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What does the renal reserve mean?

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The concept of the renal functional reserve stems from the observation that in normal humans, the "resting" glomerular filtration rate may be acutely raised following several stimuli. This extra excretory capacity, represented by the rise in GFR from baseline to maximum, might be regarded as a reserve upon which the kidney could call in times of stress. As a corollary it seemed likely that whenever a kidney was damaged and lost filtration capacity, this unused reserve would be depleted before the resting GFR fell. Measuring the degree to which the GFR could respond to stress—its renal functional reserve (RFR)—would therefore provide an early measure of renal damage. It would also be rational to believe that once the GFR was impaired this response would be lost.

Since this hypothesis was proposed it has become obvious that it was flawed. It has been clearly shown that the response is not lost in disease states and that therefore its does not represent a true "reserve". The response itself is also heterogeneous. The glomerular filtration rate can be induced to rise by a variety of stimuli using different mechanisms. The most commonly used stimuli to test the RFR are a high protein meal or an intravenous (or oral) amino acid infusion. Dopamine infusions have also been used to provoke the response, but there is little evidence that the response is mediated in the same way.

This article will chiefly deal with the physiological mechanisms involved in the renal haemodynamic response to a meat meal or amino acid infusion and confine to these responses the convenient appellation "renal functional reserve".

The response itself

Changes in renal function following a meal were noted in 1923 [1]. It has been consistently shown since this time that the GFR rises either following a meal of animal protein or after an infusion of amino acids. Various investigators have attempted to define these stimuli more carefully and also to decide whether the response is direct or is mediated by other substances.

The nature of the stimulus

Type of protein

Different types of protein: tuna [2], raw [3] and cooked beef [4], soy and lactoprotein [5] all stimulate the RFR in normal individuals. Bilo et al [3] compared the effect of 80 g protein in various forms (soy, lactoprotein and raw beef). Beef induced the largest rise in GFR (19%) while soy and lactoprotein stimulated similar but smaller rises of 13.6% and 10.9%, respectively. It is generally agreed that animal protein produces the largest rise in GFR.

Which amino acid?

Many workers using intravenous amino acids as stimulants of the RFR have utilized proprietary mixtures of amino acids, [3, 6–8]. More recently there has been considerable and renewed interest in looking at the response to smaller mixtures or single agents (it has been known since 1944 that glycine stimulates the GFR [9]). Premen [10] infused serine, alanine and proline into anaesthetized dogs. The mixture caused an acute rise in GFR. Both oral and intravenous arginine stimulate a rise in GFR when given alone; the oral stimulus seems more active than the intravenous infusion [11]. No single amino acid has been implicated as the sole stimulant to the RFR when administered intravenously although glycine seems particularly potent. Amino acids have also been infused in different ways: intravenously, intraportally, intrarenally and into the isolated perfused kidney in attempts to untangle the actual mechanism of the response.

Dose-response

The amount of protein administered alters the magnitude of the response. Rodríguez-Iturbe [12] showed that the RFR was present when only 43 g of cooked beef was given and that there was a dose-response relationship up to 107 g. It is not clear how high the response can be pushed. A partial dose response relationship has also been observed with amino acids [3].

The hemodynamic response

Following a maximal stimulation with a meat meal the mean GFR rises by as much as 66 to 95 ml/min (62 to 81%) [4, 12]. Most observers report smaller rises and mean values of 10 to 30% are more usual [13, 14]. In almost all studies the ERPF and RBF also rise [13], although this has not been a universal finding [6, 15]. In general, filtration fraction appears to be unaltered while renal vascular resistance falls [6, 13, 14, 16], indicating that renal vasodilatation is the main mechanism for the rise in ERPF and hence GFR [13].

In the dose-response study by Rodríguez-Iturbe, however, filtration fraction rose when high doses of protein were administered, implying that the rise in GFR is proportionately higher than the rise in RPF. This suggests that changes in RPF cannot completely account for the protein-induced rise in GFR. It may

be that there is also a change in intra-glomerular haemodynamics, since dextran sieving data suggests that ΔP, the transcapillary hydraulic pressure gradient, rises following a meal [15]. The response is associated with a natriuresis and possibly a kaliuresis, but the fractional clearance of these electrolytes is unchanged [13].

Another explanation for the response has been that the resting kidney has a population of "dormant nephrons" which normally contribute little or nothing to filtration. Under stress, these nephrons are called into play and the GFR and renal blood flow rise. Although this is an attractive hypothesis there is no evidence to support it and at present no way of gathering the evidence, particularly in humans.

The time course of the RFR

The change in renal hemodynamics is frequently seen within the first hour after a protein load, and the maximum response in GFR is generally seen about 2 to 2.5 hours following a meat meal [4, 14].

Mechanisms

Most work on the mechanism of the renal functional reserve indicates that the response is not directly due to the intrarenal effects of the stimulus. When amino acids are infused into anaesthetized dogs, intrarenal infusion has no effect while intraportal and intravenous infusion provoke the RFR [10]. These *in vivo* data are not entirely supported by work on the isolated perfused kidney, which suggests that the normal decay in glomerular filtration rate can be prevented and even reversed by a mixed amino acid solution [17], while single amino acids cause vasodilation without a change in the GFR, possibly by acting as direct metabolic substrates [18]. Nevertheless, Premen's work [10] suggests strongly that the *in vivo* physiological response is not due to direct stimulation of the renal vasculature by amino acids. It appears that metabolism or a secondary message is necessary before amino acids cause the RFR.

Glucagon and pancreatic hormones

Plasma glucagon concentrations rise after a meal, a fact confirmed rather belatedly by nephrologists [3, 19] (Fig. 1). In addition, pharmacological doses of glucagon induce a rise in GFR and ERPF. Consequently it is not surprising that glucagon has been intensively investigated as a mediator of the RFR. Pancreatectomized dogs and humans have no RFR [8, 20]. Similarly, somatostatin, which (among other things) blocks glucagon secretion, blocks the protein meal and amino acid-induced RFR in normals [7, 8, 19].

Castellino et al [7] have studied humans using a technique that others have referred to as the "pancreatic clamp", blocking endogenous hormone secretion with somatostatin and providing a combination of glucagon, insulin and growth hormone in a manner designed to mimic the changes seen following an amino acid infusion. They conclude that the RFR is dependent on a factor inhibited by somatostatin and restored by replacement of the combined hormone infusion.

The necessary hormone out of the three is glucagon. In a clearly thought out series of experiments, Premen used anaesthetized pancreatectomized dogs [20]. In these animals, amino acids alone provoked no RFR. Physiological doses of glucagon similarly provoked no RFR. Only when amino acids were

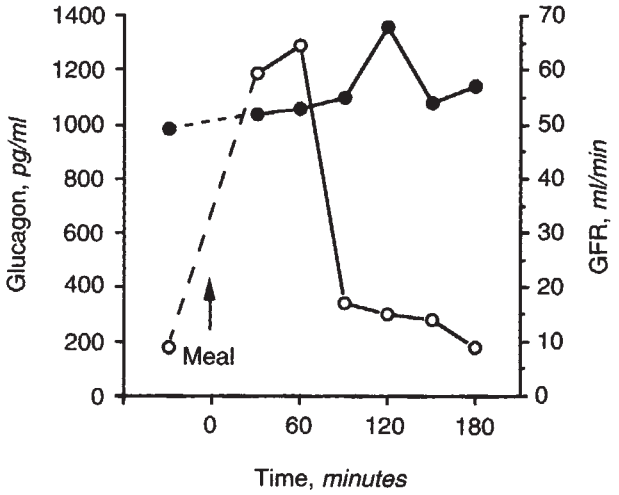

Fig. 1. *Changes in plasma glucagon (open circles) and glomerular filtration rate in children following a meat meal.* Redrawn from Brouhard et al 1987 [19].

Table 1. Possible mediators of the renal reserve (references in text)

Glucagon	+
Growth hormone	−
Insulin	−
Prostaglandins	+
Renin/angiotensin system	+/−
Kinins	?
Nitric oxide	probably
Dopamine	−
"Glomerulopressin"	hypothetical

infused together with physiological (post-prandial) doses of glucagon did GFR and RBF rise, although to lower levels than that induced by amino acids in control animals. The conclusion from these results is that glucagon is a necessary modulator of the RFR but is not the prime mediator. Friedlander et al, experimenting on humans with and without pancreatectomy [8], has also concluded that glucagon is essential for amino acid induced hyperfiltration. Unfortunately the replacement doses of glucagon administered following pancreatectomy or somatostatin are pharmacological rather than physiological, so it is difficult to come to any firm deduction from the data. They do show clearly, however, that intrarenal glucagon does not directly affect renal hemodynamics.

The necessity for glucagon has been challenged [21]. Dogs whose insulin and glucagon levels were "clamped" were subjected to a complex experimental protocol. When amino acids were infused together with low levels of glucagon equivalent to the unstimulated state, the animals could be shown to have a renal functional reserve. Glucagon alone in these doses did not provoke a renal functional reserve. Amino acids infused with a "post-prandial" level of glucagon provoked a greater RPF response than the lower dose but a similar GFR response. This study omitted a control group in which amino acids were infused in the absence of glucagon so these data are entirely consistent with a facilitative role for glucagon.

It is of interest that 30 g arginine orally provokes an apparent RFR with no rise in plasma glucagon [11] while i.v. arginine

provokes a rise in glucagon with no change in renal hemodynamics. It may be that the response to the individual amino acid is not the same as the RFR.

Growth hormone

Patients with growth hormone deficiency or a deficient hypothalamo-hypophyseal axis appear to have no renal reserve in a small scale preliminary study [22]. This has been contradicted in two studies [23, 24]. Rather unusually, however, the RFR in one study [23] was taken as the response following a seventeen hour amino acid infusion, so it is possible that the hemodynamic response measured was more analagous to prolonged high protein feeding rather than an acute RFR. In the other study arginine HCl alone was used as the stimulus, so again this may not reflect the usual RFR response. The fact that glucagon replacement alone restores the RFR in individuals on a somatostatin infusion suggests that growth hormone is not a mediator.

Prostaglandins

There is no change in the excretion of prostaglandin E_2 [25, 26] and 6-ketoPGF$_{1\alpha}$ when the RFR is elicited. Indomethacin may, however, attenuate or abolish the RFR in normal individuals [25–28]. This has led to the suggestion that the normal response is mediated in part by vasodilatory prostaglandins. Indomethacin had no effect on the post-prandial rise in glucagon in one study [27] but completely abolished the rise in another [29].

Renin/angiotensin system

The evidence for the a role of the renin/angiotensin system in the RFR is conflicting. Following the meat meal, neither angiotensin II activity [16] nor plasma renin activity (PRA) rise but there is a rise in plasma aldosterone [15, 25, 30]. In normals, pre-treatment with ACE-inhibitors is reported not to affect RFR [25] or to attenuate the response [31]. In disease states the effects are equally contradictory; augmentation of the response is reported in diabetes [32] but no change was seen in a group of patients with chronic renal impairment [33]. Under other circumstances the renal response to ACE inhibitors is dependent on a degree of sodium depletion in the subject [34] and it may be that the same is true of the RFR. Certainly subjects on a low sodium diet have little or no RFR [35], and in these conditions pre-treatment with captopril both reduces baseline hemodynamics and restores the RFR.

Kinins

Urinary kinin excretion increases and kallikrein falls following a casein meal in normal subjects [36]. This is not sufficient data to support more than a casual link so far, but there is evidence that the kallikrein-kinin system is vasodilatory in the isolated perfused kidney [37], and these compounds merit further investigation.

Nitric oxide

There is little published evidence implicating the ubiquitous vasodilator nitric oxide (NO) in the RFR response. It is becoming increasingly clear that the substance is an important mediator of renal vasodilatation. In animal models, inhibition of NO synthesis generally produces a fall in GFR, ERPF and ultrafiltration coefficient (K_f) while causing a rise in blood pressure, transcapillary hydraulic pressure (ΔP), efferent and afferent arteriolar resistance. It seems that nitric oxide acts in a number of areas as the final local mediator of many vasodilator substances. Perhaps it is not surprising therefore that in the isolated perfused kidney, L-nitro arginine methyl ester (L-NAME), which inhibits nitric oxide synthesis, inhibits the effects of amino acids on the inulin clearance [17], and that in rats L-NAME blunts glycine induced hyperfiltration [38]. It is tempting to implicate the nitric oxide precursor arginine in the amino acid response, but other unrelated amino acids produce hyperfiltration [9] and rather surprisingly, intravenous arginine (unlike oral arginine) produces no rise in GFR or ERPF [11]. Possibly the substance is involved as a vasodilatory mediator in the physiological RFR, but understanding this may only be to understand the beginning and end links in the chain.

Dopamine

Dopamine has been used as a stimulant of the RFR [39]. Although low dose dopamine has somewhat similar effects on renal hemodynamics as a meat meal or amino acid infusion, in that GFR and ERPF rise [40], there is little evidence to link it with the meat meal response. Indeed there is also a qualitative difference in the response since dopamine causes a relatively greater increase in ERPF than GFR and thus filtration fraction falls. It is generally assumed that urinary dopamine excretion rises following a meal but the evidence for this in humans is not so clear-cut. Urinary dopamine following a tuna meal was just higher than baseline in one study [2] but no difference in excretion rate has been found by others [25]. Somatostatin analogues block the amino acid stimulated rise in GFR but not the dopamine stimulated rise [23]. It would seem that the dopamine stimulated response is analagous but not identical to the meat meal/amino acid response.

Glomerulopressin

There have been suggestions that the meat meal response is mediated by a hormone synthesized in the liver [41]. There are really very little data to support this assertion.

The RFR in renal impairment

It was concluded by Bosch, Lower and Glabman [42] using a meat meal and by others using dopamine infusions [39, 43], that in chronic renal impairment the RFR was lost when the GFR fell to less than 50 to 70 ml/min. These findings have not been confirmed in a series of later studies in children [44] and adults [3, 15, 45, 46], and it therefore seems to be the case that the RFR is still present in chronic renal impairment. All these studies have defined the RFR using a high protein meal or amino acids.

Recent studies have not always found however that the response is the same as in normal controls. In children De Santo et al [44] have shown a significantly larger (in percentage terms) rise in GFR and ERPF following the meal. The children with disease were chronically ingesting less protein, however, and it may be that the protein load was effectively a larger stimulus for them. Other studies have shown no difference in relative terms (% rise in GFR from baseline) between controls and diseased individuals [45, 46] and did not appear to be correlated with percent sclerosis [45] or baseline GFR [46].

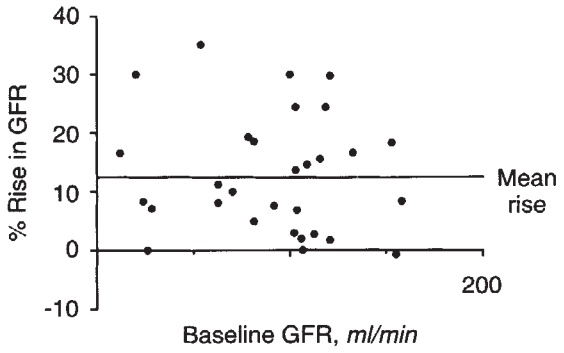

Fig. 2. *The renal reserve in patients with chronic renal disease.* Graph drawn from data in Bosch et al 1984 [42].

Increasingly it would appear that the response to acute protein loading is maintained down to low levels of GFR. It is interesting to replot the data presented in Bosch's 1984 paper (Fig. 2). It clearly shows that in percentage terms the RFR was also maintained in his patients even at low levels of GFR.

Dietary protein

Although a low protein diet reduces the "resting" GFR it does not appear to alter the relative RFR [47].

The RFR in specific conditions

There is limited evidence concerning the RFR in specific conditions. As with so many clinical studies, it has proven easier to assemble groups of subjects with similar levels of renal function and similar diagnoses than to compare groups with identical diagnoses. Nevertheless some data exist, particularly with regard to diabetes, IgA nephropathy and polycystic kidney disease.

In a group of polycystics with a very wide range of GFRs, amino acid infusion caused a rise in GFR, measured plasma clearance of inulin [48]. Surprisingly, in the same study no RFR could be elicited in subjects with "glomerular disease"—IgA nephropathy, type I diabetes and type II diabetes. It is difficult to know how to interpret these data. They conflict with much other information published elsewhere. In addition they do not use standard experimental technique and are therefore difficult to compare directly. It is interesting, however, that patients with IgA nephropathy and chronic renal impairment may not have the standard hemodynamic response to dopamine [39].

Diabetes

Measuring RFR in diabetics can be difficult since high glucose levels themselves stimulate hyperfiltration [49] and the two effects need to be dissociated. When blood sugar is not adequately controlled it appears that diabetic patients with nephropathy do not exhibit an RFR (**Note added in proof,** A). Similarly patients showing extreme hyperfiltration appear to have no RFR [50, 51]. Under normoglycaemic conditions, however, insulin-dependent diabetics without nephropathy or with microalbuminuria appear to have a renal functional reserve [52], although some authors find it somewhat attenuated [51]. There is a suggestion that this response is exaggerated by captopril in well controlled, non-hyperfiltering insulin dependent diabetics [32]. Non-insulin dependent diabetics without nephropathy have normal RFRs [**Note added in press,** B].

Individuals with single kidney

Following contralateral nephrectomy, the remaining kidney undergoes compensatory hypertrophy. This is a situation of particular interest since in rats the remnant kidney undergoes progressive glomerulosclerosis and eventually fails. It is this observation which lies at the heart of the hyperfiltration theory of progressive glomerular damage. Kidney donors have been reported to have a renal functional reserve which is present but attenuated [53] when creatinine clearance is used as the GFR marker. Another study shows an apparently normal RFR [54] but has no control group. The reserve still appears to be present when individuals with a single kidney have impaired function [55].

The significance of the RFR

The original hypothesis that the hyperfiltration response to a meat meal or amino acid infusion was evidence for the existence for a renal functional reserve had many implications. First, the resting kidney could adapt to (in the loosest term) stress. Secondly in disease states the reserve would be used before resting filtration capacity was diminished. Finally, in chronic renal impairment, the renal functional reserve would be lost.

From the evidence cited it is clear that only the first of these propositions is true. The normal human kidney is not working at full capacity and under certain conditions it adapts by hyperfiltering. The capability to adapt is generally not lost in disease states, however, although the absolute size of the response falls in proportion to the GFR. The concept of the spare capacity being a true reserve is therefore undoubtedly limited.

The only situations in which the reserve filtration capacity seems to be lost or attenuated are those in which the kidney is already maximally stimulated: hyperfiltrating diabetics and possibly live kidney donors. It is conceivable that in these groups prolonged hyperfiltration could indeed mediate renal damage. It may follow from this that if there are disease states in which hyperfiltration contributes to progressive renal damage, the loss of the RFR could be used as a marker of hyperfiltration. This is illustrated graphically in Figure 3.

If the response is not a reflection of a true reserve, then it becomes necessary to view it as an adaptive mechanism. Normal humans have a lower GFR when on a low protein or vegetarian diet than on a normal diet [4, 47]. Plasma creatinine is unchanged, however. The same seems to be true of patients with renal disease [56]. It seems possible that chronic changes in GFR reflect creatinine (or rather nitrogen) homeostasis and that the acute response to a meat meal is an acute form of the same process.

Studying protein-induced hyperfiltration is therefore a legitimate and interesting physiological exercise. To call this response a functional reserve is, however, something of a misnomer and the term should be abandoned.

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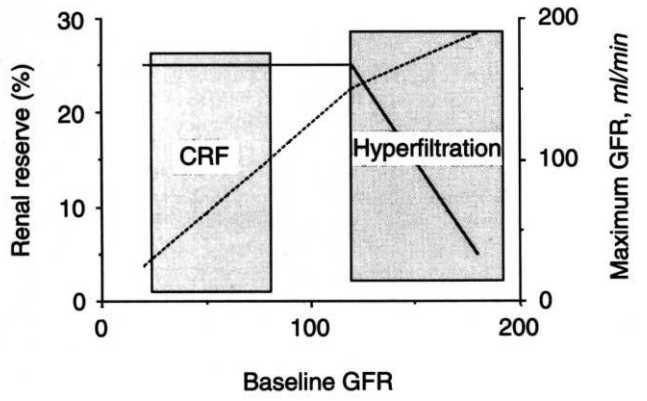

Fig. 3. *Diagrammatic representation of protein-induced hyperfiltration and its relationship to baseline GFR.* The solid line represents the maximum response in percentage terms, suggesting that the response is usually fixed but diminishes if hyperfiltration is present. The dashed line represents the maximum stimulated GFR in ml/min.

Note added in proof

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