Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis

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Abstract

**Background.** Atherosclerotic renovascular disease is increasingly recognized as an important cause of renal failure in patients over 60 years of age but the processes leading to renal dysfunction have not been defined. We have examined the relationship between renal artery stenosis and individual renal function in patients with atherosclerotic renal artery stenosis.

**Methods.** In this prospective descriptive study over a 25-month period, we examined the relationship between the presence of renal artery stenosis and single kidney glomerular filtration rate (SKGFR). SKGFR was measured using a novel method of synchronous 51-Chromium ethylenediamine tetraacetic acid glomerular filtration rate (51CrEDTA-GFR) and 99mTechnetium dimercaptosuccinic acid (99mTcDMSA) scintigraphy. We studied 79 patients with a mean age of 68.9 years (25.2–88.2), 44 males and 35 females. The mean age of the males was 70 years (60–80) and females 67 years (25.2–88.2).

**Results.** We found that the precision of the SKGFR was 2 ml/min. For paired kidneys we found: (i) no significant difference between kidneys with stenosis (17.3 ml/min) compared to those without stenosis (13.6 ml/min) ($P=0.22$); (ii) kidneys with occluded renal arteries had significantly less function (2.6 ml/min) than those without occlusion (24.5 ml/min) ($P<0.05$). When degree of renal arteries stenosis was correlated with SKGFR there was a reduction with an increasing degree of stenosis (<30% 27 ml/min, 30–60% 17.7 ml/min, >60% stenosis 15 ml/min, $P=0.016$).

**Conclusions.** These data demonstrate that SKGFR provides a reproducible measure of individual kidney function. There was a similar impairment of function in paired kidneys with and without renal artery stenosis, but occlusion was associated with significant reduction in function compared to the contralateral kidney. This suggests that there is a process causing renal dysfunction in patients with atherosclerotic disease independent of renal artery narrowing.

Key words: radioisotope scintigraphy; renovascular disease; single kidney glomerular filtration rate

Introduction

Atherosclerotic renovascular disease has become increasingly recognized as an important cause of renal failure in the elderly population [1,2]. Revascularization of patients with severe renal dysfunction and renal artery stenosis has resulted in improvement in renal function [3]. Jacobson [4] suggested that the term ‘ischaemic nephropathy’ should be applied to patients with renal dysfunction due to renal artery stenosis. However, in atherosclerotic renal artery stenosis Toto [5] and Textor [6] have observed that the natural history and the processes leading to renal dysfunction have not been defined. We set out to examine the relationship of renal artery stenosis and individual kidney function in patients with atherosclerotic renal artery stenosis. Strategies to improve renal function in these patients with atherosclerotic renovascular disease must start with an understanding of the relevance of the renal artery narrowing to the renal dysfunction. We have used a novel combination of two nuclear medicine techniques to provide a measure of individual renal function in these patients SKGFR [7]. This is the first investigation to examine the relationship between individual kidney function, rather than overall renal function, in patients with arteries affected by atherosclerotic disease.

Patients and methods

We prospectively studied 79 patients with renovascular disease in the Guy’s and St Thomas’ renal unit over a 25-month period. The mean age was 68.9 years (25.2–88.2), 44 males and 35 females. The mean age of the males was 70 years (60.5–80.1) and females 67 years (25.2–88.2). The patients were recruited from nephrology clinics and underwent renal angiography due to the clinical suspicion of renal artery stenosis. The vast majority of these patients as shown in Figure 1 suffered from atherosclerotic renal artery stenosis but patients with fibromuscular hyperplasia are included in...
Fig. 1. Scatter plot of single kidney GFR against degree of stenosis in atherosclerotic renal artery stenosis. (solid lines represent mean for each sample).

Fig. 2. Precision of individual GFR on repeated measurements in normal kidneys.

Figures 1 and 2. The results are expressed as individual kidneys and not the total number of patients. The unit has a policy of not treating patients with renovascular disease with ACEI or ARB blockers and thus the results are in the absence of either agent. All patients underwent intra-arterial digital subtraction angiography.

Renal angiography

Renal angiography was performed using digital subtraction image intensification with selective views taken of each renal artery. All patients had oblique views of their renal arteries in order to accurately assess both the presence and degree of stenosis in the renal arteries. The degree of stenosis was graded with renal arteries placed into one of five categories: normal, no evidence of renal artery stenosis; mild, 0–30% stenosis; moderate, 30–60% stenosis; severe, >60% stenosis; and occluded, no evidence of patent renal artery. The relative distribution of the various levels of renal artery stenosis are shown in Figure 1. There were two further categories of angiographic findings: post angioplasty and fibromuscular dysplasia. It is important to note that all patients with 'normal renal arteries' had atherosclerotic or fibromuscular renal artery stenosis on the contralateral side and thus the term 'normal' only applies to the renal artery architecture.

Single kidney glomerular filtration rate (SKGFR)

A number of investigators had used methods to determine individual kidney GFR. Jensen et al. [8] used two nuclear medicine investigations to determine individual kidney function but did these at different times. We sought to use a combination of nuclear medicine tests which would individually be accurate and well-validated [9,10], but could also be performed in a single sitting to enable the test to be applicable widely. Thus, the combination of two readily available tests, $^{51}$Chromium ethylenediamine tetraacetic acid GFR ($^{51}$CrEDTA-GFR) and $^{99m}$Technetium dimercaptosuccinic
Acid (\(^{99m}\)TcDMSA) scintigraphy were used to provide an accurate assessment of SKGFR by combining both investigations on a single visit. This investigation can therefore be made available to physicians by most nuclear medicine departments. We have previously reported preliminary observations with its use [7,11].

Divided function is calculated from 5 min, anterior and posterior images acquired 2 h after intravenous injection of 80 MBq \(^{99m}\)TcDMSA. Regions of interest are drawn around each kidney on both views with background regions below the renal region. Background geometric means were compared to express the divided function (D) of each kidney as a percentage of overall function where:

\[
D = \left( \text{geometric mean of counts from kidney/sum of geometric mean counts from both kidneys} \right) \times 100\%.
\]

GFR is measured following the administration of 3 MBq \(^{51}\)CrEDTA diluted to 10 ml in 0.1% w/v excess EDTA solution. Injections are administered just prior to \(^{99m}\)TcDMSA. Venous blood samples (10 ml) are taken from the opposite arm 2, 3 and 4 h after injection. Samples are centrifuged and 3-ml aliquots taken and counted at least 72 h later. The delay in counting was to allow decay of the \(^{99m}\)Tc which has a half-life of 6 h compared to a half-life of 27 days for \(^{51}\)Cr. Counts are measured with standards and background blanks in an automated gamma counter. GFR was calculated from the slow exponential of the bi-exponential plasma clearance curve and multiplied by a correction factor of 0.87 because of underestimation of the plasma integral by this method. The formula for calculation of the GFR was as follows:

\[
\text{GFR} = 0.87 \times Vd \times k
\]

\(Vd\) = volume of distribution = 100/l; \(L\) = intercept of the slow exponential; \(K\) = slope of the slow exponential = \(\ln 2/t\); \(t1/2\) = half life of the slow exponential.

The SKGFR was calculated from the divided function of that kidney multiplied by the overall body surface area corrected GFR. Divided function was acquired using static scintigraphy (\(^{99m}\)TcDMSA) 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 \(^{99m}\)TcDTPA or Mercaptoacetyltriglycine (MAG3) thereby reducing statistical error in this measurement. In addition, acquisition of both anterior and posterior views allows more accurate assessment of divided function than is possible with single view dynamic imaging when the kidneys lie at different depths from the surface.

**Statistical analysis**

Descriptive demographics are expressed as means, standard deviation and range; comparisons between groups were calculated using the \(t\)-test. Precision was calculated as the standard deviation of the two measurements expressed as the coefficient of variation, \(CV = SD \times GFR/GFR \times 100\%\).

**Results**

The SKGFR combines two tests which are widely accepted as being both reproducible and accurate [9,10]. This investigation was well tolerated by the patients under investigation. The precision of the investigation was 2 ml/min (Figure 2). It is important to note that the precision is independent of renal function. The fact that some kidneys with normal renal arteries had significant reductions in renal function illustrates the issues raised by Figure 3 that the absence of renal artery stenosis in atherosclerotic patients does not mean an absence in decrement in renal function.

Figure 3 demonstrates the relationship between the presence of stenosis and SKGFR. The mean SKGFR of the kidneys with a stenosed renal artery was 17.32 ml/min compared to the kidneys without renal artery stenosis, ‘normal’ renal arteries, of 13.6 ml/min and this was not statistically significant (\(P = 0.22\)). The presence of an occluded renal artery was associated with severe renal dysfunction, mean SKGFR 2.6 ml/min when compared to the SKGFR of 24.5 ml/min of the contralateral kidney without occlusion.

Figure 1 demonstrates the correlation between SKGFR and degree of stenosis in a larger number of patients including those with bilateral renal artery stenosis. There was a reduction in GFR with increasing degree of stenosis (\(< 30\%\) 27 ml/min, \(30–60\%\)

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**Figure 3.** Individual kidney GFR against presence of stenosis in atherosclerotic nephropathy.
Individual kidney function in atherosclerotic nephropathy

17.7 ml/min, > 60% stenosis 15 ml/min, \( P = 0.016 \). These patients include those reported previously in a different analysis [7,11]. For comparison the SKGFR post angioplasty in both atherosclerotic renal artery stenosis and fibromuscular dysplasia are shown.

There is a theoretical possibility that renal function may be affected by angiography with contrast nephropathy or atheroembolic disease. This obviously cannot apply to the paired kidney data in Figure 3 where each kidney would undergo the same insult. We have previously reported that there is little positive or negative effect of angioplasty on individual kidney function as performed at our institution [11].

**Conclusion**

The data in this paper present a number of important findings in atherosclerotic nephropathy. The first is that the test of SKGFR can be applied to patients with atherosclerotic disease as a useful measure of divided renal function which is repeatable, well tolerated and precision is independent of level of renal function. The second is that renal function may be impaired in kidneys with atherosclerotic disease even in the presence of an anatomically normal renal artery. Atherosclerotic renal artery stenosis is invariably associated with aortic wall atheroma proximal to the origin of both renal arteries.

An initial hypothesis would be that in patients with atherosclerotic renal artery stenosis the individual kidney function would be equal between the two kidneys until the degree of stenosis was sufficient to cause a decrement in renal function. This hypothesis would also suggest that if reduced renal perfusion was the important event then renal function would be preserved in the kidney with a normal renal artery. Thus, one would expect to see findings where the function in the stenotic kidney was either equal to, or lower than, the kidney without stenosis. Figure 3 demonstrates that in paired kidneys the presence of renal artery stenosis has no effect on the individual renal function. In fact the data show that it is just as likely that there is better renal function in the stenotic kidney than the kidney with normal renal artery. The overall data show a slightly higher renal function in the kidney with renal artery stenosis suggesting the intriguing possibility of a protective effect from processes such as atheroembolic disease of the stenosis! However, the degree of stenosis is important in determining divided renal function when the most severe degree of renovascular disease occurs; occlusion. The importance of the paired kidneys is that the other risk factors, such as genotype, hypertension, lipid levels and smoking, will be identical in both kidneys. This demonstrates that there are two processes occurring in a kidney with atherosclerotic renal artery stenosis. One is related to renal artery narrowing, ischaemic nephropathy, and one is unrelated to renal artery narrowing. The different expressions of these two processes explain the variable result from restoration of renal artery diameter with revascularization or angioplasty [6,11–13]. These reports have suggested that improvement in overall renal function will not occur in all patients after renal angioplasty in one series [12] and in the minority of patients in another [6]. We have shown that in the short-term measurement of SKGFR improvement is as likely to occur in those kidneys without intervention as in those with angioplasty [11]. We have also shown that in some patients with initially successful angioplasty, progressive renal dysfunction occurs in the absence of re-stenosis [13]. These data suggest that processes in these patients, other than reduced renal blood flow due to renal artery narrowing, cause renal parenchymal damage. If the kidney undergoing revascularization has already been damaged by these processes then a response to angioplasty or surgery may not occur. However, Figure 3 also demonstrates that occlusion is associated with severe impairment renal function compared to the contralateral kidney which is not the case in renal artery stenosis. Thus, if renal artery stenosis progresses to occlusion then renal dysfunction due to ischaemia will predominate and prevention of this will be a useful therapeutic procedure.

The data in Figure 1 shows a correlation between the degree of stenosis and SKGFR. These data are more difficult to interpret than the data in Figure 3 as these include individuals who have bilateral disease. In this group the kidneys with stenosis do not all have paired kidneys with normal renal arteries. The correlation with the degree of stenosis seen could suggest that ischaemia is playing a role in the renal dysfunction. This is supported by the observation in Figure 3 that the most severe degree of renal artery narrowing is associated with poorer function in paired kidneys. However, it may also be that the more severe stenoses are in those patients with the most long-standing disease. It is well-described that the renal artery narrowing in atherosclerotic disease is a progressive process [14,15]. These kidneys with high-grade stenosis and thus long-standing disease may have greater non-stenosis related renal damage due to the duration of their disease as seen in those kidneys without stenosis in Figure 3. It is also clear from Figure 1 that there is a wide range of renal function with each degree of renal artery narrowing. It is widely accepted that the definition of the degree of renal artery stenosis on angiography may be difficult as the stenosis may in fact be asymmetrical within the lumen of the renal artery as shown by intravascular ultrasound [16]. However, both Figures 1 and 3 demonstrate that the most severe form of renal artery stenosis, that is occlusion, is associated with worse function in both analyses. The small number of kidneys examined with fibromuscular dysplasia show relatively good function post angioplasty when compared with those with atherosclerotic disease post angioplasty. However, the fibromuscular dysplasia patients were younger than those with angioplasty and so other factors have to be taken into account when making a comparison.

The processes which may play a part in the renal damage in these kidneys could include hypertension
and atheroemboli. We do not have biopsy data on the kidneys with renal dysfunction without stenosis. It is also possible that other downstream effects of the atheromatous aorta including cytokine and cholesterol crystal release may be important. The atherosclerotic plaque is a potent source of both [17]. Future efforts will be needed to identify and produce therapeutic regimes for the processes causing renal dysfunction in patients with atherosclerotic aortic disease independent of renal artery narrowing. There is one report that suggests that lipid lowering may improve renal function in atheroembolic disease [18] and this may prove an important area for investigation. The data showing poor function in kidneys with occluded renal arteries do support the use of angioplasty in high-grade stenoses as the rate of progression to occlusion is related to the degree of stenosis [19]. However the management of the parenchymal disease associated with severe aortic disease still remains an important therapeutic question.

References


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