Clinical Kidney Journal

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Clinical Kidney Journal, 2018, vol. 11, no. 5, 623–654

doi: 10.1093/ckj/sfy022
Advance Access Publication Date: 13 April 2018
CKJ Review

CKJ REVIEW

Haemodynamic or metabolic stimulation tests to reveal the renal functional response: requiem or revival?

Bart De Moor[1,2], Johan F. Vanwalleghem[2], Quirine Swennen[1], Koen J. Stas[2] and Björn K. I. Meijers[3,4]

[1]Faculty of Medicine and Life Sciences, University of Hasselt, Diepenbeek, Belgium, [2]Department of Nephrology, Jessa Hospital of Hasselt, Hasselt, Belgium, [3]Department of Nephrology, Universitair Ziekenhuis Leuven, Leuven, Belgium and [4]Department of Immunology and Microbiology, Faculty of Medicine, Katholieke Universiteit Leuven, Leuven, Belgium

Correspondence and offprint requests to: Bart De Moor; E-mail: bart.demoor@uhasselt.be

ABSTRACT

Renal stimulation tests document the dynamic response of the glomerular filtration rate (GFR) after a single or a combination of stimuli, such as an intravenous infusion of dopamine or amino acids or an oral protein meal. The increment of the GFR above the unstimulated state has formerly been called the renal functional reserve (RFR). Although the concept of a renal reserve capacity has not withstood scientific scrutiny, the literature documenting renal stimulation merits renewed interest. An absent or a blunted response of the GFR after a stimulus indicates lost or diseased nephrons. This information is valuable in preventing, diagnosing and prognosticating acute kidney injury and pregnancy-related renal events as well as chronic kidney disease. However, before renal function testing is universally practiced, some shortcomings must be addressed. First, a common nomenclature should be decided upon. The expression of RFR should be replaced by renal functional response. Second, a simple protocol must be developed and propagated. Third, we suggest designing prospective studies linking a defective stimulatory response to emergence of renal injury biomarkers, to histological or morphological renal abnormalities and to adverse renal outcomes in different renal syndromes.

Keywords: protein stimulation test, renal functional reserve, renal functional response, renal stimulation test, renal stress test

INTRODUCTION

Glomerular filtration rate (GFR) is considered the best overall index of kidney function. It is dependent on age, gender, ethnicity, body composition and diet [1] as well as nephron endowment [2]. GFR is determined by the measured clearance of certain exogenous markers or endogenous waste products. In everyday practice, clinicians usually rely on estimated GFR (eGFR) calculated from a single serum marker measurement, mostly creatinine. However, such estimates have several limitations. Estimating equations are valid only in steady-state conditions. Moreover, analytical variation of serum creatinine measurements (2% for enzymatic assays), variation in tubular secretion and dependency on muscle mass [3] should be factored in.

Received: 2.11.2017. *Editorial decision:* 26.2.2018

Often ignored, GFR is not constant, as the kidneys do not continuously function at maximum filtration capacity [4]. It is estimated that in healthy subjects, kidneys usually operate at ~75% of their maximal GFR. Renal function is influenced by diurnal cycles [5] and is stimulated by protein-containing meals. Thus, single-point assessments of renal function ignore varying rates of glomerular filtration, as kidneys are capable of adjusting their performance to haemodynamic and metabolic demands.

In 1930, Verney mentioned the reserve forces of the kidney [6]. In analogy with myocardial and pulmonary function, a redundant or dormant renal reserve was hypothesized, intended to cope with extraordinary haemodynamic and metabolic demands. Fifty years later, Bosch called this the renal functional reserve (RFR), defined as the difference between the baseline GFR and the stimulated GFR, measured 2 h after a protein meal [7].

Over the years, enthusiasm for the RFR concept abated [8–12], until Ronco and colleagues [4, 13–15] and Molitoris [16] recently revived interest in this concept. They postulate that diminished RFR contributes to the susceptibility for recurrent acute kidney injury (AKI). These authors argue that evaluation of the degree of functional recovery post-AKI is not only clouded by the loss of muscle mass but also by stimulated single-nephron GFR to compensate for nephron loss. Testing the renal functional response in these recovered patients could possibly unveil this undetected loss of functional units and could identify patients at risk for progression to chronic kidney disease (CKD). This hypothesis was discussed and reviewed at the Fifth International Conference of the French Society of Intensive Care [17, 18].

Additionally, a deficit in RFR has been incriminated in pregnancy-related kidney disease [19]. Further, study of the diagnostic and prognostic utility of RFR has been mentioned in the roadmap for global kidney health 2017, issued by the International Society of Nephrology [20]. Finally, the promotion of high-protein diets to lose weight stimulated renewed attention to the postprandial behaviour of the GFR.

Reviewing the literature on RFR is impeded by a myriad of definitions and stimulatory tests. This article aims to propose a synthesizing lexicon and tries to offer a variety of protocols for future directions of research.

LEXICON

The RFR (also referred to as renal reserve capacity) is defined as the difference between the stimulated GFR and the baseline GFR. This difference can be expressed in absolute terms (mL/min) or in relative terms (percentage of increment relative to the baseline GFR). Although a straightforward and simple definition at first sight, terminologies and definitions are quite confusing. Table 1 proposes a revised nomenclature in the context of renal functional testing. The expression of RFR should be replaced by renal functional response.

The baseline or basal GFR is sometimes referred to as unstimulated GFR (as opposed to stimulated GFR) or unstressed GFR (to better differentiate it from the GFR in stressed circumstances) and finally resting GFR. While the resting GFR is the lowest normal GFR, it is not identical to the baseline GFR used in the context of AKI, which is usually defined as the best or highest GFR preceding an AKI episode [17, 21].

To maximally guarantee an unstimulated (lowest) GFR, patients are often instructed to adhere to a low-protein or vegetarian diet in preparation for a renal stimulation test. If the person is not instructed to do so, the test results (actual GFR and maximal increase) should be interpreted in the light of the usual protein intake of the subject. This can be derived from the urea nitrogen level in timed urine collection. Coincidentally, patients with CKD often follow a low-protein diet. This increases the value of a stimulatory test.

Table 1. Suggested terminology and alternatives in the context of a renal stimulation test

Unstimulated GFR	Random GFR	Stimulated GFR
Unstressed GFR	Uncontrolled GFR	Stressed GFR
Basal GFR	Actual GFR	Peak GFR
Baseline GFR	Reference GFR	Maximal or maximized GFR
Resting GFR		Maximal filtration capacity
Minimal GFR		

Renal functional response = stimulated GFR – baseline GFR (either in mL/min or in percentage of baseline GFR), i.e. renal functional reserve, renal reserve capacity, renal reserve filtration capacity.

The stimulated or stressed GFR is the measured GFR following a stimulus, including an oral protein load, an intravenous amino acid (AA) solution, a glucagon infusion or a dopamine drip [22]. Rodríguez-Iturbe *et al.* [23] defined a tubular stress test, describing the tubular secretion of intravenously injected creatinine. Regretfully, a creatinine solution marketed for intravenous use in human experiments is currently not available (personal inquiry). As creatinine is readily absorbed by the gastrointestinal tract, an oral creatinine load is safer and might result in a comparable tubular challenge [24]. Recently a furosemide stress test was applied to patients with progressive AKI, discriminating recovery from progression [25]. Thus renal stimuli are either of a metabolic or haemodynamic nature. A protein meal, when composed of cooked meat, challenges the kidney with both AA and creatinine. This stimulus can be considered a combination of both a metabolic and a tubular stimulus.

Descriptions of the numerous alternative tubular challenges (sodium, potassium, phosphorus, acid, water deprivation and water loading) is beyond the scope of this review.

After stimulation and in healthy subjects, the GFR can reach 180–200 mL/min. Some authors refer to GFR in this range as hyperfiltration. Cachat *et al.* [26] reviewed the literature in 2015 and Tonneijck *et al.* [27] recently described the mechanisms of diabetic hyperfiltration. These authors correctly differentiate between whole kidney function as opposed to single-nephron function. On a single-nephron level, hyperfiltration is assumed when the intraglomerular pressure is elevated, causing albuminuria and in the long-term leading to progressive glomerulosclerosis. Single-nephron hyperfiltration does not automatically translate into whole-kidney hyperfiltration, quite the opposite: glomerular hyperfiltration is often intended to preserve a waning whole-kidney GFR in the face of a diminishing nephron number [28]. More recently, high GFR values were also noted in septic intensive care unit (ICU) and post-operative patients. We advocate the use of augmented renal clearance for seemingly physiological adaptations and the use of stimulated GFR in the context of RFR.

PHYSIOLOGY OF METABOLIC RENAL STIMULATION

For a more extensive overview of the functional compensation after a protein meal, we refer the reader to excellent reviews by Gabbai [29], Bankir *et al.* [30], Helal *et al.* [31], King and Levey [1] and Premen [32].

Any metabolic stimulus triggers the kidneys to increase the GFR primarily by reducing the overall renal vascular resistance (RVR) and inducing a postprandial renal hyperaemia. This increase of the renal blood flow results from systemic mediators as well as paracrine factors, both acting on the whole kidney level as on the single-nephron GFR. Initially, recruitment of quiescent glomeruli in ill-perfused regions was hypothesized, hence the term 'renal functional reserve' [7, 33]. Later it was concluded that the increased GFR results from a higher filtration effort of all single nephrons, almost exclusively attributed to a higher effective renal plasma flow (ERPF).

The feed-forward stimulus after a protein load or an increase in AA plasma levels originates from the pancreas and the liver [30]. A higher ratio of glucagon to insulin stimulates the liver in favour of nitrogen handling and helps the kidneys in the disposal of urea. The hepatic production of cyclic adenosine monophosphate (cAMP) operates as a second messenger. On the single-nephron level, glucagon and cAMP cooperate to reduce the tubular solute concentration at the macula densa. In this way, the tubuloglomerular feedback is downregulated. As a result, vasodilation of the pre-glomerular arteries and arterioles induces an increase in the single-nephron GFR. Intrinsic renal autoregulation with nitric oxide, vasodilating prostaglandins and kinins is responsible for this action. Inhibition of renal autocrine prostaglandin synthesis with indomethacin counteracts the vasodilatory effects of AAs. The hypothalamic–hypophyseal axis contributes to this process. Vasopressin or the antidiuretic hormone (ADH) is also active in stimulating the GFR after a protein meal. Together with glucagon, this hormone helps in the processing of protein metabolites. The role of growth hormone seems of less importance, as a protein meal equally elicits a functional renal response in growth hormone–deficient patients [34, 35].

In the long term, the afferent arteriole is evidently the weak spot in these consecutive events, as this site harbours the first signs of hypertensive hyalinosis, impeding maximal relaxation [36]. Arterial stiffness proved to be an independent predictor of adaptive glomerular hyperfiltration after kidney donation [37]. If the ERPF is not able to keep pace with the increased demands, the efferent vasoconstriction gradually prevails, leading to a higher intraglomerular pressure and filtration fraction (FF). This additive mechanism, triggered by the renin–angiotensin system with thromboxane A2 and endothelin-1 as cofactors, leads to a cascade of negative events. In the long run, a higher FF might lead to glomerular as well as tubular injury and a loss of nephrons. Treatment with an angiotensin-converting enzyme (ACE) inhibitor has been shown to restore the GFR response after a protein stimulation [38].

METHODOLOGY OF RENAL STIMULATION TESTS

Table 2 provides an overview of the chronology and methodology of a renal stimulation test. The numerous stimuli and modes of GFR measurements are described in the following paragraph.

Measurement of unstimulated GFR

Several factors may influence the unstimulated GFR. First, hydration status [39] is a very important confounding variable. Spinelli *et al.* [40] advise the use of bio-impedance measurements to identify dehydrated subjects. For this reason, most protocols adopt a strict oral hydration policy, starting with 10–20 mL/kg plain water and replacing each voided urine sample with an equal amount of oral fluids. Hypovolaemia also blunts the renal response after stimulation [38]. Second, the body must remain in the fasting state for at least 8 h (overnight fasting). A low-protein or vegetarian diet for 10 days preceding the test is advised by some authors to ascertain a true unstimulated GFR. Doubt remains if this interval succeeds in normalizing glomerular hypertrophy caused by a chronically high-protein diet. If the investigator does not advocate this preparatory phase, habitual protein intake can be estimated from urea nitrogen in a 24-h urine collection [41] and the extent of GFR stimulation must be interpreted with this knowledge. Finally, besides a thorough non-pharmacological preparation, some drugs must be paused, as they interfere with renal vascular adaptation. These include non-steroidal anti-inflammatory drugs (NSAIDs) [42], ACE inhibitors and angiotensin receptor blockers.

Selecting the proper stimulus

Measuring the stimulated GFR requires maximal recruitment of the so-called reserve GFR. Several approaches have been advocated, which—broadly speaking—can be divided into haemodynamic and metabolic stimuli.

In humans, a significant increase of the GFR has been described with glucagon infusions at a rate of 10–20 ng/kg/min. More frequently, dopamine is used. This vasoactive drug augments the ERPF and hence the GFR without affecting cardiac output or systemic vascular resistance. The FF usually drops slightly when dopamine is infused at a dose of 2.0 μg/kg/min. This is the result of afferent and preferentially efferent arteriolar dilation [43]. At the single-nephron level, the increased filtration seems totally attributable to higher plasma flow in combination with lower transcapillary pressure. Sometimes dopamine is the only renal stimulus used, for instance, in a dopamine-induced glomerular response test [44].

Dopamine provocation may be combined with a metabolic stimulus. When combined with an AA infusion, the effects are additive [45]. During the AA infusion, ERPF and GFR increase proportionally with a predominant afferent arteriolar dilation resulting in a constant FF. The composition of the AA solution depends on local availability, but gluconeogenic AA should be present [46], whereas branched-chain AAs do not alter GFR or FF [47]. The infusion rates reported in the literature are disparate. The AA infusion can begin the night before the test day, but the GFR response is already present after a 1- or 2-h infusion time. A dose–response curve for AA stimulus was constructed by Giordano *et al.* [48]. Within the physiological range, incremental AA concentrations cause a stepwise increase in the GFR, whereas this effect levels off in the pharmacological range.

The administration of a single AA to elicit a change in GFR is also reported. Arginine [49, 50] and glycine have been used, each acting via different pathways. Arginine causes systemic and renal vasodilation, while glycine operates via the *N*-methyl-D-aspartate glutamate receptor (NMDA-R) [29]. This receptor is localized in the proximal tubule and functions as a calcium channel, causing local vasodilation.

A more natural approach is to stimulate the GFR by a protein meal. This short-term oral protein loading should consist of at least 1 g/kg of protein [51]. Rodríguez-Iturbe *et al.* [52] studied three quantities of protein meals: 1.3, 1.1 and 0.55 g/kg. The filtration fraction rose significantly with the moderate and large protein load but not with the lower protein load.

Animal proteins are preferred, so most centres prepare a cooked beef hamburger. Red meat, however, contains 3.5–5 mg/g

Table 2. How to perform a renal stimulation test?

Variables	Preparatory phase: instruction and informed consent	Test day: Part 1, measuring unstimulated GFR	Test day: Part 2, stimulus	Test day: Part 3, measuring stimulated GFR
Location	Home	Hospital: recumbent position		
Duration	1 day: starting urine collection 2–3 days: when CACrC is opted 10 days: when a low-protein diet is advised	2–4 h	30–60 min to cover ingestion and digestion	2–4 h
Diet	Diet 1: habitual diet until the night before RFR testing	Fasting for at least 8 h		
	Diet 2: controlled low-protein diet for at least 10 days before RFR	Fasting for at least 8 h		
Fluids	Drinking according to thirst	Drinking is stimulated: 10–20 mL/kg at start	Drinking in equal amounts to match diuresis	Drinking in equal amounts to match diuresis
PO	Start cimetidine (when CACrC is chosen) according to the Hilbrands protocol Stop NSAID, preferentially pause ACE i or angiotensin receptor blocker		Stimulus option 1: 1 g/kg protein offered as cooked meat (containing creatinine) Stimulus option 2: 1 g/kg protein offered as egg whites or a commercial protein solution (not containing creatinine)	
IV		Introduce two separate IV lines	Stimulus option 3: a 10% IV AA solution at a rate of 4 mL/kg/h during 3 h Stimulus option 4: IV dopamine at a rate of 2 μg/kg/min (can be combined with stimulus 3) Stimulus option 5: IV glucagon at a rate of 10–20 ng/kg/min during 1 h	
Clinical exam		Weight, height, hydration status, blood pressure	Blood pressure and heart rate at regular intervals	
Blood as well as urine samples in combination with timed urine collections	24-h urine collection for reference creatinine clearance, sodium excretion and urea nitrogen appearance	GFR option 1: plasma or urinary clearance of an exogenous marker Urine collections and samples: every 30–60 min bracketed with serum samples		
		GFR option 2: urinary CrC (with or without cimetidine correction) Urine collections and samples: every 30–60 minutes bracketed with serum samples		Urine collections and samples every 30–60 min bracketed with serum samples
Result		Unstimulated GFR or CrC: mean of at least three measurements		Stimulated GFR or Stimulated CrC: highest of at least three measurements

PO, by mouth; IV, intravenous.

creatine. By cooking, a non-metabolic conversion of creatine to creatinine occurs [53]. This metabolite is easily absorbed and the rising serum levels result in increased tubular secretion until the tubular transport maximum is reached [54]. Accordingly, the more pronounced response (after a protein challenge) of creatinine clearance (CrC) compared with inulin clearance is due to a higher input and increased tubular secretion of creatinine.

Alternatives for animal protein are dairy products and egg-white proteins. These are more practical in paediatric subjects [55]. Vegetable proteins, for instance soy products or bean curd, are less effective in stimulating the GFR [56]. Many reasons for this difference have been postulated, including a different AA mixture, less sulphur-containing AA, less oxidative stress or acid load, lower maximal AA serum levels, faster internalization in the cells due to a different insulin/glucagon surge, less sodium and more potassium content. An elaborate description of the renal benefits attributed to a vegetarian diet is beyond the scope of this article. The reader is referred to excellent reviews by Kalantar-Zadeh *et al.* [57] and Snelson and Fouque [58].

The renal response after a haemodynamic stimulus is immediate while the maximal effect of a metabolic stimulus is noted after 1–3 h. Recent evidence shows that in obese non-diabetic subjects, the maximal rise in GFR after a protein stimulus is postponed [59].

Over the years, no major side effects of renal stimulation tests have been observed. In the different studies, blood pressure and heart rate were carefully monitored, especially when dopamine was used as a stimulating agent. After the stimulus has waned renal function returns to its unstimulated state. Intravenous perfusion of a hyperosmolar AA solution has been found to cause local pain and phlebitis. No increase in urinary neutrophil gelatinase-associated lipocalin or proteinuria has been documented in the protein stimulation experiments performed by Sharma *et al.* [51]. N-acetyl glucosaminidase (NAG) has been studied in immunoglobulin A nephropathy (IgAN) during RFR testing [60], but the serial documentation of damage biomarkers, including albuminuria, remains largely unexplored.

Measuring GFR during renal stimulation tests

The Achilles heel of renal function testing is the method used for GFR determination [61]. Urinary inulin clearance remains the most extensively reported method in renal stimulation tests. This classic mode of GFR measurement is often combined with para-aminohippuric acid (PAH) clearance to document the ERPF. Delanaye *et al.* [62] delineates the difficulties of this technique, including costs, variances in lab techniques and availability. Zitta *et al.* [44] succeeded in studying GFR behaviour after AA infusion via the plasma kinetics of sinistrin and hippurate supplied to a two-compartment computer model. The advantage of this technique is the elimination of urine collections.

The easiest alternative for the use of inulin is to monitor urinary CrC by timed urine collections (30 or 60 min), considering known caveats when using this biomarker. At least three clearance calculations are advised. The CrC overestimates true GFR because of additive tubular secretion, leading to a mean bias of 14 mL/min or 25% [63]. The overestimation depends on baseline kidney function. However, when subjects are asked to adhere to a low-protein diet of 0.5 g/kg/day, calculated CrCs are similar to inulin clearance [64, 65]. When urinary CrC is used not only as a GFR estimator but also to track accessory tubular secretion, the intake of drugs that inhibit the tubular secretion of creatinine must be avoided (e.g. trimethoprim–sulfamethoxazole, cimetidine and possibly fenofibrate). On the other hand, when the investigator wants to capture solely the dynamics of glomerular filtration, tubular secretion of creatinine can be blocked by cimetidine. This results in the cimetidine-aided CrC (CACrC). In the publication by Hilbrands *et al.* [66], cimetidine was started 1–4 days prior to the GFR stimulus according to a dosing protocol determined by the actual renal function.

Irrespective of the methodology, investigators must ascertain complete voiding or resort to placing a bladder catheter (mostly done in children, which increases the invasiveness of the test).

We do not advocate GFR estimating formulas (Chronic Kidney Disease Epidemiology Collaboration formula or Cockcroft–Gault formula] to document the renal functional response. Some authors propose cystatin C measurements [67, 68]. The kinetics of this functional biomarker have been tested after protein meals, with conflicting results [69, 70].

Alternative possibilities for measuring the GFR before and after a stimulus are urinary or plasma clearances of isotopes, e.g. ^{51}Cr-labeled ethylenediaminetetra-acetic acid (Cr-EDTA), ^{125}I-labeled iothalamate [45] and ^{99m}Tc-labeled diethylenetriaminepenta-acetic acid (Tc-DTPA) (see Tables 4 and 5 for references). Most protocols choose the urinary clearance of a subcutaneously injected or continuously infused radioisotope. Alternatively, calculation of the GFR by decaying plasma levels after an intravenous bolus can be performed. However, this technique requires the investigator to invite the test person on two separate days, one for an unstimulated GFR test and one for a stimulated GFR test. Other drawbacks are the exposure to radiation and the additional costs. Recently an elegant technique of urinary clearance of iohexol was tested in an ICU population with varying GFRs [71]. The protocol describes a bolus injection followed by a continuous infusion of a low dose of iohexol combined with regular plasma and urine sampling. This technique seems applicable in renal function testing.

In the meantime, progress is being made in the development and validation of fluorescent markers for GFR determination. These intravenously injected compounds behave as an ideal renal filtration marker. Their plasma disappearance curves match glomerular filtration and can be read transdermally thanks to their fluorescent properties. In this way, an almost real-time GFR evaluation is possible [72, 73].

Table 3 describes in more detail the advantages and disadvantages of the numerous options.

Alternatives to GFR measurements

Magnetic resonance imaging (MRI) holds great promise, as it allows for simultaneous measurements of both the GFR and renal plasma flow (RPF) [74], as well as providing estimates of single-nephron GFR. Additionally, MRI could be used to quantify renal fibrosis, as recent evidence suggests [75].

Doppler ultrasound can detect the decrease in RVR occurring in healthy kidneys after a protein challenge [76, 77]. This has led investigators to study the renal resistive index variation (RRIV) before and after an AA infusion. A similar decrease in RVR can be documented when pressure is applied to the retroperitoneal vasculature. This autoregulatory reflex is intended to preserve the GFR. Maximal renal vasodilation was recorded when a saline bag representing 10% of the body weight was placed on the abdomen. The maximal RRIV observed in these experiments correlated with the RFR, thus offering a non-invasive real-time evaluation of the changing RVR [78].

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Tabe 3. Advantages and disadvantages of the different options mentioned in Table 1

Option	Pros	Cons	Evaluation
Diet 1: habitual diet	Easiest protocol. Protein intake can be evaluated by the urinary nitrogen appearance	Unstimulated GFR is influenced by the protein content of the habitual diet. The renal response may be lower	Simplicity: high Duration: low Costs: low Validity: lower
Diet 2: 10 days of low-protein or vegetarian diet	Best guarantee of approaching unstimulated or resting GFR	Requires the effort of a dietician and the subject's compliance	Simplicity: low Duration: long Costs: higher Validity: higher
Stimulus option 1: oral protein load in the form of cooked meat	Easiest to prepare. Oldest and most extensively documented challenge	Subjects must ingest the meal in 30 min. In case of gastric emptying disorders, digestion can be slower	Simplicity: high Duration: low Costs: low Validity: neutral
Stimulus option 2: oral protein load without creatinine	The taste can be adapted to subjective wishes. Can be used in children	Requires the effort of a dietician to compose the meal. The tubular secretion of creatinine is missed	Simplicity: neutral Duration: low Costs: low Validity: neutral
Stimulus option 3: IV dopamine	Low-dose dopamine augments the renal plasma flow more than the GFR	Only offering a haemodynamic stimulus. Mostly used in combination with an AA infusion. Requires an extra IV line and clinical follow-up. Dopamine has fallen into disuse	Simplicity: low Duration: low Costs: high Validity: lower
Stimulus option 4: IV AA infusion	If AA plasma levels are more than tripled, this stimulus offers the best guarantee of maximal GFR simulation	AA composition must match those used in literature. Infusing AA may cause phlebitis	Simplicity: low Duration: high Costs: high Validity: highest
Stimulus option 5: IV glucagon	Shortest stimulus. Physiologically logical stimulus	Requires glycaemic controls. Misses simultaneous insulin secretion as in normal physiology. Less experience and literature support	Simplicity: low Duration: low Costs: high Validity: lower
GFR option 1: exogenous marker	Best GFR measurement. Current literature proposes a bolus/continuous infusion protocol for the evaluation of unstable renal function	In case of a single bolus injection: unstimulated and stimulated GFR measurements must be scheduled on two separate days.	Simplicity: low Duration: neutral Costs: high Validity: highest
GFR option 2: creatinine clearance	Easiest protocol. Evaluates glomerular filtration as well as tubular secretion	CrC overestimates true GFR	Simplicity: high Duration: neutral Costs: low Validity: neutral
GFR option 2: CACrC	If tubular inhibition is maximal, CACrC matches measured GFR	Maximal tubular inhibition of creatinine secretion cannot be guaranteed. Potential side effects of cimetidine (allergy and tolerance). The tubular contribution to overall clearance is blocked	Simplicity: lower Duration: higher Costs: higher Validity: high

IV, intravenous.

CLINICAL SUPPORT OF RENAL STIMULATION TESTING

Over the last three decades, numerous publications have reported on the renal stimulation test in various healthy and diseased populations (summarized in Tables 4 and 5). An exhaustive literature search of RFR testing proves very challenging because of the heterogeneous nomenclature, necessitating several surveys and meticulous scrutiny of the references. Surprisingly, only a minor fraction of studies investigated >50 subjects. Molina *et al.* [79] decided on a sample size of 384 children, considering a standard deviation of the GFR of ±20 mL/min to find a pre–post difference of at least 2 mL/min. Despite this fundamental statistical consideration, most papers omit biological variance and inter-person variability in their discussions.

The first studies were performed in healthy individuals (Table 4). Several different stimuli were used. It was shown that inulin clearances could rise to 130–150 mL/min while CrCs reached 160–180 mL/min [7]. These studies also demonstrated that the protein content of the habitual diet influences unstimulated GFR and determines the absolute extent of the GFR increase after a protein load [80–82]. Hypovolaemia is an appreciated cause of a blunted response [38]. Healthy elderly individuals show a lower GFR and less effect after stimulation, most probably because they rely on fewer nephrons [83–85]. Recently Denic *et al.* [86] demonstrated that the single-nephron GFR (in unstimulated circumstances) remained remarkably stable in a large cohort of living kidney donors until the age of 70 years. The age-dependent decline of the GFR in elderly donors was attributed to a lower nephron count and a lower metabolic need without the presence of kidney disease.

Table 4. Current experience with renal stimulation testing in subjects without kidney disease (for reference list, see Supplementary material)

			Type of stimulus				Type of GFR measurement			
Confounding variables	Reference	Number	Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	Summary of the results
	Bosch 1983[1]	5: normal protein diet 8: vegetarian diet			X		X	X		GFR reached a maximal level of 171 ± 7.7 mL/min after 150 min. In patients with reduced number of nephrons, RFR may be diminished or absent
	Graf 1983[2]	5 receiving parenteral nutrition		X				X		Endogenous CrC increases during infusion of AA
	Bosch 1984[3]	16			X			X		CrC increases from 123 ± 13 to 157 ± 13 mL/min
	Rodriguez-Iturbe 1985[4]	44			X			X		CrC increases from 108.5 ± 6.45 to 161.5 ± 9.39 mL/min
	ter Wee 1986[5]	9	X	X					IOTH 1	Infusion of AA and dopamine show additive effects: dopamine lowers FF, while during AA infusion the FF remains unchanged
	Hostetter 1986[6]	10			X		X			GFR increases from 101 ± 7 to 114 ± 6 mL/min. RVR decreases
	Castellino 1986[7]	13		X			X			GFR increases from 107 ± 5 to 128 ± 4 mL/min. Somatostatine blocks this increase
	Bosch 1986[8]	7			X		X			GFR increases from 122 ± 10 to 151 ± 15 mL/min
	Solling 1986[9]	Healthy male physicians and students			X				IOTH 1	Eight subjects received a meat meal while seven were challenged with an AA infusion. GFR and RPF increased and FF as well as albumin excretion remained unchanged
	Mansy 1987[10]			X	X			X		Same increase of CrC after AA, 80 g meat and 80 g milk protein
	Rodriguez-Iturbe 1988[11]	37			X		X			Subjects were given, three quantities of protein load: mild protein load, 0.55 g/kg; moderate protein load, 1.08 g/kg; high protein load, 1.35 g/kg. The effect on the GFR was incremental: the largest increase of GFR was observed when a high protein load was served. To accomplish this GFR increase, the

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus				Type of GFR measurement			Summary of the results
			Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	
										filtration fraction was significantly increased
	Rodriguez-Iturbe 1988[12]	10			X			X		A protein meal and not a carbohydrate meal stimulates the CrC and is associated with a parallel increase (doubling) in plasma immunoreactive ANF
	Hirschberg 1988[13]	12 subjects	(Glucagon)	X (Arg)			X			Glucagon and IV infusion of arginine induce an increase in GFR that is blunted by NSAIDs
	Castellino 1988[14]	18		X			X			The renal haemodynamic response following AA infusion is dependent on insulin/glucagon/growth hormone replacement and can be blocked by somatostatin
	Laville 1989[15]	9			X		X	X		Simultaneous measurements of GFR and CrC showed a peak in GFR after 127 min and a maximal CrC after 189 min. This was caused by a subsequent increase of tubular secretion of creatinine (contributing 15%)
	Olsen 1990[16]	12 volunteers		X					EDTA 1	AA increased GFR by a primary effect on renal haemodynamics or, less likely, by reducing the signal to the TGF. The increase in proximal tubular outflow was compensated for in the distal tubules
	Tam 1990[17]	12 healthy medical students			X			X		Three protein meals were offered and compared with a control meal. Regardless of the protein content, an increase in CrC is observed
	Braendle 1990[18]	10			X		X			Oral protein concentrate and an oral mixture of AA induce a similar increase in GFR
	Wada 1991[19]	7 normal subjects tested twice with		X				X		Branched-chain AA induces no increase of CrC, while a mixture of AA elicits the expected

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus				Type of GFR measurement			Summary of the results
			Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	
		a different AA compositoin								functional response. Only the infusion of a mixture of AA is accompanied by an increase in serum glucagon levels
	Cirillo 1998[20]	25 healthy adults			X		X			GFR and urinary sodium excretion increase over baseline after a protein meal of 2 g/kg. A net decrease in sodium balance is observed
	Luipold 2000[21]	12 volunteers		X			X			AA infusion increases GFR and RPF. Pretreatment with domperidone marginally influences while sulpiride completely blocks the renal response. Sulpiride acts as a centrally and peripherally acting D_2-like receptor antagonist
	Barai 2008[22]	109 kidney donor candidates		X					DTPA 1	Lower mean GFR in healthy adult Indians than whites. No difference between sexes. Similar increment of the GFR after AA stimulation: 27.3 ± 10.01%
	Bird 2008[23]	20			X				EDTA 2	Comparison of iohexol with Cr-EDTA. Fasting and non-fasting. BSA versus ECV. The only significant increase of GFR was observed when GFR/BSA was considered
	Sharma 2016[24]	18			X			X		Similar increase of CrC after 1 and 2 g/kg protein load and 1 g/kg protein powder. No appearance of urinary NGAL
	Rodenbach 2017[25]	18			X			X with cimetidine	IOH 1	Protein loading stimulates iohexol clearance and CACrC after a beef-or milk-based meal. Cystatin C eGFR changes are smaller
Age	Fliser 1993[26]	10, median age 70 years (up to 80 years)		X			X			Lower GFR and ERPF in elderly. The median percent increase (17%) was not different from younger controls. Higher RVR and FF in the elderly

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus				Type of GFR measurement			Summary of the results
			Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	
	Böhler 1993	12 non-renal patients ages 60–80 years		X			X			Baseline GFR is lower in the elderly compared with young adults. However, RFR is well maintained in elderly human subjects
	Pecly 1999[27]	13: 20–39 years 13: 40–59 11: 60–68			X			X		Ageing decreases the increment of CrC. Increased bradykinin seems responsible for the GFR adaptation
	Fuiano 2001[28]	10 young 11: 65–76 years 15 young donors 11 older donors	X	X			X			In older subjects, GFR is lower. After combined stimulus, a smaller increase was seen in older subjects. More arteriosclerosis and interstitial fibrosis in older patients.
	Esposito 2007[29]	6 (25–37 years) 6 (44–74 years) 7 (81–96 years)	X	X			X			GFR and RPF were slightly reduced in elderly individuals, which resulted in increased FF. In the elderly as opposed to young and middle-aged subjects, neither GFR nor RPF increased after maximal stimulation
	Musso 2011[30]	5: 20–40 years 6: 64–74 years 5: > 74 years			X			X with cimetidine		Renal functional response was present in all age groups. Its magnitude was significantly higher in healthy compared with older subjects
Gender	No data									
Ethnicity	No data									
Diet [low protein (LP), normal protein (NP), high protein (HP)]	Bosch 1984[3]	10 (LP = 0.7–0.8 g/kg/d, NP 1.0–1.5 g/kg/d)			X			X		CrC on low protein (LP) diet is lower: 97 ± 34 versus 109 ± 37 mL/min. Peak GFR is similar at 122 ± 45 mL/min
	Castellino[7]	6 (LP = 40 g/d, NP 1.2–1.5 g/kg/d)		X			X			GFR is lower on LP diet. Increment after stimulus is equal
	Viberti 1987[31]	6 (LP: 43 g/d, NP: 75 g/d)			X		X			GFR is lower on LP diet: more relative increment but not reaching peak GFR on normal protein diet. Unchanged FF

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus: Dopamine	Type of stimulus: Amino acids	Type of stimulus: Protein meal	Type of stimulus: Creatinine IV	Type of GFR measurement: Urinary inulin (+ PAH) clearance	Type of GFR measurement: Urinary CrC	Type of GFR measurement: Exogenous marker	Summary of the results
	Kontessis 1990[32]	17 healthy subjects (3 weeks vegetarian versus animal protein)			X		X			GFR is lower after a 3-week course of vegetarian protein. Soy proteins induce less GFR increase than meat proteins while serum AA levels are comparable. A meal containing animal protein induces a higher and more sustained increase in glucagon levels
	Nakamura 1993[33]	6 healthy females and 6 type 2 diabetics			X				IOTH 1	Comparison with 0.7 g/kg tuna fish and the same or double amount of boiled egg white. GFR increases only after ingestion of tuna fish both in normal controls and diabetics. Only AA Gly and Ala rose differently after this meal
	Nakamura 1989[34]	11 healthy 20 diabetics			X			X		Comparison with 1.0 g/kg tuna fish versus bean curd. Vegetable protein could not induce an increase of the CrC in healthy subjects or in diabetics.
	Nakamura 1990[35]	10 healthy volunteers 6 type 2 diabetics			X			X		Comparison with 0.7 g/kg tuna fish versus boiled egg white, cheese of tofu (bean curd). An increased GFR was only observed after tuna fish. This was accompanied by an increase in glucagon and growth hormone as well as three AAs (alanine, glycine and arginine)
	Simon 1998[36]	8 healthy volunteers			X		X			A chicken or equivalent beef meal induces identical GFR and RPF response. RVR decreases as GFR and RPF increase. FF remains unchanged
	Orita 2004[37]	6 healthy male subjects		X			X			Offering a beefsteak or the same amount of skim soy with soy sauce results in an identical enhancement of GFR. AA analysis revealed no differences between the two protein challenges

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus				Type of GFR measurement			Summary of the results
			Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	
Low sodium diet (20 mmol/d and furosemide 80 mg once)	Ruilope 1986[38]	11		X			X			No increment of GFR when salt-depleted. Recovery when captopril is given. No recovery under indomethacine
Low sodium diet (0.5 g) and furosemide 25 mg for at least 3 days	Memoli 1991[39]	8 paired observations	X	X			X			In control conditions, both GFR and RPF increase (+31.5% and +41%) after dopamine and AA stimulation. After salt depletion, GFR and RPF are impaired mainly by an increased vascular resistance. After dopamine and AA, both GFR and RPF increase (+37% and +31%)
Low hydration/ high hydration	Hadj-Aissa 1992[40]	10 paired observations. High hydration: 1st h 10 mL/kg, 2nd h 7.5 mL/kg and 5 mL/kg/30 min			X		X			High hydration resulting in a low urinary osmolality blunts a protein-induced response of GFR
	Claris-Appiani 1999[41]	7 adults tested 6 times			X		X			The renal haemodynamic response is blunted when hypotonic saline is infused (0.23–0.45%)
	Anastasio 2001[42]	12 paired observations. High hydration means 5 mL/kg/30 min. Low hydration means 0.5 mL/kg/30 min			X		X			High hydration lowers GFR and preserves response versus low hydration (with a higher unstimulated GFR and lower response)
Medication	Krishna 1988[43]	9: tested 3 times (placebo, indomethacine, enalapril		X			X			GFR increased from 101 ± 7 to 118 ± 4 mL/min. Smaller increase after indomethacine. No effect of enalapril
	Herrera 1988[44]	10 healthy subjects, twice stimulated without and with indometacine			X		X			A protein load induces an increase in GFR from 107.2 ± 6.05 to 146.4 ± 6.79 mL/min/1.73 m^2 and an increase in RBF. No effect of indomethacine
	Vanrenterghem 1988[45]	6 subjects			X		X			Indomethacine blunts the GFR increase

(continued)

Table 4. Continued

Confounding variables	Reference	Number	Type of stimulus				Type of GFR measurement			Summary of the results
			Dopamine	Amino acids	Protein meal	Creatinine IV	Urinary inulin (+ PAH) clearance	Urinary CrC	Exogenous marker	
	Chagnac 1989[46]	12 healthy subjects before and after enalapril			X			X		CrC increases from 114.3 ± 4.5 to 137.1 mL/'/1.73 m^2 after a protein load. On the enalapril intake day, the increase of CrC was lower
	Mizuiri 1994[47]	6 controls 10 controls and 10 IgAN patients before and after captopril		X (L-Arg)			X			L-arginine infusion leads to a significant decrease in RVR and a significant increase in RPF and GFR in all groups. An increase in plasma glucagon levels was observed. Captopril pretreatment in healthy subjects attenuates this effect
	Pritchard 1997[48]	23 patients with hypertension (four-way crossover)	X	X			X			Tandolapril 2 mg and indomethacine 3 times 25 mg: no effect on GFR or ERPF after dopamine and AA
Body composition	Deibert 2011[49]	10 male patients with the metabolic syndrome 10 controls			X		X			The obese subjects show a higher baseline GFR and RPF. The protein load induced a significant increase in GFR and RPF in healthy controls and even more in patients with metabolic syndrome
	Anastasio 2017[50]	28 obese 20 controls			X		X			Delayed glomerular response in obese patients
Time of day	Buzio 1988[51]	7			X			X		Best CrC stimulatory effect when protein load is administered at lunch (instead of supper)
	Buzio 1989[52]	10			X			X		Circadian rhythm. No effect of placebo when given in the evening

IOTH 1 (^{125}I-iothalamate): IV bolus followed by a continuous infusion. Urinary and plasma clearances (to correct for incomplete voiding). HPLC measurement (in later studies); IOTH 2 (^{125}I-iothalamate): single subcutaneous injection. Plasma clearances. Gamma counter measurement; IOH 1 (iohexol): IV bolus followed by a continuous infusion. Plasma clearances. HPLC measurement; EDTA 1 (^{51}Cr-EDTA): IV bolus followed by a continuous infusion. Urinary clearances; EDTA 2 (^{51}Cr-EDTA): single IV bolus. Plasma clearances; DTPA 1 (^{99m}Tc-DTPA): single IV bolus. Plasma clearances. BSA, body surface area; HPLC, high-performance liquid chromatography; IV, intravenous; NGAL, neutrophil gelatinase-associated lipocalin.

Table 5. Current experience with renal stimulation testing in subjects with kidney disease (for reference list, see Supplementary material)

				Type of stimulus				Type of GFR measurement			Result
Clinical context	Condition	Ref	Number	Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
Hyperechogenicity	Potential kidney donors	Fouda 2011[53]	34 potential kidney donors with Grade 1 hyperechogenicity, 10 matched healthy donors	X	X					MAG 3	The renal reserve is comparable in the two groups. In 41% of 17 biopsies of the donors with abnormal ultrasound, morphologic abnormalities are present, compared with only 1 of 8 biopsied controls
Single kidney	Post-donation	Bosch 1984[3]	5			X			X		CrC increases from 70 ± 14 to 83 ± 4 mL/min
		Iturbe 1985[4]	25			X			X		CrC increases from 115.4 ± 11.6 to 137.4 ± 11.6 mL/min
		ter Wee 1986[5]	9	X	X					IOTH 1	GFR shows only increment on double stimulation
		Solling 1986[9]	8 meat meal 7 amino acid		X	X		X			Short-term protein load and AA, increased RPF and GFR and decreased RVR. The permselectivity of the GBM was unchanged
		ter Wee 1987[54]	18 after uninephrectomy, 10 kidney donors (pre and post)	X						IOTH 1	GFR increases 4.5% versus 10% in controls. After donation in paired observations, the GFR increase decreases from 12.4% before to 5.9% after nephrectomy
		Cassidy 1988[55]	12			X			X		Lower CrC in donor group but comparable increase on placebo.
		Amore 1988[56]	6 patients after unilateral nephrectomy 8 healthy subjects			X			X		Patients with single kidneys show albuminuria at baseline, while their CrC is normal. After a protein load, albuminuria increases while their CrC response is lower than in controls
		ter Wee 1990[57]	20 pre and post observations	X	X					IOTH 1	After donation: 65% of pre-donation GFR, lower FF. Dopamine: increase of GFR, with 13.8% before versus 5.3% after donation. AA-induced increase: 11.2% before versus 9.6% after. Combined: 20% increase before versus 12.6% after donation. ERPF helps maintain GFR
		Heering 1994[58]	8 controls 8 renal graft recipients 8 after nephrectomy		X			X			A RFR is shown in healthy controls but a grossly diminished response is seen in patients with a single kidney

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		ter Wee 1994[59]	15 pairs (donor/recipient) 12 long-term follow-up	X	X					IOTH 1	Preserved increase in GFR on AA stimulus, less after dopamine. Long-term RFR is preserved, less due to increased ERPF than to glomerular hypertrophy
		Rodriguez-Iturbe 2001[60]	14 normal controls 7 donors 11 after kidney transplantation				X		X	IOTH 2	An IV bolus of creatinine stimulated tubular secretion in controls (11.3 times), in donors (4.3 times) and in transplanted patients (2.5 times)
		Rook 2006[61]	125 kidney donors 120 days before and 57 days after donation	X	X					IOTH 1	GFR post-donation was predicted by GFR_{pre}, GFR_{max} and age
		Rook 2008[62]	178 kidney donors, 4 months before and 2 months after donation	X						IOTH 1	Dopamine-induced increase in GFR was reduced from 11 to 5% after nephrectomy. Dopamine-induced increase correlated negatively with donor age and BMI
		Spinelli 2017[63]	7 pairs donor/recipient			X			X		Sum of stimulated CrC of donor and recipient equals pre-donation stimulated CrC
		Van London 2018[64]	105 female kidney donors ages <45 years 51 donors with a BMI >25 kg/m^2	X						IOTH 1	Donors were tested 4 months before and 2 months after donation. Female donors with a BMI >25 kg/m^2 showed an absent functional response. BMI correlated with RFR
	After resection of Wilms tumour	Bhisitkul 1991[65]	12			X			X		No differences in CrC before and after oral protein load in single kidneys versus controls
		Regazzoni 1998[66]	37 after nephrectomy in childhood			X		X			Long-term follow-up shows stable GFR but decreasing increase of GFR after oral protein load
		Donckerwolcke 2001[67]	11 patients after nephrectomy			X		X			GFR and ERPF are well preserved. At rest, tubular secretion of creatinine is stimulated. Two patients show maladaptation with loss of RFR
	Renal agenesis	De Santo 1997[68]	21 adults with unilateral renal agenesis (3 groups with declining GFR)			X		X	X		Higher blood pressure and proteinuria in patients with lowest GFR. Normal response after protein load in all groups. CrC overestimated GFR by 32.7%
Renal transplantation		Cairns 1988[69]	9 renal transplants on cyclosporine	X	X					EDTA 1	After a protein load, azathioprine-treated renal transplantation

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
			9 azathioprine-treated renal transplants								showed a significant increase of GFR and ERPF compared with cyclosporine treated renal transplants
		Nunley 1991[70]	6 RT on cyclosporine 7 RT on azathioprine			X		X			Cyclosporine alters the renal response to a protein meal
		Rondeau 1993[71]	18		X			X			RFR: increase from 50 to 60 mL/min. No effect of ACE inhibitors. Less RFR if cyclosporine treatment
		Ader 1994[72]	12 patients studied at 20 days and 7.6 months 8 single kidneys 12 controls		X			X			Renal transplant patients show a GFR increase after AA stimulus
		Shokeir 1994[73]	152 donor/recipient pairs: 40 paediatric recipients, 112 adult recipients	X	X					DTPA 2	The GFR of paediatric recipients is significantly lower. The functional response of the transplanted kidney was assessed after 4–8 months. Also, graft functional reserve proved lower in paediatric recipients
		Chagnac 1995[74]	6 on cyclosporine before and after 2 weeks with high-dose nifedipine		X			X			High-dose nifedipine increases renal perfusion, decreases FF and RVR but RFR remains absent
		Hansen 1995[75]	9 healthy volunteers 9 on cyclosporine 9 without cyclosporine		X					DTPA 1	A 10-week dietary supplementation with fish oil did not induce significant renal function improvement. On low-dose cyclosporine, a well-preserved renal response is demonstrated
		Pluvio 1996[76]	16 transplanted patients on cyclosporine 6 nephrectomy patients 7 on cyclosporine 9 controls		X			X			No renal functional response on cyclosporine treatment, both transplanted and non-renal patients. Basal GFR correlates with renal allograft volume (measured by ultrasound)
		Hansen 1996[77]	8 on cyclosporine 8 on azathioprine	X	X					DTPA 1	Low-dose cyclosporine A does not attenuate the renal response after dopamine or AA infusion
		Englund 1996[78]	36 renal transplanted children, 15 donors and 15 single kidneys			X		X			Baseline GFR and ERPF is lower in transplanted patients. Increases are similar. Stimulated GFR and ERPF correlated with kidney length

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Maranes 1998[79]	11 patients with 'en bloc' transplantation 10 controls (single kidney transplants)		X			X			Patients having received an 'en bloc' pediatric kidney transplantation show a greater renal response (and a lesser risk of hyperfiltration)
		Fagugli 1998[80]	25 kidney transplanted patients 8 controls			X		X			A group of renal transplants shows no RFR but rather a reduction of GFR, a higher FF and a high level of thromboxane
		Zhang 1999[81]	5 normal volunteers 21 renal transplants on cyclosporine (10 with normal renal function)		X (L-Arg)			X			L-Arg increased GFR from 103 ± 9 to 122 ± 7 mL/min/1.73 m^2 in control subjects. In transplanted patients, no increase of GFR was observed
		Englund 2000[82]	30 children 7 recipient/donor pairs			X		X			Stable GFR and preserved increase on repeated measurements. Donors tend to show a higher response. Max GFR is related to kidney volume
		Bertoni 2001[83]	40 grafted with a kidney younger than 55 years 40 grafted with a kidney older than 55 years						X		CrC increases at 6 months and after 1 year. The increase in the CrC is higher in kidneys from younger donors. This increase is inversely related to donor baseline GFR
		Delclaux 2001[84]	11 out of 14 patients, >20 years after transplantation		X				X	EDTA 1	7 of 11 patients show an RFR that is lower than median. No correlation was found with morphological data (unless a slightly higher glomerulosclerosis rate in this population). In 4 of 11 patients a functional response is present, even >20 years after renal transplantation
		Fulladosa 2003[85]	32 transplanted patients on cyclosporine	X	X			X			Correlation of renal response with renal biopsy. The presence of arterial hyalinosis is the only histological parameter associated with impaired renal response
		Kamar 2006[86]	10 patients on FK and sirolimus 7 patients on FK and MMF		X			X			Similar GFR and renal functional response after 6 and 12 months post-transplantation. No correlation with histology.
		Saurina 2006[87]	14 patients before and 8 months after conversion to sirolimus		X					DTPA 1	More proteinuria and higher calculated glomerular filtration pressure after conversion of CNI to sirolimus

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
Heart transplantation		Ader 1996[88]	12 renal and 13 heart transplants 8 single K and 12 controls		X			X			Maximal increase of GFR after heart transplantation (7 months) is lower than in controls. No increase in ERPF was seen in heart transplanted patients
Heart Failure		Magri 1998[89]	10 (mild HF, compensated)		X			X			No vasodilatory response on AA in mild HF. Restored response after treatment with RAS blocker
		Frangiosa 1999[90]	9 patients with end-stage HF (ACE inhibitors, diuretics) 18 controls			X		X			GFR and ERPF are higher in normal controls, but the percentage increase after a protein load is conserved (27%) in HF patients, although they show a high FF (35%)
Coronary artery disease		Fuiano 2005[91]	15 patients with an indication for coronary angiography 15 kidney donors as a control group		X			X			Unstimulated: lower ERPF in CAD, higher FF. Lower RPF dependent on severity of CAD After AA infusion: no increase of GFR in CAD. After 2 years: decrease in GFR and RPF. Unchanged response to AA.
Cardiac surgery		Mazzarella 1991[92]	11 adult patients scheduled for coronary artery bypass graft			X			X		Patients were tested before, as well as 9 days and 6 months after cardiac surgery. At 9 days, no significant renal response could be shown. The renal response was restored at 6 months
Pregnancy		Ronco 1988[93]	29 pregnant subjects were tested at different stages			X		X	X		Resting CrC increases during pregnancy. Increment in CrC decreases during pregnancy. Peak GFR is 160 mL/min
	Late gestation compared with 3 months post-partum	Barron 1995[94]	14: protein challenge 8: carbohydrate challenge			X		X			GFR is higher during gestation and even higher than post-protein load in post-partum women. Placebo during pregnancy is less effective
	Early and late gestation compared with 3 months post-partum	Sturgiss 1996[95]	14: AA infusion 7: crystalloid		X			X			GFR increases in early and late pregnancy. Percentage increase is not different from post-partum. Unstimulated GFR is 40% higher during pregnancy
		Heguilén 2001[96]	8 pregnant women (15 weeks) 5 controls			X			X		Pregnant women still show an increased CrC on protein loading
	Mid-term	Heguilén 2007[97]	8 hypertensive pregnant, 5 non-hypertensive, 8 controls			X			X		After protein challenge, hypertensive pregnant women show a lesser increase of CrC than normal pregnant women

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Cohen 2012[98]	Healthy pregnancy = 15 Pregnancy and CKD = 25 Non-pregnant women = 8			X			X		In controls, baseline CrC increases from 99.8 ± 2.9 to 149 ± 4 mL/min. In healthy pregnancy, baseline CrC increases from 118.5 ± 3.2 to 223.4 ± 5.2 mL/min, a 90% increase. In CKD pregnancy, baseline CrC increases from 132 ± 7.6 to 186 ± 10.3 mL/min, a 40% increase
Liver cirrhosis		Hirschberg 1984[99]	8			X			X		No increase of the GFR after a protein load
		Rodriquez 1999[100]	10 patients with Child A liver cirrhosis 10 controls		X			X			GFR and ERPF are lower in patients with cirrhosis. The functional reserve is similar. Higher levels in cGMP and NO were seen in patients, probably to compensate for angiotensine II effects
		Woitas 2002[101]	22 patients with decompensated liver cirrhosis and ascites		X			X			Baseline GFR and ERPF were low. After AA infusion the GFR increases by 67% and ERPF by 29%
		Woitas 1997[102]	12 patients with liver cirrhosis and portal hypertension		X			X			Baseline GFR and ERPF were lower. In both groups GFR and ERPF are increased after AA infusion. The degree of ERPF increase is higher in cirrhotic patients
Liver transplantation		Badalamenti 1995	13 treated with fish oil 13 with corn oil, during 2 months		X (L-arg)			X			Two months treatment with fish oil improves renal hemodynamics, no effect on RFR.
Nephrotoxicity	Occupational exposure to lead	Roels 1994[103]	76 male lead workers			X			X		Both controls and lead workers showed a significant increase in CrC of 15%. Baseline and stimulated CrC is higher in lead workers
Genetic risk of essential hypertension		O'Connor 2001[104]	26 normotensives with positive familial risk of hypertension 13 controls		X			X	X		RFR is already blunted in still normotensive subjects at genetic risk of hypertension. Potential explanations: insulin resistance to the amino acid–translocating effects of this hormone, baseline hyperfiltration and decreased proximal tubular reabsorption during amino acid infusion
Hypertension		Losito 1988[105]	34 mild to moderate HT (22 controls)		X				X		Less increase in CrC after AA infusion. Some patients show no RFR: CrC correlates with albuminuria in these patients

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Valvo 1990[106]	15 hypertensives 12 healthy subjects			X				IOTH 2	RFR is identical to controls. ACE inhibitor does not influence the amount of RFR
		Buzio 1994[107]	16 hypertensives with apparently normal GFR with and without nifedipine and captopril			X				IOTH 1	Nifedipine increases GFR, ERPF as well as urinary excretion of proteins after a protein load, while captopril decreases GFR and proteinuria
		Cottone 1994[108]	16 newly diagnosed patients with essential hypertension 10 healthy controls		X				X		Among 16 patients, 13 showed an increased CrC after AA infusion. No correlation was found with plasma renin activity, aldosterone concentration, circulating norepinephrine and endothelin-1
		Tietze 1997[109]	12 controls 14 patients with essential hypertension		X			X			GFR increases in healthy controls with and without ramipril. In hypertensive patients, ramipril inhibits the increase in RPF. Long-term treatment with ACE inhibitor blunts the response of GFR and RPF
		Belsha 1998[110]	33 normotensive adolescents 29 hypertensive adolescents			X			X		Normal functional response in hypertensive adolescents. No renal pathology even with left ventricular hypertrophy
		Zitta 2000[111]	15 controls, 16 hypertensive patients			X		X			No increase of GFR in hypertensive patients unless partial recovery after carvedilol and not after fosinopril treatment
	Obesity + hypertension	Pecly 2006[112]	14 obese and AHT 9 lean and AHT			X		X			In obese patients, GFR and RPF are higher. Response after protein load is lower
		Teunissen-Beekman 2016[113]	Out of 79 overweight individuals with untreated hypertension and normal GFR, 27 on maltodextrin and 25 on protein mix participated			X		X			Greater decrease in FF after a protein supplemented breakfast following a 4-week course of protein supplementation
		Gaipov 2016[114]	10 hypertensive nephropathy 14 hypertensive without nephropathy 11 controls			X			X		Lower RFR in hypertensive patients. Correlation with renal resistive index and proteinuria
ADPKD		Harrap 1992[115]	19 ADPKD 20 controles			X		X			Lower ERPF in ADPKD patients, also stimulated renin–angiotensin system and higher body sodium load. Non-significant increase in GFR after oral protein load

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
Scleroderma		Livi 2002[116]	21 scleroderma patients with normal creatinine 10 controls		X				X		Unstimulated: lower CrC Stimulated: less increase of CrC. The response is dependent on MAP and unstimulated CrC
		Livi 2011[117]	28 normotensive sclero-derma patients		X				X		19 patients had an RFR defect and 9 showed a normal RFR. Those patients had a lower BP. After 5 years: 13 of 19 showed a reduction of CrC >2mL/min/year
		Amin 2012[118]	30 patients with scleroderma 30 controls			X				DTPA 2	High prevalence of lower RFR in scleroderma patients. Pulmonary hypertension correlated with abnormal RFR
SLE	No CKD	Khusnutdinova 2014[119]	30 versus 40 controls	X					X		RFR was 41% in controls and lower in SLE
Poststreptococcal GN	No CKD on follow-up	Iturbe 1985[4]	35 patients			X			X		CrC rose from 82.0 ± 6.45 to 90.3 ± 5.3 mL/min
Chronic glomerulonephritis	No CKD	Tietze 1994[120]	13 biopsied CGN 13 controls		X					IOTH 1	Renal response and glomerulo-tubular balance are intact. Abnormal lack of suppression of the renin–angiontensin–aldosterone system after AA infusion
IgA nephropathy		Bach 1994[121]	7 with modest impairment 2 nephrotic 9 controls		X			X			GFR and ERPF increased in controls and patients without nephrotic syndrome. No increase in the two nephrotic patients
		Beukhof 1985[122]	32	X						IOTH 1	Dopamine induces GFR-only effect when baseline GFR > 73 mL/min/1.73 m^2
	GFR 64 mL/min,Diet: 0.9–1.3 g/kg/d protein	Pluvio 1996[123]	7 stage II, 8 stage III-IV and 12 controls		X			X			RFR 20% in Stage II comparable to normals. No RFR in Stages III–IV
		De Santo 1997[124]	10 proteinuric IgAN patients 20 controls			X		X	X		GFR was lower and FF was higher at baseline in patients. GFR increase following protein load was comparable
		Sulikowska 2004[125]	20 patients before and 1 year after treatment with Omega-3	X					X		Omega-3 polyunsaturated acids improve dopamine-induced GFR response and lower proteinuria and NAG excretion
		Sulikowska 2008[126]	50 15 controls	X					X		Less response on dopamine, higher NAG and FeUA
		Sulikowska 2012[127]	46 patients 15 controls	X					X		Lower DIR in patients. Correlation of EPO with uric acid clearance: more EPO and reduced urate clearance

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Sulikowska 2015[128]	46 non-nephrotic IgAN patients 15 controls	X					X		IgAN patients were separated in subjects showing a decrease in EPO levels versus those showing an increase in EPO levels. A decreasing EPO level was associated with a preserved CrC response, less proteinuria, less NAG and lower uric acid and blood pressure while kidney biopsy findings were comparable
HIV nephropathy		Marques 1998[129]	6 healthy 9 asymptomatic carriers of HIV			X			X		CrC increases in healthy subjects. In HIV carriers a lower response is observed
Sickle Cell anaemia		Herrera 2002[130]	16 sickle cell A 20 controls				X		X	IOTH 2	SCA patients have a higher GFR at baseline, but no increase in tubular secretion of creatinine
CKD	Altered renal function	Bosch 1983[1]	6			X			X		Some have RFR while others not
	CKD1a, CKD1b, CKD2, CKD4	Bosch 1984[3]	CKD1a (4), CKD1b (13), CKD2 (9), CKD4 (5)			X		X	X		CKD1a: from 149 ± 12 to 165 ± 13 mL/min CKD1b: from 109 ± 8 to 124 ± 16 mL/min CKD2: from 70 ± 14 to 86 ± 12 ml/min CKD4: from 22 ± 6 to 24 ± 6 ml/min
	CKD 1, CKD 2-3, CKD 4	ter Wee 1985[131]	CKD 1: 9 CKD 2–3: 11 CKD 4: 7	X	X					IOTH 1	
	Variable GFR	Bosch 1986[8]	10			X		X			GFR increases from 63 ± 29 to 76 ± 37 mL/min dependent on severity
		Colome 1987[132]	16 controls (13 adults and 3 children) 31 patients (22 adults and 9 children)			X			X		No response if clearance is <40 mL/min and in patients with acquired or congenital solitary kidney. The presence of proteinuria is not associated
	CGN	Chan 1988[133]	12 patients 12 controls			X		X			No acute effect on glomerular barrier size selectivity
	Reduced number of functioning glomeruli	Zuccala 1989[134]	20 with 15–70% sclerotic glomeruli 10 with acquired single kidney 5 with surgical ablation of >50% of renal mass 24 controls			X		X			RFR is not necessarily reduced or absent in patients with a reduced number of functioning glomeruli
	CKD	Krishna 1991[135]	15 CKD			X		X			Preserved renal reserve in CKD patients not influenced by enalapril
		Uemasu 1991[136]	8 healthy subjects 9 subjects with CGN and baseline GFR >90 mL/min 8 subjects with baseline GFR between 40 and 90 mL/min	glucagon						THIO	Normal controls show an increase in GFR and ERPF. CGN with preserved GFR showed no increase in ERPF, while patients with lower GFR showed no effect on GFR while ERPF increases

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Loo 1994[137]	32 with CKD 19 post-transplantation 12 kidney donors 62 healthy controls			X			X		Renal response in healthy subjects was 31 mL/min. Lower response in CKD patients: 13.5 mL/min. Same response in transplant recipients. Lower response in donors: 5.4 mL/min
		De Santo 1997[138]	10 healthy subjects 10 CKD patients (GFR = 40 mL/min)			X		X			Similar increase of GFR in healthy and CKD patients. Renal tubules contribute to the acid/base balance in both groups by reabsorbing most of the bicarbonate load
	CKD on low protein diet	Cianciaruso 1994[139]	14	X		X		X			Lower effect of stimulus in patients even after low-protein diet, while in controls an increased effect is seen on a low-protein diet
	CKD 1-2CKD 3CKD 4	De Santo 1995[140]	CKD 1–2 = 115 CKD 3 = 85 CKD 4 = 73			X		X			Compared with 85 healthy subjects, renal disease patients peak later after a protein meal. Cumulative GFR increase is less in renal disease
		Herrera 1998[141]	12 controls 7 donors 8 CKD			X		X	X		Comparison of inuline and CrC reveals that there is a limited tubular secretion of creatinine dependent on renal mass
		De Nicola 1999[142]	21 proteinuric CKD patients: 11 for 6 months on L-arginine and 10 controls		X			X			No improvement of 6 months treatment with arginine supplementation on renal functional response
		Barai 2010[143]	25 controls 100 CKD		X					DTPA 1	Control mean renal reserve = 23.4% CKD 1 = 19.08% CDK 2 = 15.4% CKD 3 = 8.9% CKD 4 = 6.7%
Diabetes		Bosch 1986[8]	18			X		X			GFR decreases from 118 ± 46 to 102 ± 37 mL/min
	Insulin-dependent (type 1)	ter Wee 1987[144]	14	X	X					IOTH 1	130 mL/min baseline GFR, lesser increase after AA than controls dependent on baseline GFR (negative correlation)
	Type 2 DM	Nakamura 1989[34]	A: no albuminuria B: micro C: macro			X			X		No albuminuria: normal GFR increase. Microalbuminuria: no GFR increase. Macro: GFR decreases after placebo
	Type 1 DM	Nosadini 1989	15 IDDM (>9 years), 8 with and 7 without albuminuria 8 controls		X					EDTA 1	Comparison of AA and ketone body infusion shows that renal response in long-standing DM type 1 patients is not present

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
	Type 2 DM with nephropathy	Brouhard 1990[145]	8 patients on low-protein (0.6 g/kg/d) and 7 on normal diet			X		X			RFR measured at 6-month intervals during 1 year decreased as well as resting GFR in patients on normal diet
	Type 1 DM	Dedov 1991[146]	10 patients with type 1 DM without diabetic nephropathy 7 healthy controls			X			X		Patients with normal RFR show a lower baseline GFR. Patients with no RFR have a higher resting GFR and demonstrate hilar glomerular lesions with severely expanded mesangium, apparently preceding overt nephropathy
	Type 2 DM	Tuttle 1992[147]	12 diabetic patients without insulin treatment 9 normal subjects		X			X			Diabetics show a higher baseline GFR and ERPF, as well as a more prominent RFR. This does not change after 36 h of insulin infusion. A 3-week course of insulin therapy diminishes the exaggerated renal response and the volume of the right kidney without normalizing it
		Sackmann 1998[148]	33 patients: 14 early stage, 10 microalbuminuric, 9 late stage 12 controls		X			X			Early stage (at high GFR) and late stage (proteinuric and lower GFR) show less response
	Type 1 DM	Sackmann 2000[149]	10 with nephropathy, 10 without 15 controls		X			X			Less increase of GFR in patients with nephropathy (proteinuria and hypertension) even when GFR is preserved
	Type 2 DM	Guizar 2001[150]	181 recently diagnosed type 2 -> 28 studied, 7 controls			X		X			75% of patients show microalbuminuria. Studied microalbuminuric patients lose response on protein load
	Type 2 DM	Earle 2001[151]	9 African-Asian diabetes 9 white patients		X			X			Less response in patients of African-Asian descent due to defective NO production or bioavailability
	Type 1 DM	Assan 2002[152]	285 IDDM treated with cyclosporine 100 IDDM not treated with cyclosporine		X			X			10–12% functional response, conserved even after 7 and 10 years of low-dose cyclosporine treatment
	Type 1 DM	Tuttle 2002[153]	12 DM type 1 12 controls		X			X			Diabetics have a higher GFR and FF. AA and glucagon induce GFR to rise via a different pathway. Glucagon can be inhibited by indomethacine

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
	Type 1 DM	Zaletel 2004[154]	22 patients without renal disease			X		X			Renal response is inversely related to CRP, linking endothelial dysfunction with renal haemodynamic behaviour
	Type 1 DM	Sulikowska 2007[155]	30 sulodexide and 13 not	X					X		Sulodexide helps in improving dopamine-induced GFR response and lowering of NAG
		Mueller 2009[156]	28 diabetic patients			X		X			Preserved RFR in 6 of 28 patients. No correlation with cystatin C
Children (< 18 years)											
		Hellerstein 2004[157]	89 studies in 78 children			X			X + cimetidine		Follow-up of CACrC after a meat-free protein meal is non-invasive and inexpensive
	Solitary kidneys	Peco-Antic 2012[158]	22 patients 30 controls			X			X + cimetidine		CACrC and cystatin C were compared. Half of the patients had decreased RFR. Cystatin C was a strong predictor. Also, blood pressure was a determinant
	CKD	Molina 1988[159]	Normal: 386 CKD: 21			X		X	X		A normogram was constructed with p10 and p90. Negative correlation of stimulated GFR with unstimulated
		De Santo 1990[160]	Normal: 11 10 children with mean creatinine 2.6 mg/dL			X		X			Earlier peak GFR in healthy children. Greater increase of GFR and RPF in diseased children
	Offspring of hypertensive parents	Grunfeld 1990[161]	21			X			X		Lack of GFR increment in offspring of hypertensive parents is associated with higher albuminuria
	Type 1 DM	Semiz 1998[162]	22 patients (11 with >5 years of diabetes, 11 with shorter duration) 15 healthy controls			X			X		Renal functional response is lower after a longer duration of diabetes. This pathology is present without albuminuria
		Raes 2007[163]	51 diabetic children 34 controls	X				X			Unstimulated GFR is similar, increased FF. Lower RFR in patients
	Previous post-streptococcal GN	Cleper 1997[164]	36 patients (5–21 years old) without renal function anomalies 12 controls (2–12 years old)			X			X		Similar basal CrC. The functional response is lower in patients after a post-streptococcal GN
	Previous HUS	Perelstein 1990[165]	17: previous HUS 11: single kidney 15: controls			X			X		Children with a history of HUS show an abnormal RFR
		Tufro 1991[166]	16			X		X			Protein content in the diet influences CrC

(continued)

Table 5. Continued

Clinical context	Condition	Ref	Number	Type of stimulus				Type of GFR measurement			Result
				Dopamine	AA	Protein meal	Creatinine IV	Urinary Inulin (+PAH) clearance	Urinary CrC	Exogenous marker	
		Dieguez 2004[167]	26: tested two times 15 controls			X			X + cimetidine		CACrC rises after a protein load in both patients and controls. When distinction is made between responders (> 36% increase) and not, non-responders develop proteinuria. They had a longer oliguria period during their HUS
		Bruno 2012[168]	33 children with previous HUS (18 males, 15 females) with normal CrC			X				EDTA 2	Half of the children showed a GFR increase of at least 20%, judged as a normal response
	Reflux nephropathy	Coppo 1993[169]	28 children with surgically corrected bilateral vesico-ureteric reflux		X						Children with severe renal parenchymal scarring had greater albuminuria and beta-2 microglobuline in basal conditions. Both increased after AA infusions. CrC increases also
		Matsuoka 2009[170]	35 patients with reflux nephropathy, glomerular size evaluated on renal biopsy	X						THIO	When glomerular size was normal, DIR was good and ERPF was unchanged When GS was enlarged, GFR and ERPF increased both When GS was extremely enlarged, both GFR and ERPF remained unchanged
	Unilateral uretero-pelvic junction obstruction	Montini 2000[171]	4 boys and 1 girl after pyeloplasty with contralateral kidney as control			X		X			GFR at baseline was greater in normal than in surgically treated kidney. Aspirin decreases GFR in operated kidneys. Lower GFR increase after protein loads in operated kidneys
	Posterior urethral valve	Ansari 2011[172]	25 patients, at least 6 weeks after fulguration of posterior urethral valve			X				DTPA 1	In more than a third of patients, RFR is depleted. They had more bladder dysfunction and more severe vesicoureteral reflux

IOTH 1 (^{125}I-iothalamate): IV bolus followed by a continuous infusion. Urinary and plasma clearances (to correct for incomplete voiding). HPLC measurement (in later studies);IOTH 2 (^{125}I-iothalamate): single SC injection. Plasma clearances. Gamma counter measurement; IOH 1 (iohexol): IV bolus followed by a continuous infusion. Plasma clearances. HPLC measurement; IOH 2 (iohexol): single IV bolus. Plasma clearances. HPLC measurement; EDTA 1 (^{51}Cr-EDTA): IV bolus followed by a continuous infusion. Urinary clearances; EDTA 2 (^{51}Cr-EDTA): single IV bolus. Plasma clearances; DTPA 1 (^{99m}Tc-DTPA): single IV bolus. Plasma clearances; DTPA 2 (^{99m}Tc-DTPA): single IV bolus. Isotope renography; MAG 3 (^{99m}Tc MAG 3): single IV bolus. Isotope renography; THIO (thiosulfate sodium): IV bolus followed by a continuous infusion. Urinary clearances. Measurement by the method of Brun. GN: glomerulonephritis; HUS, Haemolytic uraemic syndrome.

Overweight people show an increased unstimulated GFR and less exploitable filtration capacity [87].

Kidney donors as well as patients with a congenital single kidney were extensively studied (Table 5). The expected response after a fixed protein meal or an AA infusion is generally preserved in single kidneys, even several years after nephrectomy. Dopamine accomplishes less stimulatory effect, as ERPF is already maximally increased [45]. Long-term follow-up reveals that the gradual increase in the GFR in the post-transplant period is achieved by glomerular hypertrophy instead of an increased ERPF [88]. Regazzoni *et al.* [89] described an unchanged GFR several years after a nephrectomy in childhood. However, an oral protein load proved gradually less effective in evoking an adequate response. Transplanted kidneys show less response to a protein stimulus when treated with cyclosporine compared with patients treated with a calcineurin-free regimen, mostly azathioprine [90]. The extent of the GFR increment after a stimulus correlated with kidney size (i.e. length or volume). Kidneys from younger donors exhibited a better renal response after a stimulus and this was dependent upon the unstimulated GFR of the donor [91]. The native kidneys of patients after a heart transplantation tended to show less response than the single transplanted kidney [92]. This was attributed to pre-existent cardiovascular damage, absence of renal denervation or a slightly higher cyclosporine trough level.

Hypertensive patients challenged with a protein meal, demonstrate a weaker or absent renal response. The presence of albuminuria indicates subclinical damage with abolished filtration reserve. A significant negative correlation was shown between the renal response and the renal resistive indices, evaluated by ultrasound [77]. In the offspring of hypertensive parents, the RFR proved lower and was associated with albuminuria [93]. Fifteen patients planned for a coronary angiography were matched with as many healthy peers. Their ERPF was lower and correlated with the extent of coronary lesions [94]. No response on AA infusion could be documented in patients with coronary artery disease.

IgAN cases were studied after AA and dopamine infusions. A diminished renal response was present in patients with more prominent histological lesions (with >50% of the glomeruli showing proliferation and >15% of the glomeruli with crescents or segmental lesions) [95]. Another study correlated a lower GFR increase to injury biomarkers such as proteinuria and NAG excretion [60].

Livi *et al.* [96] studied patients suffering from systemic sclerosis and found that they displayed a lower stimulated GFR. Followed for 5 years, scleroderma patients without increasing GFR at the start lost kidney function at a faster rate of >2 mL/min/year. This study is one of the rare prospective reports. Children tested after a previous episode of haemolytic uremic syndrome showed variable response after a protein meal. Low responders (<36% increase) developed proteinuria later in life [97].

When renal function is decreasing, the amount of exploitable filtration capacity decreases but stays measurable even in patients with Stage 4 CKD [98]. This contrasts with the former theory of RFR, claiming that the reserve capacity is fully utilized before the GFR drops below 50 mL/min [80].

In a small study, 10 compensated patients with mild heart failure showed no vasodilatory response after AA infusion. The response was restored after initiation of an ACE inhibitors [99].

A higher GFR is observed in diabetics with hyperglycaemia. In these circumstances, the renal blood flow and the filtration fraction are increased, resulting in a higher intraglomerular pressure. This leads to transient or permanent albuminuria [27]. Diabetic patients with overt proteinuria fail to respond with a GFR increase when challenged with a protein meal [100–103].

In pregnancy, the induced augmented renal clearance (we deliberately avoid using the phrase 'hyperfiltration') is observed because of an increased ERPF thanks to relaxin, a vasodilating hormone produced by a healthy placenta. Pregnancy offers the most extensive increment of GFR [104]. The filtration fraction of kidneys in pregnancy is normal or decreased [105]. Only normotensive gravida display a functional response [106]. Failure to fully dilate the afferent arteriole and augment ERPF may lead to pre-eclampsia or pregnancy-related hypertension [104]. Hence the interest in examining the RFR in women with kidney disorders consulting with a pregnancy wish.

CRITICAL APPRAISAL OF RENAL STIMULATION TESTING

The idea of a dormant and exhaustible RFR was flawed as soon as it became obvious that single and transplanted kidneys still show a functional improvement after a protein load [10]. This observation led to waning interest in renal function testing and resulted in incomplete scientific explorations: not all renal syndromes have been thoroughly tested. Correlations with histological findings are hardly reported. Moreover, there are no reference data in sickness or in health. Furthermore, longitudinal data linking a decreased stimulatory effect to unfavourable outcomes are scarce. Today, the use of RFR measurements has no place in routine clinical care.

A second criticism is the missing of a renal distress signal, making renal and cardiac stress testing hard to compare. An absent functional response and/or the demonstration of a higher filtration fraction could be viewed as a surrogate for renal maladaptation, potentially leading to progressive nephron loss. This parameter can only be documented when renal clearances of a filtration and a perfusion marker (PAH or ^{131}I-hippuran or ^{99M}Tc-mercaptoacetyltriglycine) are followed simultaneously. Without the emergence of injury biomarkers, a normal renal response after a protein load implies normal protein tolerance.

In contrast to cardiac stress testing providing the clinician with an early diagnosis allowing for targeted treatment, renal function testing offers the clinician a suggestion of subclinical pathology, but without therapeutic consequences.

A concern is the terminology used. The literature is with confounding nomenclature and consensus definitions are missing.

Renewed interest in renal function testing has been stimulated by nephrologists involved in AKI care. A metabolic challenge could be valuable in assessment of the renal recovery. However, the causative link of diminished renal protein tolerance to a higher susceptibility for recurrent AKI remains debatable.

Finally, renal function testing is relatively labour intensive and requires the allocation of resources. Because the test remains in the experimental context, it is not reimbursed. Spinelli *et al.* [40] performed a cost calculation of a simple RFR test using cooked beef as a stimulus and four urine CrC measurements added to 8 h of a nurse's workload. The total cost was €91 for a single RFR estimation. Costs were predominantly driven by the nursing workload, so actual costs may vary substantially between different regions of the world.

FUTURE DIRECTIONS OF RESEARCH

The first step to be taken is deciding on a common vocabulary. We propose to use the terminology of unstimulated GFR (when

Table 6. Suggested research topics for renal stimulation testing (adapted and complemented from Molitoris [16])

Clinical category	Specific situation	Diagnostic information
1. Prior to renal mass reducing surgery	Before kidney donation	Risk of CKD post-donation
	Before nephrectomy for other reasons	Need for nephron-sparing surgery or alternative therapies (e.g. radiofrequency ablation)
2. In case of congenital or acquired lower renal mass	Congenital anomalies of the kidney and urinary tract	Long-term prognosis
	After kidney transplantation	Long-term prognosis
	After kidney donation	Risk of progressive renal failure
3. In case of suspected renal frailty	Before major surgery	Risk of AKI
	Before pregnancy in high-risk situations	Risk of gestational hypertension and pre-eclampsia
	Before or during chemotherapy or treatment with nephrotoxic drugs	Early nephrotoxicity? Need for dose reduction or change of therapy?
	In high-risk patients (cardiovascular disease, COPD, OSAS, diabetes, scleroderma, etc.)	Early diagnosis of CKD
	In geriatric patients	Discerning renal ageing from genuine CKD
	In patients after cystectomy and urinary diversion	Early diagnosis of tubulointerstitial nephritis
	In patients with the cardiorenal syndrome	Distinction between worsening renal function and true AKI
	Follow-up after an AKI episode	Fully recovered or not
	Follow-up after inflammatory glomerulonephritis	Fully recovered or not
4. In case of suspected whole kidney hyperfiltration	Obesity	Maladaptive hyperfiltration or not
	Diabetes type 1 and type 2	Maladaptive hyperfiltration or not
	Septic patients	Augmented renal clearance resulting in alternative dosing of antibiotics

COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome.

all confounding variables are controlled for), random GFR and stimulated GFR. We also advocate rephrasing the terminology of RFR, although firmly embedded in the literature, to renal functional response.

Second, two standard protocols of renal function testing can be proposed, varying in complexity from an elaborate research methodology (encompassing exogenous markers) to a simple scheme with calculated renal CrCs by the means of timed urine collections. However, recent evidence points to the important contribution of tubular secretion in the clearance of protein-bound retention products [107]. The tubular contribution to overall renal clearance can be evaluated by simultaneously measuring the clearance of creatinine and an exogenous filtration marker, either after a protein meal or a creatinine load. Alternative stimuli should be explored, for instance serelaxin [108].

Third, prospective studies in different disease entities are necessary to link an abnormal renal response to major adverse renal endpoints and provide us with reference values. In Table 6 we present four clinical situations in which the absent response after stimulation might yield meaningful diagnostic and prognostic information: subjects before kidney mass reducing surgery or known to have a diminished number of nephrons, patients in which renal disease is assumed and individuals with an augmented renal clearance. When the eGFR is low, a significant stimulatory response indicates a sufficient nephron quantity. In the case of a diminished or absent increase, CKD can be ascertained. Subjects at high cardiovascular risk may present with a preserved eGFR. If a renal stimulation test fails to induce an increment of glomerular filtration, these patients can be diagnosed as having subclinical kidney disease. A lower as well as a higher GFR have been associated with increased cardiovascular risk [109]. No renal response might indicate single-nephron hyperfiltration in both circumstances.

The complexity of the stimulation protocol should match the importance of the anticipated result. Hence the study of kidney donor candidates might receive the greatest attention: maximal stimulus (dopamine in combination with an AA infusion) combined with measured GFR by an exogenous marker. Women at high risk for pre-eclampsia or pregnancy-induced hypertension might be solicited to participate in a simple protein challenge study with urinary CrC. Also, patients applying for bariatric surgery might be tested: an absent functional response could provide the multidisciplinary team with a sense of urgency. Will these patients regain their glomerular reactivity along with the expected reduction of proteinuria [110]? Tubular function testing can be interesting in patients with chronic obstructive pulmonary disease or obstructive sleep apnea, with both showing a high prevalence of kidney disease. Can RFR testing before and after starting nocturnal continuous positive airway pressure sort out the questions in this syndrome regarding cause, effect or merely association? Post-AKI patients can be evaluated before they leave the ICU by means of an AA infusion and timed urinary CrCs. In this way, their renal recovery status is better documented and can be correlated with future events. Doig *et al.* [111] published a randomized controlled trial in an ICU population of an AA infusion as a preventive strategy for AKI: the primary endpoint was negative but eGFR and urine production increased. Repetitive testing of the glomerular and tubular reserve by a protein load in patients after cystectomy and urinary diversion, might elucidate progressive tubulointerstitial damage even before serum creatinine rises.

Finally, to broaden the scientific foundation of renal function testing, studying the behaviour of renal damage biomarkers during renal stimulation might offer more insight into glomerular and tubular adaptation. Moreover, functional data should be coupled to histological information. Morphological details acquired by MRI or ultrasound can provide additional elements. Obviously these lines of research will greatly amplify the cost of renal function testing and can only be initiated in the context of a study. Eventually comparison of these divergent diagnostic procedures can guide us in choosing the most cost-effective procedure to gain deeper insight into renal health. Several relevant clinical trials (www.clinicaltrials.gov) are under way or are awaiting publication. One trial (NCT03190070) includes 30 participants and is testing a liquid protein load in normal and CKD subjects. A second trial (NCT03190070) included 110 patients scheduled for cardiac surgery and performed RFR testing 1 day before and 3 months after the procedure as well as urinary TIMP2-IGFPB7 analysis. Another trial (NCT03190070) plans to monitor 100 patients with a partial laparoscopic nephrectomy and intends to compare the renal protective effect of total versus segmental renal artery clamping by studying the RFR.

CONCLUSIONS

This article offers the most extensive review of renal function testing to date. The authors propose a synthesizing lexicon and advocate a limited number of protocols applicable in future research.

A renal stimulation or stress test aims to document the capacity of an individual to increase his or her kidney function in response to a metabolic need. The stimuli that are proposed are derived from both physiological and experimental evidence. Offering a short-term oral protein load, for instance, mimics a normal meal and probes the integrity of the gut–liver–kidney axis. This protein challenge tests glomerular as well as tubular function. Confirmation of an increasing GFR after a stimulus is meaningful. It implies an associated decrease of RVR. To accomplish this, the kidneys' vascular reactivity as well as a critical number of pre-glomerular arterioles must be preserved.

This dynamic test of a vital organ, shows analogies with stress tests in other clinical domains. Preservation of a renal haemodynamic and/or metabolic response might imply overall vascular health to overcome planned or unintentional injurious events.

With the available evidence, measurement of the renal functional response remains restricted to research purposes. Without prospective studies delivering reference data and acknowledging that renal iconographic and biomarker research is moving at great speed, a requiem rather than a revival for renal function testing is equally possible.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The authors thank P. Delanaye for the stimulating discussions.

CONFLICT OF INTEREST STATEMENT

None declared.

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