

## Individual kidney function in renovascular disease

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### Introduction

This review assesses the importance of various methods of measurement of individual renal function in renovascular disease. It describes the important advance in understanding how individual kidney function is affected by atherosclerotic renovascular disease.<sup>[1–5]</sup> The approach to this problem used in our unit is also described.<sup>[6]</sup>

Renal disease is usually bilateral and affects both kidneys uniformly. This assumption forms the basis of the routine practice of renal biopsy where only one kidney is sampled. Patients will often ask when presented with the results of a renal biopsy if the other kidney is affected. In conditions which may be unilateral, such as reflux nephropathy or renovascular disease, asymmetry of renal function is a common diagnostic feature which differentiates them from other causes of renal disease.

Intervention in the majority of renal disease is aimed at treating the systemic features. For instance, in systemic lupus erythematosus (SLE), treatment is aimed at suppressing an immunological process, which would otherwise affect both kidneys as well as other organs. Control of blood pressure is the basis of management of all forms of kidney disease and the outcome of treatment is the result of its action on both kidneys. In interventions such as the use of angiotensin-converting enzyme inhibitors (ACEI) in diabetic nephropathy the presumption is that the effect will be on both kidneys.<sup>[7]</sup> The effect of an intervention in renovascular disease, however, in a large number of cases, will be asymmetrical. An intervention on one side may result in improving systemic features such as blood pressure or plasma creatinine as a surrogate for renal function. However, the presumption that this is due solely to the effect on the kidney undergoing intervention is flawed. For example, unilateral renal angioplasty could result in

renal artery occlusion and ablation of function in that kidney. This could, however, result in improving blood pressure control and thus an overall improvement in renal function; this would be regarded as a positive outcome. Interventions in unilateral renal disease also presume that the dominant functioning kidney can be identified reliably. The presumption is that a unilateral renal artery stenosis will lead to a decrease in renal function on the side affected. When there is the possibility of intervention it is important to understand what the effect will be on the treated kidney and what contribution this kidney makes to overall renal function.

### Methods for estimating individual kidney function

There are various methods for measuring unilateral renal function. Most tests will need to combine estimation of both overall renal function and individual kidney function.

The creatinine clearance is a good indicator of overall function but is prone to error in collection of the 24 h urine sample. Estimation of creatinine clearance using the Cockcroft and Gault formula<sup>[8]</sup> can provide a reasonable estimation of glomerular filtration rate (GFR) but is not as precise as the methods subsequently discussed.

#### *Glomerular filtration rate*

The 'gold standard' for measurement of overall renal function is inulin clearance or, in the clinical setting, the <sup>51</sup>Chromium ethylene-diamine-tetra-acetic acid (<sup>51</sup>Cr EDTA) plasma clearance method for GFR. Both of these, however, depend on the injection of a foreign substance and the measurement of its clearance. The

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$^{51}\text{Cr}$  EDTA GFR is more commonly performed than the inulin clearance which depends on an inulin assay not universally available. These two tests are regarded as the best measures of global renal function available.<sup>[8]</sup>

The relative function of each kidney can be measured in a number of ways. One method is to catheterize each ureter individually and measure output. Although this can be useful for the investigation and documentation of haematuria it requires some form of anaesthetic and is an invasive technique not practicable in routine clinical practice. Routine quantification of differential renal function depends on the adoption of nuclear medicine methodology.

### Single kidney glomerular filtration measurement by nuclear medicine methods

In practice the most convenient and reliable method of measuring individual renal function is a combination of two readily available nuclear medicine investigations:  $^{51}\text{Cr}$  EDTA GFR and Technetium dimercaptosuccinic acid ( $^{99\text{m}}\text{Tc}$  DMSA) scintigraphy which can be performed on a single visit. This so-called single kidney glomerular filtration rate (SKGFR) test can be readily performed by the vast majority of nuclear medicine departments.

#### $^{99\text{m}}\text{Tc}$ DMSA method

For calculation of divided function, 5 min anterior and posterior images are acquired 2 h after the intravenous injection of 80 MBq  $^{99\text{m}}\text{Tc}$  DMSA. Regions of interest are drawn around each kidney on both views together with representative background regions for subsequent subtraction. Background corrected, geometric means of total counts from each kidney are then compared to express the divided function ( $D$ ) of each kidney as a percentage of overall function where:

$$D = \left\{ \frac{\text{geometric mean of counts from kidney}}{\text{sum of geometric mean counts from both kidneys}} \right\} \times 100\%. \quad (1)$$

This method is used to measure divided function as it is possible to acquire a much higher number of counts from each kidney than is possible with the functional phase of dynamic renal imaging with either  $^{99\text{m}}\text{Tc}$ -diethylenetriamine penta-acetic acid (DTPA) or MAG3, thereby reducing the statistical error in this measurement. In addition, the acquisition of both anterior and posterior views allows more accurate assessment of divided function than is possible with single view dynamic imaging, especially when the kidneys lie at different depths from the surface.

### GFR method<sup>[9]</sup>

GFR is measured following intravenous injection of 3 MBq  $^{51}\text{Cr}$  EDTA as 10 ml of tracer solution. The injection is given just prior to  $^{99\text{m}}\text{Tc}$  DMSA. Ten millilitres of whole blood are taken from the opposite arm at 2, 3 and 4 h, the exact times being noted. Separated 3 ml plasma samples are counted with appropriate standards and background blanks in an automated gamma counter at least 72 h later (to allow for decay of  $^{99\text{m}}\text{Tc}$ ).

From the resultant biexponential plasma clearance curve the GFR is calculated from:

$$\text{GFR} = 0.87 VDk, \quad (2)$$

where  $VD$  = volume of distribution calculated from the intercept ( $I_0$ ) of the slow exponential

$$VD = 100/I_0 \quad (3)$$

and where  $k$  = clearance constant derived from the slow exponential curve half-life ( $t_{1/2}$ )

$$k = \ln 2/t_{1/2}. \quad (4)$$

Because this model underestimates the plasma integral, the GFR is overestimated and requires a correction by a factor of 0.87. GFR can be expressed in absolute units of  $\text{ml min}^{-1}$  but is often indexed to body surface area and expressed as  $\text{ml/min}/1.73 \text{ m}^2$ .

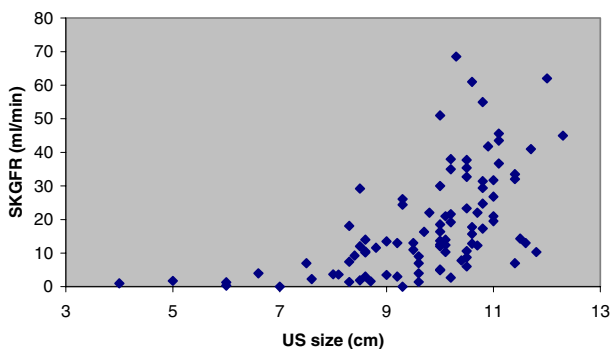
The precision error for SKGFR<sup>[4]</sup> is approximately 2–3  $\text{ml min}^{-1}$  and is independent of the GFR value. This therefore provides a robust, clinically applicable test for individual kidney function in patients with a range of absolute renal function. It displays obvious advantages over surrogate markers of individual function such as renal length measured by ultrasound or indeed simple measurements of overall renal function for the reasons discussed above. In patients with low GFRs it may be advisable to take late plasma samples (e.g. at 6 h) for  $^{51}\text{Cr}$  EDTA clearance in order to obtain a more accurate estimate of the slow exponential.

#### Individual kidney function and renal artery stenosis

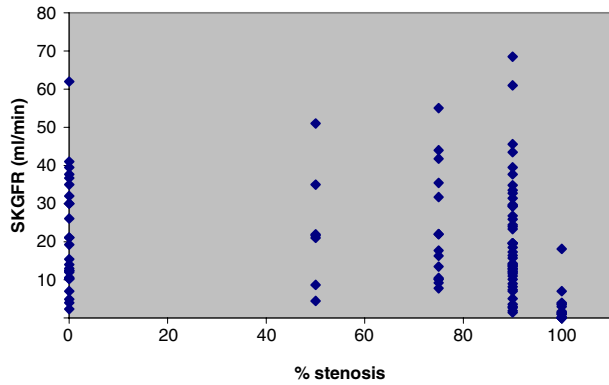
The presumption with the experimental data on renal function and renal artery stenosis is that any kidney with renal artery stenosis will potentially suffer renal damage. The original Goldblatt studies showed reversible renal parenchymal damage with renal artery clipping.<sup>[10]</sup> Subsequent studies have confirmed these findings but have also shown that the same improvement in renal function in the kidney with renal artery obstruction can be achieved by removing the normal contralateral kidney.<sup>[11,12]</sup> This suggests that the processes are complex. Few studies have tried to examine individual kidney function in patients with renal artery stenosis.

We demonstrated that in asymmetrical renal artery stenosis (ARAS) there was no correlation between renal size and renal function.<sup>[3]</sup> It is important to make clear that the results in this study were those from routine clinical assessment rather than from a formal trial. It is also important to point out that the early observation that revascularization in very small kidneys is not disputed.<sup>[13]</sup> Two important results stand out. First, in the important clinical range of kidneys with lengths of 9–11 cm renal function was not related to length and was very variable. Second, this applied to kidneys with renal artery stenosis, post-angioplasty and with ‘normal’ renal arteries in the presence of severe atherosclerotic disease. Figure 1 shows the values for all kidneys with atherosclerotic nephropathy independent of renal artery anatomy. It clearly delineates the wide spread of renal function in the 9–11 cm length group. We do not contend that kidneys of 5–7 cm have dysfunction but these are not of clinical importance. Figure 2 shows that the degree of renal artery stenosis short of occlusion does not determine the renal function in that kidney. Our data<sup>[4]</sup> show that in paired kidneys with unilateral renal artery stenosis the size of stenosis does not predict the renal function in that kidney. This is supported by the data in Fig. 3 where individual values for all the kidneys studied are shown. There is a significant difference in the SKGFR in kidneys with fibromuscular dysplasia (FMD) with or without stenosis compared with their unaffected pair. However, in ARAS there is little difference among the three groups.

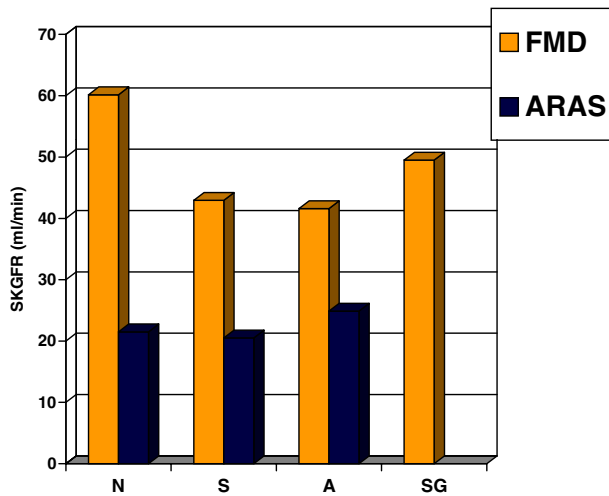
These studies suggest that, as previously reported, there is a complex process of renal damage in kidneys supplied by an atherosclerotic aorta with or without renal artery narrowing,<sup>[14]</sup> which we term atherosclerotic nephropathy.



**Figure 1** The plot of SKGFR for all forms of renal artery anatomy in patients with atherosclerotic renal disease. The ultrasound size is that recorded in routine clinical reporting. We have previously reported this in relation to normal, stenosed and angioplastied renal arteries.



**Figure 2** Degree of stenosis related to SKGFR. Stenosis was assessed on angiography.



**Figure 3** The SKGFR in kidneys of patients with atherosclerotic disease and those with non-atherosclerotic disease. The latter group is predominantly FMD but include patients with middle aortic syndrome. N = normal renal arteries (ARAS,  $n = 26$ ; FMD,  $n = 7$ ), S = stenosed renal arteries (ARAS;  $n = 30$ ; FMD,  $n = 7$ ), A = angioplastied renal arteries (ARAS,  $n = 52$ ; FMD,  $n = 10$ ), SG = surgically operated on renal arteries (FMD,  $n = 2$ ).

*Renal artery stenosis, intervention and renal function*

Since the original animal work by Goldblatt<sup>[10]</sup> hypertension and renal dysfunction have been linked to renal artery narrowing. The data on revascularization and hypertension in FMD are well established.<sup>[15]</sup> In this condition cure of the hypertension is a reasonable expectation. In atherosclerotic renal artery stenosis the relationship has become less clear with the publication of randomized studies.<sup>[16–18]</sup> These suggest that hypertension is not significantly altered by angioplasty. Renal dysfunction in fibromuscular disease is relatively rare except as a consequence of hypertensive renal damage. However, atherosclerotic renal artery stenosis is

now thought to be a major cause of renal dysfunction in the elderly population.<sup>[19]</sup> The relationship between intervention and improvement in renal dysfunction has been less clear. Many authors have used the reciprocal plot of plasma creatinine before and after intervention to ascertain the effect of intervention. Probably the best early study is that of Harden *et al.*<sup>[20]</sup> who showed in a group of patients with severe renal dysfunction and predominantly bilateral disease that there was an improvement in the rate of change of renal function. This has recently been confirmed by Watson *et al.*<sup>[21]</sup> in patients with 'global renovascular disease' where intervention improved the rate of change in renal function. Radermacher *et al.*<sup>[22]</sup> sought to use the resistive index of the contralateral kidney to predict the outcome of intervention. These studies are very impressive but include many patients with excellent renal function at no risk of renal failure. However, in all of these studies there was no randomization and unilateral intervention was interpreted by the effect on overall renal function. At the present time a number of randomized trials are underway and their results are awaited.

There have been a few investigations of individual kidney function and intervention in renovascular disease. Those from our group will be discussed separately; there are two other reports. The first was Jensen *et al.*<sup>[1]</sup> who reported in 1995 the results of Cr-EDTA GFR and I-Hippuran scanning. This group of patients were those predominantly having renal angioplasty for hypertension and included both FMD and ARAS. The improvement in renal function was made with the revascularized kidney. However, they noted that the change in blood pressure control was worse in patients with renal insufficiency. From the data presented it would also appear that only 13 of the kidneys with ARAS had GFRs less than 30 ml min<sup>-1</sup> and of these only five seemed to see an improvement in renal function. In keeping with the published data the best improvements in hypertension control and GFR were in those kidneys with FMD.

A second group has recently reported similar findings. La Batide-Alanore *et al.*<sup>[5]</sup> have used either synchronous inulin clearance or <sup>51</sup>Cr EDTA clearance and <sup>99m</sup>Tc-DTPA scintigraphy. Thirty patients were reported, 18 with ARAS and 14 with FMD. Intervention was performed in all patients and improvement was noted in SKGFR in 29 patients. However, the corrected average clearance was 72 ml/min/1.73 m<sup>2</sup> for those with ARAS and 95 ml/min/1.73 m<sup>2</sup> for those with FMD. These studies suggest that in relatively good renal function improvement can be demonstrated in individual kidney function.

We reported a group of patients with the vast majority of renal function in a single kidney, who post-angioplasty saw a deterioration in function.<sup>[23]</sup> Re-stenosis was suspected but not found at angiography and progressive decline in renal function occurred in the absence of

renal artery obstruction. It is important to note that these patients had modest proteinuria indicating underlying renal parenchymal damage, which we term atherosclerotic nephropathy.<sup>[24]</sup> We have reported on a group of older patients with severely impaired renal function who did not as a group benefit from angioplasty.<sup>[2]</sup> Within this group, however, there are a number of kidneys that appeared to improve in function. In fact, the pattern of decline and improvement is very similar to the data presented by Harden *et al.*<sup>[20]</sup> where the average improvement in the rate of change of renal function masked a number of patients with stable or worsening renal function. These results at first sight would appear different from the Swedish group.<sup>[25]</sup> However, none of the patients in our series underwent angioplasty for the treatment of hypertension but rather in an attempt to improve renal dysfunction. The group with similar characteristics in the Swedish study also showed a similar lack of improvement in renal dysfunction. It must also be stressed that renal failure and the requirement for dialysis treatment is unlikely in a patient with two kidneys each of which have 50 ml min<sup>-1</sup> of GFR. Those most at risk of developing renal dysfunction have been shown by Baboolal *et al.*<sup>[26]</sup> to be those with significantly impaired renal function at presentation. In this group of patients the role of intervention is unclear but potentially very beneficial.

### Other uses of individual kidney function estimation

At present these techniques have not been widely applied to renal disease. The measurement of divided function has been used in the assessment of patients with hypertension and small scarred kidneys. We have more recently used the technique in nephron-sparing surgery in Von Hippel Lindau Syndrome. It is possible that in future these techniques will be more widely applied.

### Conclusion

The use of tests of individual kidney function has helped delineate the importance of the cause of renal artery narrowing in progressive renal dysfunction. It has shown that in ARAS there are many factors independent of renal artery narrowing. This may prove important in the understanding of the pathophysiology of ARAS. It has also provided a method of assessment of renal function allied to intervention. We believe that these methods will become widely used in the assessment of renovascular disease.

### References

- [1] Jensen, G, Zachrisson, BF, Delin, K, Volkmann, R, Aurell, M. Treatment of renovascular hypertension: one year results of renal

- angioplasty. *Kidney Int* 1995; 48: 1936–45.
- [2] Farmer, CKT, Reidy, J, Kalra, PA, Cook, GJR, Scoble, J. Individual kidney function before and after renal angioplasty. *Lancet* 1998; 352: 288–9.
- [3] Scoble, JE, Mikhail, A, Reidy, J, Cook, GJR. Individual kidney function in atherosclerotic renal-artery disease. *Nephrol, Dial Transplant* 1998; 13: 1048–9.
- [4] Farmer, CKT, Cook, GJR, Blake, GM, Reidy, J, Scoble, JE. Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis. *Nephrol, Dial Transplant* 1999; 14: 2880–4.
- [5] La Batide-Alanore, A, Azizi, M, Froissart, M, Raynaud, A, Plouin, PF. Split renal function outcome after renal angioplasty in patients with unilateral renal artery stenosis. *J Am Soc Nephrol* 12; 1235–41.
- [6] Scoble, JE, Cook, GJR. Individual kidney function in atherosclerotic nephropathy. *Nephrol, Dial Transplant* 1998; 13: 842–4.
- [7] Lewis, EJ, Hunsicker, LG, Bain, RP, Rohde, RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329: 1456–62.
- [8] Cameron, JS, Greger, R. Renal function and testing of function. *Oxford Textbook of Clinical Nephrology*, Vol.1 (Eds A M Davison, J S Cameron, J P Grunfeld, D NS Kerr, E Ritz and C G Winerals). Oxford, Oxford University Press, 1998: 39–69.
- [9] Blake, GM, Roe, D, Lazarus, CR. Long-term precision of glomerular filtration rate measurements using 51-Cr EDTA plasma clearance. *Nucl Med Commun* 1997; 18: 776–84.
- [10] Goldblatt, H, Lynch, J, Hanzal, RF, Summerville, WW. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934; 59: 347–78.
- [11] Grone, HJ, Warnecke, E, Olbricht, CJ. Characteristics of renal tubular atrophy in experimental renovascular hypertension: a model of kidney hibernation. *Nephron* 1996; 72: 243–52.
- [12] Gobe, GC, Buttyan, KRL, Ethridge, MR, Smith, PJ. Clusterin expression and apoptosis in tissue remodelling associated with renal regeneration. *Kidney Int* 1995; 47: 411–20.
- [13] Lawrie, GM, Morris, GC, Glaeser, DH, de Bakey, ME. Renovascular reconstruction: factors affecting long term prognosis in 919 patients followed up to 31 years. *Am J Cardiol* 1989; 63: 1085–92.
- [14] Scoble, JE. Atherosclerotic nephropathy. *Kidney Int* 1999; 56: S106–9.
- [15] Ramsay, LE, Waller, PC. Blood pressure response to percutaneous transluminal angioplasty for renovascular hypertension: an overview of published series. *Br Med J* 1990; 300: 569–72.
- [16] Plouin, PF, Chatellier, G, Darne, B, Raynaud, A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis. *Hypertension* 1998; 31: 823–9.
- [17] Webster, J, Marshall, F, Abdalla, M *et al.* Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with renal artery stenosis. *J Hum Hypertens* 1998; 12: 329–35.
- [18] Van Jaarsveld, B, Krijnen, P, Bartelink, A *et al.* The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study: rationale, design and inclusion data. *J Hypertens* 1998; 16: S21–7.
- [19] Scoble, JE, Hamilton, G. Atherosclerotic renovascular disease. *Br Med J* 1990; 300: 1670–1.
- [20] Harden, PN, MacLeod, MJ, Rodger, RSC *et al.* Effect of renal-artery stenting on progression of renovascular renal failure. *Lancet* 1997; 349: 1133–6.
- [21] Watson, PS, Hadjipetrou, P, Cox, SV, Piemonte, TC, Eisenhauer, AC. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. *Circulation* 2000; 102: 1671–7.
- [22] Radermacher, J, Chavan, A, Bleck, J *et al.* Use of Doppler ultrasonography to predict the outcome of therapy for renal artery stenosis. *N Engl J Med* 2001; 344: 410–7.
- [23] Mikhail, A, Cook, GJR, Reidy, J, Scoble, JE. Progressive renal dysfunction despite successful renal artery angioplasty in a single kidney. *Lancet* 1997; 349: 926.
- [24] Makanjuola, AD, Scoble, JE. Ischemic nephropathy—is the diagnosis excluded by heavy proteinuria? *Nephrol Dial Transplant* 1999; 14: 2795–7.
- [25] Jensen, G, Aureil, M. Individual kidney function before and after angioplasty. *Lancet* 1998; 352: 1150–1.
- [26] Baboolal, K, Evans, C, Moore, RH. Incidence of end-stage renal disease in medically treated patients with severe bilateral atherosclerotic renovascular disease. *Am J Kidney Dis* 1998; 31: 971–7.