper limit of what the true GFR is under steady-state conditions. A more accurate

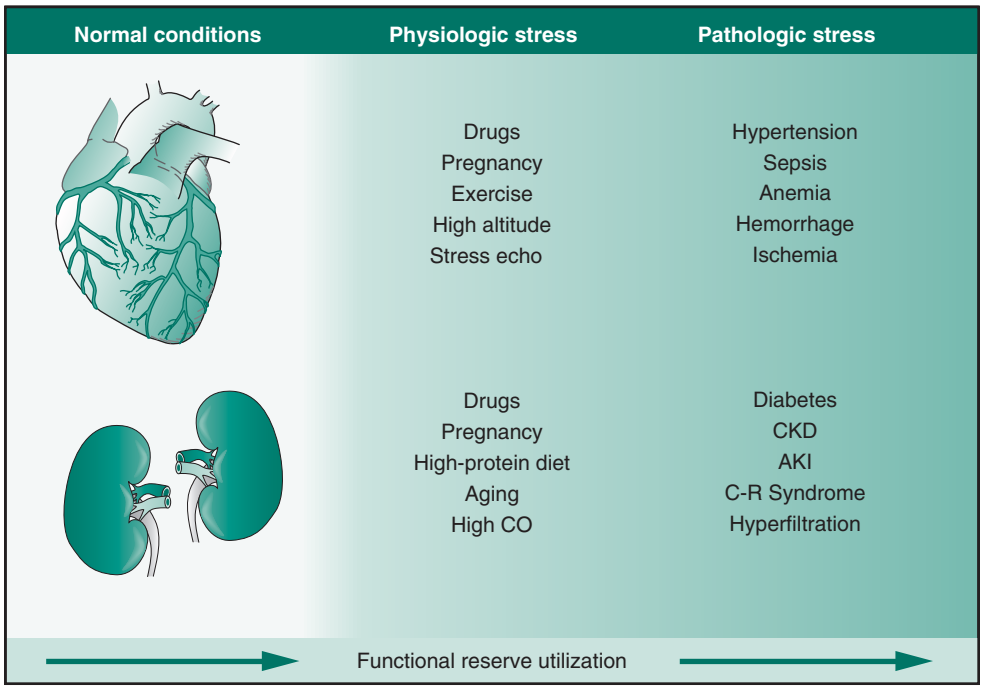

FIGURE 9.5 The concept of physiologic stress and pathologic stress for the kidney can be expressed by a parallel example of what happens in the heart. *AKI,* Acute kidney injury; *CKD,* chronic kidney disease; *CO,* cardiac output; *C-R,* cardiorenal syndrome.

determination of GFR would require measurement of the clearance of inulin or a radiolabeled compound.[7] Unfortunately, these tests are not routinely available. However, for clinical purposes, *determining the exact GFR is rarely necessary*. Instead, it is important to determine whether renal function is stable or getting worse or better—which can be accomplished usually by monitoring serum creatinine value alone.[8] Furthermore, because patients with ARF are not in a steady state, creatinine clearance does not accurately reflect GFR.

When the patient has preexisting renal disease, the baseline GFR and serum creatinine value are different from those predicted by the MDRD study equation. Also, the relative decrease in renal function required to reach a level consistent with the diagnosis of ARF is less than that in a patient without preexisting disease. For example, a patient with a baseline serum creatinine value of 1 mg/dL (88 µmol/L) has a steady-state serum creatinine value of 3 mg/dL (229 µmol/L) once 75% of GFR is lost. By contrast, in a patient perfectly matched with the preceding one for age, race, and sex who has a baseline creatinine of 2.5 mg/dL (221 µmol/L), a mere 50% decrease in GFR corresponds to a serum creatinine value of 5 mg/dL (442 µmol/L).

The problem with these criteria is that the first patient may have had a baseline GFR of 120 mL/min decreasing to 30 mL/min, and the second patient a baseline GFR of 40 mL/min decreasing to 20 mL/min. It would be confusing to regard the first patient, with a GFR of 30 mL/min, as having ARF, and the patient with a GFR of 20 mL/min as not having ARF. Thus it seems that either a different set of criteria is needed in patients with preexisting disease or some absolute creatinine criteria must be integrated into the classification system. One possible approach would be to use a relative change in creatinine (e.g., threefold) as the primary criterion, with an absolute cutoff (e.g., 4 mg/dL or about 350 µmol/L) as a secondary criterion when the baseline serum creatinine value is abnormal. Separate criteria should be used for the diagnosis of AKI superimposed on chronic renal disease. An acute rise in serum creatinine (of at least 0.3 mg/dL) to more than 4 mg/dL (350 µmol/L) identifies most patients with AKI whose baseline serum creatinine values are abnormal.

All of these considerations have been used to come up with a definition of ARF or AKI that could serve for prospective studies as well as for stratification of patients according to severity of the syndrome and of the organ damage.

RENAL FUNCTIONAL RESERVE AND RENAL STRESS TESTING

As part of the human evolutionary development, many human organ systems have innate mechanisms to adapt to increased "work demand" or stress. At rest, organ systems operate at baseline capacity, and this capacity can be increased to a certain maximum capacity. A familiar example of this concept is cardiac function. In a healthy person at rest, cardiac output is approximately 5.0 L/min. However, when a healthy person exercises, the cardiac output can double or even triple. Similarly, the kidney has reserve capacity of its multiple physiologic functions (Fig. 9.5). The ability to test the reserve of an organ system is often an excellent diagnostic tool to uncover subclinical disease (e.g., treadmill test). Similarly, stress testing of the kidney appears to generate insights into the presence or absence of kidney disease and parenchymal loss resulting from injury and potentially fibrosis. The two main domains of kidney stress testing are glomerular and tubular. In a healthy kidney, these two components of the nephron work in concert. However, when the kidney is diseased or injured, the glomerular and tubular function may be affected equally, or its form and functional capacity may

diverge. An assessment of glomerular and tubular function may be more informative than just one of these domains. Glomerular reserve testing has been well established but is used infrequently in routine clinical care. Tubular function diagnostic testing is relatively new and in its clinical "infancy." However, tubular assessment appears to hold significant promise for the assessment of chronic and acute kidney disease.

Renal Functional Reserve—Glomerular

Because of the common use of estimated GFR equations, there is a tendency for nonnephrologists to think that the GFR is a constant. In fact, the actual GFR changes throughout the day, particularly after meals, based on physiologic needs.[24] One of the kidney's primary roles is to effectively remove nitrogenous waste, and as a consequence, the consumption and metabolism of protein results in an increase in GFR.[25] GFR also can be increased through other mechanisms that work along the protein metabolic pathway. For instance, an intravenous infusion of amino acids will result in an increase in GFR.[26] This increase in GFR over baseline GFR is known as renal functional reserve-glomerular (RFR-G).[27] Protein ingestion, particularly red meat, is a potent stimulant for increasing GFR, and the teleological explanation is likely related to an adaptive response to increased protein in the diet.[28]

Bosch et al. first described RFR-G in 1983.[27] In this seminal paper, Bosch et al. demonstrated that the consumption of protein, not carbohydrates or fat, results in a substantial increase in GFR in patients with healthy kidneys. Multiple subsequent studies have confirmed these findings. The clinical implications of RFR-G will be reviewed.

Baseline (Unstressed) GFR

Glomerular filtration rate (GFR) is used normally as a surrogate of kidney function in healthy subjects as well as in patients with kidney disease. Studies[29] in healthy subjects under the age of 50 have identified the average baseline normal values of GFR to be between 100 to 130 mL/min/1.73 m^2. Evaluation of population-wide "normal" values is useful, but the concept of "normal" GFR in the single individual is more nuanced (Fig. 9.6). It is important to recognize that a person's GFR at any given point in time will vary in relation to the physiologic demands of dietary and hemodynamic conditions. Baseline value for GFR (bGFR) also depends on age, sex, and body size, with considerable variation among healthy individuals. Overall, the average daily GFR is remarkably stable over years, although there is an age-related decline in GFR physiologically by 0.8 mL/min/1.73 m^2/year, after the age of 30 years.[30,31]

In general, serum creatinine tends to remain relatively normal even in the presence of kidney damage, until approximately 50% of nephrons are lost or simply when bGFR approached 60 mL/min/1.73 m^2, (Fig. 9.7).[32] For this reason serum creatinine cannot be considered an accurate marker of renal function when GFR is above 60 mL/min/1.73 m^2. Similarly, GFR estimation (eGFR) by creatinine-derived equations (e.g., MDRD[33]) cannot be considered a sensitive index for early detection of renal disease during the early phases of parenchymal damage. A good example of this can be seen in patients who donate a kidney; despite a halving of their nephron mass, their serum creatinine and calculated eGFR are "normal."[33,34] Therefore, when renal disease becomes apparent because of an elevated serum creatinine, this occurs only after the residual nephrons can no longer compensate for the functional loss.[32]

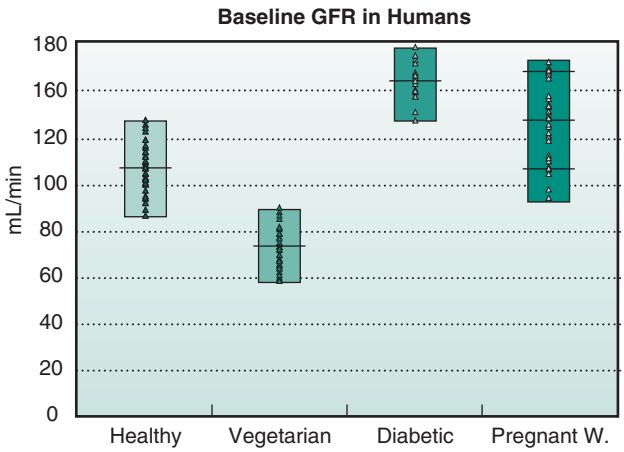

FIGURE 9.6 Different levels of baseline glomerular filtration rate (GFR) can be observed in healthy subjects depending on diet or other concomitant situations. In case of pregnancy, the baseline GFR depends on the period of the pregnancy that is considered (the three lines represent three baseline GFR levels observed in the average pregnant population and the first, second, and third trimester).

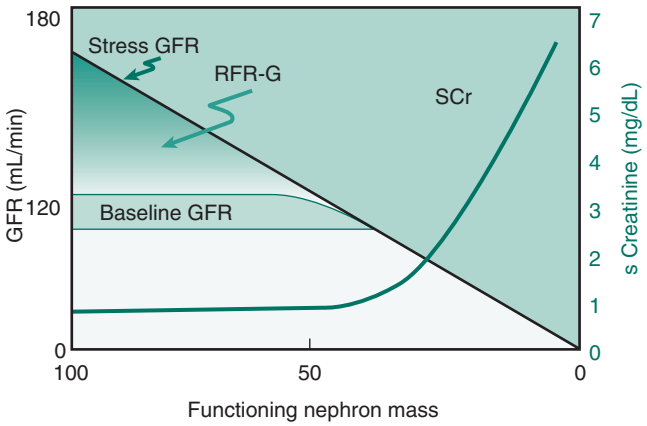

FIGURE 9.7 The concept of renal functional reserve (RFR). The baseline glomerular filtration rate (GFR) depends on many factors, including diet and fluid intake. Nevertheless, each person has the capability to increase GFR in response to different stimuli to a level that depends on the amount of intact renal mass. The difference between maximum GFR (maxGFR or stress GFR) and baseline GFR (unstressed GFR) describes the renal functional reserve (RFR). When renal mass is lost, maxGFR declines in an almost linear function. Serum creatinine (SCr) tends to increase when more than 50% of the renal mass is compromised. RFR is still present any time the baseline GFR is lower than the maxGFR at a given value for functioning renal mass.

Renal Functional Reserve

Healthy subjects display a significant increase in GFR 1 or 2 hours after an acute protein load (1–1.2 g/kg) over their baseline GFR. The difference between peak or "maximum" GFR (maxGFR) and baseline GFR describes the RFR-G (Figs. 9.7 and 9.8). Fliser et al.[34] compared the baseline and maxGFR in young and elderly healthy subjects and found that RFR was significantly lower in elderly than

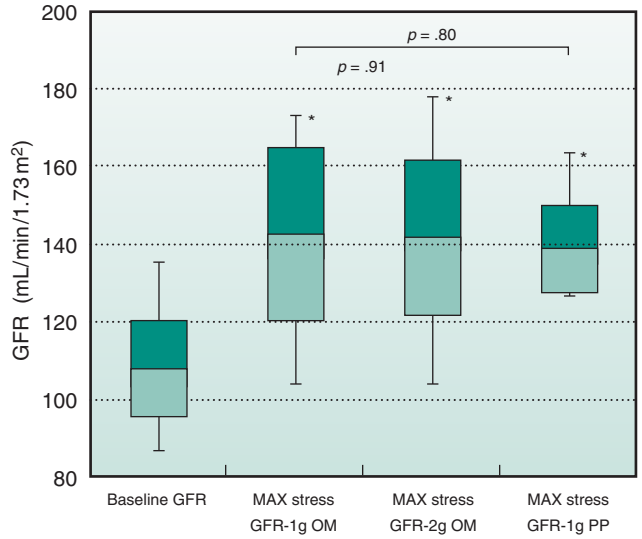

FIGURE 9.8 Typical response of GFR after stimulation with oral meal (1 g/kg bw, 2g/kg bw of meat proteins or 1g/kg bw of powder protein. * denote statistical significance. *bw,* Body weight.

in young healthy individuals, while virtually all baseline GFR values of elderly were within the reference range. The renal reserve as assessed by RFR-G is a measure of the kidney's capacity to increase GFR by a combination of nephron recruitment and increases in renal blood flow coupled with hyperfiltration.[35–38]

The stimulus to "tap" into this reserve capacity can arise from adaptive physiologic needs such as pregnancy or the presence of solitary kidney. Use of RFR in nondisease states is best illustrated by pregnancy. In pregnancy, GFR significantly increases during each trimester, such that there is a significant rise in bGFR from first to last trimester. Studies done on healthy pregnant women in each trimester have shown a progressive increase of baseline GFR with a parallel reduction of RFR as a result of its progressive utilization.[36] MaxGFR in normal pregnant women, however, does not change. However, pathologic states also can initiate processes that increase GFR above the normal baseline. Primary hyperfiltration in kidney disease has been shown in patients with diabetes mellitus, polycystic kidney disease, secondary focal segmental glomerulosclerosis, sickle cell anemia, high altitude renal syndrome, and obesity, hypertension, nephrotic syndromes, and glomerulonephritis.[39] In physiologic states of diminished RFR, the observed hyperfiltration is likely because of recruitment of more nephron units, whereas in pathologic states, hyperfiltration is probably the result of an increase in single nephron filtration fraction. This, in part, is the basis of angiotensin II blockade in CKD and often is demonstrable by a drop in GFR when ACE inhibitors are given to patients with CKD.

A current limitation on the use of RFR-G assessment is that these assessments have not been conducted in large cross-sectional cohorts; thus the population variability of the RFR response is not known. Several investigators have estimated RFR by measuring the difference between protein-stimulated GFR and baseline GFR after a protein load.[27] In a separate study, Bosch et al.[40] demonstrated the estimation of RFR by a short-term oral protein loading method. De Nicola et al.[41] demonstrated that the estimation of RFR can be assessed by amino acid infusion. Our own group has pointed out the methodology to perform a complete renal reserve stress test.[42–43]

Numerous mechanisms have been hypothesized for the increase in GFR after protein load. In their study, Woods[44] showed that protein loading increases GFR because digested protein raises plasma amino acid levels, which then are filtered at the glomerulus, thereby stimulating proximal tubular absorption. In addition, filtered amino acids change the sensitivity of macula densa sensing mechanisms, causing release of nitric oxide (NO) and prostaglandins locally resulting in vasodilation, increasing renal blood flow and GFR. In our laboratory we analyzed the response to acute protein loading, and we detected an increase in GFR proportional to an increase in renal blood flow with a constant of filtration fraction. This observation seems to support the hypothesis that an overall increase in blood flow is the main mechanism rather than a temporary hemodynamic perturbation in the afferent/efferent tone and equilibrium.

Stress testing with a protein load is the definitive way to assess for the loss of RFR-G, but the significance of renal reserve is not just a diagnostic consideration. It is important to recognize that the loss of renal reserve also may manifest as a loss in autoregulation capacity in the kidney. This loss of autoregulation may increase the vulnerability of those patients with CKD to volume depletion and certain nephrotoxins (e.g., NSAIDs). Population studies suggest that increased creatinine variability, which could be due to the loss of autoregulation, predicts progression to ESRD.[45]

Kidney Stress Test of Glomerular Function in Clinical Practice and Future Research

Assuming RFR-G represents the difference between maxGFR and bGFR, a protein load is the basis of a kidney stress test forcing the kidneys to use the entire filtration capacity. This technique can be used to "reveal" subclinical kidney disease. MaxGFR and bGFR assessment with protein loading has been studied extensively and can be used in the clinic to assess RFR-G in patients with kidney disease. Because dietary protein raises GFR, establishing bGFR is important when attempting to assess RFR-G; developing standardized protocols to accomplish this is an important research recommendation.

There is another approach that would allow single GFR assessment instead of having to conduct a baseline and a stimulated stress test. In this approach, the maxGFR would be assessed among healthy patients across a wide age range, ethnic range, and in both genders. Once these data were known, then normative values could be determined for maxGFR. These data would be used for diagnostic purposes for patients who underwent a kidney stress test to achieve maxGFR. Those patients that could not achieve the appropriate age, gender, and race maxGFR metrics could be referred for further workup.

As part of the future research plan, the safety of repeated protein loading inpatients with CKD also should be assessed. Because protein is a stimulant for GFR, the effects of repeated protein loading in patients with CKD is unknown. The exposure of repeated high levels of protein in patients with CKD may be deleterious but may also "condition" the kidney as well and stimulate restorative or protective effects; this concept should be studied further.

The idea of assessing renal reserve has been present for decades but is used infrequently in clinical practice, whereas the cardiac stress test is used routinely. Why is this the case? In our view, the simple reason is that cardiologists perceive that they can intervene in patients with diminished cardiac reserve (e.g., heart failure treatment), whereas the

nephrology community may not feel that an intervention is available and therefore may be unwilling to perform an extra test. We hypothesize that patients with loss of renal reserve are at risk for CKD. Future trials should assess whether early identification of diminished renal reserve can reliably predict the risk of progression to CKD. If this can be shown, early screening of renal reserve may prompt early intervention and forestall the development of CKD.

Tubular Function Assessment in Kidney Disease

The renal tubule portion of the nephron is tasked with an enormous variety of responsibilities. Chief among those chores include the handling of electrolytes, water, and amino acids; catabolism of various proteins; and the active secretion of endogenous and exogenous acids. Tubular function assessment may be more informative than glomerular reserve in patients who already have advanced kidney disease. When patients do not have obvious kidney disease, the loss of glomerular reserve (RFR-G) can be an indicator of loss of nephron mass. However, once a patient has kidney injury/disease, glomerular reserve already is reduced substantially and therefore is less informative.

In patients with decreased GFR, tubular function appears to be more variable. One reason for this observation may be renal fibrosis. During the assessment of a kidney disease by tissue biopsy, the level of interstitial fibrosis is one of the strongest predictor of renal survival.[46,47] Interstitial fibrosis can represent scarred tubules that are fibrosed and/or the secretion of matrix that fills in between the nephrons. However, because chronic kidney disease generally is marked by a reduction of kidney size, this makes the possibility of "extra" matrix an unlikely sole explanation for fibrosis (an exception to this would multiple myeloma). In most forms of kidney disease, the kidneys shrink and become more echogenic over time. Based on this observation, we believe that it is more likely that diseased tubules are replaced by matrix and fibrosis. To test the notion that tubular function may identify patients that are increased risk for worse outcomes, various studies in patients with both acute and chronic kidney disease have been conducted to determine the utility of tubular secretion capacity to predict outcomes.[48,49]

Different aspects of tubular function can be investigated in various ways, depending on what feature of tubular function is being assessed. For instance, the tubule's capacity to secrete acid or sodium can be assessed via acid or salt loading. The tubule's concentrating capacity can be assessed via water deprivation or exogenous administration of desmopressin (DDAVP). Among these different techniques, thus far the primary methodology to assess tubular functional capacity in patients with kidney disease has been assessed via tubular secretion of either creatinine or an exogenous drug (e.g., furosemide).

Tubular Function Assessment in Chronic Kidney Disease

The first studies of tubular functional capacity in patients with chronic kidney disease used the difference between creatinine clearance and inulin clearance as an assessment of tubular function. Herrera et al.[49] developed an elegant study to demonstrate the potential use of tubular secretion. In this study, the investigators took three cohorts of patients: normal patients, renal allograft donors (uninephrectomized), and those with chronic kidney disease. In these subjects, baseline creatinine clearance and inulin-based GFR were measured and then reassessed after a protein meal. They found that healthy patients and patients with CKD were able to increase their inulin-measured GFR in response to a protein meal: as expected, healthy patients could increase their GFR after stimulation much more than CKD patients. Similarly, healthy patients were able to increase their tubular secretion of creatinine (TScr), but CKD patients were unable to increase their TScr. When all three groups of patients were compared, uninephrectomized patients were able to increase their TScr (but to a lesser degree than healthy subjects), whereas CKD patients were unable to increase their TScr. These data are consistent with previous studies that show that patients with CKD maintain some glomerular renal reserve at all levels of baseline GFR. In addition, this study demonstrated that CKD patients likely operate near their maximum TScr, and thus are less able to increase their TScr when challenged with a protein meal.

In a second trial, this same group of investigators assessed TScr by infusing intravenous creatinine into normal subjects and kidney donors.[50] They found that creatinine infusion did not increase GFR and that an infusion of intravenous creatinine resulted in an increase TScr in healthy patients but not in kidney donors. Thus a tubular functional assessment with a challenge of intravenous creatinine had the capacity to reveal the subjects with decreased nephron mass (i.e., kidney donors) who otherwise had normal serum creatinine levels.

In aggregate, preliminary studies suggest that tubular stress tests that measure the secretory capacity of the renal tubule are informative and predictive of outcomes.[48–51] However, it should be noted that tubular stress tests remain research tools and have not yet been deployed into the clinic for CKD.

Tubular Assessment in Acute Kidney Injury

The aforementioned studies in CKD used creatinine secretion to assess tubular functional assessment. In patients with AKI, many factors including lack of steady state, increased catabolism, and concurrent medications that interfere with creatinine secretion preclude the use of TScr as a reliable measure of tubular secretion. One approach uses intravenous furosemide to assess tubular function. Furosemide, a loop diuretic, has pharmacokinetic properties that make it an appealing functional tool. In contrast to other drugs cleared by the kidney, furosemide is not filtered effectively by the glomerulus. As an organic acid, furosemide is bound tightly to albumin and gains access to the tubular lumen by active secretion via the human organic anion transporter (hOAT) system in the proximal convoluted tubule.[52,53] Once in the tubular lumen, furosemide blocks luminal cation-chloride cotransport throughout the thick ascending limb of Henle, thereby preventing sodium reabsorption and resulting in natriuresis and increased urine flow.[54–56] Based on these properties, furosemide-induced increases in urine output represent a methodology to assess the integrity of the renal tubular function in the setting of AKI. This methodology was developed by Chawla et al.[48] and is referred to as the furosemide stress test (FST).

The FST has been assessed prospectively in a single cohort study of critically ill patients with AKI and was found to have good diagnostic performance. In that study, Chawla et al.[48] administered a standard dose of intravenous furosemide (1.0–1.5 mg/kg) to critically ill patients with KDIGO stage I or stage II AKI and then assessed the urine output response. This study showed that the 2-hour urine

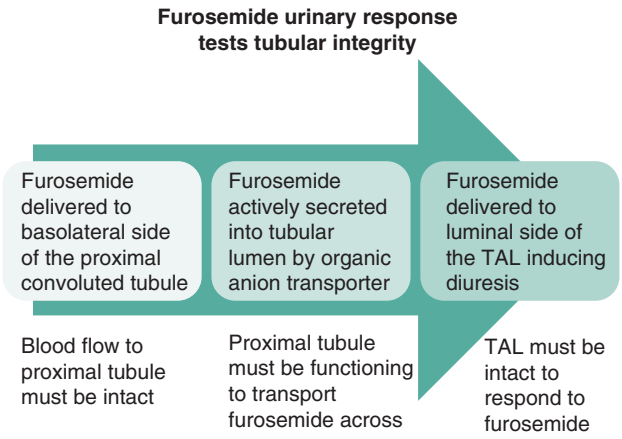

FIGURE 9.9 Kidney tubular integrity is described by the furosemide stress test through different mechanisms.

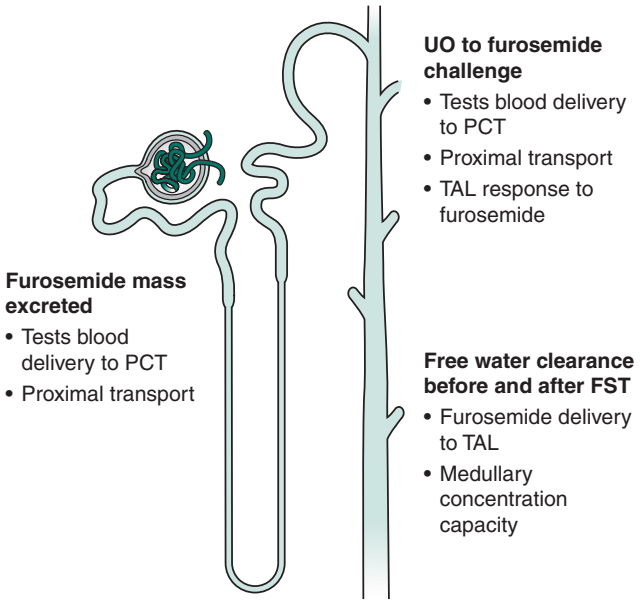

FIGURE 9.10 Mechanisms involved in the tubular stress test performed with furosemide. *PCT,* Proximal convoluted tubule; *TAL,* thick ascending limb; *UO,* urine output.

output response to a furosemide challenge was able to predict progression to KDIGO stage III within 14 days with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.87 (standard error 0.05). At a cutoff of 200 cc at 2 hours, the sensitivity and specificity of the FST were 87.1%, and 84.1%, respectively. In a follow-up study of the same cohort, the same research group showed that FST performed better than known AKI biomarkers. Importantly, the follow-up study demonstrated that the FST performance improves when used in patients with increased levels of AKI biomarkers.[56] These data suggest that the combination of AKI biomarkers with tubular functional assessment are informative and can be used at the bedside to assist clinicians in assessing the severity of AKI. It remains unclear whether the FST reveals the severity of AKI, or the loss of tubular functional capacity. An important caveat to the FST is that the subject must be euvolemic for the test to be safe and valid, and any volume losses induced by the diuresis should be replaced.

A version of the FST also has been analyzed in patients with advanced stage AKI requiring renal replacement therapy to determine if a standardized furosemide challenge can predict renal recovery. Van der Voort et al. reported that a standardized 4-hour infusion of furosemide was also an excellent predicator of renal recovery.[51,58] This analysis was a post-hoc assessment of a randomized clinical trial, which compared a 4-hour infusion of furosemide to placebo as an intervention to promote renal recovery for patients who are on continuous renal replacement therapy. In this post-hoc analysis, the authors assessed the intervention arm of the trial (i.e., the patients randomized to furosemide) and found that the mean urine output was much higher in patients destined to recover (654 mL vs. 48 mL, $p = .007$) and had a diagnostic performance AUC-ROC of 0.84. These two studies demonstrate that the urine output response to furosemide is informative about renal tubular function throughout the phases of AKI (progression and recovery). Another advantage of the FST is that it does not just measure the tubule's secretion capacity but actually assesses integrated renal function[59] (Figs. 9.9 and 9.10). For furosemide to increase urine output, furosemide must be secreted actively into the proximal lumen, and the thick ascending limb, luminal patency, and collecting duct function must be intact.[60] Because the FST requires an intact nephron for full function, the FST does readily identify the location of the defect in cases in which the FST response is poor.

The aforementioned studies of FST are of modest size and currently are undergoing larger-scale validation (NCT01275729). However, the FST is based on the bedside practice of many clinicians, which involves challenging patients with a loop diuretic and assessing the clinical response. The FST, as currently devised, is simply a framework around this common bedside practice. The FST also is being assessed by the "*0 by 25*" initiative spearheaded by the International Society of Nephrology (ISN). In an austere medical environment, simple diagnostic tools such as serum urea and creatinine are not readily available. As such, the use of FST in euvolemic patients with oliguria may allow a thoughtful way to triage patients who may need more advanced care. Because furosemide is inexpensive and available worldwide, this physiologic assessment may allow for broader use of this diagnostic approach.

In summary, kidney stress testing can be accomplished by assessing glomerular and tubular domains. These assessments are safe and relatively inexpensive and can be done at the bedside or in the clinic. Importantly, these assessments have been shown to be informative in acute and chronic kidney disease. However, neither of these stress tests currently is used routinely at the bedside or the clinic. The role of assessing RFR-G can, and in our opinion, should be used to reveal the loss of RFR in patients at risk for kidney disease. Tubular functional testing has been less developed, but early studies demonstrate good diagnostic performance. However, large validation studies are still needed. Because tubular testing may have the capacity to assess multiple anatomic domains of the nephron, we believe that noninvasive kidney stress testing may allow clinicians to identify phenotypes, prognosticate regarding, and better follow patients with kidney disease.

Key Points

1. Glomerular filtration rate is the main parameter to describe kidney function.

2. The mechanisms that regulate glomerular ultrafiltration are numerous and complex. The final regulation is achieved through a fine regulation of the transcapillary pressure gradient and the membrane permeability coefficient.
3. The measurement of glomerular filtration rate is complicated, and in clinical settings, simplified methods or even estimations from serum creatinine using special formulas can be used.
4. Baseline and maximal glomerular filtration capacities may be different. The difference between the two values describes a third parameter called *renal functional reserve.*
5. Measurement of glomerular filtration rate and its modification over time is an important method in determining the level of acute kidney injury.

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