



## ORIGINAL ARTICLE

# Split renal function in patients with unilateral atherosclerotic renal artery stenosis—effect of renal angioplasty

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## Abstract

**Objective:** To evaluate the effect of percutaneous transluminal renal angioplasty (PTRA) on split renal function (SRF) in patients with unilateral atherosclerotic renal artery stenosis (ARAS).

**Methods:** We performed a retrospective analysis of all consecutively examined patients at our centre with significant ARAS undergoing PTRA during 2002–07. A significant ARAS was defined as a lesion with a trans-stenotic mean arterial pressure gradient of at least 10 mmHg or a diameter stenosis >50% on angiography. Ambulatory (24 h) systolic and diastolic blood pressure (ASBP and ADBP, respectively) and calculated SRF using  $^{99m}\text{Tc}$ -DTPA renal scintigraphy were evaluated before (baseline) and 4 weeks after PTRA.

**Results:** ASBP and ADBP were significantly lower 4 weeks after PTRA compared with baseline levels. Although total estimated glomerular filtration rate (eGFR; four-variable Modification of Diet in Renal Disease equation) had not changed by PTRA, analysis of SRF showed significantly increased eGFR in stenotic kidneys and a comparable reduction in eGFR in non-stenotic kidneys 4 weeks after PTRA.

**Conclusions:** In patients with unilateral ARAS, PTRA significantly improved eGFR in stenotic kidneys and decreased filtration in contralateral, non-stenotic kidneys. These potentially beneficial effects may not be apparent when total renal function remains stable. The clinical significance of these findings needs to be evaluated further.

**Key words:** colour duplex sonography, renal angiography, renal artery stenosis, renovascular hypertension, split renal function

## Introduction

Atherosclerotic renal artery stenosis (ARAS) is relatively common in patients with generalized atherosclerotic disease and may lead to renovascular hypertension (RVH), reduced glomerular filtration rate (GFR) and eventually end-stage renal disease

[1]. The pathophysiological mechanisms causing impaired renal function in patients with RVH are multiple and not fully understood [2]. Chronic renal hypoperfusion and the term ‘ischaemic nephropathy’ have been used generally to describe renal injury and impairment of function beyond a stenotic lesion in the renal artery [2, 3]. Endovascular treatment by percutaneous

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transluminal renal angioplasty (PTRA), with or without stenting, is a commonly used treatment of renal artery stenosis (RAS) in selected patients. However, despite successful restoring of vessel patency by PTRA, randomized controlled trials have shown no beneficial effect of revascularization in preserving renal function when added to a background of optimal medical treatment [4, 5]. Notably, data from current studies of ARAS show a relatively slow progression of renal impairment with estimated GFR (eGFR) losses of 1–2 mL/min/1.73 m<sup>2</sup>/year [4, 6]. This, at least partly, can be explained by the fact that most cases of ARAS are unilateral. The reduction in GFR in a stenotic kidney may be compensated by hyperfiltration of the contralateral non-stenotic kidney. Thus the use of both kidneys 'total renal' GFR is plausibly flawed and poorly reflects the effects of the disease and the impact of revascularization on the stenotic kidney [7].

Taken together, our hypothesis is that PTRA would improve GFR in stenotic kidneys and decrease filtration in contralateral, non-stenotic kidneys. The aims of the present retrospective study are to evaluate the short-term impact of PTRA on split renal function (SRF) in patients with unilateral ARAS and to identify potential predictors of outcome after PTRA.

## Materials and methods

### Study participants

Patients were recruited for the present retrospective study from the candesartan in RAS study programme that was described previously [8]. In brief, this was a randomized, open, investigator-initiated trial at two Swedish centres (Department of Nephrology at Sahlgrenska University Hospital in Gothenburg and Department of Vascular Diseases at Malmö University Hospital) between 2003 and 2008 to study the effects of candesartan in patients with ARAS who had undergone PTRA. Thus, according to the study design, patients with residual hypertension 4 weeks after PTRA were eligible for randomization to antihypertensive treatments based on either candesartan or a regimen without inhibitors of the renin-angiotensin-aldosterone system (RAAS). In the present retrospective study, only patients from Sahlgrenska University Hospital were included, as the patients from Malmö University Hospital lacked SRF data. Indications for renal angiography were hypertension (accelerated, refractory, malignant or with intolerance to medication), a progressive increase in plasma creatinine concentrations [unexplained or during treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB)] or recurrent hypertensive pulmonary oedema, together with a positive screening test for RAS duplex ultrasonography or by computed tomography (CT) or magnetic resonance (MR) angiography. A significant stenosis was defined as a lesion with a trans-stenotic mean arterial pressure gradient (MAPG) of at least 10 mmHg or >50% diameter stenosis on angiography in those cases in which the MAPG was not measured because of technical difficulties due to high-grade stenosis and luminal occlusion during the procedure. To avoid pharmacological interference with the RAAS, patients in whom treatment with ACE inhibitors, ARBs or aldosterone receptor antagonists was clearly indicated (e.g. patients with congestive heart failure or diabetic nephropathy) were excluded [8]. Hence, included patients were not on any of these RAAS-inhibiting drugs during the study period starting from 2 weeks prior to renal angiography. In addition, only patients with unilateral ARAS were included in the present study and individuals with RAS of other aetiology or with either bilateral RAS or stenosis of a solitary kidney were excluded. No modifications of dietary intake, including salt intake, were made during the study period.

### Protocol and measurements

All patients were subjected to baseline measurements 1 day before angiography (baseline) and 4 weeks after PTRA. Analyses included office blood pressure (BP), ambulatory BP (ABP), biochemical analyses, eGFR and renography for assessment of SRF.

### Measurements

Systolic and diastolic office BP (SBP and DBP, respectively) were measured after 5 min of rest in the sitting position. Ambulatory SBP (ASBP) and DBP (ADBP) were measured for 24 h by an ABP system (Model 90217, Spacelabs Healthcare, Snoqualmie, WA, USA). eGFR was calculated according to the four-variable Modification of Diet in Renal Disease (MDRD) equation [9].

### Biochemical analyses

Standard laboratory methods at the Department of Clinical Chemistry at Sahlgrenska University Hospital (Sweden's national accreditation body, SWDAC, approved according to European norm 45001) were used for routine biochemical analyses. Plasma renin activity (PRA) was measured by a radioimmunoassay (RIA) kit (DiaSorin, Stillwater, MN, USA), with inter- and intra-assay coefficients of variation (CVs) <10%. Plasma concentrations of angiotensin II (Euro-Diagnostica, Malmö, Sweden) were measured by RIA kits.

### Renography

Renographic examinations were performed on hydrated patients in the supine position using a large-field gamma camera (APEX 415, Elscint, Israel). In total, 96 frames (64 × 64 pixels) of 10 s each were recorded after an intravenous bolus injection of 100 MBq <sup>99m</sup>Tc-DTPA. Time-activity curves for the regions of interest over the kidneys were created. Renograms were corrected for the extrarenal background signal and normalized for kidney area. Relative function was estimated by means of the uptake index, as previously described [10]. Individual kidney eGFR was calculated by multiplying the percentage of SRF by total eGFR.

### Colour duplex sonography

Colour duplex sonography was carried out using a Sequoia 512 with a V4 transducer (Acuson, Mountain View, CA, USA). The equipment was used by experienced technicians with the patient in the lateral decubitus position. After B-scanning for determination of kidney size, blood flow velocities were localized within interlobar arteries.

Blood flow velocity spectra were registered for at least 4–8 s with the patient holding his/her breath at the end of a normal expiration. During the examination at least three measurements in different interlobar arteries covering the upper pole, the mid-portion and the lower pole of each kidney were registered and an average value was calculated. As described previously [11], velocimetric indices from the analysis of Doppler waveforms were estimated as follows:

Resistive index (RI) = (peak systolic velocity – end diastolic velocity)/peak systolic velocity during a cardiac cycle.

Side-to-side difference in RI ( $\Delta$ RI) = RI in non-stenotic kidney – RI in stenotic kidney.

Maximal acceleration of blood flow during the early systolic phase ( $ACC_{max}$ ) = the visually judged maximum derivative of the early systolic upstroke.

All patients in the present study were examined in the present single centre by a very few experienced technicians in a strictly standardized manner.

### Renal angiography and angioplasty

Digital subtraction angiography was used for evaluating renal arteries. The procedures of renal angiography and PTRAs have been described previously [12]. A 4 French catheter was used for measurements of intra-arterial pressure gradients. The diameter of stenosis was estimated manually in all cases. Indications for stent placement were angioplasty failure (elastic recoil or flow-limiting dissection resulting in >30% residual luminal narrowing, absence of antegrade flow or significant residual MAPG) or restenosis.

### Statistics

Differences between baseline data and 4 weeks after PTRAs were analysed with paired t-test or Wilcoxon signed-rank test. Pearson's or Spearman's correlation coefficient tests were used to evaluate correlations. Chi-square tests were used to evaluate the distributions of categorical data. A percentage change was calculated to represent the relative change between the baseline value of a variable and the value 4 weeks after PTRAs [(value 4 weeks after PTRAs – baseline value/baseline value) × 100]. All tests were two-tailed and  $P < 0.05$  was considered statistically significant. Data are presented as mean ± SD. SPSS Statistics for Windows, version (IBM, Armonk, NY, USA) was used for statistical analysis.

### Results

All 52 patients from Sahlgrenska University Hospital with significant unilateral ARAS on angiography were included in the present study. Demographic and clinical data for the study population are given in Table 1.

#### Effects of PTRAs on BP, PRA and angiotensin II (Table 2)

Office SBP and DBP remained unchanged 4 weeks after PTRAs, whereas ASBP and ADBP decreased significantly. The number of antihypertensive drugs was reduced after PTRAs, yet not statistically significant. Both daytime and night-time ASBP and ADBP were significantly reduced 4 weeks after PTRAs, whereas the nocturnal dipping in ASBP and ADBP remained unchanged (data not shown).

There were no significant changes in PRA or in plasma levels of angiotensin II 4 weeks after PTRAs. However, baseline levels of PRA and plasma angiotensin II were significantly correlated to percentage changes in ASBP [ $r = -0.35$ ,  $P < 0.05$  (Figure 1A) and  $r = -0.52$ ,  $P < 0.01$  (Figure 1B), respectively] and ADBP [ $r = -0.35$ ,  $P < 0.05$  (Figure 1C) and  $r = -0.59$ ,  $P < 0.01$  (Figure 1D), respectively]. There were no correlations between baseline levels of PRA or plasma angiotensin II with the degree of RAS assessed by MAPG on angiography or by velocimetric Doppler indices of the stenotic kidneys (RI,  $\Delta$ RI and  $ACC_{max}$ ) from colour duplex sonography (data not shown).

Percentage changes in ASBP 4 weeks after PTRAs significantly correlated with  $\Delta$ RI [ $r = -0.40$ ,  $P < 0.05$  (Figure 2)] and  $ACC_{max}$  and RI (data not shown) in stenotic kidneys assessed by colour duplex sonography. Similarly, percentage changes in ADBP 4 weeks after PTRAs significantly correlated with  $\Delta$ RI, but the correlation with  $ACC_{max}$  and RI in stenotic kidneys did not reach statistical significance (data not shown). There were no

**Table 1.** Characteristics of the study population at baseline

Characteristics	ARAS (n = 52)
Age (years)	63 ± 9
Male/female (male %)	38/14 (73)
Diabetes mellitus, n (%)	9 (17)
Current cigarette smoking, n (%)	16 (31)
Office SBP (mmHg)	157 ± 21
Office DBP (mmHg)	86 ± 11
Serum creatinine (μmol/L)	116 ± 39
eGFR, (mL/min/1.73 m <sup>2</sup> )	57 ± 21

Data are presented as mean ± SD, unless stated otherwise.

**Table 2.** Effects of PTRAs on blood pressure and renal function

	Baseline (n = 52)	4 weeks after PTRAs (n = 52)	P-value
Antihypertensive drugs (n)	2.6 ± 0.9	2.3 ± 1.1	0.09
Office SBP (mmHg)	157 ± 21	155 ± 21	0.50
Office DBP (mmHg)	86 ± 11	86 ± 11	0.87
ASBP (mmHg)	145 ± 14	138 ± 16	0.005
ADBP (mmHg)	80 ± 9	77 ± 11	0.005
PRA (ng/mL/h)	2.09 ± 2.04	1.90 ± 2.51	0.26
P-Ang II (pg/mL)	13.5 ± 8.2	11.9 ± 6.3	0.37
tU-albumin (mg/day)	117 ± 183	125 ± 274	0.85
Serum creatinine (μmol/L)	116 ± 39	117 ± 41	0.81
eGFR (mL/min/1.73 m <sup>2</sup> )	57 ± 21	58 ± 21	0.77
Stenotic renal function (%)	38 ± 19	41 ± 19	<0.0001
Non-stenotic renal function (%)	62 ± 19	59 ± 19	<0.0001
eGFR stenotic kidney (mL/min/1.73 m <sup>2</sup> )	22 ± 14	26 ± 17	0.004
eGFR non-stenotic kidney (mL/min/1.73 m <sup>2</sup> )	37 ± 16	34 ± 15	0.026

Data are presented as mean ± SD.

P-Ang II, plasma angiotensin II; tU-albumin, total urinary excretion of albumin.

correlations between RI in non-stenotic kidneys and changes in ASBP and ADBP 4 weeks after PTRAs (data not shown). There were no significant correlations between baseline demographic data (age, gender, smoking and presence of diabetes mellitus) and percentage changes in ASBP and ADBP (data not shown).

#### Effects of PTRAs on total and SRF (Table 2)

Serum creatinine levels and total eGFR were not significantly affected by PTRAs. However, analysis of SRF showed significantly increased eGFR in stenotic kidneys and comparable reductions in eGFR in non-stenotic kidneys 4 weeks after PTRAs.

The percentage changes in eGFR in stenotic kidneys were correlated only with baseline levels of PRA [ $r = 0.39$ ,  $P < 0.05$  (Figure 3)] 4 weeks after PTRAs. There were no significant correlations between baseline demographic data and the percentage changes in eGFR in stenotic kidneys 4 weeks after PTRAs (data not shown). In addition, there were no significant differences in the percentage changes in eGFR in stenotic kidneys 4 weeks after PTRAs, between patients with RI >0.80 and those with RI <0.80 assessed non-stenotic (25.6 ± 59.3 versus 15.6 ± 35.3,

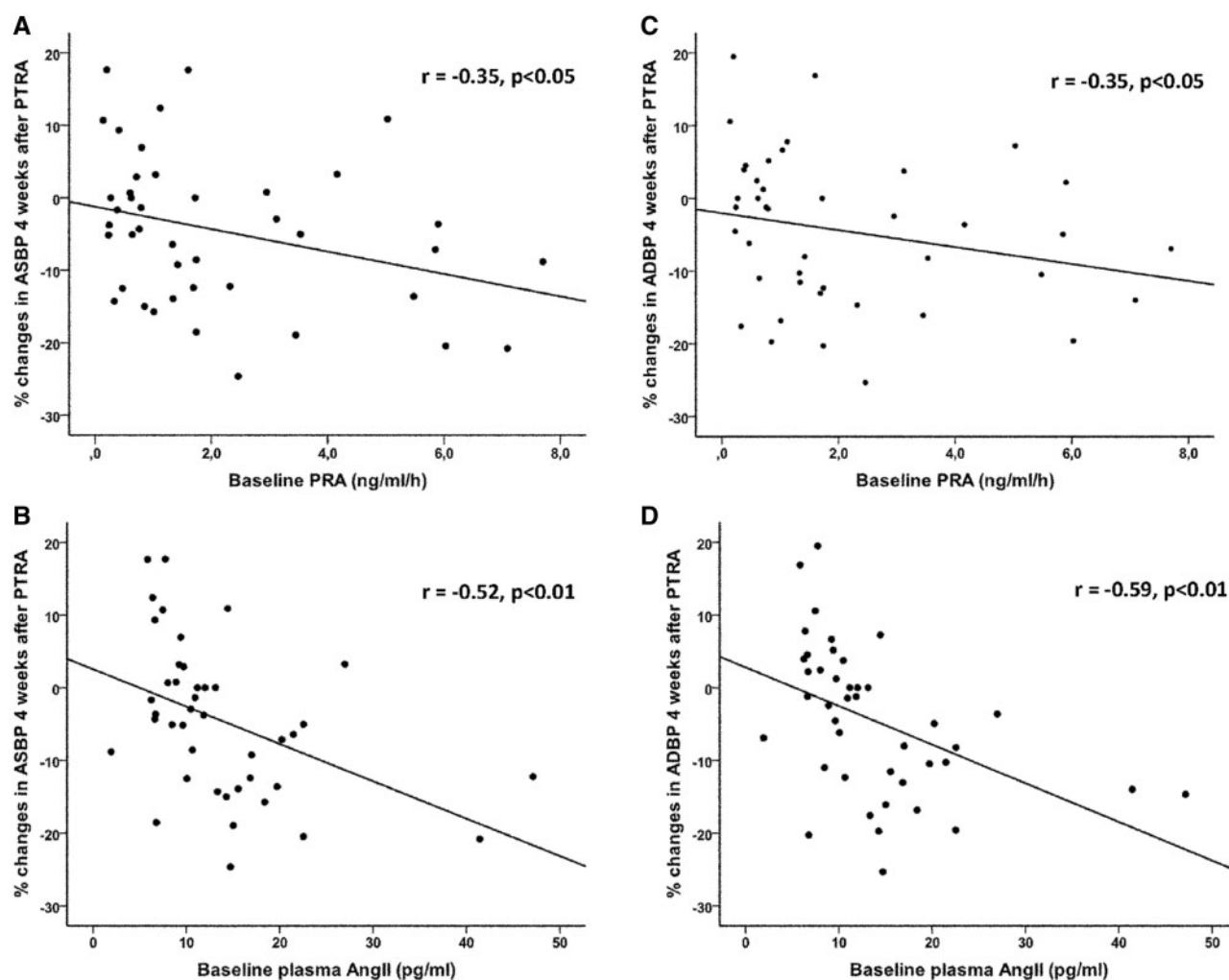


Fig. 1. Correlation of baseline PRA and angiotensin II (Ang II) with the percentage changes in ASBP and ADBP 4 weeks after PTR in patients with unilateral ARAS.

respectively;  $P = 0.75$ ). There were no correlations between RI in non-stenotic kidneys and the percentage changes in eGFR in stenotic kidneys 4 weeks after PTR (data not shown).

## Discussion

The main findings of the present study were that in hypertensive patients with unilateral ARAS, total eGFR was not affected by PTR after short-term follow-up. Nevertheless, PTR significantly improved eGFR in stenotic kidneys and decreased filtration in contralateral, non-stenotic kidneys. In addition, despite the fact that office SBP and DBP remained unchanged after PTR, ASBP and ADBP decreased significantly. Our finding regarding the lack of beneficial effect of PTR on total eGFR is in line with the results of the major randomized controlled trials, including the two largest trials, Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), that have shown no beneficial effect of revascularization in improving renal function when added to a background of optimal medical treatment [4, 5]. However, there are some considerations that might explain why these trials could not show improvement of renal function by PTR. One major concern is that these trials included a large number of patients with normal or mildly

reduced renal function. This may reduce the likelihood of finding beneficial effects of PTR on renal function. Another important concern is that in patients with unilateral ARAS, the stenotic kidney has a reduced GFR, while the contralateral non-stenotic kidney likely undergoes hyperfiltration as a response to elevated BP. Improvement of renal perfusion by PTR would likely increase GFR in the revascularized stenotic kidney while the filtration in the contralateral kidney decreases [3, 13–15]. Due to these opposing effects of PTR on the two kidneys, it is plausible that PTR would not have an obvious impact on total eGFR in patients with unilateral ARAS. In accordance with the present study, Jensen *et al.* [16] previously showed a similar magnitude of improvement in relative GFR in stenotic kidneys measured by renography with  $^{131}\text{I}$ -hippuran in 117 patients with ARAS 1 year after PTR. However, in contrast to the present study, Jensen *et al.* also showed significant improvement in total GFR measured as plasma clearance of  $^{51}\text{Cr}$ -EDTA by PTR. Thus the divergent effects of PTR on the two kidneys seen in the present study were not evident in the study by Jensen *et al.* Nevertheless, in accordance with the present study, in 27 patients with unilateral ARAS, Coen *et al.* [17] showed significant improvement in the percentage of GFR in stenotic kidneys and reduction of percentage GFR in contralateral kidneys 1 year after PTR, measured by renography with  $^{99\text{m}}\text{Tc}$ -DTPA or

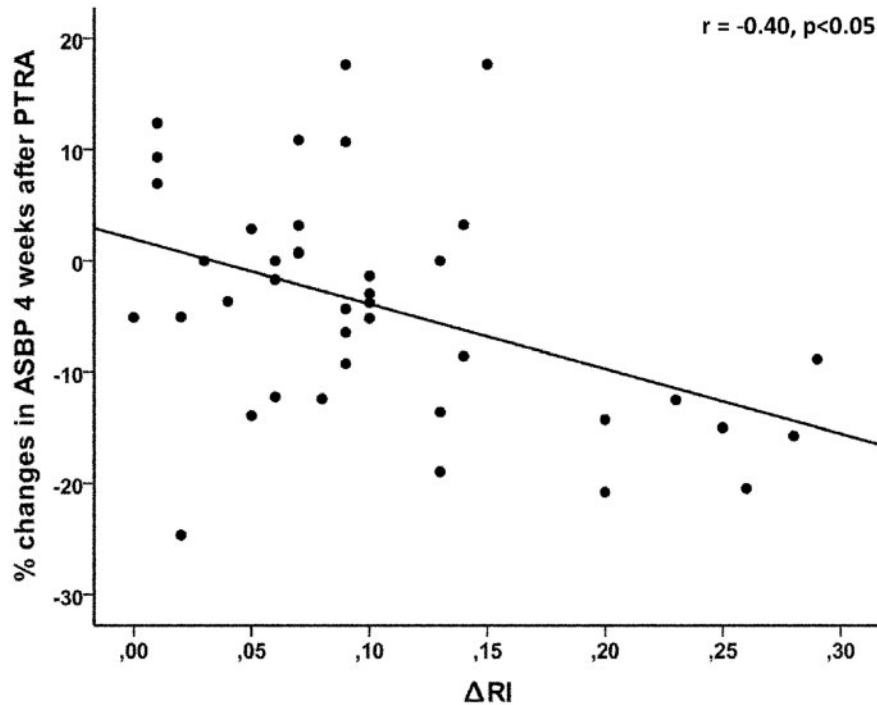


Fig. 2. Correlation of degree of RAS assessed by  $\Delta RI$  (RI in non-stenotic kidney – RI in stenotic kidney) from the analysis of Doppler waveforms of colour duplex sonography with the percentage changes in ASBP 4 weeks after PTR in patients with unilateral ARAS.

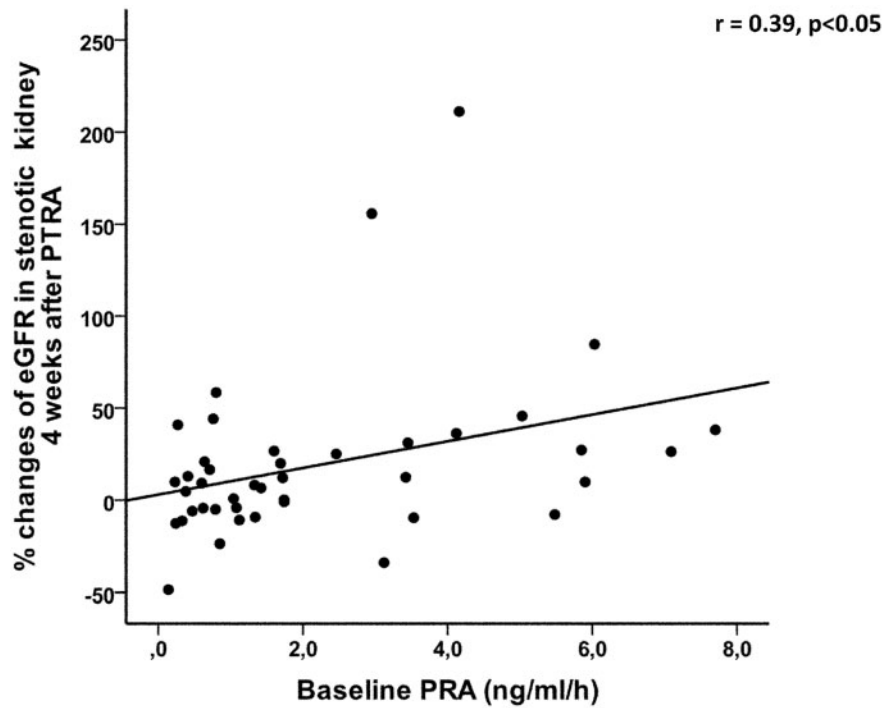


Fig. 3. Correlation of baseline PRA with the percentage changes in eGFR in stenotic kidneys 4 weeks after PTR in patients with unilateral ARAS. Individual kidney eGFR was calculated by multiplying the percentage of SRF by total eGFR according to the four-variable MDRD equation.

with  $^{99m}Tc$ -MAG3, whereas renal creatinine clearance as an estimate of the total GFR remained largely unchanged.

Chronic renal hypoperfusion and ischaemic renal injury have been used generally to describe the pathophysiology of kidney injury and impairment of function in patients with ARAS [2, 3]. On the other hand, hypertensive renal injury in the

contralateral non-stenotic kidney due to hyperfiltration has also been described in these patients [2, 3, 14]. Thus it is plausible to speculate that such opposing effects of PTR on the two kidneys seen in the present study may have a beneficial renal effect not only by improvement of renal perfusion and GFR in the stenotic kidney but also by a potential protective effect from

hypertensive glomerular injury in the contralateral non-stenotic kidney.

Activated RAAS in response to reduced renal perfusion in unilateral RAS is one of the most important counterregulatory pathways directed towards restoring renal perfusion and GFR [18]. However, in the present study, the reduction in PRA after PTRA was not statistically significant. A possible explanation is that blood samples for baseline PRA were taken while the patients were lying flat in bed in the morning in the hospital. In contrast, blood samples for PRA, 4 weeks after PTRA, were taken in a sitting position as outpatient follow-up. Thus a possible postural augmentation of PRA at 4 weeks after PTRA may have masked a more apparent reduction in PRA by PTRA [19]. Nevertheless, baseline plasma levels of PRA and angiotensin II were significantly correlated to percentage changes in ASBP and ADBP 4 weeks after PTRA. In addition, the baseline plasma level of PRA was the only variable that correlated significantly to percentage changes in eGFR in stenotic kidneys 4 weeks after PTRA. These findings are suggestive of the pathophysiological role of RAAS in patients with unilateral ARAS. Interestingly, baseline PRA was not correlated to baseline ABP, total eGFR or SRF. In addition, there were no correlations between baseline PRA and the degree of RAS assessed by MAPG on angiography or by velocimetric indices of the stenotic kidney (RI,  $\Delta$ RI and  $ACC_{max}$ ) from colour duplex sonography. One can speculate that an attenuated response to reduced renal perfusion and release of renin from juxtaglomerular cells in stenotic kidneys may reflect advanced renal vascular damage and hence a lack of effect of PTRA on GFR. On the other hand, a more adequate response and release of renin to renal hypoperfusion in stenotic kidneys may reflect intact renal vasculature and hence improvement of GFR by PTRA. However, as is evident from the depicted correlation on the scatterplot in Figure 3, baseline PRA cannot be used reliably to predict those patients with ARAS who will or will not benefit from PTRA with improved eGFR in stenotic kidneys. Radermacher *et al.* [20] showed that an  $RI \geq 0.8$  served as a negative prognostic predictor for revascularization outcome. However, these results were not consistently confirmed in different studies. In contrast to Radermacher *et al.*, there were no significant correlations between baseline RI in non-stenotic kidneys and changes in ABP and eGFR in stenotic kidneys after PTRA in the recent study. In accordance with our findings, Zeller *et al.* [21], in 241 patients with unilateral ARAS, showed significant improvement in renal function and BP control after PTRA in 39 patients with an  $RI \geq 0.8$ . Interestingly, a reduction in ASBP by PTRA significantly correlated to indices of the degree of RAS by colour duplex sonography (RI,  $\Delta$ RI and  $ACC_{max}$ ) but not by MAPG on angiography. This could be explained, at least in part, by the notion that renal Doppler indices reflect not only the degree of RAS but rather are a product of multiple renal and non-renal factors. Extrarenal factors reflecting the stiffness/compliance of major arteries and hence the likelihood of BP response to revascularization, may have a significant impact on renal Doppler indices [22].

There are some limitations of the present study. First, it is a retrospective study and there is no control group. However, this was partly compensated for by the fact that the study population comprised all patients from a prospective cohort in one centre with pre-specified inclusion and exclusion criteria. In addition, the significance of ARAS was assessed objectively by measuring the trans-stenotic MAPG on angiography. Second, the short-term follow-up duration limits the clinical significance of our findings. Yet, the present study shows clearly the opposing effects of PTRA on the stenotic and contralateral non-stenotic kidneys, which may explain the lack of impact of PTRA on total eGFR in the clinical trials.

In conclusion, in patients with unilateral ARAS, PTRA significantly improved eGFR in stenotic kidneys and decreased filtration in contralateral, non-stenotic kidneys. These potentially beneficial effects of revascularization may not be apparent when total GFR remains stable. In addition, augmented PRA may be suggestive of improvement of eGFR in stenotic kidneys and ABP control. The clinical significance of these findings needs to be evaluated further.

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## Conflict of interest statement

None declared.

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