Glomerular Filtration Rate and Renal Functional Reserve

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Summary

Glomerular filtration rate (GFR) is usually accepted as the best overall index of kidney function in health and disease. Normal GFR varies according to age, sex, and body size. In young adults it is approximately 120-130ml/min/1.73 m² and declines with age[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), while an abrupt reduction of GFR possibly transient in nature may be used to describe acute kidney injury (AKI). Below 60 ml/min/1.73 m², the prevalence of complications and the risk of cardiovascular disease seem to increase both in CKD and in AKI[2-4] (see Table I and II for classification of CKD according to e-GFR).

The physiological mechanism of glomerular filtration is generally clearly understood. A more complex issue however, is the measurement of GFR in clinical practice and especially the definition of "normal" renal function. In fact, one cannot define "renal function" just relying on glomerular filtration rate since 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 may not be a fixed function, but may rather display significant variations among individuals or even in different moments within one individual. All these aspects have an important impact on the diagnosis and staging of chronic kidney disease, but they are similarly important in the evaluation of kidney function in ICU patients with or without acute kidney injury. We will try to elucidate some of the aspects related to glomerular filtration rate in the clinical setting.

The mechanism of glomerular filtration

The process of glomerular filtration[1] is a typical model for transcapillary ultrafiltration. Ultrafiltration is a process where plasma water containing solutes and crystalloids but not cells or colloids is separated from whole blood by mean of a pressure gradient through a semipermeable membrane. The pressures involved in the process are typical Starling forces i.e. 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.

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

Obviously, Jw 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)

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

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 (GBM), and the filtration slits between the glomerular epithelial cell foot processes. Anatomic alterations of various components of the glomerular filtration barrier play a crucial role in determining glomerular hydraulic conductivity and hence glomerular filtration in disease states.

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

For the same reason, the permeability coefficient is also difficult to determine but calculations can be done 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, chronic ureteral obstruction, puromycin aminonucleoside-induced nephrosis, and chronic protein malnutrition can all affect K_f. In addition, the hydraulic permeability of the GBM is inversely related to $\overline{\Delta P}$, suggesting that K_f may be directly affected
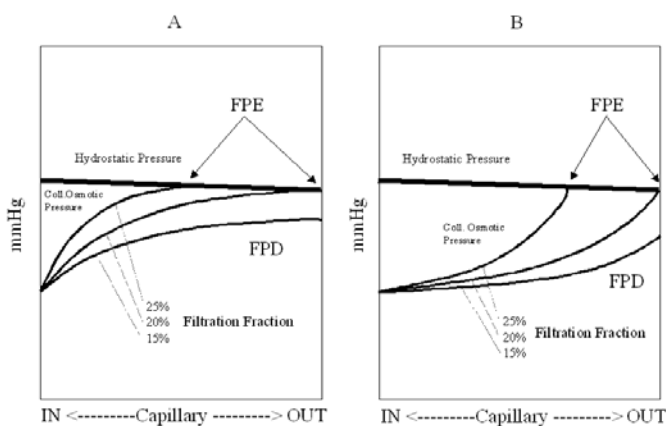
Figure 1. The concept of filtration pressure equilibrium (FPE) in the glomerular capillary. As blood moves through the capillary, water is removerd from blood by ultrafiltration. This result in a progressive increase in protein concentration that is paralleled by an increase in colloid osmotic pressure. Two possible profiles of colloid osmotic pressure have been hypothesized and they are descrbed in panels A and B. Independently of the profile, colloid osmotic pressure increases until it equalizes the hydraulic pressure inside the capillary and filtration ceases. The point of filtration pressure equilirium moves along the length of the capillary in response to different blood flows. While FPE is maintained, filtration fraction is faily constant. When filtration pressure equilibrium is lost (FPD) then filtration fraction changes. These findings are mostly in relation to the hydration status and the flow autoregulation mechanism.

by $\overline{\Delta P}$. The hydraulic conductivity of the GBM and K_f are also affected by the plasma protein concentration.

The behaviour of the pressure in the glomerular capillary is interesting and it has been considered to be similar to that 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 the hydraulic pressure in the blood compartment with a parallel increase in the counter pressure generated by the progressive increase in plasma proteins. Different profiles can be postulated for the colloid osmotic pressure (Fig. 1) but it has been demonstrated that in fluid depleted animals filtration pressure equilibrium occurs along the length of the capillary[1]. This means that hydrostatic and colloido-osmotic 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 filtration pressure equilibrium points towards the end of capillary until a point in reached when such equilibrium does not occur any more. Changes in glomerular filtration rate and filtration fraction 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 approach obtained relatively good correlation with experimental data in animals. The anatomy of the glomerular capillary network is far more complex, however, with capillary loops having varying lengths. Even when the data suggest that the overall network is at filtration pressure disequilibrium, filtration pressure equilibrium

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), Remuzzi and co-workers found that calculated values of K_f from the homogeneous model are somewhat lower than those obtained from the network model. This discrepancy becomes greater as filtration pressure equilibrium is approached. Therefore, it is evident that the permeability coefficient of the glomerular membrane can only be studied in conditions where filtration-pressure equilibrium 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 filtration pressure equilibrium along the length of the capillary correspond to different levels of filtration fraction and have significant consequences on the proximal and distal tubular physiological response. At the same time, it becomes clear that all conditions altering blood flow to the capillary (ischemia, sepsis, cardiac dysfunction) can be tolerated only to the point in which renal blood flow autoregulation is intact. When autoregulation is lost or the delicate equilibrium between afferent and efferent arteriolar tone is altered, both blood flow and filtration fraction are consequently altered and so are the intraglomerular hemodynamics and the process of ultrafiltration. This 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, while approximately 70% of the hydraulic pressure drop between the glomerular capillaries and the renal vein takes place along the efferent arterioles. Thus, these two anatomical sites are important determinants of the intraglomerular hemodynamics.

Another important concept to underline is the tubulo – 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 ideally suited for a feedback system whereby a stimulus received at the macula densa might 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 now 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 decreases in filtration rate of the same nephron. This goes under the name of tubulo-glomerular feedback. Agents that interfere with NaCl transport in the macula densa cells inhibit the feedback response and consequently alter the physiological regulation of glomerular filtration rate.

Another important mechanism is the neural regulation of glomerular filtration rate. The renal vasculature, including the afferent and efferent arterioles, the macula densa cells of the distal tubule, and the glomerular mesangium, are richly innervated. Innervation includes renal efferent sympathetic adrenergic nerves and renal afferent sensory

fibers. Neurological stimuli may contribute to the alteration of the vascular tone, vasoconstriction mediated by rennin secreation and altered tubular glomerular feedback.

A variety of hormonal and vasoactive substances influence glomerular ultrafiltration modifying the tone in the arcuate arteries, interlobular arteries, and afferent and efferent arterioles. Vasoconstrictor 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 can also be regulated by mesangial cell activity (production of 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 by 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 5'-triphosphate (ATP), endothelin, vasopressin, serotonin, and epidermal growth factor.

A special mention should be made for norepinephrine since its use in the critically ill patient with septic shock and acute kidney injury is often 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 resulting in a decrease in blood flow. An increase in intraglomerular pressure, however, prevents a flow-induced decrease in GFR and frequently preserve diuresis in septic patients.

Among vasodilator substances we should mention nitric oxide (NO). Endothelial cells of both arteries and veins release an EDRF that is NO or an unstable nitroso compound that yields NO. EDRF formation in the vascular endothelium is stimulated by excess of vasoconstricting agents. EDRF plays a major role in modulating renal hemodynamics and systemic blood pressure and it is also involved in the mechanism of hyperfiltration in some conditions such as diabetes. Other vasodilators are prostaglandins: The vasodilator prostaglandins PGE_1, PGE_2, and prostacyclin generally increase RPF but not necessarily GFR since they may not affect intraglomerular pressure. Histamine is a potent vasodilator of the renal circulation that promotes large increases in RPF and RBF mediated by H_2 receptors. It activates adenylate cyclase, increasing cellular concentrations of the vasodilator cAMP. Despite this, histamine does not substantially alter GFR. Bradykinin is a potent renal vasodilator and 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 increases urinary cGMP excretion, and the renal and systemic vasodilation induced by acetylcholine is now thought to be mediated to a large extent through the stimulation of EDRF production. Also acetylcholine does not alter significantly GFR. Insulin and glucocorticoids also increase renal blood flow and possibly GFR. The effect seems to be EDRF mediated. Other vasodilating factors include insulin-like grow factor, calcitonin-gene related peptide, cyclic adenosine monophosphate,

Finally, another series of hormones seen to affect GFR. These include, PTH, PTH related protein, natriuretic peptides, adenosine, and adrenomedullin.

The Measurement of Glomerular Filtration Rate

It is well known that we use "clearance" as a tool to estimate GFR. Why do we use clearance to estimate GRF? Human beings were not created equal. Teleologically speaking however they have organ function designed to maintain life parameters as close as possible to norma. Kidneys are not an exception to this rule. They might 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, of solute excretion or urine output cannot describe the real "function" of the organ. It takes an integration of all these parameters that, appropriately combined, allow for a simple computation of "clearance"[5,6]. Thus clearance is a tool to compare renal function among different individuals independently (at least in great part) on 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. For this reason, for the computation of clearance as a surrogate of GFR, we need a molecule with ideal features: fully filtered by the glomerular membrane (sieving = 1), absent reabsorption or secretion in the tubular part of the nephron and easily measurable. Of course if we use an exogenous substance, this must be non toxic for the organism[7].

Recently the new England Journal of Medicine[8] has reported that measuring GFR with ideal exogenous marker molecules is expensive, complex and it leads to 5 - 20% errors in different 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 hr urine collection is involved. In a steady state condition, the serum level of an endogenous marker is correlated to the reciprocal of the level of GFR making possible for GFR estimation to occur without urine collection[9,10]. When this is done with creatinine, however, variations of the amounts of tubular secretion, altered extrarenal elimination and variable generation rates make the use of a single reference range for serum creatinine inadequate to distinguish between normal and abnormal GFR[11]. Recent studies have proposed Cystatin C as a better filtration marker than creatinine but this is still controversial and no definite 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 where clearance can be quantitated precisely. This measurement, unfortunately, can only be used to compare different treatments efficiency in a given moment but not as a tool to establish the effect of treatment on the patient. The reason for this is that extracorporeal clearance cannot be compared to a GFR unless the treatment is continuous as in CVVH or CAPD. In all other techniques, serum le-

Table I. KDIGO definition of CKD.

Structural or functional abnormalities of the kidneys for ≥3 months, as manifested by

1. Kidney damage, with or without decreased GFR, as defined by
   Pathologic abnormalities
   Markers of kidney damage
      Urinary abnormalities (proteinuria)
      Blood abnormalities (renal tubular syndromes)
      Imaging abnormalities
   Kidney transplantation
2. GFR <60 ml/min/1.73 m^2, with or without kidney damage

CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

Table II. Current CKD classification based on severity.

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	< 15 (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

vels 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), National Kidney Foundation (NKF) and American Society of Nephrology (ASN) recommend estimating GFR (eGFR) from serum creatinine using the MDRD Study equation[2,14,15,16]. This equation[16] uses serum creatinine in combination with age, sex and race to estimate GFR and therefore improves upon several of the limitations with the use of serum creatinine. The MDRD Study equation has been rigorously developed and validated, is more accurate than measured creatinine clearance from 24-hour urine collections[15,16].

The equation is:

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

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 4-variable equation has an R2 value of 89.2%, with 91% and 98% of the estimated values in the MDRD Study falling within 30% and 50% of measured values, respectively. Thus, GFR can be estimated using different equations that include race, gender, age and body size. The MDRD 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 chronic kidney disease. Both equations, however, have been reported to be less accurate in patients without chronic kidney disease[8,17]. In several conditions, estimated GFR (from MDRD formula) can be significantly lower than direct measurements of renal clearance. This potentially leads to a false positive diagnosis of chronic renal disease (eGFR < 60 ml/min/1.73m^2) with important consequences[17]. This phenomenon has been particularly evident in Europe compared to United States and a possible explanation among others is a different calibration of serum creatinine assays among laboratories[18] (Tab. I and Tab. II).

The MDRD Study equation was validated in a group of patients with chronic kidney disease (mean GFR 40 ml/min/1.73 m^2) who were predominantly Caucasian and did not have diabetic kidney disease or kidney transplants[15]. The MDRD Study equation has now been validated in diabetic kidney disease, kidney transplant recipients, and African Americans with non-diabetic kidney disease[19,20]. The MDRD Study equation has not been validated in children (age <18 years), pregnant women, the elderly (age >70 years), racial or ethnic subgroups other than Caucasians and African Americans, in individuals with normal kidney function who are at increased risk for CKD, or in normal individuals. Furthermore any of the limitations with the use of serum creatinine as related to nutritional status or medication usage are not accounted for in the MDRD Study equation[8,15,16]. Despite these limitations, GFR estimates using equations are more accurate than serum creatinine alone. Understanding these limitations should help clinicians interpret GFR estimates. If more accurate estimation of GFR is necessary, one should obtain a clearance measurement (e.g. creatinine, iothalamate, iohexol, inulin).

At this point we have two important points to clarify: first, we know from different studies that even minimal reductions of GFR may result in an increased risk for mortality, cardiovascular disease and hospitalization[21,22]. The evaluation and management of such complications definitely pertains to the nephrologist who is well aware of the full spectrum of problems in these circumstances. For this reason, an early referral to the nephrologists may result in better management of chronic kidney disease 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 considerations, monitoring GFR and capturing an early reduction may become quintessential in the whole prevention of kidney and cardiovascular disease. The impact on health care systems and providers, together with the benefits for the entire population are clearly evident. Second, based on potential GFR underestimation from inaccurate serum creatinine measurements (or better, calibrations) we might be facing a "false epidemic" of mild chronic kidney disease with a tremendous overload of nephrological centres from a series of referrals done by the general practitioners according to our own 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 or lab calibration changes. This may have a little impact on subject with overt renal dysfunction but it might be crucial in subjects with GFR estimates between 60 and 90 ml/min/1.73m^2. In these circumstances, exogenous markers clearance may be the solution or at least it may represent an important auxiliary tool[7].

The 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 CVD[22]. In addition, decreased GFR in the elderly requires adjustment in drug dosages, as in other patients with CKD. In general, drug dosing is based on GFR levels that are not adjusted
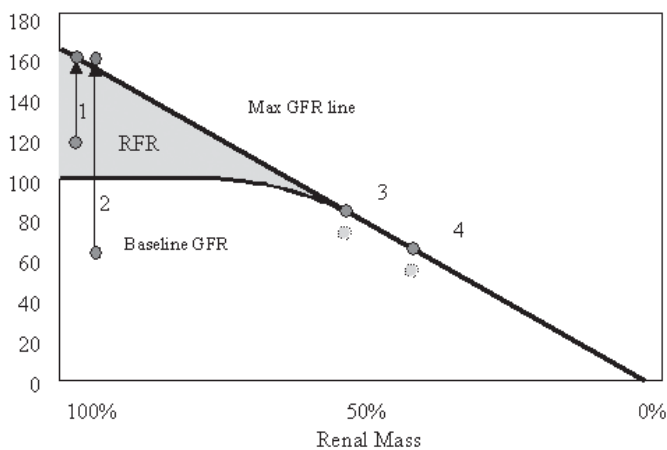
Figure 2. The concept of renal functional reserve (RFR). Every subject has a baseline glomerular filtration rate that depends on many factors including diet and fluid intake. Nevertheless, each individual has the capability to increase GFR in response to different stimuli. The difference between Max GFR and baseline GFR describes renal functional reserve. When nephron mass is lost, Max GFR declines according to an almost linear function. Renal functional reserve is still present any time the baseline GFR is lower than the max GFR at a given amount of functioning nephron mass.

for body surface area. In practice, adjusted GFR estimates are adequate except in patients with body size that is very different than average. In these patients, unadjusted estimated GFR can be computed by the following formulas:

$$BSA = W^{0.425} \times H^{0.725} \times 0.007184/1.73 \text{ m}^2$$
$$GFR = \text{estimate (ml/min)} = GFR \text{ estimate}$$
$$(\text{ml/min}/1.73 \text{ m}^2) \times BSA$$

All these considerations must be made once GFR is evaluated in the critically ill patients where a pre-existing GFR decline could have been present, hormonal and nutritional disorders are present, and finally a significant pharmacological support may be present with enormous potential of physiological interactions.

Renal functional reserve

In all this discussion, we have taken for granted a series of aspects which deserve a more detailed analysis. Is clearance of an appropriate molecule a good measure GFR and therefore of kidney function? If so, can we define a "normal" kidney function from GFR under normal circumstances? Or even better; is a normal GFR a sign of normal kidney function?

We know that so-called normal values are related to age, sex and body size and they are identified as 130 and 120 ml/min/1.73 m² in man and woman respectively. But can we really give a number for normality of GFR in a single measurement? And above all, can we extrapolate normal kidney conditions from a normal GFR?

Glomerular filtration rate is not a fixed parameter in subjects with normal renal function. Because several factors may affect the regulation of the afferent and efferent arteries and thus filtration fraction, the resulting effect is that glomerular filtration rate may vary even in the presence of a normal glomerulus and a normal kidney.

Experiments performed on normal subjects in 1983[23], demonstrated that there is a baseline GFR whose value (in

the absence of disease) is dependent on several factors including circulating prostaglandins and other vasoactive substances and ultimately, at steady state, the level of protein intake. Subjects on vegetarian diet present GFRs as low as 45-50 ml/min while subject on large animal protein intake may have a GFR as high as 140-150 ml/min[24].

In all subjects, baseline GFR can be incremented by an exogenous stimulus that causes a constriction in the efferent artery or a vasodilatation in the afferent one. This effect is exactly the opposite of the one observed when ACE inhibitors are administered to a subject who is in a condition of hyperfiltration. In this circumstance, the already vasoconstricted efferent artery is dilated by the ACE inhibitor and filtration fraction ceases and GFR falls[25].

It is not clear what is the maximal value of GFR but it can certainly be approached in a subject receiving an acute load of at least 1.2 g of animal protein or an i.v. infusion of a mixture of essential aminoacids with addition of hystidine.

The concept of a baseline and maximal GFR in humans has been defined by the so called "renal functional reserve".

In order to better explain this concept, a series of examples can be described in a GFR /functioning renal mass domain graph.

GFR can be considered a continuous function which is maximal in subjects with 100% renal mass and absent in anephric patients. We have a condition in which renal mass is by definition 50% and this is in a patient with a monolateral nephrectomy.

Once the curve of maximal GFR has been drawn, various conditions of baseline GFR can be imagined (Fig. 2).

Patient 1 has a baseline GFR of 120 ml/min. His renal mass is intact and if stimulated, he can increase its GFR to values as high as 170 ml/min[23-26]. Patient 2 is a vegetarian and his baseline GFR is 65. When stimulated he can also increase GFR to values close to 170. In other words, the renal functional reserve in these two patients is different because they are using their GFR capacity at a different level as indicated by the baseline GFR. Nevertheless, baseline GFR cannot tell us if the renal function is fully preserved.

Patient 3 has been operated of monolateral nephrectomy because of a renal cancer. His baseline GFR corresponds to his maximal GFR under unrestricted dietary conditions. If moderate protein restriction is applied to his diet, his baseline GFR may decrease and some degree of renal functional reserve becomes evident. The same concept is true for patient 4 where, however, the only possibility to restore some functional reserve is to apply a severe protein restriction. In some cases even under such ultra-low protein intake regime, renal functional reserve cannot be restored.

In conclusion, baseline GFR does not necessarily correspond to the extent of functioning renal mass. A test of stimulation to reach maximal GFR might be helpful to define the real situation of the subject in terms of renal function.

Only maximal "test" GFR describes fully the level of renal function and baseline GFR might be misleading if not well interpreted on the basis of diet and drug regimes.
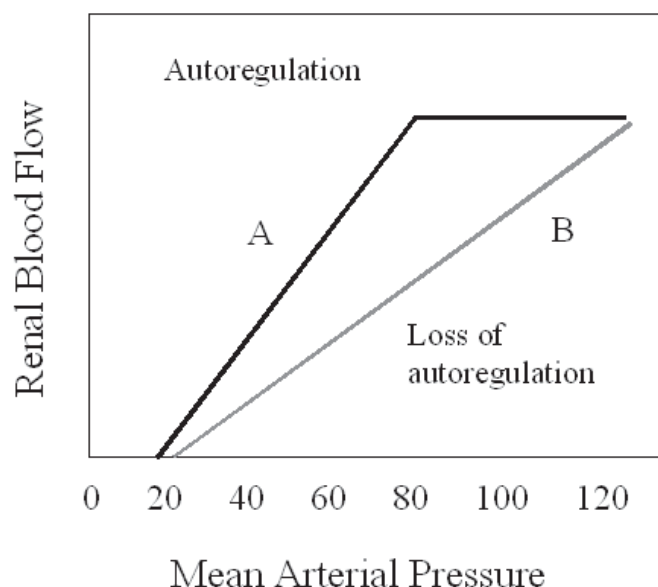
Figure 3. The concept of renal blood flow autoregulation. Renal blood flow is maintained fairly constant in the presence of significant variations of renal perfusion pressure (line A). When a pathological event occurs, the mechanism is lost and even small variations of perfusion pressure result is significant variations of renal blood flow (line B)

GFR and eGFR in Acute Kidney Injury

In patients with AKI eGFR has not been validated yet; furthermore, it should be clearly stated that eGFR is not an equivalent measure of GFR but only a transformation of creatinine value into a parameter which is static in nature and is not immediately related to the physiology of the glomerular function in a specific moment[27].

Accurate estimation of GFR from serum creatinine 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 is used alone, in the MDRD Study equation or in other estimating equations such as Cockroft-Gault formula. However, serum creatinine 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 is rising, and underestimates GFR when serum creatinine is falling. In general, if the serum creatinine doubles within one day, then the GFR is near zero.

Based on what we mentioned above, the definition of ARF may be seen in light of the physiological concepts of "normality", the presence of residual renal functional reserve and finally on the dynamic modifications of GFR within hours of the clinical course.

GFR regulation and measurement in acute kidney injury

In different clinical conditions, renal blood flow is maintained at steady levels due to a mechanism called autoregulation (Fig. 3). Significant variations of 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 that is also maintained constant by a mechanism called tubular-glo-

merular feedback[1]. In detail, glomerular filtration rate depends on transcapillary pressure gradient which is regulated by a fine tuning of the tone of afferent and efferent arteries. This mechanism permits to compensate for changes in plasma flow through a variation in filtration fraction. Filtration fraction is the ratio between the glomerular filtration rate and the plasma flow rate. While this parameter is regulated to maintain its value around 20%, significant variations of FF, may allow GFR to remain stable in the presence of plasma flow variations. The final result of a combined effect of autoregulation and filtration fraction result in the quantity and composition of the urine. In the so-called syndrome of pre-renal dysfunction, the loss in renal perfusion due to arterial underfilling produces a temporary decrease in glomerular filtration and lower sodium content in the tubular lumen which is rapidly counterbalanced by an increased reabsorption of sodium and water (leading to a decreased fractional secretion of sodium, high urine osmolality and oliguria) while glomerular hemodynamics are adjusted to increase filtration fraction although GFR may decrease and creatinine may rise.

If the patient receives a fluid infusion and extracellular volume expansion these conditions may be reversible and the original equilibrium can be restored. In some pathological conditions, however, or when arterial underfilling remains untreated for longer times, the original alteration, 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, and the GFR decrease with a progressive increase of the fractional excretion of sodium and a progressive reduction in urine osmolality.

It should be speculated that subjects with partial or total loss of renal functional reserve due to previous damage or loss of nephron mass, are more exposed than others to have a rapid passage from the pre-renal to the renal phase of acute kidney injury. In the absence of previous baseline and test GFR determinations, this might explain the variability of responses observed among patients to ischemic insults, to hypovolemia and to fluid infusion.

Because urea or BUN is such a non-specific indicator of renal function, it is a very poor marker of GFR relative to creatinine and will not be discussed further. However, a serum creatinine (S_{Crt}) of 1.5 mg/dL (133 mmol/L), at steady-state, corresponds to a GFR of about 36 ml/min in an 80 y/o white female, but of about 77 ml/min in a 20 y/o black male. Similarly, a serum creatinine of 3.0 mg/dL (265 mmol/L) in a patient suspected of having renal impairment would reflect a GFR of 16 ml/min in the elderly female but 35 ml/min in the young male. In both cases, a doubling of serum creatinine corresponds to an approximate decrease in GFR by 50% (exactly a 55% decrease in the above example) because there is a linear relationship between GFR and 1/Cr. Thus, while every classification of ARF in the literature relies on some threshold value for serum creatinine concentration, *no single creatinine value corresponds to a given GFR across all patients*[27]. Therefore, it is *the change* in creatinine that is useful in determining the presence of ARF.

Unfortunately, like creatinine clearance, the S_{Crt} is not an

accurate reflection of GFR in the non-steady state condition of ARF. During the evolution of dysfunction, S_{Crt} will *under-estimate* the degree of dysfunction. Nonetheless, the degree to which S_{Crt} changes from baseline (and perhaps the rate of change as well) will, to some degree, reflect the change in GFR. S_{Crt} is readily and easily measured and it is reasonably specific for renal function. Thus, S_{Crt} (or creatinine clearance) is a reasonable approximation of GFR in most patients with normal renal function[8]. Creatinine is formed from non-enzymatic dehydration of creatine in liver and 98% of 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 include conditions of increased production such as trauma, fever, and immobilization; and conditions of decreased production including liver disease, decreased muscle mass, and aging. In addition, tubular reabsorption ("back-leak") may occur in conditions associated with low urine flow rate. Finally, the volume of distribution (V_D) for creatinine (total body water) influences S_{Cr} and may be dramatically increased in critically ill patients. There is currently no information on extrarenal creatinine clearance in ARF and a non-steady state condition often exists.

Once glomerular filtration has reached a steady state it can be quantified by measuring a 24-hours 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 (S_{Crt}) 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 two-fold difference). Therefore creatinine clearance represents the upper limit of what the true GFR is under steady-state conditions. A more accurate determination of GFR would require measurement of the clearance of inulin or a radio-labelled compounds[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. This can usually be determined by monitoring S_{Crt} alone[8]. Furthermore, since patients with ARF are not in a steady state, creatinine clearance will not accurately reflect GFR.

When the patient has pre-existing renal disease the patient's baseline GFR and serum creatinine will be different from those predicted by the MDRD equation. Also, the relative decrease in renal function required to reach a level consistent with the diagnosis of ARF will be less than that of a patient without pre-existing disease. For example, a patient with a serum creatinine of 1 mg/dL (88 mmol/L) will have a steady-state serum creatinine of 3 mg/dL (229 mmol/L) when 75% of GFR is lost. By contrast, a mere 50% decrease in GFR in a perfectly matched patient for age, race, and sex with a baseline creatinine of 2.5 mg/dL (221 mmol/L) corresponds to a creatinine of 5 mg/dL (442 mmol/L). The problem with these criteria is that the former patient may have had a baseline GFR of 120 mL/min decreasing to 30, whereas the latter patient has a GFR of 40 mL/min decreasing to 20. It would be difficult to consider the first patient with a GFR of 30 mL/min as

having ARF whereas the patient with a GFR of 20 mL/min does not. Thus, it seems that either a different set of criteria will be needed in patients with pre-existing disease or some absolute creatinine criteria will need to be integrated into the classification system. One possible approach would be to use a relative change in creatinine (e.g. three-fold) as the primary criterion, with an absolute cutoff (e.g. 4 mg/dL or about 350 mmol/L) as a secondary criterion when baseline creatinine is abnormal. Separate criteria should be used for the diagnosis of ARF superimposed on chronic renal disease. An acute rise in S_{Crt} (of at least 0.5 mg/dL or 44 mmol/L) to more than 4 mg/dL (350 mmol/L) will serve to identify most patients with ARF when their baseline S_{Crt} is abnormal[27-28].

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