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Renal Stress Testing in the Assessment of Kidney Disease

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As part of human evolutionary development, many human organ systems have innate mechanisms to adapt to increased "work demand" or stress. This reserve capacity can be informative and is used commonly in cardiology to assess cardiac function (e.g., treadmill test). Similarly, the kidney possesses reserve capacity, which can be demonstrated in at least 2 of the following renal domains: glomerular and tubular. When appropriate stimulants are used, healthy patients with intact kidneys can significantly increase their glomerular filtration rate and their tubular secretion. This approach has been used to develop diagnostics for the assessment of renal function. This article reviews both glomerular and tubular kidney stress tests and their respective diagnostic utility.

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As part of 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 liters/min. However, when a healthy person exercises, the cardiac output can double or even triple. Similarly, the kidney has reserve capacity of its multiple physiological functions (Figure 1). 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 due to injury and potentially fibrosis. The 2 main domains of kidney stress testing are glomerular and tubular. In a healthy kidney, these 2 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 their form and functional capacity may diverge. An assessment of both glomerular and tubular function may be more informative than just 1 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 both chronic and acute kidney disease.

Renal Functional Reserve–Glomerular

Because of the common use of estimated glomerular filtration rate (GFR) equations, there is a tendency for non-nephrologists to think that the GFR is a constant. In fact, the actual GFR changes throughout the day, particularly after meals, based on physiological needs.[1] 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.[2] GFR can also be increased through other mechanisms that work along the protein metabolic pathway. For instance, an i.v. infusion of amino acids will result in an increase in GFR.[3] This increase in GFR over baseline GFR is known as renal functional reserve–glomerular (RFR-G).[4] Protein ingestion, particularly red meat, is a potent stimulant for increasing GFR, and the teleologic explanation is likely related to an adaptive response to increased protein in the diet.[5]

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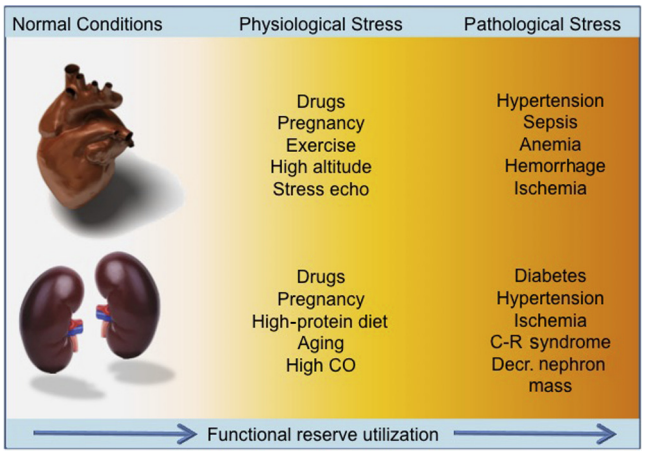

Figure 1. Comparison of stressors in the heart and kidney. C-R, cardiorenal.

Bosch and colleagues first described glomerular functional reserve (RFR-G) in 1983.[4] In this seminal paper, Bosch and colleagues 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

GFR is normally utilized as a surrogate of kidney function in healthy subjects as well as in patients with kidney disease. Studies in healthy subjects under the age of 50 have identified the average baseline normal values of GFR to be between 100 and 130 ml/min per 1.73 m^2.[6] Evaluation of population-wide "normal" values is useful, but the concept of "normal" GFR in the single individual is more nuanced. It is important to recognize that a person's GFR at any given point in time will vary in relation to the physiological 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 per 1.73 m^2 per year, after the age of 30 years.[6,7]

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 approaches 60 ml/min per 1.73 m^2 (Figure 2).[8] For this reason serum creatinine cannot be considered an accurate marker of renal function when GFR is above 60 ml/min per 1.73 m^2. Similarly, GFR estimation (eGFR) by creatinine-derived equations (e.g., MDRD[9]) 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."[10] Therefore, when renal disease becomes apparent due to an elevated serum creatinine, this occurs only after the residual nephrons can no longer compensate for the functional loss (Figure 3).[8]

Renal Functional Reserve (RFR-G)

Normal 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 renal functional reserve of glomerular function (RFR-G). Fliser and colleagues[11] compared the baseline and maxGFR in young and elderly healthy subjects and found that RFR was significantly lower in elderly than 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.[12–15]

The stimulus to tap into this reserve capacity can arise from adaptive physiological needs like pregnancy or the presence of a solitary kidney. Utilization of RFR in non-disease 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 normal pregnant women in each trimester have shown a progressive increase of baseline GFR with a parallel reduction of RFR due to its progressive utilization.[13] MaxGFR in normal pregnant women, however, does not change. However, pathological states can also 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

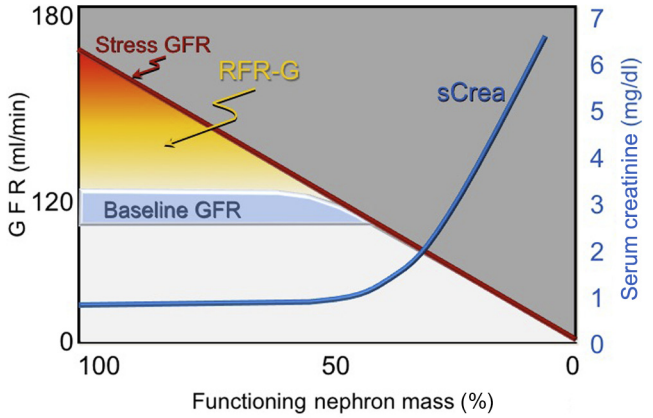

Figure 2. Relationship between glomerular filtration rate (GFR) and serum creatinine changes. RFR-G, renal functional reserve–glomerular.