Original Article

Multimarker assessment for the prediction of renal function improvement after percutaneous revascularization for renal artery stenosis

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Background: Identifying patients likely to have improved renal function after percutaneous transluminal renal angioplasty and stenting (PTRA) for renal artery stenosis (RAS) is challenging. The purpose of this study was to use a comprehensive multimarker assessment to identify those patients who would benefit most from correction of RAS.

Methods: In 127 patients with RAS and decreased renal function and/or hypertension referred for PTRA, quantification of hemodynamic cardiac stress using B-type natriuretic peptide (BNP), renal function using estimated glomerular filtration rate (eGFR), parenchymal renal damage using resistance index (RI), and systemic inflammation using C-reactive protein (CRP) were performed before intervention.

Results: Predefined renal function improvement (increase in eGFR ≥10%) at 6 months occurred in 37% of patients. Prognostic accuracy as quantified by the area under the receiver-operating characteristics curve for the ability of BNP, eGFR, RI and CRP to predict renal function improvement were 0.59 (95% CI, 0.48–0.70), 0.71 (95% CI, 0.61–0.81), 0.52 (95% CI, 0.41–0.65), and 0.56 (95% CI, 0.44–0.68), respectively. None of the possible combinations increased the accuracy provided by eGFR (lower eGFR indicated a higher likelihood for eGFR improvement after PTRA, P=ns for all). In the subgroup of 56 patients with pre-interventional eGFR <60 mL/min/1.73 m^2, similar findings were obtained.

Conclusions: Quantification of renal function, but not any other pathophysiologic signal, provides at least moderate accuracy in the identification of patients with RAS in whom PTRA will improve renal function.

Keywords: Natriuretic peptides; C-reactive protein (CRP); resistance index (RI); renal artery stenosis (RAS); renal function; angioplasty

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Introduction

Renal artery stenosis (RAS) is a relatively common problem in patients with systemic atherosclerosis and may lead to uncontrolled arterial hypertension, renal insufficiency, and cardiac disorders, including flush pulmonary edema and heart failure (1). The progressively impaired renal function in patients with RAS is assumed to be caused not only by reduced blood flow to the kidney but also by loss of microvascular renal perfusion induced by hypertensive and ischemic nephropathy (2). The pathophysiological concept is based on the fact that the reduction of perfusion pressure to the kidney activates the renin-angiotensin system, adrenergic stimuli, and volume expansion. Furthermore, the coexistence of hypoperfusion, atherosclerosis, and cardiovascular risk factors activates several additional deleterious proinflammatory and profibrotic pathways that have been implicated in progression of renal damage in hypoperfused kidneys (3).

The effect of percutaneous transluminal renal angioplasty and stenting (PTRA) for hemodynamic relevant RAS on renal function as well as the prediction of patients in whom PTRA improves renal function is a matter of debate (1,4,5).

We aimed to investigate a comprehensive multimarker assessment with quantification of hemodynamic cardiac stress using B-type natriuretic peptide (BNP), quantification of renal function using estimated glomerular filtration rate (eGFR), quantification of parenchymal renal damage using resistance index (RI), and quantification of systemic inflammation using C-reactive protein (CRP) in the prediction of renal function improvement. This is a prospective, two-center cohort study.

Methods

Patient population

This prospective, two-center study included 127 consecutive patients undergoing PTRA for RAS from August 2004 to December 2007 at the University Hospital Basel, Switzerland, and the Herz-Zentrum Bad Krozingen, Germany. Indications for renal arterial endovascular treatment were unilateral or bilateral RAS ≥50% with arterial hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or on any antihypertensive drug therapy) (n=71) and/or renal insufficiency (eGFR ≤60 mL/min/1.73 m^2) (n=56). Assessment of RAS was based primarily on duplex ultrasound using a Philips ATL, HDI 5000 (Philips, Best, Netherlands). As described previously, RAS was classified as hemodynamically relevant if the renal/aortal velocity ratio was ≥2.5 (6). For unilateral RAS the side-to-side difference in intrarenal RI =1-[end-diastolic velocity/peak systolic velocity] between the 2 kidneys >0.05 was also used to classify hemodynamically relevant RAS. Before intervention, duplex ultrasound was always confirmed by intra-arterial angiography showing a percent diameter stenosis ≥50% by measuring the ratio between the diameter of the narrowest segment of the imaged renal artery and the diameter of a normal segment of the artery proximal to the stenosis or distal to poststenotic dilation. Alternatively, an intra-arterial, trans-lesional systolic pressure gradient of ≥20 mmHg was considered as hemodynamically relevant and was assessed in 31 patients (6). A RAS ≥70% was documented in 84% of all patients and mean systolic pressure gradient was 72±46 mmHg.

The study was carried out according to the principles of the declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all participating patients.

Revascularization procedure

For atherosclerotic renal artery lesions a stent placement procedure with and without pre-dilatation using a guiding catheter technique via the femoral access and a variety of balloon expandable renal stents were used, such as Hippocampus™ (Invatec), Dynamic renal™ (Biotronik) or Palmaz blue™ (J&J Cordis). Procedural success was defined as <30% residual luminal narrowing or residual peak trans-lesional pressure gradient <10 mmHg. Antiplatelet therapy was started at least 1 day before the intervention and routinely consisted of 75 mg of clopidogrel daily for 4 weeks and 100 mg of aspirin indefinitely.

Follow-up and definitions

Baseline evaluation before PTRA and follow-up examinations 6 months after the revascularization procedure included duplex ultrasound with measurement of the renal/aortal velocity ratio and intrarenal RI at both the sides, measurement of serum creatinine, 24-hour ambulatory blood pressure monitoring (BSI, SpaceLab Medical Inc., Issaquah, WA, USA), and documentation of antihypertensive drugs. To estimate the eGFR, we used the formula for creatinine clearance calculated by the abbreviated modification of diet in renal disease study equation (7).

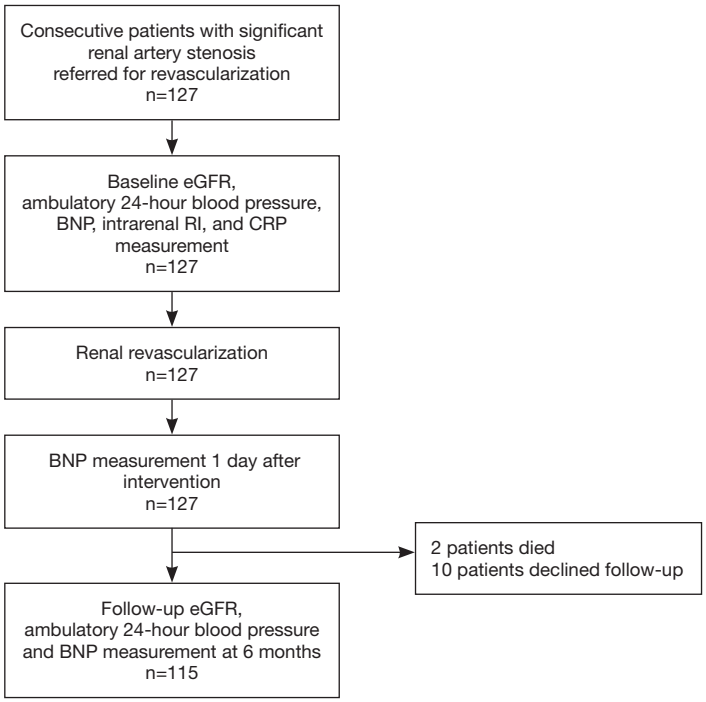

Figure 1 Flow diagram of patients with renal artery stenosis referred for revascularization.

Two patients died during the follow-up period and 10 patients had no follow-up data after PTRA (*Figure 1*). Therefore, follow-up data was available from 115 patients (91%). Improvement in renal function at 6 months after PTRA was predefined as increase in the absolute value of the eGFR by ≥10% compared to pretreatment values (8). Decrease in renal function at 6 months after treatment was predefined as deterioration in the absolute value of the eGFR by ≥10% compared to the pretreatment value. A change in the absolute value of the eGFR within ±10% was predefined as no change in renal function. Patient with no change or decrease in renal function were summarized as no improvement in renal function.

Blood sampling and laboratory methods

A specimen of venous blood for BNP measurement was drawn before the intervention, 1 day and 6 months after the intervention. These samples were collected in plastic tubes containing EDTA and were centrifuged at 3,000 g and analyzed immediately. BNP concentration was determined using the commercially available Biosite assay (Biosite Diagnostics, La Jolla, CA, USA). Precision, analytical sensitivity, and stability characteristics of this fluorescence immunoassay have been previously described (9). In brief, the coefficient of variation for intra-assay precision has been reported to be 9.5%, 12.0%, and 13.9%, and the coefficient of variation for interassay precision is known to be 10.0%, 12.4%, and 14.8% for BNP levels of 28.8, 584.0, and 1,180.0 pg/mL, respectively. The analytic sensitivity was <5.0 pg/mL, with a measurable range of 0 to 5,000 pg/mL. As previously described, age and gender-specific median levels (25^{th} and 75^{th} percentiles) of plasma BNP using the same Biosite assay in 767 normal subjects in sinus rhythmu without cardiovascular disease or cardiac dysfunction were 27 (range, 15–43) pg/mL and 11 (range, 5–20) pg/mL for women and men of 55 to 64 years of age, and 29 (range, 19–52) pg/mL and 18 (range, 7–37) pg/mL for women and men of 65 to 74 years of age, respectively (10).

The laboratory technician who measured BNP was blinded to patient information.

Statistical analysis

The primary objective of this study was to examine whether pre-interventional BNP levels, eGFR, intrarenal RI at the side of the stenosis and CRP predicted improvement in renal function by the 6 months follow-up end point in

the overall study cohort and in the subgroup with renal insufficiency at baseline (eGFR ≤60 mL/min/1.73 m^2). The secondary endpoint was to examine whether the decrease in BNP level one day after intervention predicted improvement in renal function at 6-month follow-up.

Statistical analyses were performed using IBM SPSS/PC (version 19.0, SPSS Inc., Chicago, IL, USA). Discrete variables were expressed as numbers and percentages, continuous variables as mean ± SD or median and interquartile range (25^{th} to 75^{th} percentiles) when the sample data was not normally distributed. Univariate analysis of patients with renal function improvement compared to patients without renal function improvement were made using analysis of variance (ANOVA) or Mann-Whitney U test for continuous factors as appropriate and Chi-square tests for categorical factors. Paired *t*-test or Wilcoxon signed-rank test as appropriate were used to compare measurements before and after PTRA. Area under the receiver operating characteristic curve was used to estimate the value of baseline BNP, eGFR, intrarenal CRP, and CRP for the prediction of renal function improvement. The comparison of ROC-curves was performed using the method of DeLong on MedCalc (version 11.2.1.0, MedCalc Software, Ostend, Belgium). Multivariable logistic regression analyses were performed to assess the association of renal function improvement with pre-intervention BNP level, eGFR, intrarenal RI, and CRP (adjusted for age and sex).

Results

Baseline characteristics and renal artery intervention

The baseline clinical characteristics are shown in *Table 1*. Mean baseline eGFR was 65±27 mL/min/1.73 m^2 and baseline eGFR <60 mL/min/1.73 m^2 was documented in 56 patients (44%). Seven patients (7%) had chronic kidney disease stage 4 or 5 according to KDOQI classification before intervention. Hemodynamically relevant bilateral stenosis was found in 13 patients (10%). The majority of all lesions were atherosclerotic ostial stenoses (78%). PTRA secondary to fibromuscular dysplasia of the renal arteries (11) has been performed in 14% of patients. The overall primary technical success rates for renal revascularization were 100%.

There was no procedure related death. Two patients died from acute myocardial infarction during the follow-up period (*Figure 1*). We observed four major procedural complications: Intrarenal bleeding successfully treated with embolization; acute occlusion of the main renal artery one week after stent implantation with spontaneous reopening; perforation of the main renal artery treated with extended balloon dilation; dissection of main renal artery distal from stent implantation with occlusion of a segmental arterial branch.

Renal function response

As shown in *Table 1*, eGFR increased from baseline value of 65±27 mL/min/1.73 m^2 before intervention to 69±29 mL/min/1.73 m^2 after PTRA at 6-month follow-up (P<0.05). Renal function improvement was documented in 37% of patients (42/115 patients), no change in renal function was found in 44 patients (38%), and decrease in renal function was documented in 29 of patients (25%). In the four patients with major procedural complications only one had a decrease in renal function; two patients had no change and one patient an improvement in renal function. Mean systolic and diastolic blood pressure in all patients decreased from baseline values of 147±17 and 81±13 mmHg before intervention to 137±16 and 77±11 mmHg after renal angioplasty at the 6-month follow-up (P<0.001 for both). The number of antihypertensive agents significantly decreased from 2.9±1.3 to 2.6±1.4 (P=0.009). Differences in baseline characteristics between patients with and without (no change or decrease) renal function improvement are shown in *Table 1*.

Multimarker assessment

BNP

Median BNP before revascularization was 97 pg/mL (IQR, 35–254) and decreased significantly within one day after PTRA to 63 pg/mL (IQR, 24–179) (P<0.001), remaining at 75 pg/mL (IQR, 31–190) at the 6-month follow-up (P=0.03 compared to pre-intervention). BNP levels at baseline, after revascularization, and 6 months post procedure in patients with and without renal function improvement are shown in *Table 2* and *Figure 2*. The AUC for the ability to predict renal function improvement was 0.59 (95%CI, 0.48-0.70; P=0.101) for pre-intervention BNP (*Figure 3*).

eGFR

Mean baseline eGFR was significantly lower in patients with compared to patients without renal function improvement (54±23 *vs.* 73±28 mL/min/1.73 m^2, P<0.001).

Table 1 Baseline characteristics of all consecutive patients and the subgroup with impaired renal function at baseline undergoing renal artery revascularization with and without renal function improvement during follow up

Characteristics	Overall cohort (n=127)			P value	Subgroup with baseline eGFR <60 mL/min/1.73 m^2 (n=56)		P value
	All patients (n=127)	Improvement in renal function (n=42)	No improvement in renal function (n=73)		Improvement in renal function (n=27)	No improvement in renal function (n=22)	
Age, years	63±13	66±11	61±14	0.06	69±11	69±11	0.94
Female [n, (%)]	58 [46]	20 [48]	32 [44]	0.70	12 [44]	5 [23]	0.14
Diabetes mellitus [n, (%)]	21 [17]	8 [19]	9 [12]	0.41	7 [26]	5 [23]	1.00
Hypercholesterolemia [n, (%)]	93 [73]	27 [66]	58 [80]	0.12	20 [74]	20 [91]	0.16
Smoker [n, (%)]	52 [41]	16 [38]	32 [46]	0.55	10 [37]	13 [62]	0.14
Obesity [n, (%)]	45 [35]	17 [41]	24 [33]	0.43	11 [41]	9 [41]	1.00
Co-morbidities							
CAD [n, (%)]	48 [38]	14 [33]	28 [39]	0.69	11 [41]	11 [52]	0.56
Cerebrovascular disease [n, (%)]	21 [17]	6 [14]	12 [17]	0.79	4 [15]	3 [13]	1.00
PAD [n, (%)]	45 [36]	13 [31]	30 [41]	0.32	10 [37]	12 [54]	0.26
LVEF <40% [n, (%)]	6 [5]	1 [3]	5 [8]	0.66	1 [4]	4 [18]	0.14
CRP (mg/L)	7.0±9.7	8.1±8.3	6.9±11.0	0.53	10.5±9.3	12.0±17.9	0.70
Renal function							
Baseline serum creatinine (μmol/L)	112±59	128±53	104±63	0.04	155±48	168±83	0.48
Follow-up serum creatinine (μmol/L)	110±76	101±41	116±90	0.33	121±37*	192±135	0.011
Baseline eGFR (mL/min/1.73 m^2)	65±27	54±23	73±28	<0.001	40±12	41±12	0.71
Follow-up eGFR (mL/min/1.73m^2)	69±29†	70±31†	68±28	0.71	53±18*	39±14†	0.004
Baseline eGFR <60 mL/min/1.73 m^2, n [%]	56 [44]	27 [64]	22 [30]	<0.001	27 [100]	22 [100]	NA
CKD stage 1 (GFR >90 mL/min/1.73 m^2)	23 [18]	2 [5]	20 [27]	0.002	NA	NA	-
CKD stage 2 (GFR 60–89 mL/min/1.73 m^2)	48 [38]	13 [31]	31 [42]	-	NA	NA	-
CKD stage 3 (GFR 30–59 mL/min/1.73 m^2)	47 [37]	22 [52]	18 [25]	-	22 [82]	18 [82]	0.49
CKD stage 4 (GFR 15–29 mL/min/1.73 m^2)	8 [6]	5 [12]	3 [4]	-	5 [18]	3 [14]	-
CKD stage 5 (GFR <15mL/min/1.73 m^2)	1 [1]	0 [0]	1 [1]	-	0 [0]	1 [4]	-
Arterial hypertension							
SBP at baseline (mmHg)	147±17	151±20	146±16	0.13	152±20	150±15	0.68
SBP at follow-up (mmHg)	137±16*	136±16*	137±19*	0.69	136±19*	134±16*	0.62
DBP at follow-up (mmHg)	77±11*	74±9†	79±12†	0.02	71±9†	76±13	0.13

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Overall cohort (n=127)			P value	Subgroup with baseline eGFR <60 mL/min/1.73 m^2 (n=56)		P value
	All patients (n=127)	Improvement in renal function (n=42)	No improvement in renal function (n=73)		Improvement in renal function (n=27)	No improvement in renal function (n=22)	
Number of antihypertensive drugs at baseline	2.9±1.3	3.1±1.2	2.8±1.3	0.23	3.2±1.3	3.0±1.4	0.70
Number of antihypertensive drugs at follow-up	2.6±1.4†	2.7±1.6	2.6±1.3	0.83	2.6±1.5†	2.9±1.2	0.59
Renal anatomy and physiology							
Kidney length (mm)	103±13	103±13	103±14	0.88	101±13	97±13	0.27
Renal/aortal ratio at baseline	5.3±1.9	5.1±1.8	5.4±1.9	0.49	5.4±1.5	5.8±1.6	0.52
Renal/aortal ratio at follow-up	1.9±0.9*	2.0±0.8*	1.9±1.0*	0.78	1.9±0.8*	1.7±0.6*	0.21
Intrarenal RI at baseline	0.63±0.10	0.63±0.11	0.62±0.09	0.91	0.64±0.11	0.65±0.11	0.74
Contralateral intrarenal RI at baseline	0.70±0.08¶	0.72±0.09¶	0.69±0.08¶	0.09	0.73±0.08¶	0.72±0.07¶	0.64
Intrarenal RI at follow-up	0.71±0.08*	0.72±0.07*	0.69±0.07*	0.21	0.75±0.10*	0.73±0.07*	0.61
Bilateral stenosis [n, (%)]	13 [10]	6 [14]	7 [10]	0.54	6 [22]	2 [9]	0.27
≥70% stenosis [n, (%)]	105 [84]	38 [90]	58 [84]	0.40	25 [93]	21 [91]	1.00
Ostial stenosis [n, (%)]	97 [78]	30 [73]	58 [80]	0.49	20 [77]	21 [96]	0.11
Stent placed [n, (%)]	106 [85]	38 [90]	59 [81]	0.19	27 [100]	20 [91]	0.20
Fibromuscular dysplasia [n, (%)]	18 [14]	5 [12]	12 [16]	0.59	1 [5]	1 [4]	1.00

Data are expressed as mean±SD, or number (percentage) of patients. *, P<0.001 compared with baseline; †, P<0.05 compared with baseline; ¶, P<0.05 compared with RI on the stenotic side. BP indicates blood pressure; CAD, coronary artery disease; PAD, peripheral artery disease; LVEF, left ventricular ejection fraction, eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RI, resistance index.

Table 2 B-type natriuretic peptide levels in patients with and without renal function improvement during follow up

BNP levels	All patients	Improvement in renal function	No improvement in renal function	P value
Overall cohort	[n=127]	[n=42]	[n=73]	
BNP pre-intervention (pg/mL)	97 [35, 254]	103 [48, 366]	95 [31, 193]	0.10
BNP 1 day post-intervention (pg/mL)	63 [24, 179]*	87 [35, 217]*	55 [22, 144]†	0.15
%BNP decrease	−31 [−57, 6]	−35 [−55, −1]	−29 [−52, 15]	0.33
BNP 6 months post-intervention (pg/mL)	75 [31, 190]†	114 [41, 181]†	60 [23, 103]	0.47
Patients with baseline eGFR <60 mL/min/1.73 m^2	[n=56]	[n=27]	[n=22]	
BNP pre-intervention (pg/mL)	164 [65, 352]	168 [60, 399]	182 [93, 362]	0.82
BNP 1 day post-intervention (pg/mL)	118 [50, 238]†	124 [48, 235]†	139 [59, 411]	0.47
%BNP decrease	−26 [−59,10]	−30 [−60, 0]	1 [−50, 23]	0.12
BNP 6 months post-intervention (pg/mL)	125 [62, 194]†	125 [46, 181]†	169 [87, 361]	0.18

*, P<0.001 compared with BNP pre-intervention; †, P<0.05 compared with BNP pre-intervention. BNP, B-type natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fraction; RAS, renal artery stenosis. Data are expressed as median [25th and 75th percentiles), or number [percentage) of patients.

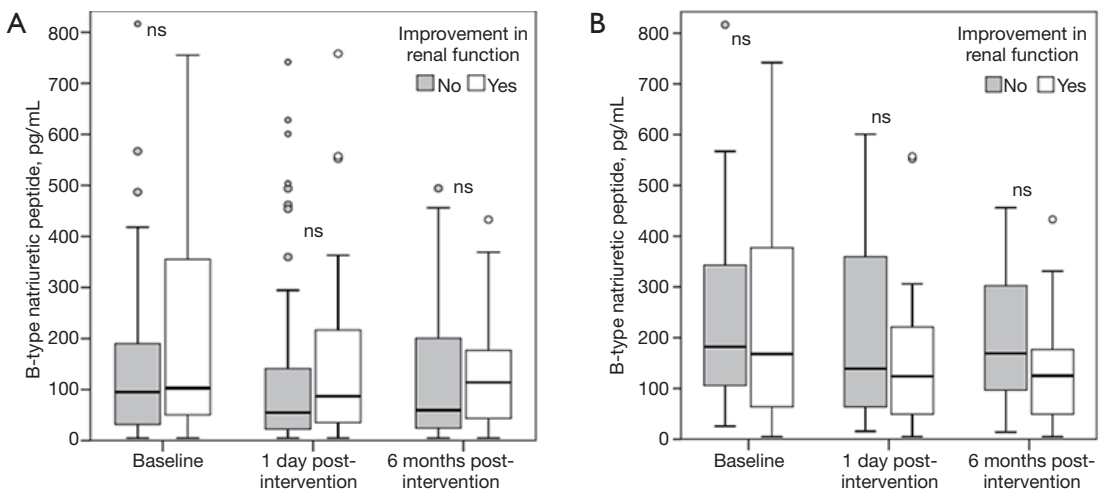

Figure 2 Box plot indicating the median (25th to 75th percentiles) and 5th–95th percentiles of BNP levels before and after percutaneous revascularization for renal artery stenosis in patients with (white) and without (gray bar) renal function improvement. (A) BNP levels in the overall cohort (n=127); (B) BNP levels in patients with impaired pre-interventional renal function (eGFR <60 mL/min/1.73 m^2) (n=56). NS indicates not significant. BNP, B-type natriuretic peptide.

The AUC for the ability to predict renal function improvement was 0.71 (95% CI, 0.61–0.81; P<0.001) for pre-intervention eGFR (*Figure 3*).

RI

Mean intrarenal RI and mean contralateral intrarenal RI at baseline was similar in patients with and without renal function improvement (0.63±0.11 *vs.* 0.62±0.09, P=0.91and 0.72±0.09 *vs.* 0.69±0.08, P=0.09). The AUC for the ability to predict renal function improvement was 0.52 (95% CI, 0.41–0.65; P=0.66) for pre-intervention RI (*Figure 3*) and 0.61 (95% CI, 0.49–0.73; P=0.06) for contralateral RI.

CRP

Mean CRP level at baseline did not significantly differ between patients with than without renal function improvement (8.1±8.3

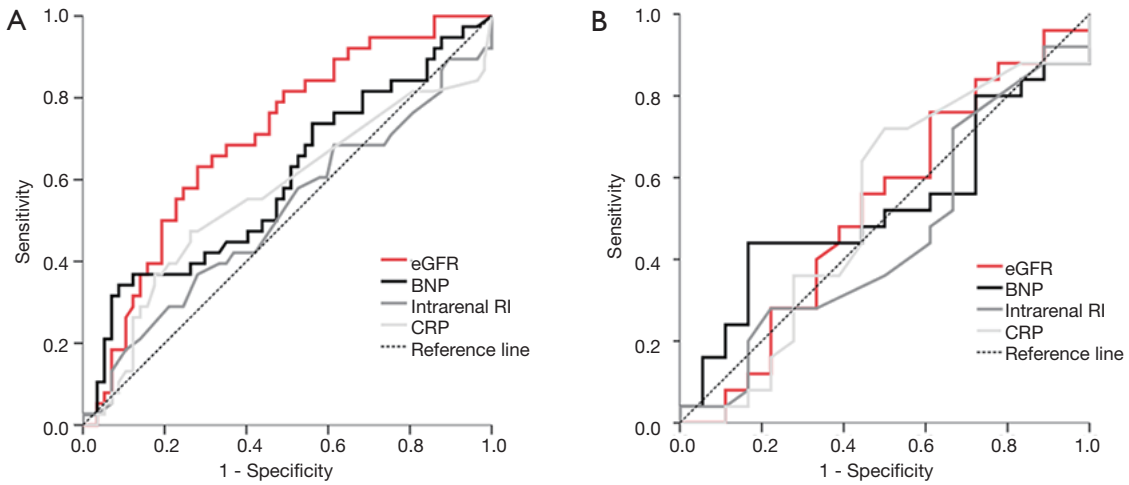

Figure 3 ROC curves for pre-interventional eGFR, BNP, intrarenal RI, and CRP for the prediction of renal function improvement at 6 months after renal angioplasty and stenting for renal artery stenosis. (A) The area under the ROC curve for the overall cohort (n=127) was 0.71 (95% CI, 0.61–0.81; P<0.001), 0.59 (95% CI, 0.48–0.70; P=0.101), 0.52 (95% CI, 0.41–0.65; P=0.66), and 0.56 (95% CI, 0.44–0.68; P=0.30), respectively; (B) the area under the ROC curve for patients with impaired pre-interventional renal function (eGFR <60 mL/min/1.73 m^2) (n=56) was 0.55 (95% CI, 0.39–0.72; P=0.53), 0.48 (95% CI, 0.32–0.65; P=0.817), 0.52 (95% CI, 0.34–0.69; P=0.84), and 0.43 (95% CI, 0.26–0.60; P=0.42), respectively. Diagonal line, no discrimination. ROC, receiver operator characteristic; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; RI, resistance index; CRP, C-reactive protein.

vs. 6.9±11.0 mg/L; P=0.53). The AUC for the ability to predict renal function improvement was 0.56 (95% CI, 0.44–0.68; P=0.30) for pre-intervention CRP (*Figure 3*).

Combination of marker

The AUC of the combination of baseline eGFR and BNP or RI or CRP for the ability to predict renal function improvement was 0.71 (95% CI, 0.60–0.79), 0.72 (95% CI, 0.61–0.80), and 0.71 (95% CI, 0.60–0.79), respectively. None of these combinations increased, however, the accuracy provided by eGFR (P=ns for all).

As shown in *Table 3*, multivariate logistic regression analysis including pre-intervention eGFR, BNP, intrarenal RI, and CRP (adjusted for age and sex) shows that only decreased pre-intervention eGFR was significantly associated with renal function improvement (OR, 0.96; 95% CI, 0.94–0.99; P=0.003).

Subgroup analysis in patients with pre-interventional impaired renal function

The clinical characteristics in patients with and without renal function improvement of the subgroup with baseline eGFR <60 mL/min/1.73 m^2 are shown in *Table 1*. In this subgroup renal function improvement was documented in 55% (27/49 patients), no change in renal function was found in 13 patients (27%), and decrease in renal function was documented in 9 patients (18%).

BNP

As shown in *Table 2* median BNP before revascularization was elevated at 168 pg/mL (IQR, 63–355) and decreased significantly within one day after PTRA to 121 pg/mL (IQR, 51–244) (P<0.001), remaining at 127 pg/mL (IQR, 60–197) at the 6-month follow-up (P=0.006 compared to pre-intervention) in this subgroup with decreased baseline eGFR.

BNP level was also not significantly different in patient with and without improvement in renal function [168 pg/mL (IQR, 60–399) *vs.* 182 pg/mL (IQR, 93–362), P=0.82] (*Figure 2B*). The decrease in BNP one day after revascularization was not significantly different in patient with than without improvement in renal function [–30% (IQR, –60 to 0) *vs.* 1% (IQR, –50 to 23), P=0.12]. The area under the receiver operating curve for the ability to predict blood renal function improvement was 0.48 (95%CI, 0.32–0.65; P=0.817) for pre-intervention BNP (*Figure 3*).

eGFR, RI, CRP

In this subgroup mean baseline eGFR, RI, and CRP did not significantly differ between patients with than without renal

Table 3 Multivariate analysis for the prediction of renal function improvement during follow up

Variables	Odds ratio (95%CI)	P value
Overall cohort (n=127)		
Age	0.99 [0.95-1.05]	0.83
Male sex	1.72 [0.67-4.42]	0.26
eGFR pre-intervention (mL/min/1.73 m^2)	0.96 [0.94-0.99]	0.003
BNP pre-intervention (pg/mL)	1.00 [0.99-1.01]	0.22
Intrarenal RI pre-intervention	0.05 [0.001-14.1]	0.30
CRP pre-intervention (mg/L)	0.65 [0.39-1.08]	0.10
Patients with baseline eGFR <60 mL/min/1.73 m^2 (n=56)		
Age	0.99 [0.92-1.08]	0.90
Male sex	4.04 [0.93-17.66]	0.06
eGFR pre-intervention (mL/min/1.73 m^2)	1.00 [0.93-1.08]	0.96
Intrarenal RI pre-intervention	0.01 [0.00-46.5]	0.28
BNP pre-intervention (pg/mL)	1.00 [0.99-1.01]	0.24
CRP pre-intervention (mg/L)	0.64 [0.36-1.15]	0.14

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide.

function improvement (*Table 1*).

The AUC for the ability to predict renal function improvement for baseline eGFR, RI, and CRP was 0.55 (95% CI, 0.39–0.72; P=0.53), 0.52 (95% CI, 0.34–0.69; P=0.84), and 0.43 (95% CI, 0.26–0.60; P=0.42), respectively (*Figure 3*).

Combination of marker

As shown in *Table 3*, multivariate logistic regression analysis in this subgroup including pre-intervention eGFR, BNP, intrarenal RI, and CRP (adjusted for age and sex) shows that none of these parameters are significantly associated with renal function improvement.

Discussion

This prospective study in unselected consecutive patients with hemodynamically relevant RAS and renal insufficiency and/or arterial hypertension referred for PTRA, evaluated the utility of a comprehensive multimarker assessment with quantification of hemodynamic cardiac stress, renal function, parenchymal renal damage, and systemic inflammation using BNP, eGFR, sonographic RI measurement, and CRP in the prediction of renal function improvement after successful revascularization.

We report five major findings. First, renal function improvement 6 months after intervention was documented in 37% of patients in the whole study cohort and in 55% of patients in the subgroup of patients with pre-interventional impaired renal function (eGFR <60 mL/min/1.73 m^2). This is in line with previous reports of 11 observational studies which showed improvement of renal function after PTRA in 39% (range, 17–60%) (12). Similarly, Zeller *et al*. demonstrated in larger study cohort improvement of renal function after stent-supported angioplasty of severe ostial RAS in 52 % of patients (13). Most of these studies, however, investigated the effects on renal function measuring serum creatinine rather than eGFR as in our study and as recommended by current guidelines (8).

Second, pre-interventional BNP is elevated in most patients with RAS and decreased significantly one day after revascularization supporting the pathophysiological concept that hemodynamically significant RAS is associated with hemodynamic cardiac stress. Third, pre-interventional BNP and decrease of BNP level after successful revascularization, however, have shown poor accuracy in the prediction of renal function improvement at 6 months. Similarly, other markers as pre-interventional intrarenal RI and CRP are not predictive for renal function improvement. Forth, only decreased pre-interventional eGFR level was associated with renal function improvement at the 6-month follow-up endpoint, independent of other clinical, laboratory and duplex sonographic parameters. Fifth, in the subgroup of patient with pre-interventional impaired renal function none of the investigated markers are predictive for renal function improvement after PTRA.

PTRA is a treatment option for patients with RAS and can be helpful in certain patient populations for improvement of renal function (1). The results of the CORAL study demonstrated no appreciable benefit with regard to the prevention of clinical events in patients with atherosclerotic RAS undergoing renal artery stenting in addition to medical therapy in comparison to those with medical therapy alone (14). In this trial during follow-up only a minimal though significant decrease was demonstrated with regard to systolic blood pressure when performing renal artery stenting in addition to medical therapy as opposed to medical therapy alone. Observational studies and larger controlled trials have shown that up to 50% of patients may have some benefit from RAS treatment with PTRA (12). As these results showed, selection of the appropriate subgroup is key when considering patients for PTRA and unselected PTRA based on the pure detection of RAS is not recommended (4,5,15). It has been suggested that those patients with a decreased renal function may benefit from RAS treatment with PTRA (16). The concept of a variety of markers to help select the appropriate patients with a high likelihood of improving renal function post-intervention is appealing. The results of this prospective non-randomized cohort trial essential reveal that a multimarker assessment with the investigated biomarkers may have only a limited benefit for RAS patient subgroup selection to undergo PTRA.

In fact, eGFR appears to be the most useful prognostic biomarker according to this trial. The patients who harbored a decreased kidney function prior to the procedure, improved markedly in their post-PTRA renal function. Previous studies are in line with these findings and have shown that particularly patients with decrease renal function can benefit from PTRA (17). Zeller *et al*. already demonstrated that baseline creatinine level and left ventricular function was an independent predictor for improved renal function after PTRA in their large cohort of patient with RAS (18). According to current guidelines eGFR, however, is a more accurate marker then creatinine level alone for renal function assessment as it in-cooperates age, gender, race information and creatinine level (19,20). This result also supports previous hypotheses why particularly patients with kidney injury benefit most from PTRA with regard to renal function improvement. Zeller *et al*. argued that reversal of RAS is most effective if hemodynamic compromise is severe enough to cause renal dysfunction or if there is a coexisting systemic prerenal component (18).

The neurohormone BNP is, therefore, an interesting biomarker in the setting of RAS. The synthesis and release happens from the bilateral ventricular myocytes secondary to volume expansion or pressure overload (21). BNP has been established in the clinical arena for assessment and follow-up of congestive heart failure patients (22,23). Prior studies demonstrated the value of BNP in RAS for prediction of blood pressure improvement post renal artery revascularization (24,25). Zeller *et al*. also demonstrated that patients with impaired left ventricular function benefit most from RAS revascularization with regard to renal function improvement (18). In this study BNP revealed not to be an accurate biomarker for renal function prediction post-PTRA. However, BNP decreased significantly in all patients and in the cohort with improved renal function post intervention. This was true for both the overall cohort and the cohort of patients with a baseline eGFR of less than 60 mL/min/1.73 m^2. A possible reason while BNP turned out not to be an accurate predictor might be related to the multi-morbid patient population with a variety of confounding factors which may impact ventricular stretch leading to alterations in BNP levels. Essentially BNP is a relative unspecific though sensitive biomarker as demonstrated by the results of this and other studies (26,27).

The RI is another potential sonographic biomarker which did not show significance for prediction of renal function improvement in this study. Previous studies showed that a pre-procedural RI of less than 0.75 enables prediction of superior clinical outcomes post-PTRA (15). Another study found similar results with a RI of more than 0.80 being reliable to determine those patients whose renal function will not be improved post renal revascularization therapy (which was either surgery or renal artery angioplasty) (28). This, however, has been challenged by prospective cohort studies (29). The RI is a biomarker of vascular impedance derived from ultrasound Doppler, hence measuring arterial stiffness (30). Previous studies revealed a correlation of the RI with irreversible renal parenchyma histological changes of the glomerular and tubulo-interstitial system (31). Therefore, people with high RI may already suffer from advanced renal parenchymal disease and most likely do not profit from PTRA (32). One reason why RI did not correlate with clinical outcome in our study could be that patients with very high RI over 0.8 were pre-selected and not referred for PTRA.

CRP turned out to be unhelpful for prediction of renal function improvement post-PTRA in RAS patients. CRP is a highly sensitive but unspecific biomarker for

inflammation and ischemia (33). CRP is influenced by a multitude of factors and had be investigated in a variety of clinical settings including the presence of RAS as a serial biomarker for assessing the inflammatory and ischemic status of patients as well as predicting cardiovascular and cerebrovascular events (34-37). CRP was included in the study to evaluate its predictive value in a multimarker assessment approach. However, the inflammatory component measured by serum CRP level seems not to be related with renal function improvement post intervention.

Study limitations

Several limitations apply to this study. In this prospective, non-randomized cohort study all of the patients received percutaneous revascularization of RAS without inclusion of any control group. Therefore, we cannot preclude that factors other than RAS may have contributed to the elevation and decrease of BNP after PTRA. However, median levels of BNP in our cohort with RAS were elevated compared to a previously published healthy control group as well as to a patient population with severe essential hypertension (10,38). Furthermore, we also estimated the eGFR based on creatinine value using an established equation and we did not measure eGFR directly using ^{125}I-iothalamate which has been shown to be more sensitive and reliable for detecting meaningful changes in eGFR after PTRA (39). Furthermore, we did not assess renal mass by ultrasonography as an additional marker for renal function. However, the use of eGFR has been accepted in the guidelines for the assessment of renal function after PTRA and is well established also in larger randomized controlled trials (14).

Another limitation of the prospective study was the follow-up time of 6 months post-PTRA and no standardized optimized medical therapy was performed in all patient universally as recommended by recent trials (4). In future studies longer follow-up times post intervention and standardized optimized medical/conservative therapy are warranted to further validate the results of the current study.

Conclusions

Quantification of renal function, but not any other pathophysiologic signal, provides at least moderate accuracy in the identification of patients with RAS in whom PTRA will improve renal function. Lower eGFR indicates a higher likelihood for eGFR improvement after PTRA. Further studies are needed to improve the selection of patients with RAS who benefit most from PTRA.

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Footnote

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