

Article

Sequential determination of individual renal function in atherosclerotic renal artery stenosis

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Abstract

Background: Atherosclerotic renovascular disease has been increasingly recognised as a common cause of end-stage renal failure in elderly people. The optimum management of this condition is unclear. The aim of this study was the prospective evaluation of the long-term renal outcome in kidneys with atherosclerotic nephropathy.

Methods: We have performed sequential individual GFR (glomerular filtration rate) measurements in 115 kidneys where it or its contralateral kidney had angiographically proven atherosclerotic renal artery stenosis over a mean period of 19.37 ± 15.1 months (range 2–66 months). The individual renal function was measured by a synchronous combination of ⁵¹chromium ethylene-diamine-tetra-acetic acid GFR (⁵¹CrEDTA GFR) and technetium dimercaptosuccinic acid (^{99m}Tc DMSA) scintigraphy, the so-called single kidney (SK) GFR test. According to the angiography findings, individual kidneys were divided into four groups: normal, stenosis, occlusion and those treated with balloon angioplasty with or without stent employment.

Results: We have calculated the annualised rate of SKGFR change in the four groups of kidney (2.89 ± 8.93 ml/min/year in the normal group, -0.19 ± 4.99 ml/min/year in the stenosis group, 0.66 ± 3.21 ml/min/year in the occlusion group and -1.81 ± 14 ml/min/year in the group of kidneys undergoing percutaneous revascularisation) and no statistically significant difference was found ($p > 0.05$). For paired kidneys with at least one undergoing balloon angioplasty, the percentage of change between the SKGFR measured before and after revascularisation did not differ between the kidneys revascularised and the contralateral ones ($p > 0.05$).

Conclusions: Our data showed no significant difference in long-term renal outcome in kidneys with and without renal artery narrowing and in the ones undergoing percutaneous revascularisation. The data also show a relatively slow decline in function in kidneys with untreated renal artery stenosis when followed in a specialist clinic. This suggests that other pathological mechanisms as well as renal artery narrowing can injure the renal parenchyma in atherosclerotic renal artery stenosis.

Keywords: Atherosclerotic renal artery stenosis; renal outcome; single kidney glomerular filtration rate.

Introduction

Atherosclerotic renovascular disease (ARVD) is becoming a relatively common condition especially among elderly people^[1]. It can cause systemic hypertension, kidney function impairment, flash pulmonary oedema or

can be silent and therefore diagnosed only in patients undergoing angiography for peripheral vascular^[2] or coronary artery disease^[3].

The relationship between renal function and atherosclerotic renal artery stenosis (ARAS) is quite complex and not yet well understood. In contrast to fibromuscular

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dysplasia (FMD) where a correlation of renal function with renal artery narrowing has been shown and percutaneous transluminal renal angioplasty (PTRA) is the treatment of choice because of the high percentage of success^[4–7], in ARAS the natural history of renal function in respect of the degree of the stenosis can vary largely^[8,9] and the indications for PTRA are still a matter of debate. The same probability of improvement, stabilisation or worsening in renal function has been observed after successful percutaneous revascularisation of atherosclerotic renal artery stenosis^[10–12] but these studies have had no control group.

The few randomised trials that have compared percutaneous revascularisation with conservative treatment were intended to examine the effect on blood pressure control and overall renal function was good^[13–15]. However, the degree of narrowing of the renal artery, as well as the associated atherosclerotic nephropathy, can be asymmetrical on the two kidneys and the reduced function of one side can be hidden by the compensatory GFR increase of the contralateral one. Consequently, the use of overall renal function measurement can conceal the difference in function of the two kidneys and might fail to show any significant change in renal function.

Our investigation was designed to evaluate the long-term trend of the individual renal function in patients with ARAS treated with PTRA or with medical therapy alone. For this purpose, we carried out a prospective study in which patients with bilateral or unilateral ARAS were investigated with sequential SKGFR measurements in order to unmask any significant difference of the individual function in kidneys with different renal artery condition (normal, stenosis, occlusion, PTRA). The patients were not randomised and were managed by what was considered best medical practice of the unit. This is the first report with a relatively long follow-up period that examined individual renal outcome also in the sample of kidneys in which the renal artery stenosis did not undergo percutaneous revascularisation. Following this study all such patients have been entered into ASTRAL (Angioplasty or Stent for Renal Arterial Lesions). This is a randomised trial that aims to recruit 1000 patients with ARAS in order to elucidate the role of revascularisation treatment in ARAS in different groups of patients^[16].

Patients and methods

We prospectively followed-up a population of 57 patients (40 males, 17 females) with renovascular disease referred to the Guy's and St Thomas' Renal Unit for a period of 19.37 ± 15.1 months (range 2–66 months). All patients underwent renal angiography and we included only patients in which atherosclerosis was the cause of renal artery narrowing. The mean age was 68 years (44–97); the mean age of the males was 67.7 years (44–97) and females 68.5 years (52–88) (Table 1). Thirty-five of the 57 patients had bilateral ARAS and diabetes was present

in 23.5% of patients. Fifty-three percent of patients were on a lipid-lowering medication (statin) and 24% on ACE-inhibitors/angiotensin-II-antagonists. The unit has a policy of not using ACE-inhibitors or angiotensin-II-antagonists in patients with renovascular disease and the main reasons that a part of the population was on these agents were uncontrolled hypertension with other classes of antihypertensive drugs or severe congestive heart disease. Note that the results refer to the overall number of individual kidneys and not patients.

Renal angiography

All patients underwent intra-arterial angiography using digital subtraction image intensification; selective views were taken of each renal artery, especially oblique views in order to have an accurate assessment of the presence and of the degree of stenosis in the renal arteries. The patients were divided into four groups in respect to the angiography findings, as follows:

1. *Normal*: kidney with no stenosis but the side had renal artery narrowing of any degree.
2. *Stenosis*: kidneys with ARAS of 50% or greater of the luminal diameter.
3. *Occlusion*: kidneys with no evidence of patent renal artery.
4. *Angioplasty with or without stent*: kidneys treated by endovascular revascularisation using balloon angioplasty with or without stent implantation.

The unit policy is to not perform stent placement if arteriography after angioplasty shows a good technical result.

Single kidney glomerular filtration rate (SKGFR)

In order to evaluate the glomerular filtration rate of each kidney, we performed a synchronous combination of two universally used nuclear medicine investigations, ⁵¹chromium ethylene-diamine-tetra-acetic acid glomerular filtration rate (⁵¹CrEDTA GFR) for estimation of overall renal function and technetium dimercaptosuccinic acid (^{99m}Tc DMSA) scintigraphy scan for estimation of differential function, as described by Scoble *et al.*^[17]. Previous investigations have used this combination of nuclear medicine test for the assessment of SKGFR in patients with renal artery stenosis and, in particular, Farmer *et al.* showed that it is a useful and repeatable tool, whose precision is not affected by the level of renal function^[9].

Table 1 Baseline characteristics of the patients with ARAS (means \pm SD). Overall single kidney: 115

Characteristics	
Age, year (range)	68 \pm 9.2 (44–97) M = 67.7 \pm 9.2 (44–97) F = 68.5 \pm 9.5 (52–88)
Gender, M/F (%)	70.4/29.6
DM (%)	23.5
Bilateral RAS (%)	61.4
ACE-i/AII antagonist (%)	24.3
Statin (%)	53
Antiplatelet therapy (%)	67.8
Follow-up, month (range)	Overall: 19.4 \pm 15.1 (2–66) Normal: 16.4 \pm 11.7 (2–50) Stenotic: 19.9 \pm 16.4 (4–51) Occlusion: 21 \pm 13.8 (7–48) PTRA: 19.8 \pm 16.6 (2–66)

DM = Diabetes mellitus; RAS = renal artery stenosis.

Statistical analysis

Descriptive demographics are expressed as means, standard deviation and range; comparisons between groups were calculated using the T-test.

Table 2 Annualised rate of SKGFR change in the normal, stenosis, occlusion and PTRA groups. The differences are not statistically significant ($p > 0.05$)

SKGFR annualised change rate (first- last SKGFR), means \pm SD (range)		
Group	Annualised rate (ml/min/year)	Follow-up (month)
Normal	2.89 \pm 8.93 (from -10.8 to 35.6)	16.4 \pm 11.7 (2–50)
Stenosis	-0.19 \pm 4.99 (from -11.7 to 12)	19.9 \pm 16.4 (4–51)
Occlusion	0.66 \pm 3.21 (from -1.68 to 12)	21 \pm 13.8 (7–48)
Post-PTRA	-1.81 \pm 14 (from -53 to 28.4)	21.4 \pm 16 (3–61)

Results

We followed-up 115 single kidneys; the mean observation period was 19.37 \pm 15.1 months and the longest follow-up was 66 months. The mean follow-up period in normal, stenosis, occlusion and PTRA groups is shown in Table 1.

We have calculated the annualised rate of SKGFR change in the four groups of kidneys: the results are shown in Table 2. Of the total group of 115 kidneys, 13 were not considered in this analysis because they had only one GFR determination after PTRA. We performed a mean number of SKGFRs of 2.91 \pm 1.09 (2–7) with a mean period between each determination of 10.91 \pm 7.47. The mean annualised rate of SKGFR change was 2.89 \pm 8.93 ml/min/year in the normal group, -0.19 \pm 4.99 ml/min/year in kidneys with a stenosed renal artery, 0.66 \pm 3.21 ml/min/year in case of occlusion

and -1.81 \pm 14 ml/min/year in the group of kidneys undergoing PTRA. In the latter case the annualised rate of SKGFR change was calculated considering the first measurement after revascularisation and the last one. The mean annualised rates of SKGFR change of normal, stenosis, occlusion and PTRA do not significantly differ ($p > 0.05$).

Figure 1 compares the annualised rate of SKGFR change in kidneys with renal artery stenosis against the opposite kidney whatever the anatomy of the contralateral renal artery was. No difference in mean annualised rate of individual GFR change between the stenotic kidneys and the opposite ones was reported: the annualised rate was -0.04 \pm 5.23 ml/min/year in the stenosis sample and 0.37 \pm 6.52 ml/min/year in the contralateral side. The range of the rate can vary from -11.7 to 12 ml/min/year in the group of kidneys with a renal artery stenosis and from -20 to 12 ml/min/year in the opposite side.

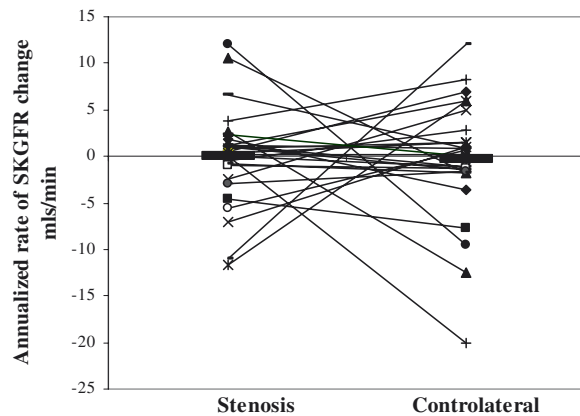
**Figure 1** Annualised rate of SKGFR change in the normal group against the contralateral side (solid lines represent mean for each group).

Figure 2 compares the percentage of individual GFR change in kidneys treated with PTRA with the contralateral kidneys. We have calculated both the changes in GFR between the determination preceding revascularisation and the first immediately after and between the measurement preceding PTRA and the last one. Thirty-two paired kidneys were considered in this analysis. The mean observation period was 6.1 \pm 4.6 months in the short-term follow-up and 20.2 \pm 17 month in the longer one. In the short period, the mean SKGFR change was 21.42% in the revascularised kidneys compared to 12.75% in the contralateral side; in the longer follow-up the mean SKGFR change was 21.45% in the PTRA group compared to -6.73% in the opposite kidneys. The results were not statistically significant in the short period ($p > 0.05$), were at the limit of statistical significance in the longer one ($p = 0.059$). We have observed a wide range of variability: in the short period, the SKGFR change varying from 332% to -75% in PTRA sample and from 396% to -100% in the opposite kidney; in the long-term, from 332% to -89%

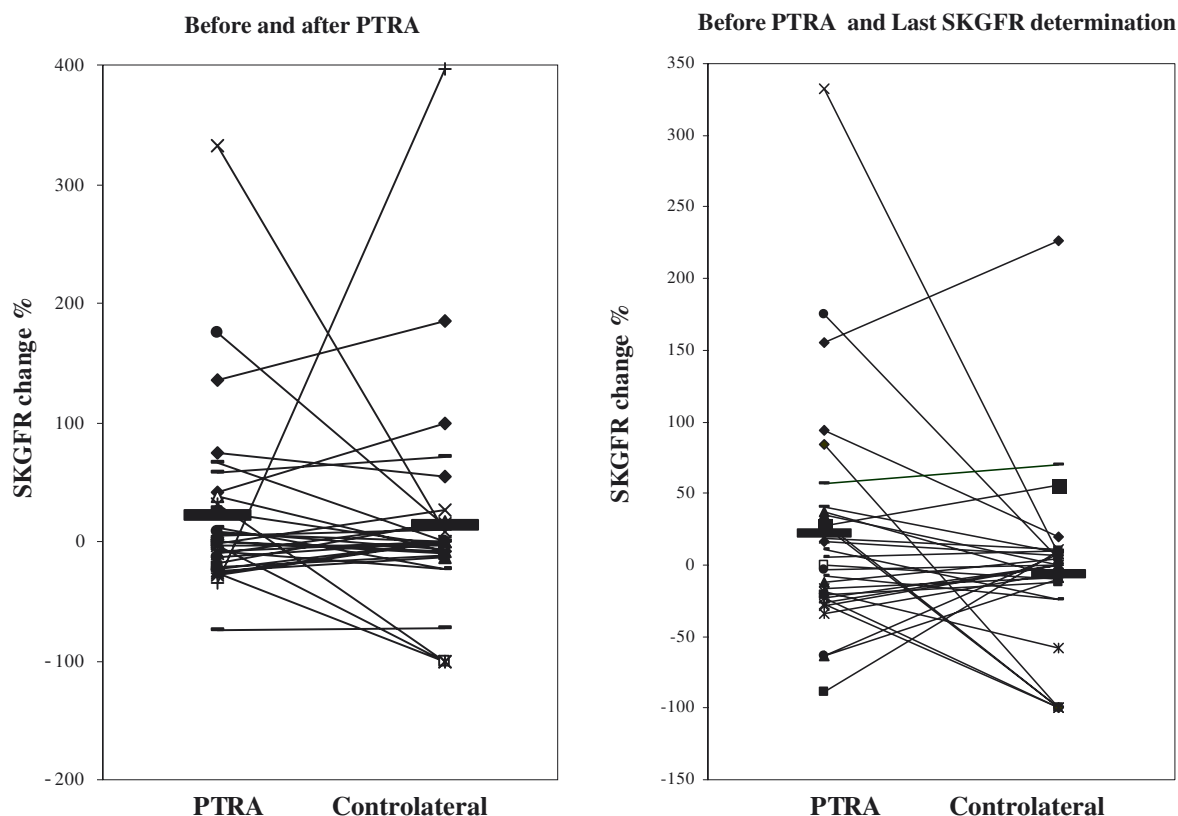


Figure 2 Individual kidney GFR change in the PTRA group against the contralateral side: short- and long-term follow-up (solid lines represent mean for each group).

in the PTRA group and from 226% to -100% in the contralateral kidney.

Discussion

ARVD is the underlying cause of end-stage renal failure in up to 20% of older patients starting dialysis treatment^[18–20]. Although balloon angioplasty has become a widespread tool in ARAS management since its introduction in 1978 by Grüntzig^[21], the selection of patients which may benefit from percutaneous revascularisation is still an issue and little is known about the natural course of renal function in ARVD.

In the last few years some investigations on individual renal function in patients with ARAS have begun to be published. In particular, Farmer *et al.* have paradoxically found a better renal function in the kidney with atherosclerotic renal artery narrowing than in the side without renal artery stenosis^[9] and they have shown a lack of renal function improvement after PTRA in the short-term^[22]. The original aspect of our study is the long-term evaluation of individual renal survival and for this purpose we have sequentially performed individual GFR measurements, thus determining the annualised rate of SKGFR change in groups of kidneys with different conditions of renal artery anatomy (normal, stenosis, occlusion, PTRA). There are two main findings in this

paper. First of all, we have observed no statistically significant difference in renal survival in the four groups of kidneys: the renal function is quite stable in all groups regardless of the presence of a renal artery stenosis (Table 2). In particular, Fig. 1 shows that the mean long-term renal survival does not differ between the stenotic kidney and the other side, whatever the renal artery condition is. However, it is also evident that there is a wide range of annualised individual GFR change rates both in kidneys with stenosis and in the other ones. The second main result relates to the group undergoing revascularisation treatment, where we have considered both a short-term and long-term follow-up in order to verify if the timing of GFR determination after revascularisation could be important in revealing any change in kidney function. There was no significant difference in terms of GFR change between the PTRA kidneys and the opposite side in both short and long observation periods (Fig. 2); moreover a broad range of renal function outcome in the PTRA and in the contralateral group was observed. Therefore PTRA does not seem to improve significantly the renal survival whatever the measurement timing is and we can expect either improvement or worsening or stabilisation in individual renal function despite successful revascularisation.

However these data raise some questions: why individual kidney function may not be related to the

presence of renal artery stenosis in ARAS and therefore a similar impairment of renal function can be present in kidneys with and without renal artery narrowing? And finally, why is the renal outcome after PTRAs so unpredictable? We believe that the answer can be found if we consider the overall renal injury of 'atherosclerotic nephropathy'. In fact, nephrologists are now aware that the progressive renal dysfunction that can occur in ARAS is not only the effect of the reduced blood supply to the kidney as initially thought^[23,24]. It is well recognised that pathological processes other than renal ischaemia, often associated with ARVD, can also variably affect the kidney, causing parenchymal damage and a consequent impairment of its function. Hypertension and widespread atherosclerosis are common features in patients with ARAS and aortic atherosclerosis in its turn can cause renal atheroembolic disease, either spontaneously or precipitated by PTRAs. More recently, some investigators have focused their attention on some cytokines, such as TGF- β and plasminogen activator inhibitor-1: they can be produced by atherosclerotic plaque and might contribute to renal disease progression in ARVD through profibrotic effects and by altering tissue remodelling^[25]. These factors can variably affect kidneys causing different degrees of function impairment; interestingly the stenosis might have a protective role on the kidney from these systemic pathological conditions preserving the individual function as suggested by Scoble^[26]. On the contrary, when progress to occlusion occurs, parenchymal damage due to ischaemia will be predominant and this explains the worse function in the higher degree of renal artery stenosis observed^[9]. Therefore it is not easy to predict which kidneys may benefit from revascularisation on the basis of the degree of the renal artery stenosis because it will depend also on the parenchymal damage that can have already occurred. Moreover, the renal outcome after technically successful PTRAs might be negatively influenced by the downstream effects of cholesterol embolisation that can be precipitated by PTRAs itself, making it even more difficult to predict the renal outcome. New data from other vascular territories have shown a significant improvement in outcome with the use of protection devices to prevent vessel wall fragments embolising peripherally^[27,28]. It is possible that there is an improvement in kidney function in a similar manner to that seen in fibromuscular dysplasia but that this is masked by damage due to peripheral embolisation which is not seen in FMD^[29].

In conclusion, this study has provided new understanding on long-term renal survival in atherosclerotic nephropathy; however, it has also confirmed the need for parameters for selecting patients likely to benefit from percutaneous revascularisation. Therefore, we are now looking forward to the results of large and long-term randomised trials that will elucidate whether or not the progression rate of renal function can be positively influenced by revascularisation. It is also possible that

randomised trials with renal protection devices may be required before the true effect of angioplasty and stenting in the atherosclerotic renal artery is defined.

References

- [1] Mailloux, LU, Napolitano, B, Bellucci, AG *et al.* Renal vascular disease causing end-stage renal disease, incidence, clinical correlates and outcomes: a 20-year clinical experience. *Am J Kidney Dis* 1994; 24: 622–9.
- [2] Missouriis, CG, Buckenham, T, Cappuccio, FP *et al.* Renal artery stenosis: a common and important problem in patients with peripheral vascular disease. *Am J Med* 1994; 96: 10–14.
- [3] Harding, MB, Smith, LR, Himmelstein, SI *et al.* Renal artery stenosis: prevalence and associated risks factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol* 1992; 2: 1608–16.
- [4] La Batide-Alanore, A, Azizi, M, Froissart, M *et al.* Split renal function outcome after renal angioplasty in patients with unilateral renal artery stenosis. *J Am Soc Nephrol* 2001; 12: 1235–41.
- [5] Jensen, G, Zachrisson, BF, Delin, K *et al.* Treatment of renovascular hypertension: one year results of renal angioplasty. *Kidney Int* 1995; 48: 1936–45.
- [6] Birrer, M, Do, DD, Mahler, F *et al.* Treatment of renal artery fibromuscular dysplasia with balloon angioplasty: a prospective follow-up study. *Eur J Vasc Endovasc Surgery* 2002; 23: 146–52.
- [7] 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.
- [8] Suresh, M, Laboi, P, Mamtora, H *et al.* Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol, Dial Transplant* 2000; 15: 631–6.
- [9] Farmer, CKT, Cook, GJR, Blake, GM *et al.* Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis. *Nephrol, Dial Transplant* 1999; 14: 2880–4.
- [10] Dorros, G, Jaff, M, Mathiak, L *et al.* Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. *Circulation* 1998; 98: 642–7.
- [11] Lederman, RJ, Mendelsohn, FO, Santos, R *et al.* Primary renal artery stenting: characteristics and outcomes after 363 procedures. *Am Heart J* 2001; 142: 314–23.
- [12] DeJani, H, Eisen, TD, Finkelstein, FO. Revascularization of renal artery stenosis in patients with renal insufficiency. *Am J Kidney Dis* 2000; 36: 752–8.
- [13] 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 Human Hypertens* 1998; 12: 329–35.
- [14] Plouin, PF, Chatellier, G, Darne, B *et al.* Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis. *Hypertension* 1998; 31: 823–9.
- [15] van de Ven, PJ, Kaatee, R, Beutler, JJ *et al.* Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. *Lancet* 1999; 353: 282–6.
- [16] Wheatley, K. ASTRAL-the story so far. *J Renovasc Dis* 2003; 2: 1–2.
- [17] Scoble, JE, Cook, GJR. Individual kidney function in renovascular disease. *J Renovasc Dis* 2002; 1: 1–5.
- [18] Mailloux, LU, Napolitano, B, Bellucci, AG *et al.* Renal vascular end-stage disease. In: *Renal Vascular Disease*. (Eds A Novick, J Scoble and G Hamilton). London, W.B. Saunders, 1995: 315–21.
- [19] Appel, RG, Bleyer, AJ, Reavis, S *et al.* Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int* 1995; 48: 171–6.
- [20] van Ampting, JM, Penne, EL, Beek, FJ *et al.* Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. *Nephrol Dial Transplant* 2003; 18: 1147–51.

- [21] Grüntzig, A, Kuhlmann, U, Vetter, W *et al.* Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal artery stenosis. *Lancet* 1978; 1: 801–2.
- [22] Farmer, CK, Reidy, J, Kalra, PA *et al.* Individual kidney function before and after renal angioplasty. *Lancet* 1998; 352: 288–9.
- [23] Goldblatt, H, Lynch, J, Hanzal, RF *et al.* The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med* 1934; 59: 347–78.
- [24] Jacobson, HR. Ischemic renal disease: an overlooked clinical entity? *Kidney Int* 1988; 34: 729–43.
- [25] Chade, AR, Rodriguez-Porcel, M, Grande, JP *et al.* Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. *Arteriosclerosis Thrombosis Vasc Biol* 2003; 23: 1295–301.
- [26] Scoble, JE, Cook, GJR. Individual kidney function in atherosclerotic nephropathy. *Nephrol, Dial Transplant* 1998; 13: 842–4.
- [27] Mas, JL, Chatellier, G, Beysen, B. EVA-3S Investigators. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Stroke* 2004; 35(1): e18–20.
- [28] Baim, DS, Wahr, D, George, B *et al.* Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-cornary bypass grafts. *Circulation* 2002; 105: 1285–90.
- [29] Scoble, JE. Do protection devices have a role in renal angioplasty and stent placement? *Nephrol, Dial Transplant* 2003; 18: 1700–3.